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Dissolution Studies of Drug Formulations Using Ion-Selective Electrodes as Sensors in an Air-Segmented Continuous Flow Analyzer

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Abstract □ The application of drug ion-selective electrodes as sensors for the direct determination of the released drug in a continuous-flow analyzer for automated dissolution studies is described. Flow-through electrodes, selective to chlorpromazine, amitriptyline, propantheline, cimetidine, and ranitidine, have been constructed and used for the dissolution studies of 18 dosage forms using the rotating basket apparatus. The dissolution profiles are obtained in the form of potential peaks versus time.

It is now well established that the clinical effectiveness of a drug product depends not only on the amount of active substance contained in the product, but also on its availability to the body.[1,2] In the case of solid dosage forms, particularly those with dissolution rate-limited bioavailability, dissolution testing can serve as a reliable, rapid, and economical technique to indicate the in vivo rate and extent of drug release and, also, as an important tool in the design, evaluation, and quality control of the products.[3]

In order to accommodate the increased effort for dissolution studies, numerous dissolution systems with automated sampling and analysis have been designed and tested.[4] In these systems, a filtered sample is pulled from a vessel more or less continuously and may be diverted through the vial rack of an autosampler,[5] through a spectrophotometric cell,[6] or a sampling valve, for introduction into a high-performance liquid chromatograph,[7] a flow injection analyzer,[8] or an air-segmented continuous flow analyzer.[9–12] The detectors in the above systems are mainly spectrophotometers. Selective chemical reactions are used in order to avoid spectral interferences from the excipients or other drug(s) contained in the dosage forms.

Ion-selective electrodes (ISE) are electrochemical transducers that respond selectively, directly, and continuously to the activity of the free ion of interest in solution. Theoretical and practical aspects of ISE technology and methodology are reviewed regularly by Koryta every 2–3 years.[13] The electromotive force (E_{cell}) of an electrochemical cell consisting of an ISE for the ion i and a reference electrode is described by the Nernst equation:

$$E_{cell} = E_{constant} + \frac{2.303\ RT}{zF} \log \alpha_1 \qquad (1)$$

where $E_{constant}$ is a constant term, R is the ideal gas constant, T is the absolute temperature, z is the charge of the ion i, F is the Faraday constant, and α_i is the activity of the ion. When the ionic strength of the solution is fixed at a constant value or at concentrations of $i < 10^{-2}$ M, the activity values can be replaced by concentration values in eq 1.

Besides the membrane electrodes selective to the common inorganic anions and cations, which are commercially available, a great number of ISEs have been constructed by several research groups which are selective to organic ions of pharmaceutical interest.[14] Ion-selective electrodes have some inherent advantages, such as, sufficient selectivity and sensitivity, wide analytical range of analyte concentrations (three or four decades), insensitivity to optical interferences (useful for the analysis of colored or cloudy sample solutions), low cost, fast response, and flexibility in constructing flow-through sensors for analyzers. Despite these advantages and their wide usage in routine analysis, the application of ISEs in dissolution monitoring is very limited. The potassium ISE has been used to monitor the dissolution rate of potassium chloride tablets.[15–17] Dissolution studies of active substances found in tablets as salts with inorganic counter ions have been carried out indirectly by measuring the counter ion with an ISE. For example, the sodium ISE has been used for the dissolution studies of formulations of sodium warfarin, salicylate, and butobarbital,[18,19] and the chloride ISE has been used for the dissolution studies of pseudoephedrine hydrochloride tablets.[20] These electrodes were mainly dipped in the dissolution medium and the electrode potential was recorded.

In this paper, ion selective electrodes are used as sensors for the direct determination of the released drug in an air-segmented, continuous-flow analyzer, interfaced to the USP single-rotating-basket apparatus. New membrane electrodes, assembled as tubular flow-through types, selective to chlorpromazine (CPM), amitriptyline (AMT), propantheline (PRO), cimetidine (CIM), and ranitidine (RAN), were used for the dissolution studies of 18 commercial solid formulations at two different pH values.

Experimental Section

Apparatus—A schematic diagram of the air-segmented, continuous-flow system used for the dissolution studies is shown in Figure 1. The dissolution apparatus consisted of a 250-mL double-wall thermostated glass vessel and a 45-mesh cylindrical stainless steel basket (height 5.5 cm, diameter 2.6 cm), centered within the vessel 2 cm above the inside bottom. The basket was rotated at 60 rpm. A peristaltic pump (pump III, Technicon Instruments Corp.) was used to continuously pump solutions through the electrode assembly. The sampler was purchased from Hook and Tucker, UK (A40 sampler II). The electrode sensors were tubular flow-through PVC matrix membrane ISEs, the construction of which is described below, with a Ag/AgCl wire as an internal reference electrode. The external reference electrode was a saturated calomel electrode (Corning). All potentiometric measurements were carried out with a Corning model 12 Research pH/mV meter and recorded on a Radiometer strip chart recorder (REC 21) through a high sensitivity unit (REA 112) interface. In all experiments, the sampling rate was 22 samples/h, with a sample-to-wash ratio of 1:1. With this configuration, a sample volume of 0.80 mL was aliquoted at each time of sampling.

Construction of Tubular Flow-Through PVC Matrix Membrane ISEs—A small part (4 mm) of the wall of a 4-cm long PVC tube

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(0.89-mm id; e.g., the tubing coded orange-orange by Technicon) is replaced by the PVC matrix membrane of the ISEs using the method previously described by Meyerhoff and Kovach.[21] The polymer ISE membrane casting solution used was prepared by adding 1 mL of the liquid ion exchanger and 0.2 mL of bis-2-ethylhexylphthalate in a solution of 85 mg of PVC in 3 mL of tetrahydrofuran. The electrode body consisted of a plastic test tube (10-cm height, 1.5-cm id). Two holes were opened with a hot nail through the test tube. The PVC tube was then inserted through these holes (with the ion-selective membrane facing the bottom of the test tube) and sealed in place with Araldite epoxy resin glue. The internal reference solution (see below in the reagent section) was introduced into the electrode body (test tube) and a Ag/AgCl wire was immersed. The complete tubular flow-through ISE is presented in Figure 2a.

Instead of the tubular flow-through PVC matrix membrane ISE, a new, completely different configuration, flow-through liquid membrane ISE was also designed and used in the case of ranitidine. The construction of this configuration is described below.

Construction of Flow-Through Liquid Membrane ISE—This ISE consists of two pieces (A and B) of plexiglas (3.2 × 1.8 × 1.5 cm). Five holes (numbered from 1 to 5) are drilled through piece A, as shown in Figure 2b. The stream flows through a hole drilled 0.5 mm below the upper surface of piece B (tangentially to the surface). A thin plexiglas layer over the stream hole is removed, in a 0.3-cm long area, with a hot nail. In this manner, a hole is created on the upper surface of piece B which is covered with a cellulose acetate membrane (Figure 2b). A piece of the Beckman standard microzone electrophoresis cellulose acetate membrane is imposed between pieces A and B and then the pieces are stacked together by fastening the screws (holes 1 and 2 of A and B). The internal reference solution is introduced into hole 4. Holes 3 and 5 are filled with the drug liquid ion exchanger and serve as reservoirs.

Reagents—All chemicals used were of analytical reagent grade, and deionized, distilled water was used in solution preparation. Pure substances of the hydrochloride salts of chlorpromazine, amitriptyline, ranitidine, and cimetidine, and the bromide salt of propantheline, were obtained from various manufacturers and were used to prepare standard solutions.

Sodium tetraphenylborate, eosin yellow, tetrakis (*m*-chlorophenyl) borate, *o*-nitrotoluene, *p*-nitrocumol, bis-2-ethylhexyl phthalate, and tetrahydrofuran (THF) were obtained from Fluka. Polyvinyl chloride (PVC) of very high molecular weight was obtained from Aldrich Chemical Co.

Liquid Ion Exchangers—The liquid ion exchangers for chlorpromazine and amitriptyline were their mixed salts with eosin and tetraphenyl borate dissolved in *p*-nitrocumol. For propantheline, the liquid ion exchanger was its ion pair with tetraphenyl borate

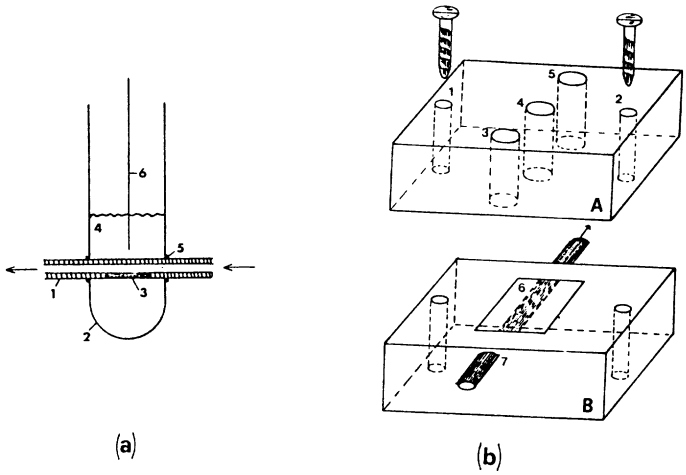

Figure 2—(a) *Schematic diagram of the tubular flow-through PVC matrix membrane ISE:* (1) *PVC tube;* (2) *plastic test tube;* (3) *sensing membrane;* (4) *internal reference solution;* (5) *Araldite glue;* (6) *Ag/AgCl wire.* (b) Liquid membrane ranitidine flow-through electrode: (1) *and* (2) *screw holes;* (3) *and* (5) *liquid ion-exchanger reservoir holes (3 mm, id);* (4) *internal reference solution hole (3 mm, id);* (6) *cellulose acetate membrane;* (7) *flowing stream hole (2 mm, id). The arrows show the direction of the flowing stream.*

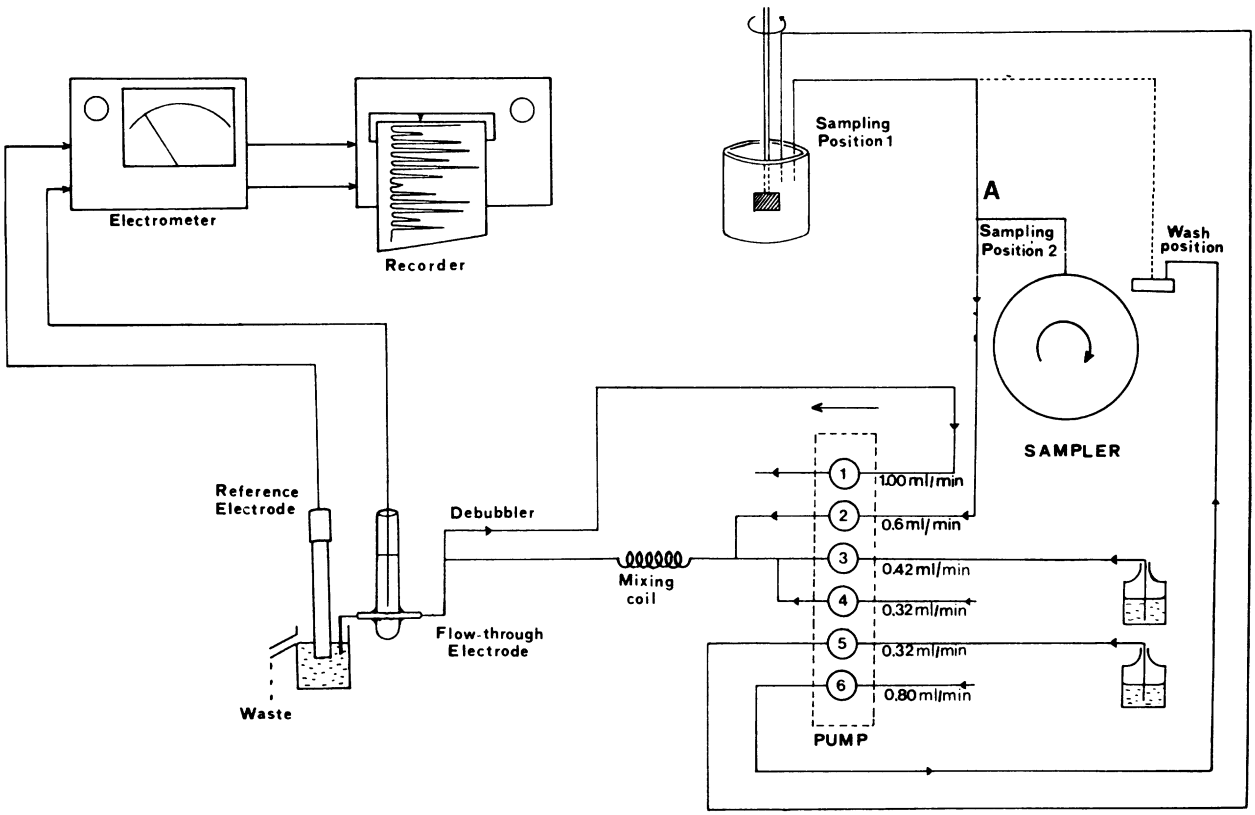

Figure 1—*Diagram of the continuous-flow automated system for dissolution studies. The pump channels correspond to the following:* (1) *debubbling;* (2) *sample;* (3) *ISA/pH adjustor;* (4) *air;* (5) *dissolution medium;* (6) *standard wash solution.*

dissolved in *o*-nitrotoluene. For ranitidine and cimetidine, the liquid ion exchangers were their salts with tetrakis(*m*-chlorophenyl) borate dissolved in *p*-nitrocumol. The selection and preparation of the liquid ion exchangers, and the study of selectivity and other analytical characteristics of the electrodes, as well as their applications to the potentiometric determination of the above drugs in formulations and in serum and urine, have been described elsewhere.[22,23]

Internal Reference Solutions—These solutions were 0.010 M with respect to the measured drug and 0.10 M with respect to sodium chloride saturated with silver chloride.

Buffers—The following buffers were used: acetate (0.30 M, pH 5.2); phosphate (0.40 and 0.010 M, pH 6.5); and phosphate (0.010 M, pH 7.2). They were prepared from the corresponding acid or acid salt and 18 M sodium hydroxide solution.

Wash Solutions—The wash solutions were prepared to contain a drug concentration that was approximately equal to one third of the final drug concentration after the completion of the dissolution of the tested formulation in the dissolution medium used. The drug concentration of each wash solution is shown in Table I.

Drug Formulations—For the dissolution studies, commercial formulations were obtained from local suppliers and are shown in Table II.

Procedures—*Calibration Curves*—Calibration curves were obtained before and after each dissolution test in the following manner. The sample tray was loaded with aqueous standard drug solutions (all in duplicate) and the pump was turned on allowing the reagents to flow through the system (sample probe immersed into the wash solution). After a few minutes, a steady baseline potential was observed and sampling was started. The difference in potential between each sample and wash solution was recorded as a peak on the recorder chart. Peaks corresponding to drug concentrations lower than that of the wash solution appear below the baseline, while those corresponding to concentrations higher than the wash solution appear above the baseline. Peak heights for each standard drug solution of concentration C were plotted versus $-\log[C]$ to give the calibration graph.

Dissolution Studies—The sample tray was replaced by the dissolution apparatus. A volume of 200 mL of the dissolution medium was pipetted into the dissolution vessel which was thermostated at 37 ± 0.5 °C. The pump was turned on with the sample probe positioned in the wash solution. When the baseline potential was stabilized, the rotating basket, containing the dosage form as well as the pump channel (tube 5), was immersed into the dissolution medium and immediately the sampler was initiated. Channel 5 replaced the dissolution medium removed during sampling and therefore the dissolution volume remained constant throughout the test. The experiment proceeded automatically and was stopped manually after complete dissolution of the drug (this is shown by the stabilization of the peak heights recorded).

Calculations—The baseline traces of electrode potential at the beginning and end of the dissolution test were joined graphically with a straight line. This line was taken as the baseline of the experiment. The baseline usually deviated slightly from parallelism to the time axis because of the electrode drift, especially during the experiments with sustained-release dosage forms. This fact does not influence the results.

The peak height (mV) was taken as the distance of the peak from the baseline. From the height of the k^{th} peak and calibration graph, the corresponding concentration, C_k, of the drug in the dissolution medium was calculated. The amount of the dissolved drug in the vessel is then given by the product V_oC_k, where V_o is the constant volume of the dissolution medium. The cumulative amount, m_k, of drug dissolved is given by eq 2, which takes into account the amount withdrawn during the (k − 1) previous samplings:

Table II—Values of $t_{50\%}$ for Various Formulations of Chlorpromazine, Amitriptyline, Propantheline, Ranitidine, and Cimetidine at Two pH Values

Formulation[a]	$t_{50\%}$ ± SD (n = 3), min	
	pH 1	pH 6.5
Chlorpromazine		
Ancholactil	6.3 ± 0.3	5.6 ± 0.3
Solidon	14.2 ± 1.3	10.3 ± 0.1
Largactil	41.4 ± (7.2)[b]	18.0 ± (1.2)[b]
Zuledin	21.6 ± 2.3	5.9 ± 0.8
Antistress	27.3 ± 3.9	21.1 ± 1.0
Amitryptyline		
Amitriptyline	<2	5.1 ± 0.5
Stelminal	4.1 ± 0.4	3.2 ± 0.2
Minitran	58.9 ± 4.9	70.7 ± (5.1)[b]
Somnium	5.7 ± 0.9	8.9 ± (0.2)[b]
Limbitrol	<2	<2
Saroten Dragees	24.6 ± (2.6)[b]	40.6 ± (3.8)[b]
Saroten retard	108 ± 8	106 ± (6.3)[b]
Propantheline		
Pro-Banthine	3.2 ± 0.3	3.2 ± 0.8
Pro-Banthine with Dartalan	41.4 ± 6.0	41.1 ± 1.2
Flogonevrin	97.6 ± 8.3	80.7 ± 6.0
Ranitidine		
Zantac	13.0 ± 3.0	11.7 ± 1.0
Baroxal	10.8 ± 0.2	13.2 ± 1.8
Cimetidine		
Tagamet	4.3 ± 1.1	3.7 ± 0.6

[a] Formulations (lot no. in parentheses): Ancholactil, 1.00 mg CPM/tab., Antibiotiki, (577–161); Solidon, 100 mg CPM/tab, Adelco (13); Largactil, 100 mg CPM/tab, Rhone-Poulene (229–7); Zuledin, 100 mg CPM/tab, Demo (80121); Antistress, 100 mg CPM/tab, Pefanic (7601); Amitriptyline, 25 mg AMT/tab, Erfar (84015); Stelminal, 25 mg AMT/tab, Coup (160); Minitran, 25 mg AMT and 4 mg perphenazine/tab, Adelco (2/79); Somnium, 12.5 mg AMT and 5 mg chlordiazepoxide/tab, Pefanic (79/8401); Limbitrol, 12.5 mg AMT and 5 mg chlordiazepoxide/tab, Roche (H001E); Saroten Dragees, 25 mg AMT/tab, Tropon (402001); Saroten retard capsule, 75 mg AMT/caps, Tropon (3474); Pro-Banthine, 15 mg PRO/tab, Searle (4534 8 9); Pro-Banthine with Dartalan, 15 mg PRO and 3 mg thiopropazate/tab (9J039); Flogonevrin, 15 mg PRO/tab, N. Zikidis (179); Zantac, 150 mg RAN/tab, Glaxo (3222 F4); Baroxal, 150 mg RAN/tab, Glaxo (486022); Tagamet, 200 mg CIM/tab, Smith Kline and French Labs (4029). [b] Range of two values.

Table I—Conditions for the Calibration Curves and the Dissolution Studies

Ion-Selective Electrode	ISA/pH Adjustor Solution	Wash Solution, M[a]	Linear Response Range, M, and Slope, mV[b]
Chlorpromazine	Na_2SO_4, 0.10 M HCl, 0.30 M	1.10^{-4}	4.10^{-5}–6.10^{-3} (52)
Amitriptyline	Na_2SO_4, 0.10 M HCl, 0.30 M	1.10^{-4}	6.10^{-5}–6.10^{-3} (45)
Propantheline	Na_2SO_4, 0.10 M	3.10^{-5}	3.10^{-6}–6.10^{-3} (58)
Ranitidine	Phosphate Buffer 0.40 M, pH 6.5	1.10^{-4}	1.10^{-5}–5.10^{-3} (53)
Cimetidine	Acetate Buffer 0.30 M, pH 5.2	4.10^{-4}	4.10^{-5}–8.10^{-3} (49)

[a] Solutions of the drug salt in the dissolution medium. [b] Slope is shown in parentheses.

$$m_k = C_k V_o + V_s \sum_{i=1}^{k-1} C_i \quad (2)$$

where C_i is the concentration of dissolved drug at the i^{th} sample collection and V_s is the volume of sample used for the assay (V_s is always 0.80 mL). The percent of drug dissolved is equal to $(m_k/m_m) \times 100$, where m_m is the amount of the drug in the tablet as stated by the manufacturer.

Results and Discussion

Dissolution studies of propantheline, ranitidine, and cimetidine formulations were carried out at pH values of 1.0 (0.10 M HCl) and 7.2 (0.010 M phosphate buffer); those of chlorpromazine and amitriptyline were conducted at pH values of 1.0 (0.10 M HCl) and 6.5 (0.010 M phosphate buffer). Other experimental conditions for the calibration and the dissolution studies are presented in Table I. The last column of Table I contains the linear response ranges and the slopes of the constructed flow-through electrodes. The potential stability at each of the concentration levels falling into the linear response range is $\sim\pm0.2$ mV. This corresponds roughly to $\pm1\%$ error in concentration. The reference electrode potential is constant, irrespective of the composition of the solution in the waste beaker (Figure 1). So, the effluents of the continuous-flow system which are directed into that beaker by no means affect the accuracy of the measurements.

Typical dissolution profiles of various commercial formulations are presented in Figures 3 and 4, along with the peaks of standards used for the calibration curves.

In the dissolution profiles, some peaks appear below and others above the baseline. This means that at the beginning of the experiment the concentration of the dissolved drug is lower than the concentration of the wash solution (baseline) and the peaks are below the baseline. As dissolution progresses, the concentration of the dissolved drug increases and after the point which corresponds to equal concentration of the dissolved drug and the wash solution, all peaks are above the baseline. We have selected the wash solution concentration in each case so as to obtain stable baseline recordings and for rough equality of peak heights below and above the baseline. With water as the wash solution, the electrode baseline would be unstable and noisy.

For the calculation of the percentage of the drug dissolved with time, only potential readings (peak heights) which lie in the linear response range of the electrodes are used (Table I).

Some dissolution experiments may last up to 2 h or more. During this time, the baseline may shift from its initial value due to the drift of the flow-through electrodes. The electrode drift does not affect the results, if the baseline of the whole

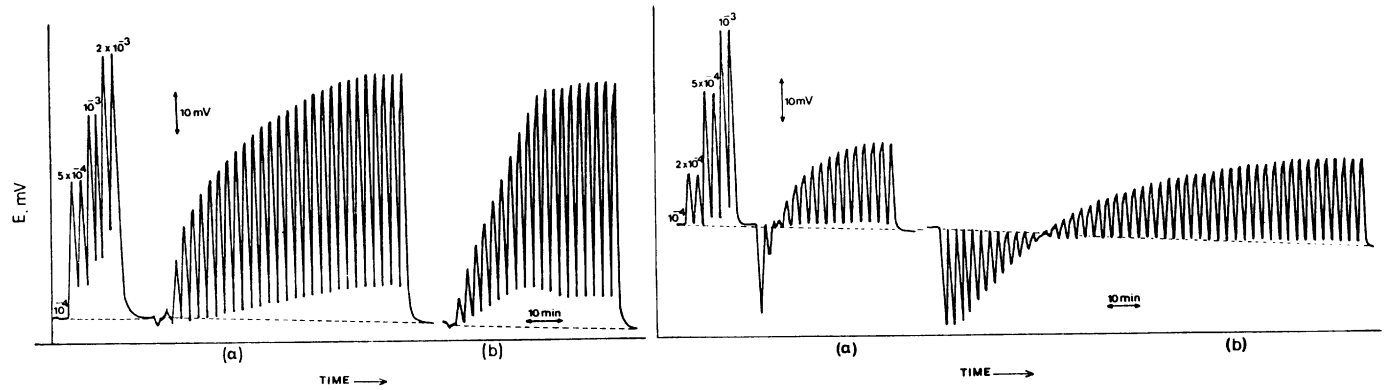

Figure 3—*Left panel: typical dissolution profiles of* (a) *Largactil and* (b) *Antistress at pH 6.5, along with the peaks for the calibration curve. Right panel: typical dissolution profiles of* (a) *Amitriptyline and* (b) *Minitran at pH 1.0, along with the peaks for the calibration curve.*

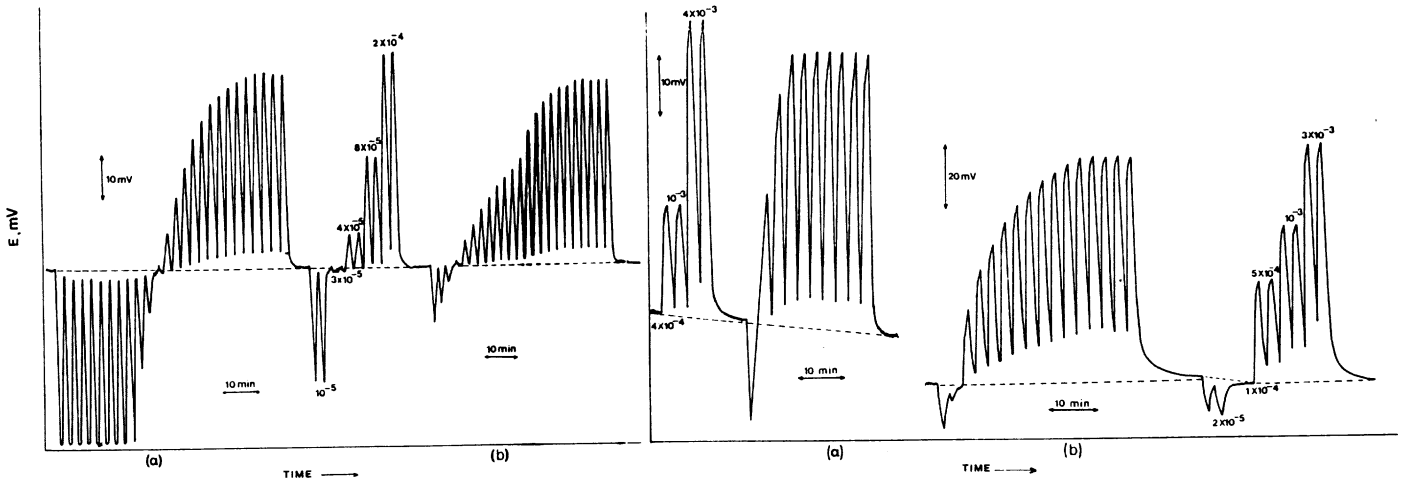

Figure 4—*Left panel: typical dissolution profiles of* (a) *Pro-Banthine with Dartalan and* (b) *Flogonevrin at pH 1.0, along with the peaks for the calibration curve. Right panel: typical dissolution profiles of* (a) *Tagamet and* (b) *Zantac at pH 7.2, along with the peaks for the calibration curves.*

experiment is graphically constructed as described previously and as shown in Figures 3 and 4.

Experiments with calibration graphs constructed before and after various dissolution studies, have shown that the changes in the electrode slope are ≤0.2 mV during a dissolution experiment. Such changes are considered insignificant and do not affect the accuracy of the results to any considerable extent.

In Figures 5 and 6 the percentage of the dissolved drug versus time is presented for the formulations tested and for two pH values. From these diagrams, the time at which 50% of the active compound has dissolved was calculated ($t_{50\%}$), and the results are summarized in Table II. In the proposed system, the sampling time was always 80 s. For this reason, a reliable estimation of $t_{50\%}$ is not possible for formulations which dissolve almost immediately, and $t_{50\%}$ is reported as $t_{50\%}$ <2 min. The variation in the values of $t_{50\%}$ is due to the precision of the analytical system used and to the within-lot variability of the formulations tested.

It was noticed that drug formulations which contain the same active compound but are from different manufacturers demonstrate statistically significant differences in their dissolution rates. This was verified by applying the unpaired t test criterion to the values of the $t_{50\%}$ calculated in each case. In some cases, the differences were dramatic. For example, the $t_{50\%}$ values for Largactil and Flogonevrin are 7 and 30 times greater than those for Ancholactil and Pro-Banthine, respectively (Table II). Differences for the other formulations tested are illustrated in Table II. The differences in the dissolution rates of formulations containing the same active compound are not unexpected. They reflect differences in the manufacturing process and the excipients used. Sometimes, such differences are desirable for the manufacturing of drugs with slow, intermediate, or rapid release of the active compound in the gastrointestinal tract. On the other hand, these observations stress the usefulness of in vitro dissolution testing as an objective indicator of the bioavailability of the formulation and as an independent quality control procedure.

As shown in Figures 5 and 6 and in Table II, for most drugs the pH effect on the rate of dissolution is minimal. The exceptions are the formulations Largactil, Zuledin, Antistress, Saroten Dragees, and Amitriptyline. The Zuledin tablets dissolve faster at pH 6.5 ($t_{50\%}$ = 5.9 min) than at pH 1.0 ($t_{50\%}$ = 21.6 min). The Antistress tablets have about the same value of $t_{50\%}$ at pH 1.0 and 6.5, but the shape of the dissolution curve is different at the two pH values (see Figure 5). The Saroten Dragees tablets have a higher dissolution rate at pH 1.0 compared with that of pH 6.5 (Figure 5). Significant differences in the dissolution rates at pH 1 and 6.5 have also been noticed for the formulation Amitriptyline. At pH 1.0, the tablets dissolve almost immediately ($t_{50\%}$ < 2 min), but at pH 6.5, the dissolution is slower ($t_{50\%}$ = 5.1 min).

The differences in the dissolution rates of some formulations at the two pH values tested cannot be attributed to differences in the ionic species present due to different ionization constants of the drugs. For all drugs tested, the main species in solution, even at pH 6.5, is the monoprotonated base. The differences are presumably due to differences in the excipients used and the manufacturing details. No effort was made to study the pH effect in more detail.

The selectivity of the electrodes used in this report was studied in detail and is mentioned elsewhere.[22,23] We have previously shown that the excipients of the formulations

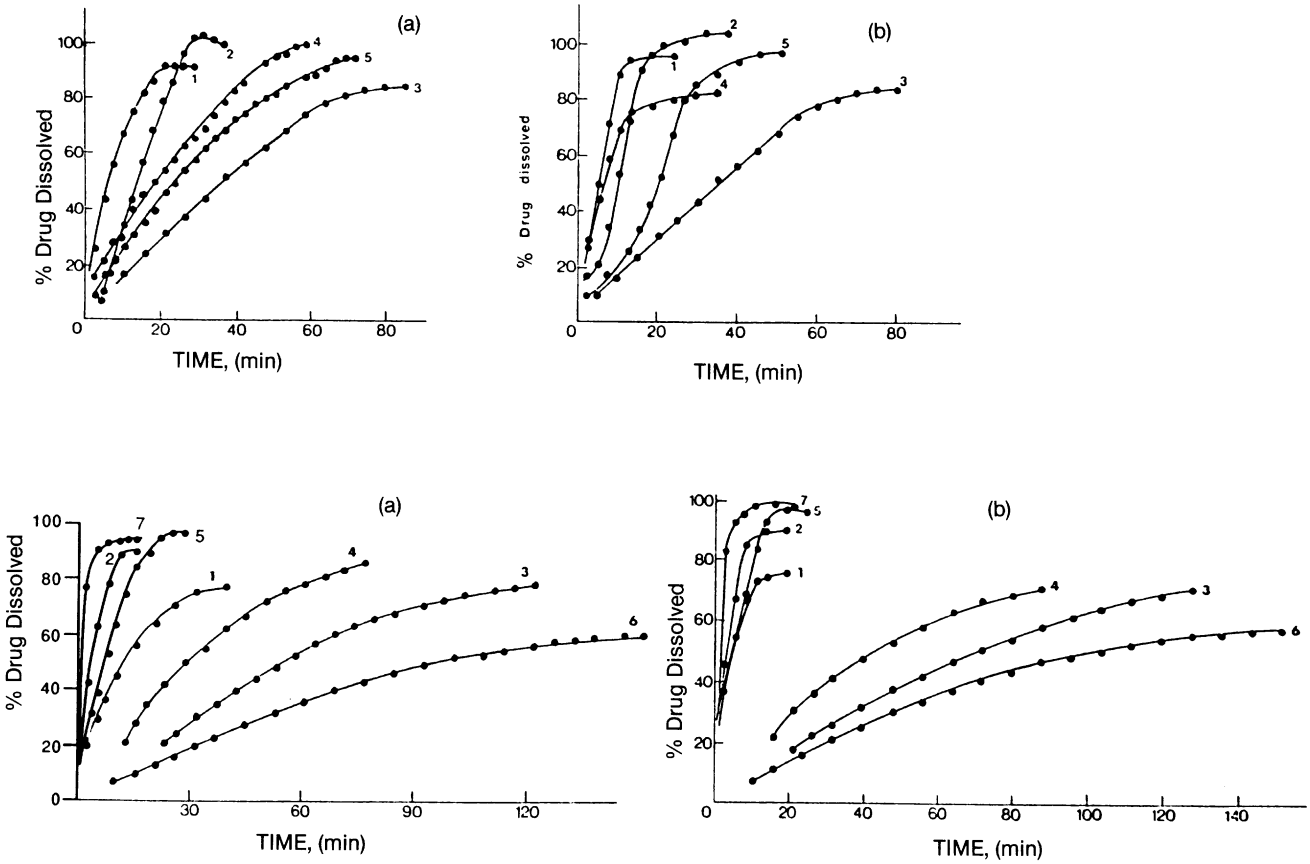

Figure 5—*Upper panel: dissolution curves of chlorpromazine dosage forms at pH* (a) *1.0 and* (b) *6.5:* (1) *Ancholactil;* (2) *Solidon;* (3) *Largactil;* (4) *Zuledin;* (5) *Antistress. Lower Panel: dissolution curves of amitriptyline dosage forms at pH* (a) *1.0 and* (b) *6.5:* (1) *Amitriptyline;* (2) *Stelminal;* (3) *Minitran;* (4) *Saroten Dragees;* (5) *Somnium;* (6) *Saroten retard;* (7) *Limbitrol.*

used and the drugs that may be present in mixtures with the drug of interest do not interfere. This was verified by analyzing the drug content with the respective ISE and by an official analytical procedure. The results of such comparisons were in excellent agreement.[22,23]

To further evaluate the accuracy of the proposed methods, the results of the dissolution study of chlorpromazine formulations were compared with those obtained using a manual sampling and analysis technique, according to the USP official procedure. The mean differences of the two methods expressed as percentage of the dissolved drug at each sampling point were $<\pm 3.5\%$. This difference can be considered reasonable.

The flow-through electrodes of the tubular type have the advantage of using a PVC membrane (instead of a liquid ion exchanger) which is part of the tube containing the measuring stream. This is important because the dead volume of the measuring cell can be considered as zero. Moreover, the tubular PVC electrodes demonstrate a fast response and their other response characteristics are similar to the conventional dip-type PVC or liquid-membrane electrodes. The only disadvantage of these tubular devices is the slightly lower slope which is noticed for some of the electrodes constructed. The procedure for constructing tubular flow-through electrodes is very simple. Their operating lifetime is ~15 d. This is not a serious disadvantage because the replacement of an old membrane with a new one can be done easily and with minimal time. The option of using a liquid-membrane flow-through unit is also given. This unit can be constructed very easily, is reusable, and can be used for any drug electrode provided that a suitable liquid ion exchanger exists.

Procedures which have already been published and use ion-selective electrodes in dissolution studies[15–20] have the following deficiencies. (*a*) The stirring of the dissolution medium with the rotating basket is not sufficient to guarantee homogeneity of the solution. This can lead to electrode potential noise and instability when the electrodes are dipped directly into the dissolution medium. Additionally, with these systems, the construction of a calibration curve under the same experimental conditions is difficult. (*b*) In some dissolution studies it may be necessary to work at experimental conditions at which the electrode response is poor (e.g., at a pH value where the electrode potential depends strongly on pH). In our system, the final analytical measurement is carried out under the optimum electrode response conditions. This is achieved by adding to the sample stream an ionic strength/pH adjustor (ISA/pH adjustor). With appropriate optimization, possible interferences from other compounds which are also present in the formulation tested can be minimized or even eliminated. (*c*) With the electrodes dipped into the dissolution medium, there is always the possibility of errors which are due to electrode drift, especially for drugs which dissolve slowly. This is not a problem in our system because the baseline potential used for every peak corresponds to that sampling time. The wash solution which is aspirated during the experiment after every peak is equivalent to a recalibration process with one standard drug solution. (*d*) In all the dissolution studies presented here, an ion-selective electrode is used to selectively monitor the active compound released in the dissolution medium. Most active compounds are present in the pharmaceutical preparations as salts with counter ions such as halides (the cations) or alkali metals (the anions). In this

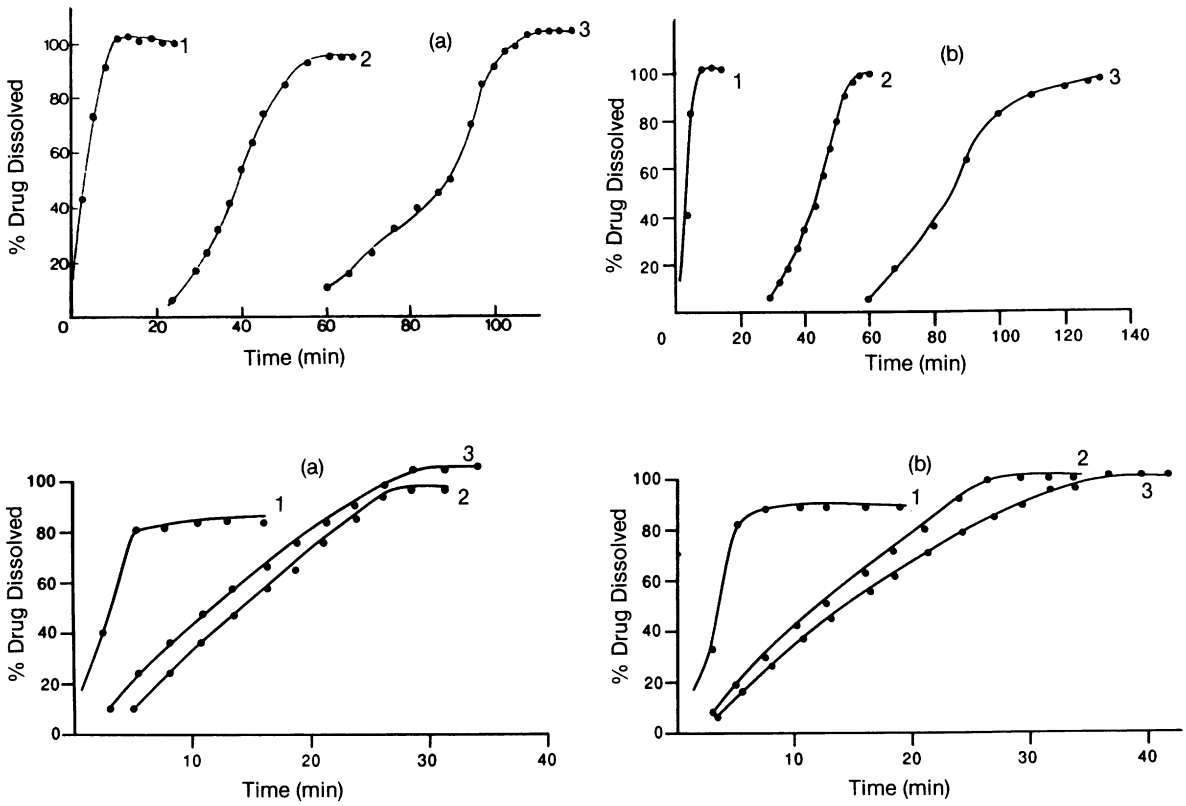

Figure 6—*Upper panel: dissolution curves of propantheline tablets at pH* (a) *1.0 and* (b) *7.2. Tablets:* (1) *Pro-Banthine;* (2) Pro-Banthine with Dartalan; and (3) *Flogonevrin. Lower panel: dissolution curves of ranitidine and cimetidine tablets at pH* (a) *1.0 and* (b) *7.2. Tablets:* (1) *Tagamet;* (2) *Zantac;* (3) *Baroxal.*

case, the dissolution process can also be followed by measuring the counterion concentration in the dissolution medium versus time. This practice has been followed by many investigators,[17-20] but the results can be compromised for the following reasons: (*i*) in the case of mixtures of two or more active compounds containing the same counterion, much faster dissolution rates will be observed for a simple active compound, if the counterion is assayed during the experiment (in fact, in such cases, the calculation of the rate of release of each active compound from the formulation is not feasible); and (*ii*) it is possible that the active compound and the counterion are released from the formulation with a different rate.

In conclusion, the proposed dissolution procedures combine the well-known advantages of ion-selective electrode potentiometry with those of continuous-flow analysis. The final result is a new operational system which could be proven useful for the direct and reliable in vitro dissolution testing of pharmaceutical formulations. Modification of the proposed system to increase productivity (e.g., adaptation to a six-station dissolution test apparatus) probably can be done without any major difficulties.

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