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New Method for the Evaluation of *in Vitro* Dissolution Time and Disintegration Time

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A new model-independent method is proposed for evaluating the *in vitro* dissolution time and disintegration time of solid dosage forms. The mean *in vitro* dissolution time (*in vitro* MDT) is defined as the first moment of the dissolution rate-time curve, that is, $MDT = \int_0^\infty t(dm/dt)dt \Big/ \int_0^\infty (dm/dt)dt$, where dm/dt is the dissolution rate of a drug at time t. The mean *in vitro* disintegration time (*in vitro* MDIT) is defined by subtraction of MDT for drug powder from that for its tablet or capsule. The MDT is correlated with the parameters of several dissolution models.

Keywords——moments; mean *in vitro* dissolution time; mean *in vitro* disintegration time; model-independent; convolution

The characterization of the *in vitro* dissolution-time curve is essential to assess the properties of a drug formulation, to compare the standard and various test preparations, and to predict the bioavailability and *in vivo* behavior. Several equations, which are based on modeling of the dissolution process or empirical relationships, have been used to analyze dissolution curves. The cube-root model, zero-order kinetic model, and first-order kinetic model have often been discussed.[1,2] Wagner introduced the log-normal distribution curve[3] and Langenbucher proposed the use of the Weibull function[4] for the approximation of dissolution curves. Such model-dependent evaluation, however, has a fundamental disadvantage; it is not always easy to select a dissolution model. The choice of model is sometimes arbitrary. Several solid dosage forms can give different shapes of dissolution curves which are best fitted by different equations. This makes it difficult to compare the dissolution properties of these dosage forms using the same parameters. In such a case, a model-independent method would be advantageous to characterize the dissolution-time curve.

Statistical moments, which are model-independent characteristics, can be defined for all statistical distribution curves. Cutler[5] and Yamaoka *et al.*[6] applied the moments to analyze *in vivo* time course curves such as plasma concentration-time curve and urinary excretion rate-time curve. Riegelman and Collier proposed the mean *in vivo* dissolution time (*in vivo* MDT) for bioavailability evaluation.[7]

The dissolution phenomenon includes a stochastic feature; a drug molecule in a tablet or a capsule transfers with a certain probability from the solid state to the dissolved state. We observe the total behavior of numerous drug molecules, each of which has its own transit probability. Thus the dissolution-time curve represents a statistical cumulative distribution. Therefore, moment analysis can also be applied for the characterization of the *in vitro* dissolution-time curve as well as the *in vivo* time course curves. The mean *in vitro* dissolution time (*in vitro* MDT) is defined as follows.

$$MDT = \int_0^\infty t(dm/dt)\,dt \Big/ \int_0^\infty (dm/dt)\,dt \qquad \text{Eq. 1}$$

or

$$MDT = \int_0^{m_\infty} t\,dm/m_\infty \qquad \text{Eq. 2}$$

where m is the amount, concentration, or fraction of drug dissolved in solution at time t, dm/dt is the dissolution rate, and m_∞ is the total amount dissolved or final concentration at infinite time.

The *in vitro* MDT is calculated in the same way as the mean *in vivo* residence time (MRT) of the urinary excretion rate-time curve by using trapezoidal integration.[6] Table I presents the relationships between MDT and parameters involved in several dissolution models. Using Table I, the dissolution data from different sources where different models are adopted can be systematically compared in terms of MDT.

TABLE I. Relationships between MDT and Several Dissolution Models

Models	Equations	MDT
First-order kinetics[2]	$m=m_\infty[1-\exp\{-k(t-t_0)\}]$	$MDT=1/k+t_0$
Zero-order kinetics[2]	$m=k_0(t-t_0)\quad t_0\leq t\leq m_\infty/k_0+t_0$	$MDT=m_\infty/2k_0+t_0$
Cube-root model[1]	$m=m_\infty-[m_\infty^{1/3}-K(t-t_0)]^3$	$MDT=m_\infty^{1/3}/4K+t_0$
Weibull function[4]	$m=m_\infty[1-\exp\{-(t-t_0)^b/a\}]$	$MDT=1/b\cdot a^{1/b}\Gamma(1/b)+t_0$

Key ; m, mass of drug dissolved in solution at time t; m_∞, total mass dissolved at infinite time; t_0, lag time; k, first-order dissolution rate constant; k_0, zero-order dissolution rate constant; K, cube-root constant; a, scale parameter; b, shape parameter; $\Gamma(x)$, gamma function.

Cf; $\int_0^\infty t^y \exp(-t^x/a)dt=1/(y+1)\cdot a^{(y+1)/x}\cdot\Gamma((x+y+1)/x)$

Langenbucher[4] defined the dissolution time, T_d by a term, $a^{(1/b)}$, where a is a scale parameter and b is a shape parameter of the Weibull function (see Table I). T_d represents the time interval necessary to dissolve 63.2% of the material. T_d coincides with MDT if the dissolution rate-time curve can be approximated by a mono-exponential equation.

The dissolution of a drug from a solid dosage form involves a disintegration step prior to release from the dispersed drug. Nelson and Wang[8,9] determined the time course of tablet disintegration by a deconvolution using the dissolution curves of a tablet and primary drug particles. The convolution expression for the dissolution rate-time curves becomes

$$u(t)=\int_0^t r(\theta)v(t-\theta)d\theta \qquad \text{Eq. 3}$$

where $u(t)$ and $v(t)$ represent the dissolution rate at time t of a tablet and that of drug powder, respectively. $r(t)$ is the disintegration rate of a tablet. The first moments corresponding to Eq. 3 are simply given as follows.[6]

$$MDT_{tablet}=MDIT_{tablet}+MDT_{powder} \qquad \text{Eq. 4}$$

where MDIT is the first moment of the disintegration rate-time curve, which we call the mean *in vitro* disintegration time. MDT_{tablet} and MDT_{powder} are calculated by linear trapezoidal integration of the dissolution rate-time courses of the tablet and the powder, respectively.[6] $MDIT_{tablet}$ is estimated by subtracting MDT_{powder} from MDT_{tablet}. In the case of acetaminophen,[9] Nelson and Wang have already fitted the Weibull function and an exponential equation to the dissolution-time data of the tablet and the powder, respectively, and they give the estimated parameters of those equations. Thus, MDT of an acetaminophen tablet and the primary drug particles are evaluated as 2.96 min and 0.55 min, respectively, using the parameters given by Nelson *et al.* and the relationships in Table I. The MDIT of this tablet is estimated as 2.41 min, which demonstrates that the disintegration is the rate-determining step in the dissolution process of the acetaminophen tablet.

Correlation of *in vivo* bioavailability and *in vitro* dissolution is practically important. The *in vivo* MDT and *in vivo* MDIT have been used as a basis to understand *in vivo* dissolution and disintegration phenomena,[7,10] and it may be useful to compare *in vivo* MDT and MDIT

with *in vitro* MDT and MDIT. Therefore, moment analysis could be valuable in studies of quantitative *in vivo–in vitro* correlations relating to drug release.

References and Notes

1) A.W. Hixon and J.H. Crowell, *Ind. Eng. Chem.*, **23**, 923 (1931).
2) M. Gibaldi and S. Feldman, *J. Pharm. Sci.*, **56**, 1238 (1967).
3) J.G. Wagner, *J. Pharm. Sci.*, **58**, 1253 (1969).
4) F. Langenbucher, *J. Pharm. Pharmacol.*, **24**, 979 (1972).
5) D.J. Cutler, *J. Pharm. Pharmacol.*, **30**, 476 (1978).
6) K. Yamaoka, T. Nakagawa, and T. Uno, *J. Pharmacokin. Biopharm.*, **6**, 547 (1978).
7) S. Riegelman and P. Collier, *J. Pharmacokin. Biopharm.*, **8**, 509 (1980).
8) K.G. Nelson and L.Y. Wang, *J. Pharm. Sci.*, **66**, 1758 (1977).
9) K.G. Nelson and L.Y. Wang, *J. Pharm. Sci.*, **67**, 86 (1978).
10) Y. Tanigawara, K. Yamaoka, T. Nakagawa, and T. Uno, presented at the first Japanese-American Conference on Pharmacokinetics and Biopharmaceutics, Tokyo, July 1981; *J. Pharm. Sci.*, in press.