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A model for linearizing drug dissolution data

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Several theoretical and empirical models are available for linearization drug dissolution profiles (Wagner, 1971; Benet, 1974; Carstensen, 1974). One of the main purposes of linearization is to express dissolution data of a drug by means of a single parameter, e.g. a rate constant. The parameter enables one to compare release rates of different dosage forms of a drug which is of importance from the viewpoint of bioavailability.

In this report, a model for linearizing drug dissolution curves together with an account of its applicability and suitability to some experimental data is presented.

The dependence of drug dissolution rate, $-\mathrm{d}M/\mathrm{d}t$, on the amount of undissolved drug, M, in the dissolution medium at any time, t, can be expressed as:

$$-\mathrm{d}M/\mathrm{d}t = kM^q \tag{1}$$

where k is a dissolution rate constant and q is a constant related to the mechanism or order of the dissolution process. If the values of 0, 2/3, and 1 are substituted for q, Eqn 1 can be integrated to the classic zero-order, cube root law, and first-order dissolution equations, respectively.

Experimental evidence has shown that none of the classical models could describe some dissolution data adequately, because the models gave unacceptably long negative lag times in dissolution which have no physical significance (Laakso et al., 1984) indicating that the above-mentioned orders were not suitable. Drug dissolution from tablets is a complex process involving steps such as wetting, water penetration, hydration and swelling of the binding and disintegrating agents, aggregation and deaggregation of granules and particles, diffusion of drug, and physicochemical interaction of drug with the excipients, all of which complicate the overall release process. Therefore, if one does not impose restrictions on the order, q, with the exception of unity a general model can be derived from Eqn 1.

The dimensions of k in Eqn 1 are [1/time (mass)$^{q-1}$]. In order to obtain a rate constant with identical dimensions for varying dissolution order, q, of a drug from its different dosage forms, Eqn 1 is written in the form:

$$-\mathrm{d}M/\mathrm{d}t = \left(kM_0^{q-1}/M_0^{q-1}\right)M^q \tag{2}$$

Eqn 2 can be expressed as:

$$-\mathrm{d}M/\mathrm{d}t = \left(K/M_0^{q-1}\right)M^q \tag{3}$$

in which $K = kM_0^{q-1}$ and has the dimension of (1/time), and M_0 is the original amount of drug in the dosage form. Assuming that the dissolution begins at time zero, the integration of Eqn 3

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between $t = 0$ and $t = t$ and subsequent rearrangements result in Eqns 4 and 5:

$$[1/(1-q)]\left[1-(M/M_0)^{1-q}\right] = Kt \text{ when } q < 1 \quad (4)$$

$$[1/(q-1)]\left[(M_0/M)^{q-1}-1\right] = Kt \text{ when } q > 1 \quad (5)$$

Plotting the left-hand sides of Eqns 4 and 5 vs time lines with slopes that equal the dissolution rate constants, Ks. Before the application of Eqns 4 and 5 the value of q should be determined. A rough estimate of q can be made from the slope of the linear form of Eqn 3:

$$\log(-\mathrm{d}M/\mathrm{d}t) = \log\left(K/M_0^{q-1}\right) + q \log M \quad (6)$$

$-\mathrm{d}M/\mathrm{d}t$ is an instantaneous rate and, in practice, one can only determine an average rate, $-\Delta M/\Delta t$, therefore, the q value obtained is not an exact value. M is the amount of undissolved drug corresponding to the midpoint of $-\Delta M/\Delta t$ determination. When an approximate value of q is known one can find its required value. This can be achieved by varying q around its approximate value, inserting into the appropriate expression (Eqn 4 or 5), and performing linear regression analysis. The q value which yields a line passing through the origin (in practice, the line with the smallest positive ordinate intercept) will be the required value.

Eqn 6 was employed in the analysis of data on indomethacin reported by Laakso et al. (1984). The average rates at 5, 20, 60, 90, and 240 min were used and equations for formulations I–IV of the drug were as follows:

Formulation I:

$$\log(-\Delta M/\Delta t) = -3.0228 + 1.4745 \quad \log \mathrm{M}$$

$$r = 0.9953$$

Formulation II:

$$\log(-\Delta M/\Delta t) = -2.2349 + 1.1439 \log M$$

$$r = 0.9991$$

Formulation III:

$$\log(-\Delta M/\Delta t) = -3.1106 + 1.7616 \log M$$

$$r = 0.9942$$

Formulation IV:

$$\log(-\Delta M/\Delta t) = -2.0048 + 1.2295 \log M$$

$$r = 0.9968$$

The dissolution rate constants, K_s, calculated from the ordinate intercepts of these lines were 0.008437, 0.01129, 0.02586 and 0.02909 min^{-1}, respectively.

The corresponding expressions (Eqn 5) for these formulations when applied to all data points reported in Table 3 of that paper were as follows:

Formulation I:

$$(1/0.544)\left[(M_0/M)^{0.544}-1\right] = 0.00016 + 0.008444\mathrm{t} \quad r = 0.9995$$

Formulation II:

$$(1/0.098)\left[(M_0/M)^{0.098}-1\right] = 0.00051 + 0.01111\mathrm{t} \quad r = 0.9990$$

Formulation III:

$$(1/0.786)\left[(M_0/M)^{0.786}-1\right] = 0.00014 + 0.02580\mathrm{t} \quad r = 0.9993$$

Formulation IV:

$$(1/0.349)\left[(M_0/M)^{0.349}-1\right] = 0.00057 + 0.02877\mathrm{t} \quad r = 0.9916$$

The rate constants obtained from Eqn 5 were in excellent agreement with those of Eqn 6. The proposed model could describe each dissolution curve by a single parameter i.e., the rate constant. There was a perfect rank order correlation between these rate constants and the amount of surfactant in the formulations, i.e., 0, 3, 6 and 9 mg. The greater the amount of surfactant the higher was the rate constant. These findings were

also supported by the data on the effect of the surfactant on the solubility of the drug (Table 1 of Laakso et al., 1984). The biphasic model of these authors described each dissolution curve by two rate constants which were not correlated perfectly with the amount of surfactant in the formulations. According to Table 6 of their paper, the rate constant of the initial phase for formulation II which had a higher surfactant content was less than that of formulation I. Also, the rate constant for the terminal phase of formulation III (with higher surfactant concentration) was less than that of formulation II.

References

Benet, L., Theories of dissolution – Multi-particulate systems. In Leeson, L.J. and Carstensen, J.T. (Eds), *Dissolution Technology*, Academy of Pharmaceutical Sciences Publ., Washington, DC, 1974, pp. 29–57.

Carstensen, J.T., Theories of dissolution – Single particulate systems. In Leeson, L.J. and Carstensen, J.T. (Eds), *Dissolution Technology*, Academy of Pharmaceutical Sciences, Publ., Washington, DC, 1974, pp. 1–28.

Laakso, R., Kristoffersson, E. and Marvola, M., Bi-exponential first order release kinetics of indomethacin from tablets containing polysorbate 80. *Int. J. Pharm.*, 19 (1984) 35–42.

Wagner, J.G., *Biopharmaceutics and Relevant Pharmacokinetics*, Drug Intelligence Publ., Hamilton, IL, 1971, pp. 104–109, 115–120.