as the labeled concentration and C_2 = 90% of this, then $-G/k_a$ is the shelf-life at temperature T_a (assuming no overage in the product).

An advantage of this method is that the activation energy and shelf-life can be estimated without assuming a particular reaction order. An average value for E can be estimated by appropriately grouping data into sets with each set having a different α value, then solving them simultaneously by weighted nonlinear regression to estimate an average E across sets and a $-G/k_a$ for each set.

An analogous technique has been used in thermogravimetric analysis (4–6), in which a number of nonisothermal experiments were performed at different linear heating rates. The logarithm of the reaction rate at a selected percentage decomposition *versus* $1/T$ was plotted using this technique. The reaction rate at a specific fraction of decomposition was estimated by linear interpolation. In the method suggested previously, t_α can be estimated similarly by linear interpolation, by alternative methods (*e.g.*, cubic splines, polynomial regression), or by assuming knowledge of the functional relationship [$f(C)$] as was done previoulsy (1).

(1) A. K. Amirjahed, *J. Pharm. Sci.*, **66**, 785 (1977).
(2) N. G. Lordi and M. W. Scott, *ibid.*, **54**, 531 (1965).
(3) S. Baker and S. Niazi, *ibid.*, **67**, 141 (1978).
(4) H. C. Anderson, *J. Polym. Sci., Part C*, **6**, 175 (1964).
(5) H. L. Friedman, *ibid.*, **6**, 183 (1964).
(6) J. Leyko, M. Maciezowski, and R. Szuniewicz, *J. Thermal Anal.*, **17**, 263 (1979).

Ian G. Tucker
Pharmacy Department
University of Queensland
St. Lucia 4067
Australia

Received October 15, 1981.
Accepted for publication January 13, 1982.

Simplified Method to Study Stability of Pharmaceutical Systems: A Response

Keyphrases □ Decomposition—determination of shelf-life using analytic methodologies, response □ Kinetics—decomposition, determination of shelf-life using analytic methodologies, response □ Stability—simplified method of study in pharmaceutical systems, response

To the Editor:

The preceding paper (1) discusses my earlier criticism, based on pragmatic reasons, of the paper (2) published by Amirjahed (3). It was suggested by Amirjahed (3) that if only 10% decomposition of a product is monitored, it is possible to ascertain the shelf-life, while using less than sophisticated analytic methodologies such as may be available in small institutional settings. My criticism that the initial concentration of the sample is important is still valid regardless of how the kinetic equation is manipulated such as reported by Tucker (1):

$$\ln(t_\alpha) = \ln(-G/k_a) + E\,(1/T - 1/T_a)/R \qquad \text{(Eq. 1)}$$

where t_α is the time to decompose from concentration C_1 to C_2, and $-G/k_a$ becomes the shelf-life at temperature T_a for a 10% concentration change. However, the assumptions involved here are self-defeating. It assumes that all preparations have similar initial concentrations and that there is no overage in the product (1). It should be reiterated that a ±5% variation in the content is routinely acceptable. This alone will discard the calculations that require identical starting concentrations. Furthermore, obtaining sufficient data points during 10% decomposition of the product (which may have several excipients) is a difficult, but not impossible, task and requires sophisticated analytic technology. Together, these arguments make such exercises as reported by Amirjahed (3) and Tucker (1) of merely academic interest and could be misleading if their use is suggested in those instances where operators may not be fully aware of these pitfalls. I would highly recommend that the authors (1, 3) use these equations with actual data collected in the laboratory and show their validity. It is only when such studies are reported that the validity of the interesting concept reported by Amirjahed (3) can be ascertained.

(1) I. G. Tucker, *J. Pharm. Sci.*, **71**, 599 (1982).
(2) S. Bakar and S. Niazi, *ibid.*, **67**, 141 (1978).
(3) A. K. Amirjahed, *ibid.*, **66**, 785 (1977).

Sarfaraz Niazi
Department of Pharmacy
College of Pharmacy
University of Illinois at
the Medical Center
Chicago, IL 60612

Received October 30, 1981.
Accepted for publication January 13, 1982.

Use of Unbound Drug Concentration in Blood to Discriminate Between Two Models of Hepatic Drug Elimination

Keyphrases □ Plasma protein binding—effect on systemic unbound blood drug concentration of orally administered drug □ Hepatic drug clearance—discrimination between two models, venous equilibrium model, sinusoidal perfusion model

To the Editor:

Two well-defined models have been proposed to describe the hepatic elimination of drugs and other compounds. These models differ in their basic hypotheses and in some of their quantitative predictions, *e.g.*, concerning the influence of blood flow, protein binding, and drug metabolizing activity on extraction ratio and hepatic clearance.

Model 1 (the equilibrium or well-stirred model) assumes that the liver is a single, well-stirred compartment, and that the concentration of unbound drug in hepatic venous blood is in equilibrium with unbound drug throughout the liver (1). Model 2 (the sinusoidal perfusion or parallel tube model) assumes that at any point along the hepatic sinusoid, the concentration of drug in the liver cell will equal

0022-3549/82/0500-0600$01.00/0

that in the sinusoid but that this concentration will fall as blood traverses the sinusoid (2).

Determination of which of the two models is the more appropriate to describe hepatic drug elimination is at present in dispute (3, 4). One of the important practical applications of these models is the calculation of intrinsic hepatic drug clearance, which measures the ability of the liver to remove drug irreversibly from liver water; for many compounds it can be regarded as an index of the activity of the drug metabolizing enzymes (5). The method of calculating intrinsic hepatic clearance differs between the two models, so that the same pharmacokinetic data may lead to two quite different answers. This is particularly true of high-clearance drugs (5, 6). Clearly, there is a need for an accurate and unambiguous method of measurement of hepatic drug metabolizing function for these high-clearance drugs, which is applicable to the intact animal rather than only to isolated liver enzyme preparations.

An extensive theoretical comparison of the two models showed that the greatest discrepancies between the predictions of the two models occur when the following parameters:

1. availability
2. steady-state drug concentration in hepatic venous blood
3. area under the blood drug concentration–time curve following a single oral dose
4. steady-state drug concentration in blood following constant oral drug administration for a highly extracted drug are examined under perturbations of either hepatic blood flow or of the degree of binding within the blood (7).

However, to date there are few experimental data available, and the evidence that is available does not single out one model as being more appropriate. For example, studies with lidocaine (3) from one laboratory using the isolated perfused rat liver preparation support the venous equilibrium model, whereas similar studies with galactose (8) from a second laboratory support the sinusoidal perfusion model. So far, experiments designed to discriminate between the two models of hepatic drug elimination have only involved examination of the effect of hepatic blood flow on the steady-state output concentration of highly cleared drugs in the perfused rat liver preparation. This is because hepatic blood flow is easily monitored and controlled in this preparation.

As a result of a series of computer simulations we have performed, relating intrinsic clearance to various pharmacokinetic indexes, another discriminant between Models 1 and 2 has emerged. The equations relating the area under the blood drug concentration–time curve following a single oral dose with the determinants of hepatic drug elimination (7) are for the venous equilibrium model (model 1):

$$AUC_{po} = \frac{D_{po}}{fu_b\, CLu_{int}} \qquad \text{(Eq. 1)}$$

and for the sinusoidal perfusion model (model 2):

$$AUC_{po} = \frac{D_{po}\,(e^{-fu_b\, CLu_{int}/Q_H})}{Q_H(1 - e^{-fu_b\, CLu_{int}/Q_H})} \qquad \text{(Eq. 2)}$$

where:

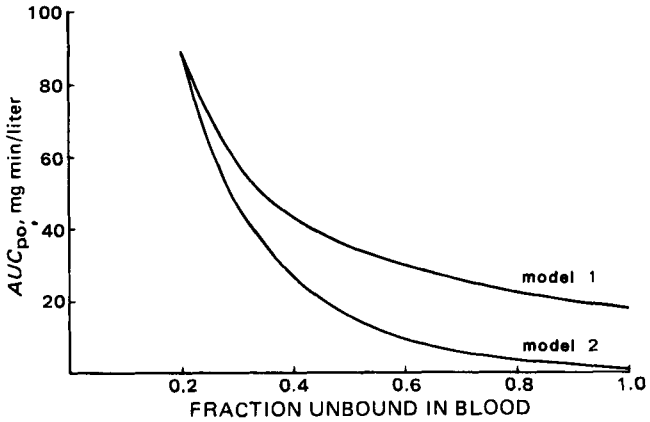

Figure 1—*Effect of fraction of unbound drug in blood on* AUC_{po} *for 200 mg of meperidine administered orally.*

D_{po} = dose administered by the oral route,
fu_b = fraction of unbound drug in blood,
CLu_{int} = intrinsic hepatic clearance of unbound drug, and
Q_H = hepatic blood flow.

From these equations, expressions can be derived which relate the area under the unbound blood drug concentration–time curve following a single oral dose ($AUCu_{po}$) with the determinants of hepatic drug elimination for model 1:

$$AUCu_{po} = fu_b\, AUC_{po} = \frac{D_{po}}{CLu_{int}} \qquad \text{(Eq. 3)}$$

and for model 2:

$$AUCu_{po} = fu_b\, AUC_{po} = \frac{fu_b\, D_{po}\,(e^{-fu_b\, CLu_{int}/Q_H})}{Q_H(1 - e^{-fu_b\, CLu_{int}/Q_H})} \qquad \text{(Eq. 4)}$$

Simulations of Eqs. 1–4 were performed for the drug meperidine and the following parameters were used:

Q_H = 1.5 liter/min
D_{po} = 200 mg
fu_b = 0.2
CLu_{int} = 11.25 liter/min (model 1)
CLu_{int} = 6.872 liter/min (model 2)

The systemic blood clearance of meperidine is ~0.9 liter/min (9), which corresponds to an hepatic extraction ratio of 0.6. Systemic blood clearance is a model-independent variable, whereas intrinsic clearance is model-dependent, *i.e.*, the value calculated depends on whether model 1 or 2 is invoked. Hence, two different values are given for intrinsic hepatic clearance of meperidine. Figure 1 shows the relationship between the fraction free in blood and AUC_{po}, according to Eqs. 1 and 2. The results are consistent with those described previously (7), in that a greater dependence of AUC_{po} on free fraction is predicted by model 2. Figure 2 shows the relationship between the fraction free in blood and area under the unbound blood drug concentration–time curve following a single oral dose, according to Eqs. 3 and 4. The $AUCu_{po}$ appears to be a much better discriminator between the two models than AUC_{po}, because $AUCu_{po}$ should be independent of free fraction in blood according to model 1 but not to model 2. These simulations present another and potentially more powerful method of discriminating between the two models using

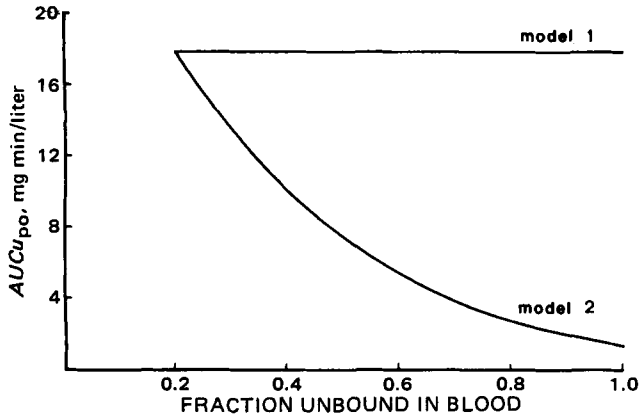

Figure 2—*Effect of fraction of unbound drug in blood on* AUC *of unbound drug concentration (*$AUCu_{po}$*) versus time for 200 mg of meperidine administered orally.*

the isolated perfused rat liver preparation. It is theoretically possible to vary the fraction of unbound drug in the perfusate by at least 10-fold for a highly bound drug, whereas the hepatic perfusion rate may only reasonably be varied by less than twofold (3). A preliminary investigation of the plasma protein binding of propranolol has been carried out using equilibrium dialysis. The results of this investigation show that it is possible to achieve a 10-fold variation of the fraction of unbound drug by varying the concentration of bovine serum albumin and α_1-acidglycoprotein in the perfusate[1].

The predictions of models 1 and 2 for the relationship between free fraction in blood and the steady-state unbound drug concentration in the reservoir of the isolated perfused rat liver preparation (Cu_{ss}) following constant-rate drug administration into the portal vein are analogous to those described for $AUCu_{po}$. The equations relating fraction of unbound drug in blood with Cu_{ss} can be derived from the equations presented by Pang and Rowland (7) and for model 1:

$$Cu_{ss} = \frac{R}{CLu_{int}} \qquad \text{(Eq. 5)}$$

and for model 2:

$$Cu_{ss} = \frac{fu_b\, Re^{(-fu_b\, CLu_{int}/Q_H)}}{Q_H[1 - e^{(-fu_b\, CLu_{int}/Q_H)}]} \qquad \text{(Eq. 6)}$$

where R is the infusion rate of drug into the portal vein.

Hence, the effect of changing free fraction of drug in perfusate on the steady-state unbound drug concentration in the reservoir following constant-rate drug administration into the portal vein in the isolated perfused rat liver preparation may also be used to discriminate between the two models.

(1) M. Rowland, L. Z. Benet, and G. G. Graham, *J. Pharmacokinet. Biopharm.*, **1**, 123 (1973).

(2) K. Winkler, S. Keiding, and N. Tygstrup, in "The Liver: Quantitative Aspects of Structure and Functions," G. Paumgartner and R. Presig, Eds. Karger, Basel, 1973, pp. 144–155.

(3) K. S. Pang, and M. Rowland, *J. Pharmacokinet. Biopharm.*, **5**, 655 (1977).

(4) L. Bass, *Gastroenterology*, **76**, 1504 (1979).

[1] D. B. Jones, D. J. Morgan, G. W. Mihaly, and R. A. Smallwood, Unpublished observations.

(5) A. S. Nies, D. G. Shand, and G. R. Wilkinson, *Clin. Pharmacokinet.*, **1**, 135 (1976).

(6) L. Bass and K. Winkler, *Clin. Exp. Pharmacol. Physiol.*, **7**, 339 (1980).

(7) K. S. Pang and M. Rowland, *J. Pharmacokinet. Biopharm.*, **5**, 625 (1977).

(8) S. Keiding and E. Chiarantini, *J. Pharmacol. Exp. Ther.*, **205**, 465 (1978).

(9) E. A. Neal, P. J. Meffin, P. B. Gregory, and T. F. Blaschke, *Gastroenterology*, **77**, 96 (1979).

Denis J. Morgan[x]
Kenneth Raymond
Victorian College of Pharmacy Ltd.
381 Royal Parade
Parkville
Victoria, Australia 3052

Received September 4, 1981.
Accepted for publication February 19, 1982.

Filter-Probe Extractor: A Tool for the Rapid Determination of Oil–Water Partition Coefficients

Keyphrases □ Filter-probe extractor—tool for rapid determination of oil–water partition coefficients □ Oil–water partition coefficients—rapid determination using filter-probe extractor □ Thermodynamics—filter-probe extractor use for rapid determination of oil–water partition coefficients

To the Editor:

The distribution of solutes between water and oil has been the subject of hundreds of studies since the end of the last century (1). The oil–water partition coefficient [or liquid–liquid distribution constant, as recommended (2) by IUPAC] is of use in separation science as it indicates the extent of extraction in a two-phase system. Also, since the partition coefficient is taken (3) as a measure of solute hydrophobicity, it is an often used parameter in, for example, preformulation and drug design (QSAR) studies. Partition coefficients have been determined by a large number of methods, including shake flask, counter-current distribution (4), and various automated methods including the AKUFVE (5) and SEGSPLIT (6) approaches.

Recently, we published a study (7) on the thermodynamics of solute oil–water partitioning, where use was made of a modification of a rapid solvent extraction method described by Cantwell and Mohammed (8) for photometric acid-base titrations in the presence of an immiscible solvent. Using various data manipulations, these workers have been able to demonstrate (9, 10) that their method provides ion-pair distribution coefficients and is of consequent use in drug analysis. Here we wish to communicate some of our experiences with a modified filter-probe for measuring oil–water partition coefficients of molecules of pharmaceutical interest, and to draw attention to the fact that the method has particular use for the examination of the effect of a large number of variables on the distribution process. It is emphasized that the apparatus here described is similar to, but not the same as, that developed by Cantwell and Mohammed.

0022-3549/82/0500-0602$01.00/0