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DESIGN OF ORAL DRUG DELIVERY SYSTEMS -- PAST, PRESENT AND FUTURE

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ABSTRACT

This paper reviews the past and the present thinking about peroral delivery research and development and how future approaches may be significantly different, both qualitatively and quantitatively. The future should involve the use of comprehensive models capable of incorporating physico-chemical data and biological information such as gastrointestinal flow, how and where drug absorption occurs, and whether and where metabolism of the drug occurs during gastrointestinal transit. Special challenges would involve the use of such models in research protocols in the optimization of drug delivery systems.

INTRODUCTION

This Symposium should be as timely as, if not more timely than, the Rutgers Symposium of 1982 on Dermal Delivery Systems. The papers presented by the various speakers here should point out

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that the approach to the design of oral drug delivery systems is evolving extremely rapidly both quantitatively and qualitatively, and the situation today might be considered to be on the threshhold of being revolutionary.

It is apparent to many of us on the scene that the role of pharmaceutical R and D from the 1950's to the 1980's has been undergoing a great deal of change. It has been evolving from a role that was primarily service oriented to one in which the pharmaceutical scientist has become increasingly involved in drug discovery or, at least, in very early drug development. The forces at play for this changing role of the pharmaceutical scientist include the great influx of new basic science concepts and methods in drug development, especially physical chemistry as applied to dosage form design and to drug absorption, metabolism and disposition. The term, "quantitative mechanistic biopharmaceutics" might be an appropriate one for the science and technology related to the behavior of the drug molecule (at the physical chemical level) after the dosage form is taken by the patient. Another factor has been that, increasingly, directors of pharmaceutical research are recognizing, for example, that they can no longer afford to regard the gastrointestinal tract as a "black box" in drug delivery systems design and evaluation. It is clear research will intensify in the areas of stomach emptying, flow down the intestinal tract, anatomical intestinal reserve length, "windows" for drug absorption, gastrointestinal transit times, and how knowledge in these areas may be used in a comprehensive rational way for drug

delivery. Such studies, when programmatically framed, will help (1) in defining delivery problems and sorting out the key variables for drug candidate compounds because critical in vitro experiments and animal and human drug absorption experiments may be identified and carried out, (2) in setting quantitative boundaries within which optimization of oral formulations may be achieved, and (3) pointing out strategies and options in drug delivery systems design.

The purpose of my presentation is to review the past and the present thinking and to discuss how recent developments may point to an essentially completely rational approach to peroral drug delivery in the future. At the risk of being overly radical or too provocative, we will follow the premise that the present state-of-the-art of oral drug delivery systems design has not been one programmed in a rational framework and that recent developments and other forces at play suggest a rapid evolution in this direction, i.e., toward pharmaceutical R and D based upon the holistic approach.

PAST AND PRESENT APPROACHES

Table 1 lists three categories of factors essential in pharmaceutical R and D with regard to drug absorption/bioavailability. These are (1) the dosage form (or drug delivery system) factors, (2) physicochemical properties of the drug itself and (3) the physiological (biological) factors. Examples of each are given. The main point here is that although the pharmaceutical scientist knows a great deal about each of these such as the pK_a of the drug molecule (and how it might affect drug species distribu-

TABLE 1.

Factors Influencing Bioavailability

(1) Physiological Factors

Membrane Transport Mechanism	Surface-Bound Enzymes
GI Motility	Bacterial Flora
Stomach Emptying	Intestinal pH Gradient
Disease State	Surface pH
Biliary & Pancreatic Secretions	Pharmacological Drug Effects

(2) Physicochemical Properties of the Drug

Lipophilicity	Chemical Stability	Complexation & Binding
Molecular Size	Enzymic Lability	Particle Size
pK_a	Solubility	Crystal Form

(3) Dosage Form Factors

Solutions	Capsules & Tablets	Properties: disintegration time;
Emulsions	Controlled-Release Systems	dissolution rates; controlled release
Suspensions	Manufacturing Variables	rates

tion in aqueous solution or the aqueous solubility of the drug) or that stomach emptying might be important in a particular situation or that particle size might be important, these factors have not been tied together in any systematic, quantitative and mechanistically meaningful manner to achieve a rational approach to drug delivery systems design.

There have been approaches, however, made to assess bioavailability and/or bioequivalence. These are listed in Table 2

Table 2. Approaches in Assessing the Bioavailability of Orally Administered Drugs

Approaches	Objectives Or Assessments
1. Basic physiochemical evaluation of drug	Basic physiochemical data for preformulation.
2. *In vitro* dissolution tests	Control of *in vitro* availability during formulation stage; optimization of release
3. Human absorption studies of drug and drug formulation	Pharmacokinetics of drug and drug formulation; evaluation and optimization of bioavailability
4. *In vitro* - *in vivo* correlation of dissolution data and plasma level data	Stochastic approach to relate *in vitro* and *in vivo* data
5. Numerical evaluation of dissolution data or plasma profiles by evolution and convolution procedures	Numerical computation of apparent "*in vivo*-dissolution" or apparent "*in vivo*-absorption"
6. *In vitro* and/or *in situ* absorption studies using animal models (rat, dog)	Mechanisms of drug absorption, rate limiting steps

and their advantages and limitations in drug delivery research and development may be pointed out. Physical chemical studies are often carried out as part of preformulation studies in drug development. Data from these studies, however, cannot be extrapolated to predict bioavailability and/or bioequivalence. *In vitro* disintegration/dissolution studies do not allow simple extrapolation to *in vivo* behavior. Classical pharmacokinetics (both human and animal), though very useful in demonstrating *in vivo* efficacy, provides little information in the rational approach to drug delivery systems design. Blood-level data correlation attempts with "beaker" studies cannot generally provide useful insights.[1] Absorption studies with isolated animal gut, when carried outside of a mechanistic framework, have not generally provided useful information for drug delivery purposes.

THE FUTURE

There should be rapid progress in the future of oral drug delivery highlighted by what the engineers call the "systems approach." In one scenario, the factors and variables in Table 1 would be integrated into a quantitative and mechanistic (behavior at the molecular level) model. Thus the influence of the drug pK_a upon dosage form behavior, drug dissolution, drug absorption (where in the intestinal tract how much will be absorbed) and, finally, upon the blood-level time pattern would be describable. Please refer to Chapter 2 where examples of both the general approaches and specific relationships have been discussed.

We are currently at a point in the evolutionary path where both new comprehensive models are being formulated and where the

parts of the whole are being better understood. Concepts at the systems level and at the molecular level are being examined by experiments. The rate of future progress will be limited only by how rapidly knowledge is gained in both of these areas and by how rapidly this new science/technology is applied "in the field" (i.e., among pharmaceutical R and D groups).

THE INTESTINAL RESERVE LENGTH CONCEPT

The pre-eminent significance of the reserve length concept is its ability to interrelate many of the factors given in Table 1 and provides, therefore, a framework for the "systems approach." The intestinal reserve length, RL,

$$RL = L - L^* \qquad \text{(Eq. 1)}$$

where L is the effective absorbing length of the intestine and L* is the length required for essentially complete absorption for a particular case. When RL is close to zero or negative, we would have a bioavailability problem. The following are the uses of the reserve length concept in oral drug delivery research:

- Points out the critical *in vitro* physicochemical, animal and human absorption studies needed to define specific problems.
- Sorts out key variables.
- Sets quantitative boundaries within which optimization of oral formulations may be achieved.
- Points out strategies and options in drug formulation design.
- Assesses bioavailability and bioequivalence in terms of biophysical and physicochemical events.

AN EXAMPLE APPLICATION OF THE RESERVE LENGTH CONCEPT TO BIOAVAILABILITY

Figure 1 shows the results of calculations of bioavailability of suspensions for which particle size, solubility, membrane permeability and intestinal flow -- all have been taken into account. This may be one of the first examples of the "systems approach." This treatment assumes that the permeability coefficient is constant along the intestinal length and that the particles flow with the fluid. The equations employed in the calculations were already tested in vitro and in the perfused rat gut segment. These calculated results may now be tested in the perfused dog and in the perfused human in vivo to demonstrate that this approach would work in predicting bioavailability. Predictions similar to those in Figure 1 may also be made for other dosage forms (e.g., sustained release, emulsions, etc.).

FUTURE RESEARCH IN GAP AREAS

In order to achieve full implementation of the "systems approach" a number of gaps have to be bridged by future research efforts. A summary of these gap areas is presented in Table 3. The topics mentioned should be considered in light of the discussions in foregoing chapters, and comments can, therefore, be brief.

Although already considerable knowledge on the rates of gastrointestinal flow is at hand, still more work has to be done for full understanding and characterization of flow regime, mixing, techniques together with invasive techniques (such as gastrointestinal perfusion of nonabsorbable markers through

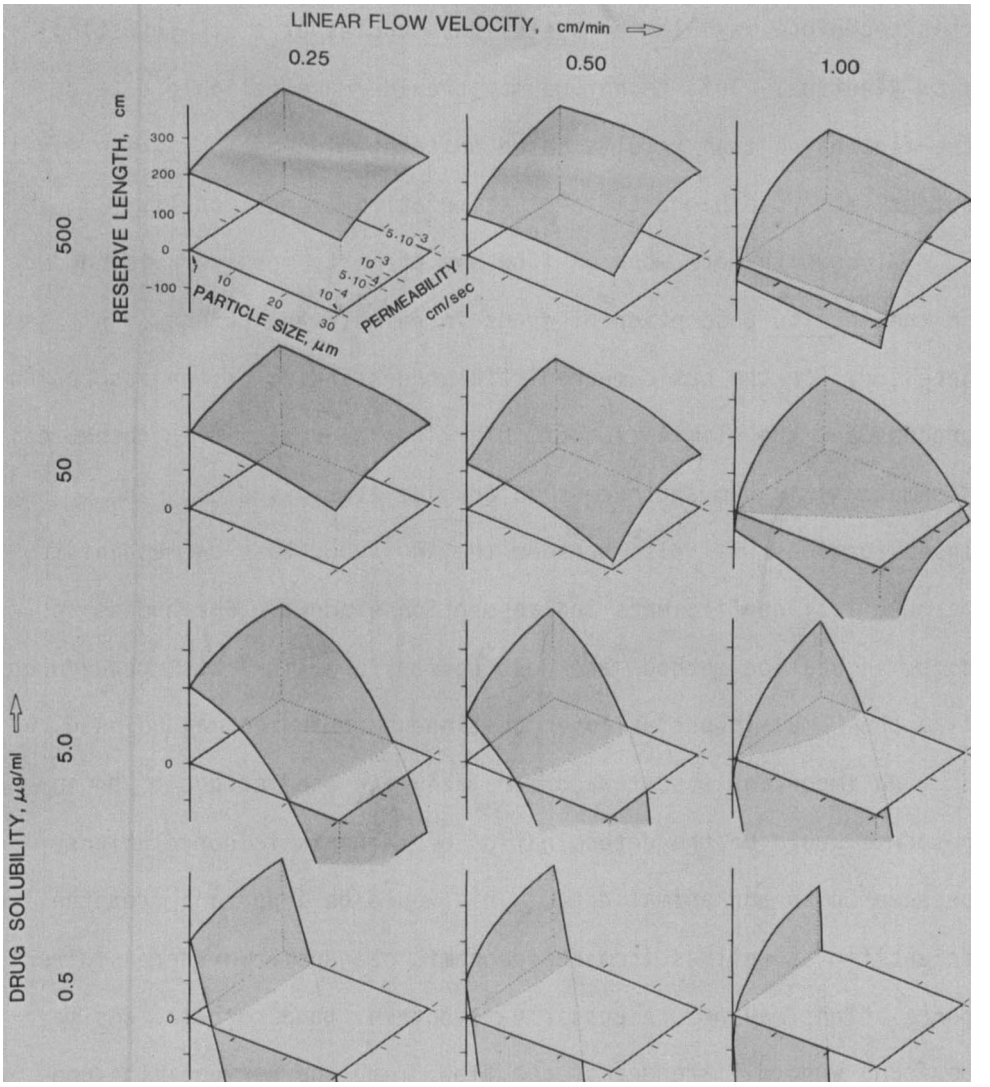

Figure 1

intubation). The most promising non-invasive technique at hand is scintigraphy using suitably radiolabeled solutions or dosage forms. This technique has so far been mostly used to study gastric emptying (Digenis et al., 1976, 1977, 1980; Heading et al., 1973; Fell et al., 1982).[2-6] However, more recent work indicates that

this technique may also be useful for studies of small intestinal flow kinetics. This technique may provide more reliable data on the flow rates than results based on intubation methods which may suffer from possible artificial stimulation of gut motility.

Along with more work on flow and transit, more work is needed on the in situ absorption of drugs in animals and humans. This is necessary for the basic mechanistic understanding of the absorption process and the elimination of "black box" concepts or hypothetical assumptions in our approaches to drug delivery studies. Such investigations will also broaden the knowledge base on mechanisms, permeability coefficients and absorption windows. For humans and dogs, intubation methods are most appropriate; for rats, procedures like the Doluisio-perfusion or continuous perfusion may be used.

An important step toward more accurate predictions of human response would be the determination of mechanistic correlations between human and animal data. This would be important from the scientific as well as from the economic standpoint. Whereas direct correlations may not be possible to obtain, good correlations may be found when differences of gut flow, membrane permeability and windows are taken into account in the models. Additionally, such correlations would be more meaningful and better suited for interpolation and extrapolation of data than when based on "black box" concepts. If such correlations can be successfully established, they would be useful for practical dosage form and drug delivery systems development.

An important focus of immediate and future work should be research on mechanisms to increase the residence of drug particles

or drug/excipient particles in the small intestine. As this will effectively increase transit times, absorption will be more complete and the effective reserve length will be increased. This consideration will be especially important for controlled release preparations mainly with regard to the question of completeness of absorption in the small intestine. Indication that this approach might be possible with the use of high density pellets have been presented by Bechgaard and Ladefoged (1978).[7] However, other authors have raised doubts about this approach, suggesting that prolonged small intestinal stay could be due to the fact that only ileostomy patients were studied. Other studies with normal subjects did not show similar effects (Bogentoft et al., 1982).[8]

Other research should be directed to prolonging the residence of small particles in the small intestine. Such improvement could be brought about by specific or non-specific particle/gut wall interactions during the intestinal passage of the particles. Although any discussion of possible mechanisms is speculative at the moment, the expectations are appealing. Specific interactions might be the most interesting, e.g., carbohydrate interactions mediated by calcium ions or by lectins. Although considerable knowledge about such interactions is available from fields like targeting of microparticulate carriers to cells or in bacterial attachment, they have not been proposed for the improvement of small intestinal residence.

Finally, data bases need to be established for assessing drug metabolism in and along the intestinal tract. The influences of bacterial flora in the terminal ileum and in the large intestine on

bioavailability need to be understood and quantified. Studies mapping out the enzyme systems with emphasis on location/distribution should be high priority.

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