precision obtained with the longer colorimetric method. The new method does not require extraction steps or the addition of reagents, both of which take considerable time.

The method described is similiar to the method of Jones *et al.* (6) in that it is based on the electrochemical reduction of the nitro functional group in nitrofurantoin. The rotating platinum electrode method has the advantage over a previously used electrochemical method of not requiring a differential pulse polarograph or differential polarograph; it requires only a simple direct current polarograph, because of the relatively high sensitivity possible with a rotating electrode.

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Simple Transformation Method for Predicting Plasma Drug Profiles from Dissolution Rates

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Abstract □ A transformation factor is described which related *in vitro* drug dissolution from a preparation to the corresponding *in vivo* plasma drug concentrations. This factor, derived from the dissolution profile and the corresponding *in vivo* plasma concentration of a single formulation, was used to predict plasma concentration profiles of similar formulations simply from dissolution data.

Keyphrases □ Plasma drug profiles—predicted from dissolution rates, transformation factor described □ Dissolution rates—transformation factor described for prediction of plasma drug profiles

Frequently, the *in vivo* dissolution rate of an oral dosage form controls the rate at which a drug appears in plasma, and similar formulations of the same drug can have different therapeutic equivalences. Since drug absorption studies in humans are expensive and time consuming, *in vitro* dissolution data are frequently correlated with the biological availability of a drug from different preparations. The times to achieve 50% drug dissolution (t_{50}) usually are correlated with either maximal plasma drug concentrations or the areas under the plasma concentration–time curves (1).

Although these latter methods are useful, they are not designed to predict the plasma time course of a drug following administration of different preparations. One method of predicting plasma drug concentrations involves a detailed pharmacokinetic study of drug distribution and elimination after an oral aqueous dose and the derivation of an explicit function to describe *in vitro* drug dissolution from various preparations (2).

Alternatively, a curve follower or variable diode function generator can be used to input *in vitro* dissolution data directly into a pharmacokinetic model programmed on an analog computer (3).

To avoid detailed pharmacokinetic studies in humans, a simple transformation method was investigated for predicting plasma drug concentrations from *in vitro* dissolution data.

THEORY

Two independent functions of time, $f_1(t)$ and $f_2(t)$, can be related to each other at some specific value of time by an arbitrary transformation factor, $m(t)$, so that at time t:

$$f_1(t)m(t) = f_2(t) \qquad \text{(Eq. 1)}$$

Relating the two functions (Eq. 1) in this way does not necessarily imply a specific relationship between them. Similarly, *in vitro* dissolution characteristics of an oral drug preparation can be related to the corresponding *in vivo* plasma drug concentrations.

Without defining the distribution and elimination processes in the body, the plasma concentration of a drug obtained with some drug input process into the body can be related to the drug input by an operator, $m(t)$, such that:

$$\text{drug input}(t) = m(t)\ [\text{plasma drug concentration}(t)] \qquad \text{(Eq. 2)}$$

In Eq. 2, m is a collection of numbers which, together with the drug input, uniquely determines the plasma drug concentration for all $t \geq 0$. When considering plasma drug concentrations obtained after oral administration of a dosage formulation, Eq. 2 becomes:

$$\text{amount of drug released } \textit{in vivo} \text{ from formulation}(t) = m_i(t)\ [\text{plasma drug concentration}(t)] \qquad \text{(Eq. 3)}$$

where m_i is a collection of numbers which, together with the amount of drug released from the preparation at time t, uniquely determines the plasma drug concentration at time t for all $t \geq 0$.

Similarly, *in vitro* drug dissolution from an oral formulation can be related to the corresponding *in vivo* drug dissolution by an operator, $m_j(t)$:

$$\text{amount of drug dissolved in } \textit{in vitro} \text{ dissolution test from dosage formulation}(t), \textit{i.e.}, \text{dis}_j(t) = m_j(t) \times \text{amount of drug released } \textit{in vivo} \text{ from formulation}(t) \qquad \text{(Eq. 4)}$$

Combining Eqs. 3 and 4 gives:

$$\text{dis}_j(t) = m_i(t)m_j(t)[\text{plasma drug concentration}(t)] \quad \text{(Eq. 5)}$$

and from Eq. 5:

amount of drug dissolved at time t in *in vitro* dissolution test = $H(t) \times$ plasma drug concentration at time t obtained with oral drug preparation (Eq. 6)

Plasma drug concentrations are a function of both the pharmacokinetics of the drug within the body and the amount of drug absorbed. Since the latter is also a function of the amount of drug released from the preparation, H (Eq. 6) can be regarded as a transformation factor which simultaneously compensates for the kinetics of the drug and relates *in vitro* drug dissolution to *in vivo* drug dissolution.

If linear drug pharmacokinetics are assumed with respect to the dose, then H (Eq. 6) is a specific operator, and for two different formulations of the same drug:

$$\text{dis}_1(t) = H(t)C_{p1}(t) \quad \text{(Eq. 7)}$$

and:

$$\text{dis}_2(t) = H(t)C_{p2}(t) \quad \text{(Eq. 8)}$$

where C_{p1} and C_{p2} are plasma drug concentrations obtained with two different oral preparations of the same drug, and dis_1 and dis_2 are the corresponding amounts of drug released *in vitro* from these preparations.

The transformation factor H (Eq. 7) can be evaluated at different values of t from one *in vitro* dissolution curve and the corresponding *in vivo* plasma drug concentrations (Eq. 7). Calculated values of H can then be used to predict plasma drug concentrations for another preparation of the same drug from a knowledge of its dissolution profile obtained under identical conditions as those used for the first preparation.

EXPERIMENTAL

To demonstrate the application of Eqs. 7 and 8, the serum concentrations of total alprenolol were calculated from the data of Johansson *et al.* (4), and the results were compared with experimental observations (Table I). Johansson *et al.* (4) recorded the total serum concentration of alprenolol and its metabolites obtained with three sustained-release preparations (A, B, and C) at 0.25, 0.5, 1.0, 1.5, 2.0, and 3.0 hr after drug administration and measured the *in vitro* dissolution at time 1.0, 2.0, 4.0, and 6.0 hr.

Estimates of the *in vitro* drug dissolution at times corresponding with serum sample times were obtained by linear interpolation between the quoted values. The *in vitro* data (4) also were curve fitted to a polynomial using a least-squares fit by orthogonal polynomials, and the numerical value of the polynomial function itself was used in the calculation.

From the *in vivo* and interpolated *in vitro* data for Preparation A (dose ≡ 100 mg of alprenolol hydrochloride), the transformation factor of H was calculated at different times (Table I). This transformation factor was then used in conjunction with the interpolated *in vitro* data for Preparation C (dose ≡ 100 mg of alprenolol hydrochloride) to predict the *in vivo* serum concentrations.

Further examples of the application of Eqs. 7 and 8 are given in Fig. 1; predicted serum digoxin concentrations for two brands of digoxin tablets and predicted serum alprenolol concentrations for two sustained-release preparations [B and C (4)] are presented. Predicted serum drug concentrations are also compared with experimentally determined concentrations in Fig. 1. *In vitro* dissolution data and serum drug concentrations used in the calculations on digoxin were obtained from Fraser *et al.* (5), Preparation 3 was used to calculate H, and the serum levels of digoxin for Preparations 6 and 8 are predicted.

DISCUSSION

As indicated in Table I, the predicted serum drug concentrations (Fig. 1) obtained by the application of transformation factors (Eqs. 7 and 8) are in excellent agreement with the *in vivo* measurements. The discrepancies between predicted and measured digoxin

Table I—Calculation of the Transformation Factor H at Various Times (Eq. 7) from the *In Vitro* Dissolution of Alprenolol and *In Vivo* Serum Alprenolol Concentrations of Preparation A and the Application of H to the Prediction (Eq. 8) of the Serum Concentrations of Alprenolol Obtained with Preparation C[a]

Hours	Drug Released *In Vitro* from Preparation A (*i.e.*, dis_1), %		Serum Alprenolol Concentration Obtained with Preparation A (*i.e.*, C_{p1}), μg/g	$H(t) = \frac{\text{dis}_1}{C_{p1}}$		Drug Released *In Vitro* from Preparation C (*i.e.*, dis_2), %		Calculated Serum Concentration of Alprenolol for Preparation C (*i.e.*, dis_2/H), μg/g		*In Vivo* Serum Concentration of Alprenolol for Preparation C, μg/g	Difference in Calculated and Experimental Alprenolol Concentrations, %	
	a	*b*		*a*	*b*	*a*	*b*	*a*	*b*		*a*	*b*
0.25	15	17.9	0.08	187.5	223.72	7.5	8.54	0.04	0.04	0.03	+25.0	+25.0
0.5	30	32.34	0.68	44.12	47.56	15	15.65	0.34	0.33	0.32	+6.25	+3.13
1.0	60	55.56	1.56	38.46	35.62	29.5	27.58	0.77	0.77	0.77	0.0	0.0
1.5	70	72.15	1.85	37.84	39.0	36	36.85	0.95	0.94	0.9	+5.5	+4.44
2	79	83.16	1.99	39.69	41.79	42	43.80	1.05	1.05	1.00	+5.0	+5.0
3	87	92.80	1.82	47.8	50.99	50	53.03	1.05	1.04	1.1	—4.5	—5.45
4	94.5	93.11	1.48	63.85	62.91	58.5	57.9	0.92	0.92	0.98	—6.0	—6.0

[a] Columns *a* and *b* list data obtained using a linear and a polynominal interpolation of the *in vitro* dissolution data, respectively.

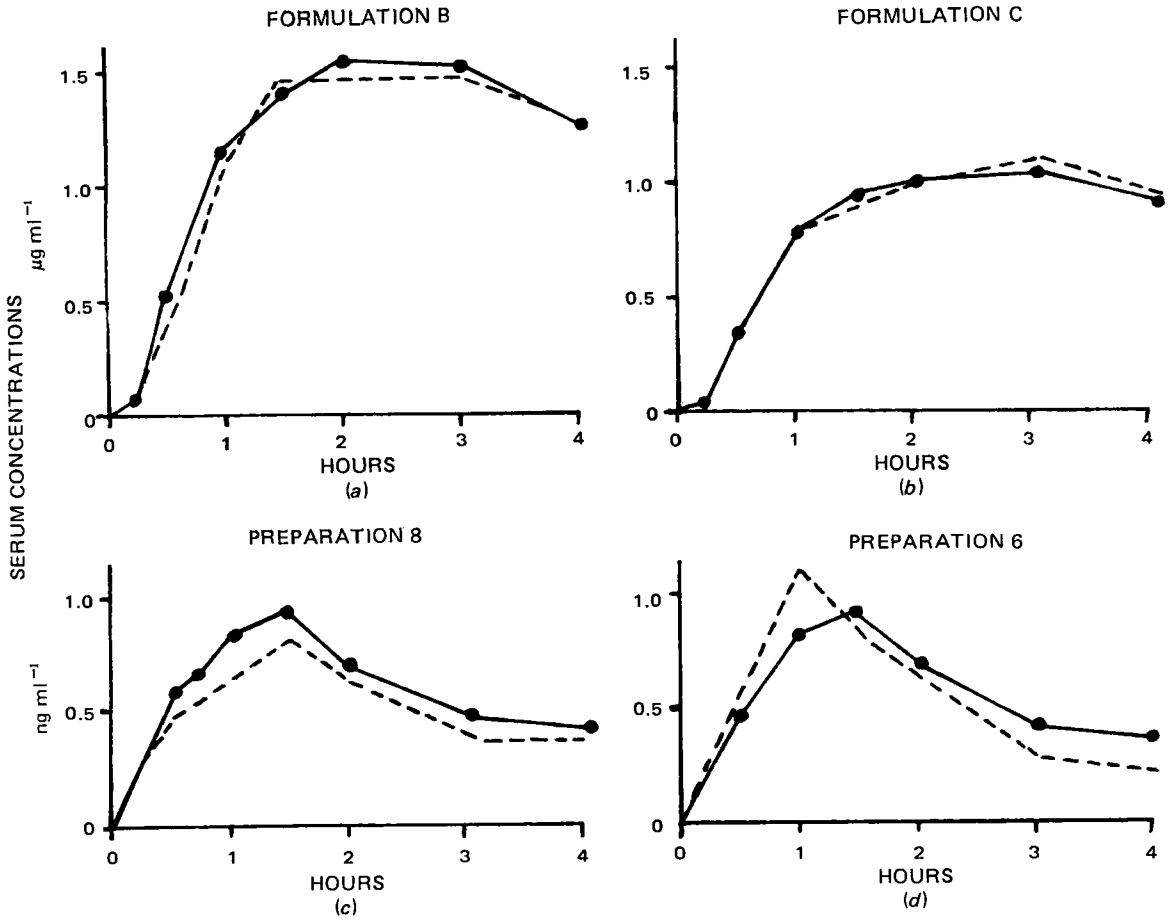

Figure 1—(a *and* b) *Predicted mean serum concentrations of total alprenolol after the administration of 100 mg of alprenolol hydrochloride in two different tablet formulations* (– ● –) *and the experimental* (- - -) *serum levels of alprenolol (experimental data from Ref. 4).* (c *and* d) *Predicted mean serum concentrations of digoxin after the administration of two brands of digoxin tablets* (– ● –) *and the experimental* (- - -) *serum levels of digoxin (experimental data from Ref. 5).*

concentrations can be largely ascribed to the errors[1] in the determination of digoxin by radioimmunoassay (5).

The transformation factors obtained by Eq. 7 and their subsequent applications (Eq. 8) are only valid during the time required to achieve complete or asymptotic *in vitro* dissolution. However, this period could be extended by decreasing the agitation rates in dissolution tests.

Since the transformation factor relates *in vivo* to *in vitro* dissolution, its application is valid only if the changes in *in vitro* dissolution mechanisms (*e.g.*, disintegration and disaggregation) between various formulations of the same drug are adequately mimicked *in vivo*. For example, transformation factors obtained from a tablet formulation are unlikely to apply to a capsule preparation since these two products could have different *in vivo* dissolution mechanisms. This restriction limits the general application of the method for predicting *in vivo* data from *in vitro* data.

However, provided the method is evaluated for a particular type of formulation, it could be applied as a control procedure for estimating the effects of *in vitro* dissolution changes on blood concentrations. This method of predicting blood concentrations (Eqs. 3 and 4) from *in vitro* dissolution data is independent of the processes governing drug release from a preparation, drug absorption, and the pharmacokinetics of drug distribution or elimination.

[1] The error is ±20–30% for serum digoxin <1 ng/ml; L. S. Culank, Clinical Chemistry Department, Queen Elizabeth Medical Centre, Birmingham B15 2TH, United Kingdom, personal communication, 1974.

In conclusion, the use of transformation factors can provide a rapid and simple method for predicting plasma drug concentrations from *in vitro* data.

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