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Application of automated flow injection analysis (FIA) to dissolution studies

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Summary

The application of FIA to dissolution studies is described. Propantheline bromide, salicylamide and sulfamethizole were chosen as model drugs to investigate the utility of FIA method for dissolution studies. In each case the FIA system with the appropriate chemistry manifold was coupled with the rotating basket apparatus. A fully automated monitoring of dissolution rates was achieved. A complete dissolution profile in tabulated form is provided by the computer of the system at the end of the experiment.

Automation of any type of solid dosage forms agitation technique can be easily acquired by adapting a FIA system.

Introduction

As the realization of the role of the dissolution process as an important factor in drug bioavailability has grown over the past two decades, the need for evaluating dissolution rates of solid dosage forms has steadily increased. Recently, the USP XX has included dissolution tests in the monographs for most of the official oral solid dosage forms. Establishment of such a requirement has expanded the need for the determination of dissolution rates. In order to accomodate this need, therefore, numerous dissolution systems with automated sampling and analysis have been designed and tested.

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Automated monitoring of dissolution process is generally performed by the direct spectral analysis technique, in which a pumping arrangement causes flow of a filtered portion of the dissolution medium to a spectrophotometer flow-cell and back to the dissolution vessel. Various systems based on this concept mechanized or automated to varying degrees have been proposed (Schroeter and Wagner, 1962; Castello et al., 1968; Pernarowski et al., 1968; Cakiryildiz et al., 1975; Shah et al., 1973; Tingstad and Riegelman, 1970; Kent et al., 1977; Walker, 1983). However, this technique cannot be employed for drugs that lack spectral absorbance or when the excipients or other drug(s) contained in the dosage form would interfere with the spectral assay.

Air-segmented continuous flow analysis was introduced to solve the problem and the Sample Acquisition System for Dissolution Rate Analysis (SASDRA) [1] was developed (Ahuja and Spitzer, 1970; Engdahl et al., 1976). Several modifications have been made to the initial concept of air-segmented continuous flow analysis to enhance its operational utility (Lucania et al., 1976; Shah and Miller, 1976; Cioffi et al., 1976; Cioffi et al., 1979; Kirchhoefer et al., 1982).

In recent years Flow Injection Analysis (FIA), a new rapidly developing analytical technique, has come to compete with and in some cases to complete air-segmented continuous flow analysis (Ruzicka and Hansen, 1978, 1980, 1981; Betteridge, 1978; Rocks and Riley, 1982; Ranger, 1981). FIA is based on injection of a liquid sample into a moving non-segmented carrier stream of a reagent. The injected sample forms a zone that disperses on its way to a detector. The sample may be reacted with a variable number of reagents, incubated, dialyzed, distilled or extracted. The reaction product passes through a flow-cell of an appropriate detector, i.e. photometer, fluorometer, ion-selective electrode, flame atomic absorption and flame emission spectrometers, and also polarography, stripping voltametry, amperometry and luminescence devices. One of the major benefits of FIA is its capability of performing sample pretreatment functions on-line, such as dialysis, ion exchange, oxidation, reduction, solvent extraction and distillation. The only drawback of the technique is that the sample pretreatment and chemical reactions must be accomplished or proceed at a sufficient level in less than 2 min to avoid large dispersion of the sample. Various automated FIA systems have been developed and several commercial analyzers are now available [2-9].

In the present paper we describe the application of a home-made fully automated FIA analyzer to dissolution studies. Commercially available tablets of salicylamide,

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[1] Technicon Instruments Corporation, U.S.A.
[2] FIA 5020, Tecator U.S.A.
[3] Bifok, Sweden.
[4] AMFIA-2000, American Research Products Corp., U.S.A.
[5] Fiatron Systems, U.S.A.
[6] QuickChem, Lachat Chemicals U.S.A.
[7] Mark Instrument Company U.S.A.
[8] Hitachi, Japan.
[9] Breda Scientific, Belgium.

sulfamethizole and propantheline bromide were chosen as test formulations for the experiments.

Materials and Methods

Materials

Tablets of sulfamethizole [10], salicylamide [11] and propantheline bromide [12] were obtained directly from the manufacturers. All other materials were of analytical reagent grade. Deionized double-distilled water was used throughout the study.

Instrumentation

A block diagram of the automated FIA system is shown in Fig. 1. The reagent pump system consists of two 4-channel continuously variable speed pump [13] with silicone rubber tubings of 0.5–4.00 mm i.d. used with variable motor speeds to provide appropriate flow rates. The sample storage-injection system consists of a 4-way teflon rotary valve [14] operated with a pneumatic two position actuator [15]. An air supply pressure is required for operation, controlled by a microcomputer [16] through two 3-way solenoids. A 200 μl teflon sample loop was used. Disposable filter [17] was attached to the end of the sample probe to provide filtration of the dissolution medium. The sample line of the pump has only 0.5 ml dead volume and continuously circulates the dissolution medium through the sample storage loop. The analytical manifold consists of teflon tubing coils (0.8 mm i.d.) of various lengths. The spectrophotometer [18] was equipped with a 18 μl dead volume flow-cell [19] with a 10-mm length path. The spectrophotometer output signal was fed to microcomputer's interface and a chart-recorder through a log amplifier to convert transmittance to absorbance. More details on the electronic interface and the software developed to control the automated system will be published elsewhere.

Analytical methods

The determination of all drugs was based upon well-known methods which were adapted to the FIA system. The analytical manifolds used for sulfamethizole,

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[10] Urosunicol, (500 mg of sulfamethizole), Lot 770110 Athenpharm, Athens, Greece.

[11] Ilvico neo (contents: bromfeniramin maleate 3 mg, vitamin C 30 mg, propylphenazone 75 mg, caffeine 10 mg, salicylamide 150 mg), Lot U0533951 Merck, Athens, Greece.

[12] Pro-Banthine (15 mg of propantheline bromide), Lot A 21Θ81A 36 Searle, Athens, Greece. Pro-Banthine with Dartalan (15 mg of propantheline bromide, 3 mg of thiopropazate hydrochloride), Lot A 21Θ82A52 Searle, Athens, Greece.

[13] Sage, model 375A, U.S.A.

[14] Rheodyne, type 50 U.S.A.

[15] Rheodyne, type 5001 U.S.A.

[16] Rockwell AIM 65 U.S.A.

[17] Filter for pipette tips-Centraur Chemical Co. U.S.A.

[18] Bauch and Lomb, Spectronic 21 model, U.S.A.

[19] Helma Cells, Inc. model 172.12, U.S.A.

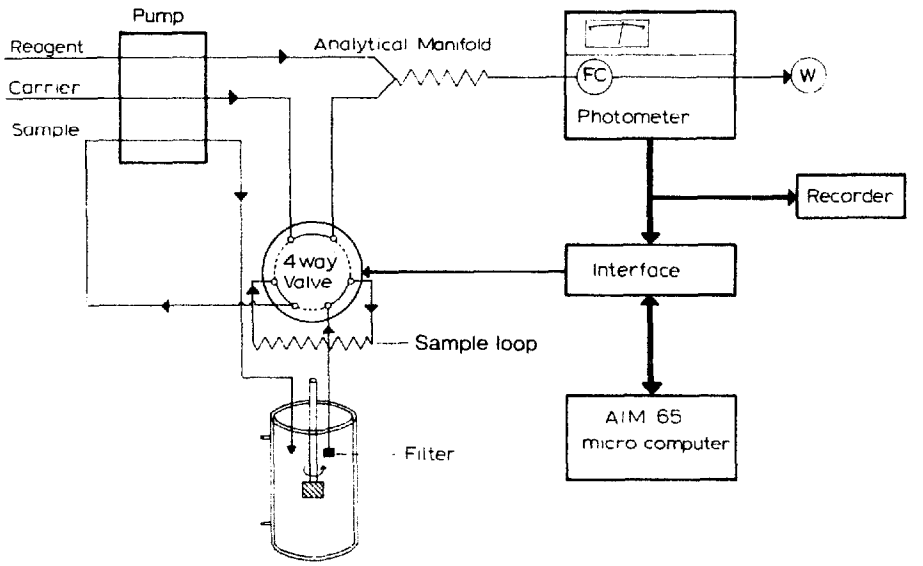

Fig. 1. Schematic diagram of the automated FIA-dissolution system. The arrows show the direction of the flow or the signal processing. Key: FC, flow-cell; W, waste.

salicylamide and propantheline bromide are shown in Fig. 2a, b and c, respectively. The Bratton-Marshall (1939) method was used for sulfamethizole, following the concentration of drug at 540 nm. Trinder's (1954) reaction was utilized to determine the concentration of salicylamide which was monitored at 540 nm. The automated photometric determination (Stenger and Kolthoff, 1935) of bromide ions which are oxidized to bromine with chloramine-T in presence of phenol red at pH 4.6 was used to follow the concentration of propantheline bromide at 590 nm.

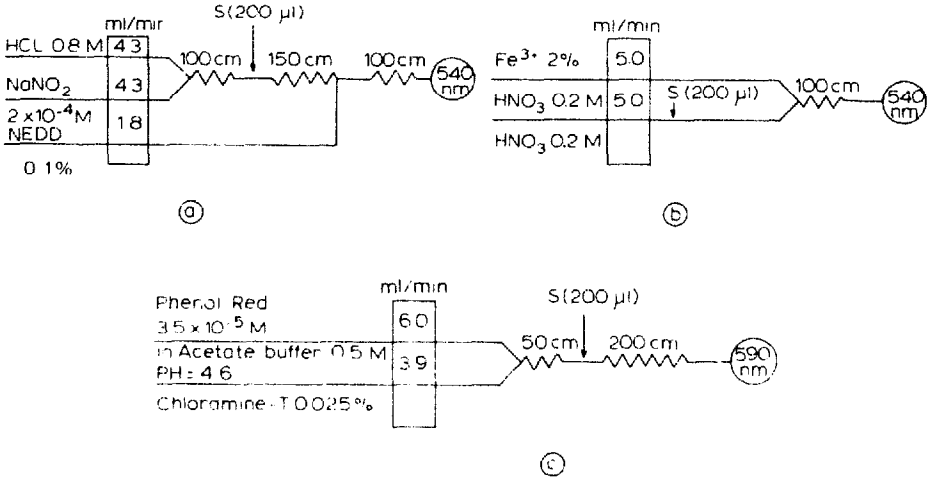

Fig. 2. Analytical manifolds for the FIA determination of: sulfamethizole (a), salicylamide (b) and propantheline bromide (c). Key: S, sample; NEDD, N-(1-napthyl) ethylenediamine dihydrochioride.

Determination of drug content was also performed on 6 tablets of each brand utilizing the analytical methods described. No interference of excipients and coexisting drugs was observed.

Dissolution

The rotating basket method was used for the dissolution studies. One tablet was placed into a 250 mesh screen basket and the whole was immersed in a double-wall beaker containing the specified volume (in the legends of figures) of HCl 0.1 N or phosphate buffer pH 7.2. The basket was rotated at 60 rpm at 3 cm distance from the bottom of the beaker. Water was circulated from a bath through the double-wall beaker ensuring a constant temperature of $37 \pm 0.5\,^{\circ}C$ throughout the dissolution experiment. A cover was used to keep the sample probe in a constant position.

Experimental procedures

In a typical experiment, a measured volume of dissolution medium is transferred into the double-wall beaker. The fluid is allowed to attain temperature equilibrium. The analytical wavelength is set on the photometer and the pump starts flowing the carrier stream and reagent(s) through the appropriate analytical manifold. The 100% transmittance is calibrated on the photometer and then using the calibration curve program 3–5 standards of the drug under study are determined. Thus, a calibration curve of absorbance peak height vs drug concentration is constructed automatically. Then, the dissolution rate program is run and the operator sets the number of samplings, the time interval and the theoretical maximum of drug concentration. The sample probe is secured in position, the rotating basket with the dosage form is immersed into the dissolution medium, and the program as well as the recorder are started. The filtered fluid is continuously circulated through the sample loop (in less than 1 s) and at the preset time is injected into the carrier stream and proceeds to the analytical manifold to be mixed with the reagent(s). The absorbance peak is recorded, its height is read by the microcomputer, while the concentration of the drug and the percentage of dissolution are calculated and printed along with the number of determinations and the corresponding time. To avoid any drift of the baseline, because of the prolonged experimental period, the 100% transmittance is automatically read by the computer before each successive determination. At the end of the experiment the dissolution profile is presented on the chart recorder as a series of absorbance peaks vs time and also on the computer's printer as a table consisting of: time, absorbance, drug concentration and percentage of dissolution.

Results and Discussion

Figs. 3, 4 and 5 show typical FIA results used for the calibration curves of drugs as well as the corresponding dissolution profiles at pH 1.0 and 7.2.

Dissolution experiments using the same methods of analysis but operated manually were also performed. The dissolution profiles obtained were identical to those obtained with the proposed system. The mean differences of the two methods

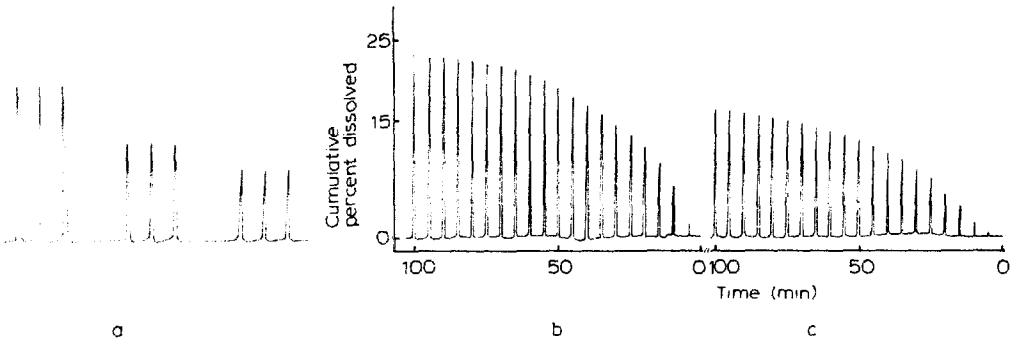

Fig. 3. Data for calibration curve (a) and dissolution profiles of sulfamethizole tablets in 0.1 N HCl (b) and 0.01 M phosphate buffer pH 7.2 (c). Sulfamethizole standard concentrations: 50, 70 and 100 μg/ml. The volume of dissolution medium was 1 litre.

expressed as percentage of the dissolved drug were less than ±3.5% for all drugs and all time points through the period of study. This difference can be considered reasonable since it includes also the content variation uniformity and the run to run variability. As an example, Table 1 shows the results obtained for sulfamethizole by the two methods.

The precision of the analytical procedures was tested by measuring sample solutions (obtained by complete dissolving of the drug in the studied tablets) as well as standard solutions. In all cases the relative standard deviations ranged from 0.2 to 0.8% (n = 10). The accuracy was also evaluated by performing recovery studies on sample solutions. The mean recovery ranged from 99.2 to 100.5%. The long-term stability of the system was studied for 1 h by measuring the concentrations of sample solutions of the 3 drugs. Because of the self-correction of the baseline by the microcomputer, the drifting of the absorbance readings was in all cases less than 2%.

Although the analytical manifolds for salicylamide and sulfamethizole were based upon the routine methods of analysis, the analysis utilized for the dissolution study of propantheline bromide tablets requires mentioning.

According to Beermann et al. (1972), propantheline bromide hydrolyzes in solution above pH 5. Thus Cumtow et al. (1977) utilized a laborious method of

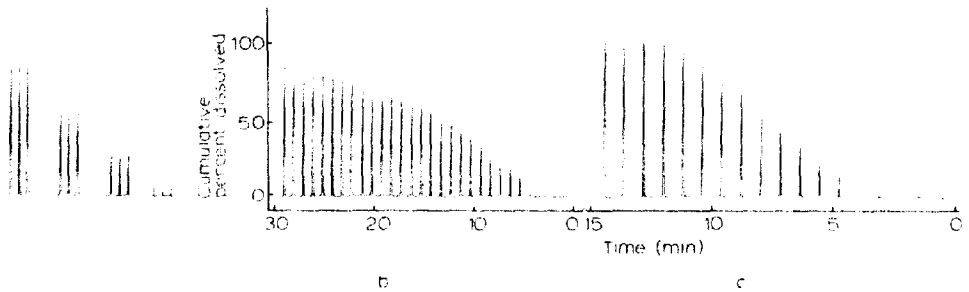

Fig. 4. Data for calibration curve (a) and dissolution profiles of salicylamide tablets in 0.1 N HCl (b) and 0.01 M phosphate buffer pH 7.2 (c). Salicylamide standard concentrations: 50, 100, 200 and 300 μg/ml. The volume of dissolution medium was 400 ml.

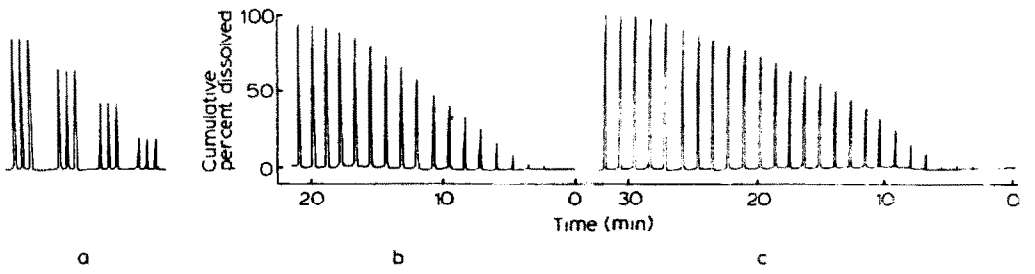

Fig. 5. Data for calibration curve (a) and dissolution profiles of propantheline bromide tablets (Pro-Banthine with Dartalan) in 0.1 N HCl (b) and 0.01 M phosphate buffer pH 7.2 (c). Propantheline bromide standard concentrations: 14, 28, 42 and 56 μg/ml. The volume of dissolution medium was 250 ml.

analysis to study the dissolution rate of propantheline bromide at pH 6.5–7.5. It is apparent, therefore, that the analytical manifold developed for the FIA of propantheline bromide offers tremendous simplicity for its determination. It is also worthwhile to mention that the tablets of propantheline bromide containing thiopropazate could not be studied either at pH 1.0 by direct spectral analysis at 243 nm as it is recommended for plain tablets (Chapman et al., 1980). Therefore the complexity of propantheline bromide analysis as pointed out by Charles and Ravenscroft (1983) could be coped with, at least for dissolution studies, using the method proposed in its manual or automated version.

In conclusion, the proposed interface of the automated FIA system with dissolution apparatuses furnishes new features which in summary can be delineated: (1) unattended operation—once a dissolution run is initiated, samples are selected and analyzed automatically without the need for the analyst to be present at a specific time; (2) automated data analysis—the computer calculates results at each time as soon as the reacted sample passes the photometric detector. A complete dissolution profile is available at the end of the experiment; (3) versatility in analytical methodology—any kind of analytical scheme which can be adapted to FIA can be coupled with any type of solid dosage form agitation technique to provide automa-

TABLE 1

COMPARISON STUDIES FOR THE DISSOLUTION OF SULFAMETHIZOLE WITH THE MANUAL (M) AND AUTOMATED (A) PROCEDURES

Time (min)	5	10	20	30	40	50	60	70
% Dissolved-M [a]	1.0	2.2	5.1	7.6	9.5	11.7	13.6	14.1
drug-A [b]	2.9	4.2	7.4	9.8	11.7	12.9	14.1	14.9
Difference [c]	1.9	2.0	2.3	2.2	2.2	1.2	0.5	0.8
Mean difference				1.64				

[a] Mean of 3 runs.
[b] Mean of two runs.
[c] Automated-manual value.

tion of the dissolution studies. The great number of developed automated FIA methods using a variety of detectors increases the capabilities of the system; and (4) no disturbance of agitation and volume of dissolution medium—the small sample volume required and the simplicity of the sampling process make correction for cumulative dilution not necessary and consequently the disturbance of homogeneity and agitation of medium is avoided.

Although the automated FIA system was coupled with a single unit dissolution apparatus, it can be interfaced with any device having more than one dissolution vessel provided that a mechanical changer of the sample probe able to be controlled by the microcomputer is available.

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