

THERAPEUTIC USE AND CLINICAL FEATURES OF  
NOVEL DRUG DELIVERY SYSTEMS\*

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Ever since medicinal agents have been prescribed, dosage forms have existed, as they constitute the physical-chemical form for administering a medicine. It is noteworthy that most drugs today are still prescribed in dosage forms that date back to the earliest records of pharmaceutical practice: the pill, described in Eber's Papyrus 1500 BC; the coated pill, accredited to Rhazes about AD 900; the tablet, described by Al Zahrawi during the last half of the 10th century; and the capsule, invented by Mothes in France, 1833. (Felix Theeuwes, Pharmacology and Therapeutics "Drug Delivery Systems," 13, 149-191; 1981.)

With this statement Felix Theeuwes of the Alza Corporation begins his excellent 1981 review of contemporary drug delivery systems--systems that extend man's control of dosing regimens in ways that can optimize a drug's desirable therapeutic activities while minimizing undesirable activities. These new drug delivery systems often use new routes of administration (e.g., transdermal for systemic effects) and new technologies (e.g., laser beams, computerized pumps); and are designed for careful programmed release of drugs for local effects (e.g., in the eye) or for systemic effects.

Why is it that there currently is such rapid advancement in dosage form technology after so many centuries of little advancement? The reason is that before there could be advances in dosage form design there had to be advances in analytical chemistry, clinical pharmacology, pharmacokinetics and biopharmaceutics.

Advances in Analytical Chemistry

Until recently little was known of a drug's presence in body fluids and whether a drug was eliminated unchanged by the kidney or by metabolism or by both. Since the drug's entrance and elimination could not be quantified there was little understanding of how variations in absorption and in elimination affected drug efficacy. Routes of administration, dosage forms and dosage regimens were based on observations of activity and toxicity -- a bottom line method that lacks discrimination.

The introduction of new instrumental methods of analysis (e.g., gas chromatography, high pressure liquid chromatography, mass spectrometry, etc.) allowed the quantification of drugs and drug metabolites in biological fluids, in some cases even when levels were as low as a few nanograms per milliliter.

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With the quantification came the ability to correlate a drug's presence with pharmacologic effects and to correlate pharmacologic effects with the rate processes of absorption, distribution, metabolism and excretion of an administered drug.

### Correlation of Drug Levels with Pharmacologic Effects

The pharmacologic activities of a drug are often related to its concentration at various sites of action (primary, secondary, etc.), and these drug concentrations are often related to drug concentrations in the blood. Figure 1 illustrates how patients may react to various drug administrations, i.e. there are blood levels of drug that may be subtherapeutic, there are blood levels where some patients obtain the desirable response and others do not, there are higher blood levels that provide a desired response in virtually all patients, there are higher blood levels that will start producing side effects in some patients, etc. Thus, we find that many drugs have a "therapeutic window" -- optimum blood levels that provide desirable effects. Hence, the incidence of side effects due to excessive blood levels, can be reduced if the blood levels are maintained in the optimum range. Obviously, the larger the differential between minimum therapeutic levels and toxic levels, the more latitude for dosing regimens and for drug product performance.

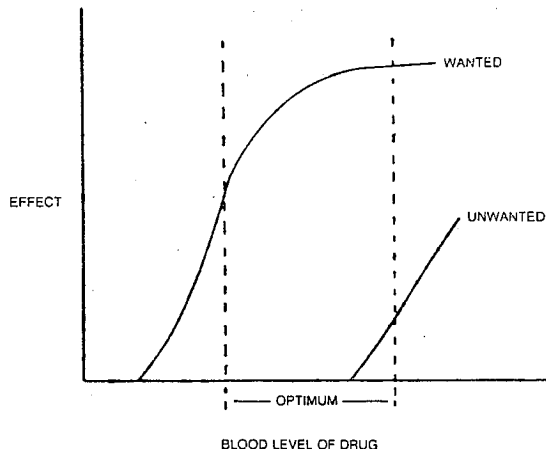


Figure 1

Table 1 lists some examples of desirable serum concentrations for some drugs. These optimum serum levels provide a target, or goal, that is useful in the rational design of dosage regimens and, importantly, in the design of novel drug delivery systems.

Table 1

<u>Drug Substance</u>	<u>Therapeutic Serum Concentrations<sup>a</sup></u>
Digitoxin	14-30 ug/l
Digoxin	0.9-2 ug/l
Diphenylhydantoin	10-20 mg/l
Lidocaine	1.5-4 mg/l
Lithium	0.5-1.3 mEq/l
Nortriptyline	5-140 ug/l
Procainamide	4-8 mg/l
Propranolol	20-50 ug/l
Quinidine	2-5 mg/l
Salicylates	150-300 mg/l
Theophylline	10-20 mg/l

<sup>a</sup>Theophylline data from Jenne et al. (1972); other data from Koch-Weser; 1972. (J.W. Jenne, E. Wyze, F.S. Rood and R.M. MacDonald, "Pharmacokinetics of Theophylline: Applications to Adjustment of the Clinical Dose of Aminophylline," Clin. Pharmacol. Ther., 13, 349-360 and J. Koch-Weser, "Drug Therapy. Serum Drug Concentrations As Therapeutic Guides," N. Engl. J. Med., 287, 227-231.)

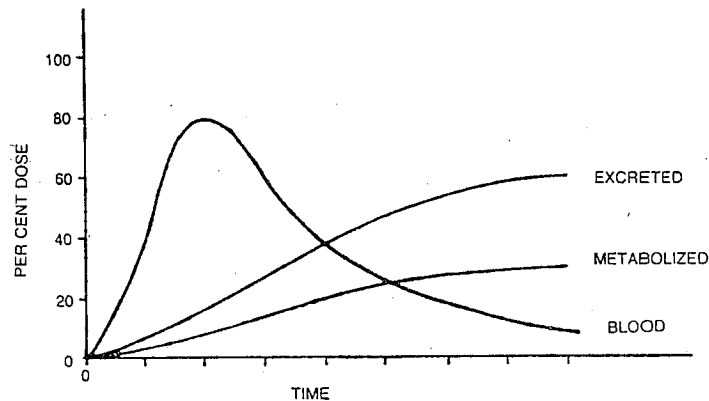


Figure 2

Figure 2 illustrates a typical blood level profile of drug following extravascular administration. When drug absorption is faster than elimination, the rise in the drug blood level is indicative of drug absorption (i.e., input of drug) and the decline is due to drug elimination (i.e., output) via metabolism and/or excretion.

The mathematics of drug absorption and elimination are quite similar to the mathematics of filling a bucket with water when the bottom of the bucket has holes. The water levels are analogous to drug-blood levels and the holes represent the elimination processes of metabolism and excretion (Figure 3). In this model, when absorption is complete, drug elimination will be monoexponential, or first-order, and describable by an elimination half-life.

If only drug-blood levels are evaluated, it could not be determined what processes were causing the decline in levels. However, if the urine is also analyzed for intact drug and metabolites (i.e., if the amount of water eliminated from each of the bucket's holes were measured), the drug elimination rate constant would be broken down into the specific rate constants that control excretion and metabolism. (In this discussion I have assumed that the body acts as a single compartment. Although a single compartment treatment of data often may be sufficient, post-absorptive drug kinetics is usually more complex than simple first-order).

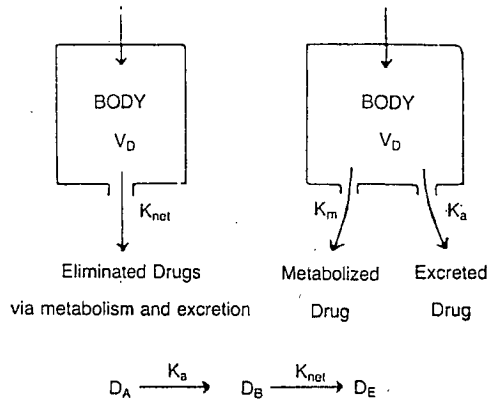


Figure 3

The relationship between drug blood levels and pharmacologic response is depicted in Figure 4. In this figure the onset of drug action occurs when the blood level reaches the minimum effective concentration and the duration of the effect will last as long as the blood levels are above the minimum effective concentration.

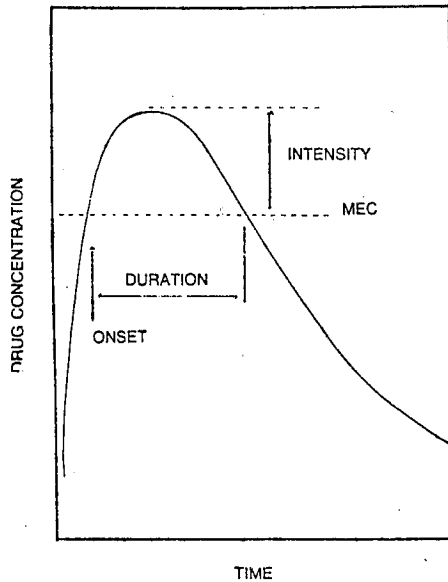


Figure 4

In some cases, but not always, the intensity of pharmacologic response is related to the extent to which the actual level exceeds the minimum effective level of drug. In other situations, minimum effective concentrations may not be obtained on a single dose, but rather a drug must be readministered so that it can accumulate to the desired blood level range. If a drug is given in a conventional dosage form it will provide a peak and valley blood level and, if administered at a fixed time interval (e.g., every six hours, every 12 hours, etc.) that allows accumulation, the blood level pattern will be as shown in Figure 5. The time of the plateau of blood level can be predicted, i.e., with a fixed time interval it takes approximately five times a drug's biologic half-life to reach the drug's plateau level. The peaks and valleys are also predictable based on the amount and rate of drug absorption, the time interval between doses and the rate of drug elimination from the body via metabolism and excretion. If drug administration is terminated, the usual drug elimination profile occurs. Thus, plateau blood levels of drug are predictable. For example, more frequent administration of smaller doses causes less "noise" in the blood levels, i.e., less difference between peaks and valleys.

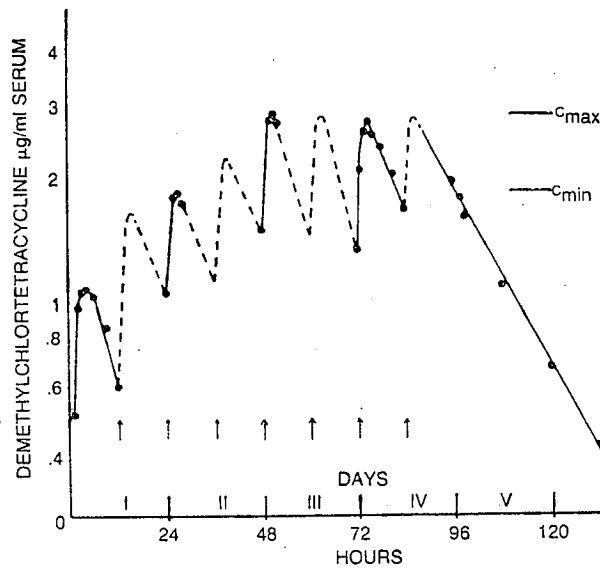


Figure 5

## Controlled Drug Delivery Forms

Basically controlled drug delivery forms, rather than conventional dosage forms, are used in the following instances.

1. When less frequent administration is desired for drugs that are eliminated rapidly from the body. These prolonged-release products initially make available to the body a quantity of drug comparable to that delivered from a single dose of the drug in a conventional dosage form, but contain additional quantities of the drug which are slowly made available to the body so as to prolong the clinical effect beyond that attainable with a single dose. Ideally, the additional drug should be absorbed constantly at a rate just sufficient to replace drug in the body that is lost by metabolism and excretion. The most obvious advantage of these dosage forms is the reduction in frequency of administration and the potential improvement in patient compliance. The prolonged-release dosage form should be most useful for drugs that are used chronically but that have relatively short half-lives and must be administered several times a day.

Bioavailability studies comparing conventional and slow-release tablets of procainamide (Figure 6) show that administration of slow-release tablets every eight hours gives the same average drug level in the plasma at steady state as do ordinary tablets given every four hours.

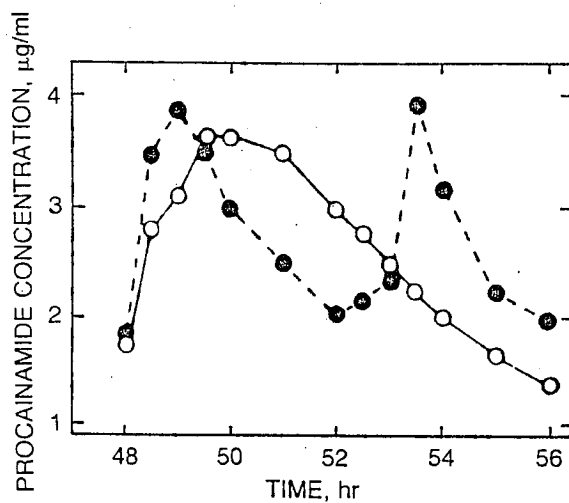


Figure 6

2. When high peak blood levels due to rapid drug absorption from conventional dosage forms are associated with adverse side effects. Thus, the use of certain drugs with relatively long half-lives in slow-release dosage forms may also be rational and advantageous if there is a question regarding the safety of giving the entire daily dose in a single administration of conventional dosage forms.

Ideally, with controlled drug delivery forms, the drug's absorption into the body should be determined by dosage form factors rather than by physiologic factors. Basically the drug's delivery into the systemic circulation is a function of the rate of drug release from the dosage form and the rate of drug passage through biological membranes (Figure 6). The slower of the two processes will be rate determining. In conventional dosage forms the physiologic factors are often rate controlling. But in controlled drug delivery forms the dosage formulation is rate controlling.

It is important to understand physiologic factors while designing controlled drug delivery systems. For example, the most used route of drug administration is oral, yet the gastrointestinal tract presents a very challenging variety of physiologic factors that can effect dosage form performance, e.g., gastric acidity and more neutral intestinal fluids, thick membranes with small surface area and poor blood supply (gastric) and thinner membranes with large surface area and good blood supply (duodenal), highly liquid environments and semisolid environments, etc. These variations are made even more challenging by changing transit times and the possibility of first pass metabolism. To render these physiologic factors less important to the rate of drug absorption than the dosage form factors is sometimes not possible e.g., for drugs that are not absorbed throughout the gastrointestinal tract or for some drugs that undergo extensive first pass metabolism.

With other drugs, however, oral dosage formulations have been successful in controlling drug delivery. Some common types of oral controlled release products include encapsulated or tableted coated pellets and various types of matrix tablets. A recent addition to oral controlled delivery forms is the osmotic pump tablet (Figure 7.) This drug delivery system consists of an osmotic core containing the drug, surrounded by a semipermeable membrane with a delivery orifice. The delivery orifice is created with a laser beam. When the dosage form is exposed to the gastrointestinal fluids, the core imbibes water osmotically at a controlled rate, determined by the permeability of the membrane and by the osmotic pressure of the core formulation. The rate of drug delivery by this system is constant (i.e., zero-order). Thus the dosage form factors can overcome physiologic factors for drugs that are good candidates for oral prolonged absorption.

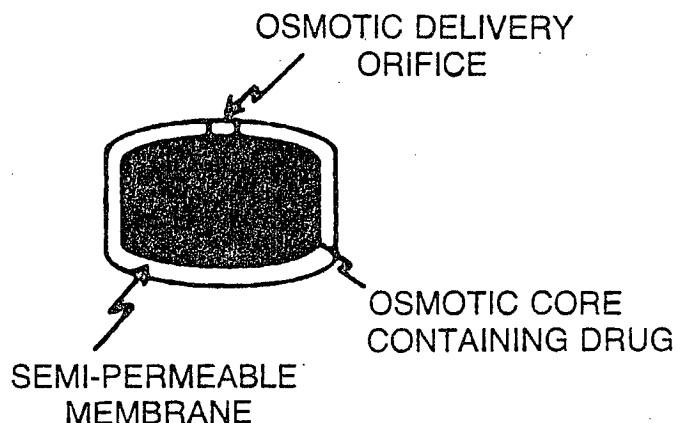


Figure 7

Understanding physiologic factors and desirable blood level endpoints has led to renewed interest in novel routes of drug administration as well as novel drug delivery systems. Nitroglycerine and scopolamine are examples.

Nitroglycerin's ability to stop the pain of angina pectoris has been recognized by the medical community for more than 100 years. Its position as the treatment of choice for this condition remains undisputed. Yet, throughout the years since the discovery of its therapeutic potential, there have been two recurring, and related, problems--the drug's high degree of volatility and its short duration of action due to rapid metabolism.

The drug's volatility causes the strength of sublingual nitroglycerin tablets to vary from tablet to tablet within the same bottle. Intravenous mixtures can lose potency while being infused into the patient. The new transdermal nitroglycerin patches--marketed by the Ciba Pharmaceutical Company, Key Pharmaceuticals, Inc. and Searle Laboratories--seem to overcome both problems. The drug's strength is retained until the patient uses the patch; and the patch releases therapeutic levels of nitroglycerin for a full 24 hours.

The three transdermal nitroglycerin products introduced in the U.S. appear to be ready-to-wear adhesive bandages containing nitroglycerin. They are actually controlled delivery systems that produce sustained blood levels for 24 hours (Figure 8).

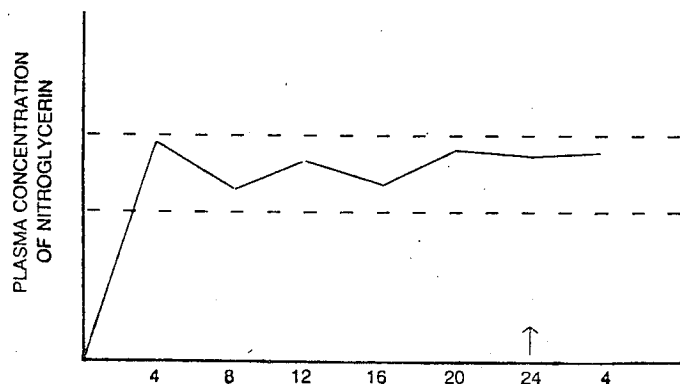


Figure 8

In a recent promotion of a nitroglycerin transdermal delivery system the manufacturer (Ciba--manufacturer of Transderm-Nitro) states: "Exclusive rate controlling membrane delivers hour-by-hour precision dosage . . . an advance beyond tablets and ointments--24 hour sustained therapeutic blood levels of nitroglycerin; precise dosage control; ease of administration; once-a-day dosage to enhance compliance; may be worn while swimming, bathing and showering."

Thus we have come to a point in modern therapeutics where there is significant appreciation for the important role that dosage forms, drug delivery systems, can play in controlling drug efficacy. Continued advances in analytical chemistry, clinical pharmacology, pharmacokinetics and dosage form technology will cause these principles to expand into new drug classes, new routes of administration and more sophisticated controlled drug delivery devices.

## Points raised during discussion

Question: Is compartmental modeling passé and should we move on to other things?

Dr. Deluisio: It all depends, you know, those of us who deal with mathematics and kinetics always like to do new things. We have marvelous computers now that can do all kinds of calculations that we would not have dreamed of 10 years ago. Whether the information affects therapeutics is another question. The ability to measure blood levels and to draw conclusions about absorption and elimination is real to a degree. It is unreal in other ways. The important thing is that whether it is a hypothetical or a real calculation, if it correlates with a toxicity or a desired effect the correlation is important. Too many people believe they are calculating real physiological numbers when they calculate pharmacokinetic values and computers have moved our ability to calculate even further. But they are still hypothetical numbers. The basic rule for the mathematical modeling of data is always to use the simplest model that works. I think the simplest model that you should start out with is a one compartment model, then move to a two compartment model, three compartment model and then one can go to more sophisticated models. When you finally publish your data, you should always publish the simplest model that works.

Question: The use of blood levels to monitor therapy and the impact of novel drug delivery systems?

Dr. Deluisio: I would not be surprised if veterinary schools do not soon establish chemical pharmacokinetic analysis laboratories to solve these kinds of problems. The blood level of digoxin, for example, does not mean anything if you do not know when it was taken. If it was taken 8 hours after administration it means one thing, if it was taken 2 hours later it means something else. This is extremely important. In the case of digoxin, the renal capacity of the individual is also extremely significant. There are certain calculations that one can do relative to mathematical modeling and predictions from these. Every once and a while you may go in and take a blood sample and say "Is the blood level where I think it should be?" Now almost every major university hospital has backup analysis laboratories in the medical center which verify these predictions. As you move into NDDS and more hypothetical pharmacokinetic predictions you would be establishing the same types of analyses to make sure that your predictions are periodically verified. But a blood level without additional information is pretty meaningless. Again, if you are giving a dosage regimen prior to the elimination of the previous dose, whether NDDS or not, you are sustaining blood levels. If the system reacts to a sustained blood level, for example, if your metabolic systems get activated and start eliminating the drug faster on chronic administration, you may go subtherapeutic.