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# IN VITRO TOPOGRAPHICAL CHARACTERIZATION AS A *PREDICTOR OF IN VIVO CONTROLLED RELEASE* QUINIDINE GLUCONATE BIOAVAILABILITY

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## ABSTRACT

The pH dissolution profiles and bioavailability data of six quinidine gluconate controlled release products were obtained, and attempts were made to identify a dissolution condition that is most indicative of in vivo bioavailability. This was achieved by graphically displaying the pH dissolution profiles of the six products in multi-dimensional graphs utilizing a topographical plotting technique. These graphs were found to be quite effective in illustrating: a) the effects of pH and buffer composition on the dissolution rate of the test products, and b) the in vitro condition that best correlates with in vivo data. It was found that for the quinidine gluconate controlled

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release dosage forms studied, dissolution carried out in pH 5.4 phosphate buffer was most meaningful in showing the differences among dosage forms and for predicting in vivo bioavailability.

## INTRODUCTION

Quinidine is the dextrorotatory isomer of quinine. Quinidine Gluconate, the gluconate salt of quinidine is indicated in the prevention and treatment of various kinds of (ventricular, nodal, and atrial) arrhythmias. In 1982, an unapproved controlled release quinidine gluconate product was found to have poor bioavailability (1), and was subjected to a Class I recall. Subsequent investigation revealed that the unapproved product, which had been formulated to match the dissolution profile of the innovator product in simulated gastric fluid (pH 1), exhibited a different dissolution profile in pH 5.4 buffer. This shows that dissolution testing conducted in only one medium may not be a reliable in vivo bioavailability predictor for controlled release products (2). Unlike immediate release formulations which usually dissolve and are absorbed rapidly in the upper gastrointestinal tract, the dissolution of controlled release dosage forms is slower. Drug absorption is prolonged and often occurs in the entire gastrointestinal tract (pH ranges from about 1 in the stomach to 8 in the distal section of the intestine). It is obvious that for controlled release formulations, the in vivo/in vitro relationship is more complex and is more difficult to discover if the pH/dissolution

relationship is not fully delineated. Since it is hard to visualize the pH effect in conventional (two dimensional) dissolution graphs, a three dimensional topographical plotting technique was used in this paper to display the topographical dissolution characteristics of six quinidine gluconate controlled release products. These three dimensional topographical graphs have been found to be quite useful in identifying the in vitro dissolution condition that is best correlated with the in vivo bioavailability of the six test products.

## EXPERIMENTAL

The pH dissolution profiles and bioavailability data were obtained from the following controlled release tablets: 1) Quinaglute (Berlex/Schering, 324 mg), 2) Duraquin (Parke-Davis, 330 mg), 3) Quinidine Gluconate (Bolar Pharmaceutical, 324 mg unapproved marketed generic formulation), 4) Quinidine Gluconate (Bolar Pharmaceutical, 324 mg reformulated formulation), 5) Quinidine Gluconate (Chelsea Laboratories, 324 mg), 6) Quinidine Gluconate (Danbury Pharmaceutical, 324 mg). All of the above controlled release products except Product 3 were approved by FDA. The dissolution data were generated from the controlled release tablets that were collected by FDA inspectors. The single dose and multiple dose bioavailability data of Products 1, 2, 4, 5 and 6 were available through Freedom of Information requests. The design of these studies are described elsewhere

(3). The bioavailability of Product 3 was determined in a single dose study conducted by Meyer et al (1). Product 1, the innovator product, was used as the reference in all the studies.

Dissolution Tests

The dissolution tests were conducted using a 6 gang unit of a commerically available dissolution equipment[1] that meets USP specifications. The USP paddle (Apparatus II) at 100 rpm, and 900 ml of dissolution fluid at 37 ± 0.5 C were employed (4). Six controlled release tablets from each firm were tested in dissolution media with pH 1.0 (simulated gastric fluid without enzymes), pH 5.4 ( phosphate buffer), pH 5.4 (acetate buffer) and pH 7.4 (phosphate buffer). For Products 1 (innovator) and 3 (unapproved controlled release tablet), an additional dissolution test was conducted in a pH 6.0 (phosphate buffer) dissolution medium. The dissolution fluids used above were prepared as described in USP (4) or Documenta Geigy (5). The dissolution rate of the tablet in each of the six vessels was measured by passing filtered dissolution medium through the cells of the spectrophotometer[2] which recorded the absorbance (235 nm) at sampling times of 0, 1, 2, 3, 4, 5, 6, 7 and 8 hours. The concentration of quinidine gluconate in the dissolution fluid was determined by comparing the absorbance of the sample to a standard curve generated using quinidine gluconate reference standards prepared in the test dissolution medium.

## Three Dimensional Topographical Plot

An IBM 3081 computer using SAS GRAPH under the MVS operating system was employed. 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 and graphic outputs. To correct for sample to sample variance, the dissolution data entered were the mean of several runs. Data were entered using the x-axis for time, the y-axis for pH, and the z-axis for percent of drug dissolved. The three dimensional graphs were generated using SAS procedures G3GRID to generate the spline interpolation of the data and G3D to generate the graphs. All procedures used were those presented in the SAS Graph User's Manual (6) and have been described in a previous paper (7).

## RESULTS AND DISCUSSION

In order to prolong absorption and to provide sustained plasma drug levels, controlled release formulations are designed to have reduced dissolution rates. Unlike the immediate release formulations which usually dissolve rapidly (80%) in a relatively short time (e.g., 1 hr), the release of most controlled release dosage forms continues to occur in the small and even in the large intestine. In these cases, the dissolution rate becomes the most important rate limiting step in the drug absorption process. For example, if the reduced dissolution rate of a controlled release product is increased

suddenly by a drastic change in the pH of the gastric or intestinal fluid following a fatty meal, dose dumping can occur and can result in toxicity. This event, however, can often be anticipated if the pH dissolution profile of the controlled release product is thoroughly investigated. In this paper, we have studied the pH dissolution profiles of six quinidine gluconate controlled release products using a multi-dimensional topographical plotting technique, and related the results to the in vivo performance of the products.

Bioavailability

The results of the in vivo bioavailability studies are summarized in Table 1A, 1B (single dose studies) and Table 2A, 2B (multiple dose studies). With the exception of Product 3 which exhibited poor bioavailability, Products 2, 4, 5 and 6 were determined to be bioequivalent to Product 1 (3), the reference innovator product. As can be easily calculated from the data shown in Table 1A, the maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) of Product 3 was only about 35% and 41% of the innovator Product.

It should be pointed out that the poorly bioavailable product, Product 3 (later subjected to a class I recall), was first introduced into the market without FDA approval and was formulated to match the dissolution profile of the innovator product in 0.1 N HCl (pH 1). It was found later that this product exhibited poor dissolution in pH 5.4 buffers. When the

TABLE 1A

Mean Plasma Data for Quinidine Gluconate Controlled Release Tablets** (Single Dose Studies)

| | Study S2 | | Study S3 | | Study S4 | |
|---|---|---|---|---|---|---|
| Parameter | Product 2 | Product 1 | Product 3 | Product 1 | Product 4 | Product 1 |
| # of Subject | 12 | 12 | 12 | 12 | 20 | 20 |
| Dose (mg) | 330 | 324 | 648 | 648 | 324 | 324 |
| Cmax (ng/ml) | 0.25 | 0.33 | 0.47 (27)* | 1.36 (25) | 0.56 (33) | 0.52 (43) |
| Tmax hr | 8.0 | 6.0 | 3.5 (19) | 3.2 (38) | 5.5 (23) | 6.1 (27) |
| AUC (mg hr/ml) | 6.10[b] | 6.10[b] | 6.39[a](27) | 15.5[a](31) | 6.37[a](42) | 6.23[a](46) |
| AUC(0- ) (mg hr/ml) | -- | -- | 8.43 (43) | 16.90 (33) | 6.90 (45) | 6.88(46) |
| T 1/2 (hr) | -- | -- | 7.60 | 5.6 | 5.6 (28) | 6.0 (20) |

* Coefficient of variation

** Product 1 - Berlex Lot #42611, Lot #1209, Lot #B1254, were used as the reference product in Studies $S_2$, $S_3$, $S_4$, respectively.
Product 2 - Parke Davis, Lot #42505
Product 3 - Bolar (unapproved), Lot #090716
Product 4 - Bolar (approved), Lot 011885

a AUC (0-24 hr)

b AUC (0-48 hr)

TABLE 1B

Mean Plasma Data for Quinidine Gluconate Controlled Release Tablets** (Single Dose Studies)

| | Study S5 | | Study S6 | |
|---|---|---|---|---|
| Parameter | Product 5 | Product 1 | Product 6 | Product 1 |
| # of Subject | 20 | 20 | 24 | 24 |
| Dose (mg) | 324 | 324 | 324 | 324 |
| Cmax (ng/ml) | 0.58 (35) | 0.62 (34) | 1.01 (31) | 0.91 (34) |
| Tmax hr | 5.5(19) | 5.0 (27) | 3.71 (23) | 3.9 (31) |
| AUC (mg hr/ml) | 6.38[a](35) | 6.84[a](35) | 12.89[b](33) | 11.55[b](37) |
| AUC(0- ) (mg hr/ml) | 7.06 (40) | 7.53 (37) | 14.20 (38) | 12.91 (42) |
| T 1/2 (hr) | 6.3 (31) | 6.2(22) | -- | -- |

* Coefficient of variation
** Product 1 - Berlex Lot #R90172, Lot #W10578 were used as the reference product in Studies $S_5$, $S_6$, respectively.
Product 5 - Chelsea, Lot PD509
Product 6 - Danbury, Lot#22769
a AUC (0-24 hr)
b AUC (0-32 hr)

TABLE 2A

Mean Plasma Data for Quinidine Gluconate Controlled Release Tablets** (Multiple Dose Studies)

| Product Parameter | Study M2 | | Study M4 | |
|---|---|---|---|---|
| | Product 2 | Product 1 | Product 4 | Product 1 |
| # of Subject | 9 | 9 | 20 | 20 |
| Dose (mg) | 660 | 648 | 324 | 324 |
| Dosing Interval | q 12 hr | q 12 hr | q 12 hr | q 12 hr |
| Cssmin(ug/ml) | 0.55(18)* | 0.54(18) | 0.41(57) | 0.44(67) |
| Cssmax(ug/ml) | 1.17(30) | 1.22(24) | 0.91(47) | 1.01(64) |
| Tmax (hr) | 3.0 | 3.0 | 4.9(40) | 4.1(33) |
| AUC (72-84 hr) (ug hr/ml) | 9.70 | 10.40 | 7.96(52) | 8.81(66) |
| AUC (72-96 hr) (ug hr/ml) | -- | -- | -- | -- |
| T 1/2 (hr) | -- | -- | 5.61(24) | 5.67(24) |

* Coefficient of variation

** Product 1 - Berlex Lot #42611, Lot #B1254, were used as the reference product in Studies $M_2$, $M_4$ respectively
Product 2 - Parke Davis, Lot# 42505
Product 4 - Bolar (approved), Lot #11885

bioavailability problem of Product 3 was discovered (1), the firm reformulated and manufactured Product 4. In contrast to the old formulation, Product 4 has good dissolution in pH 5.4 buffer and was found to have good bioavailability. The in vivo performances of Products 1, 3 and 4 in the single dose studies are illustrated in Figure 1 which clearly shows that the mean plasma concentrations-time profile of Products 1 and 3 (Study

TABLE 2B

Mean Plasma Data for Quinidine Gluconate Controlled Release Tablets** (Multiple Dose Studies)

| Product Parameter | Study M5 | | Study M6 | |
|---|---|---|---|---|
| | Product 5 | Product 1 | Product 6 | Product 1 |
| # of Subject | 19 | 19 | 24 | 24 |
| Dose (mg) | 324 | 324 | 324 | 324 |
| Dosing Interval | q 12 hr | q 12 hr | q 12 hr | q 12 hr |
| Cssmin(ug/ml) | 0.46(41)* | 0.47(44) | 0.79(49) | 0.73(42) |
| Cssmax(ug/ml) | 1.01(33) | 1.07(39) | 1.59(47) | 1.53(37) |
| Tmax (hr) | 4.2 (26) | 3.9 (44) | 3.5 (47) | 3.1(42) |
| AUC (72-84 hr) (ug hr/ml) | 8.49 (32) | 8.73 (35) | -- | -- |
| AUC (72-96 hr) (ug hr/ml) | 12.05(33) | 12.32(37) | 19.74(44) | 17.86(42 |
| T 1/2 (hr) | 6.97 (31) | 6.80 (20) | 7.76 (32) | 7.59(31) |

* Coefficient of variation
** Product 1 - Berlex Lot #R90172, Lot #W10578 were used as the reference product in Studies $M_5$, $M_6$, respectively
Product 5 - Chelsea, Lot #PD509
Product 6 - Danbury, Lot #22769

S3) are significantly different but Products 1 and 4 (Study S4) are quite similar.

When the quinidine gluconate plasma levels of the reference product were compared among the studies, we noted that its drug levels in studies (following both single and multiple doses) involving Products 3, 4, and 5 after adjusting for the dose were quite similar but those in the study of Product 2 were lower and

in the study of Product 6 higher. This inconsistency in the plasma level of the reference product is probably not due to its inconsistent performance in the studies of Products 2 and 6, but are likely due to subject differences and/or specificity of the analytical assay employed. It is noted that the same variation was exhibited by the reference product in both the single and multiple dose studies of Products 2 and 6.

Dissolution

The mean dissolution profiles of the six quinidine gluconate controlled release tablets in different dissolution media with pH of 1.0 (simulated gastric fluid), pH 5.4 (acetate buffer), pH 5.4 (phosphate buffer), pH 6.0 (phosphate buffer, only for Products 1 and 3), and pH 7.4 (phosphate buffer) are shown in Tables 3 and 4. These dissolution fluids were chosen to cover the general pH range of the gastrointestinal tract. Additionally, both acetate and phosphate buffer of pH 5.4 were used to examine any effect of buffer composition. As shown in Tables 3 and 4, the dissolution of Product 3 at pH 1 was not significantly different from the other products, and had 79% of its labeled amount dissolved in 8 hours. However, at pH 5.4 its dissolution was poor with only 24% dissolved in the phosphate buffer and 51% dissolved in acetate buffer after 8 hours whereas the other products dissolved at least 71% in phosphate buffer and 82% in acetate buffer at the same sampling time. These data show that, while the lack of dissolution of Product 3 in acetate

TABLE 3

Dissolution Profiles of Products 1, 3 and 4 in Dissolution Media of Different PHs

| Time (hr) | % Dissolved pH 1.0 (Simulated Gastric Fluid) | pH 5.4 (Acetate Buffer) | pH 5.4 (Phosphate Buffer) | pH 6.0 (Phosphate Buffer) | pH 7.4 (Phosphate Buffer) |
|---|---|---|---|---|---|
| Product 1 | | | | | |
| 1 | 39.4* | 44.6 | 43.9 | 51.6 | 14.4 |
| 2 | 53.1 | 66.3 | 59.3 | 78.8 | 20.9 |
| 3 | 62.3 | 86.4 | 67.5 | 89.3 | 31.2 |
| 4 | 68.0 | 100.0 | 72.5 | 97.9 | 35.5 |
| 5 | 74.2 | 100.0 | 76.6 | 100.0 | 39.5 |
| 6 | 79.3 | 100.0 | 79.6 | 100.0 | 43.1 |
| 7 | 80.9 | 100.0 | 82.9 | 100.0 | 46.4 |
| 8 | 85.8 | 100.0 | 84.6 | 100.0 | 50.0 |
| Product 3 | | | | | |
| 1 | 28.9 | 19.3 | 12.5 | 20.7 | 8.9 |
| 2 | 47.1 | 26.5 | 14.6 | 30.9 | 13.1 |
| 3 | 54.7 | 31.9 | 16.5 | 37.9 | 17.6 |
| 4 | 61.2 | 36.4 | 18.7 | 43.6 | 19.8 |
| 5 | 66.6 | 40.3 | 19.5 | 49.0 | 22.0 |
| 6 | 71.3 | 45.7 | 21.6 | 54.1 | 25.4 |
| 7 | 76.2 | 48.6 | 22.9 | 58.1 | 26.6 |
| 8 | 78.9 | 51.4 | 24.3 | 61.9 | 28.0 |
| Product 4 | | | | | |
| 1 | 52.0 | 50.0 | 32.0 | | 51.0 |
| 2 | 76.0 | 70.0 | 41.0 | | 56.0 |
| 3 | 91.0 | 85.0 | 48.0 | | 61.0 |
| 4 | 94.0 | 97.0 | 54.0 | | 64.0 |
| 5 | 97.0 | 100.0 | 59.0 | | 66.0 |
| 6 | 100.0 | 100.0 | 63.0 | | 69.0 |
| 7 | 100.0 | 100.0 | 68.0 | | 71.0 |
| 8 | 100.0 | 100.0 | 71.0 | | 73.0 |

* Mean of six data points

TABLE 4

Dissolution Profiles of Products 2, 5 and 6 in Dissolution Media of Different PHs

| Time (hr) | % Dissolved pH 1.0 (Simulated Gastric Fluid) | pH 5.4 (Acetate Buffer) | pH 5.4 (Phosphate Buffer) | pH 7.4 (Phosphate Buffer) |
|---|---|---|---|---|
| Product 2 | | | | |
| 1 | 43.0* | 33.9 | 33.1 | 42.3 |
| 2 | 57.0 | 46.8 | 45.3 | 48.9 |
| 3 | 66.8 | 56.0 | 53.5 | 54.2 |
| 4 | 74.2 | 63.2 | 59.2 | 56.9 |
| 5 | 80.1 | 69.0 | 63.9 | 58.5 |
| 6 | 85.1 | 74.0 | 67.5 | 59.8 |
| 7 | 89.3 | 78.3 | 70.5 | 61.0 |
| 8 | 92.9 | 82.0 | 73.2 | 62.0 |
| Product 5 | | | | |
| 1 | 41.0 | 38.0 | 33.0 | 40.0 |
| 2 | 60.0 | 59.0 | 47.0 | 45.0 |
| 3 | 72.0 | 74.0 | 55.0 | 47.0 |
| 4 | 80.0 | 83.0 | 62.0 | 49.0 |
| 5 | 88.0 | 94.0 | 67.0 | 52.0 |
| 6 | 99.0 | 97.0 | 71.0 | 53.0 |
| 7 | 100.0 | 98.0 | 74.0 | 55.0 |
| 8 | 100.0 | 98.0 | 76.0 | 57.0 |
| Product 6 | | | | |
| 1 | 45.0 | 39.0 | 39.0 | 44.0 |
| 2 | 61.0 | 55.0 | 54.0 | 52.0 |
| 3 | 71.0 | 66.0 | 63.0 | 56.0 |
| 4 | 70.0 | 74.0 | 68.0 | 58.0 |
| 5 | 87.0 | 81.0 | 72.0 | 60.0 |
| 6 | 95.0 | 90.0 | 76.0 | 62.0 |
| 7 | 100.0 | 97.0 | 81.0 | 64.0 |
| 8 | 100.0 | 100.0 | 87.0 | 65.0 |

* Mean of six data points

buffer was not quite as severe as in phosphate buffer, it still dissolved considerably slower than any other product in the same dissolution medium. At pH 7.4 phosphate buffer, the dissolution of Product 3 remained poor with only 28% dissolved in 8 hrs while the dissolution rate of the other products generally decreased and had 50% (Product 1), 62% (Product 2), 73% (Product 4), 57% (Product 5) and 65% (Product 6) of the labeled amount dissolved at that time.

These results indicate that the dissolution tests conducted in pH 5.4 phosphate and acetate buffer are most useful to discern the quinidine gluconate controlled release products. The testing in pH 7.4 phosphate buffer is not quite as good for this purpose because most of the products dissolved rather poorly at this pH. Since all the products exhibited adequate dissolution in simulated gastric fluid, dissolution testings carried out in this medium are not discriminative.

In agreement with our earlier paper (2), the results obtained in this paper again show that buffer composition can influence dissolution rate. All six controlled release tablets dissolved to a greater extent at pH 5.4 acetate buffer than in phosphate buffer. The cause of this difference is unknown but may be attributed to the solubility difference of quinidine gluconate in the two buffer solutions. As reported previously (2), it is also possible that a different kind of interaction between the acetate or phosphate ions with the constituents of

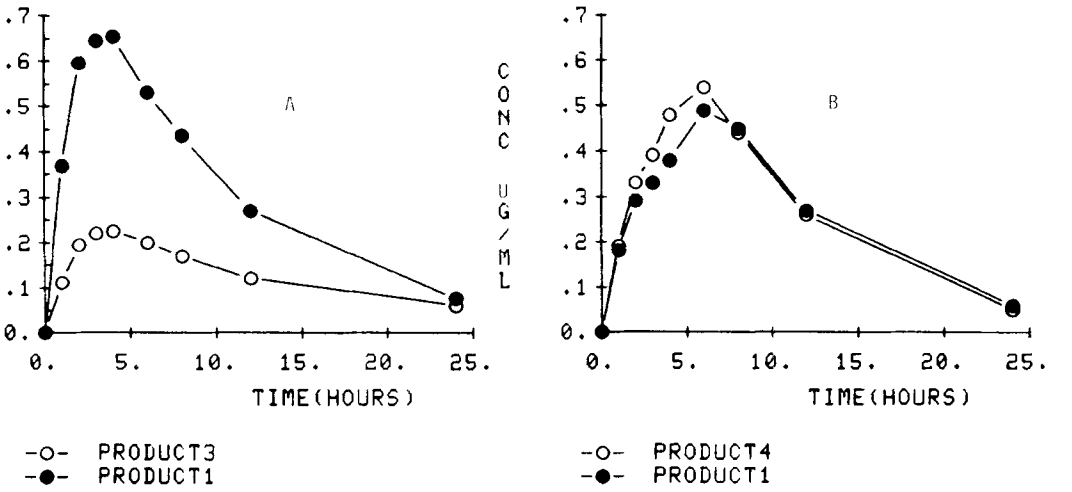


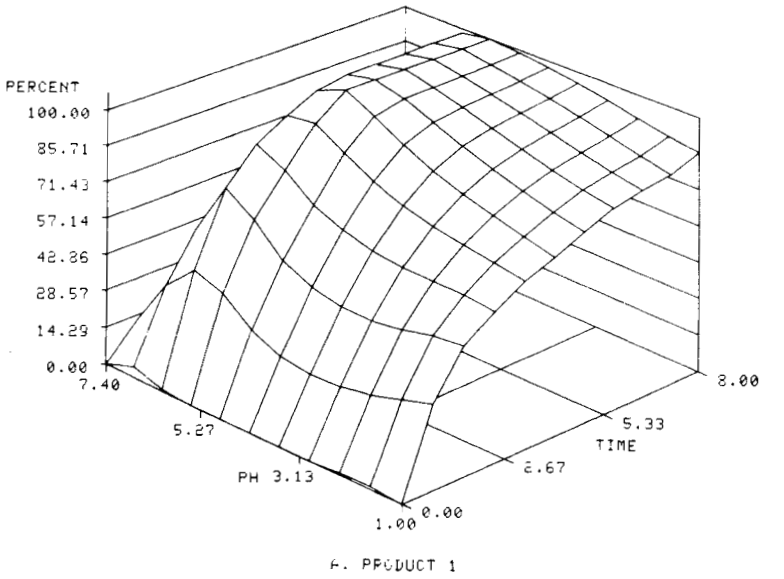

Figure 1

Mean quinidine plasma concentrations of Products 1, 3 (Study S3, Plot A) and Products 1, 4 (Study S4, Plot B). Data in Study S3 (648 mg dose) were normalized to the dose used in Study S4 (324 mg dose).

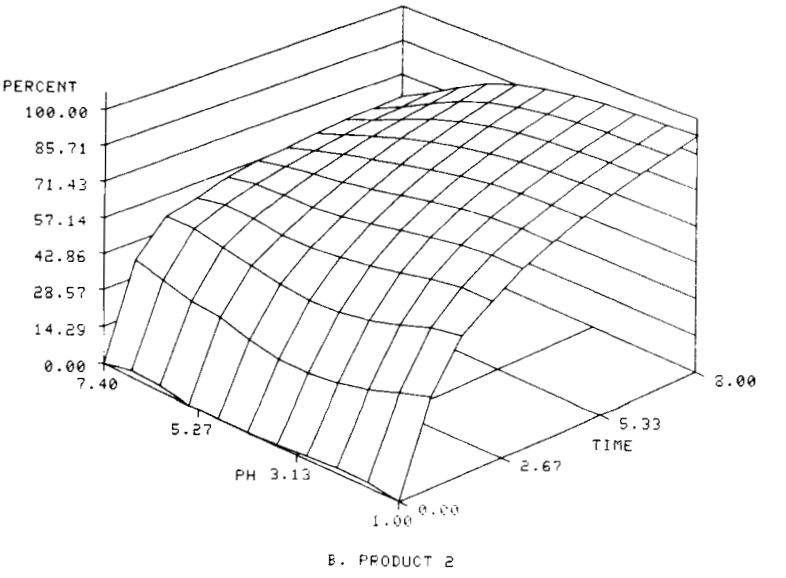
the dosage forms may lead to a larger amount of drug to dissolve in the acetate buffer. Regardless of the cause, the results of these studies have demonstrated both pH and buffer composition can play an important role in discerning differences among dosage forms, and should be considered during the developing of controlled release products.

Three Dimensional Topographical Plots and In-Vivo In-Vitro Relationships

In order to illustrate graphically how the dissolution rates of the six quinidine gluconate controlled release products are



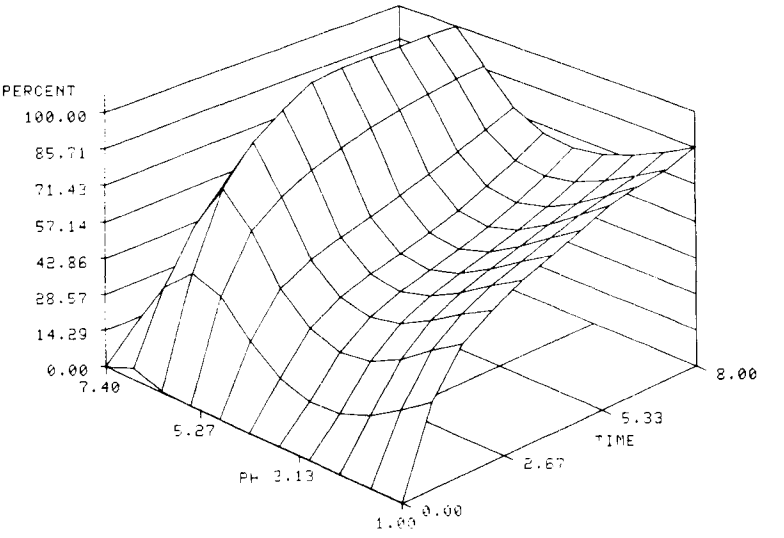

A. PRODUCT 1



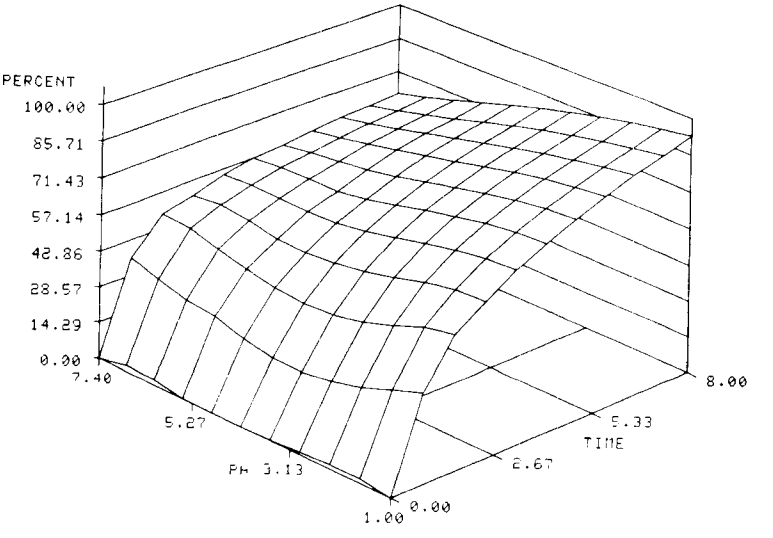

B. PRODUCT 2

Figure 2

Topographical dissolution characterization of Products 1 and 2 as a function of time and pH. Data from pH 5.4 acetate buffer were used in Plots A, B; data from pH 5.4 phosphate buffer were used in Plots C and D.

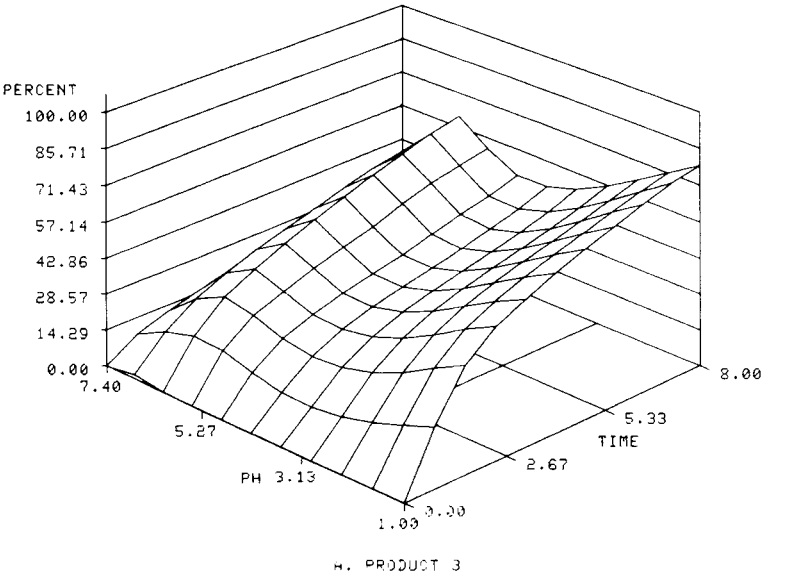



C. PRODUCT 1

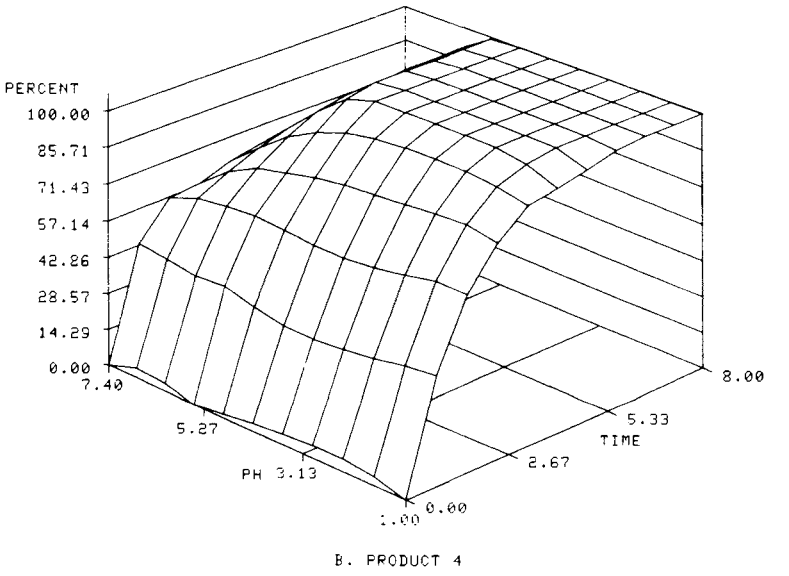



D. PRODUCT 2

Figure 2 continued.



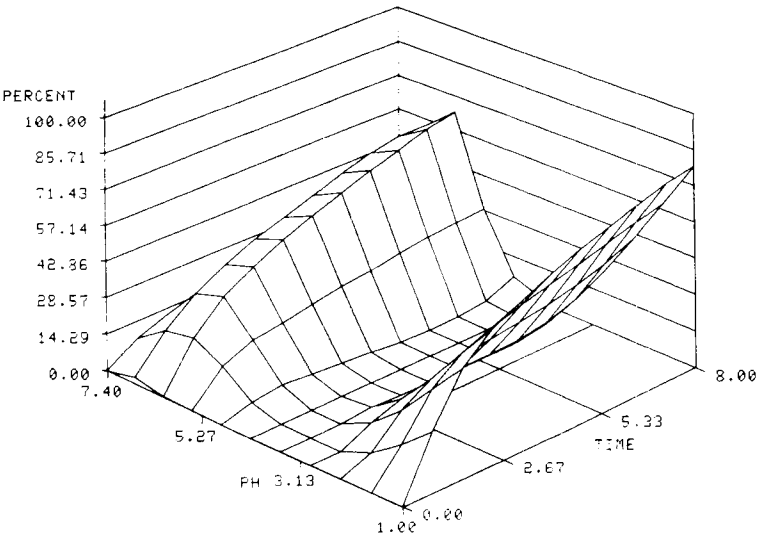

A. PRODUCT 3



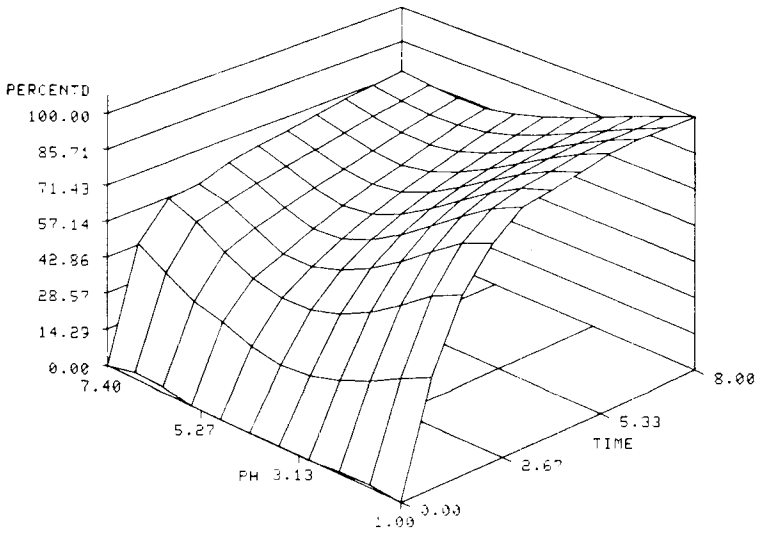

B. PRODUCT 4

Figure 3

Topographical dissolution characterization of Products 3 and 4 as a function of time and pH. Data from pH 5.4 acetate buffer were used in Plots A, B; data from pH 5.4 phosphate buffer were used in Plots C and D.

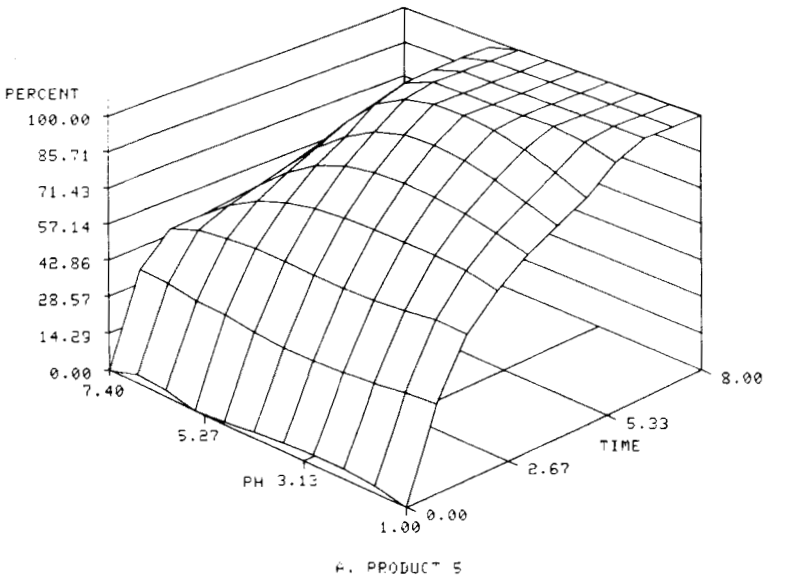



C. PRODUCT 3

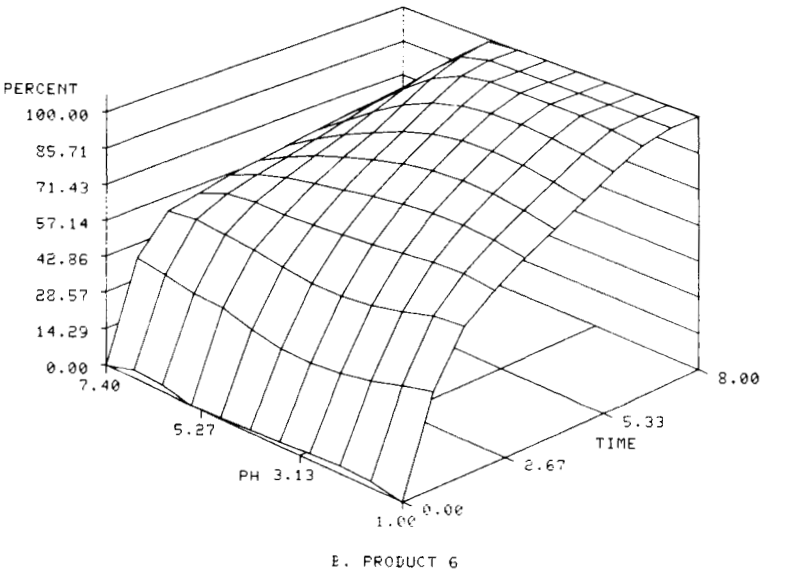



D. PRODUCT 4

Figure 3 continued.



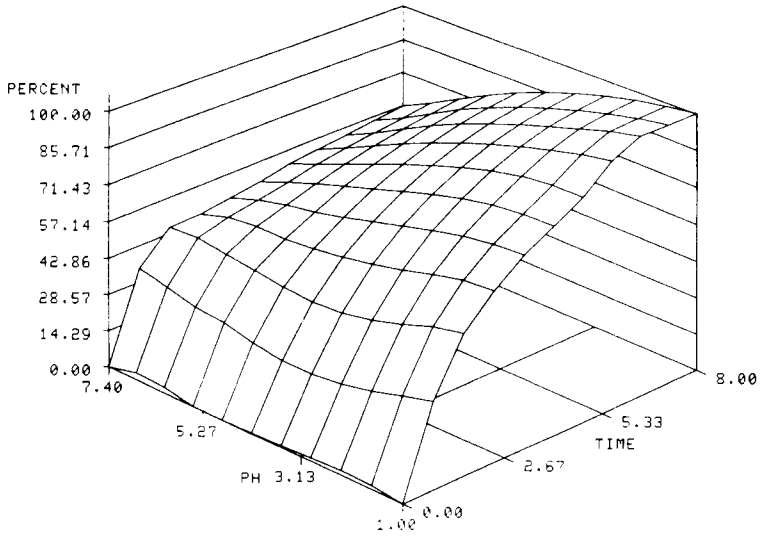

A. PRODUCT 5



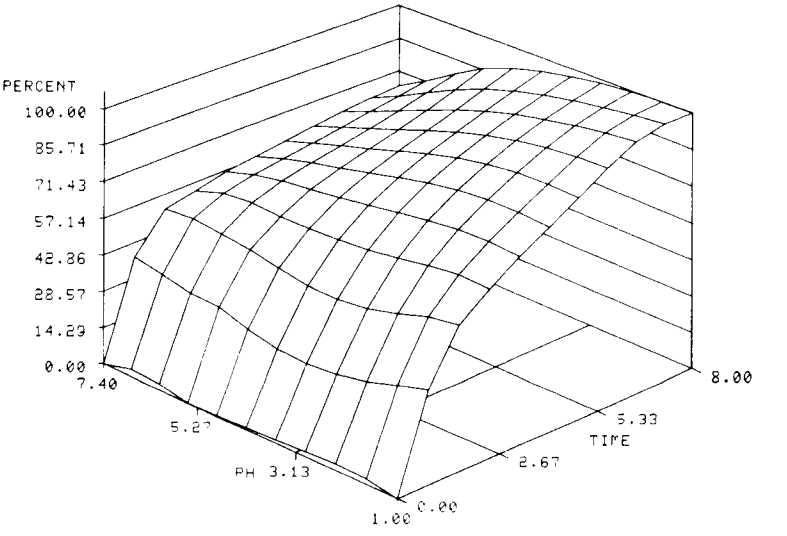

B. PRODUCT 6

Figure 4

Topographical dissolution characterization of Products 5 and 6 as a function of time and pH. Data from pH 5.4 acetate buffer were used in Plots A, B; data from pH 5.4 phosphate buffer were used in Plots C and D.




C. PRODUCT 5




D. PRODUCT 6

Figure 4 continued.

influenced by pH of the dissolution medium, three dimensional graphs were generated using the topographical technique described above. The results for Products 1 and 2 are shown in Figures 2A, 2B (using pH 5.4 acetate buffer dissolution data) and Figures 2C, 2D (using pH 5.4 phosphate buffer dissolution data). Those for Products 3, 4, 5 and 6 are shown in Figures 3A, 3B, 4A, 4B (using pH 5.4 acetate buffer data) and Figures 3C, 3D, 4C, 4D (using pH 5.4 phosphate buffer data). As shown in these graphs, the entire picture of pH effect on the dissolution profile of a product can be clearly illustrated in one plot thereby eliminating the confusion of relating a series of two dimensional graphs together. One can see from these figures that the topographical surfaces of Products 1, 2, 4, 5 and 6 are relatively flat when compared to that of Product 3 (Figures 3A, 3C) which is curved in a U shape, showing the dissolution rate of Product 3 is more influenced by pH of the dissolution fluids. Additionally, the three-dimensional topographical plots are found to be quite efficient in displaying the effect of buffer composition, and also quite useful in helping one to select the most appropriate dissolution medium. As clearly demonstrated by the topographical surfaces of Product 3 in Figure 3A (pH 5.4 acetate buffer) and Figure 3C (pH 5.4 phosphate buffer), one can conclude the pH 5.4 phosphate buffer is the most discriminating dissolution medium.

In relating the in vivo and in vitro performances of the six test products, we found the poor bioavailability of Product 3 is consistent with its poor dissolution in both pH 5.4 acetate and phosphate buffer. Based on the in vivo data and the three dimensional topographical plots of the six quinidine gluconate controlled release products, the dissolution results obtained in pH 5.4 phosphate buffer are most meaningful for discerning dosage forms and for predicting in vivo bioavailability. All four quinidine gluconate controlled release products (Products 2, 4, 5 and 6) that exhibited adequate dissolution in pH 5.4 phosphate buffer had adequate bioavailability and were evaluated to be bioequivalent to the innovator product (Product 1); while the only dosage form (Product 3) that showed poor dissolution also had poor in vivo performance. On the contrary, dissolution results obtained in simulated gastric juice (pH 1) are not discriminating and in fact are misleading if used as a predictor for in vivo bioavailability. These findings clearly show that the conventional dissolution testing using only one dissolution medium is not adequate in the design and formulation of controlled release dosage forms.

## CONCLUSION

The in vivo/in vitro relationship of controlled release formulations is much more complex than immediate release dosage forms. In order to develop a meaningful dissolution procedure that is indicative of in vivo bioavailability, the influence of

pH and buffer composition of the dissolution medium on the dissolution rate of the controlled release dosage form must be carefully studied. Their effects can be illustrated using multi-dimensional topographical plots.

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## FOOTNOTES

1 Easilift Dissolution Test Station, Model 63-734-100. Hanson Research, Research Corporation, Northridge, Ca.

2 Beckman Spectrophotometer Model 25 and Recorder Controller, Beckman Instruments, Fullerton, CA.

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