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Application of high-performance liquid chromatography in the kinetic study of α-methyldopa

Mohammed El-Sayed Metwally and Fathalla F Belal

Department of Analytical Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516 (Egypt)

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ABSTRACT

A reversed-phase high-performance liquid chromatographic (HPLC) method was developed for use in kinetic studies of α-methylopa (MD) The proposed method was further applied to the determination of MD in sustained release capsules and in the presence of its industrial impurity, 3-O-methylmethyldopa (MMD) The detector response was linear in the range 0 5–200 μg/ml for MD and MMD Replicate injections of both compounds gave relative standard deviations of 0 54 and 0 62%, respectively The mean recoveries of MD from raw material and sustained release capsules were 99 71–100 2% and 99 5–100 1%, respectively The proposed HPLC method was used to study the kinetics of degradation of MD in raw material and in sustained release capsules as a function of temperature, pH, humidity and exposure to UV radiation MD degradation followed first-order kinetics and gave a linear relationship, in agreement with the Arrhenius theory, for all the incubation media studied The activation energy for MD degradation was 93 36–105 92 kJ l mol^{-1} The disappearance of MD followed pseudo-first-order kinetics in buffered distilled water over the experimental pH range 2–13 Above pH 7 96, a base-catalysed degradation dominates, with a second-order rate constant of 190 72 ± 14 5 l mol^{-1} day^{-1} Below pH 7 96, degradation is independent of pH, with a disappearance rate constant of 6 65 (± 1 07) 10^{-4} day^{-1} at 25°C Degradation of MD raw material or ground MD beads was not enhanced by exposure to 80% humidity or to UV radiation for 21 days

INTRODUCTION

L-α-Methyldopa, [L-3-(3,4-dihydroxyphenyl)-2-methylalanine] (MD) is a competitive inhibitor of DOPA-decarboxylase [1] and can also serve as a substrate for pigment formation in the melanocytes of hair follicles [2] Owing to its phenolic nature, MD degrades easily under unfavourable storage conditions [3] and can undergo oxidation in alkaline media to a polymeric melanin-like pigment [4]

Only speculations have been made with respect to the study of MD degradation in raw material or in pharmaceutical preparations In this respect, Lippold and Jaeger [5] used a conventional UV spectrophotometer to study MD degradation They showed that the MD degradation rate increases with increasing supply of oxygen and increasing pH, but with decreasing starting concentration of the drug In addition, they found that on changing the pH, MD degrades to different products with different absorption maxima

Using the official USP method [6], Gupta and Gupta [3] claimed that although there was no difference in the stability of MD tablets after storage for 8 weeks in counting machine cells, the colour of the tablets was duller than that of the control tablets The electrochemical kinetics of MD were studied by Young *et al* [7] using an electrochemical cell They demonstrated that a melanoid pigment was formed as a final oxidation product It is, evident, therefore, that there is still a need for a comprehensive kinetic study of MD, especially in the sustained release forms owing to the exposure of the beads to a high temperature during the coating step In such kinetic studies, a stability-indicating method is essential to

Correspondence to Dr M E-S Metwally, Department of Analytical Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt

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determine whether peaks of MD degradation products overlap with MD peaks

The USP method [8] for the determination of MD in tablets does not appear to be stability indicating since an almost-degraded sample indicated that 53% of the drug was still intact compared with 0% using a high-performance liquid chromatographic (HPLC) method [9] MD has been determined in dosage forms by fluorimetry [10,11], UV spectrophotometry [12], colorimetry [13–16], PMR spectroscopy [17], potentiometry [18], thin-layer chromatography [19], ion-exchange chromatography [20], HPLC [21,22] and gas chromatography [23] These methods are not specific, are lengthy and time consuming, may require rigid experimental conditions such as pH adjustment and temperature control and/or cannot be used for the separation of MD from its degradation products

The method previously developed by Metwally [9] using a cyano-bonded column succeeded in separating MD from its degradation products and its industrial impurity, MMD Although this method would be suitable for the determination of MD in the presence of its degradation products and MMD, the half-life of the column was short, as expected [24], as the efficiency of the column decreased with time, necessitating frequent changes of the column

The aim of this work was to study the degradation kinetics of MD using a stability-indicating HPLC method The method was applied to the determination of MD in sustained release capsules and in the presence of MD degradation products and the industrial impurity MMD In addition, the data presented provide a detailed description of the kinetic behaviour of MD at different pH and humidity, after exposure to UV radiation and at different temperatures (25–80°C) Degradation rate constants, the half-lifes and the activation energies of the degradation reaction were investigated The kinetic data were compared under different media conditions

EXPERIMENTAL

Chemicals

USP reference standards of MD and MMD were used (Sigma, St Louis, MO, USA) MD raw material (checked according to the USP [8]) and MD sustained release microcapsules were supplied by Elan Pharmaceutical (Gainesville, GA, USA) Methanol (HPLC grade), acetonitrile (HPLC grade), acetic acid and sodium 1-hexanesulphonate were purchased from Aldrich (Milwaukee, WI, USA) All other chemicals were of high purity and used as received

Liquid chromatograph

A Waters (Milford, MA, USA) Model 590 solvent pump, a Rheodyne (Berkeley, CA, USA) Model 7125 20-μl loop and a Kratos Spectroflow 757 variable-wavelength detector (Schoeffel Instrument, Westwood, NJ, USA) set at 280 nm were used Compounds were separated on a 150 × 4 6 mm I D μBondapak C_8 (5 μm) analytical column (Waters) The eluted peaks were integrated by a Hewlett-Packard (Avondale, PA, USA) Model 3392A integrator

Mobile phase

A solution of methanol in water containing 2% (v/v) acetic acid and 0 005 *M* sodium 1-hexanesulphonate (18 82) was used The pH of solutions was 2 60 ± 0 05 The mobile phase was filtered by passing it through a 0 45-μm Millipore filter and degassed before use The mobile phase flow-rate was 1 5 ml/min and the temperature was ambient

Determination of water content

The water content in MD bulk powder and in the MD sustained release capsules was found to be 12 3 and 13 0%, respectively [9]

Preparation of stock solution

Stock solutions (0 1%, w/v) of MD and MMD were prepared in 0 05 *M* sulphuric acid using a simple solution method

Preparation of calibration graphs

An accurately weighed 50-mg sample of USP MD or MMD was transferred into a 100-ml volumetric flask and 50 ml of 0 05 sulphuric acid were added The flask was sonicated for 15 min, and then brought to volume with 0 05 *M* sulphuric acid Serial dilutions of MD or MMD standards covering the concentration range 0 5–200 μg/ml were made Concentrations of MD and MMD were determined in the acidified aqueous solutions using the HPLC conditions given above, and the peak heights of the standards (calibration graphs) were recorded

Quantification

All measurements were done using peak heights Concentrations of sample solutions containing MD were calculated using the slope and the intercept of the calibration graph prepared under the same conditions The slope and the intercept of the calibration graph were obtained by linear regression of peak height *vs* concentration ($y = ax + b$), where a is the slope, b is the intercept and y is the response of the analyte

Concentrations of MD and MMD were determined in the acidified aqueous solutions using the HPLC conditions listed above Concentrations were calculated by comparing the peak height with standard concentrations (calibration graphs) of both compounds The plots of the peak height *versus* concentration were linear over the range 0 5–200 0 μg/ml with a regression coefficient of over 0 999 for both compounds

Extraction of MD from sustained release microcapsules

Beads equivalent to 500 mg of MD were ground to a fine powder and transferred into a 100-ml volumetric flask, then 50 ml of 0 05 *M* sulphuric acid were added The flask was sonicated for 15 min and then brought to volume with 0 05 *M* sulphuric acid, then filtered The first 10 0 ml of the filtrate were rejected and 10 ml of the clear filtrate were diluted to 100 0 ml with 0 05 *M* sulphuric acid

Kinetic studies

pH–rate profile Kinetic studies were made in aqueous solutions containing 0 1 *M* buffer solutions [25] covering the pH range 2–12 A kinetic run at pH 13 was conducted in 0 1 *M* NaOH solution In all kinetic runs, 10-mg samples of MD were dissolved in 100 ml of the appropriate buffer solution in a 100-ml volumetric flask The flasks were kept in a thermostated water-bath at 25 ± 0 5°C At appropriate time intervals, 5 ml of sample were transferred into a 25-ml flask and 5 ml of 0 1 *M* sulphuric acid were added The mixture was adjusted to volume with deionized water and then analysed

Effect of heat on the degradation rate of MD in raw material and in solid formulations MD raw material and MD beads (finely ground) were stored at ambient temperature (25 ± 0 2), 40, 50, 60, 70 and 80°C Zero-time sample measurements were carried out when the study began only on samples from bottles to be stored under ambient conditions All original and re-bottled samples stored under accelerated conditions were not opened until the first analysis The bottles were re-closed tightly by hand between sampling For all storage conditions, the entire study was performed on duplicate bottles of MD raw material or MD microcapsules For aqueous solutions, samples equivalent to 100 mg of MD raw material were dissolved in 100 ml of 0 1 *M* buffer (pH 6) [25] Samples were diluted 1 20 using the same buffer and poured into 10-ml vials and sealed The vials were placed in ovens set at appropriate temperatures, and at specified time intervals individual samples were taken for analysis

Effect of humidity and UV radiation The effect of humidity was observed by exposing finally ground beads in an open petri dish to 80% humidity in an oven held at 60°C for 60 days, and the results were compared with those obtained with closed bottles The effect of UV radiation on MD degradation was observed by exposing finally ground beads in an open petri dish to strong UV radiation in an oven held at 25°C for 60 days, and the results were compared with those obtained with unexposed bottles

RESULTS AND DISCUSSION

The fact that MD can easily be oxidized in alkaline media, or when stored under unfavourable condition [3,5], necessitates a detailed study of its kinetics under different conditions using a stability-indicating procedure The proposed reversed-phase HPLC method utilizes a C_8 column coupled with an acidic methanol–water mobile phase containing hexanesulphonate and UV detection for the separation of MD from its degradative products and its industrial impurity, MMD (Fig 1) Under identical separation conditions, the retention times (t_R) were MD 4 35 min, MMD 8 93 min and MD degradation products 10 54, 8 12, 5 96, 5 43, 4 04, 3 41, 2 57, 1 577, 1 25, 1 15, 1 01 and 0 88 min on a 150 × 4 6 mm I D μBondapak C_8 (5 μm) analytical column

As has been observed with the CN bonded column [9], using acetonitrile as an organic modifier resulted in overlapping of one of the peaks of the degradation products of MD with that of MMD Accordingly, methanol was chosen as an organic

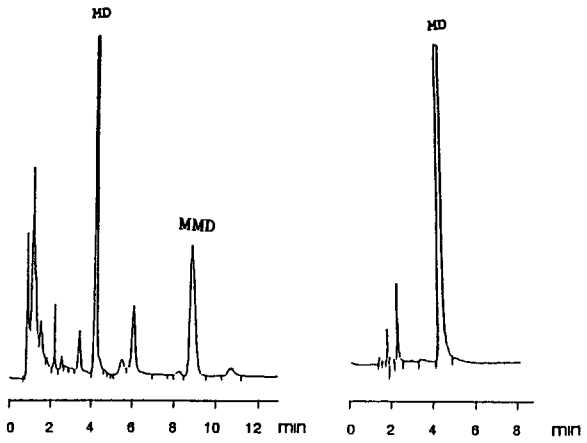

Fig 1 Chromatogram obtained from a mixture of MD (10 μg/ml, t_R = 4 35 min), MMD (10 μg/ml, t_R = 8 93 min) and degraded MD (100 μg/ml), 30 min degradation time in 0 1 *M* NaOH at 25°C, t_R = 10 54, 8 12, 5 96, 5 43, 4 04, 3 41, 2 57, 1 577, 1 25, 1 15, 1 01 and 0 88 min) Column, 150 × 4 6 mm I D μBondapak C_8 (5 μm), mobile phase, methanol–water (18 82, v/v) containing 2% (v/v) acetic acid and 0 005 *M* sodium 1-hexanesulphonate, pH, 2 60 ± 0 05, flow-rate, 1 5 ml/min, detector wavelength, 280 nm

Fig 2 Chromatogram obtained for MD sustained release capsules (t_R = 4 35 min, 90 μg/ml) Chromatographic conditions as in Fig 1

solvent modifier, whence all the degradation peaks were successfully separated from MD and MMD On the other hand, on using heptanesulphonate as a counter ion each analysis requires over 20 min, and the analysis time was shortened to 11 min by using hexanesulphonate as a counter ion

Based on the peak-height responses of standards, the method was linear in the range 0 5–200 μg/ml with regression coefficients of 0 999 for both MD and MMD

The reproducibility of the measurement of 100 μg/ml based on ten determinations showed relative standard deviations of 0 54 and 0 62% for MD raw material and MD sustained release formulations, respectively The corresponding value for the injection of 1 μg/ml were 0 92 and 1 05%, respectively

An overnight decomposed sample of MD in 0 1 *M* NaOH solution showed zero recovery by the proposed HPLC method and 53 4% by the USP spectrophotometric method, an indication of the precision of the proposed method This is in agreement with previously published data [9] Another advantage of the proposed HPLC ion-pairing method appears in the separation of MMD from MD The separation without the ion-pairing reagent was impossible In addition, the presence of excipients common to sustained release capsules [citric acid, fumaric acid, sodium lauryl sulphate, non-pareils, talc, polyvinylpyrrolidone (PVP) and shellac] did not interfere in the determination of MD in the sustained release capsules Fig 2 illustrates the separation of the active ingredients in MD sustained release capsules from excipients No MMD was found in any of the studied MD batches

In Table I, the percentage of the labelled values obtained when the proposed HPLC method was applied to the determination of MD in sustained release capsules in five different batches are compared with those obtained with the USP method with standard deviations of 0 80 and 0 94%, respectively No noticeable discrepancies were observed The mean recovery of MD from raw material and sustained release capsules ranged from 99 71 to 100 2% and from 99 5 to 100 1%, respectively

Kinetics

The short analysis time using HPLC allowed a precise study of the MD degradation with a large number of determinations per curve The kinetic studies were performed on MD raw material and on formulated beads to observe the effect of pH, manufacturing and storage temperatures, humidity and UV radiation on the degradation rate constants

pH–rate profile In the pH-rate profile study, the retention times of MD, MMD and MD degradation products were recorded every time to ensure the reproducibility and to monitor peak disappearance peak formation behaviour The patterns of the chromatograms were not stable with time (Fig 3) MD degradation products with retention times of 10 54, 8 12,5 96 and 5 43 min (which are apparently more lipophilic than MD) disappear with time with a subsequent increase in the area of the more hydrophilic products with retention times of 2 57, 1 577, 1 25, 1 15, 1 01 and 0 88 min This is consistent with Young *et al*'s findings [7], with a melanin-like pigment as the final oxidation product of MD The degradation pathway of MD became increasingly complex with time The chromatograms were carefully examined to ensure that none of the MD degradation products interfered with MD or MMD at any time during the study

TABLE I

DETERMINATION OF MD IN DIFFERENT BATCHES OF SUSTAINED RELEASE CAPSULES USING THE PROPOSED HPLC METHOD AND THE USP SPECTROPHOTOMETRIC METHOD [8]

Batch No	Sample weight[a] (μg/ml)	MD found (%)	
		HPLC method	USP method
C821	5 03	59 44	59 78
	17 94	58 58	58 83
	89 99	58 70	58 32
	165 29	58 80	59 01
	218 50	58 54	58 56
C934	3 01	59 80	59 63
	20 03	58 31	58 45
	75 01	58 29	58 07
	149 21	58 25	58 19
	250 25	58 38	58 29
C1040	20 45	58 68	59 15
	66 98	58 39	58 63
	117 43	57 99	58 21
	190 00	58 29	58 34
	298 99	59 18	59 34
176A/40	9 35	55 94	56 01
	35 10	57 04	56 23
	87 56	57 32	57 21
	187 90	57 47	57 18
	275 92	57 64	57 90
21B/11	3 29	59 27	60 00
	21 27	57 59	58 76
	69 98	57 82	57 72
	159 33	57 73	58 32
	249 57	57 71	57 67
Mean		58 21	58 31
S D		0 80	0 94

[a] Each 100 mg of beads contains 58 mg of MD

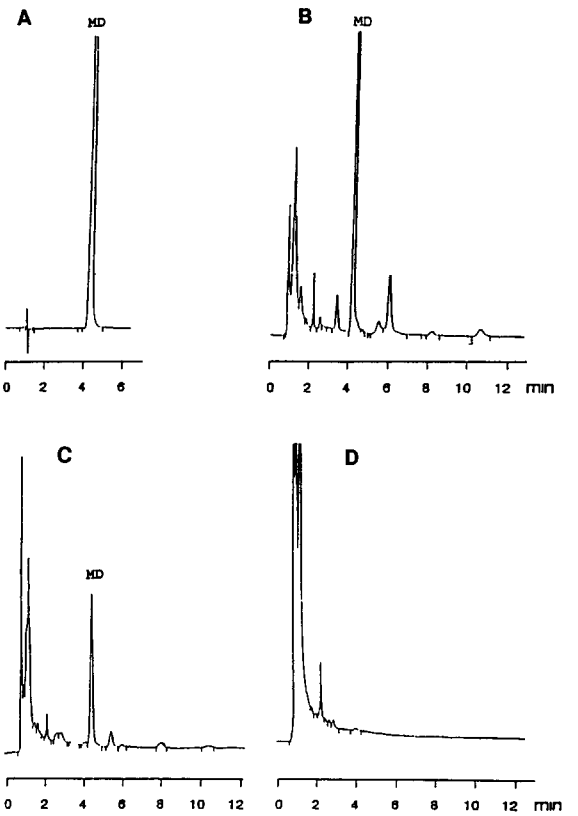

Fig 3 Chromatograms shows MD degradation products in 0 1 *M* NaOH at 25°C after time = (A) 0, (B) 30 min, (C) 2 h and (D) 8 h MD initial concentration, 100 μg/ml Retention times and chromatographic conditions as in Fig 1

The effect of initial concentration on the pH–rate profile was first studied Degradation of 5, 25, 50 and 100 μg/ml of MD in 0 1 *M* NaOH at 25°C proceeded with the same degradation rate This is different from the early findings of Lippold and Jaeger [5], who used UV spectrophotometry to study MD degradation For the remaining experiments, an initial concentration of 100 μg/ml was used to permit a longer time course

The observed first- or pseudo-first-order disappearance rate constants and the corresponding second-order disappearance rate constants for MD in 0 1 *M* non-sterile buffers in the pH range 2–13 and at 25°C are listed in Table II Fig 4 shows logarithmic concentration (ln *C*) *versus* time (*t*) for the disappearance of MD in 0 1 *M* NaOH aqueous solution and indicates a first-order degradation behaviour with a rate constant (k_{obs}) of 16 21 ± 0 14 day^{-1} and a regression coefficient of 0 994 The pseudo-first-order disappearance rate constants were calculated using a non-linear regression according to

$$\ln(C_t/C_0) = -k_{obs}t \quad (1)$$

where C_0 and C_t are the MD concentrations at time zero and t, respectively The rate constant was taken as the slope of the line obtained by a linear least-squares analysis of the data The second-order rate constant (k_2) was calculated from the equation

TABLE II

OBSERVED FIRST-ORDER OR PSEUDO-FIRST-ORDER DISAPPEARANCE RATE CONSTANTS FOR MD IN NON-STERILE BUFFERED DISTILLED WATER, USING A BUFFER CONCENTRATION OF 0 1 *M* AT 25°C

pH	r^{2a}	$k_{obs}{}^{b}$ (day^{-1})		$t_{1/2}{}^{c}$ (day)	$k_2{}^{d}$ (day^{-1} l mol^{-1})
13 00	0 994	16 21		0 043	162 10
11 98	0 995	1 810		0 383	189 53
10 88	0 995	0 150		4 621	197 74
9 91	0 991	1 600	10^{-2}	43 322	196 84
9 15	0 982	2 800	10^{-3}	247 553	198 22
8 69	0 780	9 790	10^{-4}	708 016	199 89
7 96	0 701	6 010	10^{-4}	1153 323	[e]
7 54	0 701	7 010	10^{-4}	988 798	[e]
7 00	0 695	5 190	10^{-4}	1335 543	[e]
6 09	0 691	8 340	10^{-4}	831 112	[e]
4 10	0 689	7 016	10^{-4}	987 952	[e]
1 98	0 700	6 327	10^{-4}	1095 538	[e]

[a] r^2 = Regression coefficient
[b] k_{obs} = Observed first-order rate constant
[c] $t_{1/2}$ = Half-life of the reaction
[d] k_2 = Second-order rate constant
[e] pH-independent degradation reaction

$$k_2 = k_{obs}/[OH^-] \quad (2)$$

where $[OH^-]$ is the hydroxyl ion concentration

The pH–rate profile for the degradation of MD is shown in Fig 5, which indicates that MD undergoes a neutral (pH-independent) degradation reaction over the pH range 2–7 5 with a first-order rate constant of 6 65 ($\pm$1 07) $\times$ 10^{-4} day^{-1} (n = 5) at 25°C Above pH 7 96, a base-promoting degradation reaction dominates and the reaction is first order with respect to the hydroxyl ion concentration The second-order rate constant was 190 72 $\pm$ 14 50 l mol^{-1} day^{-1} based on using data covering the pH range 8 69–13 0 The data obtained at pH 7 96 were not included in calculating k_2 because the neutral degradation rate constant still contributes seriously to the overall rate constant The data indicate the importance of incorporating acidic excipients as diluents in the sustained release formulation to prevent such degradation

Rate constants measured at room temperature and in the pH range 2–7 96 show considerable variation, presumably mainly owing to the difficulties inherent in measuring rate constants for very slow reactions

Heating Disappearance rate constants for MD in raw materials and in sustained release capsules were measured at elevated temperatures to obtain more accurate values for degradation rates at room temperature and to indicate the effect of high temperature of the manufacturing, storage and shipping conditions on the stability of MD

Activation energy The activation energy (E_a) and the frequency factor (A) were calculated using the data presented in Table III according to the Arrhenius equation

$$\ln k_{obs} = \ln A - (E_a/RT) \quad (3)$$

where R is the molar gas constant (8 3143 J^{-1} l mol^{-1}) and T is the absolute temperature The behavior of MD degradation follows the general

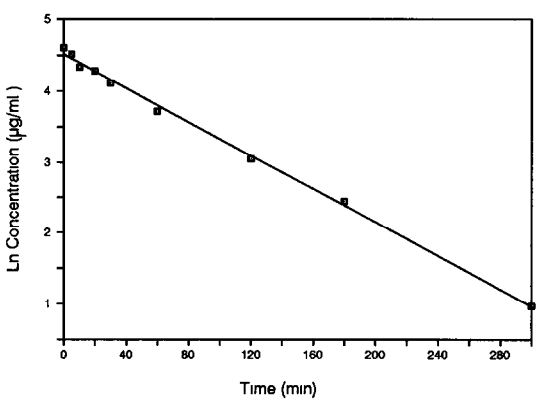

Fig 4 Plot of ln (concentration) *versus* time for the degradation of MD in 0 1 *M* NaOH at 25°C

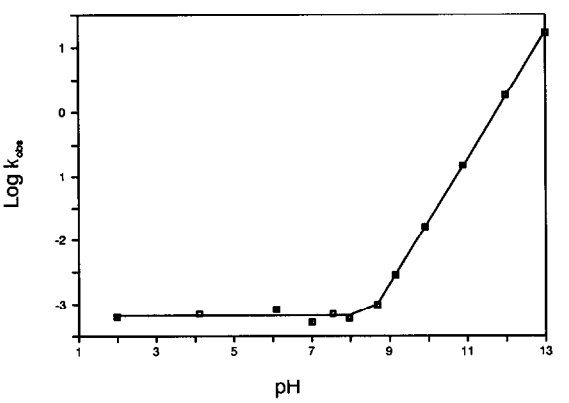

Fig 5 Plot of log (observed rate constants) *versus* pH for the degradation of MD in 0 1 *M* buffered distilled water at 25°C

TABLE III

VALUES FOR EXPERIMENTAL AND CALCULATED DEGRADATION RATE CONSTANTS AND HALF-LIFES FOR THE DISAPPEARANCE OF MD IN DIFFERENT MEDIA AND AT DIFFERENT TEMPERATURES

Sample	Temperature (°C)	r^2 [a]	k_{obs} [b] (day^{-1})	k'_{obs} [c] (day^{-1})	$t_{1/2}$ [d] (day)	$t'_{1/2}$ [e] (day)
MD aqueous solution	25	0 710	$8\,34 \times 10^{-4}$	$6\,20 \times 10^{-4}$	831 11	1117 80
	40	0 895	$3\,91 \times 10^{-3}$	$5\,01 \times 10^{-3}$	177 28	138 39
	50	0 987	$2\,91 \times 10^{-2}$	$1\,81 \times 10^{-2}$	23 82	38 29
	60	0 993	$5\,39 \times 10^{-2}$	$6\,06 \times 10^{-2}$	12 86	11 44
	70	0 998	0 190	0 189	3 65	3 67
	80	0 997	0 602	0 552	1 15	1 26
MD raw material	25	0 695	$1\,04 \times 10^{-4}$	$7\,08 \times 10^{-5}$	6664 88	9786 99
	40	0 845	$6\,79 \times 10^{-4}$	$4\,47 \times 10^{-4}$	1020 84	1552 11
	50	0 913	$9\,89 \times 10^{-4}$	$1\,39 \times 10^{-3}$	700 86	500 08
	60	0 962	$3\,26 \times 10^{-3}$	$4\,02 \times 10^{-3}$	212 62	172 46
	70	0 988	$1\,40 \times 10^{-2}$	$1\,10 \times 10^{-2}$	49 51	63 29
	80	0 989	$4\,03 \times 10^{-2}$	$2\,82 \times 10^{-2}$	17 20	24 58
MD beads	25	0 694	$1\,01 \times 10^{-4}$	$5\,83 \times 10^{-5}$	6862 84	11886 84
	40	0 897	$4\,39 \times 10^{-4}$	$3\,89 \times 10^{-4}$	1578 92	1782 34
	50	0 904	$8\,93 \times 10^{-4}$	$1\,25 \times 10^{-3}$	776 20	554 79
	60	0 963	$3\,57 \times 10^{-3}$	$3\,74 \times 10^{-3}$	194 16	185 23
	70	0 992	$1\,31 \times 10^{-2}$	$1\,05 \times 10^{-2}$	52 91	65 93
	80	0 994	$4\,01 \times 10^{-2}$	$2\,79 \times 10^{-2}$	17 29	24 88

[a] r^2 = Regression coefficient
[b] k_{obs} = Observed first-order rate constant
[c] k'_{obs} = Estimated first-order rate constant
[d] $t_{1/2}$ = Half-life of the reaction
[e] $t'_{1/2}$ = Estimated half-life of the reaction

Arrhenius relationship because linear plots of ln (rate) *versus* $1/T$ were obtained for MD raw material in both the aqueous and solid forms and for MD solid dosage forms, with regression coefficients of 0 988, 0 977 and 0 981, respectively The activation energies and the frequency factors are summarized in Table IV

Arrhenius plots (ln k_{obs} *vs* $1/T$) for the disappearance of MD in aqueous solutions and in solid forms are shown in Fig 6 Use of more precise data from runs at 40, 50, 60, 70 and 80°C to calculate the least-squares line permits extrapolation to lower temperatures, and resulted in calculating more precise rate constant estimates Values of $6\,20 \times 10^{-4}$, $7\,08 \times 10^{-5}$ and $5\,83 \times 10^{-5}$ day^{-1} for the disappearance of MD at 25°C in aqueous solution, solid-form of materials and in sustained release capsules, respectively, were obtained

It is obvious that MD degrades at a faster rate in aqueous solutions than in solid forms This could be due to the presence of dissolved oxygen in aqueous solution, which is necessary for oxidation

On heating solid beads the colour changed,

TABLE IV

ACTIVATION ENERGIES AND FREQUENCY FACTORS FOR THE DISAPPEARANCE OF MD IN DIFFERENT MEDIA

Sample	E_a [a] (kJ)	A [b] (day^{-1})	r^2 [c]
MD aqueous solution	105 92	35 38	0 989
MD raw material	93 36	28 21	0 977
MD beads	96 21	29 16	0 981

[a] E_a = Activation energy
[b] A = Frequency factor
[c] r^2 = Regression coefficient

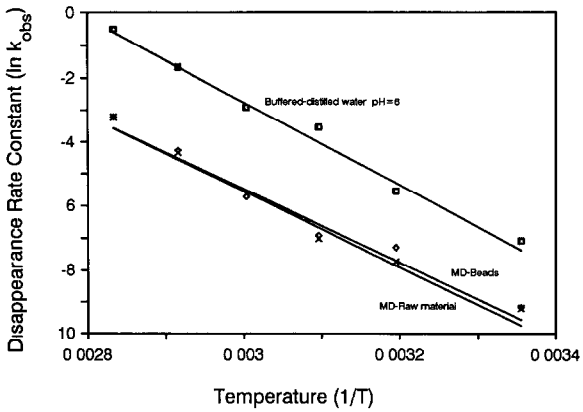

Fig 6 Arrhenius plot for the degradation of MD in (□) aqueous solution, (◇) raw material and (×) sustained release capsules

ranging from light yellow through yellow and light brown to dark brown Because only a 7% decrease in potency over 21 days at 60°C was observed, this dramatic colour change could be attributed to some sort of oxidation of the excipients rather than of the drug itself

Effect of humidity and UV radiation Kinetic runs on finely ground powder of batch C-821 sustained release capsules were conducted at 60°C and at 80% humidity It was found that changing the humidity to 80% has no effect on the kinetics of degradation of MD beads The same conclusion was also obtained for the effect of UV radiation The exposure time in both experiments was 60 days

In conclusion, the degradation of MD is a function of both pH and temperature The faster degradation rate of MD in aqueous solution than in solid form may be interpreted by the presence of dissolved oxygen in the aqueous solution In addition, the proposed method is accurate, rapid, selective and precise It gave results for MD in sustained release capsules that were in excellent agreement with those obtained by the official USP method The method was superior, however, in application to kinetics studies

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