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Short communication

Simple kinetic method for the analysis of m-dope in pharmaceutical preparations. Part II☆

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1. Introduction

Methyldopa, its structure having the 1,2-diphenolic group is usually used for the treatment of a mild moderate hypertension. Various colorimetric methods using etitration in the presence of methyl orange [7] and a titrimetric method using bromine chloride [8] as indicators have been reported.

Most of the reported methods lack the simplicity and speed needed for its determination, as is the case for the titrimetric method [8] and the assays with different oxidising reagents [1–6] in which 10–30 min are required for stability and colour formation. In a comparison of the determination of L-dopa with m-dopa, it was found that in a previous method [9] the time needed for complete determination of the drug is less than that in the case of m-dopa. Therefore, in the previous work [9] we reported on the determination of L-dopa, and the same studies were applied to m-dopa, in which the results obtained are excellent and of great interest, this is due to the fact that less attention was given to kinetic methods for the determination of m-dopa.

2. Experimental

2.1. Apparatus and reagents

All chemicals used were of analytical or pharmaceutical grade. Sodium hydroxide (0.1 mol l^{-1}) solution was freshly prepared. Double distilled water was used throughout.

2.2. Standard solution of m-dopa

Pure methyldopa 1 mg ml^{-1} or 4.2×10^{-3} mol l^{-1} was dissolved in double distilled water and the apparent purity was checked by the 1,10 phenanthroline method [2]. The stock solution of m-dopa was kept in a well closed dark container to avoid direct contact with light.

2.3. Analysis of m-dopa in preparations

M-dopa was also prepared from pharmaceutical preparations. Tablets to be analysed were powdered and dissolved in double distilled water

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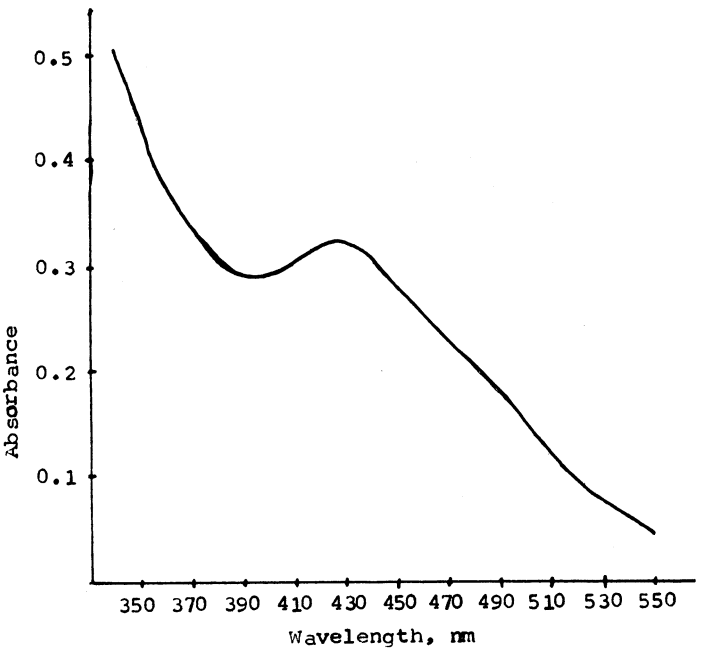

Fig. 1. Absorption spectra of m-dopa with sodium hydroxide at 293 K.

and filtered through a Whatman No. 1 filter paper. The filtrate was adjusted to a final concentration of 4.2×10^{-3} mol l^{-1}. The proposed method was then followed for the analysis of m-dopa in tablets form.

2.4. Procedure for the determination of m-dopa

Aliquots of 0.1–1.0 ml of the standard solution of m-dopa (4.2×10^{-3} mol l^{-1}) are pipetted into a series of 10 ml volumetric flasks, 1.0 ml of 0.1 mol l^{-1} sodium hydroxide is added. The solution is diluted and made up to volume with double distilled water at (293 K). After mixing, immediately transfer it to the spectrophotometric cell and after 1 min record the absorbance–time curve at λ 430 nm. Prepare a blank in the same way but omit m-dopa sample. Obtain the intercept, and slope from the initial straight line portions of these curves.

The calibration graph can be obtained by plotting Log v (rate) versus Log c (concentration) or plotting Log k (intercept) versus Log c (concentration).

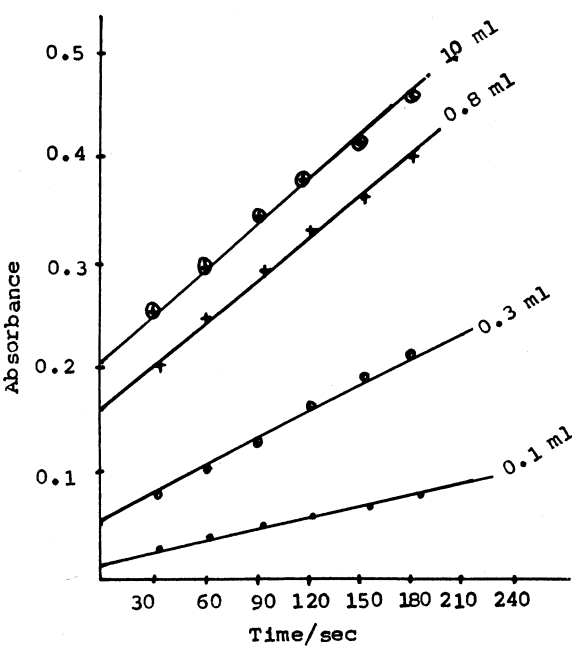

Fig. 2. Plot of log v versus log c, at 293 K, $\lambda_{max} = 430$ nm.

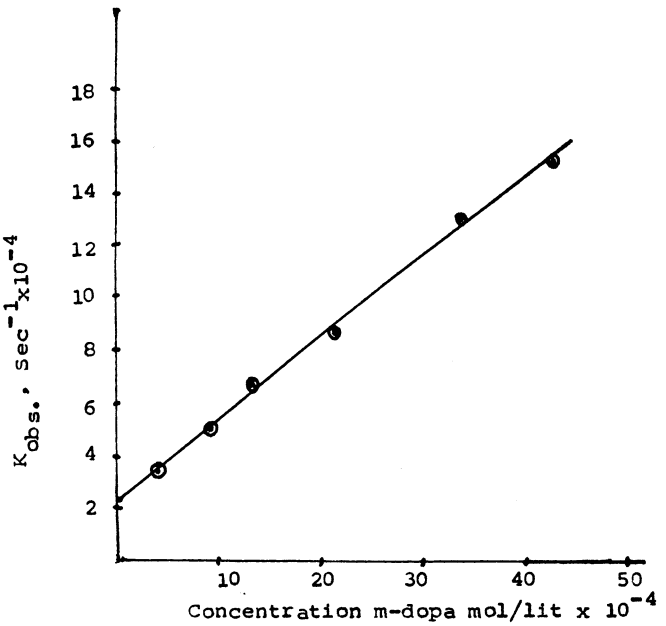

Fig. 3. Plot of log k_t (intercept) versus log c of m-dopa in mol l^{-1}.

3. Results and discussion

The reaction of m-dope (1,2 diphenolic) with sodium hydroxide gives rise to the formation of a yellow colour product, having an absorption maximum at 430 nm (Fig. 1). The intensity of the yellow colour increases with time, then starts decreasing and finally changes to light brown product. Pure m-dope in distilled water has a maxima at 280 nm, a shift in maxima is attained after adding sodium hydroxide. This type of reaction may give an account to the formation of phenoxyl ion due to the presence of 1,2 phenolic groups in the structure of m-dope.

The slope of the absorbance–time curve is used as a measure of the reaction rate, for solutions containing different concentrations of m-dope. The differential method has been used to calculate the true order. According to the rate equation, the reactions are made pseudo first order by taking one reagent in a small amount than the other. A plot of log $A_\infty/(A_\infty - A_t)$ versus t shows a linear response and utilised to calculate the reaction rate.

3.1. Features of the calibration graph

Calibration graphs, Figs. 2 and 3 are constructed by plotting Log v versus Log c and Log k_t (intercept) versus Log c, respectively. Figs. 2 and 3 show a linear relationship with respect to the concentration of m-dope in the range of 10–100 ppm. Where, v is the initial rate of reaction, c is the concentration of drug and k_t is the intercept with respect to m-dope concentration. Fig. 3 is used to calculate the rate and order of the reaction according to the equation $v = k \times c^n$, where n is the order of the reaction calculated from the slope, and k is the rate constant calculated from

Table 1
Rate constant and true order obtained by the proposed kinetic method

Reagent concentration (mol l^{-1})	Rate constant (k) (sec^{-1})	Order
m-dopa $(4.2–42.0) \times 10^{-4}$	2.7×10^{-4}[a]	0.8[a]
NaOH (0.01×10^{-1})	$1.5 \times 10 - 2$[b]	1.0[b]

[a] Values obtained from Fig. 2.
[b] Values obtained from Fig. 3.

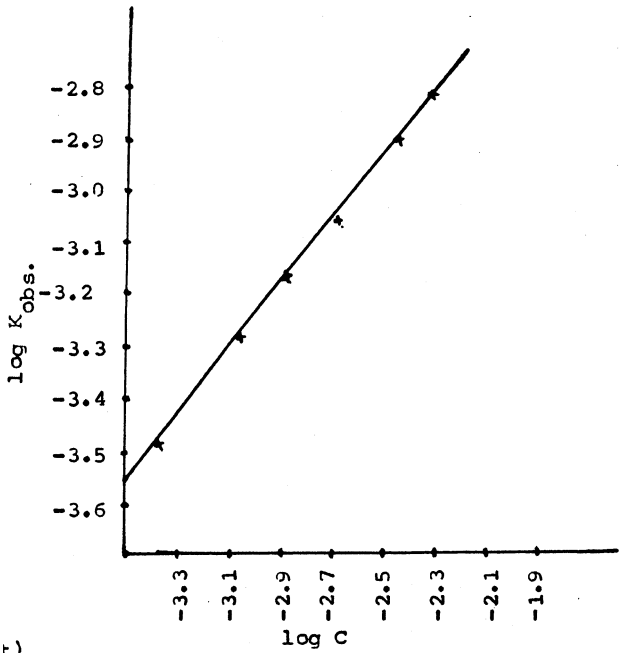

Fig. 4. Dependence of ln k on temperature at $\lambda_{max} = 430$ nm.

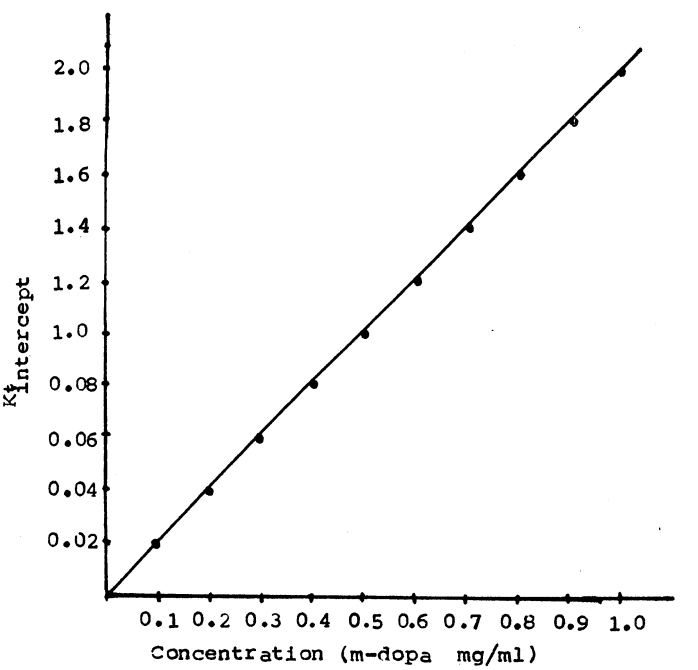

Fig. 5. Plot of k (intercept) versus c of m-dopa in mg ml^{-1} at 293 K, $\lambda_{max} = 430$ nm.

Table 2
Activation parameters for the reaction of m-dope with sodium hydroxide

$\Delta E^{\#}$ K cal^{-1} mol^{-1}	$\Delta G^{\#}$ K cal^{-1} mol^{-1}	$\Delta H^{\#}$ K cal^{-1} mol^{-1}	$\Delta S^{\#}$ cal mol^{-1} deg^{-1}
57.88	18.4	18.1	55.5

the intercept. Fig. 3 is also used for the same purpose mentioned above. Hence, a proposed equation can be suggested, i.e. k_1 (intercept) = $k \times c^n$. The values obtained from Figs. 2 and 3 are presented in Table 1.

The linearity of the calibration graphs is apparent from the correlation coefficient r obtained by determining the best fit line via a linear-square treatment. The intercepts obtained from Figs. 2 and 3 are close to 0. Therefore, the linearity is good in each instance and Beer's law is obeyed in the range of 10–100 ppm. The correlation coefficients, and the slope (m) and intercept (b) of the regression line equation, $y = mx + b$, are equal to 0.9998, 0.2 and 0.0 respectively. The molar absorptivity is found to be equal to 0.12×10^3 l mol^{-1} cm^{-1}.

3.2. Reproducibility

The reproducibility of the proposed method is carried out by running 15 replicate samples containing different concentrations of m-dope (0.5 μg ml^{-1}, 0.8 g ml^{-1}, 1.0 μg ml^{-1}) in the final solution. The mean standard deviation, mean relative standard deviation and mean % recovery are 0.48 μg ml^{-1}, 4.99 and 100.1%, respectively.

3.3. Precision and accuracy

The precision and accuracy of the proposed kinetic method have been studied for m-dope alone or in the presence of known impurities for a number of days. Solutions containing three different concentrations of m-dope are prepared and five absorbance measurements are recorded. The overall standard deviation and relative standard deviation is 0.015 μg ml^{-1} and 1.55% whereas, the mean % recovery is 96.8%.

3.4. Interference's

Some common excipients which are usually present in tablets such as lactose, starch, glucose, sucrose, and fructose, show no influence in the determination of the drug and the maximum tolerance amount (mg) are calculated. The values obtained are same as cited in the previous study [9].

3.5. Effect of reaction variables

The effect of sodium hydroxide concentration has been studied in the range of 0.01–0.3 mol l^{-1}. A plot of k (initial rate of reaction) versus NaOH concentration shows the dependence of reaction rate on sodium hydroxide. Therefore, 1.0 ml of 0.1 mol l^{-1} was used for further studies. A plot of Log A versus time (t), shows the first order kinetic system of the reaction of m-dopa with sodium hydroxide.

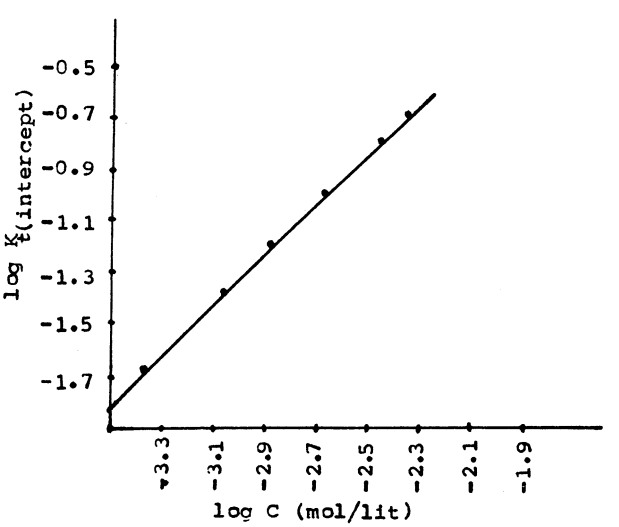

Fig. 6. Plot of log k_t (intercept) versus log c of m-dopa in mol l^{-1}.

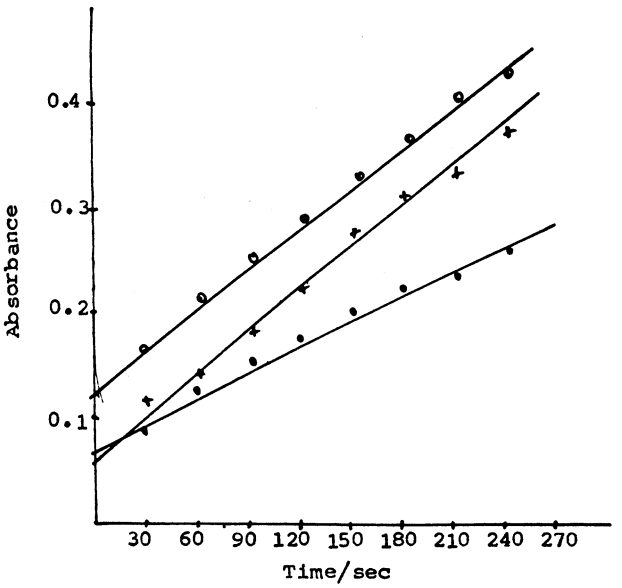

Fig. 7. Absorbance versus time curve as a function of temperature at (•) 293 (×) 308 (○) 318 K, m-dopa 2.1×10^{-3} mol/lit, $\lambda_{max} = 430$ nm.

3.6. Effect of temperature

The dependence of reaction rate on temperature has been studied between 293 and 333 K. A plot of the absorbance versus time as a function of temperature at 293 308 and 318 K using 2.1×10^{-3} mol l^{-1} of m-dopa shows the increase in absorbance with time Fig. 7. A plot of ln k versus $1/T$ (Fig. 4) gives a straight line, from which the energy of activation ($\Delta E^{\#}$) is calculated, according to Arrhenius equation:

$$K = A\ e^{-\Delta E^{\#}/RT}$$

Estimation of the free energy of activation ($\Delta G^{\#}$) from the relation:

$$K_1 = (kT/h)e^{-\Delta G^{\#}/RT}$$

(where k and h are Boltzman constant and blank constant, respectively) yielded $\Delta S^{\#}$ and $\Delta H^{\#}$ from the Gibbs-Helmholtz equation, $\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#}$. A plot of $\Delta G^{\#}/T$ versus $1/T$ is also constructed and $\Delta H^{\#}$ and $\Delta S^{\#}$ are calculated from the slope and the intercept, respectively. Therefore, the results are listed in Table 2. Working at higher temperature leads to inaccu-

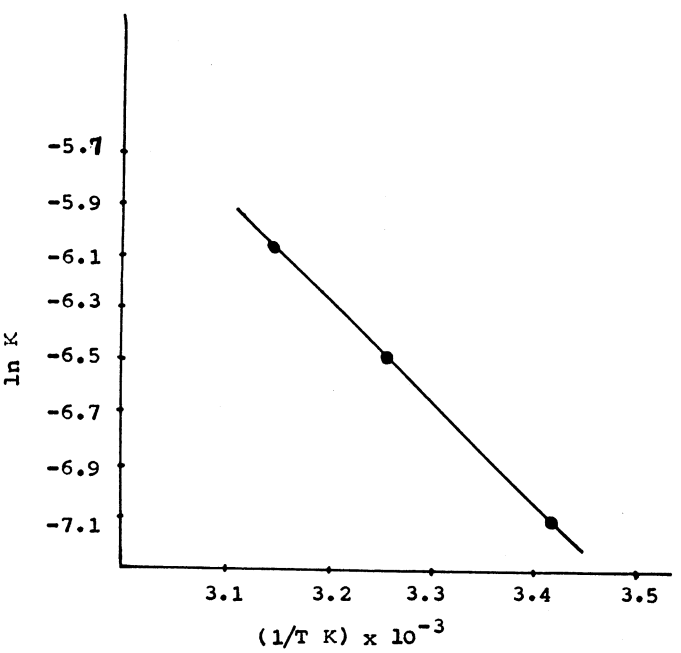

Fig. 8. Dependence of ln k on temperature at $\lambda_{max} = 430$ nm.

Table 3
Results obtained for the determination of methyldopa in dosage forms by the proposed method and compared with reference method (2)

Sample	Proposed method[a]		Reference method[a]		t[b]	F[c]
	% Recovery, SD (μg ml^{-1})	% RSD	% Recovery, SD (μg ml^{-1})	% RSD		
Emdopa (IDPL, India) 250 mg methyldopa	$100.5 \pm 1 \times 10^{-3}$	0.5	$100.0 \pm 3.8 \times 10^{-3}$	1.9	0.36 (2.447)	0.07 (6.39)
Meldopa (Dey's, India) 250 mg methyldopa	100.4 ± 0.19	0.9	98.0 ± 1.06	0.7	0.34 (2.447)	1.52 (6.39)

[a] Average of five determinations.
[b] Figure in parenthesis are the theoretical values of a t test at 95.0% confidence level.
[c] Figure in parenthesis are the theoretical values of F test at 95.0% confidence level.

rate results with a fear of decomposition of the product Figs. 5, 6 and 8.

3.7. Application of the proposed kinetic method

The proposed method has been applied to the determination of mdopa in tablets. The results obtained (Table 3) are statistically compared with those obtained by reference method [2]. The calculated 't' and 'F' test values did not exceed the theoretical values which indicate the absence of any significant differences in terms of precision and accuracy.

4. Conclusion

The major advantage of this research is the sensitivity. The concentration range was valid from 10–100 ppm, with a correlation coefficient $\geqslant 0.998$ and molar absorptivity of 0.12×10^3 l mol^{-1} cm^{-1}. The activation parameters such as ($\Delta H^{\#}$, $\Delta S^{\#}$, $\Delta G^{\#}$, $\Delta E^{\#}$) was calculated The recommended procedure was applied to the determination of m-dopa in pharmaceutical formulation and gave good results when compared with the 1,10 phenanthroline method.

References

[1] P.B. Issopoulos, Pharm. Weekble. Sci. Ed. 1166 (1989) 213.
[2] P.B. Issopoulos, Fresenius J. Anal. Chem. 336 (2) (1990) 124.
[3] P.B. Issopoulos, P.T. Economou, Ind. Drugs 29 (8) (1992) 3S5.
[4] P.B. Issopoulos, Pharm. Acta. Helv. 64 (3) (1989) 82.
[5] R.T. Sane, G.J. Bhounsule, S.V. Sawant, Ind. Drugs 24 (4) (1978) 207.
[6] G.R. Rao, A.B. Avadhanula, Ind. Drugs 23 (12) (1968) 699.
[7] K. Nicolik, M. Medenica, Farmaco 45 (9) (1990) 1037–1041.
[8] Seetharamappa, J. East Pharm. 39 (406) (1996) 131.
[9] I.H.H. Murad, N. Rahman, M.A.Q.J. Rasheed, S.M.A.-N. Eyad, J. Pharm. Biomed. Anal. 16 (1977) 269–274.