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Determination of Dopa in Pharmaceutical Dosage Forms Based on Oxidation at Tubular Carbon Electrode

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Abstract □ A method for the determination of dopa [3-(3,4-dihydroxyphenyl)alanine] in pharmaceutical dosage forms based on electrochemical oxidation at the tubular carbon electrode is presented. A comparison with a colorimetric method shows this new method to be considerably faster and simpler without a significant loss in precision or accuracy. Between 25 and 30 samples may be determined each hour, for which the variance due to the method results in a standard deviation no greater than ±0.9%.

Keyphrases □ Dopa—analysis in dosage forms, electrochemical oxidation at tubular carbon electrode □ Electrochemical analysis—dopa in dosage forms, tubular carbon electrode

The problems associated with the fluorometric or colorimetric determination of levodopa [(−)-3-(3,4-dihydroxyphenyl)-L-alanine] in pharmaceutical dosage forms were recently summarized (1). Although highly sensitive and specific, these methods are inconvenient due to lengthy procedures involving separation and other manipulative steps. A new colorimetric method by Maggi and Cometti (1), designed specifically for the determination of levodopa in dosage forms, eliminates separatory steps but requires a number of manipulations including a precisely controlled reaction for color formation. A possible alternative to the colorimetric approach may be an electrochemical method similar to the one presented for ascorbic acid (2).

The method for ascorbic acid is based on continuous analysis in flowing streams by oxidation of the drug at the tubular carbon electrode (3). This electrochemical method has advantages over other commonly employed methods of being extremely fast and simple without any significant loss in accuracy or precision. Studies (4) of the electrochemical oxidation of catecholamines, similar in structure to levodopa, suggested that the drug may be assayed in this manner. Thus, an investigation of the oxidation of levodopa at the tubular carbon electrode was undertaken with the idea of developing an analytical method. In this paper a method for the determination of dopa in pharmaceutical dosage forms is presented and compared to the colorimetric method of Maggi and Cometti (1). In addition, the utility of the new electrochemical method in continuously monitoring the dissolution of solid dosage forms is demonstrated.

EXPERIMENTAL

Instrumentation—The electrode assembly, flow system, pump, and polarography system were the same as reported earlier (2). The tablet dissolution apparatus was described by Levy and Hayes (5).

Chemicals—All chemicals were of the highest quality commercially available. Standard solutions of dopa were prepared using the powder[1].

Procedures—Current-voltage curves were determined using a tubular carbon electrode (TCE) which had previously been cleaned with ethyl acetate. Volume flow rates between 4 and 10 ml./min. were commonly employed and were controlled to ±1%. The voltage was scanned anodically from 0 v. *versus* the saturated calomel electrode (SCE) at 0.20 v./min. Standard buffers (6) were used to determine the effect of pH on the oxidation half-wave potential of the compounds studied.

Solid dosage forms were assayed by dissolving weighed quantities in sufficient 0.1 N HCl to give approximately 10^{-4} M dopa solutions. The sample solutions were pumped through a pledget of glass wool to the TCE (with the potential set at 0.90 v. *versus* the SCE) and the limiting currents were recorded. A calibration plot of the limiting current *versus* concentration was determined daily, and intermittent standards were run to check and adjust the calibration.

The accuracy of the TCE method was evaluated by comparison with a colorimetric method (1). Three tablets were weighed and powdered, and weighed aliquots were taken for analysis; the capsules were emptied and weighed, and similar aliquots were taken. The sample aliquots were dissolved in 1 ml. of 1 N HCl and diluted to 1 l. with water; then each aliquot was assayed by the colorimetric method three times. These same aliquots were then

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[1] Nutritional Biochemical Corp., Cleveland, Ohio.

Table I—Current-Voltage Scans of Possible Interfering Substances

Compound	Half-Wave Potential[a] ±0.005 v. versus SCE
Levodopa	0.250
3-Amino-L-tyrosine	0.230
Hydroquinone	0.135
Resorcinol	N.W.[b]
Tryptophane	N.W.
Tyrosine	N.W.

[a] Determined at pH 6.0, and subject to slight variance due to electrode history. [b] No wave (N.W.) before 0.60 v. versus the SCE.

Table II—Dopa Analysis

Dosage Form	Amount Declared per Sample, mg.	Mean Amount, mg. ± SD^a TCE[b] Method	Colorimetric Method[c]
Tablet (250 mg.)	20.1	20.1 ± 0.1	20.1 ± 0.1
	42.7	42.8 ± 0.2	42.6 ± 0.1
Capsule (250 mg.)	20.0	20.1 ± 0.1	20.1 ± 0.1
	38.9	38.7 ± 0.2	39.0 ± 0.2

[a] Calculated on the basis of three assays of a single aliquot. [b] With 0.1 N HCl as medium. [c] Reference 1.

diluted with 0.1 N HCl to about 10^{-4} M and assayed by the TCE method.

For the dissolution study the beaker was filled to 1 l. with 0.1 N HCl and the propeller was set at 60 r.p.m. The solution was pumped through a Swinnex-25 unit[2] without a filter to the TCE and returned to the beaker. After setting the electrode potential at +0.90 v. versus the SCE and establishing a baseline current, a tablet was added and the limiting current was recorded as a function of time. From a previously determined calibration plot, the chart paper was labeled in terms of percent dissolution (taking the plateau current to represent 100%) as well as microamperes.

RESULTS AND DISCUSSION

A typical current-voltage curve for the oxidation of levodopa at the TCE is shown in Fig. 1. The limiting current was linear with respect to concentration over the 10^{-6}–10^{-3} M range. With the volume flow rate at 5 ml./min., a typical calibration plot has a slope of 6.9 μa./10^{-4} M with a zero intercept. A plot of the logarithm limiting current versus logarithm flow rate had a slope of 0.33,
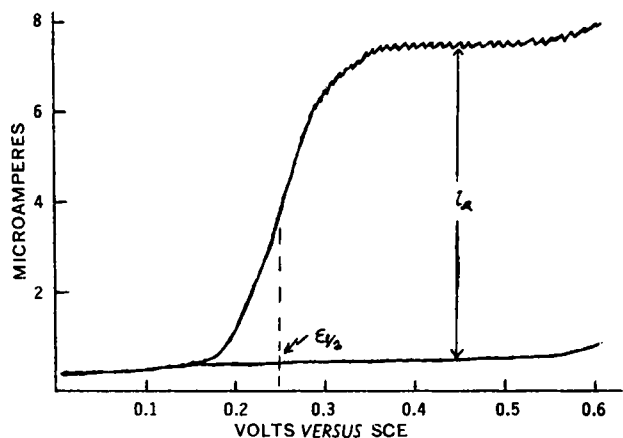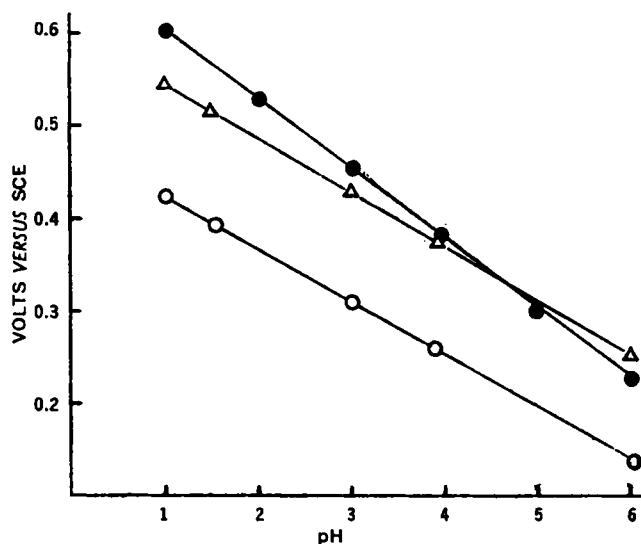
Figure 2—Half-wave potential as a function of pH. Key: O, hydroquinone; △, levodopa; and ●, 3-amino-L-tyrosine.

which agrees with theoretical considerations of the tubular electrode geometry (7).

Current-voltage scans on 10^{-4} M solutions of the compounds listed in Table I show only 3-amino-L-tyrosine to have a half-wave potential $(E_{1/2})$ close to that for levodopa. The other compounds listed, all of which have been suggested as possible interferences formed during synthesis of levodopa, have half-wave potentials significantly different from that of dopa or do not show an oxidation wave. From Fig. 2 it is evident, within the limits of experimental error, that the half-wave potentials for dopa and hydroquinone fit the relationship $E_{1/2} = E^\circ - 0.059$ pH, while the pH dependence of the 3-amino-L-tyrosine oxidation is greater. Indeed, in 1.5 M H_2SO_4 the half-wave potential for levodopa is 0.73 v. versus the SCE while the oxidation of 3-amino-L-tyrosine occurs about 0.10 v. more anodic. Although a more in-depth study was not attempted, it is surmised that the oxidation of 3-amino-L-tyrosine is suppressed by protonation of the amino group on the benzene ring. Thus, samples suspected of containing this impurity may be assayed in strong acid media. Current-voltage curves for dopamine and norepinephrine were observed to have essentially the same half-wave potential as dopa. If these compounds or other 3,4-dihydroxyphenylethylamine derivatives are considered as possible contaminants in a sample, a separation procedure must precede analysis at the TCE.

The accuracy of the TCE method in determining the dopa content of solid dosage forms is shown in Table II. It is evident that the new method gives data in agreement with the colorimetric method

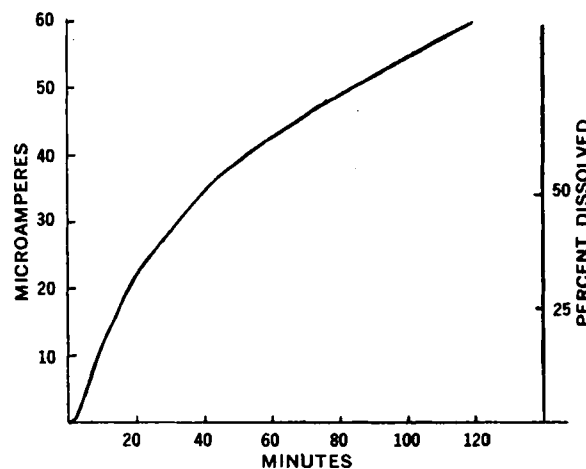Figure 1—Levodopa current-voltage curve; run at pH 6. (See text for details.)

Figure 3—Recorder trace for dissolution study. Three hours was required for 100% dissolution of the 250-mg. tablet in 1 l. of 0.1 N HCl.

and that comparable precision is obtained. In comparison with the colorimetric method, the TCE method is faster and simpler. Once the sample solutions were prepared, between 25 and 30 determinations could be run each hour. The reproducibility of the TCE, as determined by repeatedly assaying a single sample dilution, is indicated by a deviation of the mean ±0.90% for six determinations.

Figure 3 shows the current–time curve for the dissolution study. Once the tablet was placed in the beaker, no further manipulative steps were required to record continuously the tablet dissolution. Although not included here, the dissolution could be determined as a function of pH using the same analytical procedure.

In summary, it is concluded that the electrochemical method for the determination of dopa presented in this paper is more convenient, faster, and simpler to use than previously available methods without any significant loss in precision and accuracy. Although automation was not employed in this study, the method may readily be incorporated into automated or semiautomated systems because it employs continuous analysis on a flowing stream of sample. And, finally, the applicability of the analytical method in the direct and continuous monitoring of tablet dissolution is demonstrated.

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PHARMACEUTICAL TECHNOLOGY

Soft Gelatin Capsules I: Factors Affecting Capsule Shell Dissolution Rate

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Abstract □ A method to study the relationship between various factors influencing the dissolution rate of the soft gelatin capsule shell is reported. The gelatin disk method makes use of the current USP rotating-basket dissolution apparatus. The effects of agitation, temperature, dissolution medium, and shell composition on the capsule shell dissolution rate are illustrated and discussed. A knowledge of these factors and their influence on dissolution should be of assistance in the formulation of soft gelatin capsule shells for various purposes.

Keyphrases □ Dissolution rate of soft gelatin capsules—effects of agitation, temperature, dissolution medium, and shell composition □ Capsules, soft gelatin—effects of agitation, temperature, dissolution medium, and shell composition on dissolution rate □ Gelatin capsules, soft—effects of agitation, temperature, dissolution medium, and shell composition on dissolution rate

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Although soft gelatin capsules have been in mass production (1) since the introduction of the rotary die process (2), little or no work has been reported on the relationship between formulation design and dissolution rate of the capsule shell. Nevertheless, several formulations designed for specific uses have been patented (3–8) in this country. Recently, studies on comparisons of dissolution rates of drugs from soft gelatin capsules and tablets were reported (9, 10). The present report deals with a method to study the relationship between various factors influencing the dissolution rate of the soft gelatin capsule shell.

In the design and formulation of soft gelatin capsule dosage forms, one should consider the effects of components and other parameters on the dissolution rate of the capsule shell. A method that is simple, fast, able to differentiate minor but meaningful changes in dissolution rate, and readily reproducible is of great utility. Eckert et al. (11), concerned with drug availability, advocated the use of the in vitro initial-release rate to reflect this factor in the monitoring of soft gelatin capsule manufacture. The initial-release rate is adequate for such a purpose, but it lacks the sensitivity and simplicity based on the criteria of the present proposal. A more appropriate method was developed in this laboratory.

Many factors that influence the dissolution rate of the soft gelatin capsule shell may be adequately studied by the use of the Nelson (12) modification of the Noyes–Whitney equation. Using the Noyes–Whitney equation, one may write:

$$\frac{dW}{dt} = KS(C_s - C) \qquad \text{(Eq. 1)}$$

where W is the amount dissolved, t is the time, K is the solution rate constant with dimensions of distance/