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# Development of a dissolution medium for glibenclamide

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**Abstract**

A dissolution medium for slightly soluble drugs was developed using glibenclamide as a model of such drugs. The medium consists of a hydroalcoholic surfactant solution with a relatively low alcohol and Tween 80 content buffered at pH 7.4. The composition of the medium was selected on the basis of solubility data at 37°C obtained according to a central composite experimental design. The discriminating power of the medium selected (phosphate buffer pH 7.4 containing 8.5% alcohol and 0.24% Tween 80) was assessed relative to that of phosphate buffer pH 7.4, a medium usually used for the dissolution testing of glibenclamide and borate buffer pH 9.5, a medium recently recommended by the FDA. The dissolution data obtained for two commercial brands of glibenclamide tablets indicate superiority of the proposed system as a discriminatory dissolution medium for glibenclamide tablets.

*Keywords:* Glibenclamide; Dissolution medium; Hydroalcoholic surfactant solution; Tween 80; Alcohol

## 1. Introduction

Dissolution of drugs from solid dosage forms is a key parameter in assessing the product quality and uniformity at the formulation stage and throughout the product's shelf-life. For water insoluble drugs, difficulties are usually encountered in selecting a dissolution medium of acceptable volume and composition as well as a good discriminating power.

Approaches usually used in the design of dissolution media for poorly soluble drugs include: (a) bringing about drug solubility by increasing the volume of the aqueous sink or removing the dissolved drug (Gibaldi and Feldman, 1967; Katchen and Symchowicz, 1967; Chiou and Riegelman, 1970); (b) solubilization of the drug by co-solvents, up to 40% (Walkling et al., 1979; Goehl et al., 1982; U.S.P. 23, 1995.) and by anionic (Shah et al., 1989; U.S.P. 23, 1995) or non-ionic (Pandit et al., 1985; Shah et al., 1989) surfactants added to the dissolution medium in postmicellar concentrations; (c) alteration of pH to enhance the solubility of ionizable drug

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molecules. The last two approaches seem less cumbersome and have been more widely employed in pharmacopeial dissolution tests (U.S.P. 23, 1995).

The use, however, of relatively high co-solvent or surfactant concentrations may be implicated in dissolution variability as a result of potential interaction with some components of the tablet formulation and/or change in the physical properties of the dissolution medium. For instance, anomalously low release characteristics have been reported in dissolution media with a relatively high co-solvent content despite sink conditions (Guyot-Hermann and Ringard, 1981; Poirier et al., 1983; Dodge and Gould, 1987). This has been attributed to the impairment of tablet disintegration in such media (Guyot-Hermann and Ringard, 1981; Poirier et al., 1983; Dodge and Gould, 1987) and reduction in the solubility of water soluble tablet excipients, thus impeding dissolution of the drug (Corrigan, 1991).

Addition of surfactants to the dissolution medium improves the dissolution of poorly soluble drugs by facilitating the drug release process at the solid/liquid interface and micelle solubilization in the bulk (Schott et al., 1982; Abdou, 1989). However, surfactants may impair the disintegration of solid dosage forms (Heng and Wan, 1985; Pandit et al., 1985). When used in concentrations much beyond their critical micelle concentration, surfactants may reduce the dissolution rate constant due to lowering of the diffusion rate of the micelle-solubilized species resulting in a levelling-off of the dissolution enhancing effect (Parrott and Sharma, 1967; Itai et al., 1985; Pandit et al., 1985). Further, the relatively high viscosities of dissolution media with relatively high surfactant concentrations may result in a decrease in dissolution rate after a maximum is reached (Parrott and Sharma, 1967; Elworthy and Lipscomb, 1968).

In the present study, a solution containing alcohol and Tween 80 at relatively low concentration levels, was assessed as a dissolution medium for poorly soluble drugs. Glibenclamide (pka = 5.3) was selected as a model of such drugs. There was no pharmacopeial dissolution requirement for glibenclamide. Recently, a borate buffer pH 9.5 has been tentatively recommended by the FDA (U.S.P. 23-NF 18, 1995). However, such a high pH value is of little relevance to the physiological conditions at the sites of drug dissolution in the body and may reduce the discriminating power of the dissolution test.

The composition of the dissolution medium developed in this study was selected on the basis of solubility data obtained according to a central composite experimental design. The variables investigated were alcohol, Tween 80 concentrations and pH. The potential interaction of these variables may enhance their combined solubilizing effect. This would allow the use of relatively low concentrations of either a solubility enhancer and/or the adjustment of the medium pH to physiologically relevant values.

The discriminating power of the dissolution medium selected was compared to that of phosphate buffer pH 7.4, a medium usually used in the dissolution testing of glibenclamide tablets (Blume et al., 1993) and borate buffer pH 9.5, the FDA recommended medium (U.S.P. 23-NF 18, 1995), using two glibenclamide tablet brands.

## 2. Materials and methods

### 2.1. Materials

Glibenclamide (Hoechst Orient, S.A.S., Cairo, Egypt) and Tween 80 (Merck, Germany) were used in the study. All other reagents were either AR or HPLC grade. The two commercial brands of glibenclamide tablets (5 mg) tested were: brand A: Euglucon tablets (Boehringer Mannheim, GmbH, Germany, BN D5) as a standard product, and brand B: Glibenase tablets (The Arab Drug Company, Egypt, BN 106119) as a test product.

### 2.2. Solubility determination

The solubility of glibenclamide was determined in 0.1 M phosphate buffer at different pH values, with Tween 80 and alcohol concentrations as independent variables. The study was structured using a central composite experimental design for three factors (Bayne and Rubin, 1986). According

to this design, seventeen experimental units with fifteen combinations of factor levels are required. Nominal values of precoded levels of these factors are shown in Table 1 (trials 1 to 17). Also included were three experimental units (trials 18 to 20) in order to obtain response values at a higher pH level.

Excess glibenclamide (50 mg) was added to 10 ml of the different media shown in Table 1 and the mixtures were shaken for 24 h at 37°C in a thermostatically controlled water bath. After an equilibration period of 12 h at the same temperature, aliquots were filtered using a 0.22 $\mu$ Millipore membrane filter. Samples were diluted in ethanol and assayed by the HPLC method described under HPLC analysis.

### 2.3. Dissolution rate study

The dissolution rate of glibenclamide bulk powder (5 mg, particle size less than 125 $\mu$) and glibenclamide tablets of the two brands under study was determined at 37°C in 900 ml of the dissolution medium using a USP six-station dissolution apparatus (Hanson Research, Northridge, CA USA) with a paddle rotating at 50 rpm. The dissolution media used were phosphate buffer pH 7.4, borate buffer pH 9.5 and the medium proposed in this study (phosphate buffer pH 7.4 containing 8.5% alcohol and 0.24% Tween 80).

Table 1
Central composite design for the solubility study and observed values of the response (glibenclamide solubility, $\mu$g/ml at 37°C)

| Trial | % Tween 80 | % Alcohol | pH | Solubility, $\mu$g/ml |
|---|---|---|---|---|
| 1 | 0.38 | 13.5 | 6.3 | 5.55 |
| 2 | 0.10 | 13.5 | 6.3 | 4.26 |
| 3 | 0.38 | 3.5 | 6.3 | 3.45 |
| 4 | 0.10 | 3.5 | 6.3 | 1.80 |
| 5 | 0.38 | 13.5 | 4.3 | 2.90 |
| 6 | 0.10 | 13.5 | 4.3 | 1.48 |
| 7 | 0.38 | 3.5 | 4.3 | 0.00 |
| 8 | 0.10 | 3.5 | 4.3 | 0.00 |
| 9 | 0.24 | 8.5 | 7.0 | 10.29 |
| 10 | 0.24 | 8.5 | 3.6 | 2.03 |
| 11 | 0.24 | 17.0 | 5.3 | 1.44 |
| 12 | 0.24 | 0.0 | 5.3 | 0.85 |
| 13 | 0.48 | 8.5 | 5.3 | 1.79 |
| 14 | 0.00 | 8.5 | 5.3 | 0.14 |
| 15 | 0.24 | 8.5 | 5.3 | 0.85 |
| 16 | 0.24 | 8.5 | 5.3 | 0.85 |
| 17 | 0.24 | 8.5 | 5.3 | 0.85 |
| 18 | 0.48 | 8.5 | 7.0 | 15.15 |
| 19 | 0.24 | 8.5 | 7.4 | 25.70 |
| 20 | 0.48 | 8.5 | 7.4 | 36.82 |
| 21 | 0.00 | 0.0 | 7.4 | 9.90 |

Samples of the dissolution medium were filtered using a 0.22 $\mu$ Millipore filter and assayed for glibenclamide by HPLC. The dissolution experiments were carried out in triplicate.

#### 2.3.1. HPLC analysis

Glibenclamide in samples of the filtrates obtained in the solubility and dissolution experiments was assayed using essentially the HPLC method reported by Emilsson et al., 1986. A modular high performance liquid chromatograph was used. It consists of a solvent delivery system (Waters Model 501), a septumless injector (Waters Model U6K), a tunable spectrophotometric detector (Waters model 486) and a data module (Waters Model 746). The analytical column was a Bondapack C–18, Waters Associates (3.9 mm × 300 mm, 10 $\mu$). The mobile phase consisting of acetonitrile:1% acetic acid (1:1) was pumped at a flow rate of 2.5 ml/min. The retention time of glibenclamide was 5 min and the drug was detected spectrophotometrically at 227 nm.

### 2.4. Disintegration

The disintegration time of glibenclamide tablets was determined in water and in 0.1 M phosphate buffer pH 7.4 containing 0.24% Tween 80 and 8.5% alcohol.

#### 2.4.1. Tablet assay

The glibenclamide content of tablets of the two brands under study was assayed using the BP 1993 method.

## 3. Results and discussion

Solubility plays a prime role in the dissolution of a drug substance from a solid dosage form.

Correlations between solubility and intrinsic dissolution rate of different drug substances in various media are well established (Nicklasson et al., 1981; Nicklasson and Brodin, 1984). In this study, solubility data was used as a basis for the development of a dissolution medium for glibenclamide. The drug solubility was determined at 37°C in media of different pH and different concentrations of alcohol and Tween 80. pH was included as an independent variable as the solubility of glibenclamide is pH dependent (Kaali et al., 1987). The levels of the variables investigated were selected according to a central composite design (Bayne and Rubin, 1986). Combinations of the levels of variables required by the design (trials 1 to 17) and the corresponding observed response (gibenclamide solubility, $\mu$g/ml) are shown in Table 1. The results indicate that the maximum solubility value obtained was 10.29 $\mu$g/ml in trial 9 (pH 7.0, 0.24% Tween 80, 8.5% alcohol). Although the pH in this trial was 1.7 units beyond glibenclamide's pka, the increase in solubility was limited. This can also be observed in the pH-solubility profiles of glibenclamide, reported by Kaali et al., 1987. Glibenclamide solubility in trial 9 would allow complete solubility of the drug content of usual strength glibenclamide tablets (2.5 to 5 mg) in 900 ml of the medium. However, the experimental design was extended to include further factor combinations (trial 18–21) which allow a larger increase in glibenclamide solubility at a physiologically relevant pH.

A general linear model procedure (SAS/stat User's Guide, 1988) was utilized to correlate glibenclamide solubility to the independent variables using the following full second order polynomial equation with all factor interactions:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1^2 + b_5X_2^2 + b_6X_3^2 + b_7X_1X_2 + b_8X_1X_3 + b_9X_2X_3$$

where $Y$ is the response level, $b_i$ is the regression coefficient and $X_1$, $X_2$ and $X_3$ are the coded levels of pH, alcohol concentration (%w/v) and Tween 80 concentration (%w/v), respectively.

From the glibenclamide solubility data obtained, a simplified stepwise multiple regression model including the most significantly contributing factors and their interactions was developed as follows:

$$y = 51.632 - 24.084\,X_1 + 2.717\,x_1^2 + 1.038\,X_2X_3$$

The model is significant at $P < 0.05$ and $r^2 = 0.793$

As the equation indicates, pH ($X_1$) has the highest impact as a single effective variable on glibenclamide solubility and there is a significant interaction between alcohol and Tween 80 favouring glibenclamide solubilization in the range of factor levels investigated. The above equation can be used to predict solubility values at factor levels within the ranges investigated. Table 2 shows predicted and experimentally determined glibenclamide solubility values at selected levels of the independent variables (Table 2).

Table 2
Observed and predicted values of glibenclamide solubility, $\mu$g/ml, in media 18 to 20 in Table 1 (obtained using the reduced model)

| Trial | Observed | Predicted |
|---|---|---|
| 18 | 15.15 | 20.41 |
| 19 | 25.70 | 24.23 |
| 20 | 36.82 | 26.43 |

Response surface graphs (Figs. 1 and 2) were also generated to identify the range of factor levels which, in combination, produce a desirable response.

Because of the limited physicochemical data available for glibenclamide, the mechanistic understanding of the simultaneous effects of pH, co-solvent and surfactant concentrations on glibenclamide solubility requires further investigation at wider level ranges of the system variables. Generally, added alcohols exert various effects on non-ionic micelles depending on the concentration and chain length of the alcohol (Green, 1972; Nishikido et al., 1974). Lower alcohols such as methanol and ethanol increase the cmc of non-ionic surfactants (Nishikido et al., 1974), an effect attributed to the weakening of hydrophobic interactions, which is the important driving force for

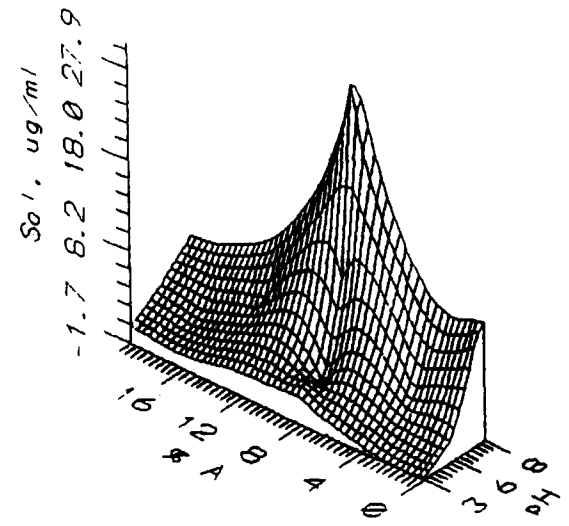


Fig. 1. Response surface graph relating glibenclamide solubility to pH values and percent alcohol.

micellization. Solubilization of short chain alcohols into the palisade layer of the non-ionic micelles was considered to be negligible (Nishikido et al., 1974). However, the cmc-increasing effect

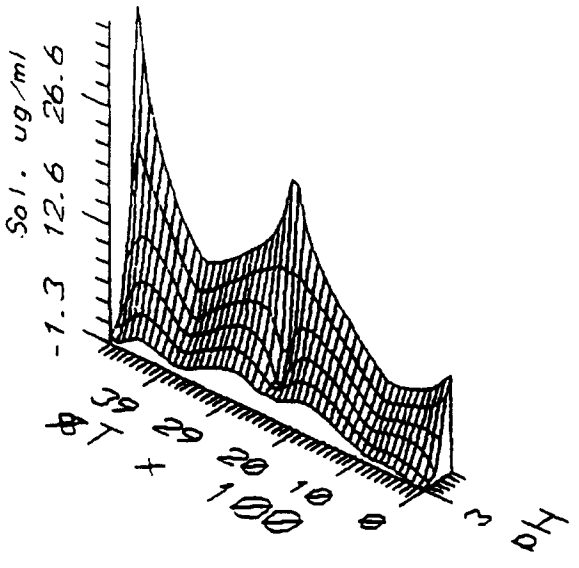


Fig. 2. Response surface graph relating glibenclamide solubility to pH values and percent Tween 80.

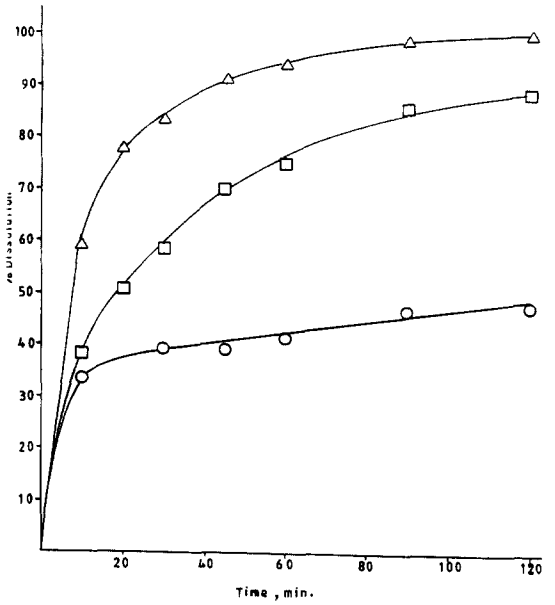


Fig. 3. Dissolution rate profiles of glibenclamide powder in different media (○) Phosphate buffer pH 7.4 (△) borate buffer pH 9.5 and (□) Phosphate buffer pH 7.4, containing 8.5% alcohol and 0.24% Tween 80.

was reported at alcohol concentrations higher than those used in the present study.

For the purpose of this study, the synergistic solubilizing effect for glibenclamide produced at pH 7.4 by a combination of alcohol and Tween 80 in the concentration ranges tested, can be made use of, in the development of a dissolution medium for glibenclamide. A medium containing 10.5% alcohol and 0.1% Tween 20 has been previously suggested by the FDA for the dissolution testing of carbamazepine tablets (FDA, 1987).

Based on the findings of the solubility study, a hydroalcoholic solution containing 8.5% alcohol, 0.24% Tween 80 and buffered at pH 7.4 was selected as a dissolution medium for glibenclamide.

The drug solubility at 37°C in this medium was 25.70 $\mu$g/ml while the solubility in phosphate buffer pH 7.4 was 9.9 $\mu$g/ml (Table 1). The latter value is consistent with previously re-

ported data (Kaali et al., 1987, Hassan et al., 1991).

Fig. 3 shows the dissolution rate of glibenclamide bulk powder in the medium selected compared to phosphate buffer pH 7.4 and borate buffer pH 9.5. The percentage dissolution at 1 h in these media was 75, 40 and 95% respectively. In the absence of the complicating formulation factors, both the rate and extent of glibenclamide dissolution in the medium under study are higher than those in phosphate buffer pH 7.4, probably due to the wetting action of Tween 80 and solubilization of the drug in the medium. However, the high pH of borate buffer (9.5) appears to outweigh the combined solubilizing effect of alcohol and Tween 80 and the wetting effect of the surfactant. These results are in agreement with those of the solubility study which showed a pronounced pH pure effect.

The dissolution rate of tablets is generally the resultant of the characteristics of the release medium including the solvent action and those of the tablet formulation. In developing a dissolution test, sensitivity of the medium to formulation and manufacturing variables considerably affects the discriminating power of the test. To assess the utility of the medium under study, in providing a discriminatory dissolution test for glibenclamide products, the medium was used for the dissolution testing of two commercial brands of glibenclamide tablets. Results of the tablet assay of both brands conformed to the BP requirements. Different dissolution profiles were obtained (Fig. 4). The medium allowed complete release of glibenclamide from the standard tablets (brand A) and did not obscure the incomplete dissolution of the test tablets (brand B). Differences observed in the rate and extent of glibenclamide dissolution from tablets of both brands cannot be attributed to the effect of the medium on tablet disintegration as the disintegration time of both brands in the medium and in water was 1 min 30 s for brand A and 5 min 20 s for brand B tablets. The discriminating power of the medium proposed was further compared with that of phosphate buffer pH 7.4 and borate buffer pH 9.5. Dissolution profiles of the two glibenclamide tablet brands (Figs. 5 and 6) indicate obvious superiority of the medium. Borate buffer pH 9.5 showed a limited discrimination ability as tablets of both brands released more than 90% of their content in 1 h (Fig. 5). In phosphate buffer pH 7.4, standard glibenclamide tablets released only 65% of their content in 1 h and 80% in 2 h (Fig. 6). These data are consistent with those of a previously reported dissolution study (Blume et al., 1993).

In conclusion, a buffered hydroalcoholic surfactant solution with a relatively low alcohol (8.5%) and Tween 80 (0.24%) concentrations has been developed as a dissolution medium for the poorly soluble drug, glibenclamide. Complete dissolution of standard glibenclamide tablets was achieved in 900 ml of the medium. Further, the developed medium offers a compromise between practical and physiological considerations and showed a discriminating power superior to that of media previously suggested for the dissolution testing of glibenclamide. Modification of the

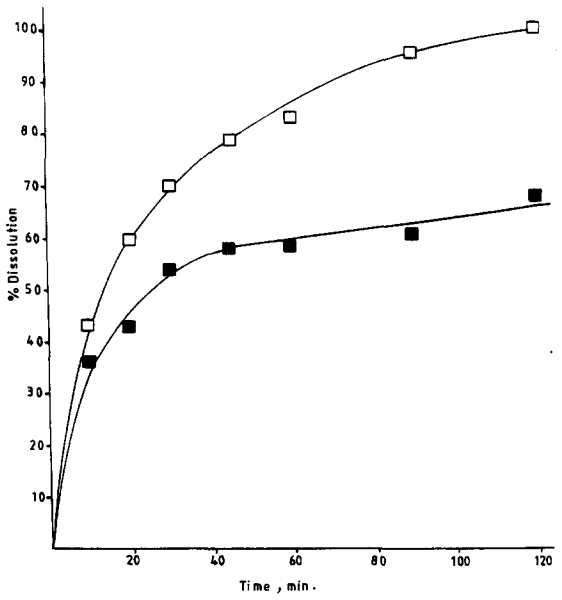


Fig. 4. Dissolution rate profiles of glibenclamide tablets (□) brand A and (■) brand B in Phosphate buffer pH 7.4, containing 8.5% alcohol and 0.24% Tween 80.

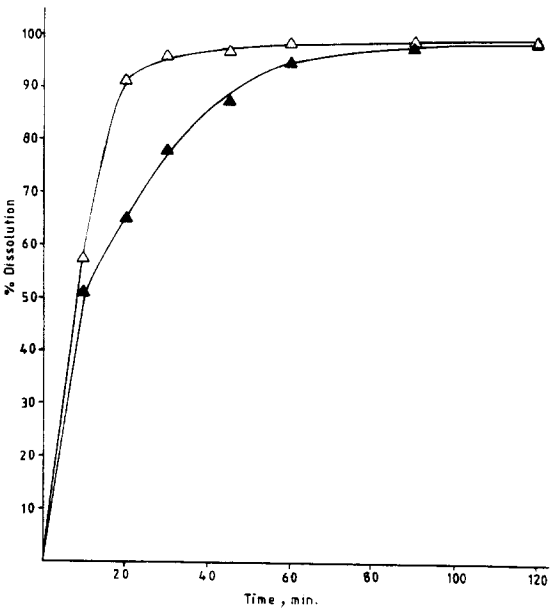


Fig. 5. Dissolution rate profiles of glibenclamide tablets (△) brand A and (■) brand B in borate buffer pH 9.5.

medium composition by adjusting the different factor levels may provide a discriminatory dissolution test for other water insoluble drugs.

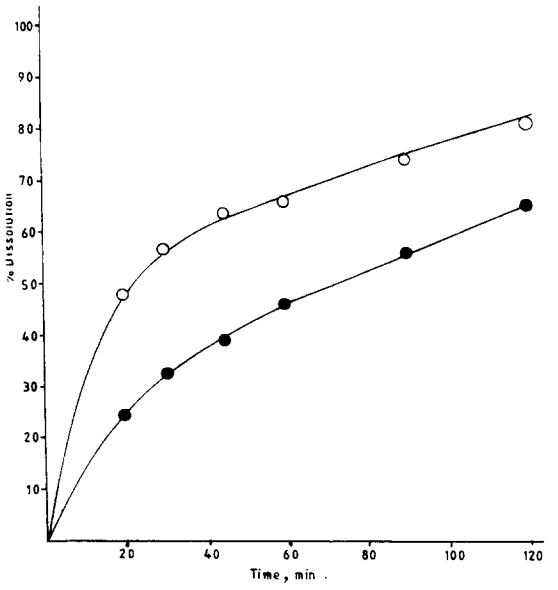


Fig. 6. Dissolution rate profiles of glibendamide tablets (○) brand A and (●) brand B in Phosphate buffer pH 7.4.

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