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THE EFFECTS OF PH, IONIC CONCENTRATION AND IONIC SPECIES OF DISSOLUTION MEDIA ON THE RELEASE RATES OF QUINIDINE GLUCONATE SUSTAINED RELEASE DOSAGE FORMS

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ABSTRACT

The dissolution profiles of some extended release quinidine gluconate products were shown to be dependent on several dissolution medium variables. It was shown that, for a quinidine gluconate wax matrix tablet, the dissolution rate has an unexpected inverse relationship to the solubility as a function of pH. The dissolution rate is also affected by the concentration of chloride ion present in the dissolution medium apparently due to the inhibition of disintegration. It was found that the nature of

the anion (inorganic vs. organic) of the dissolution buffer plays a significant role in the release of the drug. Salts of inorganic acids used as part of the buffer system lower the rate of release of quinidine gluconate from wax matrix tablets through an inhibition of disintegration. On the other hand, buffer salts of organic acids do not have any appreciable effect on the disintegration or dissolution of these tablets. Since the concentration of chloride ion in both gastric and intestinal juices is approximately 0.1M, this suggests that the use of a dissolution medium containing chloride ion represents the more appropriate approach when an in-vivo/in-vitro correlation is desired. For all the quinidine gluconate controlled release formulations studied, mechanisms of release are of at least two different types. This makes the selection of a single dissolution medium for in-vivo/in-vitro correlations either improbable or impossible.

INTRODUCTION

In-vitro dissolution testing of solid oral dosage forms under simulated biological conditions has been used for studying pharmaceutical formulations and for predicting in-vivo performance. Many dissolution investigations use media that are intended to be a simple model of in-vivo conditions, e.g., Simulated Gastric Fluid, USP or Simulated Intestinal Fluid, USP[1]. Investigators often attempt to correlate in-vitro results with

pharmacokinetic parameters such as the Cmax, Tmax or AUC[2]. Several workers have suggested that, for extended release products, deconvolution of the in-vivo plasma curve can lead to an input function that would be analogous to the dissolution profile[3,4]. Other investigators have used computer simulations to project drug level curves in plasma from a combination of pharmacokinetic data and the dissolution profiles[5].

Prasad, et al.[6] and Skelly, et al.[7,8] suggested that the dissolution of quinidine gluconate (QG) sustained release products in pH 5.4 acetate buffer could lead to a correlation with in-vivo results. They believed that this correlation could be used to predict the bioavailability of QG from any controlled release product. In their studies they concluded that the cumulative percent of quinidine gluconate released at 4 hours in acetate buffer (pH=5.4) from each of several quinidine gluconate sustained release tablets was predictive of bioavailability (AUC).

We decided to test the hypotheses that: (1) the dissolution of dissimilar formulations of quinidine gluconate would depend upon dissolution medium parameters such as pH, ionic strength and ionic species to different extents, and that; (2) differences in the respective dissolution mechanisms of different formulations would preclude the use of a single medium for the respective in-vivo/in-vitro correlations of all products.

There were several major findings from this study. First, it was shown that, for a quinidine gluconate wax matrix tablet, the dissolution rate has an unexpected relationship to the solubility as a function of pH. Second, the dissolution rate is affected by the concentration of chloride ion present in the dissolution medium apparently due to the inhibition of disintegration. Third, the nature of the anion (inorganic vs. organic) of the dissolution buffer could play a significant role in the release of the drug. Salts of inorganic acids used as the buffering system lower the rate of release of quinidine gluconate from wax matrix tablets through an inhibition of disintegration. Salts of organic acids do not have any appreciable effect on their dissolution.

When wax matrix formulations were studied, it was found that dissolution parameters such as pH, ionic species, and ionic concentration had pronounced effects on the release rate. Non-disintegrating formulations were affected by some of these dissolution media variables, but to a lesser extent.

An attempt was made in previous studies[5-8] to standardize dissolution parameters for an in-vivo/in-vitro correlation for quinidine gluconate. From the results of our investigations, it has become clear that the choice of a dissolution test medium for generalized in-vivo/in-vitro correlations must take into account both the composition of the medium and the characteristics of the formulation for each specific product.

Materials and Methods

Reagents:

Anhydrous sodium acetate, glacial acetic acid, concentrated hydrochloric acid, sodium chloride, anhydrous sodium iodide and sodium nitrate were purchased from J.T. Baker Chemical Co. and were all of ACS grade. Sodium hydroxide was purchased from Fisher Scientific and was of ACS grade. Propionic acid, butyric acid, isobutyric acid, (+)-2-methylbutyric acid, valeric acid, isovaleric acid were all obtained from Aldrich Chemical Co. and were all of reagent grade. Distilled, deionized water was produced by an Autostill (Wheaton).

Dissolution media:

Acetate buffer: 6.9 g sodium acetate/0.525 mL glacial acetic acid/L water, adjusted to pH of 5.4 with either 0.1N HCl or 0.1N NaOH.

Carboxylic acid buffers: 0.1M solutions of propionic acid, butyric acid, isobutyric acid, (+)-2-methylbutyric acid, valeric or isovaleric acid adjusted to pH 5.4 with 2N NaOH.

Procedures:

All dissolution experiments were performed at 37° ±0.5°C. using an USP XXI Dissolution Apparatus #2 (rotating paddle) at 75

rpm. The dissolution assay was automated by using a six-station dissolution tester (Hanson model 72R-QC). Detection of quinidine gluconate was accomplished by U.V. spectrophotometry at the isosbestic point (334 nm) using a diode array spectrophotometer (Hewlett-Packard 8450A) controlled by a microcomputer (Hewlett-Packard 85).

Quantitative disintegration was measured as follows: The USP Apparatus #2 (paddles) was used at 75 rpm. At selected time points (1,2,4 and 8 hours), the dissolution apparatus was stopped. The contents of each vessel was poured through a #10 screen onto a preweighed #4 filter paper in a Buchner funnel. Tablet pieces that collected on the screen were weighed and returned to their respective dissolution flask. The filter paper was allowed to dry and was reweighed to determine the weight of particles that were retained by the filter. From the cumulative weights of the disintegrated particles collected on the filters, the fraction disintegrated and the percent disintegrated at each time point was calculated. (Carstensen and co-workers used the USP baskets in an alternative procedure to quantitatively measure the disintegration of prednisone tablets[9]).

Equilibrium solubilities of quinidine gluconate in various solvents were determined at room temperature (23° ±2° C.) An excess amount of drug was allowed to dissolve, while shaking, for at least 24 hours. Filtered portions of the clear supernatant

were diluted and assayed using a UV spectrophotometer (Model 219, Varian Instrument Co.).

Formulations:

All products studied contained quinidine gluconate as their active ingredient. Quinidine gluconate experimental controlled release tablets, 486 mg (Berlex Laboratories, Inc.), Duraquin, 330 mg (Parke-Davis, Division of Warner-Lambert Co.), Quinidine Gluconate Sustained Action Tablets, 324 mg (Danbury Pharmacal, Inc.) and Quinidine Gluconate Sustained Action Tablets, 324 mg (Bolar Pharmaceutical Co., Inc.) were used in this study. The Berlex product is a wax matrix tablet. The specific composition of the other products are unknown. The Parke-Davis and the Danbury products are non-disintegrating tablets.

RESULTS AND DISCUSSION

In many cases, the dissolution rates of drug formulations are a function of solubility[10]. Since the pKa of quinidine conjugate acid is 5.4[11], the solubility of quinidine gluconate in aqueous media increases as the pH is decreased in the pH range usually employed for dissolution (i.e. pH 7.5 to pH 1.0). The solubility of quinidine gluconate as a function of pH in HCl media is shown in Table I. Based on the solubility profile, it was anticipated that an inverse relationship would be found between pH

Table I

Solubility of Quinidine Gluconate at Room Temperature

Medium	pH*	Solubility, mg/mL
Water	6.08	107
0.05N HCl	5.12	139
0.1N HCl	4.54	150
0.2N HCl	4.27	205
0.5N HCl	3.93	205
1.0N HCl	3.78	235
0.056M NaCl/Water	6.19	108
0.10M NaCl/Water	6.29	90
0.306M NaCl/Water	6.39	41
0.5M NaCl/Water	6.47	6
0.103M Sodium Acetate	6.23	112
0.31M Sodium Acetate	6.32	122
0.46M Sodium Acetate	6.37	131
0.62M Sodium Acetate	6.33	133

* pH of final solution

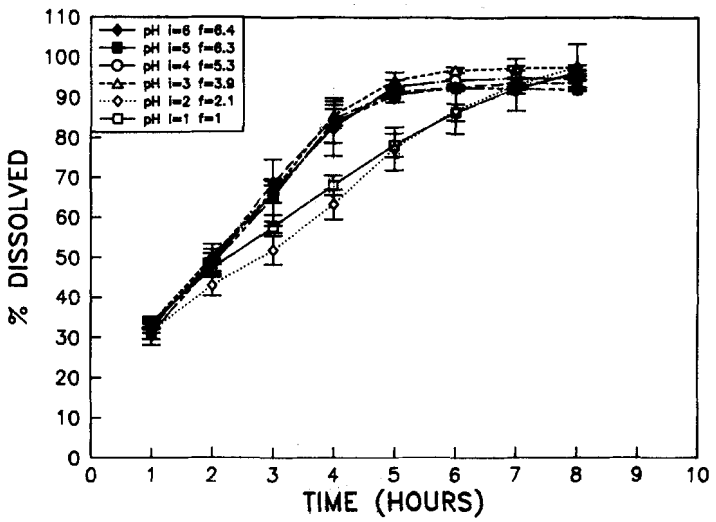

Figure 1
Dissolution of Berlex Wax Matrix Tablets as a function of pH in HCl, 0.1M Cl-. Error bars are 1 standard deviation (n=6).

and dissolution rate for all the extended release products tested in this study. However, such a relationship was not found for wax matrix tablets as is discussed below.

Effect of pH

Figure 1 presents dissolution profiles for quinidine gluconate wax matrix tablets (Berlex) where the pH of the medium was varied from 1 to 6 while the total chloride ion concentration was maintained at 0.1 M. The trend of dissolution rate as a function of pH is more easily appreciated when the data at the 3 hour time point from each of the curves from Figure 1 are plotted

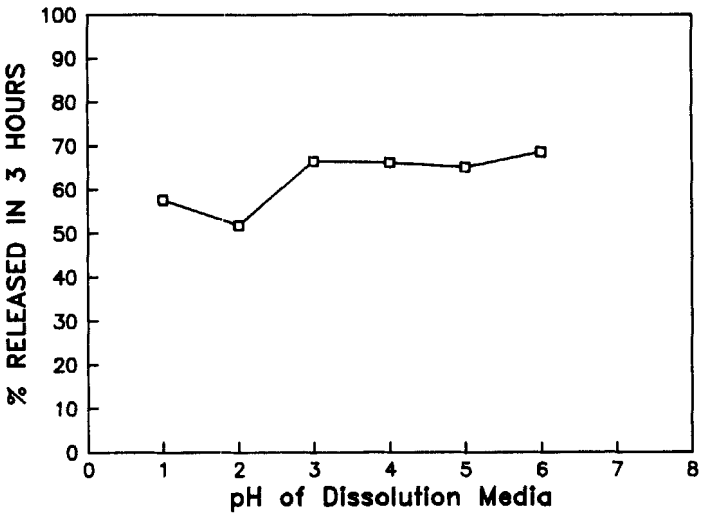

Figure 2
Dissolution of Berlex Wax Matrix Tablets as a function of pH in HCl, 0.1M Cl-.

on one graph (see Figure 2). The third hour was selected because the differences between curves are more obvious than at other time points. Figure 2 shows that, as the pH of the medium increases in the range from two to six, the percent released in 3 hours increases. Interestingly, this is contrary to what would be expected if solubility alone were controlling dissolution.

During the dissolution experiments it appeared that disintegration played an important role in the dissolution process. Therefore, all formulations were tested for quantitative disintegration in both 0.1N HCl and pH 5.4 acetate buffer dissolution media. Figure 3 shows that the extent of disintegration of the Berlex tablet is substantially greater at

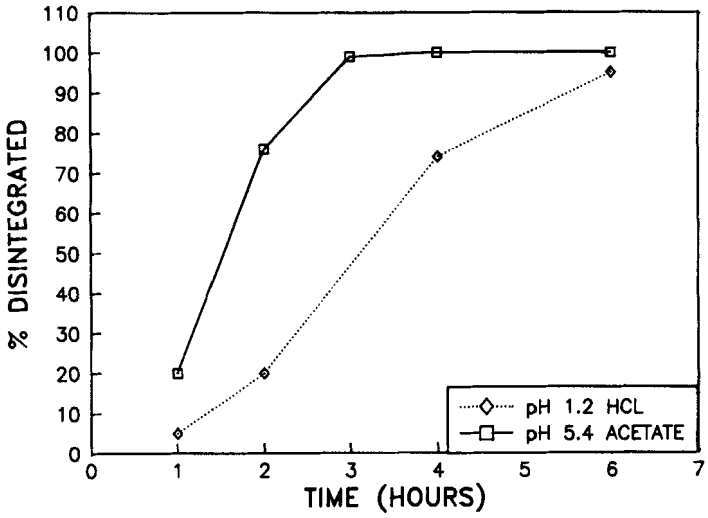

Figure 3
Disintegration of Berlex Wax Matrix Tablets as a function of pH.

pH=5.4 than at pH=1, especially after the second hour. In contrast, Figure 4 shows that the disintegration of the Bolar tablet is approximately the same at pH=1 and pH=5.4. The disintegration of both tablets resulted in an increase in the dosage form surface area as flakes and chunks came loose from the core. On the other hand, the Parke-Davis and Danbury products did not disintegrate. They remained intact and retained their tablet shape throughout the disintegration test.

Effect of Disintegration

The observation of disintegration allows some understanding of the process of drug release from the wax matrix tablets in this study. In the high pH medium, although the solubility of the drug

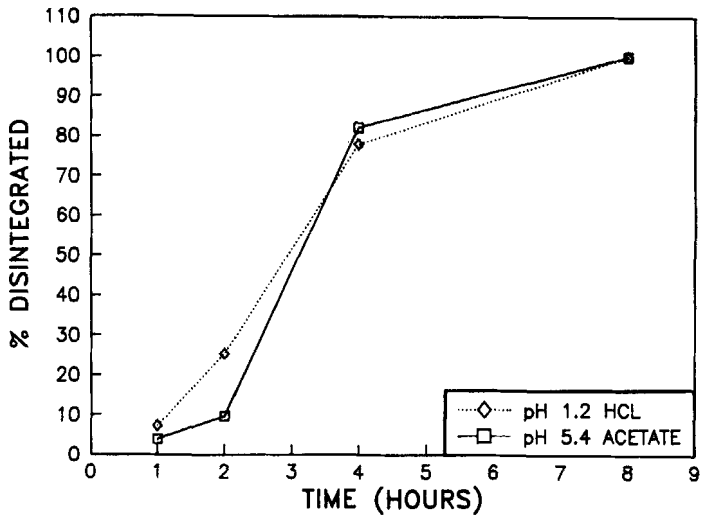

Figure 4
Disintegration of Bolar Tablets as a function of pH.

is lower, the increase in disintegration allows more drug to be released, presumably due to the increased surface area.

Effect of Chloride Ion

The relationship between pH, disintegration and the amount of drug released was explored in dissolution media employing hydrochloric acid. Experiments were performed to determine if the causal relationship is due to the concentration of the hydrogen ion, i.e. to the pH, or to the concentration of the chloride ion of the hydrochloric acid used to adjust the pH. In the previous experiment (Figure 1), the concentration of the chloride ion was kept constant as the pH was varied. In another experiment,

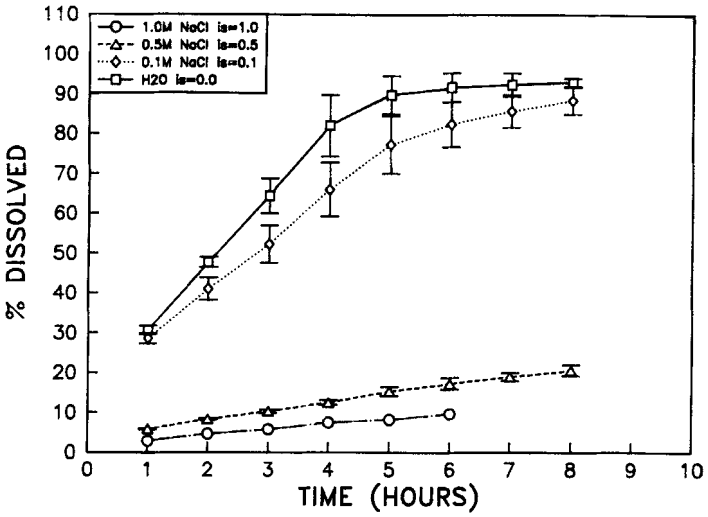

Figure 5
Dissolution of Berlex Wax Matrix Tablets as a function of chloride ion concentration in water. Error bars are 1 standard deviation (n=6).

dissolution media with various concentrations of sodium chloride in unbuffered water were used to test the Berlex wax matrix tablets. Figure 5 shows that as the chloride concentration was increased from 0 to 1.0 molar, the dissolution rates decreased dramatically. There was complete release of the drug in pure water, and less than 10 percent release in 1.0M NaCl, after 6 hours. These results indicate that the decrease in the dissolution rate with increasing chloride ion concentration is related to the decrease in the rate of tablet disintegration. Interestingly, this parallels the solubility results (see Table I). As the concentration of NaCl in water increases from 0.05M to 0.5M, the solubility also decreases from 108 mg/mL to 6 mg/mL.

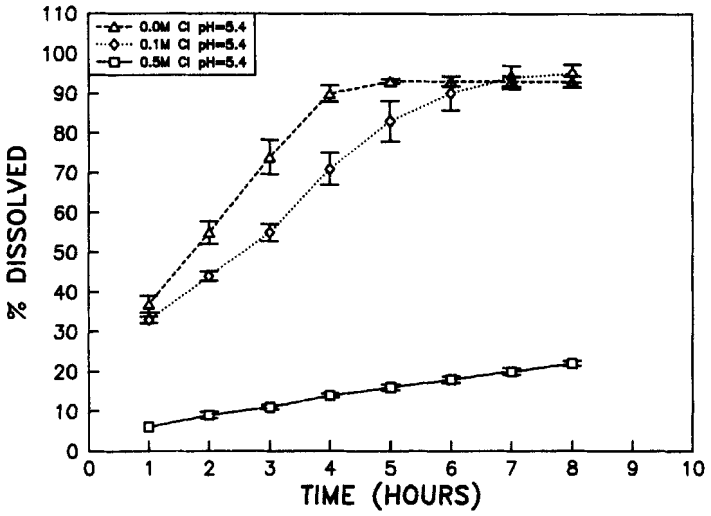

Figure 6
Dissolution of Berlex Wax Matrix Tablets as a function of chloride ion concentration in acetate. Error bars are 1 standard deviation (n=6).

Effect of Acetate Ion

The effect of ionic concentration in an acetate dissolution medium was also explored. First, the Berlex tablets were tested in pH 5.4 acetate dissolution media in which the concentration of acetate was varied from 0.0002M to 0.5M. These dissolution data were nearly identical over this 2500-fold change in acetate concentration. Second, in order to assess the competitive effects of acetate vs. chloride ions, the same dosage form was studied in 0.5M sodium acetate (pH=5.4) with various concentrations of added chloride ion. The results (see Figure 6) show that the dissolution rate slows substantially in the presence of 0.1M or 0.5M sodium chloride.

Interpretation

Thus, there appear to be two competing and inter-related phenomena that influence the release rate of the drug from a wax matrix quinidine gluconate dosage form in hydrochloric acid media of different pH values. These are solubility, which is a function of pH, and dissolution which is a function of both pH and chloride ion concentration.

A summary of these observations must take into account the relationship between pH and the concentration of the individual ions formed from the ionization of HCl. As the pH decreases, the H^+ and the Cl^- increases. The question has been: which ion has been the relevant variable, H^+ or Cl^-? It would normally be assumed that H^+ (pH) would be the most relevant. Our results have shown that an increase in H^+ (and Cl^-) yields an increase in solubility, but a decrease in dissolution. Our results have further shown that an increase in Cl^-, while H^+ remains constant, yields a decrease in dissolution. Thus it appears that the dominant effect comes from the chloride ion concentration and only a secondary effect comes from the hydrogen ion.

At pH=2 in hydrochloric acid dissolution medium, the dissolution rate is at a minimum (see Figure 2). This is the pH where the decrease in solubility, from pH 1, results in a decrease in dissolution. At the same time, there is still an appreciable

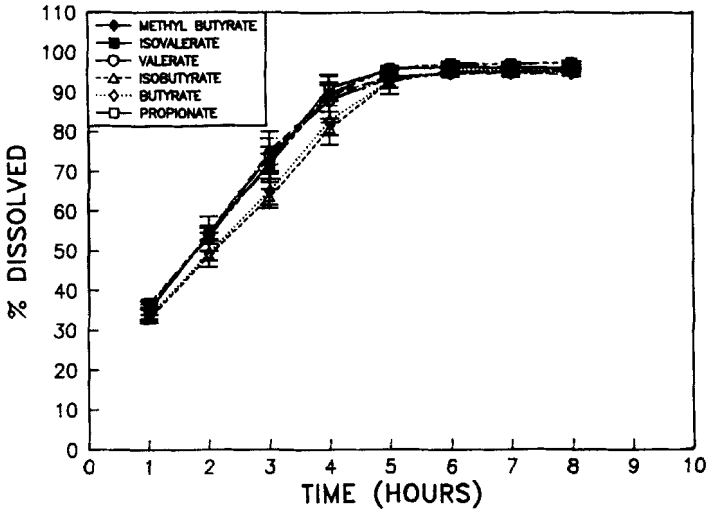

Figure 7
Dissolution of Berlex Wax Matrix Tablets in the presence of organic ions at pH 5.4. Error bars are 1 standard deviation (n=3).

amount of chloride ion present which may suppress the disintegration that is characteristic of these tablets in dissolution media with higher pH values.

Effect of Organic Anions

Beyond the study of the relationship of dissolution rate to acetate and chloride ion concentrations, the effect of using anions other than chloride in the dissolution medium was also investigated. Dissolution media were prepared using 0.1M solutions of organic acids brought to a pH of 5.4 with sodium hydroxide. Propionic, butyric, isobutyric, valeric, isovaleric

and 2-methylbutyric acids were used in the dissolution testing of Berlex tablets. The results shown in Figure 7 indicate that, although these involve different anions of organic acids, they are all similar in that they all have little effect on the release of the drug relative to either acetate buffer or pure water. In these studies the quantitative disintegration method described earlier was not used. Rather, for simplicity the time at which disintegration of the dosage form was complete was used as a qualitative endpoint. Disintegration was complete, by visual examination, within two to four hours in all media using organic ions as part of the buffer system.

Effect of Inorganic Anions

In contrast to the results with organic acid anions, when anions of inorganic acids were included in the dissolution media, the release of drug was clearly affected. Chloride, iodide and nitrate were used at various concentrations as seen in Figure 8. At concentrations of 0.5M (pH adjusted to 5.4), these ions severely impeded the release of the drug relative to the release rate in water. During the dissolution tests, disintegration of the dosage forms was not observed. Thus, it appears that the dissolution of these wax matrix tablets is unaffected by the presence of salts of organic acids, but can be severely limited by the salts of inorganic acids. Disintegration of the dosage form did not occur (visual observation) when inorganic ions were used as part of the buffer system.

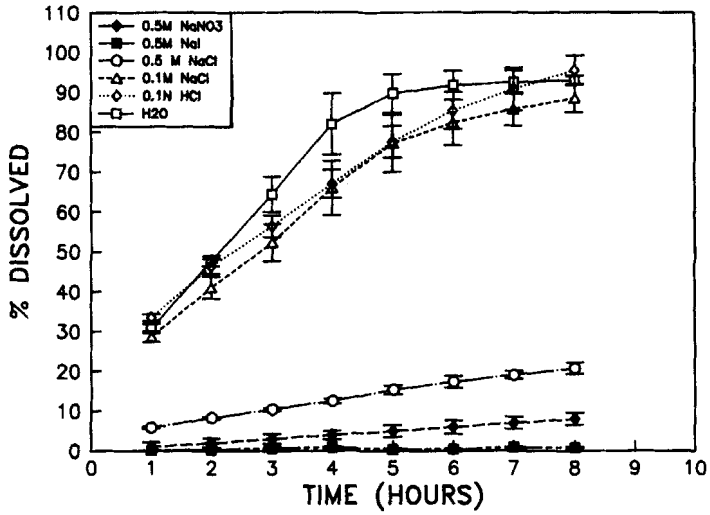

Figure 8
Dissolution of Berlex Wax Matrix Tablets in water containing inorganic ions. Error bars are 1 standard deviation (n=3).

The solubility of quinidine gluconate was determined in the presence of acetate ion in order to determine the effect of this factor on the dissolution at pH 5.4. As the concentration of sodium acetate was increased six-fold from 0.103M to 0.62M, the solubility rose only about 20% from 112 mg/mL to 133 mg/mL (see Table I). This is consistent with the observation that the Berlex tablets showed little difference in dissolution when tested in water versus acetate buffer.

Effect of Media Variables on Other Products

Having evaluated the effects of media parameters on the release of QG from the Berlex tablets, the dissolution of other

extended release quinidine gluconate products was investigated both in HCl (pH=1.0) and in acetate buffer (pH=5.4). Commercial products marketed by Parke-Davis, by Danbury and by Bolar respectively were tested in HCl brought to different chloride ion concentrations using sodium chloride. When the medium was 0.1N HCl (pH=1), each of these products demonstrated a relationship between dissolution and the chloride ion concentration that was similar to that for the Berlex wax matrix tablet relationship. The dissolution rate was generally unaffected by the chloride ion concentration (see Table II) and the tablets remained intact during the test period. On the other hand, in dissolution media buffered to pH 5.4 with sodium acetate and containing added sodium chloride, all products showed a marked decrease in dissolution rate as the chloride ion concentration increased (see Table III).

The dissolution results for the four different products, tested in 0.1N HCl and in acetate buffer (pH=5.4), are compared in Figures 9 and 10 respectively. It appears that the four dissolution profiles are similar in the hydrochloric acid medium. In the acetate buffer, there are two distinct groups of release patterns. In one group are the Berlex and the Bolar products which released drug more quickly in the acetate buffer versus the other products in either acetate buffer or in acid. Also, the dissolutions of the Berlex and of the Bolar products were complete by 6 hours in acetate buffer. The other two products released more slowly in the acetate buffer and still had incomplete

TABLE II

Dissolution at pH 1.0 as a Function of Chloride Ion Concentration

Product	Parke-Davis	Parke-Davis	Parke-Davis	Danbury	Danbury	Danbury
[Cl]	0.1 M	0.3 M	0.5 M	0.1 M	0.3 M	0.5 M
pH	1.0	1.0	1.0	1.0	1.0	1.0
Hour						
1	45	45	44	47	47	46
2	59	61	59	62	63	63
3	69	71	69	72	74	74
4	77	78	77	80	82	81
5	82	84	82			
6	87		87	90	94	93
7	91		90			
8	94		92	98	99	99

Product	Bolar	Bolar	Bolar	Berlex	Berlex	Berlex
[Cl]	0.1 M	0.3 M	0.5 M	0.1 M	0.3 M	0.5 M
pH	1.0	1.0	1.0	1.0	1.0	1.0
Hour						
1	37	42	41	34	32	32
2	52	57	58	56	56	55
3	63	72	74	57	62	55
4	75	78	91	66	71	65
5				76	79	72
6	93	99	102	83	88	80
7				89	92	84
8	97	102	102	91	96	92

TABLE III

Dissolution at pH 5.4 as a Function of Chloride Ion Concentration

Product	Parke-Davis	Parke-Davis	Parke-Davis	Danbury	Danbury	Danbury
[Cl]	0.0 M	0.1 M	0.5 M	0.0 M	0.1 M	0.5 M
pH	5.4	5.4	5.4	5.4	5.4	5.4
Hour						
1	34	35	8	36	34	8
2	48	44	10	51	42	10
3	58	48	12	61	48	13
4	64	52	14	69	52	15
5	70	55	15	74	55	17
6	74	59	17	78	58	19
7	78	60	18	82	61	19
8	82	65	19	86	66	21

Product	Bolar	Bolar	Bolar	Berlex	Berlex	Berlex
[Cl]	0.0 M	0.1 M	0.5 M	0.0 M	0.1 M	0.5 M
pH	5.4	5.4	5.4	5.4	5.4	5.4
Hour						
1	54	45	9	48	43	6
2	80	66	13	54	44	9
3	92	81	15	73	54	11
4	96	89	17	90	71	14
5	97	93	19	92	83	16
6	97	95	21	92	90	18
7	97	95	22	92	92	20
8	96	95	23	92	93	22

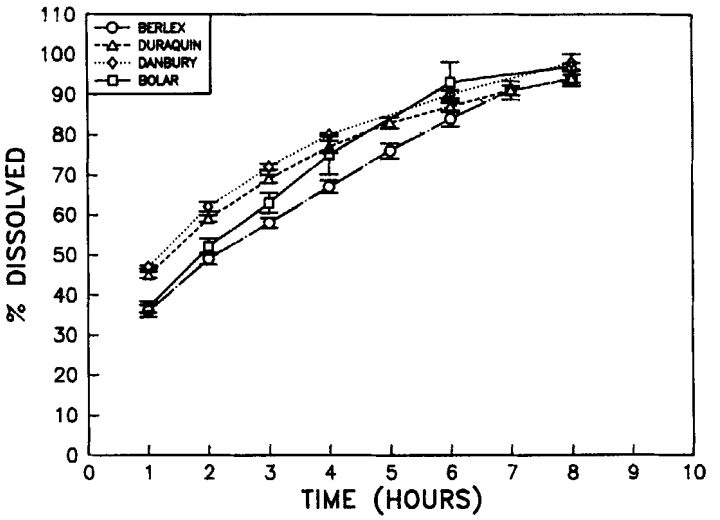

Figure 9
Dissolution results in 0.1N HCl for various formulations of quinidine gluconate extended release tablets. Error bars are 1 standard deviation (n=6).

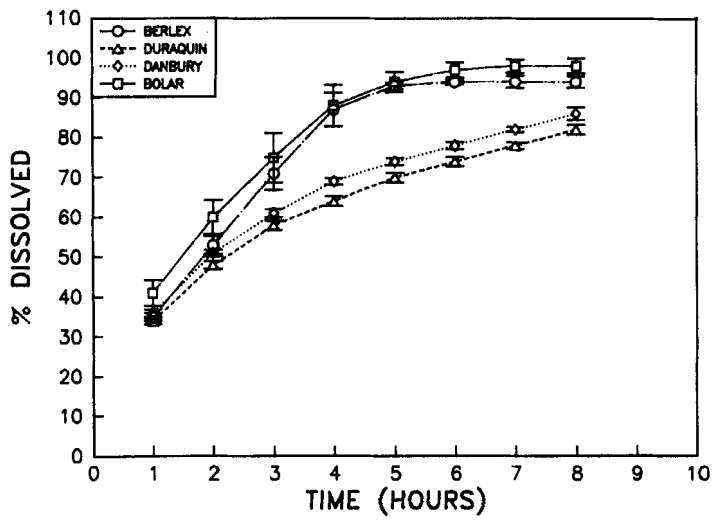

Figure 10
Dissolution results in pH 5.4 acetate for various formulations of quinidine gluconate extended release tablets. Error bars are 1 standard deviation (n=6).

dissolutions at 8 hours. The non-disintegrating products followed the relationship that dissolution rate decreased as the solubility of the drug decreased. An explanation for the results in Table III and Figures 9 and 10 requires a knowledge of the solubility of different species in the dissolution media. Quinidine hydrochloride monohydrate (QCl) has about 7 times less solubility than QG in water[11]. A review of the data in Table I shows a decrease in solubility of quinidine gluconate with an increasing concentration of sodium chloride. This is consistent with the literature data on the lower solubility of quinidine chloride noted above.

Mechanism of Dissolution

With this information we can now propose a mechanism for drug release from the Berlex tablet in acid and acetate media. As the quinidine gluconate from the formulation dissolves, it ionizes in solution.

$$QG \leftrightarrow Q^+ + G^- \qquad (1)$$
$$+$$
$$Cl^-$$
$$\downarrow$$
$$QCl\downarrow$$

The Q+ can associate with the chloride ions in solution to form the less soluble quinidine hydrochloride. The QCl species can then precipitate in the highly concentrated micro-environment inside the pores and channels of the wax matrix dosage form. The precipitate then serves to inhibit the diffusion of quinidine as

well as to inhibit the disintegration of the matrix. On the other hand, in acetate buffer medium, there is no precipitation of a quinidine salt because (as shown in Table I) the solubility of quinidine in acetate buffer is slightly higher than quinidine gluconate in water. During dissolution in this medium the soluble components, including the QG, dissolve. Thus, the wax matrix can become porous and channels can form throughout the wax. The tablet structure is thus undermined and weakens and after about two hours it disintegrates. (A relationship between porosity and disintegration has been reported previously[12]). The relative solubilities help to explain why the Berlex tablets undergo disintegration in acetate buffer, but do not do so in 0.1N HCl.

CONCLUSIONS

The results reported here have established that the dissolution of quinidine gluconate from extended release dosage forms is affected by a combination of variables. These include the pH of the dissolution medium, the concentration of buffer salts and whether the anion is organic or inorganic. The release of drug from wax matrix tablets is dependent on a combination of inter-related processes. As the pH of a hydrochloric acid dissolution medium decreases, the increasing solubility is the driving force for an increase in dissolution rate. Concomitantly, the increase in chloride concentration due to the increased level of HCl serves to impede both dissolution and disintegration of the

tablet due to a precipitation of quinidine chloride within the dosage form. These phenomena are not apparent when a dissolution medium is buffered with any salt of an organic acid since no precipitation of a poorly soluble quinidine salt occurs.

Disintegration plays a role in the overall release pattern that is different for different formulations. Non-disintegrating formulations follow the relationship that as the solubility increases in a pH-dependent manner, the release rate increases. Disintegrating formulations, on the other hand, do not necessarily follow the simple solubility relationship. In these cases, it was found that disintegration influences the dissolution pattern more strongly than solubility.

The results from these studies support both of the proposed hypotheses. First, the dissolution of dissimilar formulations of quinidine gluconate does indeed depend upon dissolution medium parameters such as pH, ionic concentration and ionic species to different extents. Second, differences in the respective dissolution mechanisms of different formulations precludes the use of a single medium for the in-vivo/in-vitro correlation of all products.

Some of the dissolution parameters tested will exert opposing effects on dissimilar formulations. If the purpose of a dissolution test is to allow an in-vivo/in-vitro correlation to be

made, the choice of a suitable dissolution medium must take into account the type of formulation that is to be studied. Since the chloride ion concentration in both gastric and intestinal juices is approximately 0.1M[13], this suggests that the use of a dissolution medium containing chloride ion represents the more appropriate approach when an in-vivo/in-vitro correlation is desired for dosage forms which are affected by chloride in the medium. In this work we have shown this to be the case for only certain QG formulations. Before one medium could be deemed suitable for use with all products to generate a global in-vivo/in-vitro correlation, all extended-release formulations must be investigated. In the case of quinidine gluconate controlled release formulations, mechanisms of release are of at least two different types. This makes the selection of a single dissolution medium for in-vivo/in-vitro correlations either improbable or impossible.

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