Role of Drug Metabolism in Drug Research and Development: Pharmaceutical Chemistry Aspects

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Abstract □ Pharmacokinetic data obtained jointly by the drug metabolism group and the pharmaceutical chemist are essential to the selection of the proper dosage form for preclinical and Phase I studies. Subsequent biopharmaceutic studies aid in the development of alternate dosage forms and in devising suitable *in vitro* procedures for ensuring batch-to-batch reproducibility in production.

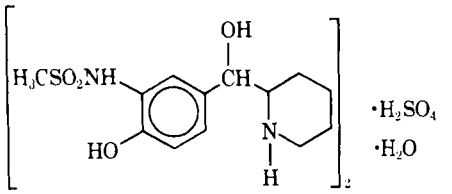
Keyphrases □ Drug metabolism—role in drug research and development, symposium □ Biopharmaceutics—development of dosage forms □ Pharmaceutical chemists—selection of dosage forms for preclinical and Phase I studies □ Dosage form development—role of drug metabolism group and pharmaceutical chemist

The objective of the pharmaceutical chemist is to formulate the new drug substance into a dosage form that can be administered to the patient. In years past the major emphasis in this work was to develop a dosage form with quality, strength, and purity beyond reproach. Recently, however, the delivery or release of the drug from the dosage form has received considerable attention.

Drug dosage forms are currently viewed as delivery systems for the drug substance. In this context, considerably more emphasis is placed on the objective measurement of the release of the drug substance from the dosage form. Although much of this work has been done in *in vitro* systems, the more relevant data have been from *in vivo* studies. These studies have been made possible by the rapid progress being made in the area of bioanalytical methodology.

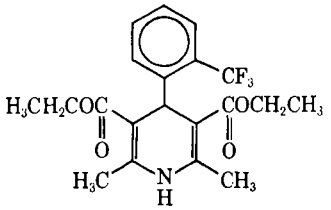
Analytical methods for determining the drug in blood and urine are usually available early in development work. A few years ago this availability was the exception. It is now possible for the pharmaceutical chemist to utilize data obtained by the drug metabolism group to design the most efficient formulation.

From the time the early preformulation work is initiated until the final dosage form comparison studies are completed, bioanalytical data are used as a guide in the dosage form development process.



Compound I:

2′-hydroxy-5′-[(hydroxy)(2-piperidyl)methyl]-methanesulfonanilide sulfate hydrate



Compound II:

2,6-dimethyl-3,5-dicarboethoxy-4-(2-trifluoromethylphenyl)-1,4-dihydropyridine

Table I—Urinary Recovery Data after Oral and Intravenous Administration to Dogs

Compound	Percent Recovered in 48 hr.	
	Oral	Intravenous
I	10, 16	62, 67
II	7.0, 7.7	41, 32

Table II—Solubility of Compounds I and II in Various Solvents

Solvent	Solubility, Concentration, mg./ml.	
	I	II
Water	>50	0.0008
0.1 *N* HCl	>50	<0.001
Intestinal fluid (pH 7.4)	>50	<0.001
Ethanol	49	>50

PREFORMULATION STUDIES

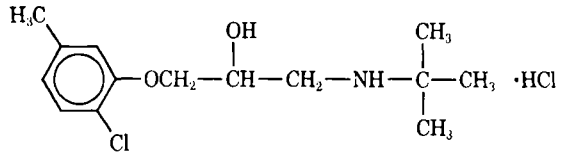
Before dosage formulation is begun, a physical-chemical characterization of the new drug substance is carried out. These data enable the formulator to proceed more efficiently toward the choice of a proper formulation. The various properties that are studied during the preformulation phase are: solubility profile, particle size, polymorphism, stability at various pH, dissolution rate, drug–excipient interactions, and partition coefficients.

These studies are designed to determine quickly if the new drug substance will be a problem in formulation. The early solubility studies give a good indication if subsequent drug absorption problems can be expected. There are many examples cited in the literature in which particle size and polymorphism have influenced drug absorption. This literature was recently reviewed (1, 2).

The stability data of the new drug substance alone and in combination with proposed excipients are essential to the eventual formulation of an acceptable drug product. If these studies indicate

Table III—Partition Coefficients of Compounds I and II at Various pH's

pH	Concentration in Cyclohexane / Concentration in Water	
	I	II
1.5	—	370
3	0.03	—
5	0.02	–
7	0.004	–
7.4	—	370



Compound III:

1-*tert*-butylamino-3-(2-chloro-5-methylphenoxy)-2-propanol hydrochloride

that problems will be encountered with a particular salt form, new salts are made and characterized.

As the pharmaceutical chemist is collecting such data, animal pharmacokinetic data useful in dosage form considerations should also be generated. Plasma and urine levels of drug after oral and intravenous administration provide data pertinent to the absorption efficiency of the compound.

To illustrate how the cooperative efforts of the metabolism group and the pharmaceutical chemistry group generate data vital to subsequent formulation work, experiences with compounds studied in this laboratory will be discussed.

In the first example, data obtained on two compounds, I and II, will be compared, since they present similar absorption profiles for different reasons.

During early pharmacokinetic studies in animals, the ^{14}C-labeled compounds were administered orally and intravenously to dogs. The tagged compound was then measured in the urine as an indication of the degree of absorption of the compound. The urinary recovery data are shown in Table I. There is a significant difference in the recoveries after oral and intravenous administration for both compounds, indicating poor absorption orally. A review of the preformulation data provides information relative to the limiting factor in the absorption.

The solubility profiles of the compounds are given in Table II. Compound I is seen to have good water solubility, while Compound II is very poorly soluble in water.

The partitioning properties of the drugs are shown in Table III. Compound I has a very low apparent partition coefficient (o/w) over a wide pH range. It was concluded from the solubility and partition data that the absorption of this compound is limited due to the poor lipid partitioning properties.

Although Compound II has favorable partitioning properties, the low water solubility is undoubtedly the limiting factor in its absorption. This indicated that formulation work should be undertaken to enhance the absorption. This work will be discussed later.

Another example of how early pharmacokinetic data aid the pharmaceutical chemist is demonstrated by experience with a β-blocker (Compound III). Recovery data after oral administration to rats indicated that about 60% of Compound III was recovered in the urine and about 40% in the feces. These data suggested a possible absorption problem. However, the compound showed an appreciable water solubility. The metabolism group then measured the biliary, urinary, and fecal excretion after oral administration to

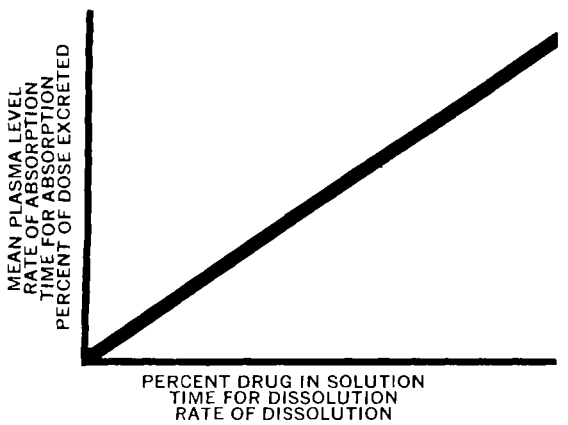


Figure 1—*Examples of parameters plotted in* in vitro–in vivo *correlations.*

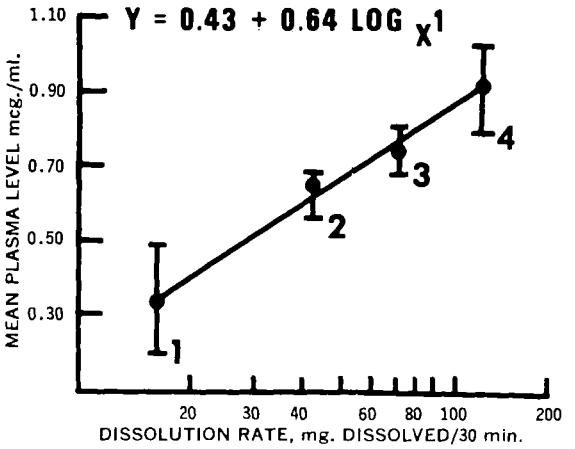


Figure 2—*Correlation of dissolution rate and mean griseofulvin plasma level. Correlation coefficient = 0.995 (p = 0.02). Brackets enclose 95% confidence intervals of regression line. Numeral beneath each point is the preparation number. (Reprinted, with permission, from* Reference 5.)

bile duct-cannulated rats. It was found that essentially 100% of the drug was recovered from bile and urine within 48 hr. The fact that very little drug was excreted in the feces indicated that absorption from the GI tract was complete.

These examples illustrate how preformulation data are utilized to make early decisions concerning the eventual formulation of the new drug substance. When these data are generated at an early date, the implications can be dealt with adequately. Different salts, solubilized systems, or other modifications can be prepared and evaluated. However, the development process is severely disrupted if data critical to the absorption of the compound are generated at a later date.

FORMULATION STUDIES

After the early preformulation and pharmacokinetic data are generated, dosage forms are prepared. The biopharmaceutical evaluation of the various formulations requires the cooperative efforts of the biochemist, pharmaceutical chemist, biostatistician, and clinical pharmacologist. The objective is to produce a dosage form with the optimum absorption profile. However, before *in vivo* testing of the formulations is initiated, they are screened by *in vitro* procedures. This minimizes the workload on the testing facility and the bioanalytical laboratory.

Numerous *in vitro* test procedures have been developed. Many of these tests are designed to simulate the agitational intensity and pH conditions of the GI tract. It has been postulated that the method most closely resembling physiological conditions should have the

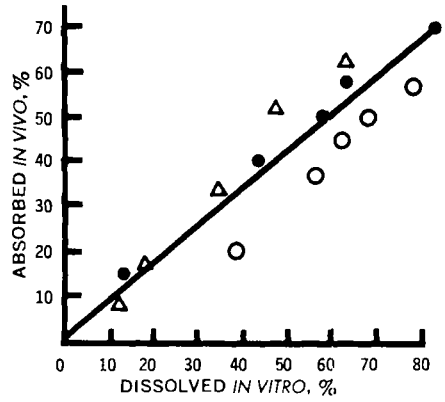


Figure 3—*Plot of percent of dose of aspirin absorbed to time* T *after drug administration* versus *percent dissolved* in vitro *at time* T. *Key:* ○, *conventional tablets;* ●, *buffered tablets; and* △, *timed-release tablets. (Reprinted, with permission, from* Reference 6.)

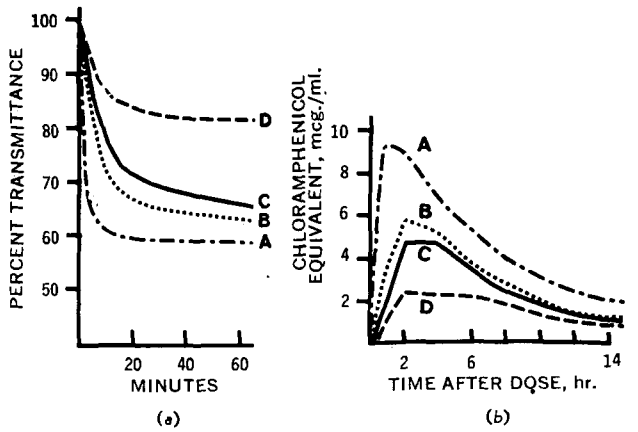


Figure 4—(a) *Plot of percent transmittance* versus *time showing the relative deaggregation rates of the four capsules in simulated gastric fluid T.S. (Reprinted, with permission, from* Reference 7.) (b) *Mean plasma levels in human volunteers of nitro compounds (chloramphenicol equivalents) following single oral doses of chloramphenicol capsules [dose 0.5 g. (two capsules), 10 subjects].*

highest probability of yielding good correlation with *in vivo* data. However, several different systems have yielded good correlation data, and a so-called "ideal system" is probably not a realistic goal. Regardless of the methodology employed, the critical factor is to correlate the rate of dissolution of the drug with some *in vivo* performance parameter.

Many examples of *in vivo–in vitro* correlation have been published and the literature has been compiled (3, 4). The usual types of correlations that are sought are seen in Fig. 1.

Studies carried out by Katchen and Symchowicz (5) on griseofulvin and by Gibaldi and Weintraub (6) on aspirin illustrate good *in vivo–in vitro* correlations. Mean plasma levels after the administration of four different griseofulvin dosage forms to 10 subjects were correlated with the amount of drug dissolved in 30 min. in simulated intestinal fluid. Excellent correlation was obtained (Fig. 2).

A plot showing the percent of dose of aspirin absorbed to time T after administration *versus* the percent dissolved *in vitro* at time T for three different dosage forms is shown in Fig. 3. Here again, it is demonstrated that *in vitro* dissolution data can be correlated with the *in vivo* performance of the dosage form.

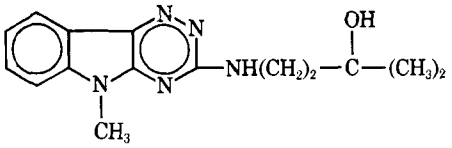
Properties other than dissolution have been measured in *in vitro* performance tests. Aguiar *et al.* (7) measured the rate of deaggregation of chloramphenicol capsules as an indicator of their bioavailability. The deaggregation was determined by measuring the decrease in transmittance of a dispersion with time. A qualitative correlation existed between the rate of deaggregation and plasma levels after the administration of the capsules (Fig. 4).

After the *in vitro* screening studies are completed, biopharmaceutical data are obtained to determine the performance of the dosage form *in vivo*. It can then be determined if a correlation exists between the *in vitro* and *in vivo* data. If the correlation does exist, specifications for the dosage form are established based on the *in vitro* test procedure. The following examples from this laboratory illustrate the utilization of biopharmaceutical data in dosage form development. The data are not intended as a full report of the studies carried out but are presented only to illustrate the use of this type of data by the formulator.

Compound II is poorly absorbed orally, has a very low water solubility, and has a high partition coefficient (o/w). Work was undertaken to enhance the absorption of the compound. A second dosing study in dogs was carried out in which the drug was administered orally as a 0.1% solution in 50% polyethylene glycol 200–50% water. A comparison of the urinary recoveries are shown in Table IV. These data indicated that urinary recovery of the drug after the oral administration of a solution was equivalent to the recovery after intravenous administration of the solution. Subsequent pharmacological tests were carried out with a 5% solution of the drug in polysorbate 80. Oral LD_{50} studies in rats and hypotensive activity studies in dogs showed the solution to be 4–5 times more active than crystalline drug. This increase in activity is of the same order of magnitude as the increase in absorption shown in Table IV for the polyethylene glycol 200 solution given orally. These studies led to the selection of a dosage form comprised of a polysorbate 80 solution filled into soft gelatin capsules.

Table IV—Urinary Recoveries of Compound II from Dogs after Various Dosage Forms

	Percent Recovered in Urine (up to 96 hr.)
Polyethylene glycol 200 solution 0.1% (intravenous)	41, 32
Crystalline drug (oral)	7.0, 7.7
Polyethylene glycol 200–water 50% of each solution 0.1% (oral)	39, 32



Compound IV:

2-methyl-4-[(5-methyl-5*H*-*asym*-triazino-[5,6-β]indol-3-yl)amino]-2-butanol

Experience with an antiviral agent, Compound IV, also demonstrated the use of *in vivo* data as a guide in formula design. The compound has a water solubility of only 0.008 mg./ml. The solubility in 0.1 *N* HCl is approximately 100 times this amount, and it was postulated that this solubility in gastric fluid would provide a reasonable dissolution rate and good absorption. However, this was not found to be the case as shown by the *in vivo* data. Two biopharmaceutical studies were carried out in which various dosage forms were administered to six subjects in a crossover study. Unchanged drug was measured in the plasma, and unchanged drug and metabolites were measured in the urine. The results of these studies are shown in Table V. A direct comparison of all the data in Table V is not entirely valid since it was generated in two separate studies. However, the data were sufficiently consistent between the two studies to permit generalizations to be made concerning the forms tested. By using the solution form as a standard, Tablet B and the suspension showed lowered recoveries. This would indicate that the base is not being readily converted to the hydrochloride salt in the stomach. Tablet B had a considerably slower *in vitro* dissolution (22% in 15 min., NF Method I, 100 r.p.m., gastric fluid) than Tablet A (100% in 15 min.), while Tablet C dissolved much more rapidly than either A or B. Tablets A and C produced total recoveries equivalent to the solution; however, their rates of availability were slower as evidenced by the lower average peak serum levels.

From a biopharmaceutical standpoint, the solution is the form of choice; however, pharmaceutically it is unacceptable due to its very low pH. Based on *in vivo* performance and pharmaceutical acceptance, Tablet C is the dosage form of choice.

It is surprising to note that the suspension form of Compound IV base showed a lower recovery and a lower average peak serum level than the rapidly dissolving tablet of the base (Tablet A). This same phenomenon of less efficient performance from a suspension as compared with a solid dosage form was reported for griseofulvin by Riegelman (8). Griseofulvin plasma levels after administration of eight 125-mg. capsules and 1000 mg. of griseofulvin in suspension

Table V—*In Vivo* Testing of Compound IV Dosage Forms

Dosage Form	Dose, g.	Urinary Recovery, % of Dose (48 hr.)	Average Peak Serum Level, mg./ml.
Solution (hydrochloride salt)	1.0	32.2	15.6
Tablet A (500 mg., base)	1.0	28.8	6.40
Tablet B (250 mg., base)	1.0	13.5	2.65
Tablet C (500 mg., hydrochloride salt)	1.0	27.4	10.8
Suspension (10%, base)	1.0	20.4	3.91

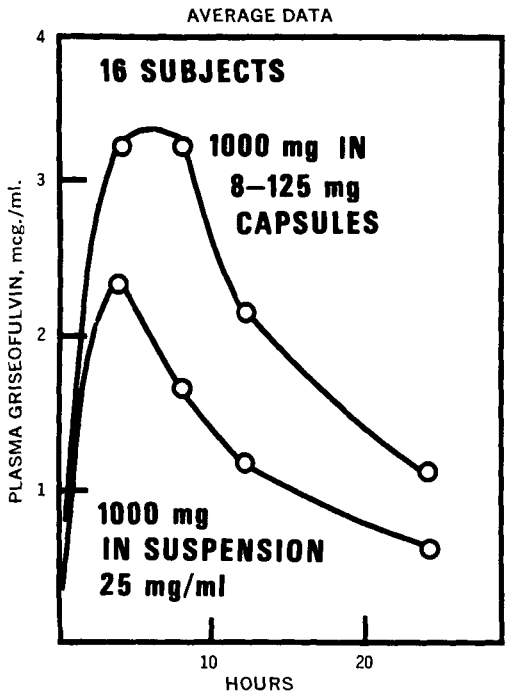


Figure 5—*Mean plasma griseofulvin levels from 16 subjects given the drug in the various dosage forms noted. (Reprinted, with permission, from* Reference 8.)

(25 mg./ml.) are shown in Fig. 5. Riegelman postulated that a major portion of the absorption of griseofulvin takes place in a limited segment of the upper intestinal tract and that intestinal transit time controls the absorption. The finely divided suspension transit time is probably less than that from the capsules and, thus, less absorption occurs from the suspension. This may also be the explanation for the lower recovery from the Compound IV suspension.

SUMMARY

The cited examples show how the pharmaceutical chemist utilizes bioanalytical data from animals and man as a guide in dosage formulation. These data, along with the physical–chemical characterization of the new drug substance, enable the formulator to produce a dosage form that maximizes the availability of the drug.

One of the most critical aspects of this total effort is timing. It is imperative that the pharmaceutical chemist, biochemist, and pharmacologist cooperate closely in the early dosing studies with the new drug substance. It is at this point where the groundwork must be laid for the eventual formulation of the most effective dosage form.

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