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Automated System of Dissolution Testing with Data Input through RS-232C Interface of a Personal Computer

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An automated system for *in vitro* drug dissolution testing was developed around the PC-9801 or PC-8801 series of personal computers. The hardware consists of the standard dissolution vessel, a ultraviolet (UV) detector, an intelligent A/D converter and a personal computer which is connected with an XY-plotter. The fluid in the dissolution vessel is recirculated between the vessel and the UV detector by a pump through fine polyethylene tubing. The signals from the A/D converter, which is connected with the UV detector, are taken into the personal computer through the RS-232C interface. A program (Automated Dissolution Measurement Program, ADMP) was written in BASIC to control the A/D converter, to store the dissolution data on floppy disk, to plot the time course of dissolution on CRT and XY-plotter, and to calculate the dissolution parameters, such as the 50% dissolution time (t_{50}) and the mean dissolution time (MDT).

Keywords——dissolution test; mean dissolution time; MDT; personal computer; bioavailability; A/D converter; RS-232C

Introduction

The importance of *in vitro* dissolution measurement of pharmaceutical formulations has been recognized for evaluation of the *in vivo* drug bioavailability, in addition to the disintegration test and the purity test of the drug ingredient in the formulations.[1] Manual measurements in the dissolution test are time-consuming and it is necessary to select an appropriate analytical method and to find the optimum experimental conditions. Therefore, the development of an automated dissolution system is very desirable. Schroeter and Wagner[2] were the first to construct a simple automated dissolution apparatus which directly plots the time course curve of dissolution on a recorder through a ultraviolet (UV) detector. There have been several attempts to develop automated dissolution systems[3-5] since their paper. There is a report on control of the dissolution measurements of several oral drugs[6] with the aid of a minicomputer. However, minicomputers are far more expensive than personal computers, and the price of special interfaces between minicomputers and analytical apparatus is high.

The purpose of the present report is to introduce an automated analysis system for *in vitro* dissolution measurement using a personal computer. Most personal computers now have an RS-232C interface for communication through telephone lines. By connecting a personal computer with the *in vitro* dissolution measuring system through the RS-232C interface, an inexpensive automated analysis system for dissolution measurement was constructed.

Experimental

Hardware——A schematic diagram of the automated analysis system for the *in vitro* dissolution measurement is given in Fig. 1. The fluid (total volume, 900 ml) in the standard dissolution vessel (USP XX), which was maintained at 37.0 (±0.5) °C, was passed though a micropore filter (0.45 μm, Dismic-25, Toyo Roshi, Japan) by a pump (model A-

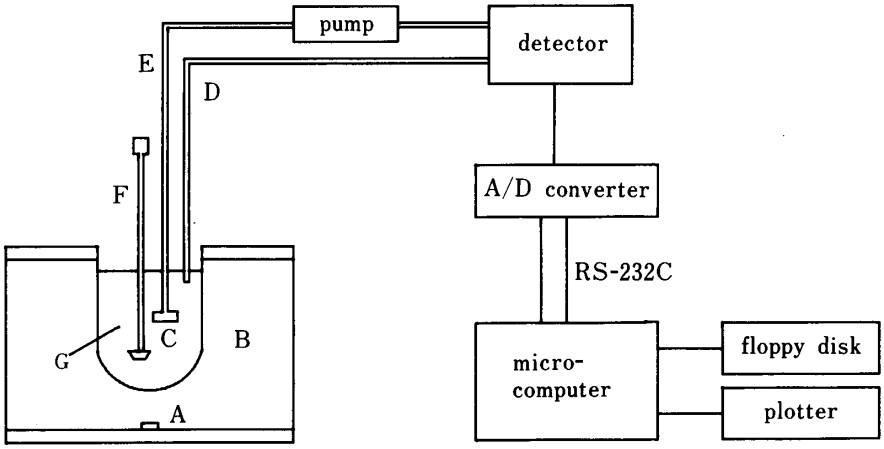

Fig. 1. Schematic Diagram of the ADMS

A, magnetic stirrer; B, water bath; C, micropore filter; D, E, polyethylene tube; F, paddle; G, distilled water.

60-S, Elilex Labs., Ca, U.S.A.) at a flow rate of 2.0 ml/min. The fluid was led through fine polyethylene tubing (0.8 mm i.d.) into the quartz cell of a UV spectrophotometer (model SPD-2A, Shimadzu, Japan) which was set at 254 nm. The fluid emerging from the UV cell was returned to the dissolution vessel. The rotation speed of the paddle in the vessel was maintained at 150 rpm. The analog signal from the UV spectrophotometer was converted to a digital signal (12 bits, 4096 resolution) by an intelligent A/D converter (model ADS-1000, Pantos Nippon Denshi Kagaku, Japan). The minimum measuring interval of the converter is 0.1 s. The digital signal was passed to a personal computer (model PC-9801F, NEC, Japan). The personal computer was connected with an XY-plotter (MIPLOT, Watanabe, Japan).

Software——The program, Automated Dissolution Measurement Program (ADMP) written in BASIC occupies about 9 k bytes for its program list. ADMP runs on both PC-9801 and PC-8801 series personal computers without any modification. The functions of ADMP may be summarized as follows:

1) Control of the A/D converter (ADS1000), including initialization and setting of the sampling time interval.
2) Uptake of digital dissolution time course data from the ADS1000.
3) Judgment of the start point of the dissolution of a drug ingredient from the drug formulation, and the end point of dissolution measurement.
4) Preservation of the data on a floppy diskette.
5) Evaluation of the *in vitro* mean dissolution time (MDT)[7] by trapezoidal integration and the time at any value of percent of drug dissolved which the user specifies.
6) Graphic plots of the time course of both dissolved amount and undissolved amount of drug on an XY-plotter.

All routines for the control of peripherals such as the A/D converter and XY-plotter and for arithmetic calculations are completely separated from the main routine in order to be replaceable simply by other subroutines when a peripheral device is replaced. MDT is a model-independent parameter for *in vitro* dissolution rate, which has been shown to have a simple linear relationship with the *in vivo* mean residence time (MRT).[8-12]

Reagents and Materials——The following drug products were used.

Product A: Ampicillin capsule (500 mg trihydrate form, Pentrex Capsules, Banyu Pharm. Co., Japan), 500 mg potency, 717 mg total weight.

Product B: Ampicillin powder in product A, 500 mg potency, 617 mg.

Product C: Ampicillin granules (500 mg Solcillin granules, Takeda Chemical Industries, Japan), 50 mg potency, 500 mg.

Product D: Cephalexin granules (250 mg Keflex, Shionogi Pharmaceutical Co., Japan), 106.5 mg potency, 250 mg. Distilled water was used as the solvent in the dissolution vessel.

Results and Discussion

Table I presents the times (min) at 20%, 40%, 50%, 75% dissolution ($t_{0.2}$, $t_{0.4}$, $t_{0.5}$, $t_{0.75}$) and the MDT values of the drug formulation. The selected sampling interval was 2 or 5 s. An *in vitro* dissolution of a drug ingredient from a formulation usually begins after a lag time. ADMP evaluates the lag time by using the following condition for the start of the dissolution.

TABLE I

Product	20%	40%	50%	75%	MDT[b]
A[a]	2.95	3.82	4.46 (3.83)	6.79 (7.69)	5.53
B	0.99	1.60	1.95 (1.78)	3.54 (3.57)	2.57
C	0.49	0.75	0.90 (1.13)	1.54 (2.27)	1.63
D	0.39	0.55	0.63 (0.48)	0.86 (0.96)	0.69

Times (min) at 20%, 40%, 50% and 75% dissolution and mean dissolution time, MDT (min), are shown. Times in parentheses are the predicted values according to the first order dissolution model with no lag time. *a*) The capsule shell was isolated from ampicillin and the UV absorption at 254 nm was tested. The contribution of the capsule shell to the UV absorption was about 5% of that of the ampicillin content. The effect of the capsule shell was ignored in the calculation of dissolution parameters. *b*) The time at a % dissolved and MDT are independent of the absolute concentration of drug. The UV absorbance is assumed to be proportional to the concentration of drug in the calculation of these parameters.

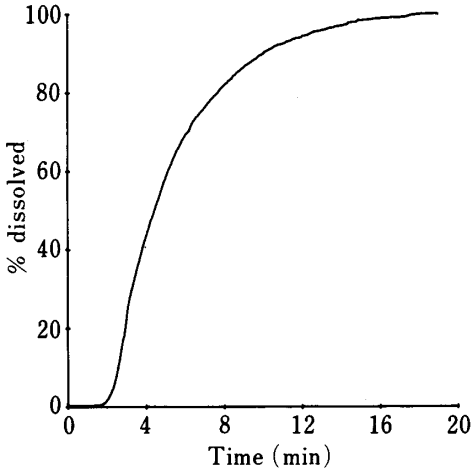

Fig. 2. The Dissolution Time Course Curve of Product A

This curve is accompanied with a large lag time.

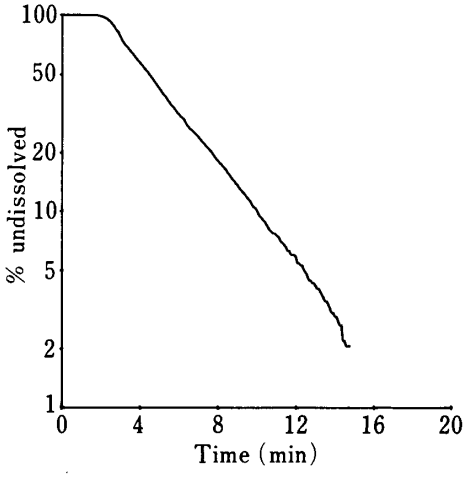

Fig. 3. The Semi-logarithmic Curve of the Calculated Undissolved Amount of Product A *versus* Time

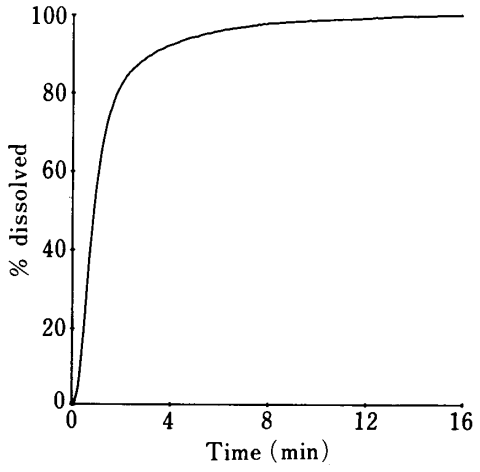

Fig. 4. The Dissolution Time Course Curve of Product C

This curve is made by 240 sampling points.

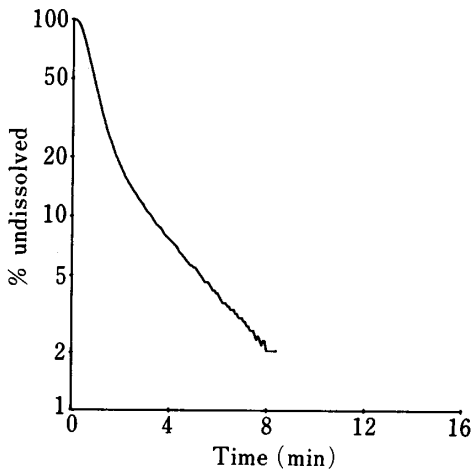

Fig. 5. The Semi-logarithmic Curve of the Calculated Undissolved Amount of Product C *versus* Time

$$\left(\sum_{i=1}^{n} dA_i/dt\right)\Big/n > E_s \quad (1)$$

where dA_i/dt is the dissolution rate, n is the number of points included in a time interval t to average the dissolution rate over the time interval and E_s is the criterion for the start of dissolution. When the condition in Eq. 1 is met, ADMP regards the time as the start point of the dissolution. The reason for averaging the dissolution rate is to eliminate "noise" in the data. The dissolution test was automatically terminated by ADMP when the following condition was filled.

$$\left(\sum_{i=1}^{n} dA_i/dt\right)\Big/n < E_e \quad (2)$$

E_e is a criterion for the end point of the dissolution.

In this experiment, the conditions ($t=60$ s, $E_s=0.01$ and $E_e=0.0001$) were selected. The void time from the dissolution vessel to the UV cell was estimated from the dissolution time course after a solution of ampicillin or cephalexin was dropped into the dissolution vessel. The estimated void time was 80 s at the flow rate used. ADMP subtracts the void time from the dissolution time course of the drug preparation. For a first-order dissolution model with no lag time, MDT is correlated to $t_{0.5}$ and $t_{0.75}$ by the following equations.

$$t_{0.5}=0.693 \text{ MDT} \quad (3)$$

$$t_{0.75}=1.39 \text{ MDT} \quad (4)$$

The figures in the parentheses in Table I are the $t_{0.5}$ and $t_{0.75}$ values predicted from MDT by using Eqs. 3 and 4. The predicted values of granules are close to the observed $t_{0.5}$ and $t_{0.75}$ values, except for products A and C. Figure 2 shows the dissolution time course curve of product A on the XY-plotter by ADMP. Figure 3 shows the semi-logarithmic curve of calculated undissolved amount *versus* time by ADMP. Figures 3 and 4 illustrate the dissolution curve of product A, which shows a large lag time. Figure 5 shows the dissolution time course curve of product C on the XY-plotter by ADMP. Figure 6 shows the semi-logarithmic curve of the calculated undissolved amount *versus* time. The time course clearly consists of two phases. Figure 6 demonstrates the reason why the predicted values using Eqs. 3 and 4 deviate considerably from the observed values. The result suggests that the dissolution process of product C is complex. This shows that the dissolution system developed by us is effective for analyzing the mechanism of the *in vitro* dissolution process of a drug formulation.

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