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Application of Clearance and Volume of Distribution to the Plateau Principle of Drugs

SAMUEL A. CUCINELL* and WILLIAM PERL†

Abstract □ The concentration of drug in plasma after continuous administration (plateau concentration, C_∞) has been defined as the relationship of the dosage per unit time and the half-life of elimination ($t_{1/2}$) to the volume of distribution (V_d) of a drug. The C_∞ determinants, V_d and $t_{1/2}$, have been determined in single-dose and continuous-infusion experiments. The data derived have been used to predict C_∞ for a series of substances when administered by continuous intravenous infusion. Alterations in V_d and $t_{1/2}$ of a drug may occur under clinical situations. This is reflected in changes in the plateau concentration, despite a constant dosage per unit time. An experimental example of deoxycholic acid decreasing the volume of distribution of bromsulfophthalein is given.

Keyphrases □ Plateau principle—plasma drug concentration □ Deoxycholic acid effect—volume of distribution □ Volume of distribution—plasma concentration plateau □ Drug administration rate—plasma concentration plateau

Drugs are often administered by continuous or repeated administration over long enough periods so that a relatively constant, or plateau concentration, of drug in the plasma is achieved and maintained. This plateau concentration will, in large measure, determine the effectiveness or toxicity of a drug. Bishydroxycoumarin,[1] quinidine, the anesthetics, antibiotics, and digitalis depend on a constant drug level in plasma to maintain their desired clinical response. In many cases, the drug may be regarded as distributed in a so-called volume of distribution into which the drug is administered at a constant rate and out of which the drug is removed by first-order kinetics. This model leads to a relationship of the plateau concentration of the drug to its rate of administration, its volume of distribution, and its first-order rate constant of removal. This relationship has been called the plateau principle (1). The purpose of this paper is to report on various types of kinetic experiments which demonstrate the self-consistency and utility of the plateau principle.

[1] Dicumarol.

THEORY

The basic formulas of the one-compartment model are summarized for convenience.

Drug is infused into the body at a constant rate, I (mg./min.). Upon entering the body, the drug is assumed to equilibrate "instantaneously" among the various body tissues, so the quantity $Q(t)$ (mg.) of drug in the body at time t (min.) is expressed as

$$Q(t) = V_d C_p(t) \qquad \text{(Eq. 1)}$$

where V_d (ml.) is by definition the constant volume of distribution and $C_p(t)$ (mg./ml.) is the concentration of drug in plasma at time t. The rate of removal $L(t)$ (mg./min.) of drug from the body, either as separation from the body or loss of identity within the body, is assumed expressible by the first-order expression

$$L(t) = GC_p(t) \qquad \text{(Eq. 2)}$$

where G (ml./min.) is by definition a constant clearance. The mass balance equation for the drug is, by Eqs. 1 and 2,

$$V_d(dC_p/dt) = I - GC_p(t) \qquad \text{(Eq. 3)}$$

which has the solution starting from zero drug plasma concentration (1)

$$C_p(t) = C_{p\infty}(1 - e^{-kt}) \qquad \text{(Eq. 4)}$$

In Eq. 4, the plateau concentration $C_{p\infty}$ (mg./ml.) is given by

$$C_{p\infty} = I/G \qquad \text{(Eq. 5)}$$

and the rate constant k(min.$^{-1}$) is given by

$$k = G/V_d \qquad \text{(Eq. 6)}$$

Equations 5 and 6 give

$$C_{p\infty} = I/kV_d \qquad \text{(Eq. 7)}$$

Substitution of the half-life $t_{1/2} = 0.693/k$ into Eq. 7 gives

$$C_{p\infty} = It_{1/2}/0.693V_d \qquad \text{(Eq. 8)}$$

If, after the plateau concentration is reached (to a given accuracy), the infusion is suddenly stopped, the decay of drug plasma concentration is described by Eq. 3, with $I = 0$, as

$$-V_d(dC_p/dt) = GC_p(t) \qquad \text{(Eq. 9)}$$

with solution

$$C_p(t) = C_{p\infty}e^{-kt} \qquad \text{(Eq. 10)}$$

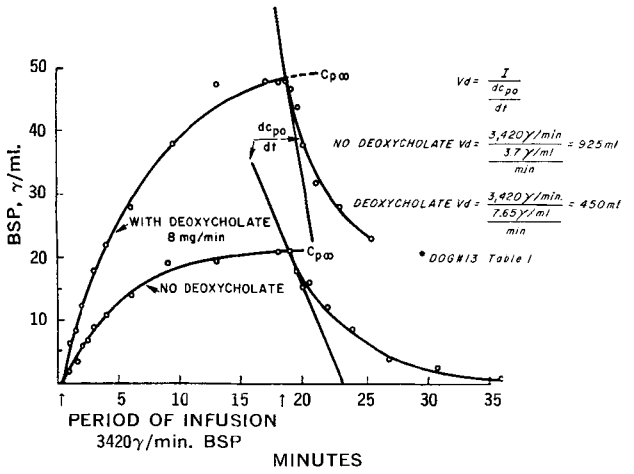

Figure 1—*Plasma BSP concentration with constant infusion.*

Just after stoppage of the infusion, the time rate of change of $C_p(t)$ changes discontinuously from the value zero just before stoppage to the value given by Eq. 9 as

$$-V_d(dC_p/dt)_0 = GC_p(0) = GC_{p\infty} \qquad \text{(Eq. 11)}$$

Substitution of G from Eq. 5 and solving for V_d give

$$V_d = -I/(dC_p/dt)_0 \qquad \text{(Eq. 12)}$$

Equations 12 and 8 yield

$$C_{p\infty} = -(dC_p/dt)_0 t_{1/2}/0.693 \qquad \text{(Eq. 13)}$$

The value of V_d from Eq. 12 applies only to a single-compartment model with monoexponential elimination. Although in practice this may be true for some drugs, additional compartments (multiexponential) may be observed, yielding a low value of V_d from Eq. 12 compared to Eq. 8 (2).

In the present constant-infusion experiments, the experimental data were I (exp.), $C_{p\infty}$ (exp.), $(dC_p/dt)_0$ (exp.), and $t_{1/2}$ (exp.) from the slope of the semilogarithmic plot of the decay curve after stoppage of the infusion (Fig. 1). $C_{p\infty}$ (exp.) was compared with the theoretical $C_{p\infty}$ obtained by Eq. 13 from $(dC_p/dt)_0$ (exp.) and $t_{1/2}$ (exp.) (Table I). Equivalently, the theoretical V_d obtained by Eq. 12 from I (exp.) and $(dC_p/dt)_0$ (exp.) was compared with the theoretical V_d obtained by Eq. 8 from I (exp.), $C_{p\infty}$ (exp.), and $t_{1/2}$ (exp.).

A series of sudden-injection experiments was also performed. Theoretical first-order kinetics (3) predicts that the response to sudden injection is essentially the time derivative of the response to constant infusion. Hence, in the present model, if the amount Q_0 of drug is suddenly injected, the plasma concentration will be

$$C_p(t) = C_{p0}e^{-kt} \qquad \text{(Eq. 14)}$$

where the zero-time intercept C_{p0} yields the volume of distribution V_d by

$$V_d = Q_0/C_{p0} \qquad \text{(Eq. 15)}$$

and the rate constant k is given by Eq. 6. The experimental data in these experiments were the amount injected Q_0 (exp.), the zero-time intercept C_{p0} of the straight-line fit of the semilogarithmically plotted plasma concentration against time, and the half-life $t_{1/2}$ (exp.) $= 0.693/k$ (exp.) from the slope of the semilogarithmic plot. Constant-infusion experiments on the same animals yielded the constant-infusion rate I (exp.) and the plateau concentration $C_{p\infty}$ (exp.). A comparison of theory and experiment was made by first calculating V_d by Eq. 15 from Q_0 (exp.) and C_{p0} (exp.) and then substituting this V_d and $t_{1/2}$ (exp.), I (exp.) into Eq. 8 to yield a $C_{p\infty}$ for comparison with $C_{p\infty}$ (exp.).

In some sudden-injection experiments, the plasma concentration decayed multiexponentially at first before becoming monoexponential (Fig. 2). In these cases the relation

$$V_d = Q_0/C_{p0}(1 + B) \qquad \text{(Eq. 16)}$$

was used instead of Eq. 15, where B is a correction derived in the *Appendix*.

In all experiments the clearance G was calculated by Eq. 6 (Table II).

If the drug is removed from the body primarily from one organ, then the rate of removal of drug can be expressed by the Fick principle as

$$L(t) = F[C_a(t) - C_v(t)] \qquad \text{(Eq. 17)}$$

where F (ml./min.) is the rate of blood flow through the organ, and $C_a(t)$ and $C_v(t)$ are the concentrations of drug, respectively, in the arterial blood inflow to and in the venous blood outflow from the organ. Equations 2 and 17 yield

$$G = \lambda EF \qquad \text{(Eq. 18)}$$

where

$$E = [C_a(t) - C_v(t)]/C_a(t) \qquad \text{(Eq. 19)}$$

is the so-called extraction ratio from whole blood and

$$\lambda = C_a(t)/C_p(t) \qquad \text{(Eq. 20)}$$

is the constant-partition coefficient of drug between whole blood and plasma.

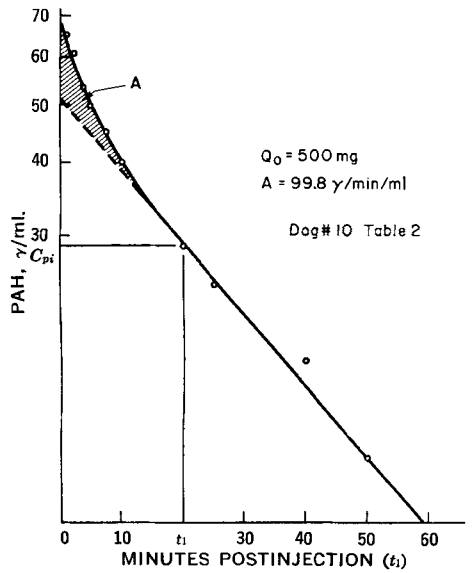

Figure 2—*Plasma decay of PAH after single dose.*

EXPERIMENTAL

Mongrel dogs of both sexes were anesthetized intravenously with pentobarbital, 50 mg./kg. Polyethylene catheters were placed in the forepaw and in the femoral veins. Isotonic solutions of bromsulfophthalein (BSP), antipyrine, *p*-aminohippuric (PAH) acid, and phenolsulfonphthalein (PSP) (all in saline) were used. In a constant-infusion experiment, the solution was infused into the paw vein at a constant rate by means of a Cambridge syringe pump. Blood was sampled from the catheter in the femoral vein into a heparinized syringe at intervals of 30 sec. for eight samples, every minute for the next four samples, and every 2 min. for the final four samples. The same schedule was followed for the single-injection experiments. There was never more than a 2% change in hematocrit throughout the experiment.

In those experiments in which two different infusions were made, the start of the second infusion was delayed until the plasma level of drug from the previous experiment had been zero for at least 2 hr. If this precaution was not taken, the BSP clearance often did not follow a first-order decay; instead the second infusion caused an almost linear rise in dye concentration throughout the 16-min. period of infusion. This suggests that the Tm for BSP had been exceeded and the rate of removal of BSP from plasma was no longer a first-order function but rather depended on liver capacity (4).

Values of V_d and k were obtained in each of six dogs by the single-injection technique. BSP (25 mg.), PSP (4.0 mg.), and PAH (500 mg.) were given intravenously as a single bolus in 5 ml. saline. Two

Table I—Continuous Infusion of BSP

Dog	Experimental			Calculated				
	I,[a] γ/min.	$t_{1/2}$,[b] min.	$C_{p\infty}$,[c] γ/ml.	$C_{p\infty}$,[d] γ/ml.	G,[e] ml./min.	V_d,[f] ml.	V_d,[g] ml.	Percent of Error of $C_{p\infty}$
4	5400	2.0	26	35	207	438	599	+25
7	9850	3.3	64	74	154	625	733	+6
9	9850	1.9	70	61	141	455	345	−8
8	9850	2.3	70	65	141	505	467	−7
10	3180	2.6	7.8	8.6	508	1370	1520	+10
	9600	2.9	27	31	355	1298	1480	+15
13	3420	3.9	21	21.5	163	925	930	−2
	3420[h]	4.0	48	45.5	71	450	440	−5
15	3820	4.0	58	57	66	382	380	−2
	3820[h]	4.2	65	77	59	300	356	+17
11	3420	4.0	26	39	131	513	759	+30
	3420[h]	3.9	42	62	81	316	458	+50

[a] I = rate of administration of BSP. [b] $t_{1/2}$ = half-life of plasma decay determined (from semilogarithmic plot) upon discontinuance of infusion. [c] $C_{p\infty}$ (experimental) = steady-state concentration (Fig. 2). [d] $C_{p\infty}$ (calculated) = obtained from $(dC_p/dt)_0$ and $t_{1/2}$ by Eq. 13. [e] G = determined from experimental values by Eq. 5. [f] V_d = volume of distribution; determined from the initial slope upon discontinuance of infusion, by Eq. 12. [g] V_d = determined from experimental values by Eq. 8. [h] Deoxycholic acid, 8 mg./min., infused with BSP.

hours after the plasma level of the test drug had reached zero, a constant infusion of the same drug was started.

In the case of antipyrine, the constant-infusion study was done 1 week after the single injection of 500 mg. The blood in the case of antipyrine was drawn every minute for the first four samples, every 5 min. for the next four samples, and every 15 min. for the next six samples.

The BSP and PSP were analyzed by diluting serum (1:3) with 0.001 *N* NaOH and reading the absorbance in a DU spectrophotometer at 560 mμ. The PAH and antipyrine were analyzed by the methods of Smith (5) and Brodie and Axelrod (6), respectively.

RESULTS

The V_d and $t_{1/2}$ were determined for a series of representative substances by both the single-injection and the continuous-infusion techniques. Data from the continuous infusion of BSP are shown in Table I. The $C_{p\infty}$ calculated from these data are in fair approximation with the experimentally observed $C_{p\infty}$. The clearance G, or volume freed of drug per unit time, was determined by Eq. 5. The volume of distribution, V_d, determined from Eq. 12 was in fair agreement with that determined from Eq. 8.

To demonstrate the consistency of these equations, deoxycholic acid was added to the infusion of BSP (Fig. 1). This caused an increase in $C_{p\infty}$ for the same dosage of BSP in the same dog which had received BSP alone 2 hr. previously. This change in $C_{p\infty}$ could have been due, by Eq. 8, to an increase in $t_{1/2}$ or a decrease in V_d. It is seen from Table I that V_d, determined from the initial slope, decreased and $t_{1/2}$ remained the same. The G must decrease by Eq. 6. Now G is also equal to $F(C_a - C_v)/C_a$, Eq. 18, with $\lambda = 1$. Either the blood flow or the fraction of BSP extracted from plasma must, therefore, have been depressed by deoxycholic acid to correspond with the depression of G. Since Demling (7), using a thermoelectric technique, was able to demonstrate that liver blood flow was not depressed by deoxycholate administration, the fraction of BSP removed from the plasma was probably decreased.

There is a tendency for the estimated $C_{p\infty}$ to be in excess of the experimental value (Table I). It may be that BSP has depots other than the plasma and liver which are more slowly filled. In this case the initial slope method, Eq. 12, would yield low values of V_d and, hence, by Eq. 8, too high values for $C_{p\infty}$.

In a similar manner, V_d and $t_{1/2}$ may be determined from Eqs. 14 and 15 by means of a single intravenous injection. Values of $C_{p\infty}$ predicted from Eq. 8, making use of V_d and $t_{1/2}$ obtained in this fashion, were in fair agreement with the $C_{p\infty}$ experimentally determined for BSP, PAH, PSP, and antipyrine by continuous infusion (Table II). The V_d and $t_{1/2}$ obtained from the single intravenous injection may be used to estimate the $C_{p\infty}$ of these substances during continuous administration. There is no consistent trend in the error of estimating $C_{p\infty}$ from the single-dose value of V_d and $t_{1/2}$.

Only in single-dose experiments with PAH was it necessary to correct for multiexponential kinetics by Eq. 16.

DISCUSSION

The clearance G determines, or is defined by, the plateau plasma concentration $C_{p\infty}$ in response to long-time, constant infusion of the drug at rate I (Eq. 5). It is clear that $C_{p\infty}$ can change, despite a constant I, if G changes. In the following, various pharmacological situations in which $C_{p\infty}$ changes are discussed in terms of G, V_d, and $t_{1/2}$. For convenience in visualization, the pair of fundamental parameters, G and V_d, may be replaced by the equivalent pair, $t_{1/2}$

Table II—Calculation of $C_{p\infty}$ from Data Obtained from Single Intravenous Injection

	V_d,[a] ml.	$t_{1/2}$,[b] min.	G,[c] ml./min.	$C_{p\infty}$, Predicted,[d] γ/ml.	I, mg./min.	$C_{p\infty}$, Experimental,[e] γ/ml.	$C_{p\infty}$, % Error
Dog 10 PAH	9400	25	250	43	10.6	53	−20
Dog 70 PAH	4600	12	264	62	16.5	66	−7
Dog 70 PSP	600	2.5	165	6.1	1.02	7.4	−19
Dog 205 BSP	300	4.5	46	72	3.30	63	+12
Dog 18 BSP	482	3.75	89	44	3.82	55	−20
Dog 14 Antipyrine	8500	100	59	58	3.4	65	−10

[a] V_d, determined from zero-time intercept after single injection by Eq. 15 or 16. [b] $t_{1/2}$, half-time of semilogarithmic plot of decay curve. [c] G, determined from V_d and $t_{1/2}$ by Eq. 6 with $k = 0.693/t_{1/2}$. [d] $C_{p\infty}$ (predicted), calculated from Eq. 8. [e] $C_{p\infty}$ (experimental), determined by constant infusion in each dog 2 hr. after completion of single dose.

Table III—Change in Values of G with Dose before and after Induction of Drug-Metabolizing Enzymes[a]

Dog	Wt, kg.	V_d, l. 50 mg./kg.	V_d, l. 20 mg./kg.	$t_{1/2}$, hr. 50 mg./kg.	$t_{1/2}$, hr. 20 mg./kg.	G, l./hr. 50	G, l./hr. 20
6	14	12	10.5	5.5	2.8	1.5	2.6 prestimulation
		15	14	2.0	1.8	5.3	5.5 poststimulation
1	10.2	10.2	5.7	7.7	1.5	1.0	2.6 prestimulation
		13.5	7.4	2.0	1.3	4.7	4.1 poststimulation
2	11.5	8.6	7.7	6.0	2.2	1.0	2.4 prestimulation
		9.6	8.0	2.5	1.8	2.7	3.0 poststimulation

[a] All data obtained from single injection.

and V_d, where by Eq. 6

$$t_{1/2} = 0.693\ V_d/G \qquad \text{(Eq. 21)}$$

For convenience in interpretation, the pair $t_{1/2}$ and V_d are assumed to be independent variables experimentally as well as theoretically. This is probably rarely if ever qualitatively correct, but one or the other predominates quantitatively.

To illustrate the utility of the concept of volume of distribution, the displacement of drugs from plasma binding sites by competing substances in the plasma may be interpreted as an increase in volume. Sulfa drugs displacing bilirubin from plasma binding sites may precipitate kernicteris in the newborn at relatively low plasma concentrations of bilirubin (8). Phenylbutazone increases the antibacterial activity of the sulfa drugs (9). In these cases, the pharmacological activity or toxicity of the drug is increased while the plasma concentration is decreased. In terms of Eq. 15, V_d has increased, causing C_{p0} to decrease at constant Q_0.

The volume of distribution may also be made to decrease. In this case, another drug may compete for binding sites in an organ other than the plasma. Thus, in Table I, deoxycholic acid when infused with BSP increased $C_{p\infty}$ and decreased V_d while $t_{1/2}$ remained unchanged. This implies (Eq. 21) a decrease in G which means that the drug is not being removed from the circulation as fast as the control, despite a constant $t_{1/2}$. Weiner *et al.* (10) have shown that methandrostenolone in man is capable of increasing the $C_{p\infty}$ of oxyphenbutazone while the $t_{1/2}$ remains unchanged. The implication that V_d is thereby decreased (Eq. 21) would indicate that methandrostenolone is capable of displacing oxyphenbutazone from extravascular binding sites. Norethandrolone and iopanoic acid appear capable of inhibiting liver storage and excretion of BSP in man (11). It is possible that this is a reflection of competition for liver binding sites. This is a case of V_d decreasing at constant I and $t_{1/2}$. Hence G is decreased (Eq. 21), which causes $C_{p\infty}$ to increase (Eq. 5).

Whereas V_d may be altered while the $t_{1/2}$ remains unchanged, the opposite may also occur. $C_{p\infty}$ may change with $t_{1/2}$ while V_d remains constant. The liver enzyme systems that metabolize a large number of drugs may be stimulated by phenobarbital or a number of other compounds (12). These enzymes will break down diphenylhydantoin, bishydroxycoumarin, and antipyrine at an increased rate after phenobarbital pretreatment. For example, an individual receiving an intravenous injection of a drug has a much longer $t_{1/2}$ before receiving phenobarbital than after receiving phenobarbital for a sufficient time. In terms of Eq. 21, G has increased.

It has been noticed that this effect is more readily demonstrated with a high dose of drug than with a low dose (13). The data in Table III demonstrate the differences observed in V_d and $t_{1/2}$ when a dog is given a 50-mg./kg. and a 20-mg./kg. dose of diphenylhydantoin intravenously. G at 20 mg./kg. was higher (2.6 l./hr.) than at 50 mg./kg. (1.5 l./hr.). Assuming that liver blood flow was not affected by the diphenylhydantoin, the fraction E of drug cleared from the blood was higher at the lower dose than at the higher dose (Eq. 18). After pretreatment of the dogs with barbiturates, the G for both dosage levels had increased (about 4 l./hr.), although the $t_{1/2}$ at the low dose was unchanged. This suggests that fraction E of the drug removed by the liver was no longer dose dependent. Also, it is clear that the induction of drug-metabolizing enzymes is prominent at low as well as high dosage levels in terms of an increase in G. The induction at the lower dose level manifests itself more as an increase in both V_d and G than as a decrease in $t_{1/2}$.

The $t_{1/2}$ may also be increased, forcing an elevation of $C_{p\infty}$, without an increase in I. Bishydroxycoumarin is capable of inhibiting the metabolism of diphenylhydantoin, thereby prolonging the $t_{1/2}$ and potentiating the effect of the anticonvulsant (14). V_d tends to remain unchanged. Thus, there is a decrease in G (Eq. 21), which in turn would cause an increase in the level of $C_{p\infty}$ (Eq. 5).

SUMMARY

The plateau principle is experimentally described for BSP, PAH, PSP, and antipyrine in terms of the volume of distribution (V_d), the half-life of plasma decay ($t_{1/2}$), and the rate of administration (I).

The plasma concentration of a drug may be altered by changes in V_d or $t_{1/2}$ despite a constant I. Deoxycholic acid infusion increased $C_{p\infty}$ for BSP by decreasing the V_d, while $t_{1/2}$ remained constant. $C_{p\infty}$ may be predicted by prior determination of V_d and $t_{1/2}$ for drugs with approximately monoexponential decay kinetics.

APPENDIX

For a single-injection experiment, a better approximation of the volume of distribution than Eq. 15 is given by

$$V_d = \left\{Q_0 - G_0 \int_0^{t_1} C_p(t)\, dt\right\} / C_{pi} \qquad \text{(Eq. A1)}$$

where C_{pi} is the drug plasma concentration at time t_1 on the final monoexponential portion of the plasma decay curve (Fig. 2). The numerator in Eq. A1 takes account of the drug which is lost from the body, by Eq. 2, at the actual (elevated) plasma concentration before the distribution of drug corresponding to the final monoexponential behavior has occurred. If the final monoexponential $C_{p0}\, e^{-kt}$ is added and subtracted to $C_p(t)$ in Eq. A1 and the integration

$$\int_0^{t_1} C_{p0}\, e^{-kt}\, dt = (C_{p0} - C_{pi})/k \qquad \text{(Eq. A2)}$$

is carried out, the result is

$$V_d C_{pi} = Q_0 - GA - G(C_{p0} - C_{pi})/k \qquad \text{(Eq. A3)}$$

where A is the area between the actual plasma decay curve and the monoexponential curve back-extrapolated to time zero (cross-hatched area in Fig. 2 measured on a linear plot). Substitution of Eq. 6 for G in Eq. A3 and solving for V_d yield

$$V_d = \frac{Q_0}{C_{p0} + kA} = \frac{Q_0}{C_{p0}(1 + B)} \qquad \text{(Eq. A4)}$$

where

$$B = kA/C_{p0} = 0.693A/t_{1/2}C_{p0} \qquad \text{(Eq. A5)}$$

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Application of Molecular Sieve Technique in Solubilization Studies of Benzoic Acid in Solutions of Cetomacrogol 1000

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Abstract □ The applicability of a new technique in solubilization studies, using a molecular sieve, was tested on a system consisting of benzoic acid and cetomacrogol 1000 (cetostearyl ether of polyoxyethylene) in aqueous solutions. The data obtained are in good agreement with those found by other methods. Some advantages of the method are outlined.

Keyphrases □ Benzoic acid—solubilization study □ Cetomacrogol 1000 solution—benzoic acid solubility □ Micellar solubilization, benzoic acid in cetomacrogol 1000—quantitative determination □ Molecular sieve technique—solubilization study □ Spectrophotometry, UV, visual—analysis

The importance of theoretical and pharmaceutical aspects of micellar solubilization of drugs has been well recognized in recent years (1–4). Nevertheless, only three methods are available in routine practice for quantitative investigation of the phenomenon.

The conventional solubility method has been used by almost all investigators either as a basic tool or comparatively. Its main disadvantage is that it is limited to saturated systems; hence the dependence of solubilization on the concentration of unbound solubilizate cannot be studied by this method. Another major disadvantage lies in the fact that many additives decrease the cloud point (4, 5). This means that although turbidity is often used as a criterion for saturation with liquid solubilizates, it is not necessarily an indication of maximum solubility (6–10). Furthermore, the determination of the turbidimetric end-point is subject to error.

Equilibrium dialysis was first introduced into solubilization studies by Patel and Kostenbauder (11). This method solved the problems encountered in the solubility method. Although widely accepted, it is time consuming and requires preliminary work on the selection of a proper membrane for each system. Nylon membranes used by Patel and Foss (12) are stated to swell and bind phenolic compounds; rubber membranes tried by Matsumoto *et al.* (13) varied in thickness; and methylcellulose membranes are attacked by certain surfactants (14).

Potentiometric titration was first used for solubilization studies of organic acids and bases by Donbrow and Rhodes (15–17). Although rapid and elegant enough to have been adopted for routine use (15–23), it is restricted to ionizing solubilizates in which only the unionized form undergoes micellar solubilization. It is thus unsuitable for studies on the solubilization of acids and bases of pronounced amphiphilic properties such as local anesthetics or acid derivatives of steroidal hormones, their ionized form, as well as the unionized, being solubilized (24).

In view of the increasing importance of studies on nonsaturated systems, additional methods of a more general nature and greater scope than potentiometric titration and quicker than equilibrium dialysis would be advantageous. Such methods would also be valuable for crosschecking.

A molecular sieve technique which promised to meet these needs, has in fact been applied to methyl *p*-hydroxybenzoate by Ashworth and Heard (25). Dextran gel, with a suitable degree of crosslinking, was used in a static way similar to a semipermeable membrane in dialysis. The small molecules (the solute) are distributed between the swollen gel and the external liquid, while the surfactant is unable to penetrate the internal gel phase and remains in the external liquid. The solute distribution normally follows a linear relation. (See also Eqs. 5 and 6 in *Results and Discussion*, and Eq. 1 in *Experimental*.)

The object of the present work is to broaden the applicability of this method by testing it on another