Use of General Partial Fraction Theorem for Obtaining Inverse Laplace Transforms in Pharmacokinetic Analysis

Keyphrases □ Pharmacokinetic theory—inverse Laplace transforms, use of general partial fractions □ Laplace transforms, inverse—use of general partial fraction theorem

Sir:

Many mathematical methods have been employed to obtain solutions to pharmacokinetic models. Among these are the classical methods of solving differential equations and using Laplace transforms, eigenvectors, and eigenvalues. During the past few years, the use of Laplace transforms has proved to be the simplest method when dealing with linear models. Although many models have been described using the Laplace derivation, the very simple general methods (1) for solving these derivations have been overlooked by most workers. This communication discusses the general partial fraction theorem, shown in Eq. 1, and illustrates how it is used to obtain inverse transforms in pharmacokinetic analysis.

If the quotient of two polynomials, $P_{(s)}/Q_{(s)}$, is such that $Q_{(s)}$ has a higher degree and contains the factor $(s - \lambda_i)$, which is not repeated, then:

$$L^{-1}\left\{\frac{P_{(s)}}{Q_{(s)}}\right\} = \sum_{i=1}^{m} \frac{P(\lambda_i)}{Q'(\lambda_i)} e^{\lambda_i t} = \sum_{i=1}^{n} \frac{P(\lambda_i)}{Q_i(\lambda_i)} e^{\lambda_i t} \quad \text{(Eq. 1)}$$

where:

λ_i's = roots of the polynomial $Q_{(s)}$
$Q'(\lambda_i)$ = derivative of $Q_{(s)}$ with the roots substituted for s
$Q_i(\lambda_i)$ = value of the denominator when λ_i is substituted for all the s terms except for the term originally containing λ_i, this term being omitted
s = standard notation used in Laplace operations

The first sum in Eq. 1 is often called Heaviside's expansion (1).

Application of this technique to compartmental analysis is shown with respect to the two-compartment model for a drug and its metabolite in Scheme I. If k_{24} is assumed to be zero, the Laplace transforms for the amount of drug in Compartment 1 (x_1) following an intravenous bolus injection of the drug is described by Eq. 2:

$$x_1 = \frac{(s + k_{21})D}{(s + \alpha)(s + \beta)} = \frac{P_{(s)}}{Q_{(s)}} \quad \text{(Eq. 2)}$$

where:

D = dose injected
$\alpha\beta = k_{21}k_{13}$
$\alpha + \beta = k_{12} + k_{21} + k_{13}$

Equation 2 may easily be derived using determinants (2), and the solution may be found in any inverse Laplace transform table. Thus, the general methods can be appropriately demonstrated for this familiar equation.

Heaviside's Expansion (First Sum in Eq. 1)—The roots of the polynominal, $Q_{(s)}$, obtained from Eq. 2 are $\lambda_1 = -\alpha$ and $\lambda_2 = -\beta$. Now the first derivative of $Q_{(s)}$ is given by: $Q_{(s)}' = 2s + \alpha + \beta$. By solving for the amount of drug in Compartment 1 (X_1) using Heaviside's expansion:

$$X_1 = \sum_{i=1}^{2} \frac{P(\lambda_i)}{Q'(\lambda_i)} e^{\lambda_i t} = \left\{\frac{D(k_{21} - \alpha)}{-2\alpha + \alpha + \beta}\right\} e^{-\alpha t} + \left\{\frac{D(k_{21} - \beta)}{-2\beta + \alpha + \beta}\right\} e^{-\beta t} \quad \text{(Eq. 3)}$$

which reduces to the familiar answer:

$$X_1 = \frac{(k_{21} - \alpha)D}{(\beta - \alpha)} e^{-\alpha t} + \frac{(k_{21} - \beta)D}{(\alpha - \beta)} e^{-\beta t} \quad \text{(Eq. 4)}$$

General Partial Fraction Theorem (Second Sum in Eq. 1)—The roots of the polynomial, $Q_{(s)}$, are $\lambda_1 = -\alpha$ and $\lambda_2 = -\beta$. The term $Q_i(\lambda_i)$ may be defined as follows. When:

$$i = 1 \qquad Q_i(\lambda_i) = (\lambda_1 + \beta) = (\beta - \alpha) \quad \text{(Eq. 5a)}$$

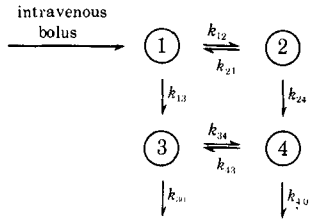
$$i = 2 \qquad Q_i(\lambda_i) = (\lambda_2 + \alpha) = (\alpha - \beta) \quad \text{(Eq. 5b)}$$

Therefore, applying the general partial fraction equation, we obtain:

$$X_1 = \sum_{i=1}^{n} \frac{P(\lambda_i)}{Q_i(\lambda_i)} e^{\lambda_i t} = \frac{D(k_{21} - \alpha)}{(\beta - \alpha)} e^{-\alpha t} + \frac{D(k_{21} - \beta)}{(\alpha - \beta)} e^{-\beta} \quad \text{(Eq. 6)}$$

The answer obtained in Eq. 6 using the general partial fraction equation is exactly that obtained in Eq. 4 using Heaviside's expansion, but the step requiring the taking of the derivative of the denominator is eliminated. The advantage of the one-step general partial fraction method might be more readily seen in the model presented by Rowland *et al.* (3) to describe the distribution of aspirin and salicylic acid following a bolus injection of aspirin as shown in Scheme I. The Laplace transform of the equation describing the amount of salicylic acid in the plasma, x_3, following a bolus injection of aspirin is given by:

$$x_3 = \frac{k_{13}(s + E_2)(s + E_4)D + A_{13}D}{(s + \alpha)(s + \beta)(s + \gamma)(s + \delta)} \quad \text{(Eq. 7)}$$



Scheme I—Compartmental model describing the distribution and elimination of a drug injected into Compartment 1. Elimination proceeds from both the central and peripheral compartments, with a metabolite, 3, undergoing analogous disposition.

where:

$E_2 = k_{21} + k_{24}$; $E_4 = k_{43} + k_{40}$; $A_{13} = k_{12}k_{24}k_{40}$

α,β = fast and slow disposition constants describing an intravenous bolus injection of aspirin

γ,δ = fast and slow disposition constants describing an intravenous bolus injection of salicylic acid (3)

A general simplified method for deriving the Laplace transform given in Eq. 7 will be published (4). At present the equation can be derived using determinants, but this derivation is not necessary to demonstrate the method of obtaining inverse Laplace transforms and it is not included here. Since there are no repeated $(s - \lambda_i)$ factors in the denominator of Eq. 7 and since the degree of s is higher in the denominator than in the numerator, the general partial fraction theorem may be used to carry out a one-step solution for the amount of drug in Compartment 3:

$$X_3 = \frac{k_{13}(E_2 - \alpha)(E_4 - \alpha)D + A_{13}D}{(\beta - \alpha)(\gamma - \alpha)(\delta - \alpha)} e^{-\alpha t} + \frac{k_{13}(E_2 - \beta)(E_4 - \beta)D + A_{13}D}{(\alpha - \beta)(\gamma - \beta)(\delta - \beta)} e^{-\beta t} + \frac{k_{13}(E_2 - \gamma)(E_4 - \gamma)D + A_{13}D}{(\alpha - \gamma)(\beta - \gamma)(\delta - \gamma)} e^{-\gamma t} + \frac{k_{13}(E_2 - \delta)(E_4 - \delta)D + A_{13}D}{(\alpha - \delta)(\beta - \delta)(\gamma - \delta)} e^{-\delta t} \quad \text{(Eq. 8)}$$

Let us review the procedure. When the factor $(s + \alpha)$ is omitted from the denominator (that is, when the root $\lambda_1 = -\alpha$ is used), all values of s in Eq. 7 are substituted by $-\alpha$ and this root appears in the exponential term $(e^{-\alpha t})$. Next, the factor $(s + \beta)$ is omitted when the root $\lambda_2 = -\beta$, *etc.* In practice, an easy way to carry out the taking of the anti-Laplace is to cover the factors in the denominator one by one with your finger while substituting the root of the covered factor for all the remaining s terms. If a single s term appears in the denominator, as when zero-order infusion equations are derived, the root for this factor is zero.

The method presented in this work is very easily used, even with complicated Laplace transform equations, so that the investigator may immediately write down the anti-Laplace without taking any derivatives and without breaking down the equation into parts that may reasonably be found in a table. A future publication (4) will contain a more extensive coverage of the method, including ways to solve anti-Laplace operations when the stated conditions of higher degree and nonrepeating factors in the denominator are not met.

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(4) L. Z. Benet, presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, San Francisco meeting, March 1971.

LESLIE Z. BENET
Department of Pharmacy
University of California
San Francisco, CA 94122

JOSEPH S. TURI
College of Pharmacy
University of Michigan
Ann Arbor, MI 48104

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Are There Spherical Micelles?

Keyphrases ☐ Micelles—nonspherical shape surfactants ☐ Surfactants—formation of nonspherical micelles

Sir:

While many shapes have been postulated for micelles in relatively concentrated aqueous surfactant solutions, it is commonly agreed that the small micelles formed at low concentrations (up to a low multiple of the CMC) are spherical (1–8). The generally accepted model for the spherical micelles is that the hydrocarbon chains of the surfactant molecules are randomly arranged in the interior of the micelle, forming a spherical core or oil droplet, and that the hydrophilic headgroups form a concentric external spherical shell surrounding the hydrocarbon core. The headgroups are hydrated and shield the hydrocarbon chains from contact with water. The core is in a liquid-like state of disorder, and the hydrocarbon chains interact with each other by van der Waals forces (1). Despite computations (4, 9) showing that spherical micelles can exist only within a limited range of aggregation numbers, interpretation of viscosity and diffusion measurements of micelles (10–12) are commonly based on a spherical shape.

The combination of simple geometric considerations with the experimentally determined micellar sizes indicates that it is unlikely that surfactants having a single normal alkyl chain as their hydrocarbon moiety form spherical micelles.

Geometric Considerations—The following parameters refer to the core of the micelle formed by the hydrocar-