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ORIGINAL ARTICLE

Novel and validated titrimetric method for determination of selected angiotensin-II-receptor antagonists in pharmaceutical preparations and its comparison with UV spectrophotometric determination

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Abstract A novel and simple titrimetric method for determination of commonly used angiotensin-II-receptor antagonists (ARA-IIs) is developed and validated. The direct acid base titration of four ARA-IIs, namely eprosartan mesylate, irbesartan, telmisartan and valsartan, was carried out in the mixture of ethanol:water (1:1) as solvent using standardized sodium hydroxide aqueous solution as titrant, either visually using phenolphthalein as an indicator or potentiometrically using combined pH electrode. The method was found to be accurate and precise, having relative standard deviation of less than 2% for all ARA-IIs studied. Also, it was shown that the method could be successfully applied to the assay of commercial pharmaceuticals containing the above-mentioned ARA-IIs. The validity of the method was tested by the recovery studies of standard addition to pharmaceuticals and the results were found to be satisfactory. Results obtained by this method were found to be in good agreement with those obtained by UV spectrophotometric method. For UV spectrophotometric analysis ethanol was used as a solvent and wavelength of 233 nm, 246 nm, 296 nm, and 250 nm was selected for determination of eprosartan mesylate, irbesartan, telmisartan, and valsartan respectively. The proposed titrimetric method is simple, rapid, convenient and sufficiently precise for quality control purposes.

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1. Introduction

Many of the active components of pharmaceutical preparations are of organic origin and contain acidic or basic groups. Such compounds can be successfully determined in their pharmaceutical preparations using titrimetric methods. The purpose of this work was to develop a simple, accurate, reproducible and rapid titrimetric method for the determination of commonly used angiotensin-II-receptor antagonists

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(ARA-IIs) such as eprosartan mesylate (I), irbesartan (II), telmisartan (III) and valsartan (IV), and applying it to the pharmaceutical dosage forms. These compounds contain either carboxylic acid group or tetrazole ring or both which act as an acidic centre and form the basis for acid–base reactions during titration. The structural formulae of these ARA-IIs are given in Fig. 1.

These ARA-IIs are safe and effective agents in the treatment of hypertension and heart failure, either alone or in conjunction with diuretics. They have been proposed as alternatives to the more traditional angiotensin converting enzyme (ACE) inhibitors because they selectively block the angiotensin type 1 (AT1) receptor, which is responsible for vasoconstriction, and salt and water retention. The angiotensin type 2 (AT2) receptor, which is thought to have cardioprotective effects and inhibitory effects on growth, is left unaffected [1–6].

Several methods that are reported for ARA-IIs compounds estimation include enzyme-linked immunosorbent assays (ELISAs) for the determination of telmisartan in human blood plasma [7], spetrofluorimetric for the determination of valsartan in human urine [8], colorimetric method [9], and UV-derivative spectrophotometric [10] for the determination of ARA-II in bulk and in tablets. Tatar and Saglik [11] compared UV- and second derivative-spectrophotometric and high-performance liquid chromatographic methods for the determination of valsartan in pharmaceutical formulation. Also, capillary electrophoresis (CE), capillary electrochromatography (CEC), micellar electrokinetic capillary chromatography (MEKC) and capillary zone electrophoresis (CZE) methods have also been reported [12–16]. High-performance liquid chromatography has been the major technique used in the determination of these compounds in different matrices with UV [17–24], fluorimetric [25–27] or mass spectrometry (MS) detections [28–30]. Validated methods which allow the determination of a single drug [31–39] or combination of ARA-IIs with hydrochlorothiazide or some of their metabolites [40–43] in urine, plasma and in pharmaceutical formulations [44] have also been published.

Although chromatographic techniques have been suggested for the determination of ARA-IIs, it requires high skilful operator and expensive instrument. In addition, most of the described procedures require expensive instrumental setup. So, there is a need to develop a simple, reliable, rapid and economical method for the determination of ARA-IIs in pharmaceuticals.

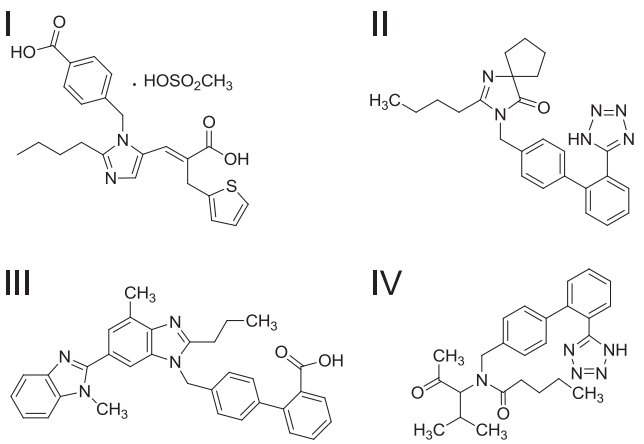

Figure 1 Structural formulae of angiotensin-II-receptor antagonists: (I) Eprosartan mesylate, (II) Irbesartan, (III) Telmisartan and (IV) Valsartan.

No titrimetric method for determination of ARA-IIs has been found in literature. In this paper, the validated titrimetric method is described for the determination of ARA-IIs in pharmaceuticals. The method is based on the titration of the drug solution in neutral ethanol:water mixture (1:1) with aqueous NaOH to a phenolphthalein end point or potentiometric equivalence point. In this paper the proposed titrimetric method is a very simple technique and adoptable for routine analysis to determine the content of ARA-IIs at milligram level in the quality control laboratories.

Because of unavailability of pharmacopial method for some of these ARA-IIs, UV spectrophotometric method has been developed for statistical comparison with results obtained by proposed titrimetric method. A comparison of results obtained by the proposed titrimetric method and those obtained by UV method shows good statistical correlation.

2. Materials and methods

2.1. Apparatus

A Jenway 3020 digital pH meter equipped with a combined pH-electrode was used throughout the study. All titrations were carried out manually. A shimadzu UV–visible recording spectrophotometer (model UV2501 PC) with 1 cm matched quartz cells was used for spectrophotometric analysis.

2.2. Reagents and materials

Eprosartan mesylate, valsartan, and telmisartan were obtained from Glenmark Pharmaceutical Ltd. Sinnar, Nasik, India; and irbesartan was obtained from Cadila Healthcare Ltd., Ahmedabad, India. These ARA-IIs were chemically pure laboratory working standards having purities of 99.8%, 99.4%, 99.6% and 99.3%. Sodium hydroxide, ethanol, potassium hydrogen phthalate, and phenolphthalein powder were obtained from Merck, India and S.D's Lab Chem & Industries, Bombay. Teveten (eprosartan mesylate), Karvea (irbesartan), Telsartan (telmisartan) and Diovan (valsartan) tablets were obtained from a local pharmacy. All chemicals were of analytical reagent grade unless otherwise stated, and doubly distilled deionised water was used throughout.

Sodium hydroxide (*0.01 M*): Accurately 0.2 g of the pure NaOH (Merck, India) was dissolved in doubly distilled water. The solution was made up to 500 mL with the same water and standardized [45].

Phenolphthalein indicator (*0.5%*): It was prepared by dissolving 500 mg of the pure phenolphthalein powder (S.D's Lab Chem & Industries, Bombay) in 50 mL alcohol and diluting to 100 mL with doubly distilled water.

2.3. Procedures

2.3.1. Potentiometric titration

Accurately weighed quantities (2.0–10.0 mg) of four ARA-IIs, namely eprosartan mesylate, irbesartan, telmisartan and

valsartan, were dissolved separately in 20 mL mixture (1:1) of ethanol and water, depending upon their molar weights. Ethanol should be previously neutralized to phenolphthalein solution. All the assay solutions were prepared prior to titrations directly in a titration cell, and titrated with standardized sodium hydroxide aqueous solution using potentiometric titration with a combined platinum ring electrode. Near the equivalence point, titrant was added in 0.05 mL increments. After each addition of titrant, the solution was stirred magnetically for 30 s and the steady potential was noted. The addition of titrant was continued until no significant change in potential on further addition of titrant. The equivalence point was determined by applying the graphical method. The amount of the drug in the measured aliquot was calculated from:

$$Amount\ (\text{mg}) = VMwR/n$$

where V is the volume of NaOH required, mL; Mw is the relative molecular mass of the drug; R is the molarity of NaOH and n is the number of moles of NaOH reacting with each mole of the drug.

2.3.2. Visual titration

Accurately weighed quantities (2.0–10.0 mg) of four ARA-IIs, namely eprosartan mesylate, irbesartan, telmisartan and valsartan, were dissolved separately in a mixture of 10 mL of water and 10 mL of neutral ethanol depending upon their molar weights. All the assay solutions were titrated with standardized sodium hydroxide aqueous solution using 2–4 drops of 0.5% phenolphthalein indicator to a pink colour end point. The amount of the drug in the measured aliquot was calculated as described under potentiometric titration.

2.3.3. Titrimetric determination of ARA-IIs from pharmaceutical preparations

Twenty tablets were weighed, and their average weights were calculated. All the tablets were finely powdered and the required amounts of these powders were dissolved in a mixture of 10 mL of water and 10 mL of ethanol. The mixture was sonicated for 5 min and filtered using Whatmann No 42 filter paper. A suitable aliquot was next subjected to analysis by potentiometry and visual titration method as described earlier.

The titrations were repeated for different amounts of each ARA-II and pharmaceutical preparation.

2.3.4. UV-spectrophotometric method

For obtaining calibration curve for UV-method, a series of solutions were prepared for each ARA-II within their Beer–Lambert's range of concentration as shown in Table 1, by diluting the respective stock ARA-II solution (0.1 mg/mL in ethanol) with ethanol in volumetric flasks (10 mL). The absorbance of each solution was determined at respective lambda max of the drug as shown in Table 1 against ethanol as blank. A calibration curve was prepared by plotting absorbance versus concentration for each ARA-II. Absorption spectra of ARA-IIs are given in Fig. 2.

2.3.5. UV spectroscopic determination of ARA-IIs from pharmaceutical preparations

Twenty tablets were weighed, and their average weights were calculated. All the tablets were finely powdered and the required amounts of these powders were dissolved in 20 mL of ethanol. The mixture was sonicated for 5 min and filtered using Whatmann No 42 filter paper. After suitable dilution, absorbance was recorded against the blank at respective lambda max of drug as shown in Table 1.

2.4. Method validation

Both potentiometric and UV spectroscopic methods were validated in compliance with ICH guidelines. The following parameters were validated.

2.4.1. Precision

The precision of the potentiometric and UV spectroscopic methods was evaluated in terms of intermediate precision (intra-day and inter-day). Three different amounts of ARA-IIs within the range of study in each method were analyzed in five replicates during the same day (intra-day precision) and five consecutive days (inter-day precision).

2.4.2. Recovery studies

Accuracy and the reliability of both methods were ascertained by performing recovery experiments. To a fixed amount of drug in formulation (pre-analyzed): pure drug at three different levels corresponding to its 80%, 100% and 120% was added (standard addition method), and the total was found by the proposed methods. Each test was repeated three times and the results obtained were compared with expected results.

2.4.3. Ruggedness

Ruggedness of both methods was done at three different concentration levels of each ARA-II within the range of study in each method.

Ruggedness of potentiometric method was expressed as the RSD of the same procedure applied by three different analysts as well as using three different burettes.

The ruggedness of the UV spectroscopic method was determined by carrying out the experiment on three different instruments and by three different analysts.

Table 1 Summary of optical characteristics and validation parameters of ARA-IIs.

Parameters	Eprosartan mesylate	Irbesartan	Telmisartan	Valsartan
Lambda max (nm)	233	246	296	250
Beer's law limit (range) (μg/mL)	6–36	2–36	4–30	2–20
Correlation coefficient (r ± S.D.)	0.999 ± 0.690	0.999 ± 0.450	0.999 ± 0.390	0.999 ± 0.560
Regression equation	$Y=0.056x+0.023$	$Y=0.036x+0.023$	$Y=0.056x+0.023$	$Y=0.0328x+0.0206$
LOD (μg/mL)	0.4142	0.5119	0.2579	0.1337
LOQ (μg/mL)	1.2552	1.5495	0.7805	0.4052

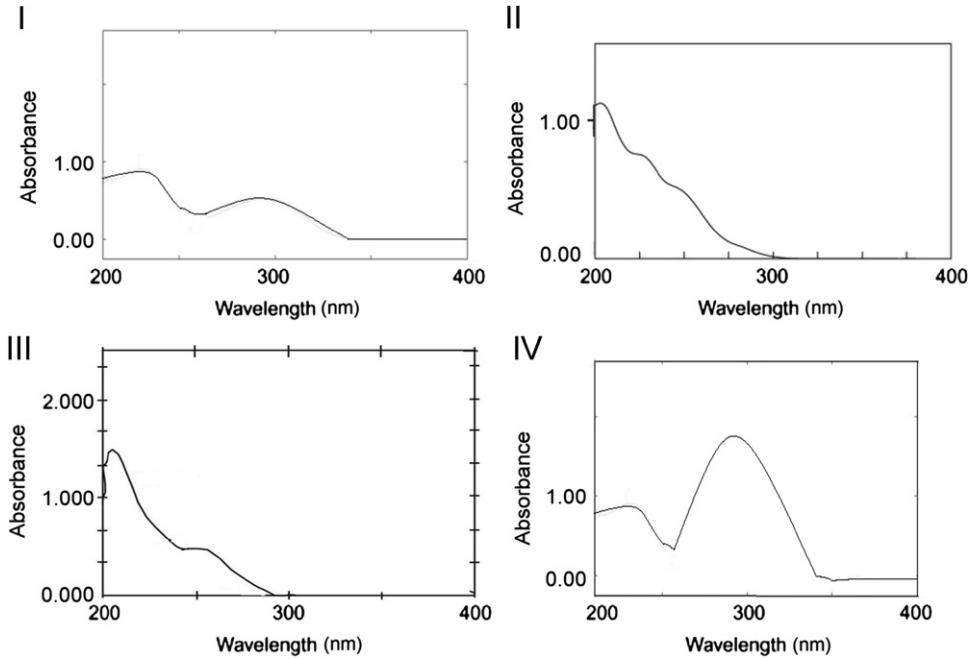

Figure 2 Absorption spectra of angiotensin-II-receptor antagonists: (I) Eprosartan mesylate, (II) Irbesartan, (III) Valsartan and (IV) Telmisartan.

2.4.4. *Linearity*

2.4.4.1. Potentiometric method. For the establishment of method linearity, five different weights of ARA-IIs test samples corresponding to 20%,40%, 60%, 80% and 100% of the about weight 20 mg were taken and analyzed potentiometrically. Calibration curve was drawn by plotting test sample weight on X axis and titre values on Y axis. The values of correlation coefficient, slope and intercept were determined.

2.4.4.2. UV spectroscopic method. Appropriate dilutions of standard stock solutions of each ARA-II were analyzed as per the developed methods. Beer–Lambert's concentration range and linearity data were determined.

2.4.5. *LOD and LOQ*

For UV method, limit of detection (LOD) and limit of quantification (LOQ) of each ARA-II were calculated as $3.3\,\partial/S$ and $10\,\partial/S$, respectively as per ICH guidelines, where ∂ is the standard deviation of the response and S is the slope of the calibration plot. The LOD is the smallest concentration of the analyte that gives a measurable response. The LOQ is the smallest concentration of the analyte which gives response that can be accurately quantified.

3. Results and discussion

3.1. *Titrimetric measurements*

3.1.1. *Potentiometric determination of standard active components*

ARA-IIs were titrated direct potentiometrically in a mixture of ethanol and water (1:1) using standardized sodium hydroxide aqueous solution as a titrant. The titration curve of ARA-IIs showed one well-defined S-shaped stoichiometric end-point (Fig. 3). The determination of the end points from the potentiometric data was carried out using the Gran's method [46].

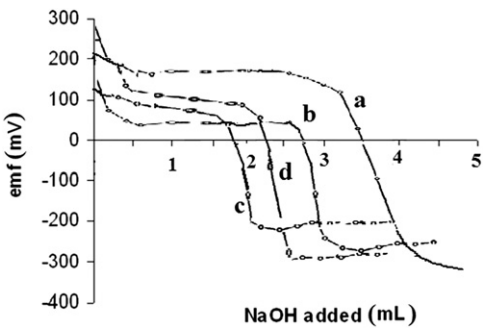

Figure 3 Potentiometric titration curve for ARA-IIs titrated with standardized sodium hydroxide aqueous solution ((a) Eprosartan mesylate, (b) Irbesartan, (c) Telmisartan, and (d) Valsartan).

Table 2 gives detail about acidic centres present in ARA-IIs which corresponds to the number of equivalent of bases required for neutralization to have the end point. For example the end point of telmisartan corresponded to one equivalent of base and was related to the neutralization of one –COOH group.

The percentage of each ARA-II (chemically pure laboratory working standard) was calculated from the potentiometric titration data. Five successive determinations were carried out for each ARA-II. The results are tabulated in Table 3. As seen from the data in Table 3, the mean values obtained by the proposed method are in good agreement with the nominal value given for each ARA-II and furthermore the relative standard deviations are less than 1%. This indicates that the accuracy and the precision of this method are satisfactory.

Table 2 Acidic centres present in ARA-IIs which take part in neutralization to have the end point.

ARA-IIs	Number of active acidic centres involved in neutralization	Site of active acidic centres involved in neutralization	Molecular weight
Eprosartan mesylate	Three	(a) Phenylic–COOH (b) Allylic–COOH (c) Mesylate (sulphonate)	520.0
Irbesartan	One	(a) Tetrazole	428.5
Telmisartan	One	(a) –COOH	514.0
Valsartan	Two	(a) Tetrazole (b) –COOH	435.0

Table 3 Titrimetric determinations of ARA-IIs which are chemically pure laboratory working standards.

ARA-IIs	Potentiometric determination (Mean ± RSD) (%)*	Visual titrimetric determination (Mean ± RSD) (%)*	Nominal value (%)
Eprosartan mesylate	99.71 ± 0.45	99.76 ± 0.32	99.8
Irbesartan	99.25 ± 0.35	99.20 ± 0.44	99.3
Telmisartan	99.52 ± 0.68	99.54 ± 0.72	99.6
Valsartan	99.42 ± 0.62	99.45 ± 0.58	99.4

*Average of five determinations.

3.1.2. *Visual titrimetric determination of standard active components*

The percentage of each ARA-II (chemically pure laboratory working standard) was calculated from the visual titration data. Five successive determinations were carried out for each ARA-II. As seen from the data in Table 3, results obtained by this method were found to be in good agreement with those obtained by potentiometric method.

3.1.3. *Titrimetric determination of ARA-IIs in dosage forms*

In order to evaluate the applicability of the above-mentioned titrimetric methods to pharmaceutical preparations, ARA-IIs were determined in their pharmaceutical preparations respectively, under the same conditions as employed for the pure anti-inflammatory agents. The fact that the mV values before the end-points in the titration curves of pure anti-inflammatory agents and their corresponding pharmaceuticals are almost identical provides evidence that the titration curves are not due to other excipients that might be present in the pharmaceutical preparations and excipients do not affect the titration curves. The excipients in the above-mentioned pharmaceutical preparation do not include acidic substances.

Table 4 summarizes the results obtained for each anti-inflammatory agent in the corresponding pharmaceuticals, expressed as percentages of the nominal contents. The results are in good agreement with the nominal contents and the RSD values are less than 1%. Thus, the reproducibility and accuracy are very satisfactory for the analysis of pharmaceutical preparations as well as bulk drugs. These results indicate that the content of each ARA-II in the pharmaceuticals can be safely determined using titrimetric method without interference from other substances in the preparations.

3.2. *UV-spectrophotometric measurements*

Lambda max, Beer's law limit (concentration range), correlation coefficient (r) and regression equation obtained by UV-spectrophotometric method for each ARA-II are given in Table 1. The proposed UV-spectrophotometric method was also successfully applied for the determination of ARA-IIs in some pharmaceutical preparations (Table 4). The results are in good agreement with the nominal contents and the RSD values are less than 1%. Thus, the reproducibility and accuracy are very satisfactory for the analysis of pharmaceutical preparations as well as bulk drugs.

3.3. *Validation*

3.3.1. *Recovery studies*

The recovery studies of standard additions to commercial pharmaceuticals were carried out in order to determinate accuracy and selectivity of the method. In these titrations, as the amount of pure standard added to commercial pharmaceuticals increases, the volume of titrant used increases linearly. The results related to these studies are presented in Table 5. It can be seen from this Table that the mean recoveries and RSD values are good evidence of the accuracy of the method.

3.3.2. *Precision*

The RSD values of intra-day and inter-day precision of the potentiometric and UV spectroscopic methods for all ARA-IIs showed that the precision of both methods was good (Table 6).

3.3.3. *Ruggedness*

The RSD values of inter analyst as well as inter instrument analysis were less than 2% for potentiometric method as well as UV spectrometric method. This proves good ruggedness of the method(Table 7).

3.3.4. *LOD and LOQ*

For UV method, LOD and LOQ of each ARA-II are presented in Table 1.

Table 4 Determinations of ARA-IIs in some pharmaceutical preparations by the proposed methods.

Pharmaceuticals	ARA-IIs	Lable claim (mg)	Percent lable claim estimated (Mean ± RSD) (%)		
			Potentiometric	Visual titrimetric	UV spectroscopic
Teveten	Eprosartan mesylate	400	100.51 ± 0.71	100.26 ± 0.28	99.990 ± 0.32
Karvea	Irbesartan	300	100.33 ± 0.52	99.16 ± 0.42	100.11 ± 0.22
Telsartan	Telmisartan	80	100.10 ± 0.42	100.55 ± 0.64	100.27 ± 0.47
Diovan	Valsartan	160	99.96 ± 0.32	100.34 ± 0.46	100.66 ± 0.57

Table 5 Recovery studies by standard additions technique.

ARA-IIs	Excess drug added to the analyte (%)	Potentiometry			UV spectroscopy		
		Recovery* (%)	RSD (%)	S.E.	Recovery* (%)	RSD (%)	S.E.
Eprosartan mesylate	80	98.71	0.66	0.22	98.55	0.26	0.81
	100	99.65	1.10	0.66	98.94	1.15	0.95
	120	99.59	0.82	0.51	98.89	0.63	1.14
Irbesartan	80	99.02	0.95	0.61	99.10	1.16	1.54
	100	99.15	1.12	0.34	99.16	1.19	0.69
	120	99.20	0.66	0.38	99.19	1.98	1.84
Telmisartan	80	99.88	0.69	0.44	99.68	1.68	1.52
	100	99.94	0.84	0.48	99.59	1.48	1.94
	120	99.79	1.12	0.39	99.54	1.50	1.80
Valsartan	80	98.99	1.19	0.47	99.94	0.94	1.83
	100	99.11	1.21	0.52	100.10	0.87	1.39
	120	99.08	0.99	0.59	99.89	1.16	1.47

*Average of three determinations.

Table 6 Precision of ARA-IIs by potentiometry and UV spectroscopy.

ARA-IIs*	Potentiometry ($n=5$)		UV spectroscopy ($n=5$)	
	Intra-day (RSD) (%)	Inter-day (RSD) (%)	Intra-day (RSD) (%)	Inter-day (RSD) (%)
Eprosartan mesylate	1.20	1.05	1.59	1.46
Irbesartan	1.85	0.95	1.29	1.90
Telmisartan	1.54	1.34	1.90	1.10
Valsartan	1.45	0.92	1.16	1.55

*Average of three concentrations of each ARA-II within the range of study in each method.

Table 7 Ruggedness of ARA-IIs by potentiometry and UV spectroscopy.

ARA-IIs*	Potentiometry (RSD) (%) ($n=3$)		UV spectroscopy (RSD) (%) ($n=3$)	
	Inter-analysts	Inter-instruments	Inter-analysts	Inter-instruments
Eprosartan mesylate	1.75	0.96	1.39	1.12
Irbesartan	1.65	1.54	1.84	1.28
Telmisartan	1.32	1.32	1.69	1.31
Valsartan	1.19	1.29	1.34	1.39

*Average of three concentrations of each ARA-II within the range of study in each method.

3.3.5. *Comparison between developed methods*

ARA-IIs were determined in pharmaceutical preparations by the developed methods and the results obtained are presented in Table 4 where excellent agreement between the three procedures can be observed. The statistical comparison of the results shows that, there is no significant difference between results of UV-spectrophotometric and potentiometric methods ($t=1.49$, $F=1.16$); UV-spectrophotometric and visual titrimetric methods ($t=1.18$, $F=1.33$) since the calculated t- and F-tests did not exceed the theoretical values ($n=5$, $p=0.05$, $t=2.23$, $F=5.05$) at the 95% confidence level (Table 8).

4. Conclusion

Statistical tests indicate that the proposed titrimetric and UV methods appear to be equally suitable for routine determination

Table 8 Linearity studies for potentiometric method only.

ARA-IIs	Correlation coefficient ($r \pm$S.D.)	Slope $\pm$S.D.	Regression equation
Eprosartan mesylate	0.999 $\pm$ 1.120	1.23 $\pm$ 0.58	$Y=1.23x+0.0017$
Irbesartan	0.998 $\pm$ 1.190	0.07 $\pm$ 0.01	$Y=0.07x+0.0003$
Telmisartan	0.999 $\pm$ 0.960	1.65 $\pm$ 0.87	$Y=1.65x+0.0003$
Valsartan	0.999 $\pm$ 1.150	1.13 $\pm$ 0.84	$Y=1.13x+0.0001$

of ARA-IIs in pharmaceutical formulation. As a result of this work, ARA-IIs can now be determined titrimetrically by the proposed method. This aqueous titrimetric assay was successfully applied to the determination of pure authentic samples and some of their pharmaceutical preparations. In the proposed method, the titrations of all ARA-IIs have shown rather well shaped end-points with high potential jumps. In conclusion, the proposed titrimetric method could be utilized readily for routine analysis of pharmaceuticals since the reported methods in literature survey suffer from drawbacks such as high cost, multiple steps and time consuming, also costly solvents (HPLC) while proposed titrimetric method offers a simple system and with the short analytical time, coupled with good reproducibility, accuracy, ruggedness and cost-effectiveness.

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