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# The effects of surfactants on the dissolution profiles of poorly water-soluble acidic drugs

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**Abstract**

The effects of types of surfactants on the solubilization and dissolution of poorly soluble acidic drugs were compared to identify the most suitable surfactant for conducting an acidic drug dissolution test. Cetyltrimethylammonium bromide (CTAB) as a cationic surfactant, sodium lauryl sulfate (SLS) as an anionic surfactant, and polysorbate 80 as a non-ionic surfactant were used in the study. And, mefenamic acid, nimesulide, and ibuprofen were selected as model drugs. The dissolution rates of these acidic drugs were substantially enhanced in medium containing CTAB. Electrostatic interactions between acidic drugs and cationic surfactants were confirmed by measuring UV spectra of each drug. Solubility of drugs in various media and the partition coefficients of drugs into micelles were found to depend on drug characteristics. For acidic drugs, the ability of media containing a cationic surfactant to discriminate rates of dissolution of acidic drugs seemed to be greater than that of media containing other surfactant types.

*Keywords:* Poorly soluble acidic drug; Dissolution; Surfactant; Cetyltrimethylammonium bromide; Sodium lauryl sulfate; Polysorbate 80

## 1. Introduction

Recently, considerable attention has been focused on the importance of dissolution testing of oral dosage forms. In vitro dissolution tests of immediate release solid oral dosage forms are used in the lot-to-lot quality control of drug products, and in the development of new formulations (FDA, 1997). The Biopharmaceutics Classification System (BCS) classifies oral drug products into four different classes based on the solubility and permeability of the drug (Amidon et al., 1995). Depending on the class of a drug, the results of a dissolution study can be closely related to in vivo results. In the case of class II drugs that have low solubility and high permeability, drug dissolution may be the rate-limiting step in the drug adsorption process (FDA, 1997). For poorly water-soluble drugs, such as, classes II and IV in the BCS classification, difficulties are encountered in terms of selecting dissolution medium with the ability to discriminate drug products, because dissolution media used generally in the laboratory cannot dissolve poorly soluble drugs completely (He et al., 2004).

Many researchers are interested in the development of an appropriate dissolution medium for such drugs to overcome solubility problems (El-Massik et al., 1996; Maggi et al., 1996; He et al., 2004). One approach to improving dissolution was to use a large amount of dissolution medium (Chiou and Riegelman, 1970; Maggi et al., 1996). A co-solvent method was also used to increase drug solubility (Itai et al., 1985; Corrigan, 1991). Other researchers have used surfactants to increase drug solubility (El-Massik et al., 1996; Maggi et al., 1996; He et al., 2004). Of the various methods investigated, the use of media containing surfactants was proposed as a suitable method for solubilizing such drugs, because various surfactants are present in the gastrointestinal fluid, e.g., bile salts, lecithin, cholesterol and its esters (Amidon et al., 1995).

The purpose of this study was to investigate the effects of various types of surfactants on the dissolution rates of poorly soluble acidic drugs, namely, mefenamic acid ($pK_a = 4.2$), nimesulide ($pK_a = 6.5$), and ibuprofen ($pK_a = 4.4$) (The Merck Index, 1996; Singh et al., 1999), and to identify an appropriate dissolution medium for these drugs. The structures of these three drugs are shown in Fig. 1. In the present study, we used cetyltrimethylammonium bromide as a cationic surfactant, sodium lauryl sulfate as an anionic surfactant, and polysorbate

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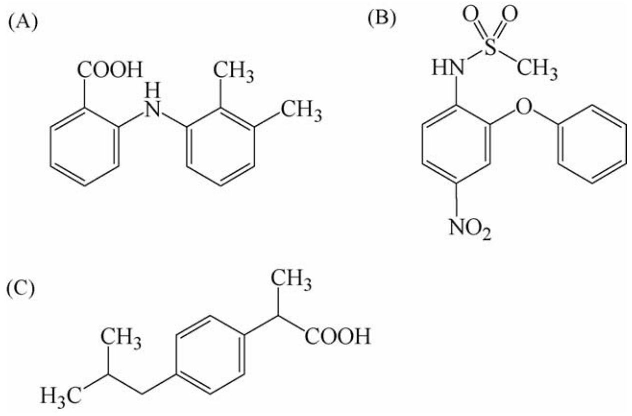

Fig. 1. Chemical structures of mefenamic acid (A), nimesulide (B), and ibuprofen (C).

80 as a non-ionic surfactant. The solubilities of drugs were measured in various media and partition coefficients of drugs between micelles and aqueous solution were calculated to study the effect of micellar solubilization.

## 2. Materials and methods

### 2.1. Materials

Mefenamic acid, nimesulide, sodium lauryl sulfate (SLS), and cetyltrimethylammonium bromide (CTAB) were purchased from Sigma–Aldrich (St. Louis, MO). Ibuprofen was obtained from Hana Pharm. Co. (Kyeonggido, Korea). Commercial tablets of mefenamic acid, nimesulide, and ibuprofen were purchased from local store. Polysorbate 80 was purchased from Junsei (Tokyo, Japan). All other chemicals were of reagent grade or above and were used without further purification.

### 2.2. Dissolution study

Drug release tests were carried out using a dissolution tester (DST 810, Labfine, Inc., Korea). The test material was placed in 900 ml of dissolution media at 37 °C using a USP dissolution apparatus II (paddle method) with the paddle rotating at 50 rpm. A pH 6.8 phosphate buffer solution (50 mM) and a pH 1.2 hydrochloric acid buffer solution were used as dissolution media. To evaluate the effects of surfactants on drug dissolution rates, 1% polysorbate 80, SLS, or CTAB was dissolved in medium, and an aliquot of medium was withdrawn at predetermined time intervals, and an equivalent amount of fresh medium was added. Withdrawn samples were centrifuged at 5000 rpm for 5 min or filtered using a 0.45 μm syringe filter. The samples were diluted with corresponding dissolution media before analysis. Drug concentrations were measured by HPLC (Shimadzu Scientific Instruments, MD) or UV spectrophotometry (UV-1601, Shimadzu, Japan).

### 2.3. Solubility measurements

An excess amount of a drug was placed into each dissolution medium in a 20 ml vial and stirred with a magnetic bar at 37 °C for 24 h. Saturated solutions were then centrifuged at 5000 rpm for 5 min or filtered using a 0.45 μm syringe filter. Drug concentrations were measured by HPLC (Shimadzu Scientific Instruments, MD) or UV spectrophotometry (UV-1601, Shimadzu, Japan).

### 2.4. UV spectroscopy

The UV spectra of mefenamic acid in pH 6.8 phosphate buffer solution with and without surfactant were obtained by UV spectrophotometer (UV-1601, Shimadzu, Japan).

### 2.5. Particle size

The particle size of the micellar solution was determined by dynamic light scattering (DLS; Zetasizer 3000, Malvern Instruments, UK) using an argon ion laser beam at a wavelength of 488 nm and a scattering angle of 90° at 25 °C. An excess amount of a drug was dissolved in dissolution medium and stirred for 24 h. Each sample was filtered through a 0.45 μm filter directly into a clean cylindrical cell.

### 2.6. Assay

Mefenamic acid and ibuprofen were analyzed by HPLC system (Shimadzu Scientific Instruments, MD) comprising a UV detector (SPD-10A), a pump (LC-10AD), and an automatic injector (SIL-10A). The wavelength of the UV detector was set at 254 nm and a reverse phase column (Luna C8, 5 μm, Phenomenex, CA) was used. The column temperature was maintained at 30 °C using a thin foil temperature controller (CH 1445, SYSTEC, MN). The mobile phase used for mefenamic acid was acetonitrile/tetrahydrofuran/50 mM ammonium phosphate buffer solution (pH 5.0) (61/14/25), and that for ibuprofen was acetonitrile/105 mM chloroacetic acid buffer solution (pH 3.0) (65/35). Concentrations of nimesulide were measured by UV spectrophotometer (UV-1601, Shimadzu, Japan) at 297 nm.

## 3. Results and discussion

In order to compare the effects of various kinds of surfactants on the dissolution profiles of acidic drugs with limited solubilities, dissolution studies were conducted using media containing 1% of a cationic, anionic, or non-ionic surfactants at pH 6.8. CTAB was used as the cationic surfactant, SLS as the anionic surfactant, and polysorbate 80 as the non-ionic surfactant. Fig. 2A shows the effects of the various surfactants on the dissolution profile of mefenamic acid. The dissolution of a mefenamic acid tablet in pH 6.8 phosphate buffer solution without added surfactant was less than 10% within 2 h, however, this increased up to 90% when 1% CTAB was added to the dissolution medium. The dissolution degrees of mefenamic acid in media containing 1% polysorbate 80 or 1% SLS were approximately 40% and 15% in 2 h, respectively. These results indicate that the extent of dissolution of mefenamic acid is significantly dependent on the surfactant used. The effects of various surfactants on the dissolution profile of nimesulide are shown in Fig. 2B. The

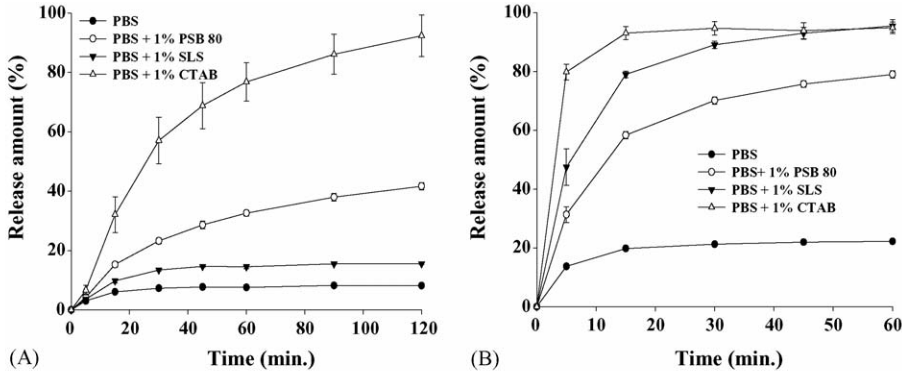

Fig. 2. Dissolution profiles of mefenamic acid tablets (A) and nimesulide tablets (B) in pH 6.8 phosphate buffer solution (PBS) with and without various surfactants. PSB80: polysorbate 80; SLS: sodium lauryl sulfate; CTAB: cetyltrimethylammonium bromide.

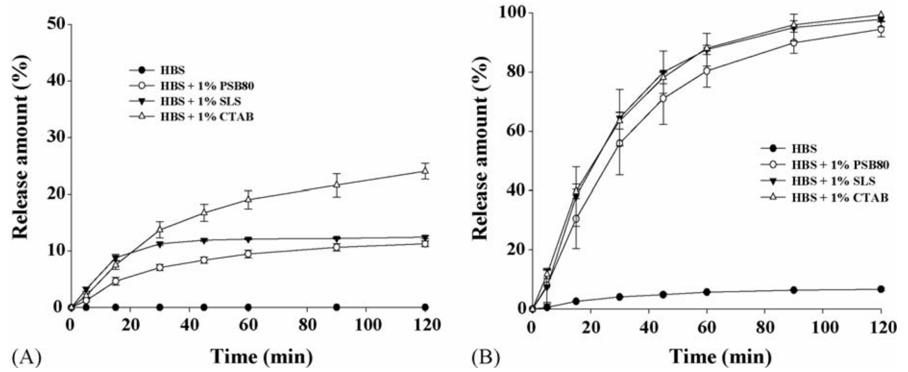

Fig. 3. Dissolution profiles of mefenamic acid tablets (A) and ibuprofen tablets (B) in pH 1.2 HCl buffer solution (HBS) with and without various surfactants. PSB80: polysorbate 80; SLS: sodium lauryl sulfate; CTAB: cetyltrimethylammonium bromide.

dissolution rate of nimesulide was significantly increased when any of the three surfactants was added to medium at pH 6.8, and was highest for CTAB followed by SLS and polysorbate 80 in order. Although SLS showed less than a two-fold increase in the dissolution rate of mefenamic acid, it increased the dissolution rate of nimesulide more so than polysorbate 80. As shown in Fig. 3, the effects of the various surfactants on the dissolution profiles of ibuprofen and mefenamic acid tablets at pH 1.2 was quite different from their effects on mefenamic acid and nimesulide at pH 6.8. The dissolution rate of ibuprofen was significantly enhanced by all three surfactants with minimal differences. The dissolution rate of mefenamic acid at pH 1.2 was much lower than at pH 6.8. Differences in the dissolution rate enhancing effect of three different surfactants were also reduced at pH 1.2. While the slowest dissolution rate was obtained in SLS solution at pH 6.8, SLS solution provided slightly higher dissolution rate than polysorbate 80 solution at pH 1.2.

In order to investigate correlations between drug dissolution rates and the surfactants used, the solubility of each drug was measured in each dissolution medium. The solubility of a drug in a medium is a major driving force when determining the dissolution rate of a drug, as is illustrated by the Noyes–Whitney equation.

$$R_\mathrm{d} = KA(C_\mathrm{s} - C) \tag{1}$$

where $R_\mathrm{d}$ is the dissolution rate, $K$ the dissolution rate constant, $A$ represents the available surface area of the undissolved drug, $C_\mathrm{s}$ the drug solubility, and $C$ is the drug concentration in the medium (Noyes and Whitney, 1897). The effects of the three

Table 1
Effects of surfactants on the solubilities (μg/ml) of mefenamic acid, nimesulide and ibuprofen

| Compound | Control | Polysorbate 80 | SLS | CTAB |
|---|---|---|---|---|
| Mefenamic acid[a] | 29.6 ± 5.48 | 236 ± 4.89 | 66.7 ± 1.90 | 4490 ± 231 |
| Nimesulide[a] | 22.8 ± 1.62 | 120 ± 6.78 | 166 ± 4.48 | 2530 ± 69.7 |
| Mefenamic acid[b] | 0.40 ± 0.14 | 33.3 ± 0.83 | 42.9 ± 3.04 | 199 ± 0.61 |
| Ibuprofen[b] | 11.0 ± 2.10 | 1415 ± 22 | 1690 ± 19.1 | 4371 ± 131 |

All surfactants were added at 1% (w/v), and no surfactant was used in the control group.
[a] Tests were conducted in pH 6.8 buffer.
[b] Tests were conducted in pH 1.2 buffer.

different classes of surfactants on the solubilities of the tested drugs are summarized in Table 1. The solubilities of all drugs tested were highest in 1% CTAB containing medium. It was speculated that an acidic drug might dissociate into an anionic form before it is solubilized in micelles formed by a cationic surfactant at pH 6.8. Then the acidic drug could easily interact with the cationic surfactant, which might facilitate its partition into micelles and increase its solubility as compared to that in media containing non-ionic or anionic surfactants. The dissolution profile of ibuprofen at pH 1.2 does not correlate well with solubility data. No significant difference in the dissolution rate of ibuprofen in spite of the large difference in solubility depending on the surfactant used may be attributable to the high solubility in all surfactant solutions. It should be noted that ibuprofen was completely dissolved in all three surfactant solutions in 2 h due to high solubility.

The UV–vis spectrophotometry was used to investigate the interaction between mefenamic acid and the surfactants (Fig. 4). As shown by Fig. 4, the absorption maximum of mefenamic acid shifted from 285.5 to 294.5 nm in the presence of CTAB, indicating that the microenvironmental polarity of mefenamic acid had been changed. This change seemed to be due to the penetration of mefenamic acid into CTAB micelles (Shah et al., 1998). A similar red shift was also observed in the presence of polysorbate 80, indicating that the drug was solubilized in the micelles of polysorbate 80. No significant shift was observed in the UV spectrum of mefenamic acid in the presence of SLS.

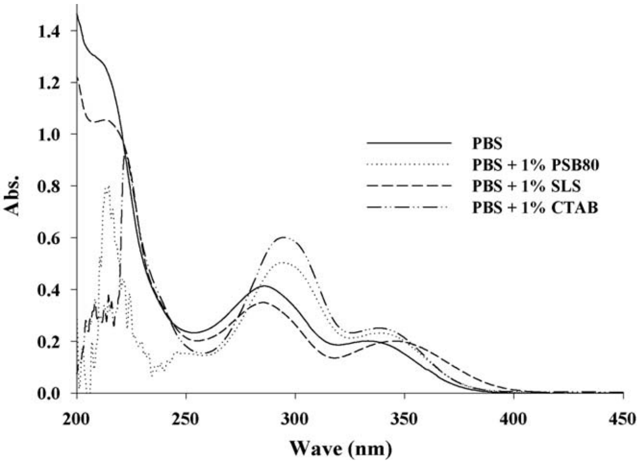

Fig. 4. UV–vis spectra of mefenamic acid in pH 6.8 phosphate buffer solution (PBS) with and without various surfactants. PSB80: polysorbate 80; SLS: sodium lauryl sulfate; CTAB: cetyltrimethylammonium bromide.

The interaction of mefenamic acid and ibuprofen with CTAB was further investigated by measuring size of the micelle. Although the size of CTAB micelle was not measurable (less than 3 nm), it increased significantly when mefenamic acid or ibuprofen was added into the solution. When mefenamic acid was added into CTAB solution at pH 6.8, the mean micellar size was 147.0 nm with the poly index of 0.404 (Fig. 5A). The zeta potential of the micelle was −2.1 mV (Fig. 5B), indicating that the cationic polar head group in the outer layer of CTAB micelle was neutralized by the anionic carboxyl group of mefenamic acid. In case of ibuprofen, no large micelle was observed and some oily drops were observed on the surface, suggesting the separation of micelle rich phase from the bulk solution. A similar phenomenon was observed when propranolol was solubilized by *n*-decylmethyl sulfoxide (Choi et al., 1991). At pH 1.2, CTAB formed a large micelle (135.1 nm) in the presence

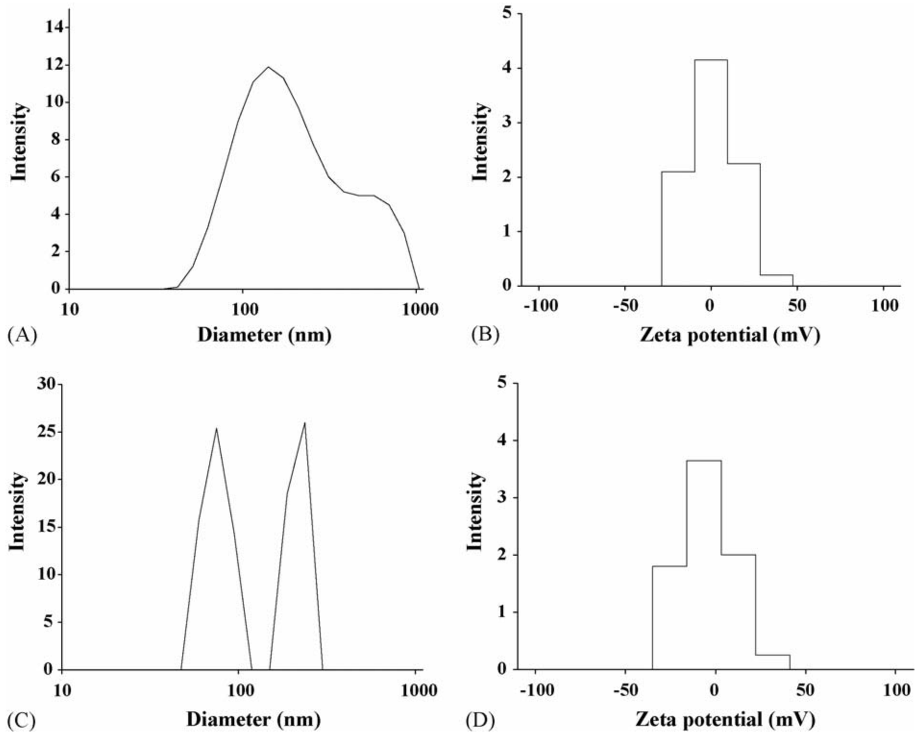

Fig. 5. Particle size distribution and zeta potential of mefenamic acid/CTAB micelle (A and B) at pH 6.8 and ibuprofen/CTAB micelle at pH 1.2 (C and D).

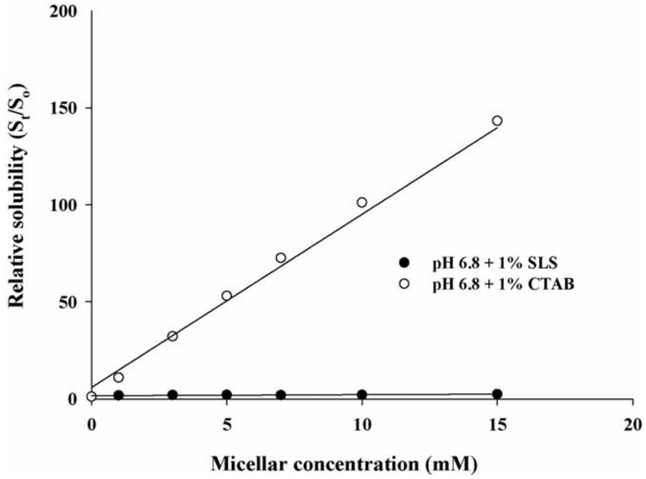

Fig. 6. Relative solubilities of mefenamic acid in media vs. cetyltrimethylammonium bromide (CTAB) micelle (open circle) and sodium lauryl sulfate (SLS) micelle (closed circle).

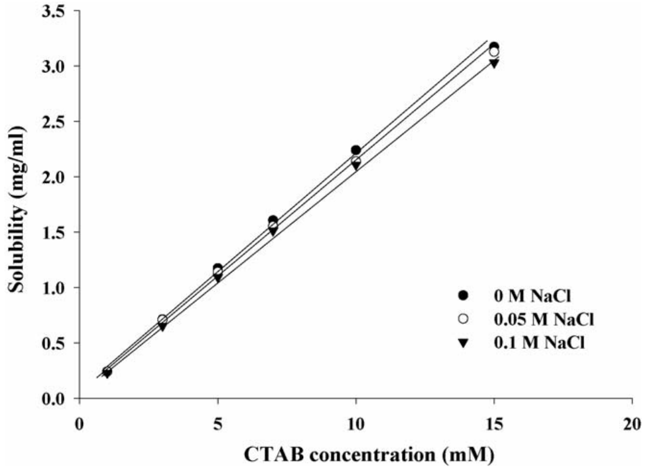

Fig. 7. Mefenamic acid solubility at different cetyltrimethylammonium bromide (CTAB) and NaCl concentrations at 37 °C.

of ibuprofen with the poly index of 0.356 (Fig. 5C) and zeta potential of −2.7 mV (Fig. 5D), however, no large micelle was formed in case of mefenamic acid.

To determine the amount of a drug partitioning into micelles, drug solubilities in surfactant containing solutions were measured at various CTAB or SLS concentrations. The data obtained were analyzed using a pseudo phase model (Alkhamis et al., 2003). Partition coefficients ($P_m$) between media and micellar pseudo phases were calculated using the following equation:

$$S_t/S_0 = 1 + P_m v[\mathrm{M}] \tag{2}$$

where $S_t$ is the total solubility, $S_0$ the intrinsic medium solubility, $P_m$ represents the micelle–medium partition coefficient, $v$ represents the partial molal volume of the micelles, and [M] is the micellar concentration (Krishna and Flanagan, 1988). Of the drugs tested, mefenamic acid was selected as a model drug. The relative solubility ($S_t/S_0$), which may be defined as the relative increase in solubility after adding a surfactant, is plotted as a function of the surfactant concentration in Fig. 6. The partition coefficient ($P_m$) was calculated by dividing the slope of the curve by the partial molal volume of micelles. The partial molal volumes of SLS and CTAB are known to be 365.4 and 246.4 ml/mol, respectively (Corkill et al., 1967). The partition coefficient of mefenamic acid between CTAB micelles and medium was calculated as $2.54 \times 10^4$ and that between SLS and medium as $2.31 \times 10^2$. Based these partition coefficients, it can be concluded that mefenamic acid dissolves over 100 times more efficiently into CTAB micelles than SLS micelles.

To investigate the locus of mefenamic acid in surfactant micelles, we studied the effect of sodium chloride on the solubility of mefenamic acid in surfactant solutions. Micelles were composed of non-polar tail group in their centers with polar head group at the periphery. The polar groups of surfactant in the periphery would be packed together more so by adding neutral electrolyte to medium, as this would reduce the repulsion between similarly charged polar head groups. Thus, if a drug is localized in micellar periphery, its solubility would be reduced by adding neutral electrolyte, and if not the drug would be located in the micellar core (Alkhamis et al., 2003). The effects of NaCl additions on the solubility of mefenamic acid in surfactant containing solution are shown in Figs. 7 and 8. A slight difference in the solubility of mefenamic acid was observed in pH 6.8 buffer solution containing CTAB as the concentration of NaCl was changed. However, increasing the concentration of NaCl significantly reduced the solubility of mefenamic acid in pH 6.8 buffer solution containing SLS. These results suggest that mefenamic acid partitioned mainly to the core region of CTAB micelles and to the periphery of SLS micelles.

The effects of surfactants on acidic drug have also been studied by other researchers. The effects of various surfactants on the micellar solubilization of gliclazide, a poorly water-soluble acidic drug, were investigated by Alkhamis et al. (2003). In this study, the aqueous solubility of gliclazide was found to be 0.8372 mg/ml in 1% CTAB solution, 0.7381 mg/ml in 1% SLS solution, 0.1294 mg/ml in 1% polysorbate 80 solution. In another study, the addition of surfactants reduced the rate of decarboxylation of *p*-aminosalicylic acid in acidic solution

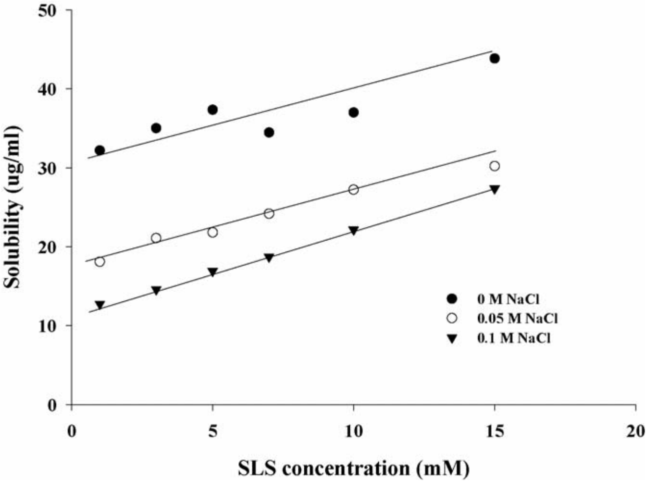

Fig. 8. Mefenamic acid solubility at different sodium lauryl sulfate (SLS) and NaCl concentrations at 37 °C.

(pH 4.88) (Plamondon and Nairn, 1997). *p*-Aminosalicylic acid would have a little opportunity to be exposed to the acidic environment once solubilized by micelles. The greatest reduction in this rate of decarboxylation was obtained in the solution containing CTAB, and this was followed by SLS and polysorbate 80 in order.

The extent of incorporation of an acidic drug into micelles appears to be dependent on the $pK_a$ of the drug and ionic nature of the surfactant. All the acidic drugs mentioned above showed highest solubility and/or fastest dissolution rate in CTAB solution due to ionic interactions. However, the surfactant that provided the lowest solubility and/or the slowest dissolution rate appeared to be dependent on drug $pK_a$. Drugs with lower $pK_a$ values, such as mefenamic acid ($pK_a = 4.2$), ibuprofen ($pK_a = 4.4$), and *p*-aminosalicylic acid ($pK_a = 3.25$) had lowest solubilities and/or poorest dissolution rates in a solution of 1% SLS. On the other hand, acidic drugs with higher $pK_a$ values, such as nimesulide ($pK_a = 6.5$) and gliclazide ($pK_a = 5.8$), had lowest solubilities and/or poorest dissolution rates in 1% polysorbate 80. Drugs with lower $pK_a$ values were mostly ionized in test solutions of pH 6.8 and thus their partitioning into anionic surfactant micelles was hindered by repulsion between the anionic charges of the drug and surfactant. On the other hand, drugs with higher $pK_a$ values do not as completely ionized as the drugs with lower $pK_a$ values and thus a proportion of these drugs remain undissociated. Moreover, ionic surfactants usually have higher surface activities and better solubilizing abilities than non-ionics (Attwood and Florence, 1983; Krishna and Flanagan, 1988; Shah et al., 1989). Thus, undissociated drugs may prefer anionic surfactant micelles, which would result in higher solubilities in solutions containing anionic surfactants. As can be seen in Table 1, ibuprofen and mefenamic acid showed higher solubility in SLS solution than in polysorbate 80 solution since both drugs are largely undissociated at pH 1.2. The effect of the degree of drug dissociation on its dissolution rate can also be observed for the dissolution of mefenamic acid at pH 1.2. When the pH of dissolution medium was lowered to 1.2, most of the mefenamic acid is undissociated, which eliminates charge repulsions and increases its solubility and dissolution rate in 1% SLS as compared with 1% polysorbate 80.

In order to determine if an increased dissolution rate can improve the power of a dissolution medium to discriminate between dissolution profiles of drug products, dissolution tests were conducted using four different products of mefenamic acid tablet in pH 6.8 buffer solution containing 1% surfactant. When 1% of SLS was used, no significant differences were observed between the dissolution profiles of the four products (Fig. 9A). However, when a buffer solution containing 1% polysorbate 80 was used as a dissolution medium, products A and C were discriminated from products B and D, as shown in Fig. 9B. Moreover, a buffer solution containing 1% CTAB was able to distinguish between products B and D, as shown in Fig. 9C. It is too early to conclude that CTAB should be used in dissolution media to maximize discriminating power without knowledge of the in vivo/in vitro relationships, however, it is believed that the CTAB may improve our ability to discriminate between acidic drug products in terms of dissolution rates.

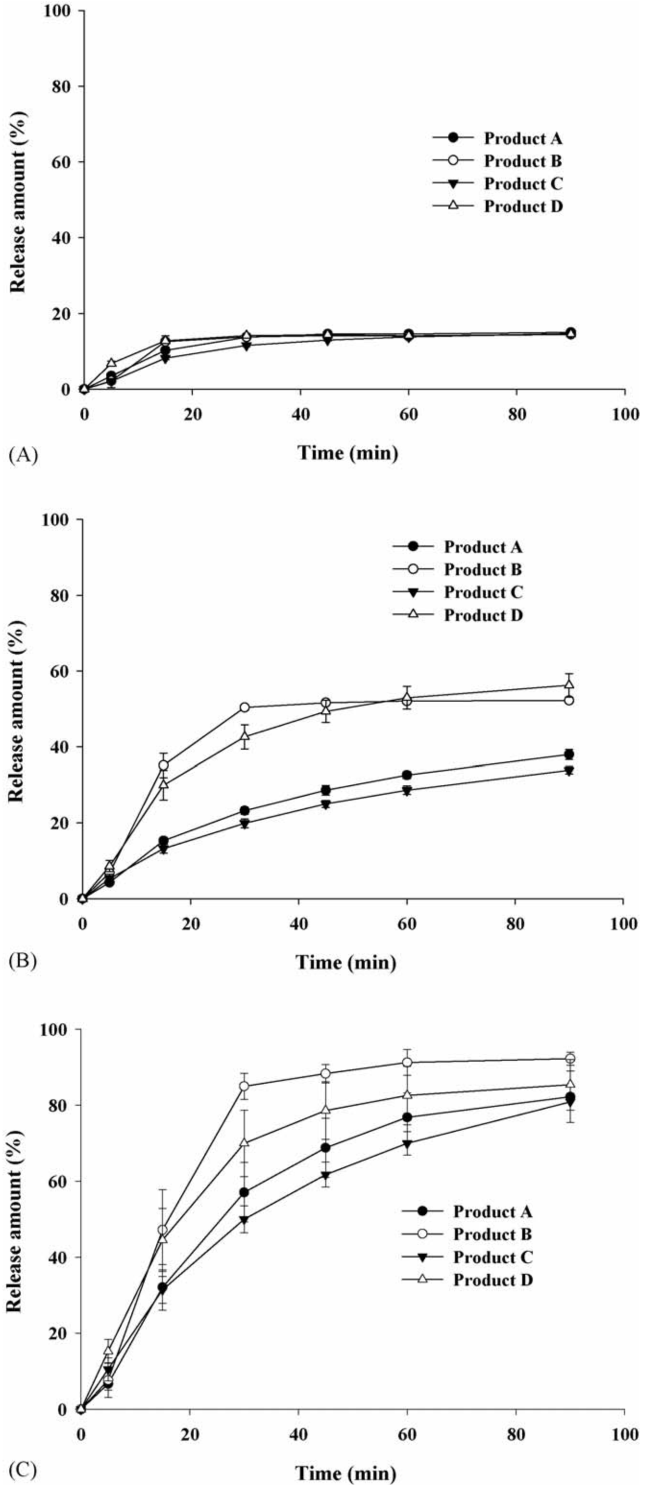

Fig. 9. Dissolution profiles of four different mefenamic acid tablets in pH 6.8 buffer containing 1% sodium lauryl sulfate (SLS) (A), polysorbate 80 (B) and cetyltrimethylammonium bromide (CTAB) (C).

Our results show that the dissolution profiles of poorly soluble acidic drugs are influenced by the class of surfactant added to the dissolution medium. The cationic surfactant, CTAB, most efficiently enhanced the dissolution rate of acidic drugs among the surfactants tested. Since the solubilities of acidic drugs in media containing cationic surfactant were several times higher than in media containing other surfactant types, it will be easier to maintain the sink condition. In particular, in the case of mefenamic acid, 1% CTAB showed greatest discriminatory power. We hope that these results will provide pharmaceutical researchers involved with the development of new dissolution media and those involved in the quality control of water insoluble acidic drug products food for thought concerning the selection of suitable surfactants.

## Acknowledgement

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