International Journal of Pharmaceutics, 13 (1983) 1–7
Elsevier Biomedical Press

Research Papers

Importance of media selection in establishment of in vitro–in vivo relationships for quinidine gluconate

Vadlamani K. Prasad, Vinod P. Shah, Patrick Knight, Henry Malinowski, Bernard E. Cabana and Marvin C. Meyer *

*Biopharmaceutics Laboratory/Bureau of Drugs, Food and Drug Administration, Washington, DC 20204 and * College of Pharmacy, University of Tennessee Center for the Health Sciences, Memphis, TN 38163 (U.S.A.)*

(Revised version received April 26th, 1982)
(Accepted April 29th, 1982)

Summary

The dissolution profiles of two different commercial formulations of controlled release 324 mg quinidine gluconate tablets were investigated and their bioavailability differences were associated with in vitro results. One of the marketed brands which was not approved by the Food and Drug Administration was alleged by some patients to have no therapeutic effect when taken orally. Dissolution profiles using the paddle method at 100 rpm in different dissolution media revealed wide differences between these two products. The dissolution rates of the two products were significantly different in water, acetate buffer pH 5.4 and phosphate buffer pH 5.4. However, the dissolution profiles were similar for the two products with respect to rate and extent in simulated gastric fluid (no enzymes) and pH 7.4 phosphate buffer. Bioavailability data for these two products showed significant differences among various in vivo parameters. A reformulated product with comparable bioavailability to the FDA-approved product also had similar dissolution profiles in the systems studied earlier. These findings confirmed the importance of the screening and judicious selection of dissolution medium as well as the predictive usefulness of a dissolution test in the quality control of sustained (or controlled) released quinidine gluconate formulations.

Introduction

Quinidine salts such as quinidine gluconate and sulfate are used clinically for their anti-arrhythmic activity. To obtain better patient compliance these drugs are

0278-5173/83/0000–0000/$03.00

formulated as sustained release tablets and are marketed under several brand names. Towards the end of 1980, a particular controlled release quinidine gluconate tablet was introduced into the market without the preclearance of the Food and Drug Administration (FDA). Because of several consumer complaints about the efficacy of this brand, the product was recalled. An investigation was initiated to establish in vivo and in vitro differences, if any, that existed between the approved, therapeutically effective product and the unapproved product.

Materials and methods

The samples of approved 324 mg quinidine gluconate tablets (Berlex Laboratories, Cedar Knolls, NJ—Brand BE—(lot no. B1209) and the unapproved product (Bolar Pharmaceuticals, Copiague, NY—Brand BO-1—(lot no. 090716) were collected by the FDA. The reformulated product BO-2 (lot no. 011885) was submitted by the firm for validation of the dissolution methodology (ANDA 1981). The same lots were used for both the in vivo and in vitro studies.

Dissolution tests

The dissolution tests were carried out using a 6-gang unit of the dissolution equipment meeting U.S.P. specifications and available commercially[1]. The paddle method (Apparatus II – at 100 rpm was used (USP, 1980a). The pH 5.4 phosphate (0.067 M) and acetate buffers (0.1 M) (Documenta Geigy, 1973), simulated gastric and intestinal fluids without enzymes (USP, 1980b) were prepared as described.

Dissolution rate profiles were determined at 37.0 ± 0.5°C in 900 ml of each of the dissolution fluids. Dissolution rate in all 6 dissolution vessels was monitored continuously by circulating filtered dissolution medium through 1 mm cells of the spectrophotometer[2] and recording the absorbance at 235 nm. Sampling times included 0, 1, 2, 3, 4, 5, 6, 7 and 8 h after the introduction of the tablet into the dissolution medium. In the experiment where the dissolution medium was changed, the tablets were stirred in simulated gastric fluid for one hour, the stirring was stopped, and the contents of the vessel were decanted or siphoned off taking care that none of the drug particles were removed. The simulated intestinal fluid (without enzymes) was added and stirring continued for an additional 7 h. The amount of quinidine gluconate in solution was calculated by comparing the absorbance of the sample with a quinidine gluconate reference standard solution prepared in the test dissolution medium.

Tablet analysis. Each of the tablets met the Abbreviated New Drug Application requirements of identification, content uniformity and assay (B.-ANDA no. 87-448 and BE-ANDA no. 85-978).

[1] Easifit Dissolution Test Station—Model 63-734-100, Hanson Research Corporation, Northridge, CA.
[2] Beckman Spectrophotometer Model 25 and Recorder Controller, Beckman Instruments, Fullerton, CA.

Bioavailability studies

A two-way cross-over bioavailability study was carried out in 12 healthy male volunteers using product BE and BO-1, the dose being two tablets. Blood samples were withdrawn at 0, 1, 2, 3, 4, 5, 6, 7, 8, 12 and 25 h after dose administration, plasma was separated and kept frozen until the time of analysis. The amount of quinidine in the plasma was determined by a HPLC procedure. Details of the bioavailability study are reported elsewhere (Meyer et al., 1982).

In another study, a reformulated product of BO (BO-2, lot no. 011885) was compared with the BE product (lot no. B1254) in a 20 subject cross-over study. In this study, a single 324 mg tablet of each product was administered to each subject. The blood samples were drawn at 0, 1, 2, 3, 4, 5, 8, 12 and 24 h and analyzed by HPLC. Both products were administered. Details of this study are reported elsewhere (ANDA Summary, 1981).

Results and discussion

Properly formulated controlled release dosage forms offer the possibility of smoother blood level–time profiles with longer intervals between doses. Since bioavailability studies involving healthy human subjects are costly and involve certain risks, it is highly desirable to carry out in vitro screening of different formulations. This in vitro screening can be achieved by a change in the pH of the dissolution medium or change in the stirring rate or change in the dissolution methodology itself. When the dissolution test is carried out under these conditions, the results may enable one to select a formulation which could be used in a bioavailability study. Such a formulation selection on the basis of in vitro results under various experimental conditions would minimize in vivo trials. Furthermore, a formulation exhibiting superior dissolution profile under the majority of the experimental conditions used is less likely to result in poor bioavailability. The comparison of dissolution rate profiles of two different brands of quinidine gluconate controlled release tablets presented here substantiates the value of such in vitro studies.

It is known that pH can influence dissolution rate, and it has recently been demonstrated that buffer composition can also have a significant effect on the dissolution rates of furosemide tablet formulations (Prasad et al., 1982). Thus dissolution studies were initiated using water, simulated gastric fluid, and phosphate (pH 7.4 and pH 5.4) and pH 5.4 acetate buffer solutions as the dissolution media. The quinidine gluconate sustained release products used in this study did not disintegrate (in the conventional sense) under any of the dissolution test conditions. The pH of the dissolution medium was checked at the end of each hour during the dissolution run. No significant change in the pH of the test medium occurred when buffers or simulated gastric fluids were used as dissolution media. However, when distilled water was the dissolution medium, its initial pH was 6.05 and the final pH was 6.75 for the brand BE and 7.40 for brand BO. The results of these studies are illustrated in Fig. 1. It is clear from Fig. 1A that substantial differences exist between the dissolution of the two tablets in distilled water. In this medium, product BO-1

Dissolution of Quinidine Gluconate

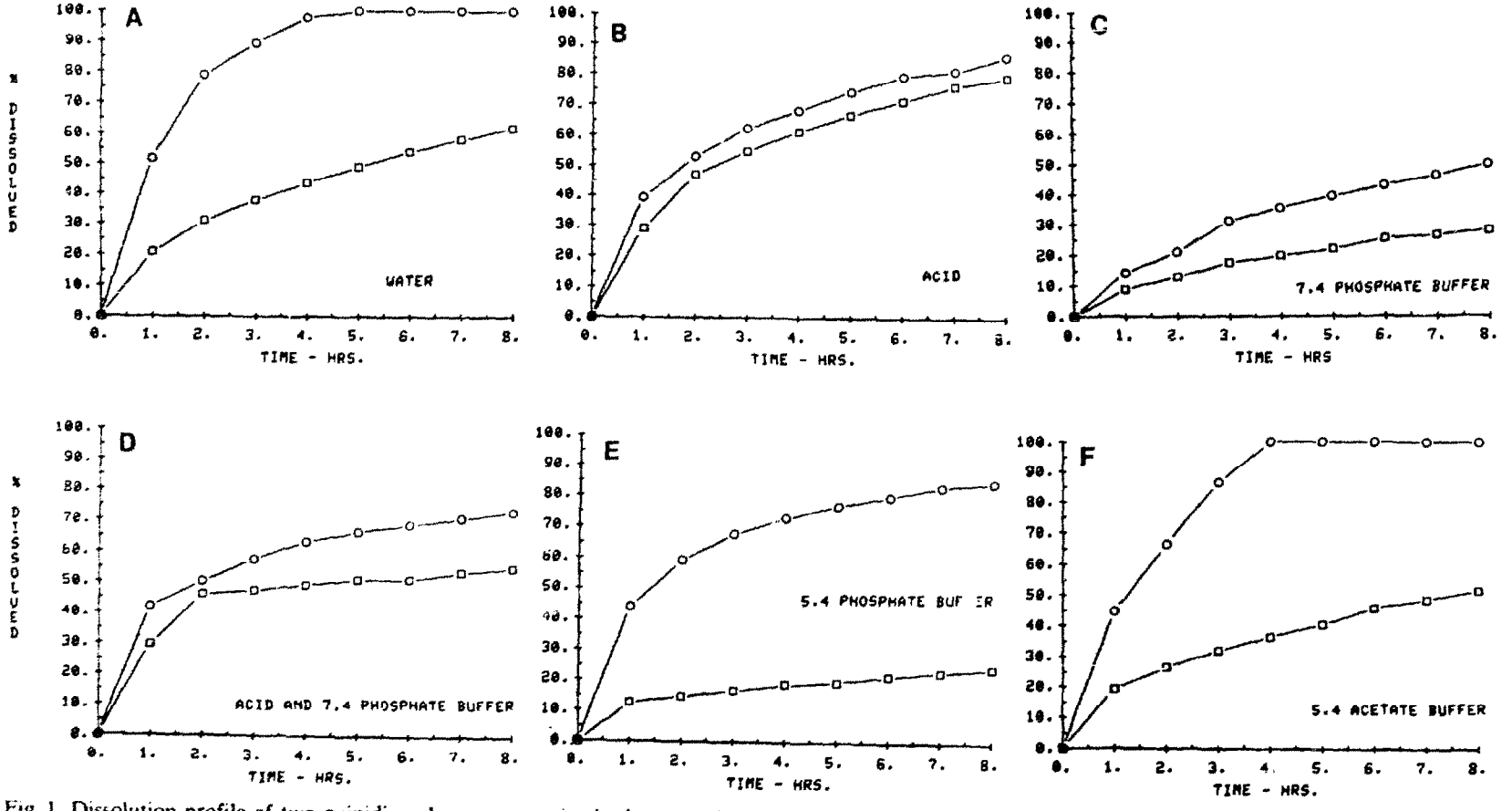

Fig. 1. Dissolution profile of two quinidine gluconate sustained release products in different dissolution media. Each data point is the mean of 12 tablets. Key: ○, product BE; □, product BO-1.

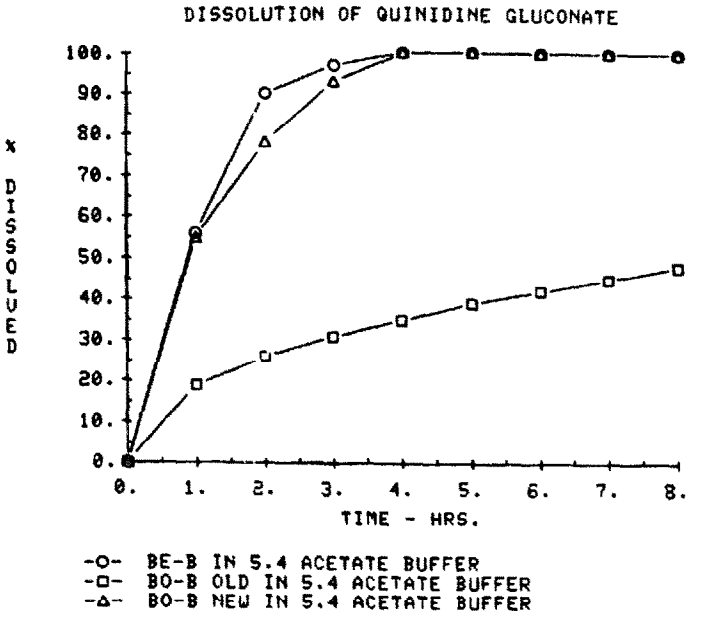

Fig. 2. The dissolution profile of 3 quinidine gluconate products in pH 5.4 acetate buffer (paddle method at 100 rpm). Key: O, product BE; □, product BO-1; △, Product BO-2.

achieves only 60% dissolution after 8 h, compared to essentially 100% dissolution in 4 h for product BE. While prolonged dissolution is to be anticipated for controlled release formulations, too slow a dissolution process may result in incomplete bioavailability. With simulated gastric fluid (Fig. 1B), little difference in dissolution was noted between the two dosage forms. Fig. 1C illustrates the dissolution in pH 7.4 phosphate buffer, which is commonly employed as a simulated intestinal fluid in dissolution studies. While in this medium differences in dissolution between BE and BO-1 did result, neither product achieved greater than 50% dissolution after 8 h. Fig. 1D shows an attempt to simulate an initial one hour exposure of the tablets to gastric fluid (simulated), followed by exposure to intestinal fluid (simulated). Both formulations exhibited better dissolution in this system than in the pH 7.4 phosphate buffer alone, although after 8 h the difference between the products was only 15%. Since the pH of the upper region of the intestinal tract of man can be mildly acidic, dissolution studies were also conducted with pH 5.4 phosphate buffer, as illustrated in Fig. 1E. It is clear that this medium has a significant effect on the dissolution process. At the end of 8 h, product BE is 87% dissolved, while product BO-1 is only 25% dissolved. In order to evaluate any effect of buffer composition, a pH 5.4 acetate buffer was also employed. Fig. 1F demonstrates that both dosage forms dissolve to a greater extent in this buffer compared to pH 5.4 phosphate buffer. Although the cause for this difference is not definitely known, a possible explanation is an interaction of the acetate or phosphate ions with constituents of the dosage forms, resulting in either retardation of dissolution by phosphate, or an enhancement of dissolution by acetate ions. The results of these studies illustrate not only that buffer composition can affect the degree to which in vitro systems can discern

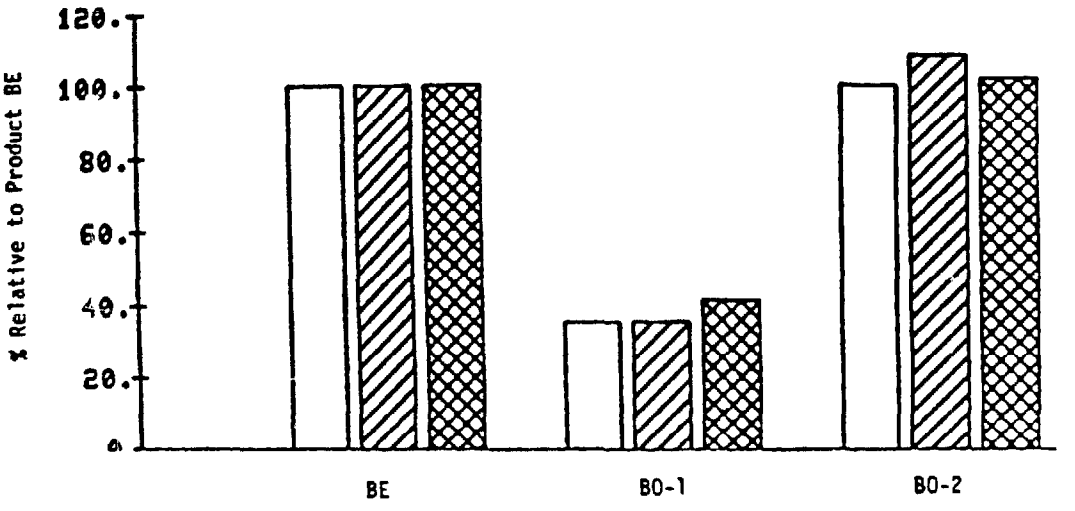

Fig. 3. In vitro/in vivo relationship for quinidine gluconate. Key: □, dissolution in pH 5.4 acetate buffer in 4 h; ▨, C_{max}; ▩, AUC.

differences among dosage forms, but they also indicate the importance of pH. Thus product BO-1 appears relatively insensitive to pH differences over the range of 5.4–7.4, while the dissolution of product BE is significantly improved at pH 5.4

TABLE 1

IN VIVO DATA FOR QUINIDINE GLUCONATE TABLETS

Parameter	Products		
	BE	BO-1	BO-1/BE × 100
Dose	648 mg	648 mg	
C_{max} (μg/ml)	1.26 ± 0.34	0.47 ± 0.13	35%
T_{max} (h)	3.18 ± 1.20	3.51 ± 0.67	
AUC (μg/ml × h)	15.5 ± 4.81	6.38 ± 2.35	41%

Each value is the mean ± S.D. of 12 subjects.

TABLE 2

IN VIVO DATA FOR QUINIDINE GLUCONATE TABLETS

Parameter	Products	
	BE	BO-2
Dose	324 mg	324 mg
C_{max} (μg/ml)	0.52 ± 0.22	0.56 ± 0.18
T_{max} (h)	6.1 ± 1.65	5.5 ± 1.27
AUC (μg/ml × h)	6.23 ± 2.87	6.37 ± 2.67

Each value is the mean ± S.D. of 20 subjects.

compared to pH 7.4. Thus dissolution studies conducted in either acid media or pH 7.4 phosphate buffer are much less effective in detecting differences between these two formulations.

Bioavailability

The bioavailability results from the first study are summarized in Table 1 where product BE was considered as the reference product. It is quite evident that product BO-1 was only 41% bioavailable in extent (Area Under Curve) (AUC) and 35% in maximum concentration achieved (C_{max}) in comparison to product BE. It is not surprising to note these in vivo differences in view of the dissolution behavior of both products. It is also quite obvious that dissolution at pH 5.4 in both acetate and phosphate buffer relates quite well to the in vivo performance of both products. For example, product BO dissolved to the extent of only 47% in the acetate buffer and is also bioavailable to similar extent (AUC = 41%) when compared to product BE. Subsequent to these studies, the BO brand of quinidine gluconate controlled release tablet was reformulated. A bioequivalency study of this product (BO-2) and product BE was performed, and the results of this study are summarized in Table 2. In vitro dissolution in pH 5.4 acetate buffer using the same experimental conditions (i.e. 100 rpm-paddle) was also carried out with BO-2. The dissolution profile for BO-2, compared to that of BO-1 and BE in pH 5.4 acetate buffer, is shown in Fig. 2. The buffer was selected for comparison because of the previously discussed close agreement between the relative dissolution data, and the extent of absorption, as measured from the area under the plasma level–time profiles.

The relative in vivo and in vitro performance of the 3 dosage forms is summarized in Fig. 3. It is evident from this figure, as well as Fig. 2, that the reformulated product BO-2 is bioequivalent to the reference product BE. Furthermore, product BO-1 is bioinequivalent with either of the two products, BE and BO-2. This in vivo performance is supported by the in vitro results at the 4 h time point in pH 5.4 acetate buffer. The mean percent dissolution and the standard deviation at four hours are: BE, (100 ± 1.2) (100 ± 1.2), BO-1 (32.7 ± 1.7) and BO-2 (98.4 ± 4.3).

Conclusions

These findings substantiate that the pH and composition of dissolution medium are quite important to make an in vitro test meaningful and consistent with in vivo results. Further, the use of the USP paddle method, at 100 rpm, with pH 5.4 phosphate or acetate buffer provided an in vitro dissolution test which was useful in distinguishing between two quinidine gluconate formulations which differed greatly in their in vivo performance.

References

ANDA no. 87-448, Summary Basis of Approval of Quinidine Gluconate Sustained Release Tablets, Food and Drug Administration, Washington, DC, 1981.

Documenta Geigy, Scientific Tables, 7th Edn., 1973, Ciba Geigy Ltd., Basle, pp. 281–282.

Meyer, M.C., Straughn, A.B., Liberman, P. and Jacob, J.T., Serious bioavailability problem with a generic prolonged release quinidine gluconate product. J. Clin. Pharmacol., 22 (1982) 131–134.

Prasad, V.K., Rapaka, R.S., Knight, P. and Cabana, B.E., Dissolution medium—a critical parameter to identify bioavailability problems of furosemide tablets. Int. J. Pharm., 11 (1982) 81–90.

The United States Pharmacopeia, XXth Revision, Mack Publishing Company, Easton, PA, 1980, (a) p. 959; (b) p. 1105.