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PHYSIOLOGICAL AND PHARMACOKINETIC FACTORS AFFECTING PERFORMANCE OF SUSTAINED RELEASE DOSAGE FORMS

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ABSTRACT

Among many workers in the drug formulation area, there is the mistaken notion that an oral product which releases drug at an idealized rate in vivo will result in drug blood levels which are relatively constant over the duration of the dosing interval. Unfortunately, intra- and inter-subject variability in physiological processes virtually ensures that under clinical conditions this will not be the case. Some of the many factors involved include: (1) differing rates of absorption dependent upon the site of drug release in the gut; (2) gastrointestinal motility and transit times, particularly gastric emptying; (3) the presence of food in the gut; (4) gastrointestinal blood flow; (5) disease and drug induced effects on gut physiology; and (6) the nature of the microflora in the large intestine.

From a pharmacokinetic view, the blood levels of drugs which are more rapidly eliminated from the body will be more sensitive to

this gastrointestinal variability than those which are more slowly eliminated. Consequently, the level of success that may be expected from a sustained release product is inversely proportional to the therapeutic need for such a product.

INTRODUCTION

A sustained release (SR) dosage form may be defined as a preparation which releases drug in vivo at a considerably slower rate than is the case from an equivalent dose of a conventional dosage form. The objective of employing a SR product is to obtain a satisfactory drug response while at the same time reducing the frequency of dosage form administration. An example of a drug which is popularly used in a SR form is chlorpheniramine maleate; in conventional form the drug may be given as 4 mg every 4 hours, or in SR form, as 12 mg every 12 hours. From the theoretical view, a SR product need only produce a satisfactory response with a less frequent rate of administration. At the pragmatic level, however, there exists a welter of issues; what is a satisfactory response, how does this relate to drug release and absorption rate, and on what criteria are these judgements based? Although of great concern, these philosophic issues are beyond the scope of the present discussion. Rather, it is the intent of the author to review and discuss those physiological and pharmacokinetic factors contributing most to the in vivo conduct of SR preparations. Purposely omitted are discussions on formulation aspects, an extremely important and exciting area, but one in which the author lacks sufficient knowledge.

Among many workers in the field of SR product development and evaluation there is the mistaken notion that on multiple dosing an

oral product which releases drug at an idealized rate *in vitro* (or even *in vivo*) will result in drug blood levels which are relatively stable and constant over the duration of the dosing interval. Unfortunately, for many drugs (*vide infra*), intra- and inter-subject variability in pharmacokinetic and physiological processes virtually ensures that this will not be the case. Some factors to be discussed herein include: (1) variability in pharmacokinetic parameters such as apparent oral clearance and half-life; (2) differing rates of absorption dependent upon the site of drug release in the gut; (3) gastrointestinal transit times, particularly gastric emptying; (4) the presence of food in the gut; (5) gastrointestinal blood flow; and (6) the nature of the microflora in the large intestine. No doubt other important factors have been omitted or overlooked, e.g., gastrointestinal pH[1]. These omissions only serve to reinforce the argument that there are so many factors interacting in such a complex fashion as to ensure variability. To the biologist, this comes as no surprise. It is a basic tenet of Neo-Darwinian thinking that species' survival requires individual variability, and that this is brought about by gene recombinations. And to add to this already protean condition, we have the stress diseases, sometimes referred to as the diseases of civilization. High blood pressure, heart disease, arthritis, diabetes, and gastrointestinal ulcers all produce biochemical and physiological changes capable of affecting drug absorption. Moreover, the diseases we are treating with drugs may very well exert an influence on the drug absorption and disposition process. For example, cardiac failure may impair the absorption of quinidine, procainamide, hydrochlorthiazide and metolazone[2]. An then there are the drugs which influence gastrointestinal

function, and thus affect their own absorption, e.g., anticholinergics. In the final analysis, our biological system may only be functionally operational since the variations tend to nullify each other.

PHARMACOKINETIC FACTORS AFFECTING PERFORMANCE OF SUSTAINED RELEASE DOSAGE FORMS

Preliminary Considerations

The relationships and importance of various pharmacokinetic parameters have been discussed in several excellent papers[3-5] and will not be repeated here. In the design and evaluation of SR products, we generally utilize very simple pharmacokinetic principles, consistent with our goals. Consider a drug with a 2 hour half-life we wish to incorporate into a SR dosage form. The drug has a desired therapeutic blood level of 6 μg/ml and is eliminated by first-order kinetics from the liver and kidney. Metabolic clearance is 178 ml/min, and total clearance (metabolic + renal) is 219 ml/min. We wish to design a zero-order release product to be given orally at 8 hour intervals. Assuming complete availability to the portal vein and liver, how much drug do we put in the formulation? The appropriate equation is:

$$\text{DOSE} = \frac{(C_B)(CL)(\tau)}{(1 - \frac{CL_M}{Q})} \qquad \text{(Eq. 1)}$$

where: C_B is the desired blood level (6 μg/ml)
CL is total clearance (219 ml/min)
CLM is metabolic clearance (178 ml/min)
τ is the dosing interval (480 min)
Q is the hepatic blood flow (1780 ml/min)

The numerator is the rate of intravenous drug administration (C_B X CL) multiplied by the dosing interval. The denominator is the fraction of drug surviving the first pass through the liver, thus adjusting (increasing) the intravenous dose for oral administration. Solving the equation, one obtains an answer of 700 mg. Note that the value of half-life (2 hrs) never even entered the calculation. We shall see, however, that the half-life does affect the apparent performance of a particular product.

Assuming now that we do have an idealized zero-order rate of release and drug absorption into the portal vein, a constant blood level of drug will be obtained provided apparent oral clearance remains constant from dose to dose and day to day, in accordance with Eq. 2.

$$\bar{C} = \frac{D}{\tau CL_O} = \frac{FD}{\tau CL} \qquad \text{(Eq. 2)}$$

where: $\bar{C}$ is the average steady state blood concentration and is constant with zero-order absorption
D is the dose
F is the bioavailability
τ is the dosing interval
CL is the total clearance
CL_O is the apparent oral clearance, (CL/F)

Unfortunately the latter assumption assuming constancy of CL_O does not appear to be true for drugs which are appreciably metabolized and have significant liver first-pass effects.[6,7] Day to day variability occurs due to changes in the external environment and/or internal physiologic parameters.

Even if intrasubject variability were not a consideration, we still have to contend with significant intersubject variability in

CL_O. Although a discussion of this topic is beyond the scope of this present work, suffice it to say that intersubject variability in CL_O is significant; some causes are genetic factors, sex, age, nutritional state, exposure to enzyme inducers, diet, state of health, influence of drugs, etc. Thus, if we administer a SR dosage form with perfect zero-order release and absorption characteristics group of subjects, variations in $\overline{C}$ would be observed consistent with variations in CL_O (for the purpose of this discussion, we are assuming homogeneity in plasma protein binding, thus simplifying our analysis.)

Influence of Pharmacokinetic Parameters on In Vivo Performance

Although generally not appreciated by researchers in the field, the pharmacokinetic behavior of a drug can have a profound effect on the suitability of a particular SR formulation. In general, the shorter the half-life of the drug, the more critical the release and absorption characteristics of the SR dosage form become. Conversely, as the half-life increases, formulation factors become less important. This is illustrated in Fig. 1, which shows a theoretical plasma concentration-time curve for a drug following single dose oral administration. Below are illustrated three rate of absorption curves; which rate of absorption curve matches the plasma concentration-time curve?

Obviously the formulations improve when going from top to bottom. The answer is that all three rate of absorption curves are consistent with the plasma concentration-time curve, but only with the half-lives so indicated. That is, if the drug had a $t_{1/2}$ of 9 hours, the top curve would describe the rate of absorption. If the drug had a $t_{1/2}$ of 3 hours, the bottom curve would describe the

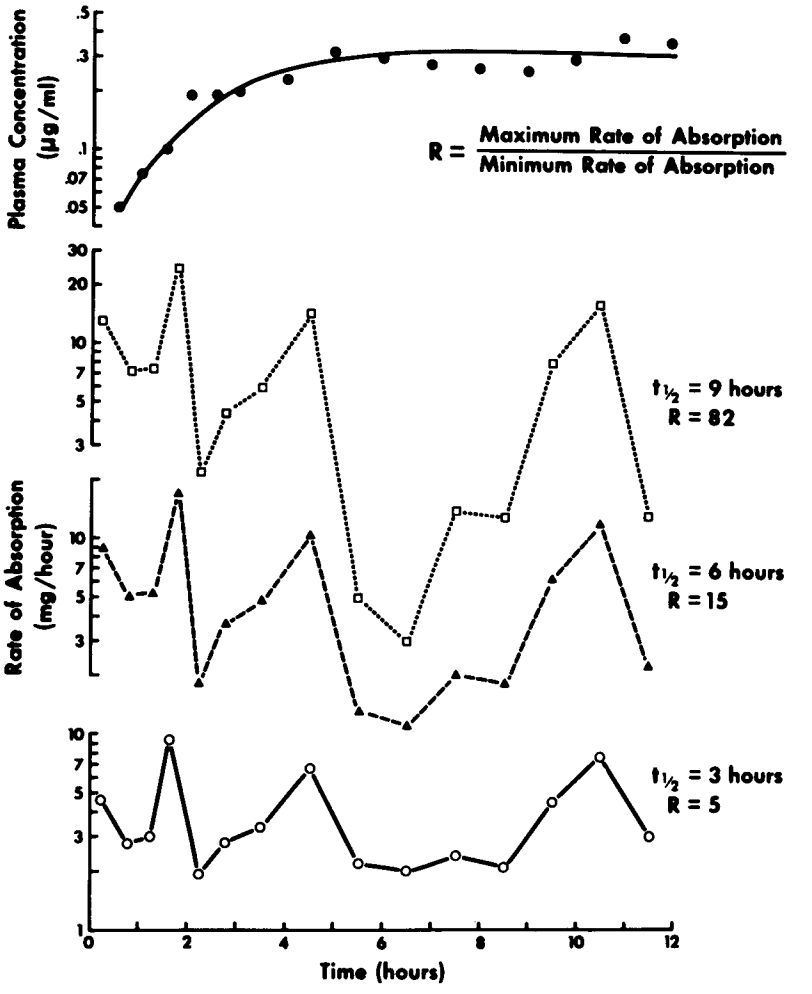

Figure 1

Rates of absorption from theoretical sustained release formulations, where the drug is assumed to have 3 sets of pharmacokinetic parameters: (1) $t_{1/2}$ = 9 hrs, Vd = 129,870 ml, CL = 10,000 ml/hr; (2) $t_{1/2}$ = 6 hrs, Vd = 86,207 ml, CL = 10,000 ml/hr; and (3) $t_{1/2}$ = 3 hrs, Vd = 43,290 ml, CL = 10,000 ml/hr. Note that CL is constant. Rate of absorption determined by the method of Wagner and Nelson.[8]

rate of absorption. Thus, it is apparent, that as half-life increases, the formulation can worsen without affecting overall performance, i.e., the plasma concentration-time curve. Intuitively, one can readily appreciate that with drugs of longer half-life, sharp dips in the plasma concentration-time curve would not occur even if absorption completely shut off over periods of time. This latter behavior may in fact be the salvation of several poorly formulated SR products presently on the market.

Looking from another perspective, the shorter the half-life, the more sensitive is the plasma concentration-time curve to the rate of absorption, and consequently, the more important it becomes to have a good formulation. And because drugs with short half-lives are the ones most in need of good formulations, we may summarize the overall situation in the following paradigm: THE DEGREE OF SUCCESS ONE MAY EXPECT CLINICALLY FROM A SUSTAINED RELEASE PRODUCT IS INVERSELY PROPORTIONAL TO THE NEED FOR THE PRODUCT. That is, it is easier to make a satisfactorily performing SR product for a drug with an 8 hour half-life than for one with a 2 hour half-life. Or, stating it in pharmacokinetic terms, the longer the half-life of the drug, the less sensitive is the plasma concentration-time curve to the rate of absorption. In a sense, the longer the $t_{1/2}$ the more buffered the plasma curve is from significant fluctuations in the rate of absorption. Conversely, the shorter the half-life, the more sensitive is the plasma concentration-time curve to the rate of absorption. In fact, for drugs with half-lives in the vicinity of 3 hours, or less, the plasma concentration-time curves generally parallel the rate of absorption curves, with a slight shift of the time axis. Figures 2 and 3 illustrate the strong dependence of the shapes of the plasma concentration-time curves on rates of absorption.

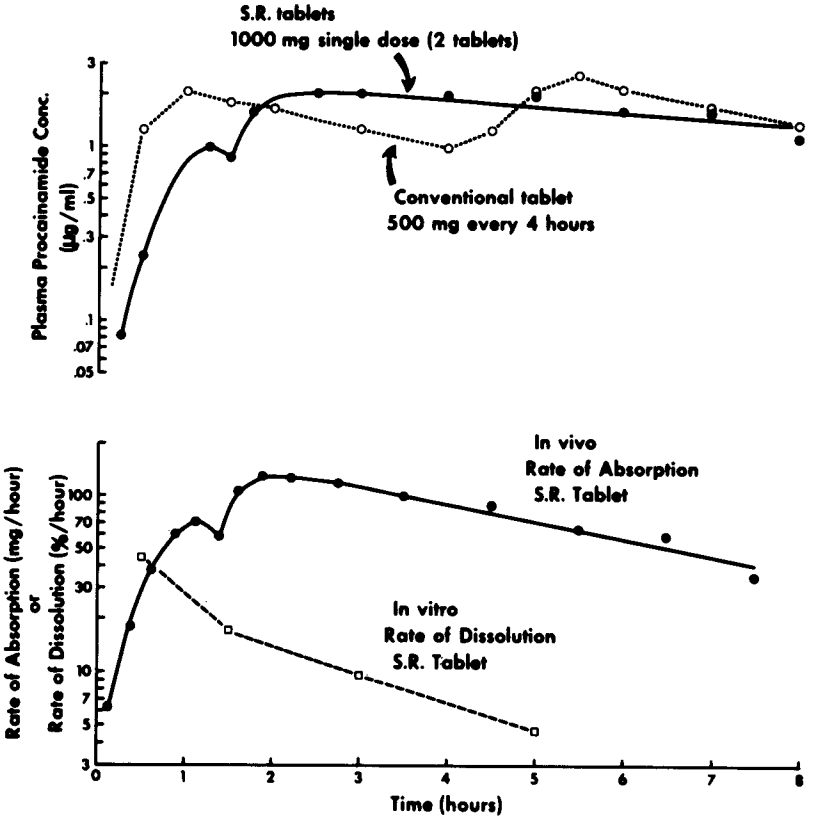

Figure 2

Averaged plasma concentration-time data, rates of absorption and rates of dissolution from an experimental procainamide SR formulation. Rates of absorption[9,10] were determined from parameters in Table I of Graffner, Johnsson, and Sjögren.[11] Procainamide data was obtained from Fig. 4 of this latter reference.

Figure 2 illustrates averaged plasma concentration-time data from a SR procainamide formulation as well as from conventional tablets. It may be noted that the rate of absorption from the SR product determines the shape of the plasma curve ($t_{1/2}$ of procainamide is 2.72 hours). Additionally, the rate of absorption curve could not have been predicted a priori from the rate of dissolution curve,

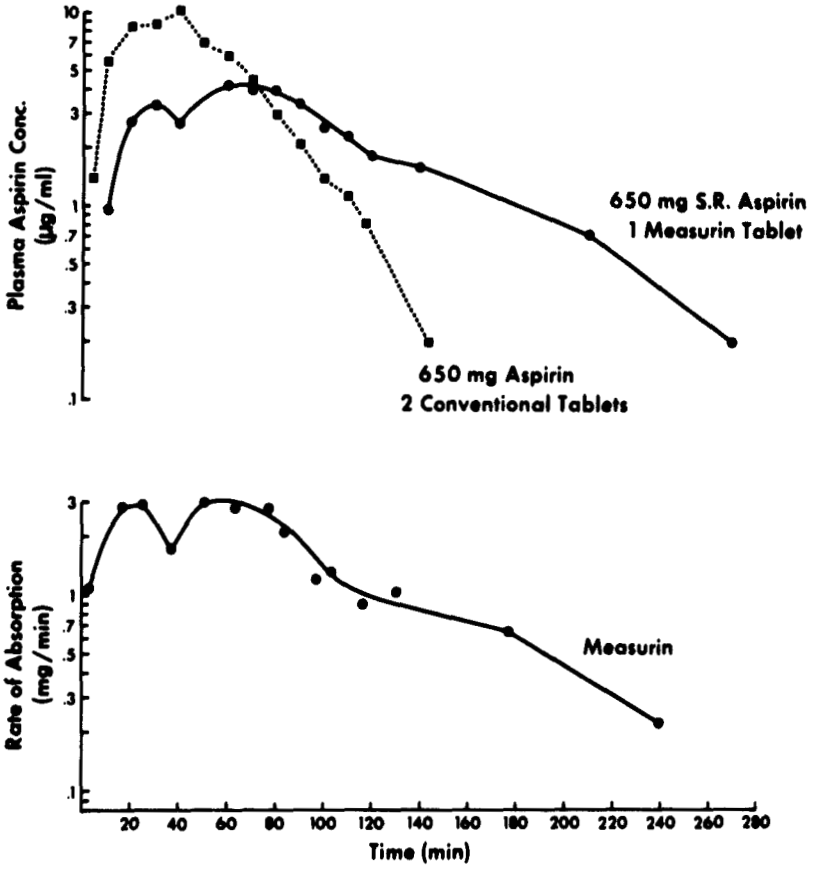

Figure 3

Plasma aspirin concentration-time curve and rates of absorption from a marketed SR aspirin product (Measurin) administered to a representative subject. Rate of absorption determined as in Fig. 3 with data from Figs. 7-8 from Riegelman.[12] Intravenous aspirin parameters for rate of absorption calculation obtained from Tables I-II (subject D) of Rowland and Riegelman.[13]

without additional experiments. It is also important to note that the plasma data were averaged from 4 subjects, and that had the data from the individual subjects been observed, considerably more scatter would be expected. Figure 3 illustrates plasma concentration-

time data and rate of absorption data following SR aspirin (Measurin) administration to a representative subject ($t_{1/2}$ of aspirin = 13.9 min). Once again it is obvious that the rate of absorption significantly determines the shape of the plasma curve. (For a general discussion on SR aspirin the reader is referred to Hollister.)[14] Also of interest is the fact that neither procainamide nor aspirin is absorbed at a zero-order rate.

Suitability of a Drug Candidate for Sustained-Release Formulation

In general, those drugs with short half-lives which are rapidly absorbed from conventional dosage forms are good candidates for SR formulation. Here we are assuming that pharmacologic activity is related to intact drug in blood, and that metabolites are inactive. Figure 4 illustrates plasma procainamide curves ($t_{1/2} \simeq 3.5$ hr) following multiple dose administration at 3 and 6 hour intervals. Taking the therapeutic window at 4-8 mg/liter,[16] it is apparent that a dosing interval of 3 hours is considerably more desirable, if not mandatory. Since this 3 hour dosing interval represents a considerable inconvenience to the patient, this drug is a good candidate for SR formulation. It should be pointed out, however, that the situation is a bit more complicated, since there is an active metabolite, acetylprocainamide[17] which is formed as a result of polymorphic procainamide acetylation.[18]

A good example of a drug for which a SR formulation is unnecessary is phenytoin (diphenylhydantoin). As illustrated in Fig. 5, dosing schedules of once daily vs. 3 times daily produced similar multiple dose plasma curves.[19] This results from both the slow absorption[20] and disposition of the drug;[21] the slow disposition is a consequence of saturable metabolism .

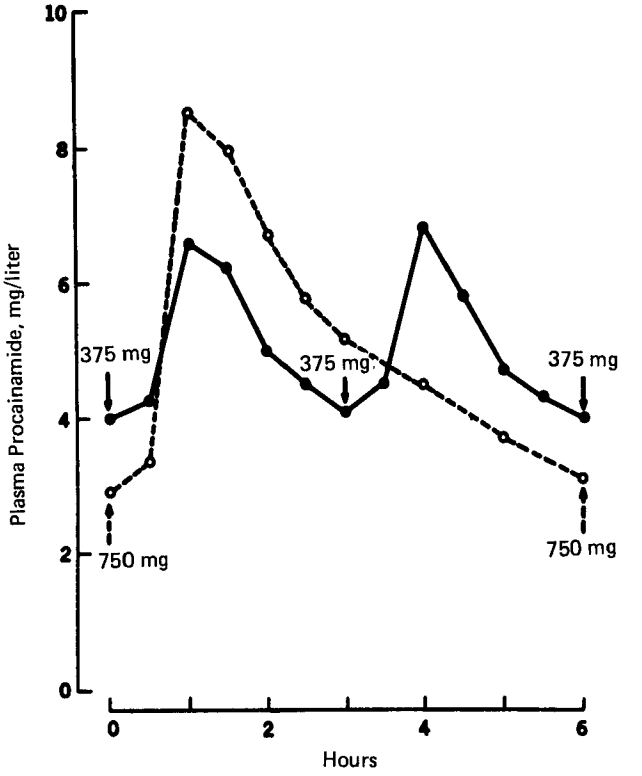

Figure 4

Steady-state plasma procainamide concentrations in a representative subject receiving 3 Gm/day at 3 and 6 hour intervals. Reproduced from Fig. 5 of Koch-Weser and Klein,[15] with permission of copyright owner (Copyright 1971, American Medical Association.)

In Vivo Evaluation of Sustained Release Products

Once a SR dosage form has undergone a satisfactory *in vitro* evaluation, it is generally tested *in vivo* using healthy subjects. Generally, these studies utilize young volunteers who are disease free. In one typical laboratory, these subjects are fasted overnight, brought into a laboratory, put to bed in the supine position, given I.V. fluids, and asked to swallow a pill with 240 ml tap

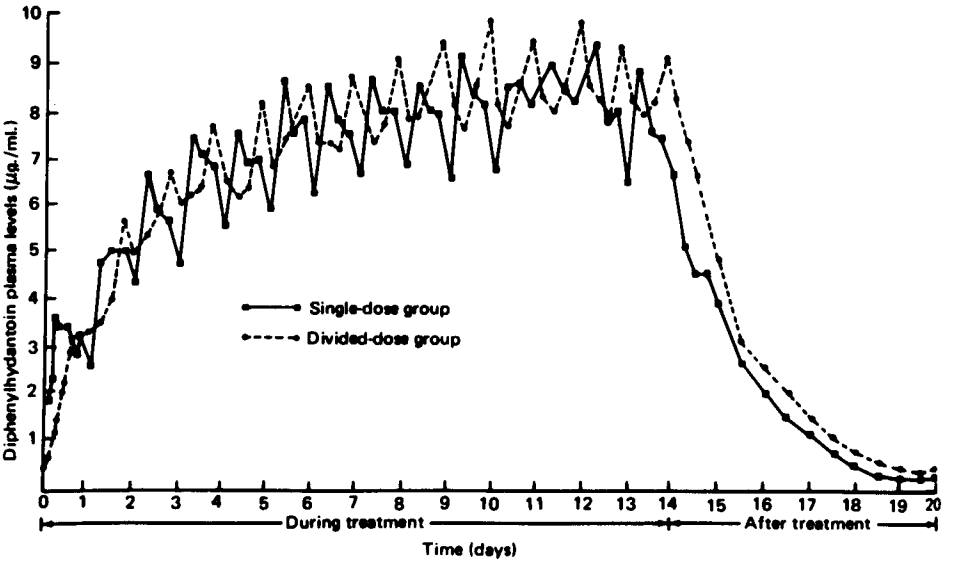

Figure 5

Mean plasma levels of phenytoin following three times daily administration (6 AM, Noon, 6 PM) vs. once daily administration. Reproduced from Fig. 1 of Buchanan and co-workers,[19] with permission of copyright owner.

water. When investigating the influence of food, the subjects receive a standardized meal. These can hardly be considered conditions representative of the situation in which the dosage form will be utilized. Consequently one may obtain data which shows considerably less intra- and intersubject variability than is observed under clinical conditions. Obviously the way to further evaluate the SR dosage form is to utilize actual patients who receive the drug under clinical conditions. Unfortunately this is not always done, and when it is, protocols tend to be faulty with respect to blood sampling, i.e., insufficient data points. Investigators should be aware of these potential shortcomings when making judgements on SR products.

PHYSIOLOGICAL FACTORS AFFECTING PERFORMANCE OF SUSTAINED RELEASE DOSAGE FORMS

Rate of Absorption at Different Sites of the Gastrointestinal Tract

As mentioned previously, there is a pervasive attitude that zero-order release produces zero-order absorption. While this may be the case for some specific drugs, there is no *a priori* reason to assume that this will be the general case. Zero-order absorption following zero-order release will only occur inasmuch as: (1) the gut behaves as a one-compartment model, i.e., a uniformly absorbing barrier, or (2) the rate of absorption from all absorbing surfaces along the tract is considerably more rapid than the rate of drug release from the dosage form, i.e., drug release rate limits drug absorption. With regard to the first point, it appears that the various segments of the gut do not afford equality of absorption rates for most drugs. Figure 6 illustrates serum tetracycline levels following administration directly into the lumen of various segments of the gastrointestinal tract (GIT) in the dog. Obviously the rate of absorption decreases from duodenum to ileum, stomach, and colon. In at least one regard, tetracycline is representative of most drugs - the duodenum has the greatest absorptive capacity. With regard to the second point previously made, considerably less information is available. However, for some drugs at least, release from the SR formulation probably rate limits drug absorption along most of the GIT.

Fluctuations in GI blood flow can conceivably affect rate of absorption. Figure 7 illustrates the influence of blood flow on the absorption of various substances from perfused jejunal loops of rat intestine.[23] In general, the absorption of very lipid soluble (e.g.,

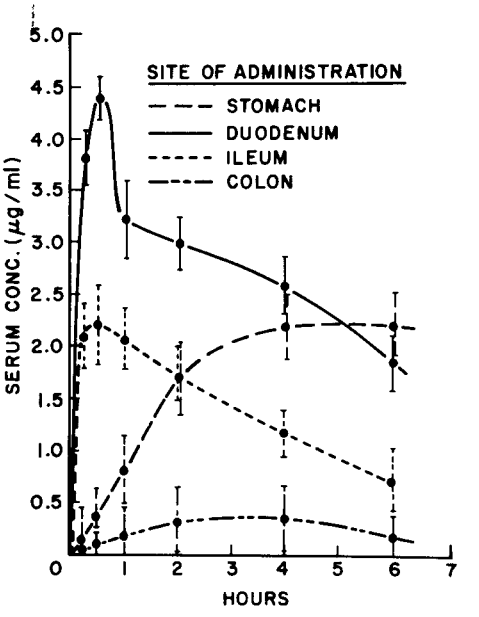

Figure 6

Tetracycline serum levels in dogs following direct introduction of the drug into various gastrointestinal sites. Reproduced from Fig. 1 of Pindell and co-workers,[22] with permission of copyright owner (The Williams & Wilkins Co., Baltimore).

aniline) or pore diffusible (e.g., tritiated water) substances is blood flow limited. Conversely, the absorption of substances with low permeability (e.g., sorbose) is blood flow independent.[2] Interestingly, in patients with acute myocardial infarction, the intestinal absorption of procainamide is generally delayed, and in some cases bioavailability may be significantly reduced.[2,15,16] This conceivably results in great measure from decreased mesenteric blood flow. Thus, the already abstruse relationship that exists *in vivo* when a drug is exposed to various segments of the GIT may be even further complicated.

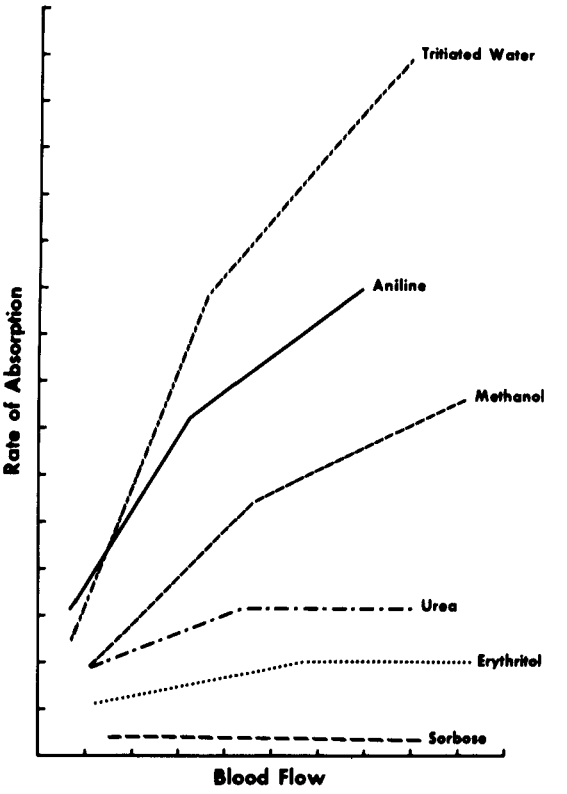

Figure 7

Dependence on intestinal blood flow of the rate of absorption of various substances from the rat jejunum. Redrawn from Fig. 4 of Winne.[23]

Gastric Emptying and Gastrointestinal Transit

That gastric emptying and GI transit can markedly affect drug absorption is well established.[1,24-27] Since most drugs are absorbed much more slowly from the stomach than from the small intestine, any factor which tends to alter gastric emptying would be expected to affect the rate of absorption. In fact, Prescott[24] has gone so far as to say that unless absorption is normally very slow, gastric

emptying is likely to be a rate limiting step in the absorption of drugs regardless of whether they are weak acids, weak bases or neutral compounds. Thus, for a given formulation (conventional or SR) absorption would be expected to proceed more readily when gastric emptying is enhanced. This is illustrated in Figs. 8-9 for alcohol

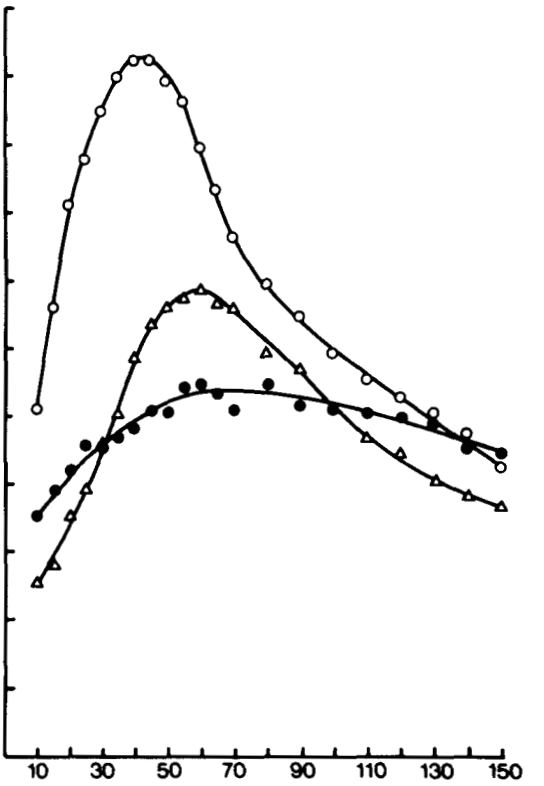

Figure 8

Blood levels of alcohol following oral administration to a representative subject showing control values (triangles) as well as those influenced by administration of metoclopramide (open circles) which enhances gastric emptying and propantheline (closed circles) which inhibits gastric emptying. Time axis in minutes. Reproduced from Finch, Kendall and Mitchard,[26] with permission of copyright owner.

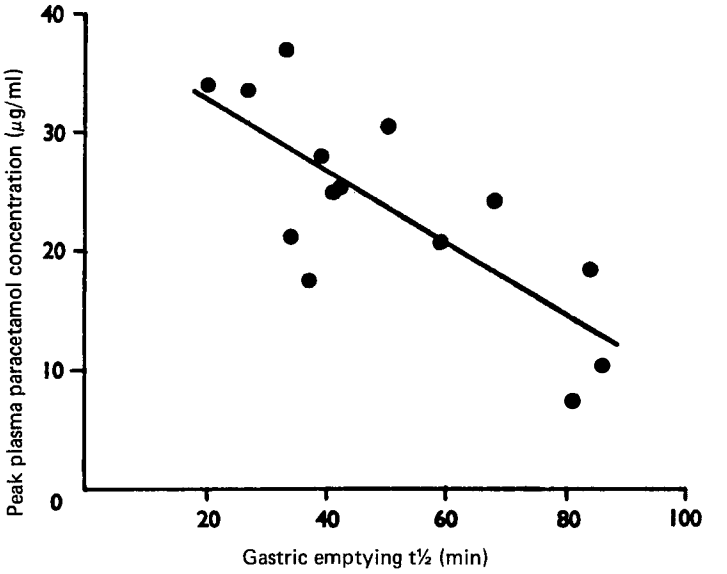

Figure 9

Relationship between gastric emptying half-time ($t_{1/2}$) and peak acetaminophen plasma concentrations. Reproduced from Heading and coworkers,[28] with permission of copyright owner.

and acetaminophen. In the case of alcohol, inhibition of gastric emptying by propantheline reduces blood alcohol levels. With regard to acetaminophen (paracetamol), enhancement of gastric emptying (lower half-times) produced higher peak acetaminophen levels (peak height is increased with more rapid absorption). Whereas neither of the two aforementioned studies utilized SR dosage forms, the illustrated principles would be applicable to SR products. This would be particularly true if premature "dumping" occurred in the stomach. Dumping refers to a SR product which releases too much of the dose in too short an interval of time.

Gastric emptying is not a parameter that can be controlled under normal clinical conditions. It may be affected by food, hormones,

posture, peritoneal irritation, severe pain, gastric ulcer, emotional state, autonomic activity, the volume, pH composition, viscosity and temperature of the contents, surface active agents, bile salts and many commonly used drugs including ethanol, anticholinergics, narcotic analgesics, ganglion blocking agents, antacids and metoclopramide.[24,27] Figure 10 illustrates the influence of food on the rate of absorption of acetaminophen administered as conventional tablets.[29] The retardation of absorption rate could be due to delayed gastric emptying, or it is conceivable that the food interferred with

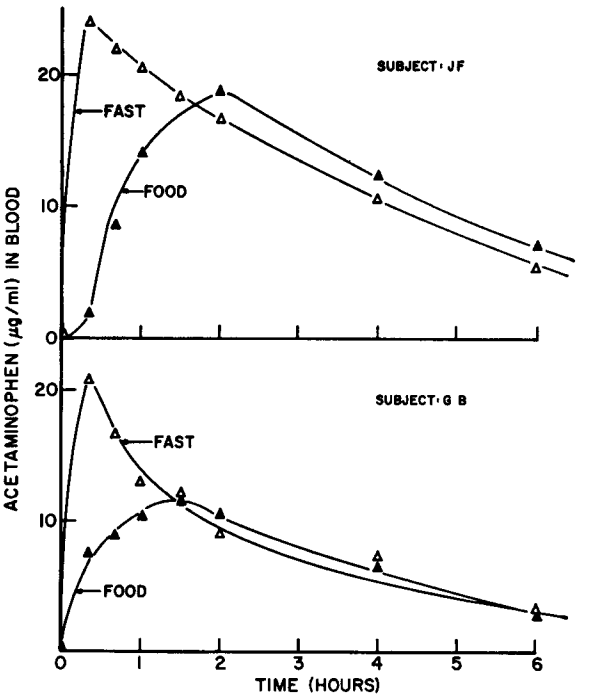

Figure 10

Effect of food on the absorption of acetaminophen in 2 representative subjects. Reproduced from Mattok and McGilveray,[29] with permission of copyright owner.

tablet disintegration and/or dissolution. Once again, it would be expected that food would interact with SR formulations in a similar or more complicated fashion.

Since GI transit can have a profound effect on drug absorption, it would be useful to have some model which describes this process. One such model is illustrated in Fig. 11.[30] The gut is divided into 4 compartments and movement of undigested residues is taken to proceed by first-order kinetics. Rate constants indicated in the figure were selected to mimic gastrointestinal transit of unabsorbed food residues in an average man consuming an average diet. The model has numerous shortcomings but at least provides the basis for some crude estimates.

Figure 12 (top) utilizes the model and shows the fraction of unabsorbed residue in the various segments of the GIT. Also illustrated is data on the excretion rate of isonicotinuric acid (INU) and isonicotinic acid (INA) following INU ingestion. Initially some INU is absorbed and excreted (first peak, 0-5 hrs), but most passes into the large intestine where bacteria hydrolyze it to INA. The INA is absorbed and metabolized by the liver back to INU. It is apparent from the gut compartment simulation that at the times that

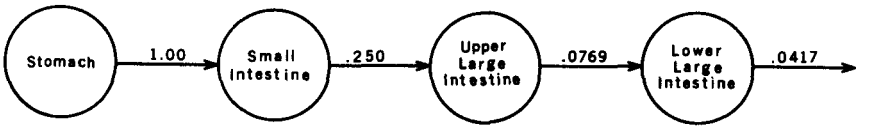

Figure 11

Catenary model illustrating gastrointestinal transit of food residues. Arrows represent first-order processes, and numbers represent first-order rate constants (hrs^{-1}). Reproduced from Boxenbaum and coworkers,[30] with permission of copyright owner.

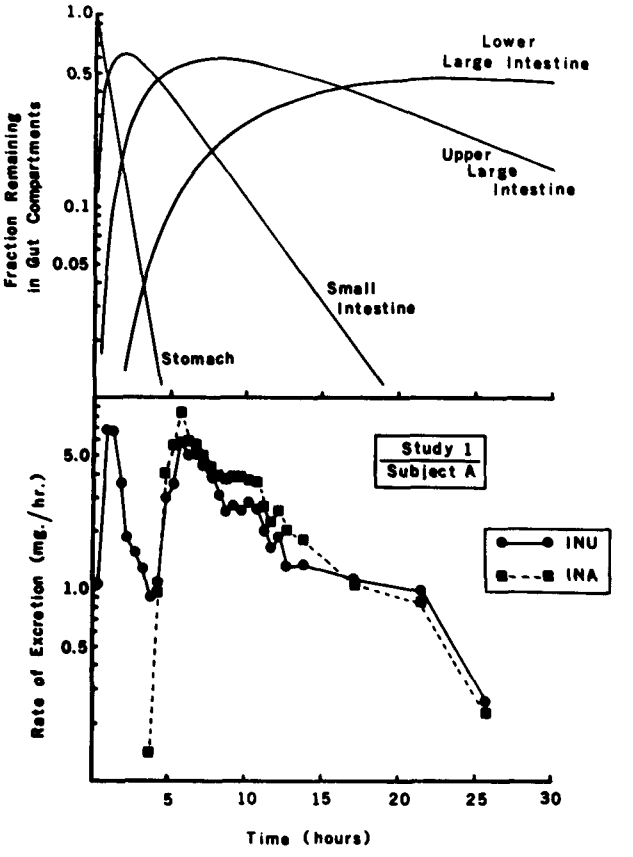

Figure 12

Relationship between rates of excretion of isonicotinuric acid (INU) and isonicotinic acid (INA) following oral administration of INU to a representative subject and fraction of food residues in GI compartments. Reproduced from Boxenbaum and co-workers,[30] with permission of copyright owner.

INA was being absorbed, much of the ingested INU would have passed into the large intestine.

Similar deductions could be made following ingestion of SR products. In one set of data made available to the author, it was apparent that drug absorption from a SR product was continuing for

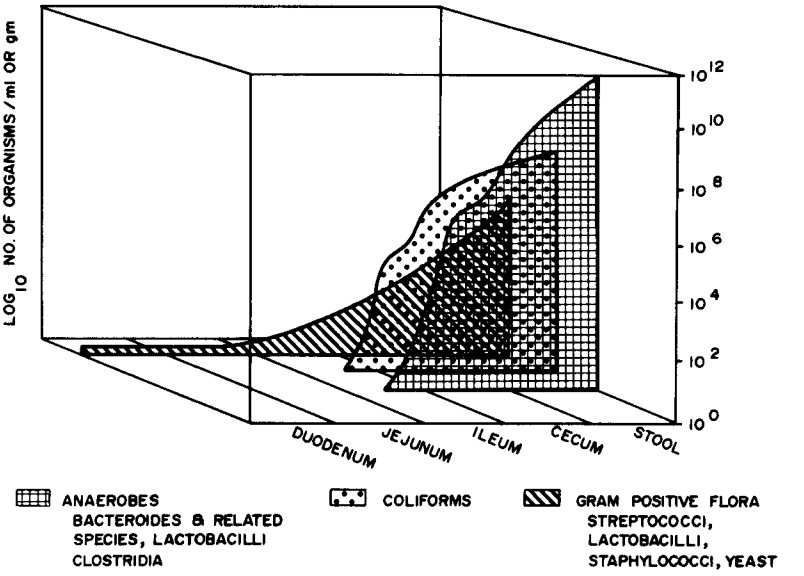

Figure 13

Diagrammatic scheme of microbial populations of the human gastrointestinal tract. Reproduced from Boxenbaum and co-workers,[30] with permission of copyright owner.

at least 14 hours post-administration. From the simulation in Fig. 12, it is clear that drug was being absorbed long after the dosage form and drug residue reached the large intestine. Even without reference to such models as these, other reports provide support. Eve[31] reported that following an ordinary barium meal the average time taken by the head of the meal to reach the cecum was 1½-2 hours and that times between 1-4 hours should be considered normal. The time required for all the barium to pass through the terminal ileum was observed to be 6 hours, although other investigators have reported 8 hours or longer. Thus, it is clear that any SR dosage form providing absorption beyond 6-8 hours post-adminis-

tration probably does so with absorption occurring from the large intestine. And therein lies the rub! Once the drug reaches the large intestine, it becomes exposed to the action of the GI flora and may be metabolized. [30,32] Figure 13 illustrates the distribution of microorganisms in the GIT (note the logarithmic scale). Once a drug or dosage form passes the ileocecal valve, it becomes exposed to large numbers of potentially metabolizing bacteria. And of course, if we are to have an 8-12 hour profile, we are going to have bacterial exposure. This is in contrast to most conventional dosage forms which release drug and have it absorbed prior to reaching the large intestine.

SUMMARY

Some of the pharmacokinetic and physiological factors affecting the performance or oral sustained release products have been discussed. In view of the fact that there are so many aspects of the problem interacting in such a complex and uncontrollable fashion, the author finds it difficult to take an optimistic stance.

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