surface energy level of surfaces with only moderate polar forces would result in a very misleading estimate of at least the dispersion forces present in that surface.

CONCLUSIONS

It is possible to characterize tablet surfaces according to their CED by using contact-angle data and applying a modification of the Zisman (15) technique. However, caution must be exercised in the interpretation of the γ_c values obtained. Particular attention should be paid to the possible effects of unbalanced polar and dispersion forces between the test liquids and surfaces investigated.

The surface energy of a tablet, as well as the types of forces present, can to some extent be predicted by studying the types of chemical components that would be present at the surface.

More work needs to be done in determining the presence and relative roles of polar and dispersion forces as they influence wetting, contact-angle data, adsorption, and adhesion.

A knowledge of the types of forces acting across the interface between the tablet surface and a film coating, their relative intensities, and the degree of interaction should greatly advance the understanding of processes involved in the formation of an adequate film coating.

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 27, 1970, from the *Department of Pharmaceutics, College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.*

Accepted for publication July 17, 1970.

This work was supported by Medical Research Council of Canada Operating Grant MA3629.

Rotating-Flask Method for Dissolution-Rate Determinations of Aspirin from Various Dosage Forms

HOWARD WEINTRAUB* and MILO GIBALDI

Abstract □ The dissolution of aspirin from different commercial dosage forms was evaluated by the rotating-flask method, and the data were correlated with previously reported absorption data. Regardless of agitation intensity, over a range from 0.9 to 2.4 r.p.m., dissolution rate was found to decrease in the following order: buffered tablets > plain tablets > timed-release tablets. The data were linearized by means of log-normal probability plots and interpreted accordingly. Aspirin dissolves from the buffered tablet about twice as rapidly as from the plain tablet and about eight times as rapidly as from the timed-release tablets. Once disintegration and deaggregation take place, the dissolution of aspirin from the capsule formulation proceeds as rapidly as from the buffered tablet. Surfactant decreased the dissolution rate of aspirin from certain formulations, in contrast to the enhanced dissolution effects observed using the beaker method where mound formation occurred. Excellent single- and multiple-quantitative correlations were observed between the dissolution data and absorption data in man.

Keyphrases □ Aspirin in dosage forms—dissolution rates □ Dissolution rates—aspirin dosage forms □ Surfactant effect—aspirin dissolution from dosage forms □ Rotating-flask method—dissolution-rate determination

A number of methods designed to measure the dissolution rate of drugs from solid dosage forms are presently available (1, 2). Interest has been particularly focused on the beaker method (3) and its variants, including the rotating-basket assembly (4) and the flask and stirrer method (5), since these methods have consistently provided data which permit some correlation with *in vivo* data (5–8).

A shortcoming of the beaker method is observed at relatively low agitation intensities, *i.e.*, <40–50 r.p.m., where the geometry of the system combined with the nature of the agitation forces the granules or particles into a mound at the bottom of the flask or beaker. The mound is more or less compact, depending upon the formulation of the dosage form, and may or may not present a markedly reduced surface area to the dissolution medium. This problem was exemplified by Levy *et al.* (6), who were concerned with the quantitative correlation of dissolution data with the gastrointestinal absorption in man of aspirin from different types of dosage forms. Clinical studies indicated that aspirin was absorbed about three times more rapidly from "plain tablets" of the drug than from a timed-release preparation. Dissolution data obtained at 50 r.p.m. gave virtually perfect correlation with respect to differences between the two dosage forms observed *in vivo*, but the dissolution rate of the drug from the plain tablet was about twice the absorption rate of the drug from the same dosage form. At 45 r.p.m., where the dissolution rate of aspirin from the plain tablet was comparable to the absorption rate of drug from this dosage form, there was only a 50% difference between the timed-

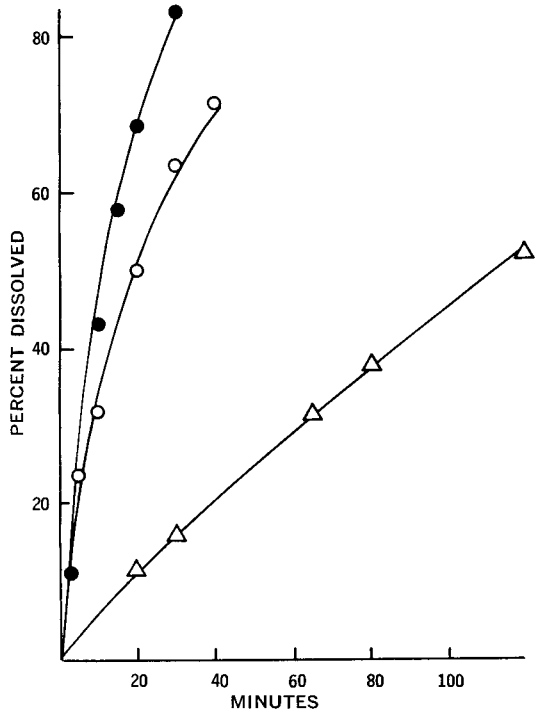

Figure 1—*Cumulative percent dissolved from aspirin dosage forms in 0.1* N *HCl at 0.9 r.p.m. Key:* ●, *buffered tablets;* ○, *plain tablets; and* △, *timed-release tablets.*

release preparation and the plain tablet, in contrast to the threefold difference observed *in vivo*. At still lower agitation rates, aspirin dissolved more rapidly from the timed-release tablets than from the plain tablets. In an attempt to overcome this problem, the rotating-flask method (9) was devised.

The philosophy underlying the development of the method is in keeping with that embodied in the development of the beaker method (3). "For tablets and other solid oral dosage forms, low intensities of agitation are highly desirable and more likely to allow distinguishing formulations and products and correlating results with *in vivo* data" (2). But at the same time, the hydrodynamics of the rotating-flask method effectively preclude mound formation, which is considered to be physiologically unrealistic. The present report concerns the evaluation of aspirin dissolution from different types of commercial dosage forms by means of this method and the correlation of these data with previously reported (6, 10) absorption data.

EXPERIMENTAL

Dosage Forms—The following were used: (*a*) rapidly disintegrating tablets, each containing 650 mg. aspirin as microencapsulated particles (timed-release tablets); (*b*) rapidly disintegrating tablets, each containing 325 mg. aspirin (plain tablets); (*c*) rapidly disintegrating tablets, each containing 325 mg. aspirin and alkaline additives (buffered tablets); and (*d*) capsules, each containing 325 mg. aspirin (capsules). Each dosage form was purchased from retail outlets.

Dissolution-Rate Determination—*In vitro* dissolution rates were determined at 37° by the rotating-flask method (9). The dissolution medium consisted of 400 ml. of 0.1 *N* HCl. In certain experiments, 0.01% polyoxyethylene (23) lauryl ether[1] was added to the medium.

[1] Brij 35 SP, Atlas Chemical Industries, Wilmington, Del.

Table I—Comparison of Aspirin Dissolution from Commercial Dosage Forms at Various Experimental Conditions

Experimental Conditions and Dosage Forms	Median Time,[a] min.	Dissolution[b] Interval, min.	*SD*[c]
0.1 *N* HCl, 0.9 r.p.m.			
Buffered tablets	12	25	0.39
Plain tablets	18	46	0.47
Capsules	19	28	0.28
Timed-release tablets	104	212	0.39
0.1 *N* HCl, 1.2 r.p.m.			
Buffered tablets	9	24	0.48
Plain tablets	10	42	0.59
Capsules	16	18	0.24
Timed-release tablets	83	211	0.45
0.1 *N* HCl, 2.4 r.p.m.			
Buffered tablets	4	15	0.60
Plain tablets	7	38	0.80
Timed-release tablets	67	186	0.48
0.1 *N* HCl + SAA,[d] 0.9 r.p.m.			
Buffered tablets	19	44	0.43
Plain tablets	30	79	0.47
Capsules	18	33	0.35
Timed-release tablets	105	209	0.38

[a] Time required to dissolve 50% of the dose. [b] Time required to dissolve 84% of the dose minus the time required to dissolve 16% of the dose. [c] Log (time required to dissolve 50% of the dose) − log (time required to dissolve 16% of the dose), *or* log (time required to dissolve 84% of the dose) − log (time required to dissolve 50% of the dose). [d] 0.01% Polyoxyethylene (23) lauryl ether.

Rotation was provided by a constant-speed motor[2] coupled to a series of gears and was varied from 0.9 to 2.4 r.p.m. A minimum of five determinations was made with each dosage form at a given rate of rotation, with the exception of the timed-release tablets where three determinations were made.

At frequent intervals after the introduction of the dosage form into the flask, rotation was briefly halted, a 1-ml. sample was taken by means of a filter pipet, and rotation was initiated once again. Elapsed time was considered to be the time during which the flask was actually rotating. Preliminary studies with the most rapidly dissolving aspirin dosage form indicated that intermittent sampling had no significant effect on the dissolution profile.[3]

Each sample was made alkaline by addition of 1 ml. 1 *N* NaOH and hydrolyzed for 1 hr. at 100°. Following hydrolysis, the pH of each sample was adjusted to pH 1 with concentrated HCl, and the samples were assayed spectrophotometrically[4] at 302.5 mμ for salicylic acid.

RESULTS AND DISCUSSION

Figure 1 is a plot of the cumulative amount (expressed as percent of dose) of aspirin dissolved as a function of time from three of the dosage forms at an agitation intensity of 0.9 r.p.m. The ranking observed—*viz.*, buffered tablet > plain tablet > timed-release tablet, agrees with the findings of Levy *et al.* (6). The same rank order was observed at 1.2 and 2.4 r.p.m. The *initial* dissolution profile of aspirin from the capsule was comparable to that observed with the plain tablet, but the time required to dissolve 80–90% of the capsule dose was considerably less than that observed with the plain tablet and, in fact, compared favorably with findings from the buffered tablet. Therefore, it was difficult to compare the dissolution of aspirin from the capsule with the data from the other dosage forms.

The interpretation of the percent dissolved–time plots adopted in this study was based on the graphical methods suggested by Wagner (11). He demonstrated that under sink conditions, the per-

[2] Dayton Electric, Chicago, Ill. Motor No. 3M095, nominally rated at 1 r.p.m., 150 in.-lb. torque.

[3] For example, the amount of drug dissolved from the buffered tablet, after 15 revolutions, at an agitation rate of 2.4 r.p.m., during sequential sampling at 5 revolution intervals was 180 ± 20 mg. (*SD*, 5 determinations), in contrast to a total amount of 154 ± 21 mg. (*SD*, 5 determinations) dissolved after 15 continuous revolutions. The difference was not statistically significant ($p > 0.2$).

[4] Hitachi-Perkin-Elmer model 139 spectrophotometer.

Table II—Regression Analysis of *In Vitro–In Vivo* Correlation According to the Equation: (% dissolved to time T) = b (% absorbed to time T) + a

Experimental Conditions and Dosage Forms	Slope (b)	Intercept (a)	Correlation Coefficient
0.1 *N* HCl, 0.9 r.p.m.			
Buffered tablets	1.32	−9.0	>0.99
Plain tablets	1.21	6.3	0.98
Timed-release tablets	0.71	5.3	0.98
All dosage forms	1.14	0.3	0.91
0.1 *N* HCl, 1.2 r.p.m.			
Buffered tablets	1.27	1.9	>0.99
Plain tablets	1.06	25.0	0.98
Timed-release tablets	0.87	4.2	0.99
All dosage forms	0.90	16.5	0.80
0.1 *N* HCl, 2.4 r.p.m.			
Buffered tablets	1.87	17.6	0.99
Plain tablets	1.44	18.4	0.99
Timed-release tablets	1.01	8.0	0.99
All dosage forms	0.85	27.3	0.78
0.1 *N* HCl + SAA,[a] 0.9 r.p.m.			
Buffered tablets	0.96	−1.7	>0.99
Plain tablets	1.20	−11.2	0.99
Timed-release tablets	0.97	0.4	0.98
All dosage forms	0.99	−1.8	0.98

[a] 0.01% Polyoxyethylene (23) lauryl ether.

cent dissolved to time T from a solid is equal to the percent of surface area generated to time T of total surface generated. Wagner proposed that the properties of the distribution of surface area available for dissolution from a capsule or tablet dosage form are similar to those of a log normal and log logistic distribution. Hence, one could plot the cumulative percent dissolved values on the probability scale (ordinate) *versus* the corresponding time values on the logarithmic scale (abscissa). If the data are described by this particular distribution function, then the points should describe a straight line. An estimate of the median dissolution time may be obtained by reading the time corresponding to the 50% point, and an estimate of the standard deviation (SD) may be obtained from the 16, 50, and 84% points by appropriate conversion of the time values to their logarithms. In the present report the difference, in units of time, between the 16 and 84% points is termed the dissolution interval.

The percent dissolved–time data obtained with the various dosage forms, with and without surfactant in the dissolution medium, at various agitation intensities were well described in each

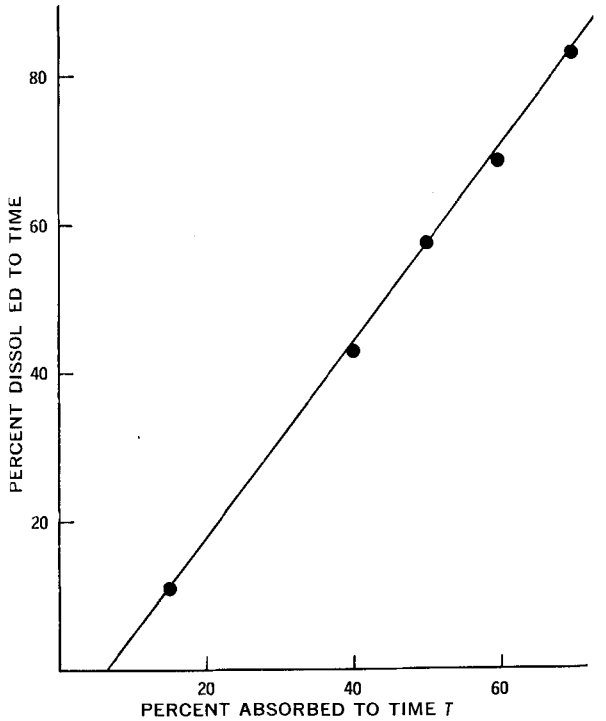

Figure 3—*Relationship between percent aspirin dissolved from buffered tablets and percent aspirin absorbed from this dosage form to the same time* T. *Dissolution data obtained in 0.1* N *HCl at 0.9 r.p.m.*

case by log–normal probability plots. Examples are shown in Fig. 2, using dissolution data obtained at 2.4 r.p.m. The critical parameters used to describe the dissolution data for all dosage forms under various experimental conditions are summarized in Table I.

As expected, for a given dosage form both the median time and dissolution interval decrease with an increase in agitation intensity; with the exception of the capsule data, the standard deviation increases with increasing agitation. Regardless of agitation intensity, the median time increases in the following order: buffered tablet < plain tablet < capsule < timed-release tablet. Comparison of the dissolution interval data suggests that aspirin dissolves from the buffered tablet about twice as rapidly as from the plain tablet and

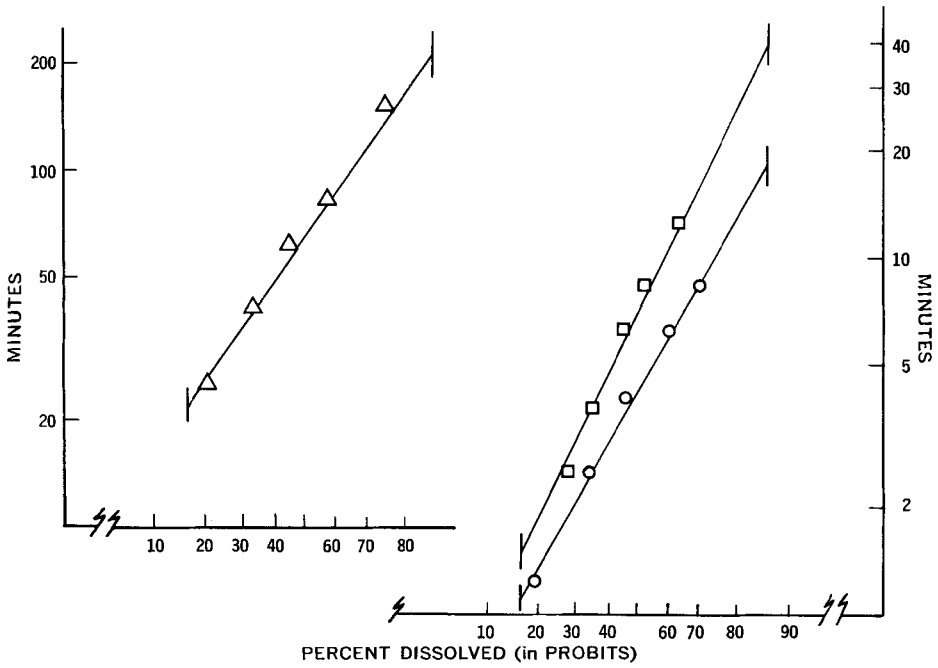

Figure 2—*Log–normal probability plots of dissolution data from aspirin dosage forms in 0.1* N *HCl at 2.4 r.p.m. Key:* ○, *buffered tablets;* □, *plain tablets; and* △, *timed-release tablets.*

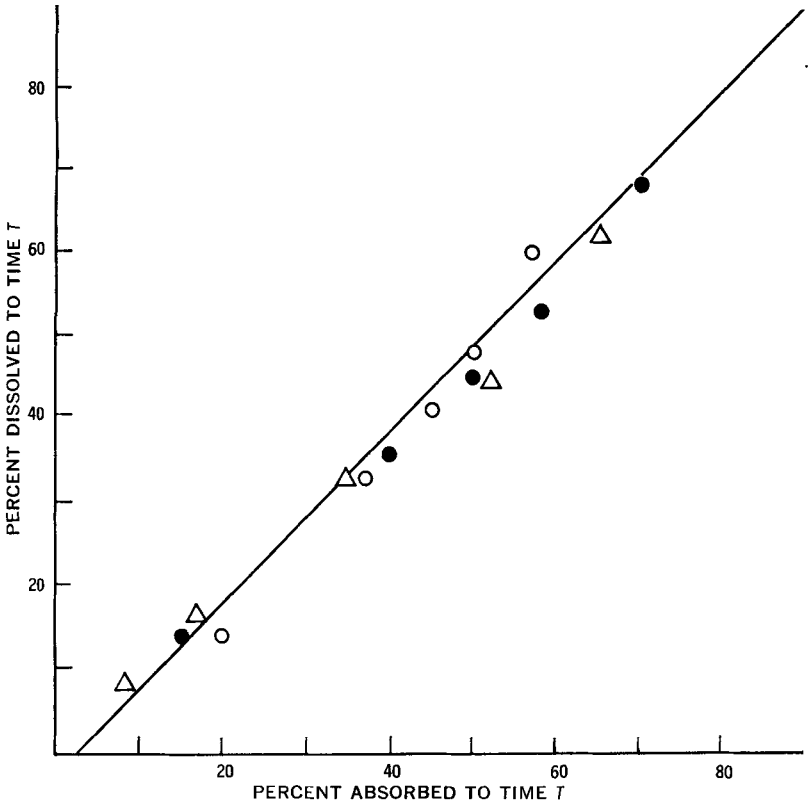

Figure 4—*Relationship between percent aspirin dissolved and percent aspirin absorbed to the same time* T. *Dissolution data obtained in 0.1* N *HCl with 0.01% polyoxyethylene (23) lauryl ether at 0.9 r.p.m. Key:* ●, *buffered tablets;* ○, *plain tablets; and* △, *timed-release tablets.*

about eight times as rapidly as from the timed-release tablet. Ratios of dissolution intervals are reasonably constant over the entire range of agitation intensities. The dissolution interval for the capsule was comparable to that of the buffered tablet. These observations suggest that disintegration and deaggregation of the capsule contents require a greater time than for similar events to occur with the plain and buffered tablets; but once these processes take place, the dissolution of aspirin from the capsule formulation proceeds as rapidly as from the disintegrated buffered tablet formulation.

The influence of 0.01% nonionic surfactant on the dissolution rate of aspirin from the various dosage forms at 0.9 r.p.m. is also summarized in Table I. Addition of the surfactant results in a considerable increase in the median time and dissolution interval for both the plain and buffered tablets but is without effect on the dissolution of aspirin from the capsule and timed-release formulations. In a previous report (12) concerned with dissolution of aspirin from the capsule and buffered tablet dosage forms using the flask and stirrer method, it was observed that 0.01% polyoxyethylene (23) lauryl ether had no effect on the dissolution of aspirin from the capsule but markedly *decreased* the median dissolution time for the buffered tablet. In the judgement of the present authors, the qualitatively different effects of the surfactant on the dissolution of aspirin from the buffered tablet, using the beaker method and rotating-flask method, are attributable to mound formation in the former and its absence in the latter.

In the beaker method, the disintegrated buffered tablet granules apparently form a rather compact mound at the bottom of the flask and give rise to a "porous plug" which the dissolution medium finds difficult to penetrate. The surfactant enhances pore penetration ostensibly by reducing the contact angle and thereby increases the effective surface area and, in turn, the dissolution rate. Since the rotating-flask method does not give rise to a mound or porous plug, one anticipates that the surfactant would not enhance the dissolution rate. This was indeed the case. The decreased dissolution rate of aspirin from the plain and buffered tablets which was observed in the presence of the surfactant may be due to a dewetting phenomenon and subsequent aggregation of the particles (13).

In a preliminary communication (9), the authors reported that the aspirin-dissolution data for the plain, buffered, and timed-release tablets obtained with the rotating-flask method provided an excellent quantitative correlation with previously reported *in vivo* absorption data (6, 10) on the same dosage forms. This type of analysis was extended, and comparisons of *in vivo* and *in vitro* data were made for the individual dosage forms as well as for the three dosage forms simultaneously under various experimental conditions. Figure 3 is an example of a single correlation. Excellent linearity is observed when the percent of dose dissolved in time T from a buffered tablet in 0.1 N HCl at 0.9 r.p.m. is plotted as a function of the percent absorbed to time T in man. The slope of the line is 1.32, and the correlation coefficient is > 0.99. Figure 4 shows the best example of a multiple correlation. Dissolution data were obtained in 0.1 N HCl with surfactant at 0.9 r.p.m. The slope of the least-squares line is 0.99, and the correlation coefficient is 0.98.

Table II summarizes the analysis for *in vivo–in vitro* correlation and includes the least-squares slope and intercept for the equation:

$$(\%\text{ dissolved to time } T) = b(\%\text{ absorbed to time } T) + a \quad \text{(Eq. 1)}$$

as well as the correlation coefficient. The latter values were computed according to Mather (14) for interclass correlation where both variables are normally distributed. In all but two cases, the correlation coefficient was greater than 0.90 and in all cases the correlation coefficient was highly significant ($p < 0.005$).

Based on the *in vivo–in vitro* correlations obtained with the aspirin dosage forms, it would appear that the rotating-flask method offers certain advantages over the beaker methods currently in use. However, before any *in vitro* dissolution method can be relied upon as an index of physiologic availability or *in vivo* absorption rate, more retrospective testing is required.

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ACKNOWLEDGMENTS AND ADDRESSES

Received May 25, 1970, from the *Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY 14214*

Accepted for publication July 22, 1970.

The technical assistance of Mr. James Mecca of the Health Sciences Instrument Shop, State University of New York at Buffalo, in the construction of the gear assembly used in this study is acknowledged.

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Theoretical Approach to Sustained-Release Multiple-Dose Therapy: Noncumulative Attainment of Desired Blood Level

JOSEPH R. ROBINSON* and STUART P. ERIKSEN†

Abstract □ Equations are presented to allow calculation of doses and dosing interval for multiple-dose therapy of sustained-release dosage forms. Both zero- and first-order release of drug from the dosage form are considered in developing these equations. Although special problems are associated with multiple dosing of sustained-release dosage forms because of their unique design, application of the appropriate equations yields relatively uniform blood levels of drug.

Keyphrases □ Sustained-release products—multiple-dose therapy □ Equations—doses, dosing intervals, calculation □ Blood levels—noncumulative multiple-dose therapy □ Theoretical approach—noncumulative blood levels, sustained-release therapy

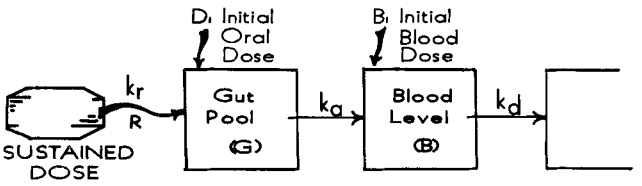
Considerable effort has been expended in the mathematical development of dosage regimens for multiple dosing of nonsustained-release dosage forms (1–7). In recent work (7), the authors developed equations to allow calculation of doses and dosing intervals to produce and maintain a desired blood level (noncumulative approach). Surprisingly, the problem of multiple dosing with sustained-release dosage forms has not been considered. In the present work, equations are presented which will allow a rational (and hopefully pragmatic) approach to such therapy.

MODEL USED

A simple four-compartment model was used throughout this study (Scheme I). All of the customary assumptions of pharmacokinetics with respect to exponential rate processes, constants, *etc.*, as well as the validity of the model are assumed in this study (see *References Ia* and *7* for a discussion of these points).

ELEMENTARY REGIMEN

The elementary regimen design, using two units initially followed by one unit each elimination half-life later, was found to be only very approximately valid for oral nonsustained-release products, as reported in another paper (7). Simple extension of this elementary concept from nonsustained- to sustained-release dosage forms suggests that for a sustained-release dosage form, which is designed to provide flat blood levels over a full treatment period, the dosing frequency, $\tau_{sust.}$, should be



Scheme I—Model used in development and evaluation of sustained-action equations

$$\tau_{sust.} = h + t_{1/2\ elimination} \qquad \text{(Eq. 1)}$$

where h is the number of hours of desired sustained effect for which one dose of the sustained-release dosage form has been designed, and $t_{1/2\ elimination}$ is the elimination half-life of the drug. Similar, but more severe, problems than those encountered with nonsustained medications are encountered here. The solution to these problems depends somewhat upon the mathematics to describe the release of drug from the dosage form, *i.e.*, zero- or first-order release, but in general involves corrections for the same difficulties present in nonsustained multiple-dose therapy, *i.e.*, accumulation of drug in the body.

As in any therapy, the interest of both the patient and the physician is safe, but rapid, and maintained relief. A therapy dependent upon accumulation does not achieve this goal. The desired sustained-action product should rapidly attain and maintain the desired blood or tissue level of drug. All subsequent doses must be designed and taken to reachieve the plateau blood level established by the first dose.

The theoretical concepts behind the design of a single sustained-action dosage form have been reported (8–10). This earlier work was designed to produce the optimum blood picture for one administered dose. While identical concepts are involved when multiple doses are to be administered, slight alterations must be made to eliminate the undesired accumulation effect.

SATISFACTORY SUSTAINED-ACTION PATTERN

The nonsustained-action definition of "satisfactory therapeutic blood level patterns" (7), *i.e.*, a rapid rise to a peak suitable to produce the desired biological action followed by a regular rise and fall between constant values, must be altered slightly for sustained-action dosage forms. Satisfactory blood level patterns, for