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IDEALIZED APPROACH TO THE OPTIMAL DESIGN, DEVELOPMENT, AND EVALUATION OF DRUG DELIVERY SYSTEMS II: OPTIMIZATION OF DRUG BIOAVAILABILITY INPUTS AND IN-VITRO DRUG RELEASE TESTING

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ABSTRACT

This report is a continuation of a previous communication concerning the role of drug bioavailability input-pharmacological response output relationships in drug delivery system design, development, and evaluation. The degree of control of ophthalmic drug action by dosage form design is exemplified with two antiglaucoma drugs. Computer simulations are presented to demonstrate the control of simultaneously occurring therapeutic and toxic drug actions which can be achieved through systemic drug input optimization. An optimally predictive in-vitro drug bioavailability testing apparatus and its mode of operation during product development studies, to function as a replacement for a panel of human subjects, is described. An overall, idealized scheme for rationally approaching the development of drug products is presented. Results of ongoing research in the authors' laboratories are provided as examples.

INTRODUCTION

Part I[1] of this two part communication described the characteristics of pharmacological data and discussed the nature and use of quantitative inter-relationships which can be established between drug bioavailability inputs and single

pharmacological response outputs. However, in designing drug delivery systems with a high level of therapeutic performance, it must be considered that few drugs elicit a single effect; most commonly two or more actions of the drug are observable and need to be simultaneously controlled. A drug input, which can be defined as the time variation of the cumulative amounts of drug released by a drug delivery system to sites of action (biophase), may produce an ideally sought therapeutic response intensity vs. time profile while simultaneously inducing magnitudes of toxic responses which are intolerable. With this in mind, an optimal drug input may be considered as inducing a preselected ideally sought time course of therapeutic action as closely as possible without exceeding predetermined safely allowable limits of any concomitantly occurring adverse drug actions. This type of pharmacological response behavior may be described as being characterized by a maximum therapeutic utility.[2,3] Computer simulations, based on actual systems are presented in this report to exemplify drug input optimizations for: 1) a case where a therapeutic and toxic response both share a common biophase; the biophase is defined as a compartment in the body which the drug must enter to elicit its effect(s),[2-7] and 2) a case of four simultaneously occurring effects each having its own separate biophase compartment. Drug inputs which are computed to be optimal can serve as ideal objectives for the drug release behavior of drug delivery systems. For oral, rectal, parenteral, and other solid drug dosage forms, the achievement of this objective can be expedited through the implementation of an optimally predictive in-vitro drug bioavailability testing method which is described.

DRUG INPUT OPTIMIZATION - SINGLE BIOPHASE

Figures 1-5 present the results of computer simulations based somewhat on the previously observed pharmacokinetic behavior of the drug tridihexethyl chloride.[2,3,8] The results demonstrate that the therapeutic and toxic response of a drug can be differentially affected by drug input rates even if both responses share the same biophase. The simulations were performed with unit pulse inputs of varying duration which physically could correspond to slow i.v. infusions of a unit dose of drug given at varying zero order rates. These inputs are shown in Figures 1 and 2. The cumulative (ramp) drug inputs in Figure 2 are the integrals of the unit pulse inputs drawn in Figure 1. Figure 3 shows the resulting biophasic

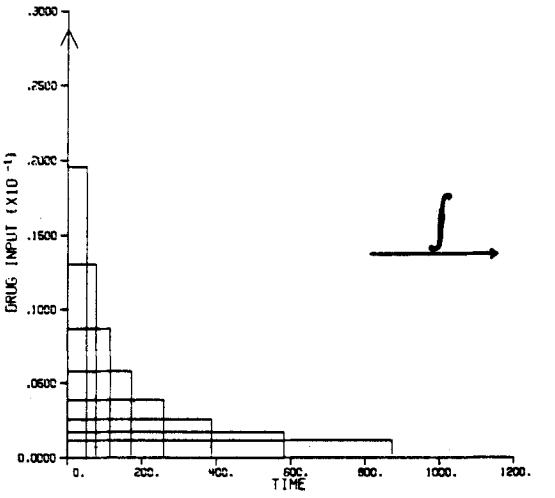


FIGURE 1

Computer plot of the unit pulse drug inputs used in a simulation study of the effect of drug input rates on the therapeutic utility of a hypothetical drug. In practice the heights and widths of the rectangles would represent the rates and durations of slow intravenous infusions of the drug.

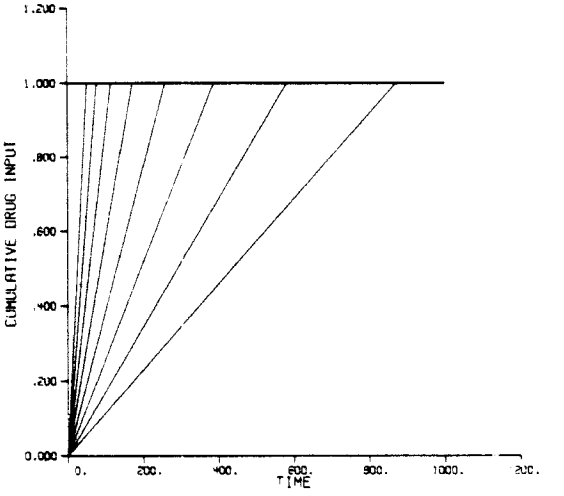


FIGURE 2

Cumulative drug inputs used in the computer simulation study of the effect of drug input rates on therapeutic utility. The ramps are the integrals of the unit impulse drug inputs shown in Figure 1.

drug level time responses which correspond to these unit pulse inputs. Figure 4 contains the dose effect curves corresponding to a therapeutic and toxic effect of the drug. The further the toxic dose-effect curve is displaced from the therapeutic curve, the higher is the therapeutic index of the drug. As discussed in Part I of this communication[1] these dose effect curves are used as calibration curves to convert the biophasic drug levels into their corresponding response intensities in a manner analogous to using a non-linear Beer's law plot to convert measured absorbances into plasma drug concentrations when using a spectrophotometric assay. If the dose-effect curve can be described by straight lines over the response range of interest, then the pharmacological data can be used directly without transformation. Figure 5 shows the

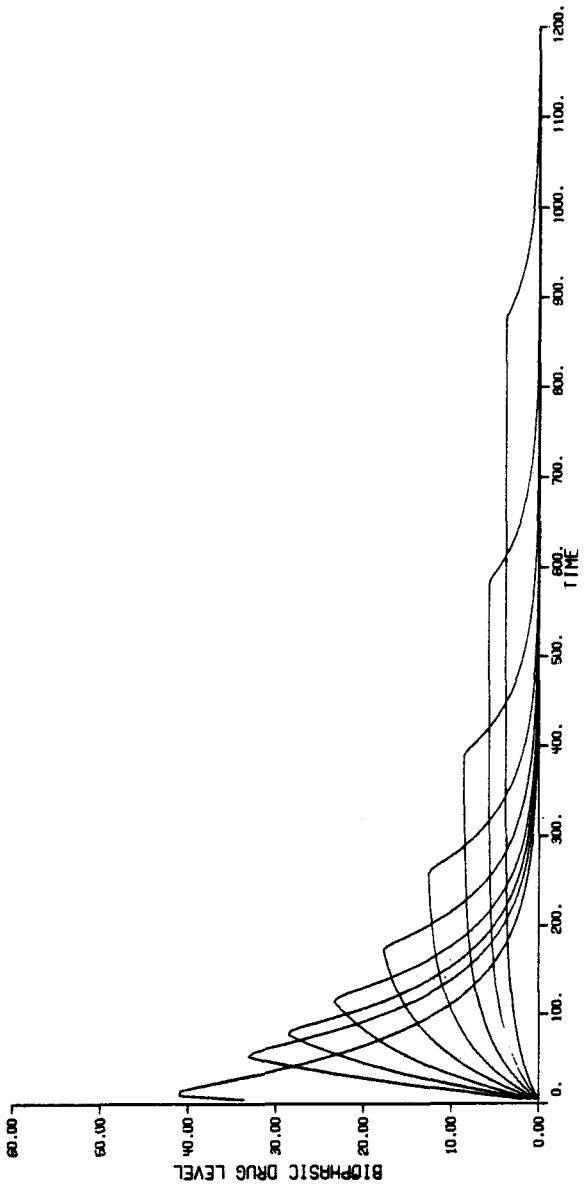


FIGURE 3

Biophasic drug level responses to unit pulse drug inputs of varying durations.

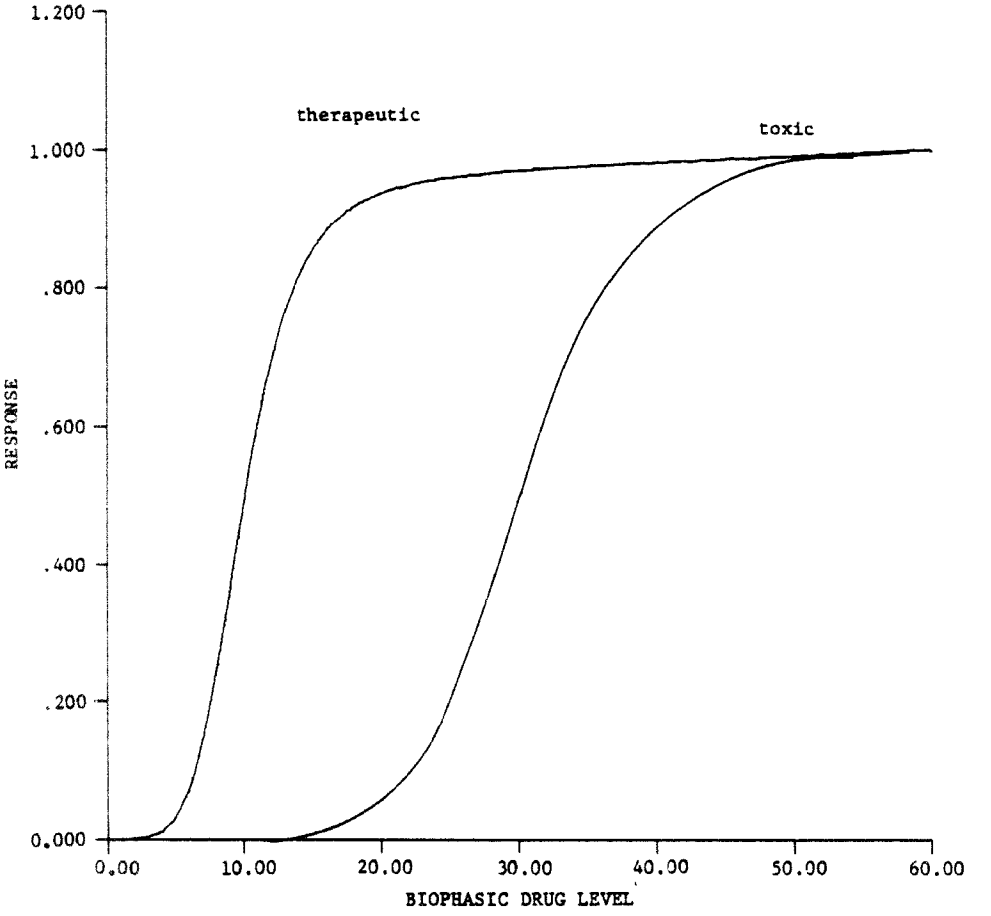


FIGURE 4

Dose–effect curves representing the transduction functions used to transform the biophasic drug levels in Figure 3 into their corresponding therapeutic and toxic response intensities.

therapeutic and toxic time response profiles corresponding to the different unit pulse inputs. The shape of these profiles obviously depends upon the shape of the dose–effect curves used to transform the biophasic drug levels which are common to both

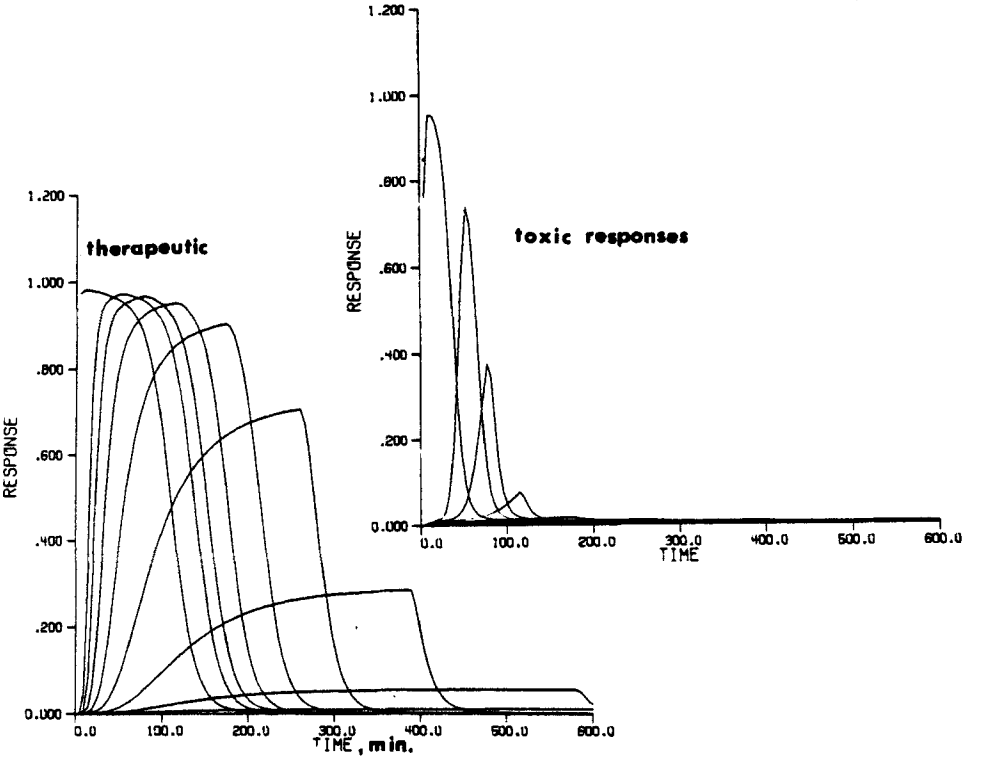


FIGURE 5

Therapeutic and toxic time response to unit pulse drug inputs of varying duration.

the therapeutic and toxic responses. It can be noted that there are considerable differences in the peak intensities and areas under the time-response curves even though the dose is the same in each case. When the infusion rate is slow enough, the responses will disappear almost entirely, therefore demonstrating the fact that although a dose of drug may be 100% bioavailable it can be entirely ineffective pharmacologically. Figure 6 shows a plot of the ratio of therapeutic to toxic peak response magnitudes and similar ratios for the areas under the therapeutic and toxic response

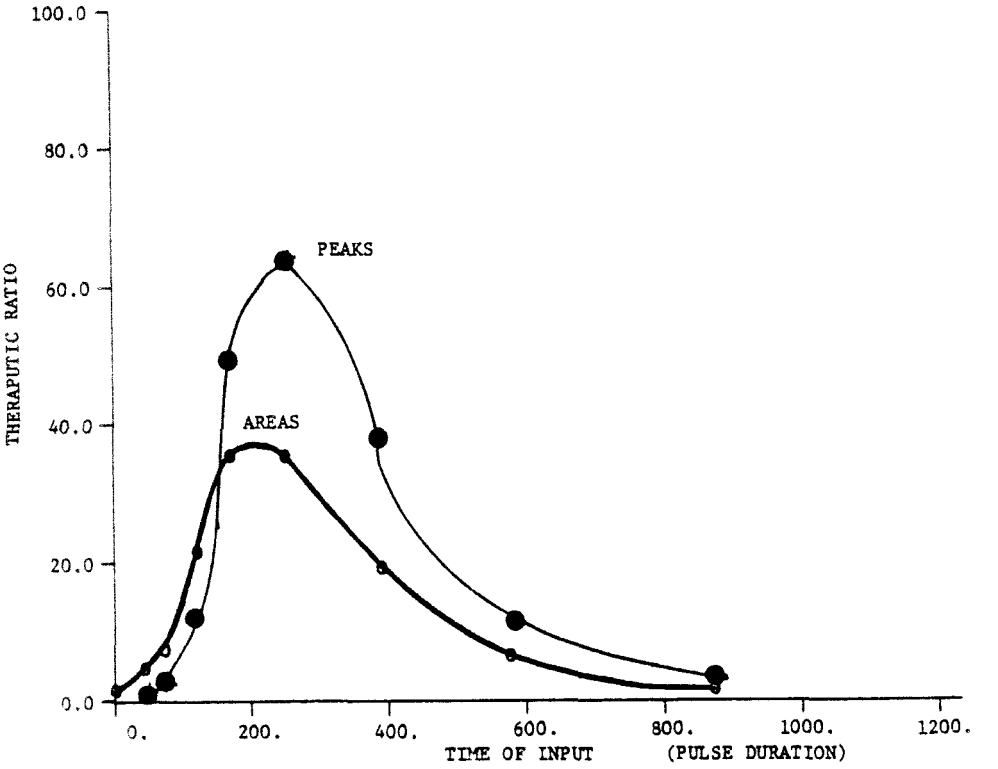


FIGURE 6

Dependency of ratios of peaks and areas under curves of therapeutic (- ● -) and (- ○ -) toxic time response intensities, for the same unit dose of drug, on the duration of time over which the drug is administered at a zero order rate of infusion.

curves corresponding to the duration of each unit pulse drug input (or the inverse of the rates of slow i.v. infusion). Using these results as criteria, an optimal zero order rate of infusion would be chosen to correspond to maximum values of these therapeutic ratios which are consistent with eliciting a desired, effective level of therapeutic activity.

TIME OPTIMAL DRUG INPUT OPTIMIZATION - SEPARATE BIOPHASES

A time optimal drug input discovery problem was also studied by computer simulation.[2,3] The problem was stated as: "Determine the cumulative drug input dynamics required to achieve an 80% of maximal therapeutic response, designated A, in minimal time without exceeding safely tolerable toxic response intensities of 50%, 40%, and 20% for responses B, C, and D, respectively." Although the system studied is hypothetical, it is realistic in that it is based on observed pharmacokinetic behavior even though the responses were for three different rather than the same drug.[2] For any real drug, the desired level of therapeutic response and the proscribed levels of toxic effects would be selected by a team of clinicians, pharmacokineticists, pharmacologists, and toxicologists having knowledge and experience with the drug.

Figure 7 shows a block diagram for the system. The $g_i(s)$ blocks symbolize the transfer functions which relate the drug input rate, $\dot{A}(t)$ to the biophasic drug levels, Q_A, Q_B, Q_C, and Q_D which are in turn related to each pharmacological response, I_A, I_B, I_C, and I_D by the transduction function blocks for each response. The details of the calculations have been reported elsewhere.[2] Unlike the previous example, each response has its own biophase. This situation usually allows a greater margin of differential control over the responses relative to the situation where each response results from the presence of the drug in the same biophasic compartment. Figure 8 shows the cumulative drug input computed to be time optimal. The drug input profile is seen to consist of a zero order input of 0.1 mcg/ml for 5.56 min. followed by

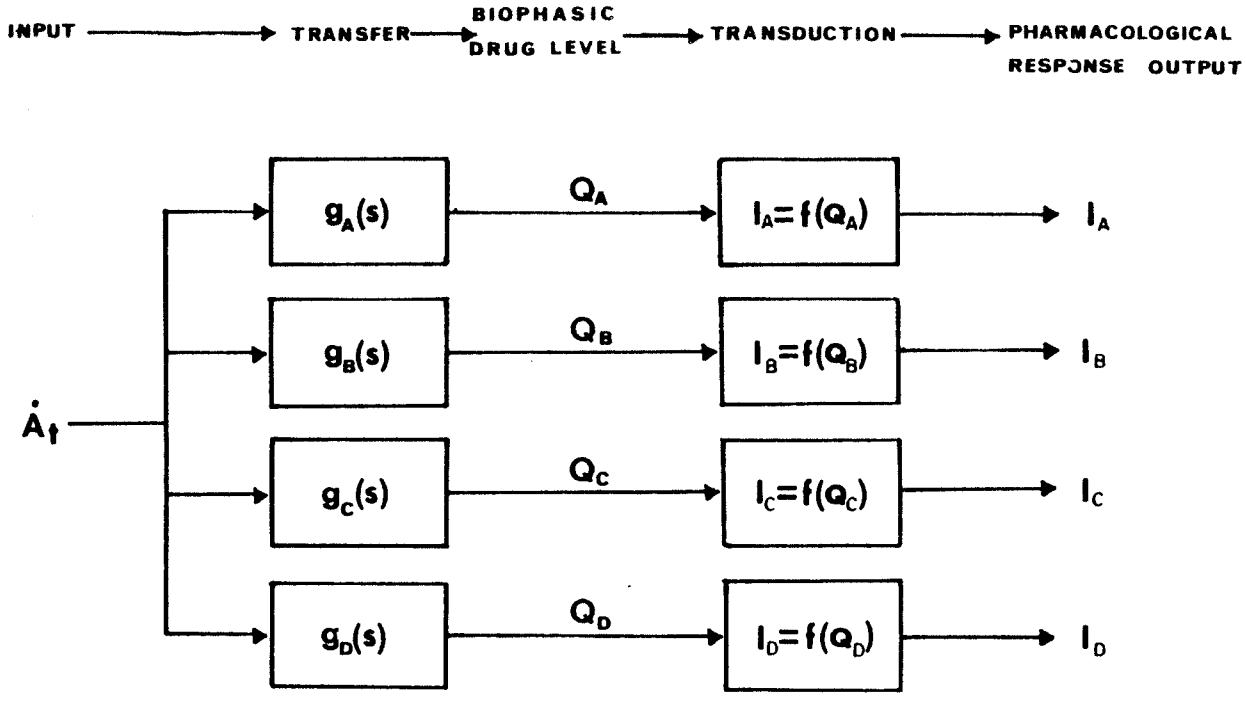


FIGURE 7

Block diagram of drug input-pharmacological response output relationships for four simultaneous responses to a single drug input.

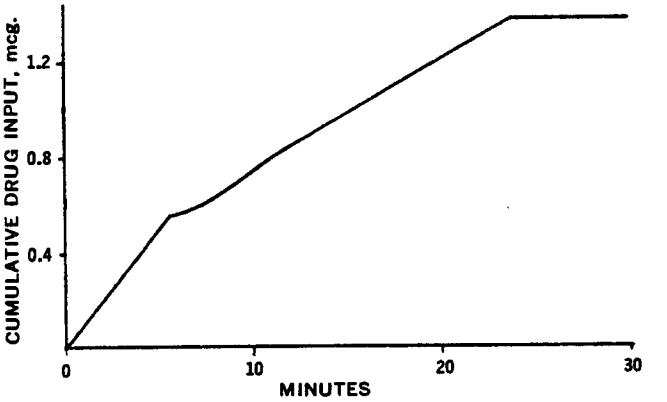


FIGURE 8

Time-optimal drug input profile.

an exponential decay into a second slower zero order infusion rate of 0.01464 mcg/min which maintains the therapeutic A response at 80%. As shown in Figure 9, the 80% A response was achieved in 5.56 minutes. If the infusion rate would merely have been set to the final value required to maintain it at a steady state at this 80% level it would have required 50 min. to reach within 1% of the 80% level. Therefore the desired level of response was achieved nine (9) times faster with the time optimal input. The maxima in the toxic responses can be noted to be well within the set limits of 50%, 40%, and 20%. The time coordinate for response D was contracted by a factor 1/4, i.e., 10 min. is actually 40 minutes. It can be seen that the toxic D response results from the presence of the drug in an apparent kinetic compartment into which it enters and is eliminated slowly. After chronic administration of the drug at uncontrolled drug inputs, the level of the drug can be expected to build up to induce a serious toxic effect

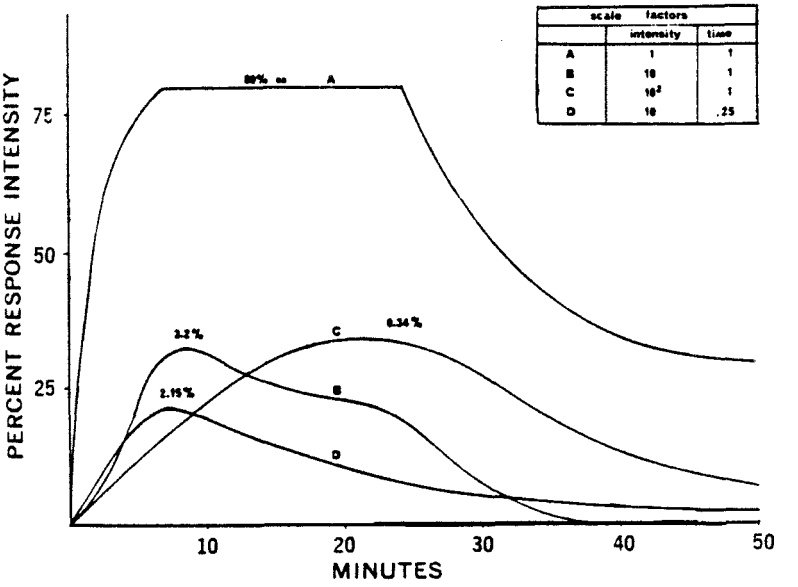


FIGURE 9

Time variation of therapeutic, A, and toxic, B, C, D, simultaneously elicited pharmacological response intensities corresponding to a time-optimal controlled drug input.

which would have a prolonged duration. On the other hand, if D was a sought therapeutic effect, it can be seen that a rapidly absorbed single dose of drug would be relatively very ineffective in producing a response. It can, therefore, occur that potentially useful drugs are discarded whereas appropriate adjustment to their dosing requirements would have allowed them to exhibit their activity. Such considerations again emphasize the importance of controlling drug inputs and thinking in terms of biophasic drug availability rather than systemic bioavailability. Theoretical drug inputs into the systemic circulation can always be precisely achieved in practice by a programmed intravenous infusion

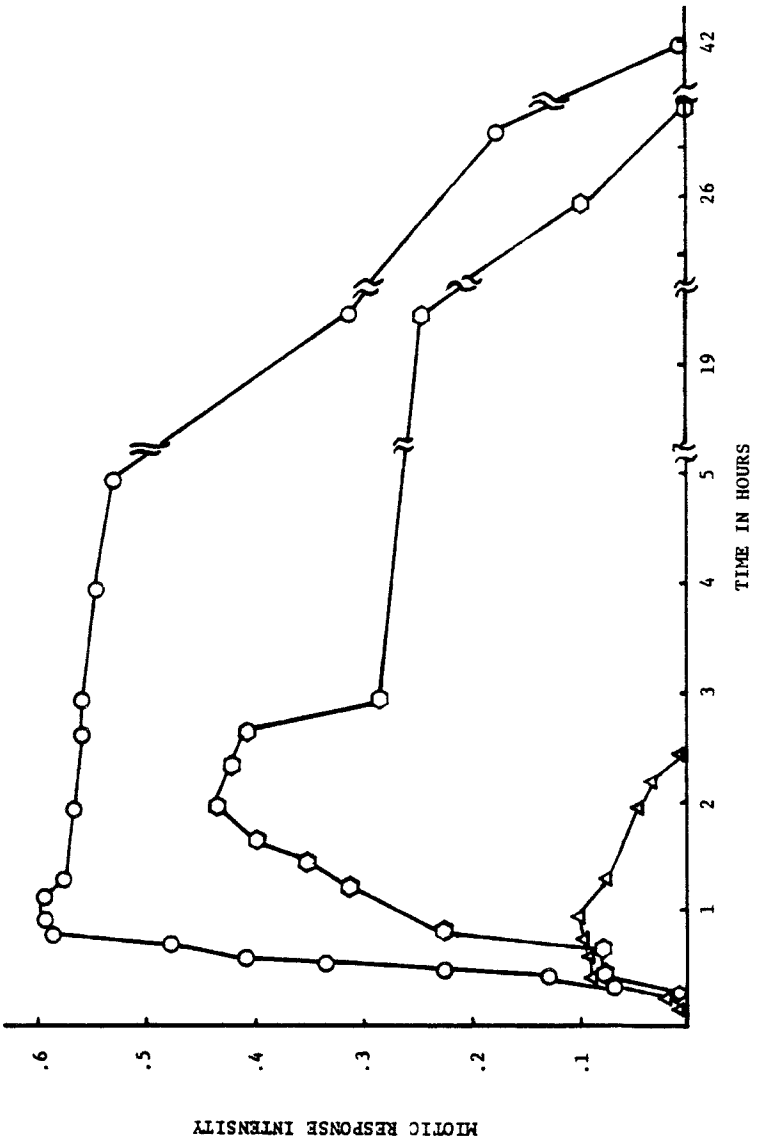
of the drug. Alternatively they could be less precisely accomplished by other routes of administration by formulating drug delivery systems which provide the drug to the systemic circulation at the required rates.

CONTROL OF DRUG INPUTS TO LOCAL SITES OF ACTION

When a drug is intended for local action at a target site at or near its site of administration as is the case with ophthalmic drugs, topical products applied to the skin and mucous membranes, intrauterine and vaginal implants, and aerosols inhaled into the lungs, for example, it is very rarely practical to even define the location and directly sample from the site(s) of the drug's action by direct assay methods. The presence of the drug in the systemic circulation merely indicates a toxic dose or a poorly designed drug delivery (dump) system. The use of pharmacological data, however, allows relationships between drug inputs and local drug actions to be established and the influence of the design and/or formulation of drug delivery systems on a drug's local therapeutic utility to be studied.

When the drug delivery is intended for local action by providing an input of drug to a local target site, direct infusion into a biophase is seldom if ever practical or even possible. Optimally sought drug inputs must therefore almost always be accomplished through the design or formulation of drug dosage forms. That such control can be achieved for ophthalmic systems is demonstrated by the experimental results shown in Figures 10 and 11, observed in the authors' laboratory.

The lower curve in Figure 10 represents the miotic response to an ophthalmic dose of 0.03% aqueous solution of echothiophate



iodide which is an antiglaucoma drug. The middle curve reflects the strong influence of the inclusion of a small concentration of a non-toxic polymeric adjuvant. The upper curve shows the even more pronounced increase in effect resulting from the administration of a much smaller dose of the drug using a controlled corneal loading drug delivery device developed in the authors' laboratory. The duration of effect is seen to be increased from approximately 2-1/2 hours for the solution alone to 42 hours even though the entirely innocuous device is removed from the eye within just a very few minutes after it is inserted.

Figure 11 shows similar results for the antiglaucoma drug carbachol. It in fact appears that similar results can be achieved for most ophthalmic drugs using the authors' drug delivery device or appropriate chemical adjuvants. It is important that in each case the increased local activity in the eye was definitely not accompanied by a concomitant increase in systemic side effects to the drug. Such adverse effects occur if the doses or concentration of the drugs, given in the form of eye drops, is merely raised to increase their local effects.

FIGURE 10

Time course of miotic response intensity following instillation of 0.1 ml. of 0.03% echothiophate iodide solution (-△-) and a 0.03% Phospholine Iodide solution containing a polymeric adjuvant (-○-) into the conjuctival sac of a rabbit. The uppermost curve represents the miotic activity observed following the several minute application and removal of a 0.03% echothiophate iodide solution treated "Controlled Corneal Loading Drug Delivery System," to the eye. No systemic effects, as gauged by measuring the miotic response to the other drug untreated control eye were observed in any of the treatments. No toxic effects in the treated eyees were noted. Each point is the average of a minimum of three determinations on different rabbits.

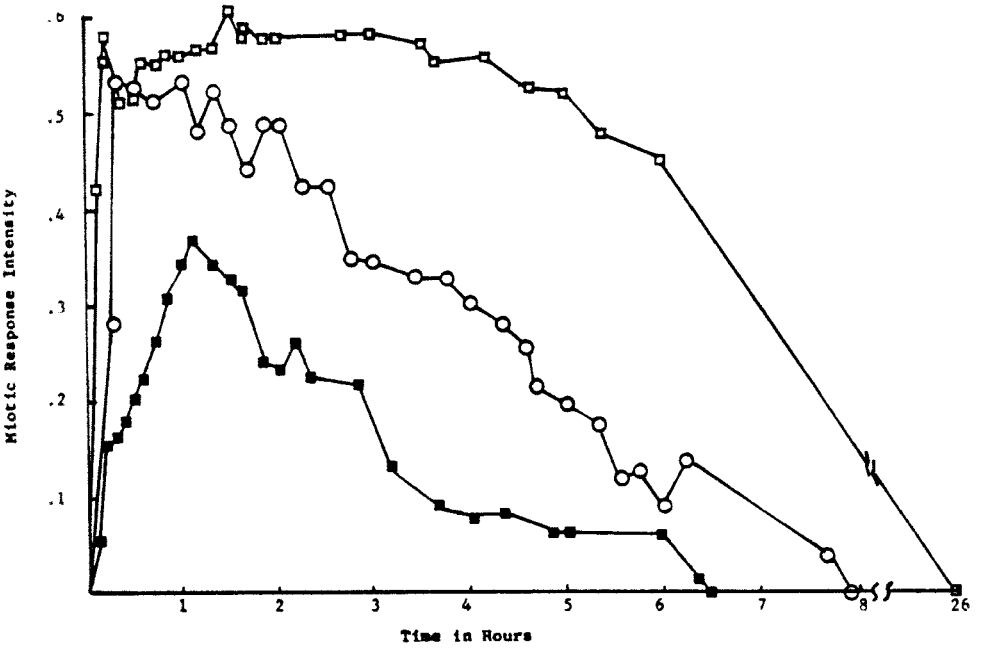


FIGURE 11

Time course of miotic response intensity following instillation of 0.1 ml. of 0.25% carbachol solution (- ■ -) and a 0.25% carbachol solution containing a polymeric adjuvant (- ○ -) into the conjuctival sac of a rabbit. The uppermost curve represents the miotic activity observed following the several minute application and removal of a 0.25% carbachol solution treated "Controlled Corneal Loading Drug Delivery System," to the eye. No systemic effects, as gauged by measuring the miotic response in the other, drug untreated control eye were observed in any of the treatments. No toxic effects in the treated eyes were noted. Each point is the average of a minimum of three determinations on different rabbits.

Figure 12 presents a block diagram representation of the ophthalmic drug transport system;[3] the symbols are similar to those previously defined. When a drug is administered to the eye a fraction of the dose is absorbed transcorneally, by route A, directly to its sites of action in the eye. This is shown in the right hand path in the diagram. It is also simultaneously

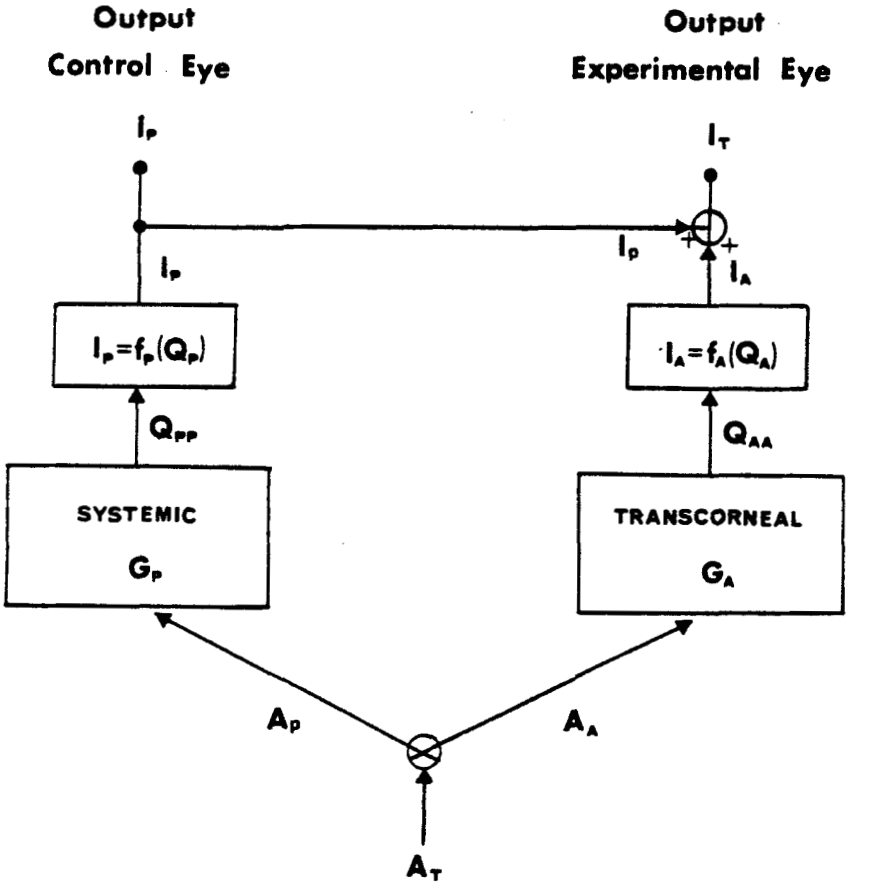


FIGURE 12

Block diagram for ophthalmic dosing drug input-miotic response output relationship; A_T is the total input; A_p and A_A are the amounts of drug absorbed systemically and transcorneally, respectively; G_p and G_A are unit step response functions, Q_{pp} and Q_{AA} are biophasic drug levels deriving from systematically and transcorneally absorbed drug, respectively; the transduction of biophasic drug levels into miotic response is represented by $I_p = f_p(Q_p)$ and $I_A = f_A(Q_A)$ where the functions are defined by intravenous and intra-aqueous dose-effect curves, respectively; I_p and I_T represent the miotic response intensity observed in the control eye (no drug) and the experimental eye into which the ophthalmic dose is administered.

absorbed systemically by route P through the schlera and by volume loss down the lacrimal nasal drainage duct; this is accounted for in the left hand path in the diagram. If the drug is administered to only one eye, the effect seen in the treated eye will be the result of the drug's reaching its site(s) of action by both routes. The untreated control eye will show only the effects of the systemically absorbed drug. The transfer (G_A and G_P) and transduction functions ($I_A = f_A(Q_A)$, $I_P = f_P(Q_P)$) for the systemic and transcorneal routes are obtained from the results of intravenous and intraaqueous dosing, respectively.

Figure 13 shows computer constructed plots of the cumulative amounts of carbachol absorbed following the administration of a 0.25% solution into the eye. The lowermost curve is the drug input resulting from systemic absorption. The middle curve represents the time course of the amounts of drug absorbed transcorneally and the upper curve represents the total absorption. Similar results obtained with the use of adjuvants or drug delivery devices are useful for the evaluation of their bioavailability performance and the elucidation of the mechnaisms of their effects. Such information is in turn valuable for the development of biophysical models which may allow a predictive capability for the control of local and systemic effects through formulation or design of the drug product to be attained.

OPTIMALLY PREDICTIVE IN-VITRO DRUG BIOAVAILABILITY TESTING

A computed theoretically optimal systemic drug input can always be achieved in practice by programmed i.v. infusion. However, in developing oral drug products to provide such optimal inputs, it is seldom that a formulator can a priori predict the composi-

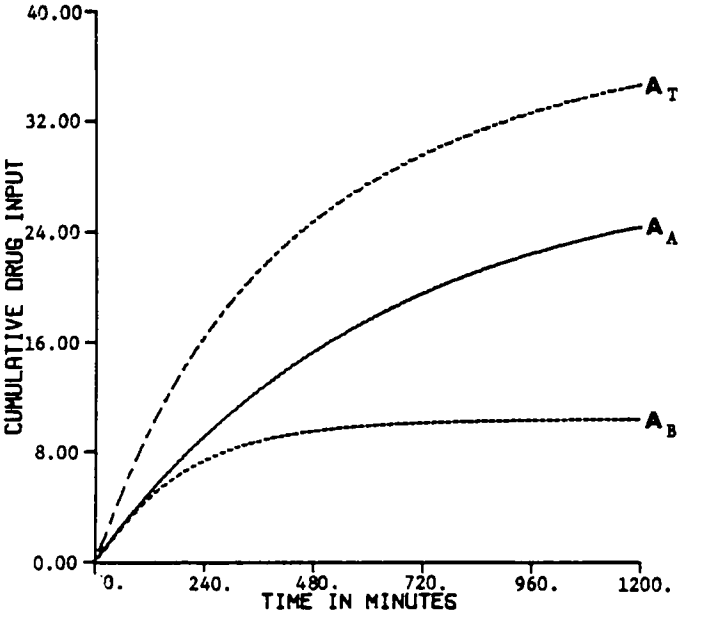


FIGURE 13

Computer-constructed plots of the cumulative amounts of carbachol absorbed transcornealy, A_A, systemically, A_B, and totals, A_T, following ophthalmic dosing of rabbits with 0.02 ml. of a 0.25 per cent w/v solution of carbachol.

tion and manufacturing conditions which will provide the oral dosage form with the sought after in-vivo drug release dynamics. The extensive trial and error screening of different formulations by human testing which would be required is generally impractical to perform. Therefore, what in effect is needed is a rapid in-vitro test which would predict the bioavailability behavior of experimental drug product formulations. Work in the authors' laboratory has been directed to this goal. Figure 14 presents a schematic diagram of the flow-thru drug release testing apparatus which was developed.[9] The conditions of the test are varied by changing

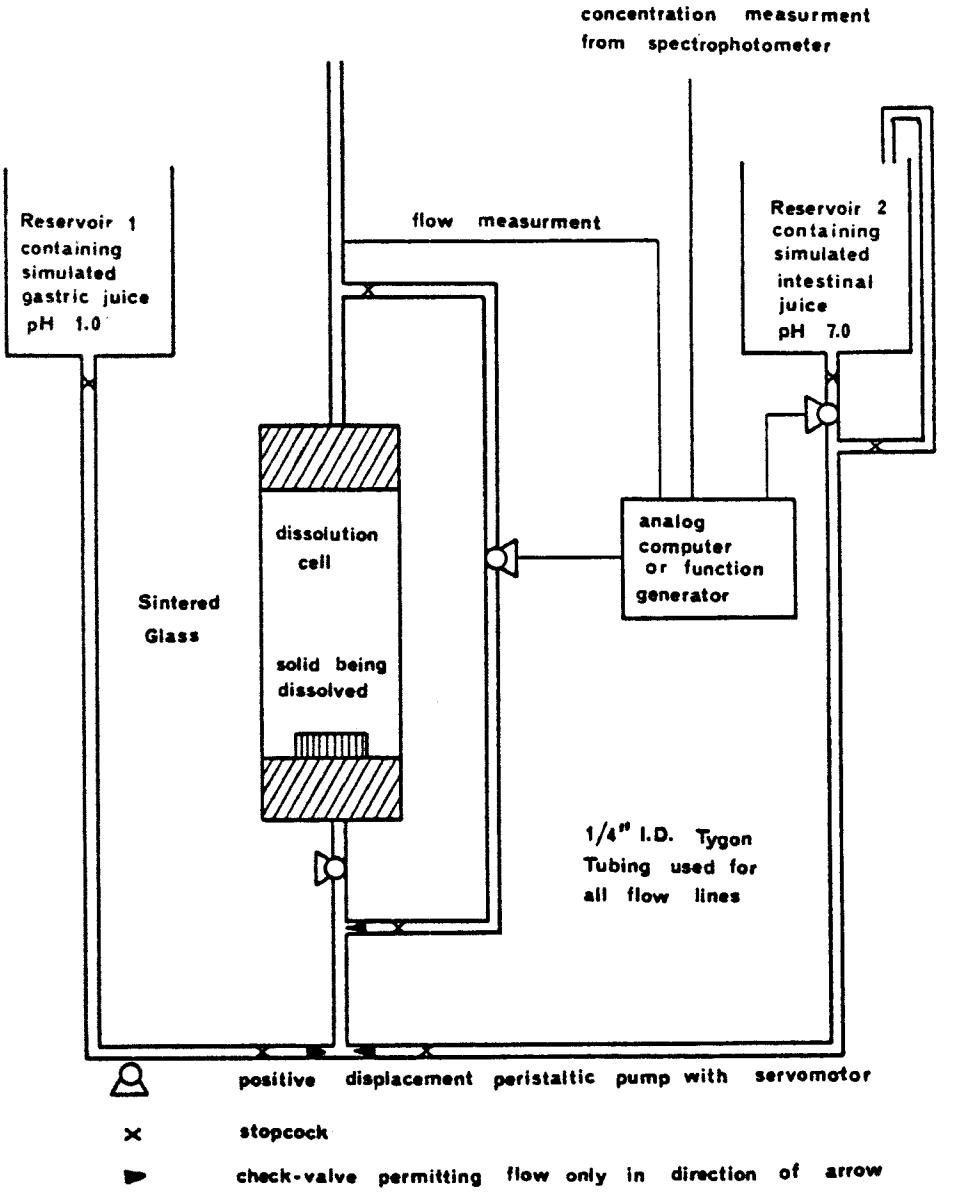


FIGURE 14

Schematic diagram of flow apparatus for optimized in-vitro drug bioavailability testing.

1) the total flow rate through the cell, 2) the composition of the media, and 3) the fraction of the flow which is recycled back through the cell. An analog computer is programmed and used to control the recycle flow rates and medium composition in an optimal manner. Figure 15 presents a block diagram description of the first, calibration stage of operation of the apparatus when it is in a closed loop, feedback controlled configuration. In this mode the apparatus is operated to simulate in-vivo bioavailability inputs previously determined for several reference dosage forms which were chosen and prepared to exhibit a broad range of differing in-vivo bioavailability rates as confirmed by testing them in a panel of human subjects. The results of operating the apparatus in this closed loop simulative mode are used to determine the optimal total flow rate, recycle flow vs. time function, and dissolution media compositions which constitute optimal conditions

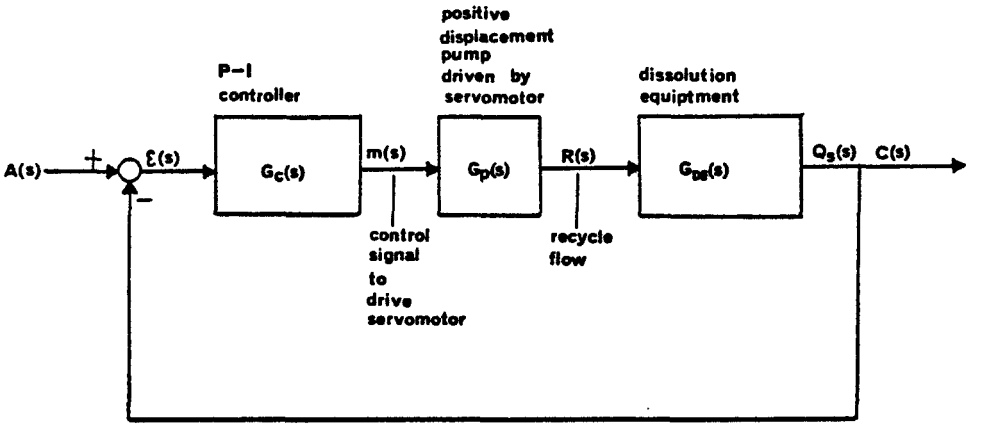
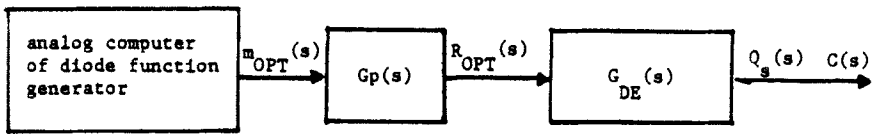


FIGURE 15

Block diagram for closed loop, feedback control of recycle flow, R(t), in the operation of the in-vitro drug release testing apparatus.

for the subsequent operation of the apparatus in the open loop, predictive mode block diagrammed in Figure 16. In other words, a minimum of human bioavailability data is used to calibrate the apparatus which is then used as a substitute for the panel of human subjects from which the data was obtained. The adequacy of the calibration of the apparatus at any stage of the experimentation leading to its ultimately optimal, predictive, performance is judged from the fidelity with which the in-vitro results reflect in-vivo bioavailability behavior; the fidelity of the performance is quantitatively judged from the evaluation of an objective function. A minimal value of the objective function corresponds to an optimal calibration of the apparatus to provide a minimal error (i.e., difference between in-vivo and in-vitro results) which is uniform and independent of time and the drug release properties of dosage forms. In other words, when the apparatus has been calibrated in this manner to reflect in-vivo bioavailability with a uniform time and dosage form independent error of known confidance limits for a minimum number of reference dosage forms of widely differing drug release properties, it can then be assumed that it will be predictive of the in-vivo bioavailability behavior of experimental dosage forms with properties falling near and within the range



open loop control generator

FIGURE 16

Block diagram for open loop programmed control of recycle flow, $R_{OPT}(t)$, during the operation of the in-vitro drug release apparatus.

of the dosage forms with which the apparatus was calibrated. Tetracycline is the first drug being studied by the authors. Although the present results are still incomplete, the predictive potential of the apparatus is demonstrated in Figure 17 which shows a comparison of the time course of average in-vivo bioavailability rates, determined from urinary excretion data obtained with 6 human subjects, with corresponding values predicted from in-vitro testing. When the operation of the apparatus is fully optimized, the systematic deviations seen between the in-vitro and in-vivo points should be eliminated. The operation of the apparatus was accelerated to provide the in-vitro results 5 to 10 times faster than in-vivo real time.

In addition to predicting in-vivo bioavailability rates, the in-vitro apparatus can also be programmed to predict blood on urine levels as well as pharmacological response vs. time profiles also at an accelerated rate relative to real time. As diagrammed in Figure 18, it can be seen that from a knowledge of the in-vivo system transfer and transduction functions, body fluid levels and/or pharmacological response profiles which are predicted by the apparatus can be interconverted to any other therapeutic or toxic effects elicited by the drug in-vivo.[2,3] In this manner it is theoretically possible to obtain an overall estimation of the in-vivo therapeutic utility of a drug dosage form from the results of predictive in-vitro bioavailability testing.[9-11].

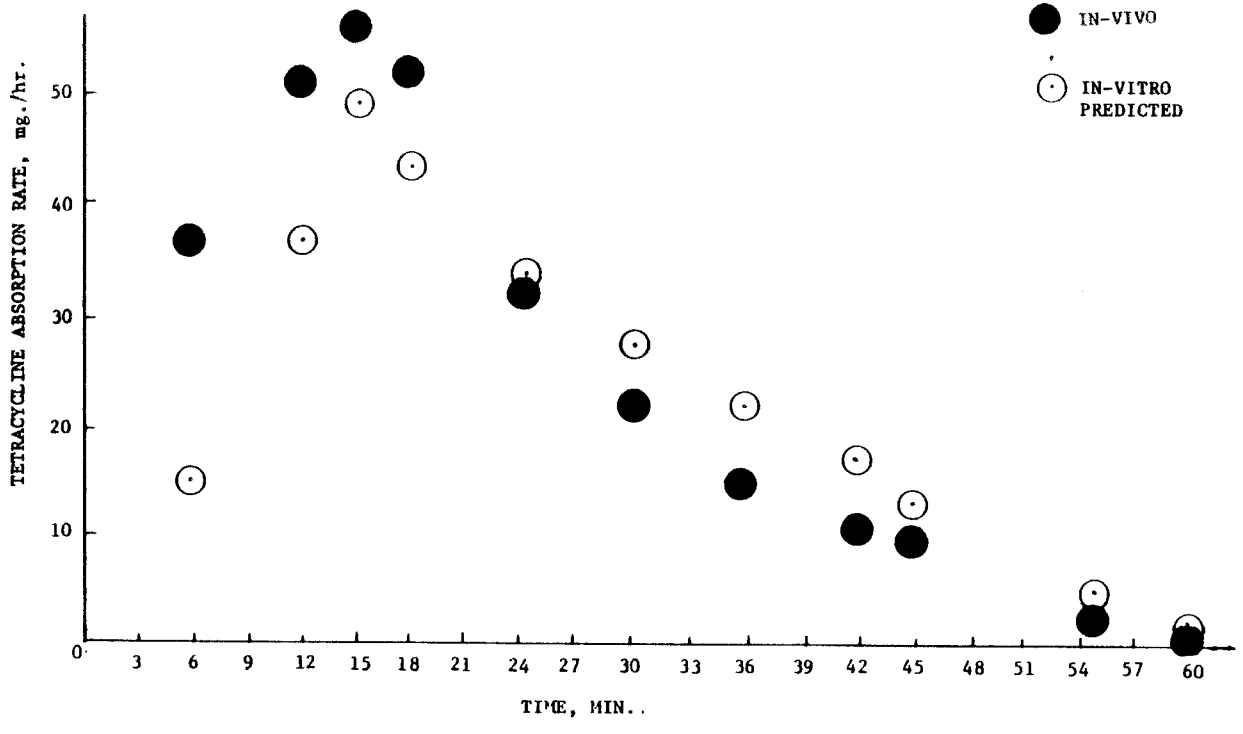


FIGURE 17

A comparison of experimentally known in-vivo with in-vitro predicted rate of absorption of tetracycline from oral tablets. The in-vivo absorption rates were computed using biexponential model from urinary excretion data obtained on six human subjects.

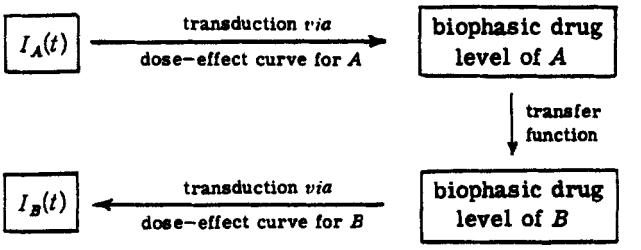


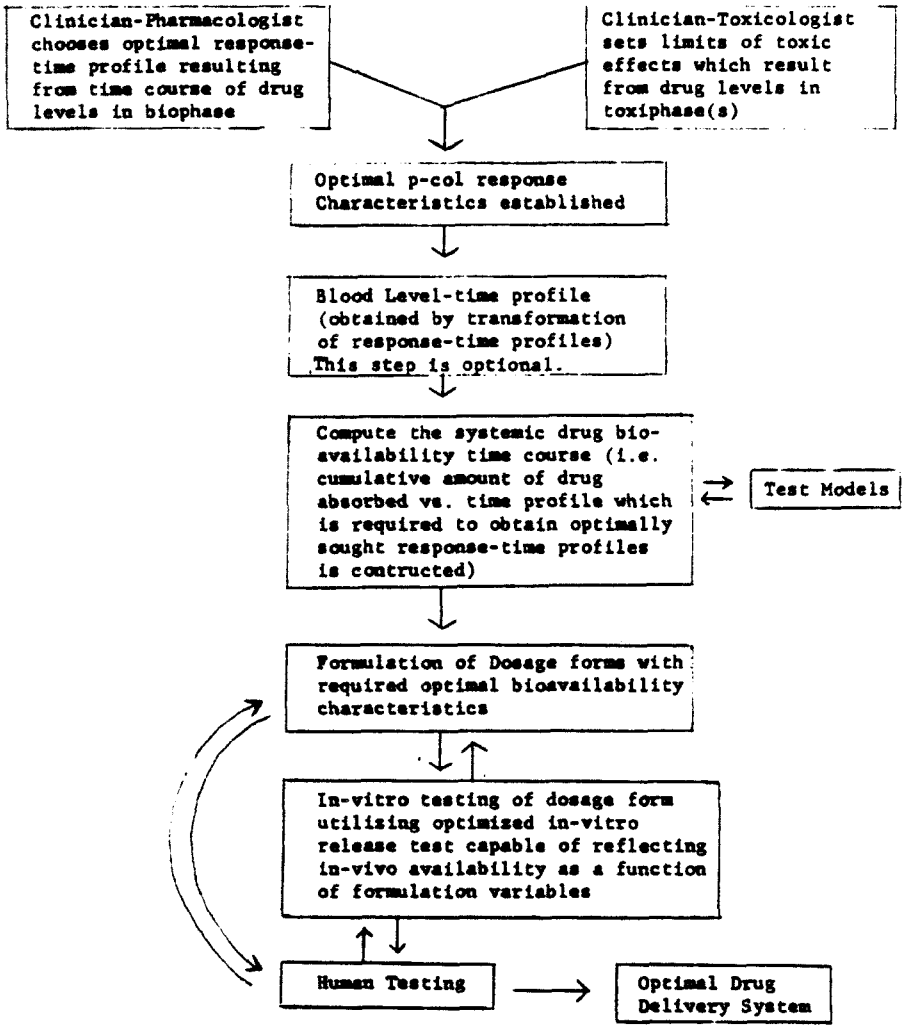
FIGURE 18

Scheme for the interconversion of measured (or predicted as, e.g., from the results of optimized in-vitro drug release testing) body fluid or pharmacological response vs. time profiles ($I_A(t)$) into any other response vs. time profiles ($I_B(t)$).

information concerning the drug's pharmacokinetic and pharmacological response behavior in humans and the difficulty and expense of experimentally obtaining it. However, there could conceivably be an economic advantage to developing optimal new drug products of still widely used important old drugs for which much information about their properties has accumulated in the literature. Drug delivery systems for these drugs could be designed to endow them with an optimal therapeutic utility. Even in this case, however, the outlined approach should best be considered rather idealized and visionary with its principal usefulness, for the present at least, being to provide goals and guidelines for the drug delivery system development methodology of the relatively near future.

SUMMARY AND CONCLUSIONS

A flow chart summarizing an idealized approach to drug product formulation is shown below. The execution of this approach may not always be practical for new drugs because of insufficient



Flow Chart Describing an Idealized Approach to Drug Product Formulation to Achieve Optimal Therapeutic Drug Response Behavior.

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