# Study of the Solubilization of Gliclazide by Aqueous Micellar Solutions

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**ABSTRACT:** It was of interest to increase the solubility of gliclazide in aqueous media. Therefore, solubilization of gliclazide in a variety of surfactants was investigated. Anionic and cationic surfactants exhibited dramatic solubilizing ability for gliclazide, whereas nonionic surfactants showed significantly lower solubilizing ability. It was found that gliclazide solubility increases with increasing the carbon chain length of cationic surfactants and decreases with increasing the carbon chain length of anionic surfactants. The solubilization data were analyzed on the basis of a pseudo-phase model with gliclazide exhibiting moderate partition coefficients into the micellar phase. The possible sites of solubilization of gliclazide in the micelle were examined by studying the effect of NaCl on solubilization and by comparing the absorption spectra of gliclazide in different solvents. The results obtained from these two experiments indicated that gliclazide is solubilized mainly in the inner core of the cationic surfactant micelles and in the outer regions of the anionic surfactant micelles.  J Pharm Sci 92:839–846, 2003

**Keywords:** gliclazide; micellar solubilization; surfactants; locus of solubilization

## INTRODUCTION

Gliclazide is a second-generation sulfonylurea used in the treatment of non-insulin dependent diabetes mellitus. It belongs to the same class of drugs as tolbutamide, glibenclamide, and glipizide. The structure of gliclazide[1] is shown in Figure 1. Gliclazide is a weak acid ($pKa = 5.8$).[2] The electronegative oxygen of the sulfonyl group or each acidic carbonyl group tends to withdraw electrons and to create a positive carbon atom. The carbon in turn attracts electrons from the nitrogen group and causes the hydrogen to be held less firmly.

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Gliclazide is shorter-acting than glibenclamide, so there is less risk of hypoglycemia, and for this reason it is preferred in the elderly.[3]

There are few complications with the clinical use of gliclazide. Previous workers have reported large variations in both the rates of absorption and the peak plasma concentrations. Variations are so wide that one worker concluded that the absorption of gliclazide in humans is somewhat more complex than that seen in other species or, for that matter, in other sulfonylureas.[2]

Gliclazide is practically insoluble in water (55 μg/mL at 37°C). Therefore, micellar solubilization is an area of investigation for the improvement of pharmaceutical formulations. Surfactants are widely used to improve the solubility of poorly soluble drugs. They also have the advantage of protecting the drug against hydrolysis. Solubilization by surfactant systems was discussed thoroughly by previous investigators.[4–6]

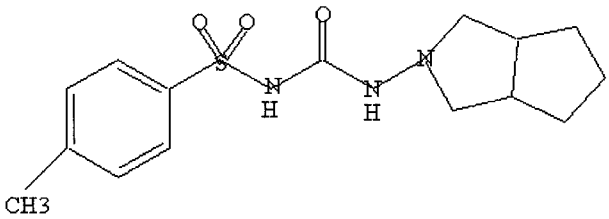



**Figure 1.** Gliclazide chemical structure.

The objectives of this work were to enhance the water solubility of gliclazide using ionic and nonionic surfactants and to specify the locus of solubilization of gliclazide in the micellar solutions.

Although some of the ionic surfactants that were used in this study might be toxic, and will not be used *in vivo*, their use is essential in determining the locus of solubilization of gliclazide.

## MATERIALS AND METHODS

Gliclazide was supplied by Dar Al Dawa'a (Amman, Jordan). Decyltrimethyl ammonium bromide (DTMAB) (99% pure), decyl sodium sulfate (DSS) (99% pure), polyoxyethylene cetylether (Brij 58), and tyloxapol were obtained from ACROS Organics Company (Fair Lawn, NJ). Dodecyltrimethyl ammonium bromide (DDTMAB) (99% pure), tetradecyl trimethyl ammonium bromide (TDTMAB) (99% pure), hexadecyl trimethyl ammonium bromide (HDTMAB) (99% pure), sodium dodecyl sulfate (SDS) (99% pure), and tetradecyl sodium sulfate (TDSS) (95% pure) were purchased from Sigma Chemical (St. Louis, MO).

Benzalkonium chloride was purchased from Scharlau (Barcelona, Spain). Other nonionic surfactants (Tween 20, Tween 80, Span 20, Span 60, and Span 80) were obtained from Jordanian Pharmaceuticals Manufacturing (Amman, Jordan).

Acetonitrile and isopropanol [high-performance liquid chromatography (HPLC) grade; Frutarom, Ltd., UK] were used for mobile phase preparation. Water (HPLC grade) obtained from Lab-Scan Analytical Sciences (Dublin, Ireland) was used in all the experiments.

### Solubilization Test

Excess gliclazide was equilibrated with various surfactant solutions in 10-mL screw-capped bottles. The bottles were closed tightly and a layer of Parafilm was placed over the top of each bottle to prevent any leakage. A layer of aluminum foil was then added to each bottle to prevent light effects. The samples were rotated (30 rpm) in a temperature-controlled water bath for a period of time in excess of that required for equilibrium (24 h). After equilibration, the samples were removed and filtered through a 0.45-μm cellulose acetate or Teflon membranes (which were installed in stainless steel filter holders). Under the experimental procedure that was used in this study, gliclazide was stable and no hydrolytic degradent of gliclazide was observed. The samples were assayed for gliclazide content with the aid of a reversed-phase HPLC system. The HPLC instrument and method of analysis are described below. Each experiment was done in triplicate and the average was used.

### Assay Method

All assays for gliclazide were performed on a Merck Hitachi chromatographic system with photodiode array detection (Merck KGaA, Darmstadt, Germany). The separation was conducted on reversed-phase C-18, 5-μm diameter and 250-mm height column (Merck KGaA). The mobile phase consisted of 50% acetonitrile, 40% potassium dihydrogen phosphate aqueous solution (0.04 M), and 10% isopropanol. The method was run under 1 mL/min flow rate, 227-nm wavelength, and 100-μL injection volume. Under these conditions, gliclazide had a retention time of 5 min. Standard solutions of gliclazide were prepared and injected at the beginning and end of the HPLC run.

### Critical Micelle Concentration (CMC) Determination and Surface Tension Measurements

The CMCs were determined by measuring surface tension change with surfactant concentration. A DuNoüy ring tensiometer (model 21; Fisher Scientific, Fair Lawn, NJ) was used to measure the surface tension. Table 1 gives the CMC and the standard deviation values obtained for the used surfactants under different experimental conditions. Each experiment was done in triplicate and the average was used.

### Spectral Test

The spectral test was done to investigate the location of gliclazide in the micelles of different

**Table 1.** CMCs of the Used Surfactants at Different Experimental Conditions

| Surfactant | CMC (mM) | SD | Conditions |
|---|---|---|---|
| $C_{10}H_{21}(CH_3)_3NBr$ (DTMAB) | 53.52 | 5.23 | 25°C, $H_2O$ |
| | 60.65 | 3.57 | 37°C, $H_2O$ |
| $C_{12}H_{25}(CH_3)_3NBr$ (DDTMAB) | 15.24 | 0.23 | 25°C, $H_2O$ |
| | 15.57 | 0.46 | 37°C, $H_2O$ |
| | 9.73 | 0.69 | 37°C, 0.03 M NaCl |
| | 5.51 | 0.69 | 37°C, 0.1 M NaCl |
| | 2.60 | 0.42 | 37°C, 0.5 M NaCl |
| $C_{14}H_{29}(CH_3)_3NBr$ (TDTMAB) | 3.27 | 0.21 | 25°C, $H_2O$ |
| | 3.57 | 0.28 | 37°C, $H_2O$ |
| | 0.57 | 0.01 | 37°C, 0.1 M NaCl |
| $C_{16}H_{33}(CH_3)_3NBr$ (HDTMAB) | 0.93 | 0.05 | 25°C, $H_2O$ |
| | 1.04 | 0.04 | 37°C, $H_2O$ |
| | 0.16 | 0.03 | 37°C, 0.1 M NaCl |
| $C_{10}H_{21}NaSO_4$ (DSS) | 26.88 | 2.71 | 25°C, $H_2O$ |
| | 30.72 | 2.71 | 37°C, $H_2O$ |
| $C_{12}H_{25}NaSO_4$ (SDS) | 7.98 | 0.49 | 25°C, $H_2O$ |
| | 8.32 | 0.49 | 37°C, $H_2O$ |
| | 2.77 | 1.85 | 37°C, 0.03 M NaCl |
| | 1.66 | 0.24 | 37°C, 0.1 M NaCl |
| | 0.55 | 0.01 | 37°C, 0.5 M NaCl |
| $C_{14}H_{29}NaSO_4$ (TDSS) | 1.90 | 0.25 | 25°C, $H_2O$ |
| | 2.53 | 0.20 | 37°C, $H_2O$ |

surfactant solutions. The ultraviolet spectrum (MultiSpec-1501; Shimadzu Corp., Tokyo, Japan) was used to determine the wavelength at maximum absorption $\lambda_{max}$ of gliclazide in each solvent or solution. SDS, DSS, TDTMAB, HDTMAB, DDTMAB, heptane, water, basic medium (pH = 11) and acidic medium (pH = 3.5) were all used in this experiment. The solubilization test was done for each solvent. The absorbances at fixed range of wavelength were obtained using the solvents as the blanks. If dilution was needed, the original solvent was used.

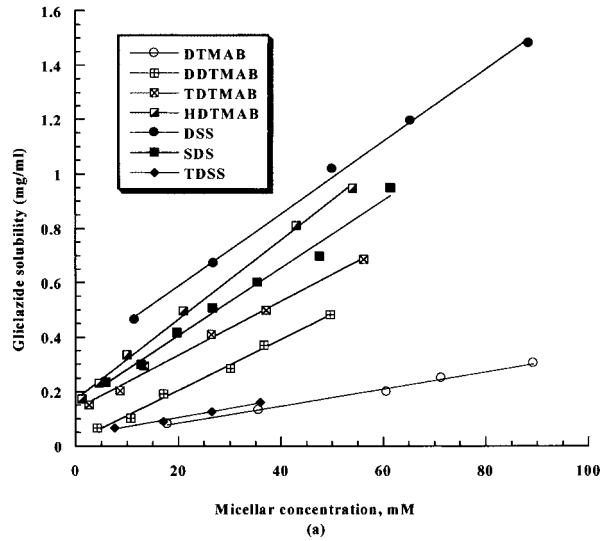
## RESULTS AND DISCUSSION

### Micellar Solubilization

A number of anionic surfactants (DSS, SDS, TDSS) and cationic surfactants (DTMAB, DDTMAB, TDTMAB, HDTMAB) showed dramatic solubilizing ability of gliclazide at both 25° and 37°C (Fig. 2a,b, respectively). For alkyl trimethyl ammonium bromides, the solubilization of gliclazide shows a significant chain length effect, HDTMAD > TDTMAB > DDTMAB > DTMAB. For alkyl sodium sulfates, however, the chain length effect on gliclazide solubilization shows a reversed behavior. The lowest chain length has the highest solubilization ability. The order of increasing solubility in anionic surfactants is DSS > SDS > TDSS.

The slopes of plotting gliclazide solubility versus micellar concentration of different surfactants at 25° and 37°C are presented in Table 2. Of all surfactants used, the one that gives the highest solubilization of gliclazide is HDTMAB, and the lowest is DTMAB. The solubilization in all ionic surfactants was higher at 37° than at 25°C. This is attributed to the increase in thermal agitation, which results in an increase in the space available for solubilization in the micelle, in addition to the increase of gliclazide solubility in aqueous phase by temperature.

Gliclazide solubility in 1% (w/v) of various surfactant solutions at both 25° and 37°C is listed in Table 3. Most of the nonionic surfactants used show a lower degree of solubilization than ionic surfactants. They improve gliclazide solubility by two- to five-fold, which is comparable to that obtained by 2% DTMAB, the one that has the lowest ionic surfactant solubility of gliclazide. However, benzalkonium chloride (a cationic surfactant) shows an increase in gliclazide solubility by about eight-fold. Based on the results presented in Table 3, it was concluded that ionic surfactants



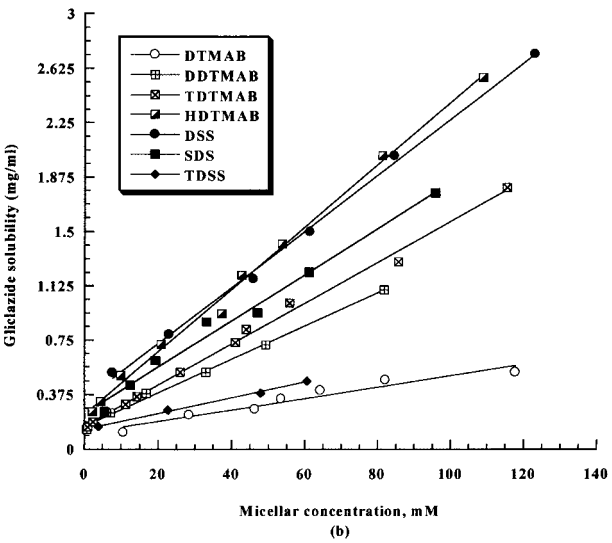




**Figure 2.** Gliclazide solubility versus micellar concentration (C-CMC) for different surfactants at (a) 25°C and (b) 37°C.

have a greater solubilizing ability for gliclazide than nonionic surfactants.

Surfactant chain length effect on solubilization of gliclazide is shown in Figure 3. An increase in the hydrocarbon chain length of cationic surfactant results in an increase in the degree of solubilization of gliclazide. This makes one expect that gliclazide is solubilized primarily in the hydrophobic micellar core. Anionic surfactants have a reversed action. Increasing the chain length showed a decrease in the solubilizing ability. This effect leads to the conclusion that gliclazide is mainly solubilized in the outer regions of the anionic surfactant micelles. It can be

**Table 2.** The Slope of the Linear Curve of Plotting Gliclazide Solubility Versus Micellar Concentration of Different Surfactants at 25° and 37°C

| Surfactant | Slope (25°C) | Slope (37°C) |
|---|---|---|
| DTMAB | 0.00315 | 0.00392 |
| DDTMAB | 0.00934 | 0.01151 |
| TDTMAB | 0.00991 | 0.01411 |
| HDTMAB | 0.01470 | 0.02154 |
| DSS | 0.01332 | 0.01937 |
| SDS | 0.01246 | 0.01594 |
| TDSS | 0.00339 | 0.00536 |

expected by now that gliclazide could be solubilized in the inner core and in the outer regions of the micelle, in a different extent depending on the nature of the surfactant.

The solubility data were also analyzed using a pseudo-phase model with gliclazide partitioning into the micellar pseudo-phase. The partition coefficient ($P_m$) between the aqueous and the micellar pseudo-phases was calculated using the following equation:

$$\frac{S_t}{S_o} = 1 + P_m \bar{\upsilon}[M] \qquad (1)$$

where $S_t$ and $S_o$ are total and intrinsic water solubilities, respectively, $P_m$ is the micelle-aqueous partition coefficient, $\bar{\upsilon}$ is the partial molal volume of the micelle, and [M] is the micellar concentration.

The relative solubility of gliclazide versus micellar concentration is shown in Figure 4. The slope of each curve was used to calculate the micellar-aqueous phase partition coefficient using pseudo-phase model with the help of eq. 1. The slope of each curve represents the partition coefficient multiplied by partial molal volume of that surfactant, which were obtained for some surfactants from literature.[7] Table 4 lists the parameter values used and $P_m$ assuming that the CMC, micellar size, and shape are unchanged when the solubilizate is present.

The calculated micellar concentration of gliclazide, that has $1.7 * 10^{-4}$ M as a molar solubility, in SDS is 0.226 M (obtained as the product of aqueous solubility and $P_m$) is comparable to the micellar concentration of some organic compounds in SDS such as *p*-Xylene which has a solubility of $1.84 * 10^{-3}$ M and $P_m$ of 1141, and biphenyl which has a solubility of $4.1 * 10^{-5}$ M and $P_m$ equal to 5122.[8]

**Table 3.** Gliclazide Solubility in Various Surfactant Solutions

| Surfactants | Gliclazide Concentration (mg/mL) 37°C | 25°C |
|---|---|---|
| Cationic surfactants | | |
| 2% (w/v) DTMAB | 0.1121 | 0.0901 |
| 1% DDTMAB | 0.3798 | 0.2871 |
| 1% TDTMAB | 0.5705 | 0.4474 |
| 1% HDTMAB | 0.8372 | 0.5822 |
| 1% Benzalkonium chloride | 0.4216 | 0.3358 |
| Anionic surfactants | | |
| 1% DSS | 0.7885 | 0.6418 |
| 1% SDS | 0.7381 | 0.6010 |
| 1% TDSS | 0.2956 | 0.1642 |
| Nonionic surfactants | | |
| 1% Sorbitan mono-laurate (Span 20) | 0.1765 | 0.1271 |
| 1% Sorbitan mono-stearate (Span 60) | 0.1956 | 0.1999 |
| 1% Sorbitan mono-oleate (Span 80) | 0.0630 | 0.0999 |
| 1% Polyoxyethylene sorbitan mono-laurate (Tween 20) | 0.1338 | 0.1114 |
| 1% Polyoxyethelene sorbitan mono-oleate (Tween 80) | 0.1294 | 0.1353 |
| 1% Polyoxyethelene-20-cetylether (Brij 58) | 0.1122 | 0.2052 |
| 1% Tyloxapol | 0.1343 | 0.0999 |

## Locus of Solubilization

It was noticed that the alkyl trimethyl ammonium bromides surfactants have a different solubility mechanism than that of alkyl sodium sulfate surfactants, and it was suggested that gliclazide is solubilized mainly in the micelle core of the cationic surfactants used and in the outer regions of the micelles of the anionic surfactants. Two tests have been made to prove these suggestions: ionic strength effect and a spectral study.

The addition of small amounts of neutral electrolyte to solutions of ionic surfactants usually increases the extent of solubilization of hydrocarbons that are solubilized in the inner core of the micelle and decreases that of polar compounds that are solubilized in the outer portion of the palisade later. The effect of neutral electrolyte

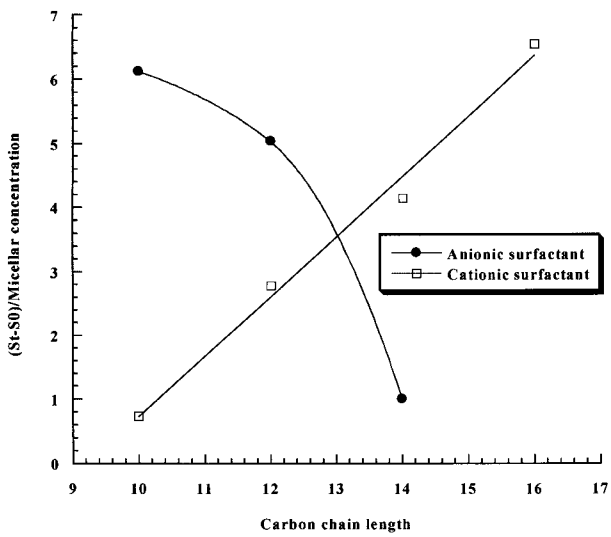



**Figure 3.** Normalized micellar solubility of gliclazide versus surfactant alkyl chain length.

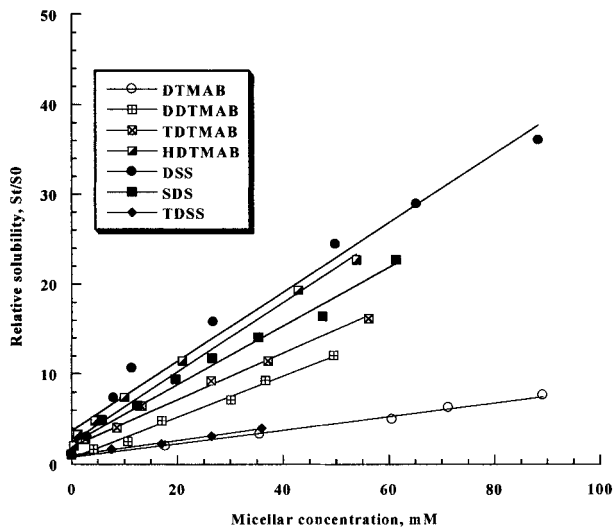



**Figure 4.** Relative solubility of gliclazide versus micellar concentration of various surfactants.

**Table 4.** Parameters Used in Micelle-Aqueous Partition Coefficient Calculation

| Surfactant | Slope ($mM^{-1}$) | $\bar{v}$ (mL/mol) | $P_m$ |
|---|---|---|---|
| DTMAB | 0.07477 | 262.3 | 286 |
| DDTMAB | 0.22759 | 295.5 | 771 |
| TDTMAB | 0.25882 | 331.2 | 782 |
| HDTMAB | 0.38723 | 365.4 | 1061 |
| DSS | 0.38808 | 212.5 | 1827 |
| SDS | 0.32702 | 246.4 | 1328 |
| TDSS | 0.08254 | 280.4 | 295 |

addition on the ionic surfactant solution is to decrease the repulsion between the similarly charged ionic surfactant head groups, thereby decreasing the CMC and increasing the aggregation number and volume of the micelles. The increase in aggregation number of the micelles results in an increase in hydrocarbon solubilization in the inner core of the micelle. The decrease in mutual repulsion of the ionic head groups causes closer packing of the surfactant molecules in the palisade layer and a resulting decrease in the volume available there for solubilization of polar compounds.

The effect of NaCl on gliclazide solubilization by DDTMAB and SDS was examined. For DDTMAB, the addition of 0.03, 0.1, and 0.5 M NaCl did not show a significant change in the solubilization power. This is shown in Figure 5a. However, gliclazide solubility in SDS was lowered as the amount of NaCl was increased. This is shown in Figure 5b.

For DDTMAB, the solubilization of gliclazide was not significantly affected by the increase in the ionic strength. This result supports the suggestion that gliclazide is mainly solubilized in the inner core of DDTMAB surfactant. Although the addition of NaCl decreased the CMC of DDTMAB and increased its aggregation number, the solubilization of gliclazide did not increase. This might indicate that the effects that favor increasing gliclazide solubility in the core were in combination with the effects that oppose decreasing solubility of gliclazide in the outer regions of the micelles. Therefore, the effect of NaCl on the solubilization power of DDTMAB was negligible.

For SDS, the solubilization of gliclazide decreased significantly by the increase in the ionic strength. This result supports the suggestion that gliclazide is mostly solubilized in the outer regions of the micelle in SDS surfactant. The addition of NaCl decreased the electrostatic repulsion

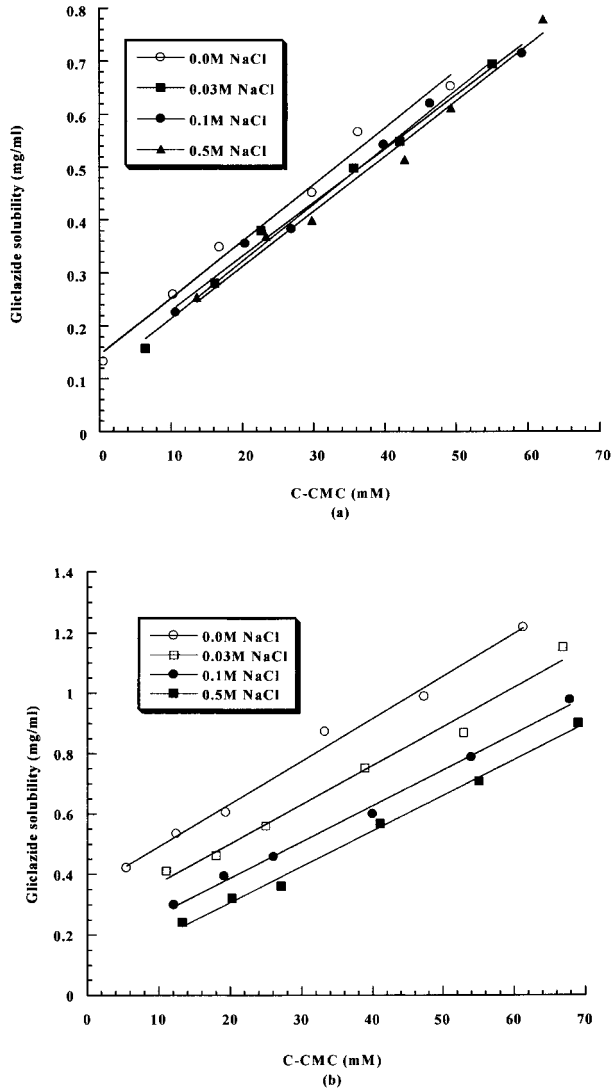



**Figure 5.** Gliclazide solubility versus micellar concentration with different concentrations of NaCl at 37°C for (a) DDTMAB and (b) SDS.

between the similarly charged ionic surfactant head groups. This effect caused a closer packing of the molecules in the palisade layer, which therefore decreased the volume available for gliclazide to be solubilized.

To further investigate the possible mechanism involved in gliclazide solubilization, a spectral study was performed. The exact location in the micelle at which solubilization occurs varies with the nature of the material solubilized and is of importance in that it reflects the type of interaction occurring between surfactant and solubilizate. Ultraviolet spectroscopy can be used to determine the location of solubilizate in the micelle, where the environment of solubilization is used to

locate the solubilizate sites. If gliclazide were to be solubilized in the inner core of the micelle, its ultraviolet spectra must indicate a nonpolar environment on solubilization. However, if gliclazide is solubilized in the outer regions of the micelle, a polar environment must be indicated.

Figure 6a is the absorption spectra of gliclazide in water, acidic (pH = 3), and basic (pH = 11) media at different wavelengths. It is shown that water spectrum exhibits a shift toward lower wavelengths. Also, changes in pH from that of water (pH = 7) do not have that much effect on the maximum wavelength of gliclazide, and their spectra are similar to that of water in their shape. Consequently, it can be assumed that gliclazide spectrum in different pHs and in water is more or less the same.

The absorption spectra of gliclazide in anionic surfactants DSS and SDS are shown in Figure 6b. The maximum wavelengths are 225.4 and 228.4 nm, respectively. These spectra indicate a polar environment, because the peaks are shifted toward that of water, which has 225.8 nm as the maximum wavelength. This supports the suggestion that gliclazide is mostly solubilized on the surface of the micelles in anionic surfactants, and it is solubilized in the outer regions of DSS micelles more than that by SDS micelles.

The absorption spectrum of gliclazide in heptane is shown in Figure 6c; the spectrum exhibits a shift toward higher wavelength, and the maximum wavelength is 236 nm. Cationic surfactants DDTMAB, TDTMAB, HDTMAB absorption spectra of gliclazide are shown in Figure 6d; the maximum wavelengths are 231, 231.6, and 232.8 nm, respectively. The spectra are shifted toward that of heptane more than to that of water, which leads to the conclusion that the solubilization environment is nonpolar. Furthermore, gliclazide is mostly solubilized in the inner core of the micelle. The shift toward heptane is more by HDTMAB than TDTMAB, which is more than DDTMAB. This indicates that the solubilization of gliclazide is more in the core because increasing

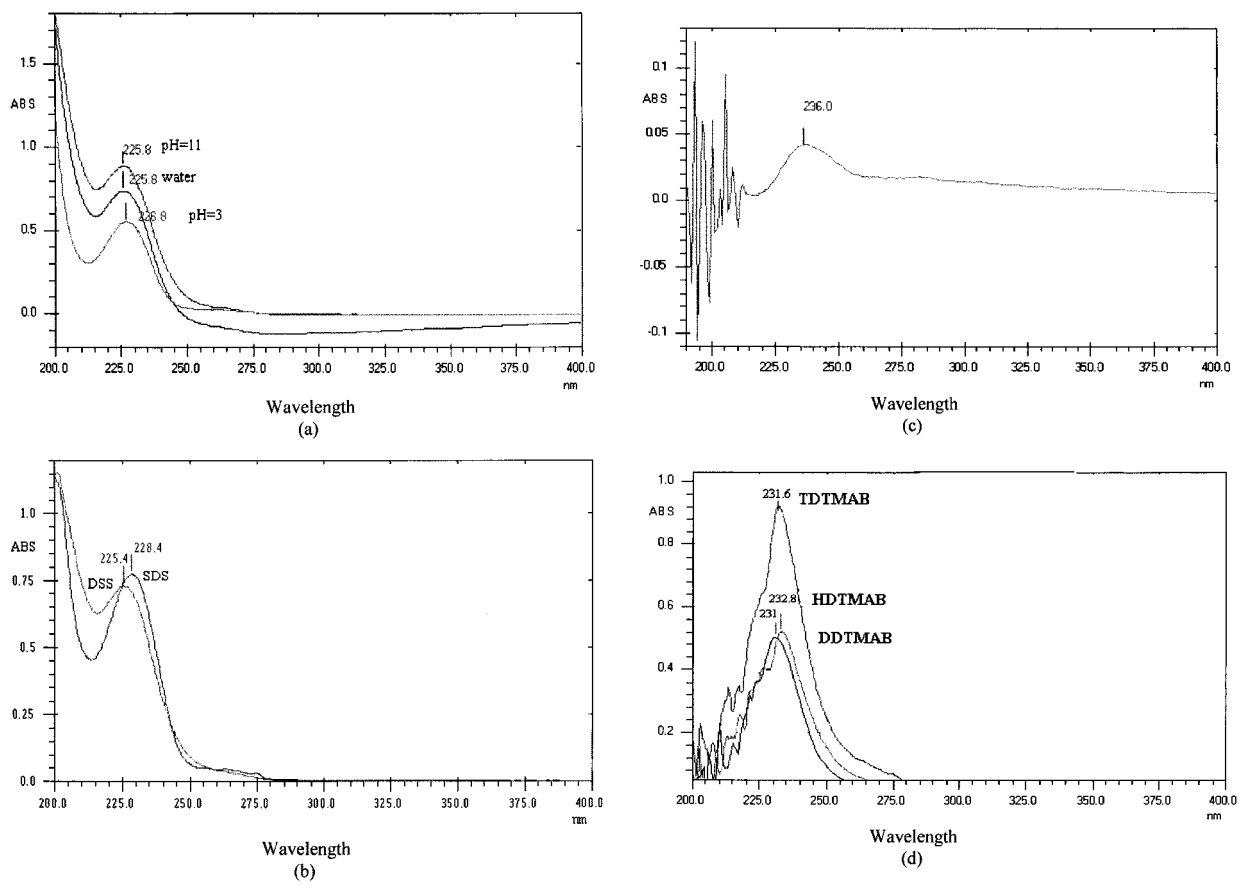



**Figure 6.** Absorption spectra of gliclazide in (a) water, acidic and basic medium, (b) DSS and SDS, (c) heptane, and (d) DDTMAB, TDTMAB, and HDTMAB.

**Table 5.** Maximum Wavelength ($\lambda_{max}$) of Gliclizide in Various Solvents

| Solvent | $\lambda_{max}$ (nm) |
|---|---|
| Water | 225.8 |
| Heptane | 236.0 |
| DSS (0.2 M) | 225.4 |
| SDS (0.2 M) | 228.4 |
| DDTMAB (0.2 M) | 231.0 |
| TDTMAB (0.2 M) | 231.6 |
| HDTMAB (0.2 M) | 232.8 |
| Acidic medium (pH = 3) | 226.8 |
| Basic medium (pH = 11) | 225.8 |

the carbon chain length results in an increase in the micelle core volume. The maximum wavelengths ($\lambda_{max}$) of absorption are listed in Table 5.

It should be pointed out that the absorbances shown in all of the figures do not give an indication of gliclazide concentration in the solvent used because different dilution factors have been used. Also, it should also be mentioned that the shape of the micelle may change with increasing the surfactant concentration but the locus of solubilizate should not change.

The specific interaction of gliclazide with the sulfate group of anionic surfactants can be explained as follows. Gliclazide is a weak acid. Based on its p*K*a and its presence in an environment such as distilled water, it is expected that at least 50% of gliclazide is unionized; therefore, there is a chance that the acidic hydrogen is interacting via ion dipole interaction with the sulfate group of the anionic surfactants.

Other investigators have previously proposed a distribution between micellar core and surface. Mukerjee and Cardinal[9,10] have described the total uptake of solubilizate by micelles to be divided into an adsorbed and a dissolved state. These investigators also used spectroscopy to establish the site of solubilization. Krishna and Flanagan[8] studied the solubilization of β-arteether in several anionic, cationic, and nonionic surfactant solutions. They found that anionic and cationic surfactants increased the solubility dramatically by micellar solubilization.

The results obtained from this investigation suggest a possible interaction between gliclazide and the polar head groups of anionic and cationic surfactants. They also indicate that gliclazide is solubilized mainly in the inner core of the cationic surfactant micelles and in the outer regions of anionic surfactant micelles. Also, significant gliclazide aqueous concentrations can be achieved using ionic surfactants.

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