DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(8&9), 1159-1175 (1986)

TOPOGRAPHICAL DISSOLUTION CHARACTERIZATION FOR CONTROLLED RELEASE PRODUCTS -- A NEW TECHNIQUE

J. P. Skelly,** L. A. Yamamoto,* V. P. Shah,*
M. K. Yau,* and W. H. Barr+

ABSTRACT

With most controlled release oral drug dosage forms, dissolution is the rate limiting step in drug release. While in vivo drug absorption and elimination involve a number of complex factors, characterization of in vitro dissolution rate under controlled conditions (pH, solvent, speed, etc.) should be able to provide valuable insights into in vivo drug bioavailability.

Frequently, the analysis of these factors becomes obscured when a variety of data are presented in conventional two dimensional plots. The choice of approval or disapproval of a new drug product based on such data becomes difficult. We have

* Division of Biopharmaceutics, Food and Drug Administration, Rockville, Maryland 20857
** To whom inquiries should be sent.
+ Virginia Commonwealth University, Richmond, Virginia 23219

0363-9045/86/1208-1159$3.50/0

therefore examined the characteristics of drug product dissolution using a multi-dimensional technique available in SAS as a means of more effectively delineating properties of dissolution rate. The results of our studies show that more definitive information can be discerned in a multi-dimensional topographic image which has been shown to be predictive of in vivo drug plasma concentrations.

INTRODUCTION

The increased emphasis on the development of a variety of new types of controlled release dosage forms has created some controversy about the methods employed to establish the bioavailability and bioequivalence of these products. One major problem, from a regulatory point of view, has been the creation and validation of in vitro methods for quality control of lot-to-lot variation and assurance of lot-to-lot bioequivalence. Even more critical is the use of in vitro method in lieu of human in vivo studies for the purpose of evaluation of minor excipient changes or changes in the site of manufacture. These difficulties arise, in part, due to the increasingly complex interactions of dosage form formulation variables with the increased physiologic variability of the absorption process due to the prolonged release.

In conventional (i.e., immediate release) drug oral dosage forms, drug absorption is usually quite rapid and most often dependent upon the concentration of the drug dissolved in the

gastrointestinal fluids of the upper GI tract (stomach, duodenum). Elimination is usually slower, such that the elimination rate constant K_e is considerably smaller than the absorption rate constant K_a. The purpose of a controlled release preparation on the other hand, is to deliver drug over a longer time interval usually over the entire intestine (jejunum, ileum and proximal colon) to prolong the drug absorption process. In contrast to immediate release products, the rate of absorption is often slower than the rate of elimination (resulting in plasma levels that are characterized by what have been called "flip-flop" models by pharmacokineticists). Thus, for most controlled release dosage forms, the in vivo dissolution and release from tablets, coated beads, nondissolving matrices, etc., becomes the most important, rate limiting step. It also becomes more difficult to simulate in vitro.

Since the controlled release drug dosage form passes through a milieu of varying pH (pH approaching 1 in the acid-secreting stomach to a pH above 7 in the distal section of the intestinal tract), pH becomes a major variable that must be considered in both the design and evaluation process. In addition, since controlled release dosage forms will usually be dosed in the presence of food as well as under fasting conditions, dramatic pH changes as well as the solubilizing influences of both bile and the highly buffered pancreatic secretions, should be

considered. Obviously, these variables can greatly influence the dissolution rate of the controlled release dosage form, and present a much more complex situation than that observed with conventional preparations. It is the complexity of the many factors involved in in vitro dissolution rate analysis that led to the development of a multi-dimensional topographical procedure as a tool for decision making.

While a number of drug controlled release products for over the counter cough and cold indications have been approved by the Agency, the first prescription product to have an approved dissolution specification for batch-to-batch approval, was Parke Davis' extended release phenytoin, Dilantin^{R}. Because of nonlinear first pass metabolism, it is possible for a fast dissolving 300 mg phenytoin dose to generate blood levels higher than would have been expected from three (T.I.D.) 100 mg administrations of the same drug, or a single administration of 300 mg of Phenytoin Extended (the slow release phenytoin) (1). Because of its slow release characteristics, the Parke Davis extended release formulation generates the same blood level profile when dosed 300 mg at one time, as it does when administered in three separate doses of 100 mg each. On the other hand, more rapidly dissolving immediate release 100 mg phenytoin formulations which are bioequivalent to the Parke Davis preparation when dosed at 100 mg T.I.D., generate

considerably higher drug blood levels when dosed 300 mg at one time.

In order to distinguish these two types of formulations, FDA proposed a dissolution window over time (2). In this case, there was only one manufacturer of the controlled release preparation. Additionally, the test methodology employed and the specification for lot to lot bioequivalence assurance was established based on the results of studies conducted in our Laboratories as well as those of Parke Davis and the USP. This dissolution test and specification has been adequate to assure the lot-to-lot bioequivalence of this product. Although for these reasons it can be regarded as a special case, it was reflective of the Agency's attempt to extrapolate the approach it had taken with conventional release formulations, to controlled release formulations. When this procedure, however, was employed for the purpose of marketing a generic version of Berlex' Quinaglute^{R} brand of quinidine gluconate, a serious bioavailability problem was discovered (3). The problem which was resolved by F.D.A. with a Class 1 recall, was interesting since both quinidine products exhibited virtually identical rates and extents of dissolution using the innovator's dissolution test (0.1N HCl), and additionally showed similar rates and extents of dissolution when tested in 0.1N HCl for 1 hour and pH 7.4 phosphate buffer for an additional seven hours (4).

At that time (1983) the Agency concluded (5) that because controlled release products which had virtually the same rate of dissolution over time, in the same media, were not equivalent when tested in vivo, conventional dissolution testing might not be a reliable predictor for controlled release products. Recently, faced with numerous requests for transferring the site of manufacture of controlled release dosage forms from sites in New York and New Jersey to the more tax advantageous Puerto Rico, without having to repeat costly human in vivo bioavailability studies, the possible predictive relationship of in vitro to in vivo data was reanalyzed. An in depth analysis indicated that if the rate of dissolution had been plotted as a function of pH, the possible lack of bioequivalence of the poorly bioavailable (inequivalent) quinidine gluconate dosage form could have been recognized. While the new variable, pH, (in addition to the time and percent dissolved variables employed for conventional preparations) could have been graphed in a multiplicity of two dimensional plots, a unique multi-dimensional topographical characterization was employed. This multi-dimensional topographical characterization effectively delineated the inadequacy of the deficient product (See accompanying paper) (6).

METHOD

Topographical dissolution characterization is described in this paper. The computer analysis was performed on an IBM 3081

computer using SAS Graph. This system has the advantage of high resolution, ease of use and excellent interpolation routines. The data were input by terminal using Time Sharing Option (TSO) and stored on a SAS data set. A Tektronix 4014 graphics terminal with a Tektronix 4631 hard copy output unit was used for most of the data entry. Data was usually entered using the x-axis for time, the y-axis for another independent variable such as rpm or pH, with percent dissolution along the z-axis. There is no limitation to the number of data points although spline interpolation becomes unwieldy with more than 100 data elements and thus expensive in terms of computer cost. Most of the data analysis was run using dissolution results at eight to ten time points spanning eight to twelve hours. Best results require at least four different pH settings for the dissolution analysis. Obviously, the choice of values should be set to reflect the range of pH values observed in vivo (i.e., physiologically significant - acid pH, neutral, and alkaline pH values).

The three dimensional graphs were generated using SAS procedures G3GRID to generate the spline interpolation of the data and G3D to generate the graphs. Several options are available using SAS Graph to present the data to provide the most useful view of the patterns. For instance the curves can be rotated or tilted around the central axis so that curvatures and surfaces can be seen in the best manner. Similarly, a

series of grid lines can be displayed to better demonstrate the topology of the graph as well as the numerical values of intermediate points. The spline interpolation of intermediate points was determined using the methods of Harder and Desmarais (7), and Meinguet (8). All procedures used were those presented in the SAS Graph User's Manual (9). SAS GRAPH also has the advantage of being easy to use and widely available to the scientific and industrial community.

RESULTS

An example of a multi-dimensional image generated showing in vitro dissolution rate vs pH is shown in Figure 1. As mentioned, this profile was created using standard SAS GRAPH commands and shows a profile of Squibb's Pronestyl-SR^{R} procainamide controlled release 500 mg Tablets. This dissolution analysis was run at four different pH values over a twelve hour dissolution time span. The profile was performed at a tilt angle of 60 degrees and a rotation angle of 45 degrees. It is readily apparent that the profile over the entire pH range is smooth and unremarkable. The advantage of multi-dimensional analysis in this particular instance is less dramatic, than shown with Bolar's quinidine gluconate in the accompanying article. Nevertheless, it clearly demonstrates the pH independent dissolution character of this controlled release formulation which has been shown by studies submitted to the FDA to be fully bioavailable. In situations where a complex

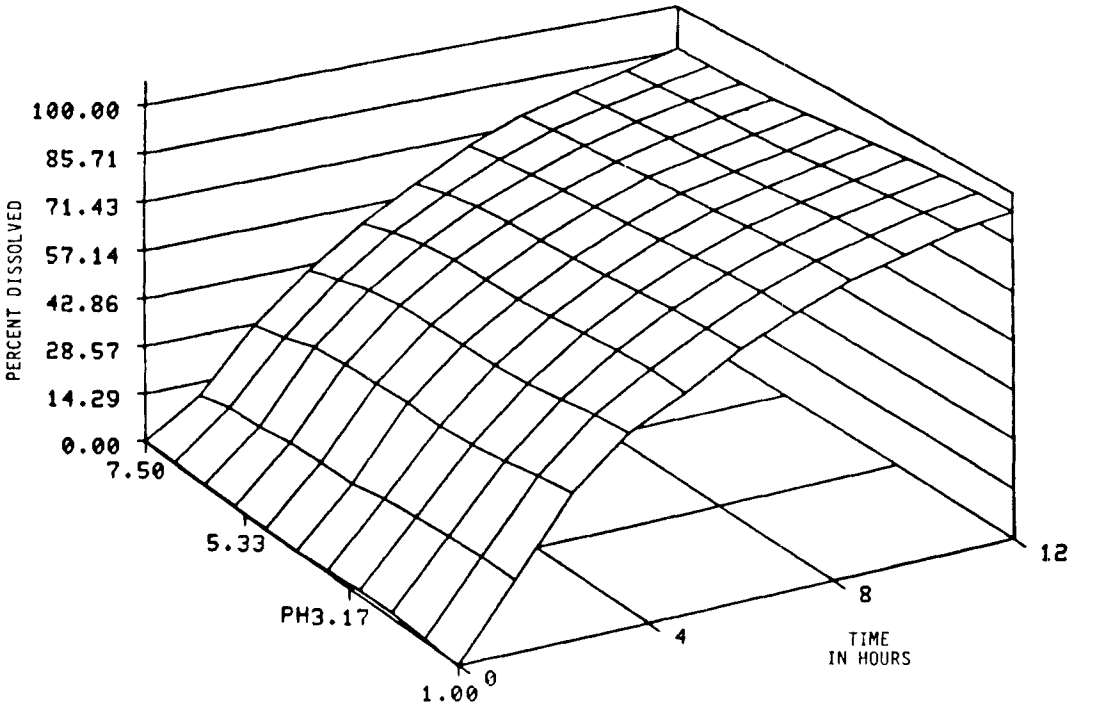

Figure 1

Topographical dissolution characterization of Squibb's Pronestyl-SR^{R} controlled release procainamide 500 mg tablets as a function of time and pH.

relationship exists between in vitro dissolution and in vivo bioavailability, and where dissolution varies as a function of pH, the advantage of topographical analysis is even more obvious.

That the use of topographical analysis as a more definitive and predictive method than two dimensional analysis, is demonstrated by the effects of pH on dissolution for product

formulations of the same drug. Additional examples will be provided and discussed in greater detail in subsequent papers.

DISCUSSION

A multifactorial graphical characterization of relevant dissolution variables is presented as being a better predictor of in vivo performance of drug product controlled release, than a single dissolution test conducted in a single medium. While not providing the assurance of a single dose or steady-state bioavailability study, this type of characterization can provide reasonable and adequate assurance of lot-to-lot uniformity and bioequivalence characterization of a formulation whose bioavailability and controlled release characteristics have been fully defined. On the other hand, relying on a dissolution test obtained from a single medium, as seen in the quinidine gluconate case, can be very misleading.

The increased complexity of the in vivo/in vitro association for controlled release drug products compared to conventional release is obvious. While the conventional release solid oral dosage form in vivo/in vitro relationship is two dimensional (i.e., the percent dissolved at a time interval versus the amount absorbed), the relationship for controlled release should be viewed as being multi-dimensional with pH being one important factor (in the case of orally administered drug).

Once the in vivo/in vitro relationship is fully characterized, one should be able to employ dissolution testing

in lieu of in vivo data for certain regulatory processes, e.g., minor equipment changes, process or manufacturing changes, site of manufacturing change, etc. If it can be ascertained that, as in the case of procainamide dissolution, the rate of dissolution for a particular drug formulation is independent of pH and speed of rotation, gastrointestinal pH changes should not affect in vivo absorption. This in vivo/in vitro relationship is characterized by the simulation in Figure 2. If one is operating on such a plateau, assurance is provided that minor changes in one parameter will have only a negligible effect on other parameters. If on the other hand, the in vitro dissolution rate over time increases as the pH of the media increases, the extent of absorption will also increase (reflective of the greater amount in solution at higher pH). Such a case may be described by the simulation in Figure 3. Where the slope is steep, a slight change in dissolution could yield quite unexpected in vivo results. If one is operating on such a slope then duplicative testing of material manufactured at the two different sites (e.g., New York and Puerto Rico) at several dissolution media pH's should be sufficient, if the data obtained are the same. If one has not pertubated their dissolution system so as to ascertain whether the topographic surface is flat or sloping, several tests may be necessary so as to determine the appropriate, sensitive variables.

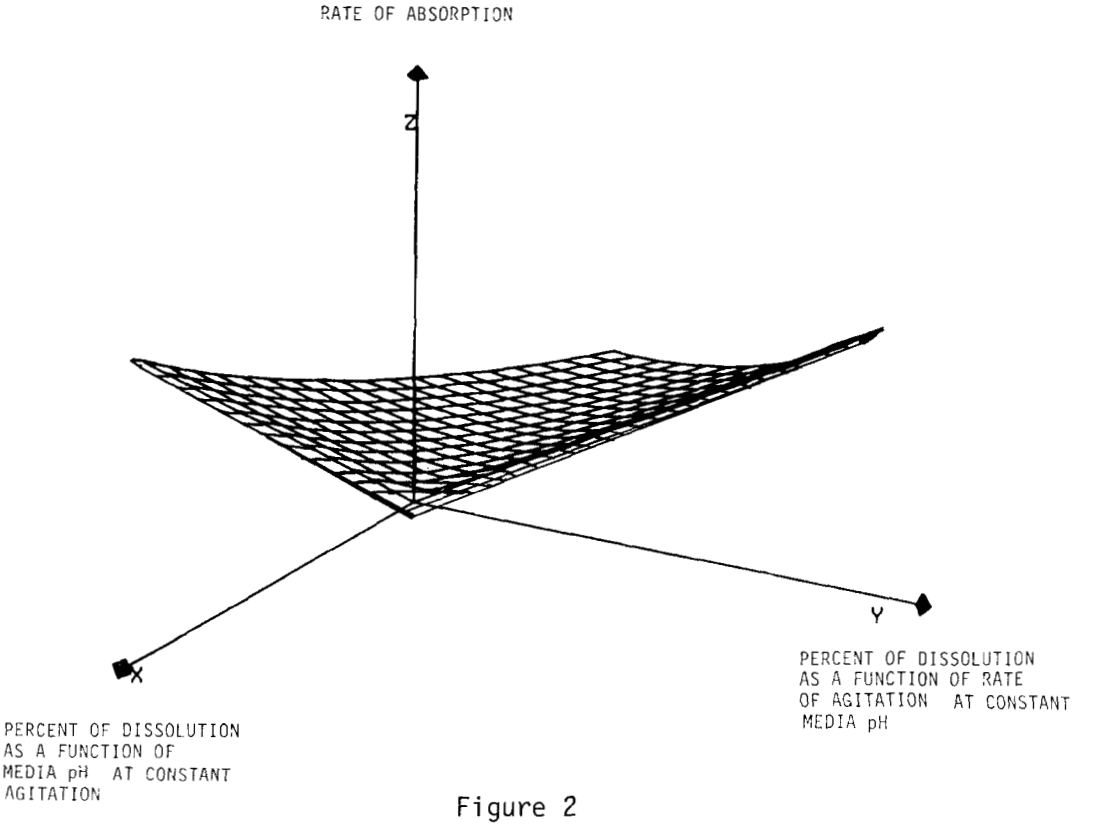

Figure 2

An example of a three dimensional in vivo/in vitro association for an oral controlled release dosage form where the dissolution rate is independent of both the rate of agitation and the pH of dissolution media.

An examination of the simulation in figure 4 illustrates a more complex relationship wherein the fluctuation within the therapeutic window is related to the apparent half-life of absorption and pH of the dissolution media. In the example illustrated, the rate of dissolution does not change as a

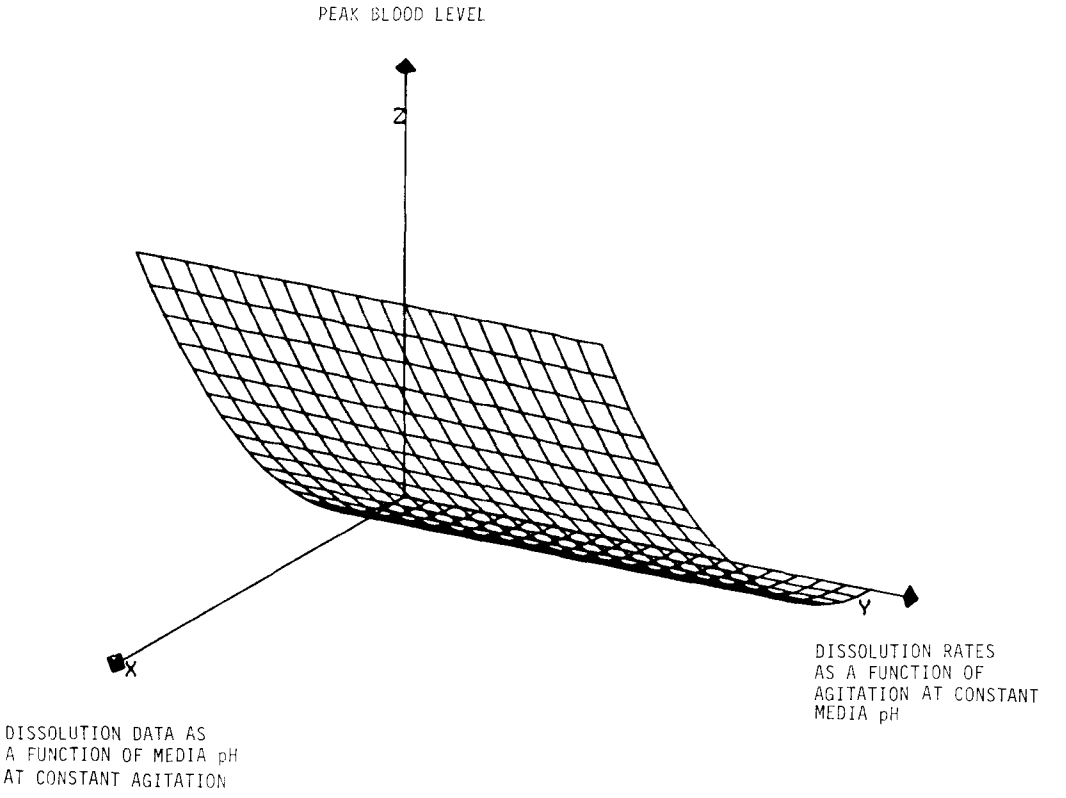

Figure 3

An example of a three dimensional in vivo/in vitro association for an oral controlled release dosage form where the dissolution rate at a particular time interval varies as a function of the pH of the dissolution media. Note that the dissolution rate at that time interval does not vary as a function of the rate of agitation.

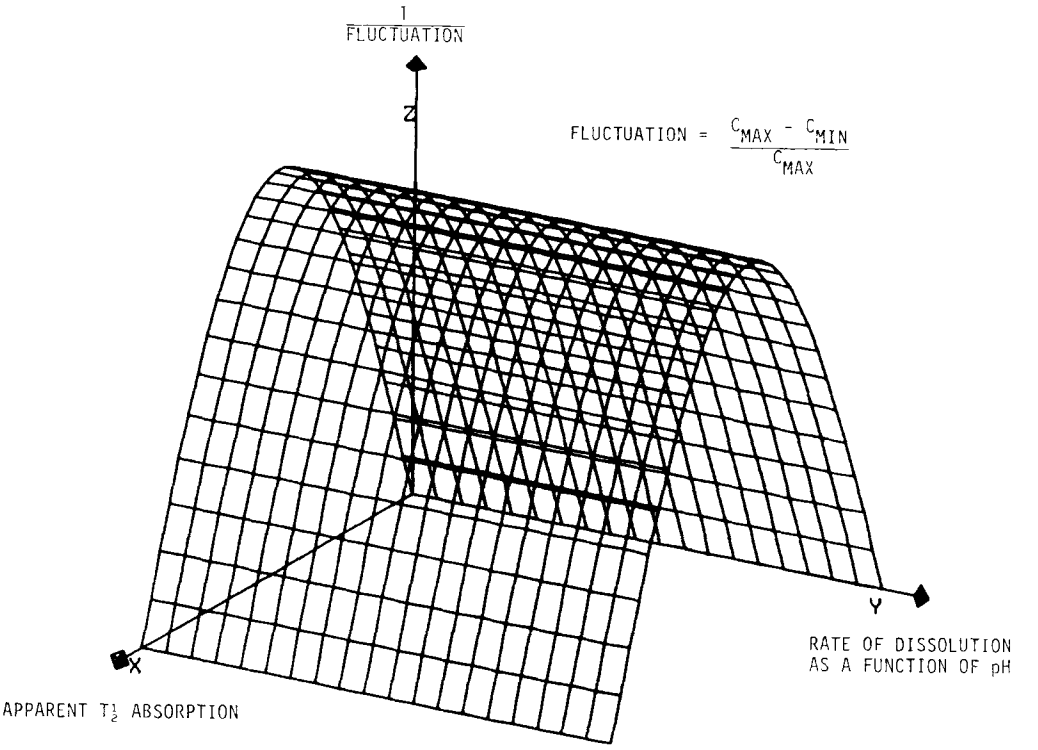

Figure 4

An example of a three dimensional in vivo/in vitro association for an oral controlled release dosage form where the rate of dissolution is independent of the pH of the dissolution media. Note that the apparent half-life of absorption is related to the inverse of the fluctuation of the drug concentration within the therapeutic window.

function of pH and therefore the media pH does not correlate the changes in the half-life of absorption or the fluctuation within the therapeutic window. On the other hand, as the half-life of absorption increases from zero to 24 hours, a bioavailability associated with minimum fluctuation is reached such that a population with specified clearance could be easily maintained within the therapeutic window. As the half-life of absorption is gradually increased above that optimum, the degree of fluctuation within the therapeutic window increases.

While in vitro topographical characterization will vary for different dosage forms (a waxy matrix being different than coated beads different than tablets, etc.), it will provide much greater assurance than a single dissolution test conducted in a single media. Relying on a dissolution profile obtained from a single media is likely better than no test, but, as was seen in the quinidine gluconate case, can be very misleading. On the other hand full in vitro topographical characterization, while not providing the assurance of a single dose or steady-state bioavailability study, can provide better assurance of lot-to-lot uniformity and bioequivalence characterization on formulations whose bioavailability and controlled release characteristics have been fully defined.

Further analysis using the topographic methodology showing its utility is demonstrated with quinidine gluconate and theophylline products and is discussed in subsequent

publications (6) (10). In summary, we feel the technique of multi-dimensional topographic analysis which is widely available to the scientific community lends itself to more accurately predicting the role of in vitro dissolution to in vivo response and should be examined more thoroughly to develop its potential.

Acknowledgment

The authors wish to thank Mrs. Marlene Shulman, Mrs. Bette Glazier and Ms. Shelley Johnson for their secretarial assistance.

REFERENCES

1. J. Gummitt, and R.J. Sawchuk, FDA Contract Number 223-76-3019.
2. V.P. Shah, V.K. Prasad, C. Freeman, J.P. Skelly, B.E. Cabana, J. Pharm. Sci., 72, 309 (1983).
3. M.C. Meyer, A.B. Straughn, P. Lieberman, J.T. Jacob, J. Clin. Pharmacol., 22, 131 (1982).
4. V.K. Prasad, V.P. Shah, P. Knight, H.J. Malinowski, B.E. Cabana, M.C. Meyer, Int. J. Pharm., 13, 1 (1983).
5. J.P. Skelly, Symposium "Critique of Proposed USP Policy on Modified Release Dosage Forms," 35th National Meeting, Academy of Pharmaceutical Sciences, Miami Beach, Florida (1983).
6. J.P. Skelly, M.K. Yau, L.A. Yamamoto, J.S. Elkins, W.H. Barr, V.P. Shah, Drug Devel. and Indus. Pharmacy, same issue (1986).

7. R.L. Harder, and R.N. Desmarais, J. Aircraft, 9, 189 (1972).

8. J.J. Meinguet, App. Math. Phy., 30, 292 (1979).

9. SAS GRAPH Users Guide Version 5 Edition, SAS Institute Inc., Cary, N.C. (1985).

10. J.P. Skelly, P.L. Hepp, C.T. Viswanathan, J. Elkins, L.A. Yamamoto, A. Noorizadeh, V.P. Shah, in preparation.