Arch Pharm Res Vol 28, No 1, 120-126, 2005

Archives of Pharmacal Research
http://apr.psk.or.kr

Surfactant Effects upon Dissolution Patterns of Carbamazepine Immediate Release Tablet

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(Received September 8, 2004)

The objective of this study was to investigate the effects of sodium lauryl sulfate upon the saturation solubility of carbamazepine, its dissolution kinetics, and $T_{50\%}$ defined as the time required for dissolving 50% of carbamazepine. Water, 0.1N-HCl, and phosphate buffers at pH 4.0 and 6.8 containing 0.1, 0.5, 1, and 2% sodium lauryl sulfate were used as dissolution media. The dissolution study was conducted by using the USP dissolution apparatus II with an agitation rate of 75 rpm. Samples of the dissolution media were taken in 7, 15, 30, 45, 60, 75, and 90 min, and the amounts of carbamazepine were determined spectrophotometrically at 285 nm. All dissolution data were fitted well into a four-parameter exponential equation: $Q = a(1 - e^{-bxt}) + c(1 - e^{-dxt})$. In this equation Q represented % carbamazepine dissolved at a time t, and *a*, *b*, *c*, and *d* were constants. This equation led to the calculation of dissolution rates at various time points and $T_{50\%}$. It was found that the dissolution rate of carbamazepine was directly proportional to the aqueous concentration of sodium lauryl sulfate. In addition, under our experimental conditions $T_{50\%}$ values ranged from 37.8 to 4.9 min. It was interesting to note that $T_{50\%}$ declined rapidly as the surfactant concentration increased from 0.1 to 0.5%, whereas it declined more slowly at concentrations greater than 1%. These results clearly demonstrated that the dissolution rate of carbamazepine and duration of its dissolution test could be tailored by optimizing the amount of sodium lauryl sulfate in a dissolution medium.

Key words: Dissolution test, Dissolution kinetics, Carbamazepine, Sodium lauryl sulfate

INTRODUCTION

The dissolution test is an important tool for validating the manufacturing process of a drug product, evaluating its batch-to-batch homogeneity, and developing a dosage formulation to provide a desirable drug release rate. The importance of dissolution testing is also implemented in regulatory affairs dealing with changes to the approved NDAs and ANDAs in relation to component & composition, manufacturing site and process, manufacturing equipment, and batch size (FDA 1995; FDA 1997a). Recently, dissolution testing has been used to establish *in vitro-in vivo* correlations, in order to predict how well a product would perform *in vivo* (FDA 1997b). These facts demonstrate that dissolution testing is invaluable in assessing the formulation quality and performance of a drug product.

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In fact, developing dissolution test methods for poorly water-soluble drug products has been an important task to formulation scientists. Problems encountered with poorly water-soluble drug products include a low extent of drug release and a slow release rate. General strategies to enhance their dissolution patterns rely upon either changing the dissolution medium pH, or adding solubilizers such as surfactants and cyclodextrin derivatives into a dissolution medium (Chen *et al.*, 2003; Qazi *et al.*, 2003; Sun *et al.*, 2003; Jain *et al.*, 2001; Castillo *et al.*, 1999; Crison *et al.*, 1997; Shah *et al.*, 1989; Aunins *et al.*, 1985; Serajuddin *et al.*, 1984). In rare cases, when the above attempts turn out to be unsuccessful, non-aqueous solvents are added into a dissolution medium. Types of surfactants that have been reported in the literature include polysorbate 20/80, cetyltrimethylammonium bromide, sodium lauryl sulfate (SLS), lecithin, sodium cholate, sodium deoxycholate, sodium taurocholate, sodium oleate, and sodium glycocholate. Among them, SLS has proved the agent of choice because it is inexpensive enough to be used at a large scale during a routine QC test, and it

possesses a good solubilizing capacity at relatively low concentrations. These might be reasons why SLS is predominantly found in compendial dissolution test methods for a variety of poorly water-soluble pharmaceuticals.

Previously, several authors reported that SLS could enhance dissolution of poorly water-soluble compounds (Sun *et al.*, 2003; Qazi *et al.*, 2003; Crison *et al.*, 1997; Shah *et al.*, 1989). Also, the carbamazepine tablet monograph listed in USP 27 recommends water containing 1% SLS as a dissolution medium. However, there are few reports on the mechanistic evaluation of SLS effects upon their dissolution patterns. In addition, it is recommended that dissolution tests be performed under sink conditions. To achieve sink conditions, one must maintain a volume of dissolution medium that is 3 to 10 times greater than a volume needed to form a saturated solution for a drug product. However, there is a dispute regarding what volume is really adequate to approximate sink conditions. Therefore, this study is aimed at investigating the effects of SLS upon the saturation solubility of the poorly water-soluble model drug carbamazepine and its dissolution pattern. It focuses on the dissolution kinetics established to describe the dissolution pattern of carbamazepine. In addition, this study has attempted to correlate SLS effects to the dissolution rate of carbamazepine and $T_{50\%}$ defined as the time required for the release of 50% of the labeled carbamazepine. To do so, the dissolution data of a carbamazepine immediate release tablet have been generated by use of a number of diverse dissolution media containing 0.1~2% SLS.

MATERIALS AND METHODS

Materials

The carbamazepine standard and SLS were purchased from Sigma Chemical Co. (St. Louis, MO, USA). A carbamazepine immediate release tablet with a dose unit of 200 mg was obtained from a Korean pharmaceutical company (lot no. 2087, Seoul, Korea). Methanol and other solvents were of analytical grade.

Determination of carbamazepine solubility

An excessive amount (40 mg) of carbamazepine was added to a screw-capped vial containing 10 mL of a dissolution medium. The vial was placed inside an oven maintained at a temperature of 37 ± 1 °C and was shaken with a rotating mixer for 24 h. The suspension was then filtered through a 0.45 μm Whatman syringe filter and diluted 40 times with the fresh dissolution medium. The absorbance of the resulting solution was measured spectrophotometrically at 285 nm (Ultraspec 2100 pro, Amersham Biosciences, Buckinghamshire, England). To make carbamazepine standard solutions, an accurately weighed quantity (60 mg) of carbamazepine was dissolved in methanol (50 mL) to produce a 1.2 mg/mL solution. Aliquots (10 mL) of this solution were transferred to a 100-mL volumetric flask and diluted 10 times with methanol. This stock solution was further diluted to make a series of standard carbamazepine solutions (3, 6, 9, and 12 μg/mL). The concentrations of unknown carbamazepine samples were calculated, based upon the standard calibration curve derived from the carbamazepine solutions with known concentrations. This experiment was repeated six times in order to calculate mean ± standard deviation (s.d.) values.

Content uniformity test

A powdered carbamazepine tablet was put into a volumetric flask containing 250 mL of methanol, which was stirred at 900 rpm for 2 h. The solution was filtered through a 0.45 μm Whatman syringe filter. One milliliter of the filtrate was diluted to 100 mL with methanol. The absorbance of the resulting solution was measured at 285 nm, and its concentration was determined from a standard calibration curve. The contents of carbamazepine in 10 tablets were determined individually as described above. Their average content and relative standard deviation are reported later.

Dissolution study

The USP dissolution apparatus II (paddle method) was used to conduct the dissolution test. The types of dissolution media used in this study included water, 0.1N-HCl, and 50 mM phosphate buffers at pH 4.0 and 6.8 (all the dissolution media contained 0.1, 0.5, 1, or 2% SLS). Total 12 carbamazepine tablets were put into 12 vessels containing 900 mL of the dissolution media. The vessels were stirred at the speed of 75 rpm, while the temperature of the dissolution media was kept at 37 ± 0.5 °C throughout the dissolution study. Aliquots (5 ml) of the dissolution media were taken in 7, 15, 30, 45, 60, 75, and 90 min. The dissolution media were then replaced with fresh ones equal to the volume removed. The dissolution samples were passed through a 0.45 μm Whatman syringe filter and diluted before the UV/Vis spectrophotometry analysis.

Dissolution data analysis

As the dissolution test continued, the amounts of carbamazepine dissolved increased exponentially to plateau as a function of time. Therefore, dissolution data were fitted into a biphasic exponential equation with four parameters as follows:

$$Q = a(1 - e^{-bxt}) + c(1 - e^{-dxt}) \quad (1)$$

where Q represented % carbamazepine dissolved at a specific time t, and a, b, c, and d were constants. A

correlation coefficient was calculated to judge the degree of curve fitting. This equation permitted the determination of $T_{50\%}$ defined as the time required for dissolving 50% of the labeled carbamazepine. The differentiation of equation (1) also helped calculate dissolution rates at various time points.

Judgment of the similarity of dissolution profiles

The similarity of dissolution profiles observed under different experimental conditions was evaluated by a model-independent approach using the similarity factor f_2, as recommended in several FDA guidelines (FDA 1997a; FDA 1997b; FDA 1995). The similarity factor f_2 was calculated as follows:

$$f_2 = 50 \bullet \log\left[\frac{100}{\sqrt{1+\frac{1}{n}\sum_{t=1}^{n}(R_t-T_t)^2}}\right] \quad (2)$$

In this equation, n is the number of time points used to measure the amount of carbamazepine dissolved, R_t is the mean % carbamazepine dissolved at a specific time t under one experimental condition, and T_t is the mean % carbamazepine dissolved at the same time t under the other experimental condition. When Qs of both the dissolution data were greater than 85% at several time points, only one of the measurements was taken for the f_2 metrics. Two dissolution profiles were judged to be similar to each other if f_2 was greater than 50.

RESULTS AND DISCUSSION

The results of the content uniformity test are shown in Fig. 1. The amounts of carbamazepine found in 10 tablets ranged from 192.8 to 208.5 mg. Their average content ± s.d. was 100.3 ± 2.7% of the label claim, and the relative standard deviation was 2.69%. The results demonstrated that the requirements for content uniformity were met because the carbamazepine content in each of the 10 tablets lied within the range of 85% to 115% of the label claim and the relative standard deviation was less than 6%.

The aqueous solubility of carbamazepine at 37 °C was determined to be 237.2 ± 5.2 μg/mL. Therefore, a sink condition would not be attained when 900 mL of water was used as a dissolution medium for one carbamazepine tablet with a 200-mg dose unit. The addition of SLS into its dissolution media resulted in a substantial increase in carbamazepine solubility, and the solubility-enhancing effect of SLS was proportional to its concentration (Fig. 2). SLS concentrations, equal to or greater than 1%, increased carbamazepine solubility more than 10-fold when compared to its solubility observed in the SLS-free aqueous solution. These results are in good agreement with the previous findings that SLS increased solubility of water-insoluble drugs via micelle formation (Sun *et al.*, 2003; Qazi *et al.*, 2003; Crison *et al.*, 1997; Shah *et al.*, 1989). Variations in the dissolution medium pH with SLS concentration remained constant, however, did not cause any considerable changes in the saturation solubility of carbamazepine. Such relatively consistent solubility might in large part be due to the fact that the ionization degree of any functional groups in carbamazepine would be unaffected by such pH changes.

The dissolution data generated by use of 4 different types of dissolution media are shown in Figs. 3~6. Increases in SLS concentration in the dissolution media resulted in a noticeable enhancement of the dissolution of carbamazepine. However, changes in pH and the type of

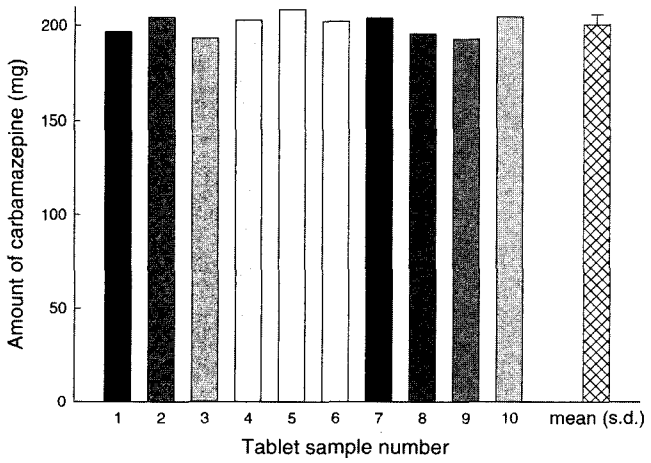

Fig. 1. Results of the content uniformity test performed on 10 carbamazepine immediate release tablets. The average content ± s.d. was 100.3 ± 2.7% of the label claim.

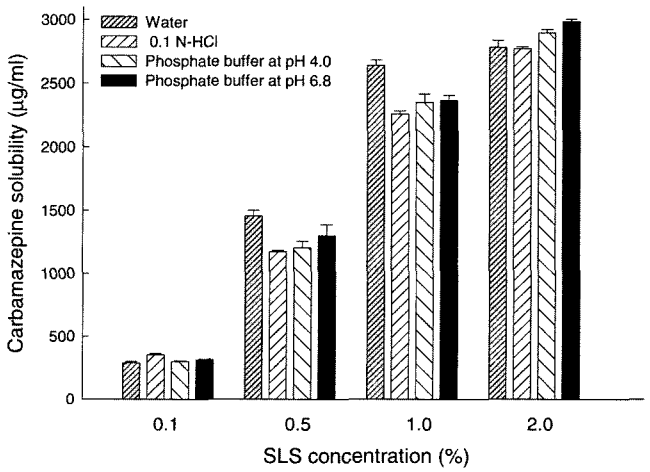

Fig. 2. Effect of aqueous SLS concentrations upon carbamazepine solubility in the four different types of dissolution media including water, 0.1 N-HCl, and 50 mM phosphate buffers at pH 4 and 6.8.

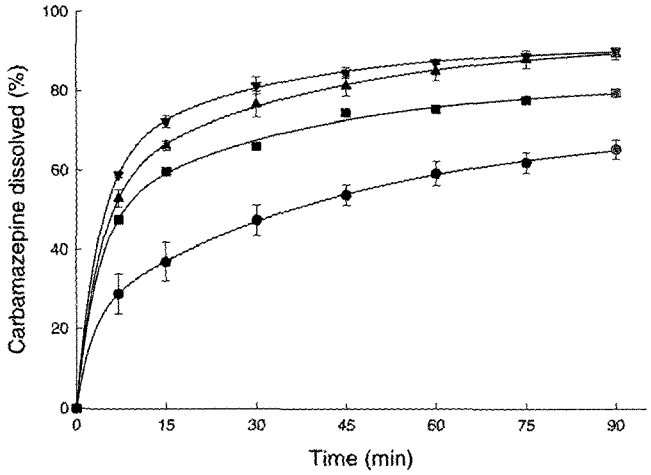

Fig. 3. Dissolution profiles observed with water containing (●) 0.1, (■) 0.5, (▲) 1, and (▼) 2% SLS.

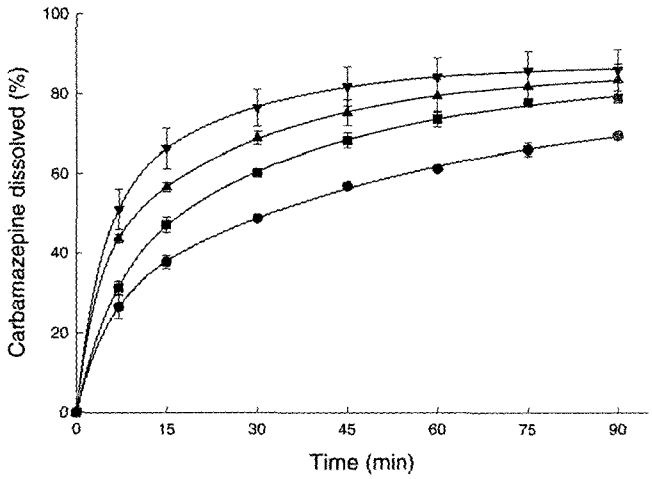

Fig. 4. Dissolution profiles observed with 0.1 N-HCl containing (●) 0.1, (■) 0.5, (▲) 1, and (▼) 2% SLS.

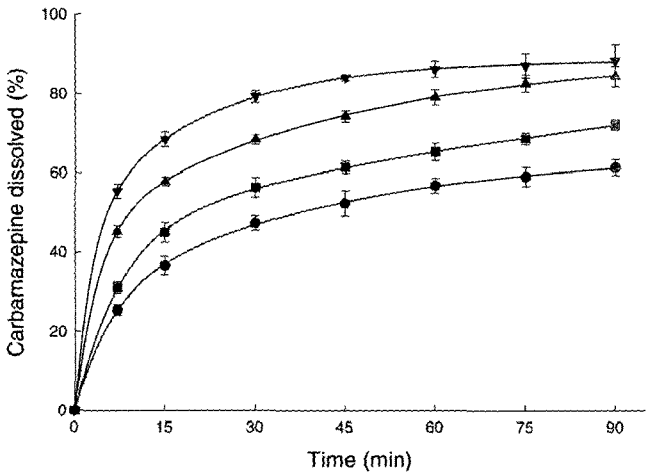

Fig. 5. Dissolution profiles observed with 50 mM phosphate buffer at pH 4.0 containing (●) 0.1, (■) 0.5, (▲) 1, and (▼) 2% SLS.

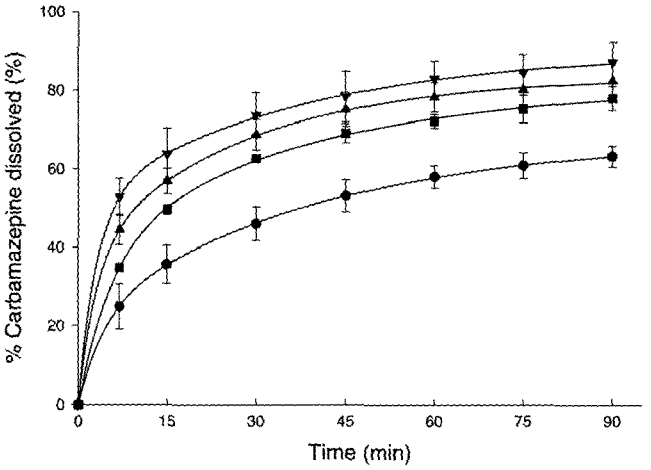

Fig. 6. Dissolution profiles observed with 50 mM phosphate buffer at pH 6.8 containing (●) 0.1, (■) 0.5, (▲) 1, and (▼) 2% SLS.

dissolution medium did not exert any substantial effects upon its dissolution, as long as the concentration of SLS remained constant. For example, Figs. 7(A) and 7(B) illustrate the similar dissolution profiles of carbamazepine observed with water, 0.1N-HCl, and 50 mM phosphate buffers at pH 4 and 6.8 containing 1 and 2% SLS, respectively. After the similarity of the dissolution profiles was further evaluated by the f_2 metrics, it was judged that their dissolution profiles were similar to one another: As shown in Table I, f_2 values determined toward various pairs of dissolution profiles were greater than 50. These results are in contrast with those observed frequently with *the solid dosage forms containing ionizable acidic/basic* drugs: dissolution medium pH plays a crucial role upon their dissolution patterns because it affects their solubility to great extents. By contrast, the similar degrees of carbamazepine solubility over the pH range of 1 to 6.8 might be responsible for the different results reported in this study. At present, SUPAC-IR recommends that the case C dissolution test for class II drugs should use five dissolution media such as water, 0.1N-HCl, and USP buffers at pH 4.5, 6.5, and 7.5. There have been arguments to such a requirement: it is too restrictive and requires a large number of unnecessary dissolution tests and relevant validation works. Certainly, our data attained with a class II drug carbamazepine are in favor of the above opinion. Reducing the number of multimedia to 2 or 3 might contribute to improving the utility of SUPAC-IR in handling postapproval changes. However, it should be cautioned that this conclusion might not be generalized for other class II drugs, particularly with ionizable groups.

It was previously reported elsewhere that drug release was quantified by the mean dissolution time (Abrahamsson *et al.*, 1994; Riegelman and Collier 1980). In other reports, dissolution data were subject to model-dependent appro-

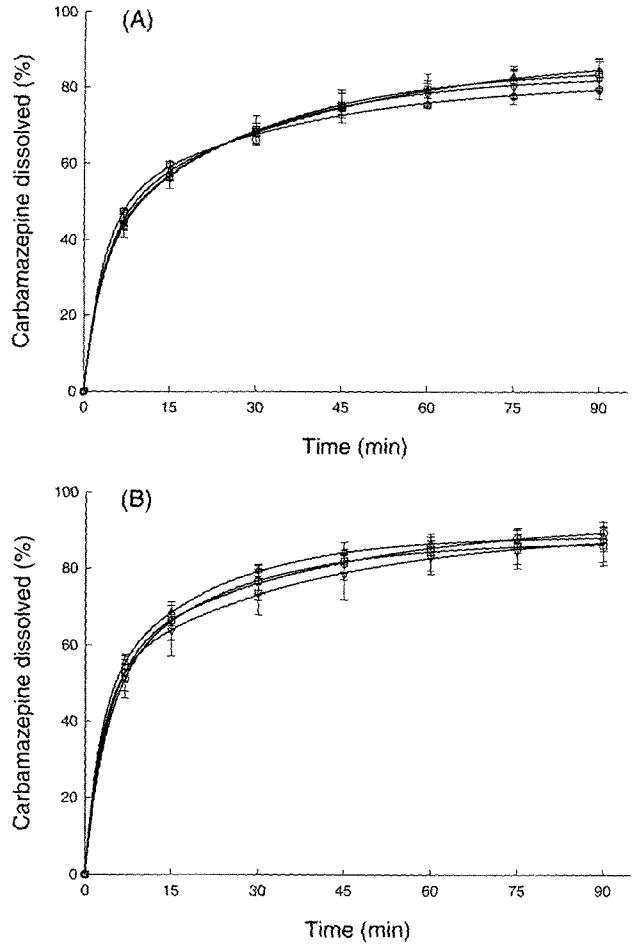

Fig. 7. Dissolution profiles observed with (○) water, (□) 0.1 N-HCl, and 50 mM phosphate buffers at (△) pH 4 and (▽) pH 6.8. The aqueous SLS concentration was (A) 1 and (B) 2%, respectively.

Table I. Comparison of the dissolution profiles observed with various types of dissolution media containing 1 or 2% SLS

A pair of profiles	f_2	
	1% SLS	2% SLS
Water vs. 0.1N-HCl	56.7	63.8
Water vs. pH 4.0	57.9	78.3
0.1N-HCl vs. pH 4.0	93.0	76.2
0.1 N-HCl vs. pH 6.8	92.6	79.5
pH 4.0 vs. pH 6.8	87.9	67.5
pH 6.8 vs. Water	55.4	59.4

aches including zero-order, first-order, Hixson-Crowell, Higuchi, Baker-Lonsdale, quadratic, logistic, Weibull, and Gompertz models (Costa and Lobo 2001; Velasco-De-Paola *et al.*, 1999; Kervinen and Yliruusi 1993; Dawoodbhai *et al.*, 1991; Rena Romero *et al.*, 1991; Langernbucher 1972). By contrast, the dissolution data obtained in this study were treated with a four-parameter biphasic exponential equation, $Q = a(1 - e^{-bx}) + c(1 - e^{-dx})$. The dissolution data were fitted quite well into the equation, and correlation coefficients greater than 0.999 were observed for every case (Table II). Based on the above equation, theoretical $T_{50\%}$ was calculated. It displays that $T_{50\%}$ tends to be shortened dramatically when a dissolution medium contains a high amount of SLS. Such a propensity was attributed to the effect of SLS upon carbamazepine solubility. To back up this supposition, $T_{50\%}$ values were plotted as a function of carbamazepine solubility determined under 16 different experimental conditions (Fig. 8): a total of 4 different dissolution media were used in this study, and each medium contained 4 different levels of SLS. It was found that $T_{50\%}$ could be correlated to carbamazepine solubility (Cs) with the following equation: $T_{50\%} = 30.02\ e^{-0.0017Cs} + 20.86\ e^{-0.0004Cs}$ ($r^2 = 0.97$). The results indicate that $T_{50\%}$ declines rapidly as an SLS concentration shifts from 0.1 to 0.5%, but it declines more slowly at SLS concentrations greater than 1%.

Table II. Results of curve fitting of dissolution data into the biphasic exponential equation (1) with four parameters and $T_{50\%}$ data calculated from the equation. All their correlation coefficients were greater than 0.999.

Dissolution medium	a	b	c	d	$T_{50\%}$(min)
pH 4.0 + 0.1% SLS	26.957	0.179	38.445	0.025	37.2
pH 4.0 + 0.5% SLS	45.331	0.135	46.836	0.009	19.6
pH 4.0 + 1.0% SLS	45.455	0.265	44.373	0.024	9.1
pH 4.0 + 2.0% SLS	46.631	0.365	41.896	0.050	5.5
pH 6.8 + 0.1% SLS	21.342	0.237	46.604	0.025	37.8
pH 6.8 + 0.5% SLS	38.390	0.175	42.704	0.027	14.9
pH 6.8 + 1.0% SLS	37.614	0.329	45.878	0.037	9.7
pH 6.8 + 2.0% SLS	51.119	0.324	38.750	0.028	6.2

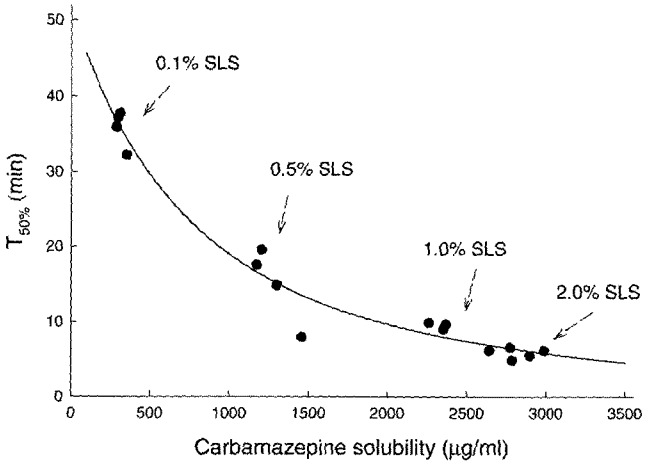

Fig. 8. Correlation of $T_{50\%}$ values to carbamazepine solubility determined under various experimental conditions. The line drawn through the data stands for the theoretical values calculated from the equation of $T_{50\%} = 30.02\ e^{-0.0017Cs} + 20.86\ e^{-0.0004Cs}$

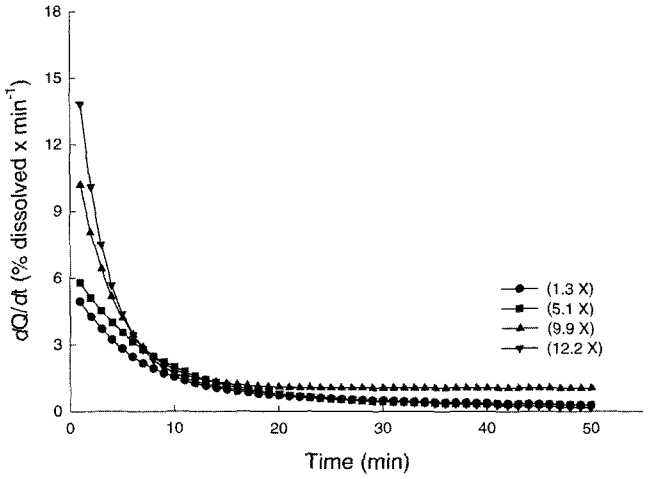

Fig. 9. Dependence of a dissolution rate upon the magnitude of sink conditions. Dissolution test was conducted by use of 50 mM phosphate buffer at pH 4 containing (●) 0.1, (■) 0.5, (▲) 1, and (▼) 2% SLS. Values inside the parenthesis represent the magnitude of sink conditions.

The effect of SLS upon the dissolution rate of carbamazepine was further evaluated by the differentiation of equation (1): $dQ/dt = a \times b(e^{-bxt}) + c \times d(e^{-dxt})$. This equation led to the calculation of dissolution rates of carbamazepine at various time points. For example, Fig. 9 illustrates the dissolution rates determined with the 50 mM phosphate buffer at pH 4 containing 0.1, 0.5, 1, or 2% SLS. It clearly demonstrates that the use of the dissolution medium containing a higher SLS concentration resulted in the attainment of a faster dissolution rate. If the solubility data in Fig. 1 are taken together into consideration, it is easy to understand how the magnitude of sink conditions affects the dissolution rate of carbamazepine.

CONCLUSION

Surfactants are known to enhance the dissolution of poorly water-soluble pharmaceuticals by improving the wettability of their dosage forms, and by increasing drug solubility via micelle formation. In this study the presence of SLS in a dissolution medium was shown to affect the saturation solubility of carbamazepine and the magnitude of sink conditions. All dissolution data were fitted well into a four-parameter biphasic exponential equation. The equation made it possible to substantiate the concentration-dependent SLS effects upon the dissolution pattern of carbamazepine, its dissolution rate, and $T_{50\%}$. The relevant results demonstrated that adjusting an SLS concentration would be very effective in tailoring the dissolution rate of carbamazepine and the duration of its dissolution test. Such information might be invaluable in developing a dissolution test as a QC tool for poorly water-soluble pharmaceuticals.

ACKNOWLEDGMENT

This work was supported in part by 2004 Catholic University of Daegu Research Fund.

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