DIRECT DETERMINATION OF SOME ADRENERGIC DRUGS BY THERMOMETRIC TITRIMETRY USING N-*BROMOSUCCINIMIDE*

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Abstract

A rapid and specific method for the determination of ephedrine HCl, norephedrine HCl, adrenaline and isopropylnoradrenaline in pure and in the presence of excipients is reported. The method is based on the oxidation reaction with N-bromosuccinimide in the acidic medium. The heat of reaction is used to determine the end point of the titration. The validity of the method was tested by comparing to those results obtained by official procedures. The accuracy and precision is analytically acceptable and the time required is less than five minutes.

Introduction

The four adrenergic drugs namely ephedrine Hydrochloride, Norephedrine Hydrochloride, adrenaline and isopropylnoradrenaline have been widely used in various pharmaceutical preparations for many years, as sympathomimetric drugs that stimulate both alpha (α) and beta (β) adrenergic receptors. They are used in therapeutic doses at the level of 15–60 mg, to produce peripheral vasoconstriction, to raise blood pressure, to prevent hypotension and to treat allergic states, catalepsy and myasthenia gravis. They are also used as antidote for poisoning by the central nervous system depressant. Methods of their quantitative analysis include nonaqueous titration[1] polarography[2], amperometry[3], spectrophotometry[4,5] and chromatography[6]. Recently a specific method has been described in the literature[7] based on the oxidation reaction of adrenaline and isopropylnoradrenaline in aqueous solution in presence of silver oxide to give a red colour measurement at 490 nm.

In pharmaceutical analysis, problems are often associated with the matrix and with the amount of active ingredients present. Dosage form of pharmaceutical products including tablets, injections, drops and capsules, etc., usually contain diluents in the form of excipients; these are starch, lactose, calcium lactates, magnesium sterate for solids and colouring agents for both solids and solutions and often flavourings to give acceptability to the product. Rapid monitoring processes, which are relatively easily automated are required. Whilst it is necessary to have high accuracy, generally ± 2% is acceptable. The presence of these materials, some coloured, some surface active, many insoluble in the aqueous or non-aqueous solutions used, render direct methods of analysis involving absorptiometry an impossibility; many electrode system used in electroanalysis are affected by the presence of the surface active agents; hence the classical or official methods used for the determination of the above drugs in various pharmaceutical preparations are usually based on extraction as a free base, followed by spectrophotometric determination[8]. Many organic compounds, drugs excipients and various organic bases, however absorb at the same wavelength and hence significantly interfere.

The determination of drugs by thermometric method has been suggested, provided that the components of the matrix do not react with the reagent used for assay of the functional group, then thermometric method can be used without separation of the matrix. It therefore, means that prior separation is not necessary. Thus many classes of the compounds have been assayed in dosage forms in our earlier work. For example determination of antihypertensive and antipyretic drugs using N-Bromosuccinimide[9]. In general the heats of reaction are such that single tablet may be assayed by thermometric methods. Thermometry is favoured for routine monitoring systems simply because of the simplicity, rapidity, precision and accuracy. Following our previous work we have developed a simple method which is based on the bromination and/or oxidation of ephedrine, norephedrine, adrenaline and isopropylnoradernaline with N-bromosuccinimide (NBS)-a well known reagent[10]. These procedures were then applied for quantitative estimation of pharmaceutical dosage forms of these compounds available locally.

Experimental

Instrumentation and procedure

The instrument was designed and constructed as described previously[11] with certain modifications. The basic electrical circuit has a simple D.C. Wheatstone bridge, having a thermistor of nominal resistance of 10 k ohms at 25°C, (Standard

Telephone and Cables Ltd, Model F-14). The off balance voltage was recorded on a potentiometer (2 mv F.S.D) via operational amplifier with a chart speed of 6 cm per minute.

For the accurate and precise delivery of the titrant and titrtrand a Mettler automatic titrator model DV 11 and 13 was coupled with the instrument. The delivery rate was monitored by gravimetry, delivering 4.47 cm^3 per minute. The titrant was maintained at constant temperature of 24 ± 0.01°C by passing it through a thermostat before it entered the titration vessel. The vessel, a thick walled polythene bottle of nominal capacity 15 cm^3, was thermally insulated in polystyrene block so that the heat losses over a period of titration were not significant. A known amount of each sample was placed in the titration vessel and was stirred until the thermal stability was achieved. The analyte was titrated with standard NBS and the amount of sample was estimated from the enthalpogram. The equivalence point was obtained by extrapolation of the linear part of the graph before and after the curvature at the end point. The length of the trace corresponding to the volume of the titrant consumed and the amount of drug was then calculated from the difference between the volumes of NBS consumed in the control blank and the actual determination as:

$$\text{mgs of drug} = (A - B)\, M/n$$

where A = volume of NBS consumed by the actual sample; B = volume of NBS consumed by the blank sample, M = molar concentration of NBS and n = moles of NBS consumed per mole of the sample.

Reagents

The ephedrine HCl, norephederine HCl, adrenaline and isopropylenoradrenaline of analar grade were obtained from Flaka, Switzerland. N-bromosuccinimide was obtained from Merck and was used without any further purification. The identity and purity of the compounds were verified by UV, m.p. and TLC[12]. An appropriate amount of each of these reagents were dissolved in 100 cm^3 of freshly prepared and cooled double distilled water. The NBS was standardised by standard sodium thiosulphate solution[13]. All the solutions were freshly prepared each time.

Effect of Variables

The effect of variables such as temperature, pH of the reaction medium, NBS concentration and the commonly used matrices have been studied to optimize

reaction conditions. The optimum concentration of NBS was found to be 0.01 M and the solution was freshly prepared.

The effect of several matrix ingredients used, such as starch, lactose, and magnesium sterate, have also been determined. There was no interference by these substances (Table.3).

Results and Discussion

The complete bromination of catecholamines with N–bromosuccinimide (NBS) is fast and quantitative, the completion of the reaction takes less than five minutes. Longer reaction time has no effect on the over all determinations and a linear correlation was obtained between the amount of drug analysed and the response of the thermistor (sensor) over the range of 10 to 50 mg. A series of thermometric titrations were carried out in 0.01N Hydrochloric acid with standard solution of oxidizing agent (NBS) in which pure drugs were used. Typical results are shown in Table 1.

The value of molar ratio has been reported earlier in the spectrophotometric studies of these compounds[14] and have also been confirmed in the present work.

The method was applied successfully to the determination of adrenergic drugs in different commercially available forms. The recoveries by the pharmaceutical codex method[8] involving a prior extraction of the free base with cyclohexane followed by spectrophotometric determination of catecholamines was also used for comparison. The results obtained by both methods are in good agreement (Table 2).

Conclusion

In previously reported method[7] for the determination of catacholemine the effect of the temperature was critical; gradual destruction of red colour was followed by distinct decrease in the absorbance due to oxidation reactions of the catecholamines at the elevated temperatures. Therefore, variation in the temperature may lead to spurious result. The proposed thermometric method for the determination of pharmaceutical compounds, offers several advantages in terms of speed, precision, accuracy and selectivity in the presence of manufacturing impurities, than the classical, potentiometric and spectrophotometric techniques. It provides analytically acceptable results for routine analysis in dosage form.

Table 1 Assay of the pure test drug by Thermometric Titrimetry

S.No.	Sample	Amount taken	Amount found	Recovery	Molar Ratio	Std Deviation	Co-efficient
1.	Ephedrine HCl	10.00	9.9	99.96	1:8	0.40	0.40
		15.00	14.85	99.96			
		20.00	20.008	100.04			
		25.00	24.95	99.82			
		30.00	29.85	99.5			
		35.00	35.01	100.04			
		40.00	39.90	99.77			
		45.00	45.01	100.04			
		50.00	49.86	99.72			
2.	Noreph-edrine HCl	10.00	10.00	100.00	1:8	0.30	0.30
		15.00	14.95	99.67			
		20.00	19.83	99.19			
		25.00	25.04	100.16			
		30.00	30.00	100.00			
		35.00	34.83	99.53			
		40.00	40.00	100.00			
		45.00	44.75	99.46			
		50.00	50.00	100.00			
3.	Adrenaline	10.00	9.94	99.42	1:8	0.17	0.17
		15.00	14.90	99.37			
		20.00	19.92	99.60			
		25.00	24.98	99.92			
		30.00	29.92	99.75			
		35.00	34.95	99.87			
		40.00	39.90	99.75			
		45.00	44.89	99.75			
		50.00	49.87	99.78			
4.	Isopropyl Noradre-naline	10.00	9.95	99.52	1:8	0.15	0.15
		15.00	14.89	99.27			
		20.00	19.94	99.73			
		25.00	24.86	99.45			
		30.00	29.91	99.73			
		35.00	34.83	99.53			
		40.00	39.89	99.73			
		45.00	44.81	99.57			
		50.00	49.86	99.73			

* Each reading is the average of 11 values quoted.

Table 2 Comparison of results for amount of drug in dosage form by use of thermometric method and official method of assay

	Official method of assay			Thermometric Method of Assay		
Sample	Amount Taken*	Amount Found	Recovery %	Amount Taken	Amount Found	Recovery %
Ephedrine HCl	0.2– 0.06	0.0199	100.0135	10–50	9.896	99.72
	0.02–0.06	0.0599			49.860	
Norephedrine	0.06–0.14	0.05	99.99	10–50	10.50	99.78
		0.1399				
Adrenaline	0.01–0.10	0.060	100.0135	10–50	9.94	99.78
	0.06	0.999			49.878	
Isopropyl Noradrenaline	0.19	0.099	100.00	10–50	9.95	99.73
		0.1899			49.865	

*Six replicate analyses e performed for each sample and method.

Table 3 Effect of added *excipients*

Compound	*Excipients*	*Amount Taken mg	Amount Found mg
Ephedrine Hydrochloride	Starch (50 mg)	40	39.8
	Lactose (50 mg)	30	29.7
	Magnesium stereate (60 mg)	20	19.9

* Each reading is mean of six readings.

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