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RESEARCH PAPER

Analysis of Mean Disintegration Time and Mean Dissolution Time by Moment Analysis Using Microcalorimetric Curves

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ABSTRACT

The mean disintegration time (MDGT; mean time required for disintegration of tablets) and mean dissolution time (MDST; mean time required for drug dissolution) of water-soluble drugs from solid dosage forms were determined by moment analysis using microcalorimetric curves. Microcalorimetric curves for heat of dilution and for heat of dissolution of the drug were prepared, and the zeroth and first moments of the calorimetric curves were then calculated. The difference between the first moments of the curves for powder dissolution and tablet dissolution was taken to be the MDGT. The difference between the first moment of the curve for heat of dilution and that of the curve for heat of dissolution was taken to be the MDST. Nicotinic acid and D-mannitol were used as model drugs. The dissolution rate was determined by the conventional beaker method and also by the deconvolution method. The dissolution process could be traced well by moment analysis, as well as by the other methods employed. Moment analysis has some advantages: (a) *both the MDGT and the MDST can be determined simultaneously;* (b) *it is applicable to many drugs that are soluble with heat evolution without the need for quantitative analysis of the drug.*

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INTRODUCTION

There are many reports concerning drug dissolution from solid dosage forms because the release of drugs from dosage forms strongly influences their efficacy (1,2). The rate of disintegration of tablets also influences the bioavailability of drugs. Simultaneous analysis of drug dissolution and disintegration of solid dosage forms is helpful in pharmaceutical development. However, there have been few reports on simultaneous analysis of both drug dissolution and disintegration characteristics of solid dosage forms in one experimental design (3). Previously, we reported a method for determining the dissolution rate of a drug using microcalorimetric curves to apply deconvolution theory (4). Since almost all solid drugs are soluble with heat evolution, analysis using microcalorimetric curves is considered to be applicable to many drugs.

In the present report, we have applied moment analysis to microcalorimetric curves and the mean disintegration time (MDGT; mean time required for tablet disintegration) and the mean dissolution time (MDST; mean time required for drug dissolution) were determined statistically. Moment analysis has been applied widely to analysis of pharmacokinetics using plasma concentration-time curves and is very useful for model-independent pharmacokinetic analysis (5–9).

A drug dissolution study by moment analysis using microcalorimetric curves has the advantage of permitting dissolution analysis without quantitative analysis of the drugs dissolved in the solvent. Results obtained by moment analysis were compared with those obtained by the conventional beaker method or the deconvolution method reported previously (4). In this manner, the usefulness of moment analysis for the study of drug dissolution was investigated.

MATERIALS AND METHODS

Materials

Nicotinic acid (Daiichi Pure Chemicals, Japan), D-mannitol (Nakarai Chemicals, Japan), and sodium chloride (Koso Chemicals, Japan) were used without further purification. Powders were sieved between 100 and 200 mesh (75–150 μm) and stored in a desiccator with P_2O_5 until use in the experiments.

Tableting

Tablets were prepared using an Instron material tester (model 1137, Instron Co., Canton, MA) at a constant plunger speed (10 mm/min). Sample powders, 0.20 g of nicotinic acid, or 0.35 g of D-mannitol were compressed under various pressures with a flat-faced punch in a die with an internal diameter of 7.0 mm.

Microcalorimetry

The calorimetric curves were prepared using a twin heat conduction microcalorimeter, model CM-204D1 (Applied Electric Laboratory, Tokyo, Japan). All measurements were carried out at 298.15 K in a room maintained at 298 K ± 1 K. Purified water (20 ml) was used as the solvent, and the test solution was stirred at 60 rpm. Other conditions were the same as those reported previously (4).

Integral enthalpy values were determined by comparing the area under the calorimetric curve with that for the heat evolved by a calibration heater. The heat of dilution of the nicotinic acid and D-mannitol solutions could not be determined under these conditions of measurement. Thus, the first moment of the heat of dilution was determined from the microcalorimetric curve obtained for the heat of dilution of a sodium chloride solution, which was taken to be representative of that of the nicotinic acid and D-mannitol solutions. This is deemed to be reasonable because the curve of the heat of dilution corresponds to the profile of conduction of heat from the calorimetric cell to the constant-temperature wall of the microcalorimeter, and the heat conduction profile seems to be independent of the sample drug.

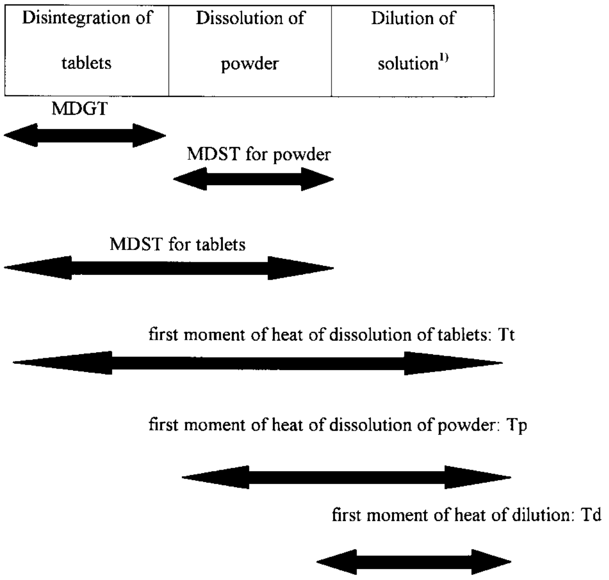
Dissolution Test

The dissolution profiles of nicotinic acid and D-mannitol were calculated by the deconvolution method reported previously (4). Dissolution of nicotinic acid was also determined by the beaker method. The conditions employed were the same as those reported previously (4), and the concentration of nicotinic acid dissolved in the solvent was monitored by means of an ultraviolet (UV) absorption spectrophotometer (UV-1300, Shimadzu, Japan).

RESULTS AND DISCUSSION

Moment Analysis Using Microcalorimetric Curves

Yamaoka et al. reported the application of moment analysis to describe the pharmacokinetics of drugs in the body (5,6). In those reports, the first moment of the area under the plasma concentration curve can be defined sta-



Scheme 1. Relationship between the first moment as determined from microcalorimetric curves and the process of dissolution of drugs [MDGT = mean disintegration time; MDST = mean dissolution time; in the scheme, 1) indicates inclusion of the process of conduction of heat from the calorimetric cell to the constant-temperature wall].

tistically as the mean residence time (MRT) of the drug in the body (Eq. 1).

$$\mathrm{MRT} = \int_0^\infty t\cdot Cpdt \Big/ \int_0^\infty Cpdt \qquad (1)$$

where t is the time, and Cp is the plasma concentration.

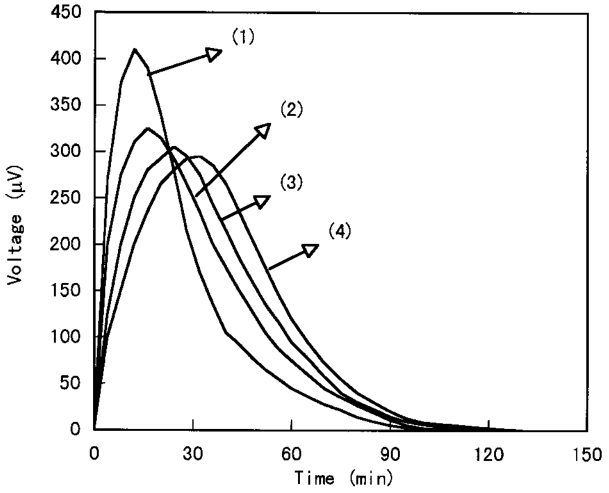


Figure 1. Microcalorimetric curves obtained for the heat of dissolution of nicotinic acid powder and tablets: (1) powder; (2) tablets (compression pressure 50 kg/cm^2); (3) tablets (compression pressure 100 kg/cm^2); (4) tablets (compression pressure 200 kg/cm^2).

Moment analysis can be applied to microcalorimetric curves in the same manner as in the case of its application to pharmacokinetics. We assumed that drug dissolution from solid dosage forms consists of three processes: disintegration, dissolution, and dilution. The relationships between the mean time required for each process are illustrated in Scheme 1 using the first moments of each process. By moment analysis, the MDGT and the MDST can be defined and calculated statistically from the calorimetric curves in Eqs. 2 and 3 (6,7).

$$\mathrm{MDGT} = Tt - Tp \qquad (2)$$

$$\begin{aligned} \mathrm{MDST} &= Tp - Td \text{ (for powder)} \quad \text{or} \\ \mathrm{MDST} &= Tt - Td \text{ (for tablets)} \end{aligned} \qquad (3)$$

Table 1

Zeroth and First Moments, Mean Disintegration Time (MDGT), and Mean Dissolution Time (MDST), of Nicotinic Acid Powder and Tablets as Determined from Microcalorimetric Curves

Sample	Zeroth Moment (cal/mol)	First Moment (min)	MDGT (min)	MDST (min)
Solution[a]	—	22.8 ± 1.3	—	—
Powder	1333.0 ± 32.5	62.5 ± 0.6	—	39.7
Tablets (50 kg/cm^2)	1425.3 ± 30.6	178.9 ± 0.8	116.4	156.1
Tablets (100 kg/cm^2)	1416.2 ± 25.3	183.0 ± 0.8	120.5	160.2
Tablets (200 kg/cm^2)	1456.2 ± 40.2	188.0 ± 1.0	125.5	165.2

Values are mean ± standard deviation for three experiments.

[a] Determined based on the calorimetric curve obtained for sodium chloride.

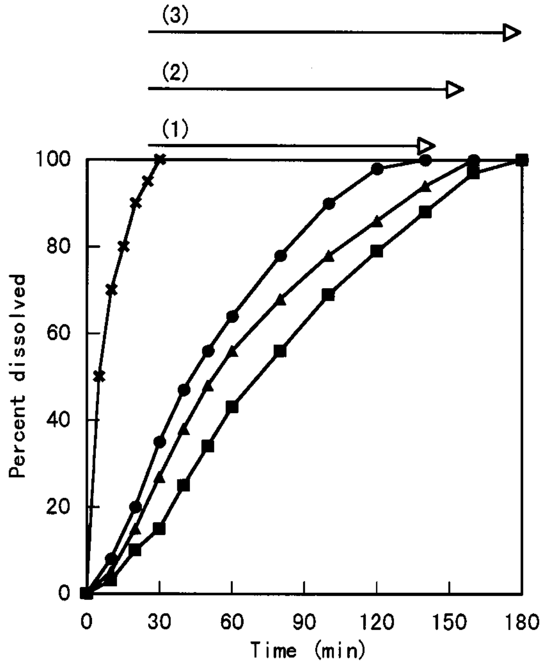


Figure 2. Dissolution behavior of nicotinic acid powder and tablets determined by the deconvolution method: ×, powder; ●, tablets (compression pressure 50 kg/cm^2); ▲, tablets (compression pressure 100 kg/cm^2); ■, tablets (compression pressure 200 kg/cm^2). (1) MDGT for tablets (compression pressure 50 kg/cm^2); (2) MDGT for tablets (compression pressure 100 kg/cm^2); (3) tablets (compression pressure 200 kg/cm^2).

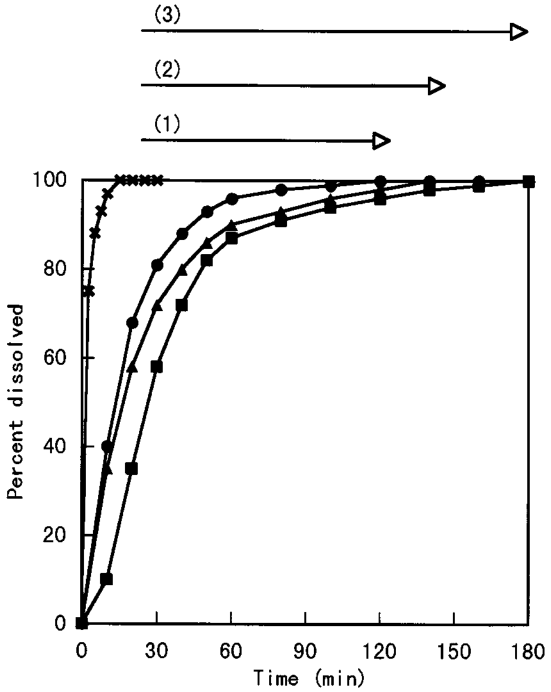


Figure 3. Dissolution behavior of nicotinic acid powder and tablets as determined by the beaker method: ×, powder; ●, tablets (compression pressure 50 kg/cm^2); ▲, tablets (compression pressure 100 kg/cm^2); ■, tablets (compression pressure 200 kg/cm^2). (1) MDGT for tablets (compression pressure 50 kg/cm^2); (2) MDGT for tablets (compression pressure 100 kg/cm^2); (3) tablets (compression pressure 200 kg/cm^2).

where *Tt*, *Tp*, and *Ts* are the first moments of the microcalorimetric curves of the heat of dissolution of tablets, the heat of dissolution of powder, and the heat of dilution, respectively.

Moment Analysis for the Dissolution of Nicotinic Acid

Figure 1 shows the microcalorimetric curves obtained for nicotinic acid powders and tablets prepared under three different pressure conditions. The microcalorimetric curves obtained for the tablets broadened with higher compression pressure, indicating that the tablets compressed at higher compression pressure showed slower dissolution rates. Table 1 shows the zeroth and first moments for the calorimetric curves obtained for dissolution of nicotinic acid samples. There were no significant changes in the zeroth moment (heat of dissolution) of nicotinic acid tablets with compression. From the first moment of the curves, MDGT and MDST were calculated, as summarized in Table 1. MDGT and MDST of the tablets increased with compression pressure.

Figures 2 and 3 show the dissolution profiles of nicotinic acid powder and tablets as determined by the deconvolution method and the beaker method, respectively.

Table 2

Comparison of the Disintegration Time of Nicotinic Acid Tablets as Determined by Moment Analysis, the Deconvolution Method, and the Beaker Method

	Moment Analysis	Deconvolution Method	Beaker Method
Tablets (50 kg/cm^2)	116.4	110	105
Tablets (100 kg/cm^2)	120.5	130	125
Tablets (200 kg/cm^2)	125.5	150	165

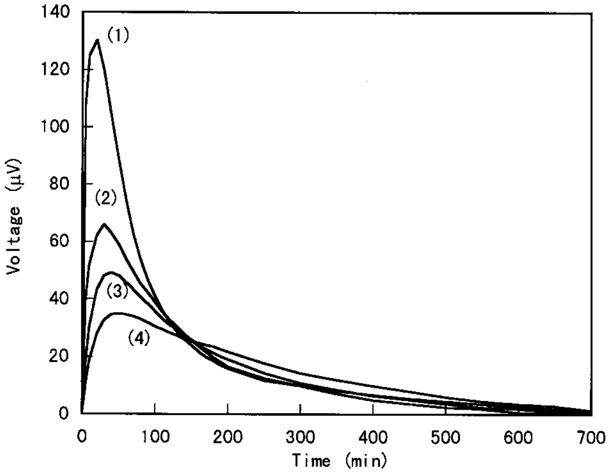


Figure 4. Microcalorimetric curves obtained for the heat of dissolution of mannitol powder and tablets: (1) powder; (2) tablets (compression pressure 1500 kg/cm^2); (3) tablets (compression pressure 2500 kg/cm^2); (4) tablets (compression pressure 3500 kg/cm^2).

Differences in time required for 100% dissolution of the powder and tablets are shown as the disintegration time in Figs. 2 and 3. Table 2 summarizes the MDGT as determined by moment analysis, the deconvolution method, and the beaker method. In all cases, the MDGT was found to increase with the compression pressure applied in preparation of the tablets.

The end point of drug dissolution, as determined by the deconvolution method (4), may include a large error because the integration errors during analysis increase

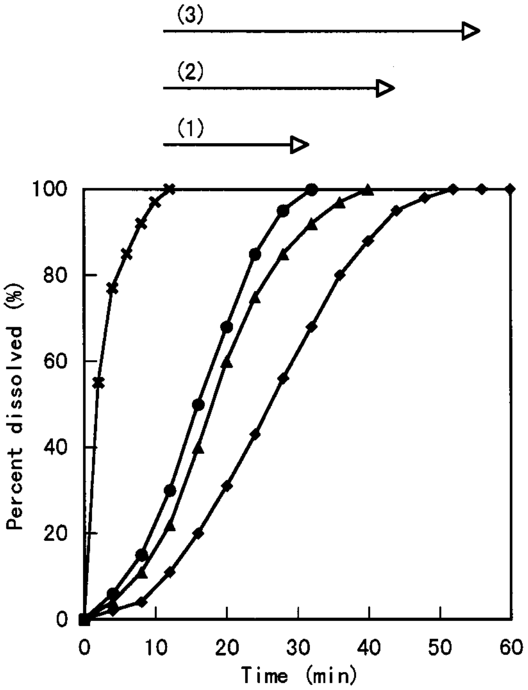


Figure 5. Dissolution behavior of mannitol powder and tablets as determined by the deconvolution method: ×, powder; ●, tablets (compression pressure 1500 kg/cm^2); ▲, tablets (compression pressure 2500 kg/cm^2); ■, tablets (compression pressure 3500 kg/cm^2). (1) MDGT for tablets (compression pressure 1500 kg/cm^2); (2) MDGT for tablets (compression pressure 2500 kg/cm^2); (3) tablets (compression pressure 3500 kg/cm^2).

Table 3

Zeroth and First Moments, Mean Disintegration Time (MDGT), and Mean Dissolution Time (MDST), of Mannitol Powder and Tablets as Determined from Microcalorimetric Curves

Sample	Zeroth Moment (cal/mol)	First Moment (min)	MDGT (min)	MDST (min)
Solution[a]	—	22.8 ± 1.3	—	—
Powder	1453.6 ± 30.2	37.3 ± 2.1	—	4.5
Tablets (1500 kg/cm^2)	1450.6 ± 17.3	37.3 ± 1.4	10.0	14.5
Tablets (2500 kg/cm^2)	1441.7 ± 15.5	40.9 ± 1.1	13.6	18.1
Tablets (3500 kg/cm^2)	1431.8 ± 10.5	52.6 ± 1.2	25.3	29.8

Values are mean ± standard deviation for three experiments.

[a] Determined on the calorimetric curve obtained for sodium chloride.

Table 4

Comparison of Disintegration Time as Determined by Moment Analysis and by the Deconvolution Method

	Moment Analysis	Deconvolution Method
Tablets (1500 kg/cm^2)	14.5	20
Tablets (2500 kg/cm^2)	18.1	28
Tablets (3500 kg/cm^2)	29.8	40

cumulatively with time. Also, precise determination of the end point of drug dissolution is difficult without interpolation by the beaker method. Interpolation seems to produce some errors. Thus, for determination of MDGT, moment analysis seems to be superior to the other methods.

Moment analysis has some advantages: (*a*) it is applicable to many drugs that are soluble with heat evolution; (*b*) not only the MDST, but also the MDGT, can be determined simultaneously from the microcalorimetric curves without the need for quantitative assay of the drug concentration by UV spectroscopy and/or high-performance liquid chromatography.

Moment Analysis for Dissolution of D-Mannitol

Figure 4 shows the microcalorimetric curves obtained for powder and tablets of D-mannitol. There were no significant changes in zeroth moment (heat of dissolution) of D-mannitol tablets with compression. From the first moment of the curves, the MDGT and MDST were calculated, as summarized in Table 3. The MDGT and MDST of the tablets increased with compression pressure. Dissolution of D-mannitol could be analyzed by moment analysis.

Figure 5 shows the results obtained for the dissolution rate as determined by the deconvolution method, and Table 4 summarizes the results obtained for the dissolution time of D-mannitol as determined by moment analysis and by the deconvolution method. Both the MDGT and the MDST of D-mannitol can be determined simultaneously by moment analysis. As mentioned before, the end point of dissolution is difficult to determine by the deconvolution method. Moment analysis is preferred for determination of the mean dissolution time of drugs.

CONCLUSION

In the present report, we describe a new method for determining MDGT and MDST using microcalorimetric curves. The dissolution behavior of nicotinic acid and D-mannitol powders and tablets could be analyzed by moment analysis. Moment analysis using microcalorimetric curves has some advantages: (*a*) both the mean disintegration time and the mean dissolution time can be determined simultaneously; (*b*) it is applicable to many drugs that are soluble with heat evolution without the need for quantitative analysis of the drug.

REFERENCES

1. M. Sugimoto, T. Okagaki, S. Narisawa, Y. Koida, and K. Nakajima, Improvement of dissolution characteristics and bioavailability of poorly water-soluble drugs by novel cogrinding method using water-soluble polymer, Int. J. Pharm., 160, 11–19 (1998).
2. K. C. Cundy, I. L. Sue, G. C. Visor, J. Marshburn, C. Nakamura, W. A Lee, and J. P. Shaw, Oral formulations of adefovir dipivoxil: in vitro dissolution and in vivo bioavailability in dogs, J. Pharm. Sci., 86, 1334–1338 (1997).
3. S. Esezobo, The effect of some excipients on the physical properties of a paracetamol tablet formulation, J. Pharm. Pharmacol., 37, 193–195 (1985).
4. E. Fukuoka, M. Makita, S. Yamamura, and Y. Yoshihashi, Use of microcalorimetry in the field of pharmaceutical sciences. I. Measurement of drug dissolution from solid dosage forms, Chem. Pharm. Bull., 42, 2139–2142 (1994).
5. K. Yamaoka, T. Nakagawa, and T. Uno, Statistical moments in pharmacokinetics, J. Pharmacokinet. Biopharm., 6, 547–548 (1978).
6. Y. Tanigawara, K. Yamaoka, T. Nakagawa, and T. Uno, Moment analysis for the separation of mean in vivo disintegration, dissolution, absorption, and disposition time of ampicillin products, J. Pharm. Sci., 71, 1129–1133 (1982).
7. S. Riegelman and P. Collier, The application of statistical moment theory to the evaluation of in vivo dissolution time and absorption time, J. Pharmacokinet. Biopharm., 8, 509–534 (1980).
8. K. Tahara, K. Yamamoto, and T. Nishihata, Application of model-independent and model analysis for the investigation of effect of drug solubility on its release rate from hydroxypropyl methylcellulose sustained release tablets, Int. J. Pharm., 133, 17–27 (1996).
9. B. Abrahamsson, D. Johansson, A. Torstensson, and K. Wingstrand, Evaluation of solubilizers in the drug release testing of hydrophilic matrix extended-release tablets of felodipine, Pharm. Res., 11, 1093–1097 (1994).