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Research paper

Effect of surfactant on dissolution of spherical particles in micellar systems

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Abstract

The influence of micelle-drug solubilization on the dissolution rate of monodisperse particles of benzocaine has been investigated. A model describing and predicting the initial dissolution rates of spherical particles was derived starting from the boundary layer theory. The dissolution rate of benzocaine spherical particles was determined in water and in solutions of sodium lauryl sulfate (SLS) under static conditions. The derived model was applied to the experimental data. The diffusion coefficients and the aqueous diffusion layer values were estimated from the experimental results and the aforementioned model. The diffusion coefficients and the boundary layer thickness values were also obtained experimentally from the rotating disk method and were used to predict the initial dissolution rates. Excellent correlations were obtained between the experimental and the calculated values at low micellar concentrations. However, obvious deviation was observed at high micellar concentrations. The results obtained from this study suggest that it is possible to predict the initial dissolution rates of monodisperse particles in micellar systems.

Keywords: Benzocaine; Micellar solubilization; Surfactants; Initial dissolution rates; Monodisperse; Particles

1. Introduction

Dissolution testing is an important tool in oral dosage form development. Under certain circumstances the dissolution data can be used instead of the in vivo data for abbreviated new drug applications. Dissolution testing is also widely used as a quality control method in pharmaceutical industry. Most rapid release oral dosage forms disintegrate into small spherical particles which must then dissolve for the drug to be absorbed [1]. The mathematics of diffusion from spheres is important in a range of pharmaceutical preparations. Various formulations contain spherical particles, and the rates at which these formulations release their active ingredients may depend on the release rates from the individual spheres [2].

The dissolution process consists of two steps. First, the interaction between the solute and the solvent molecules at the solid–liquid interface. Second, the diffusion of the solute molecules away from the interface to the bulk. The slowest step in this sequential process is the rate-determining step. If the second step is slower than the first step, then the dissolution rate is said to be diffusion-controlled. Most dissolution processes are diffusion-controlled [3].

The basic diffusion-controlled model for solid dissolution was developed in 1897 by Noyes and Whitney [1]. These investigators suggested that the dissolution rate is controlled by the rate of diffusion of a very thin layer of saturated solution that forms instantaneously around the solid particle. Factors that determine the dissolution rate constant of a specific solid were determined, three years later, by Brunner and Tolloczko. Noyes and Whitney's model was also later modified by Nernst and Brunner. The

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modification enabled these investigators to measure the thickness of the saturated film which was previously proposed by Noyes and Whitney [1].

Three diffusion-controlled models based on the film theory were reported for single spherical particle dissolution under sink conditions. The first model was derived by Hixson and Crowell and is known as the "cube-root law" with one-thirds root dependency on weight [4,5]. The cubic root law expressed the dissolution rate as a function of both concentration and surface area. The second model was derived by Niebergall et al. [6] and has a square-root dependency on weight, and finally Higuchi and Hiestand derived a model with a two-thirds root dependency on weight [7,8]. The choice of one of the aforementioned models to fit the experimental data was arbitrary. A general solution to the diffusion layer model for monodisperse spherical particles for sink and nonsink conditions was derived in 1998 by Wang and Flanagan [3]. Constant diffusion layer thickness was assumed in their derivation. The general equation derived by these investigators explained the limitations in the traditional particle dissolution expressions. The same investigators evaluated their general solution model experimentally by preparing spherical benzocaine particles, studying their dissolution behavior and applying their diffusion model to the experimental data. The experimental results of those investigators supported the applicability of their model [9]. Alternative derivation of Wang and Flanagan's model is shown in Appendix A. A new model for the dissolution of spherical particles was also derived in this work. The new equation takes into account the convection contribution to the flux. This is shown in Appendix B.

Drug dissolution characteristics can be enhanced using different methods. The selection of the enhancement method depends on the drug itself as well as the medium in which the drug will be dissolved [10]. Examples of the enhancement methods are alteration of the pH of the surrounding medium, solute–solvent complexation, the use of metastable polymorphs and micellar solubilization. Surfactants are widely used (in micellar solubilization) to improve the solubility of poorly soluble drugs. Solubilization by surfactant systems was discussed thoroughly by previous investigators [11,12].

The purpose of this investigation is to study the effect of surfactant addition on the dissolution rate of monodisperse particles of benzocaine and to predict the dissolution rate of these particles using a mathematical model.

2. Materials and Methods

Benzocaine was used as a model drug (99% pure, Acros organic company, New Jersey, USA). Sodium chloride was used in the preparation of benzocaine spherical particles (reagent grade, Scharalau Chemica, Barcelona, Spain). The surfactant used was sodium lauryl sulfate (purity >99%, Scharlau Chemica, Barcelona, Spain). Acetonitrile and methanol were used in mobile phase preparation (HPLC grade, Lab-Scan Analytical Sciences, Dublin, Ireland). Water (HPLC grade, Lab-Scan Analytical Sciences Dublin, Ireland) was used in solubility and dissolution experiments.

2.1. Preparation of benzocaine spherical particles

Benzocaine spherical particles were prepared by the hot melt dispersion according to the procedure of Wang and Flanagan [9]. Twenty-five milliliters of stirred water was heated to 90 °C. The heating temperature was higher than the melting point of benzocaine (89 °C). Benzocaine (1.5 g) was then added to the stirred hot water in a beaker. The resulted suspension was continuously heated until a melt-dispersion was formed. The dispersion was quickly diluted in a cylinder containing 1 L of water (~20 °C) layered on top of 3 L of 10% NaCl solution (~2 °C). The droplets solidified quickly to form particles. After 10 min, the top solution was carefully removed and the particles were filtered from the remaining solution, washed three times with a total of 30 ml distilled water, and dried at room temperature. The spherical particles were separated into different size fractions with standard sieves, and the size of each particle being used was determined microscopically.

2.2. Stability test

Benzocaine may degrade at the high temperatures during melting. The main degradation product that may form is ρ-aminobenzoic acid. Therefore, it was necessary to determine the stability of benzocaine at the highest temperature employed in this study. Benzocaine purity in the prepared particles was determined by the HPLC method of Narang et al. [13]. The HPLC system consisted of C18 column, a mobile phase of methanol–acetic acid–water with the ratios (40:4:56 v/v/v) at a flow rate of 1 ml/min with detection at 294 nm. Benzocaine particles (~3 mg) were weighed and dissolved in (100 ml) mobile phase, 20 μL of the solution was then injected into the HPLC system. The HPLC (10A VP) system consisted of a pump, a UV–VIS detector that is connected to a personal computer and a system controller (all Shimadzu Co., Japan). A typical chromatogram is shown in Fig. 1. Fig. 1 shows that the retention time of benzocaine is 12.95 min, and that there is no peak at the retention time of ρ-aminobenzoic acid which equals 3.7 min. Fig. 1 also shows that there are no interfer-

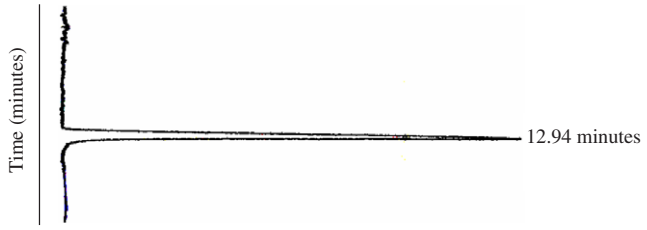

Fig. 1. Chromatogram of the dissolved benzocaine particles.

ing peaks, which indicates that the prepared spherical particles are pure.

2.3. Solubilization test

Excess amount of benzocaine 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. The samples were rotated (30 rpm) for a period of time in excess of that required for equilibrium (24 h). After equilibration, the samples were removed and filtered through 0.45 μm Teflon membranes which were installed in stainless steel filter holders. Then benzocaine concentrations were determined by using a photodiode array spectrophotometer (Multispec-1501, Shimadzu, Japan) and when required the proper dilutions were made. Each experiment was done in triplicate and the average was used.

2.4. Dissolution tests

Two types of dissolution experiments were conducted. The first was the dissolution of benzocaine spherical particles under static conditions, while the second was the intrinsic dissolution of benzocaine tablets.

2.5. Spherical particle dissolution

Particle size was determined microscopically before each run using a microscope. In each run, the spherical particle was placed inside a small cylindrical bottle of 2 cm diameter and 5 cm height. The spherical particle was surrounded from all sides with a stainless steel mesh (0.2 mm pore size) to prevent its movement. The dissolution bottle (containing 5 ml of the dissolution medium) was connected to a photodiode array spectrophotometer that contains a sipper unit. At zero time, the spherical particle was placed inside the dissolution bottle and five milliliters of the dissolution medium was then injected into the bottle. A sample of the dissolution medium was withdrawn every minute and replaced directly by the sipper unit.

Particle shape might deviate from being spherical due to its dissolution. Therefore, in order to compensate for the nonisotropic dissolution, the initial dissolution rates were obtained and the run time for each particle was less than 30 min. Each experiment was done in triplicate and the average was used.

2.6. Intrinsic dissolution by the rotating disk method

Benzocaine powder was compressed in a rotating disk die at 10,000 N for 3 min. The rotating disk was constructed of stainless steel, with a tablet diameter of 8 mm and an overall disk diameter of 53 mm. The dissolution experiments were performed at room temperature (25 °C) in dissolution vessels that were heated by a water bath to control the temperature. Sink conditions were maintained throughout the entire experiments (<5% of the solubility). Each dissolution vessel was filled with 500 ml of the dissolution medium. A sample of 1 ml of the dissolution medium was withdrawn and replaced by the same amount of the fresh solution at specified time intervals. The rotating disk dissolution experiments were run at 50, 100, 150, and 200 rpm. The surfactant solutions were prepared the day of the experiment and the benzocaine concentrations in the withdrawn samples were measured using the photodiode array spectrophotometer.

2.7. Viscosity measurements

The viscosities of the dissolution media were determined by an Ostwald viscometer. The time required for the dissolution medium to pass a specified distance was measured and was used to calculate the viscosity based on a specified correlation.

3. Results and discussion

3.1. Micellar solubilization

The CMC of SLS (at 25 °C) was previously determined in our laboratory and was found to be 7.98 ± 0.49 mM [14]. The relative solubilities (S_t/S_o) of benzocaine in solutions of different micellar concentrations above the CMCs of SLS at 25 °C are shown in Fig. 2. Fig. 2 clearly shows that as the micellar concentration increases the relative solubility of benzocaine also increases. This is due to the increase in micelles formation that leads to an increase in the solubility of benzocaine.

The binding constant, K^*, was determined by applying the following equation to the experimental data [15]:

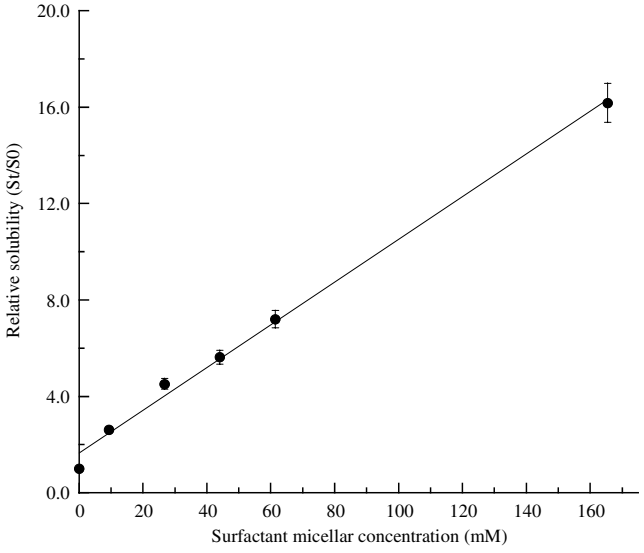

Fig. 2. Relative solubility of benzocaine versus sodium lauryl sulfate (SLS) micellar concentration.

$$\frac{S_t}{S_o} = 1 + K^* c_{m(b)} \quad (1)$$

where S_t and S_o are the total and the intrinsic solubilities, respectively, and $c_{m(b)}$ is the micellar concentration of the surfactant (SLS). The slope of the linear curve (K^*) is 0.0887 mM^{-1}. The slope of the curve represents the partition coefficient multiplied by the molal volume of the surfactant. The partition coefficient of benzocaine in SLS–water system and the molal volume of SLS were determined by previous investigators [16,17] and were found to be 486 and 248.5 ml/mol, respectively. Based on that information, the binding constant obtained by previous investigators was found to be 0.120 mM^{-1}.

3.2. Intrinsic dissolution by the rotating disk method

Knowledge of the intrinsic dissolution rate is of vital importance in screening new drug candidates as it can help immensely in optimizing new physiological effectiveness of new dosage forms. In intrinsic dissolution studies the diffusion coefficient of each species in surfactant solutions could be determined by specifying the change in dissolution rate for different concentrations of the used surfactant and in different rotational speeds. A plot of the intrinsic dissolution rate of benzocaine in water as function of the square root of the rotational speed of the disk is shown in Fig. 3. On the basis of the linear relationship and zero intercept, the dissolution is assumed to be diffusion controlled according to Levich model for the well-defined hydrodynamics of the rotating dissolution [18].

$$J = 0.62 D_i^{2/3} \upsilon^{-1/6} \omega^{1/2} C_{s(0)} \quad (2)$$

where J is the flux, υ is the kinematic viscosity of water (0.00891 cm^2/s), ω is the rotational speed of the disk, and $C_{s(0)}$ is the saturation solubility of benzocaine in water (0.84 mg/ml) and D_i is the diffusion coefficient. The diffusion coefficient of free benzocaine in water was calculated from Eq. (2) and was found to be 9.06×10^{-6} cm^2/s. The agreement with the literature value for the diffusion coefficient of benzocaine in water at 30 °C (9.9×10^{-6} cm^2/s) is satisfactory [19].

The diffusion coefficient of benzocaine–SLS micelle complex was calculated according to the following equation [20,21]:

$$\phi_{FM} = 1 + \frac{D_{sm}^{2/3}}{D_s^{2/3}} K^* C_{m(b)} \quad (3)$$

where ϕ_{FM} is defined as the total flux of the micelle-solubilized solute plus the free solute divided by the flux of the free solute, D_{sm} is the diffusion coefficient of benzocaine–SLS micelle complex, D_s is the diffusion coefficient of benzocaine in water (obtained from Eq. (2)), and K^* is the binding constant (obtained from Eq. (1)).

The reaction factor, ϕ_{FM}, (at 150 rpm) is plotted against the surfactant concentrations (SLS) in Fig. 4. Regression analysis of the data in Fig. 4 yielded an intercept which is close to the theoretical intercept of one predicted by Eq. (3). However, small deviations could be due to the model assumption of constant micelle size for all concentrations of surfactant. The diffusion coefficient of benzocaine–SLS micelle complex was calculated from the slope of the line in Fig. 4 and was found to be 3.6×10^{-6} cm^2/s. The diffusion coefficient of benzocaine–SLS micelle complex is smaller than the diffusion coefficient of benzocaine–water system (9.06×10^{-6} cm^2/s). This result was expected, since the size of the micelle is larger than the size of the free drug. The agreement with the literature value for the diffusion coefficient of carbamazepine–SLS micelle complex ($\sim 1 \times 10^{-6}$ cm^2/s) is satisfactory [20,21].

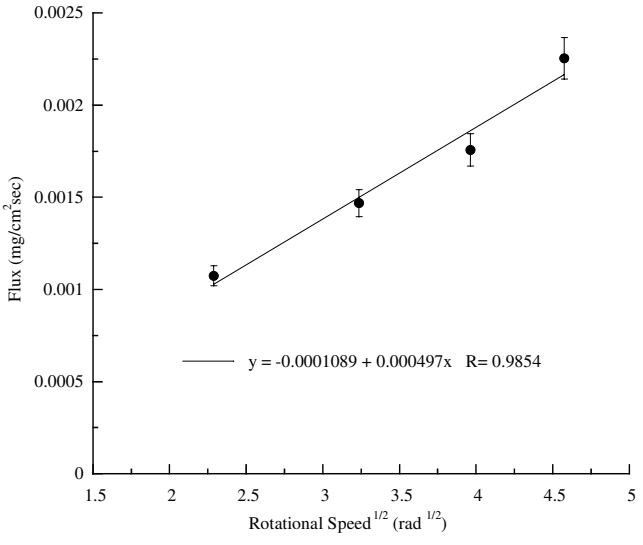

Fig. 3. Flux of benzocaine in water and as function of the square root of the disk rotational speeds.

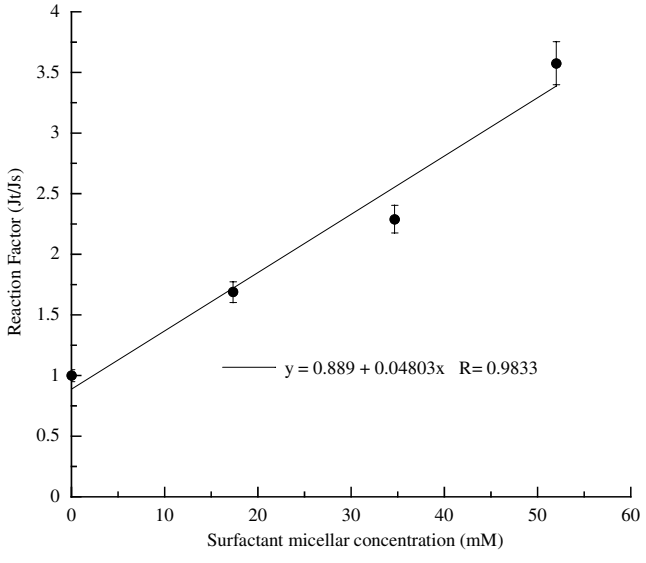

Fig. 4. Reaction factor (Φ_{FM}) as function of sodium lauryl sulfate (SLS) micellar concentration.

3.3. Dissolution of benzocaine spherical particles

The dissolution of monodisperse spherical particles of benzocaine in water was previously studied by Wang and Flanagan [9], where they have derived a general solution to the diffusion layer model for sink and nonsink conditions, starting from Fick's first law in spherical coordinate system. The following two equations were both applied to Wang and Flangan's experimental data (see Appendices A and B for derivation). For diffusions only:

$$\mathrm{DR} = \frac{4\pi D C_{\mathrm{As}} a(a+h)}{h} \tag{4}$$

or for diffusion and convection

$$\mathrm{DR} = \frac{-4\pi C D a(a+h)\ln(1-x_{\mathrm{As}})}{h} \tag{5}$$

where DR is the dissolution rate in units of mass/time, D is the diffusion coefficient, h is the diffusion film thickness, C_{As} is the saturation solubility, a is the particle radius (in case of initial dissolution) and C is the bulk solution density. The parameters obtained from those two models were identical. This result indicated that the contribution of the convection term could be neglected compared with the contribution of the diffusion term.

The dissolution of benzocaine spherical particles in water was again studied (in our laboratory). The concentration versus time profiles of benzocaine spherical particles in water are shown in Fig. 5. Fig. 5 shows that the concentration versus time profiles are linear during the experiment period. This indicates that no change in the particle shape or the form occurred during the measurement period. Initial dissolution rates of benzocaine particles in water are plotted against the particle radii in Fig. 6. It is shown from Fig. 6 that the initial dissolution rate increases by increasing the particle radius. This is expected, since the initial dissolution rates (mg/min) were used instead of the fluxes (mg/cm^2 s). The initial dissolution rates were used instead of the fluxes in order to avoid having the same variable (radius) twice.

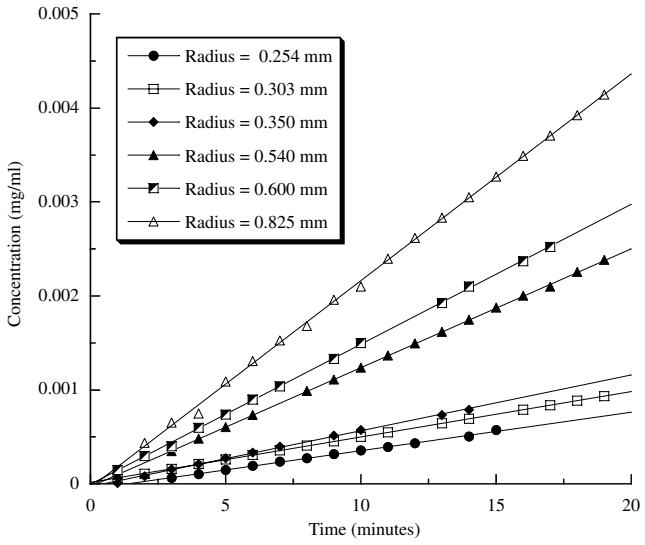

Fig. 5. Concentration versus time profiles for different particle radii in water.

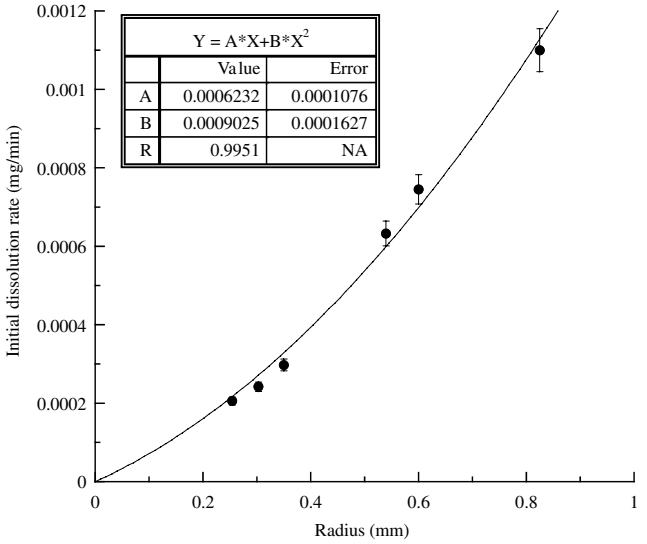

Fig. 6. Initial dissolution rates of benzocaine particles in water versus particle radii.

Eq. (4) was again applied to our experimental data. The fitted results gave a benzocaine diffusion coefficient of 9.84×10^{-6} cm^2/s and a boundary layer thickness of 690 μm. The diffusion coefficient value agrees with the result obtained from the rotating disk method (9.0×10^{-6} cm^2/s) and with the result obtained by Wang and Flanagan (1.4×10^{-5} cm^2/s). However, the boundary layer thickness value is higher than the value obtained by those investigators (110 μm). This might be due to a difference in the experimental setup and the ability to conduct the experiment under static conditions.

The dissolution of benzocaine spherical particles was also studied in different micellar concentrations of SLS. The concentration versus time profiles of benzocaine spherical particles in 0.5%, 1%, 1.5% and 5% (w/v) of SLS are shown in Figs. 7–10, respectively. Initial dissolution rates in units of (mg/min) were also calculated by multiplying the slopes of the concentration profiles equations by the micellar dissolution volume (5 ml). Fig. 11 shows the experimental initial dissolution rates versus particle radii in different SLS micellar concentrations. It is shown that as the micellar concentration increases the initial dissolution rate of benzocaine also increases. This is due to the increase in the solubility of benzocaine which leads to an increase in the initial dissolution rate.

In order to simplify the analysis of the micellar dissolution system, an assumption of a binary system was applied. This assumption will be valid only at concentrations higher than the CMC and for compounds showing a high micelle–water partition coefficient. Therefore the system was considered as a dilute solution of free benzocaine and that all benzocaine molecules are within micelles (i.e. the free

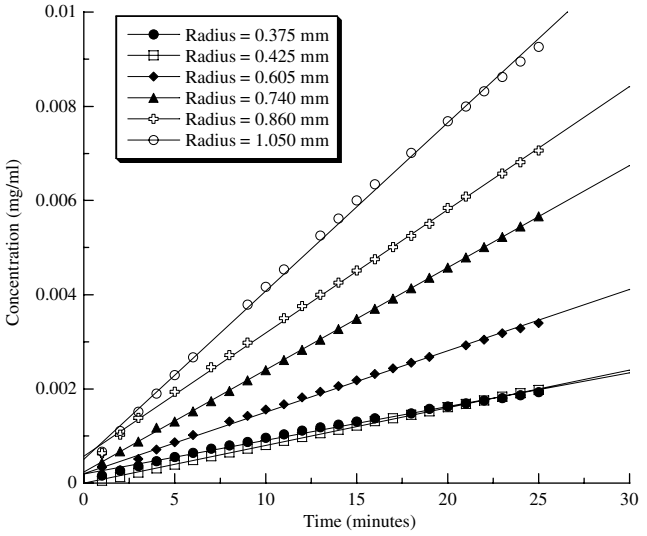

Fig. 7. Concentration versus time profiles for different particle radii in 0.5% (w/v) sodium lauryl sulfate (SLS).

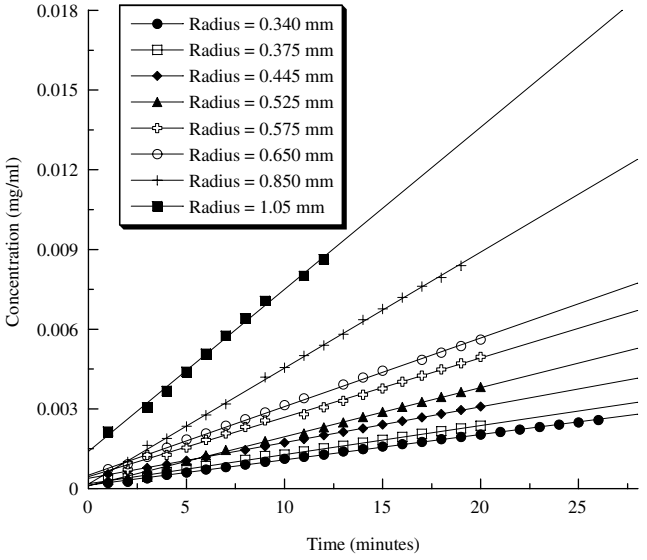

Fig. 8. Concentration versus time profiles for different particle radii in 1.0% (w/v) sodium lauryl sulfate (SLS).

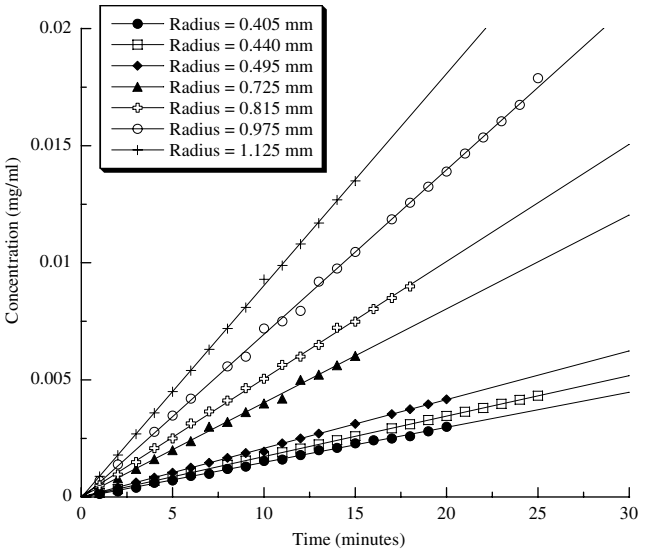

Fig. 9. Concentration versus time profiles for different particle radii in 1.5% (w/v) sodium lauryl sulfate (SLS).

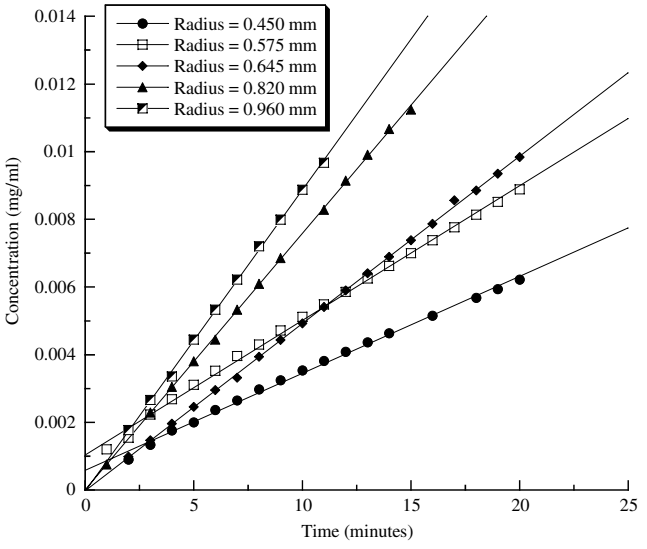

Fig. 10. Concentration versus time profiles for different particle radii in 5.0% (w/v) sodium lauryl sulfate (SLS).

drug molecules in the system are neglected and the system consists of benzocaine–micelle complex as a solute and water as a solvent). Based on the aforementioned assumption, the spherical particle dissolution model, derived from the boundary layer theory in Eq. (4), was applied to the dissolution of benzocaine particles in micellar solutions of SLS. But in order to validate the model and the previous assumption, it was necessary to estimate the diffusion coefficient and the boundary layer thickness values of benzocaine–micelle complex (drug loaded micelle) using an independent method. Benzocaine–micelle complex diffusion coefficient was calculated using the rotating disk method and was found to be 3.6×10^{-6} cm^2/s. The boundary layer thickness at the surface of the particle is a function of the viscosity of the dissolution media, the fluid velocity as well as the diffusion coefficient and temperature. During particle dissolution tests, temperature was maintained as an experimental constant, and the particle dissolution bottle provided suitable conditions for the particle dissolution model assumptions of no fluid flow and velocity distribution. Also it was found by Wang and Flanagan that the boundary layer thickness is constant, and not a function of the particle size [3]. Based on the previous assumptions, it was found that the ratio between the boundary layer thickness value in water and in micellar systems is a function of the difference between the diffusion coefficients of benzocaine in water and in SLS micellar solutions, in addition to the difference between the kinematic viscosities

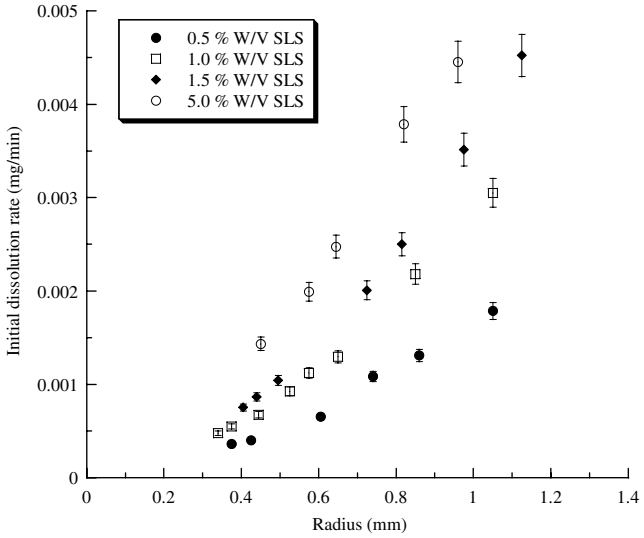

Fig. 11. Experimental initial dissolution rates versus particle radii in different SLS micellar concentrations.

of water and the micellar solutions. Hence, the following equation was assumed

$$\frac{h_s}{h_{sm}} = \frac{D_s^{1/3}}{D_{sm}^{1/3}} \frac{\upsilon_s^{1/6}}{\upsilon_{sm}^{1/6}} \tag{6}$$

where h_s and h_{sm} are the boundary layer thickness values in water and in micellar solutions, respectively. D_s and D_{sm} are the diffusion coefficients of benzocaine in water and in micellar systems, respectively, and υ_s and υ_{sm} are the kinematic viscosities of water and micellar solutions, respectively.

Based on the kinematic viscosity values of the micellar solutions, the boundary layer thickness of benzocaine–micelle complex in 0.5%, 1%, 1.5% (w/v) SLS was found to be 507 μm, while it is equal to 437 μm for 5 (w/v)% SLS.

Substituting the values of the diffusion coefficient and the boundary layer thickness of benzocaine–SLS micelle complex in Eq. (4), the theoretical initial dissolution rates were calculated. The smooth curves in Figs. 12–15 are the calculated initial dissolution rates of benzocaine particles in 0.5%, 1%, 1.5%, and 5% (w/v) SLS, respectively. It is shown from Figs. 12–14 that there is an excellent agreement between the theoretical and the experimental values which indicates that assumption of a binary system is valid. However, Fig. 15 shows an obvious deviation. This deviation is not due to the assumption of a binary system, since at 5% (w/v) SLS concentration, benzocaine will be more loaded within the micelles. The deviation between the cal-

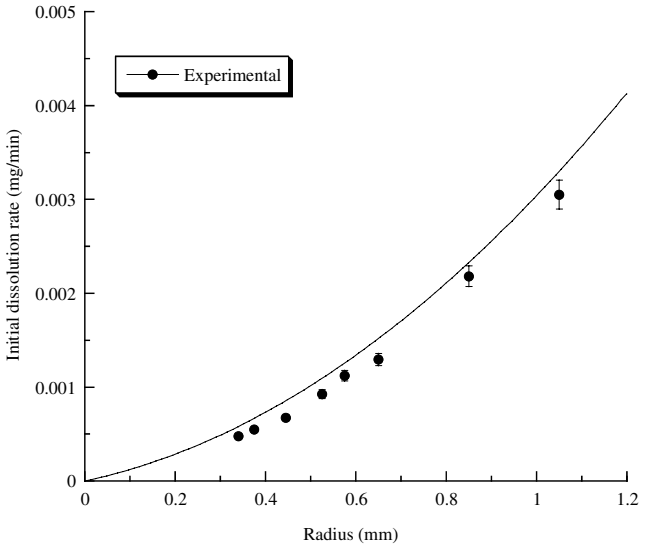

Fig. 13. Experimental and predicted initial dissolution rates of benzocaine particles versus particle radii in 1% (w/v) sodium lauryl sulfate (SLS).

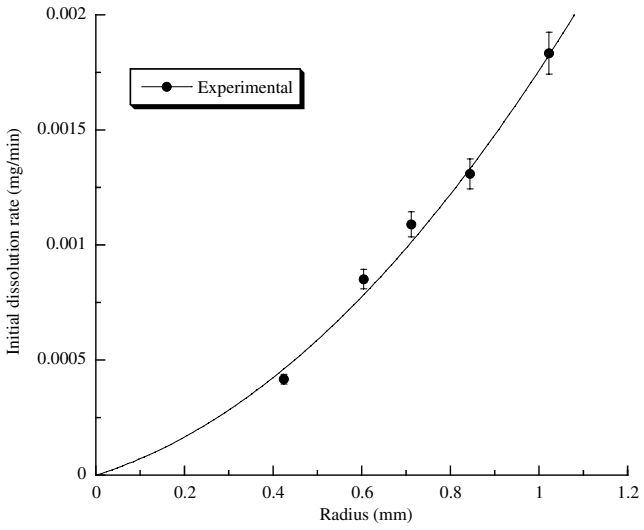

Fig. 12. Experimental and predicted initial dissolution rates of benzocaine particles versus particle radii in 0.5% (w/v) sodium lauryl sulfate (SLS).

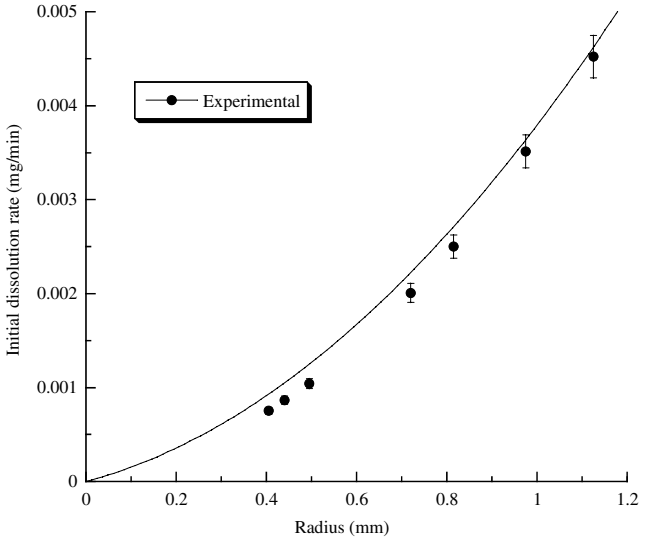

Fig. 14. Experimental and predicted initial dissolution rates of benzocaine particles versus particle radii in 1.5% (w/v) sodium lauryl sulfate (SLS).

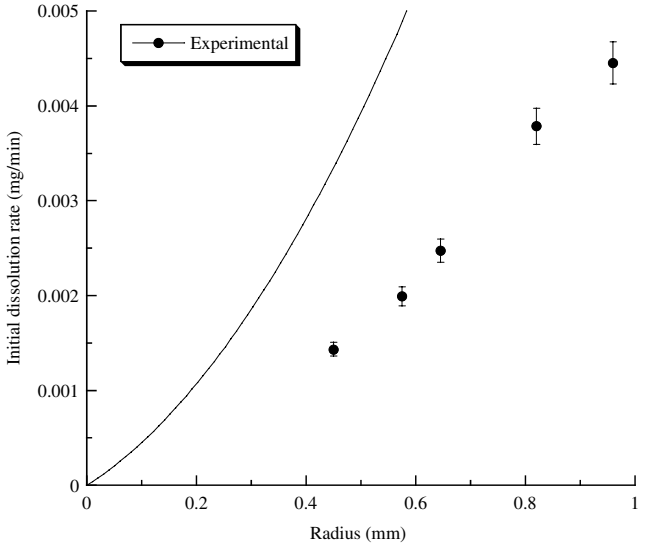

Fig. 15. Experimental and predicted initial dissolution rates of benzocaine particles versus particle radii in 5% (w/v) sodium lauryl sulfate (SLS).

culated and experimental values may be found in the assumption of constant micelle size and shape for all micellar concentrations.

4. Conclusions

In this study, a model describing and predicting the initial dissolution rates of spherical particles was validated. The results obtained from this study indicated that it is possible to accurately predict the initial dissolution rate in micellar systems at moderate surfactant concentrations.

Appendix A

The following assumptions were used in the alternative derivation of Wang and Flanagan's model [3]. The particle is spherical and dissolves isotropically. The particle is in a homogeneous solution, and there is a constant boundary layer around the particle of constant thickness (h). The concentration at the interface between the solid and the solution is saturated and equals the saturation solubility C_s. The bulk solution concentration C_b is assumed to be zero, and the diffusion coefficient D is constant throughout the diffusion layer.

The alternative derivation started from the continuity equation in spherical coordinates in terms of fluxes

$$\frac{\partial c_A}{\partial t} + \left(\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 N_{Ar}) + \frac{1}{r\sin\theta}\frac{\partial}{\partial\theta}(N_{A\theta}\sin\theta) + \frac{1}{r\sin\theta}\frac{\partial N_{A\phi}}{\partial\phi}\right) = R_A \tag{7}$$

By applying the assumptions of steady state dissolution, concentration gradient is only in the radial direction, and the detachment reaction of the solid molecules from the solid surface to form hydrated molecules at the solid–liquid interface is an instantaneous reaction. Then the continuity equation is reduced to:

$$\frac{1}{r^2}\frac{d}{dr}(r^2 N_{Ar}) = 0 \tag{8}$$

Eq. (8) is a separable first order differential equation and can be solved by separating the variables

$$\int d(r^2 N_{Ar}) = 0 \tag{9}$$

by integration

$$r^2 N_{Ar} = A \tag{10}$$

where A is an integration constant. By assuming that the flux of the solid particle is due to the contribution of diffusion only, so N_{Ar} could be defined by Fick's first law:

$$N_{Ar} = -D\frac{dC_A}{dr} \tag{11}$$

Substituting Eq. (11) into Eq. (10) gives

$$\frac{dC_A}{dr} = \frac{-A/D}{r^2} \tag{12}$$

Again solving for C_A by separating the variables

$$\int dC_A = \int \frac{-A/D}{r^2}\,dr \tag{13}$$

Solving the integration

$$C_A = \frac{A/D}{r} + B \tag{14}$$

where B is an integration constant. The integration constants A and B can be calculated by applying the following boundary conditions:

1. At the particle surface ($r = a$) benzocaine concentration equals its saturation solubility.
2. At the diffusion film thickness ($r = a + h$) there is a sink condition (i.e. $C_A = 0$).

Applying the boundary conditions to Eq. (14) gives:

$$C_{As} = \frac{A/D}{a} + B \tag{15}$$

$$0 = \frac{A/D}{a+h} + B \tag{16}$$

Solving Eqs. (15) and (16) simultaneously gives:

$$A = \frac{DC_{As}a(a+h)}{h} \text{ and } B = \frac{-C_{As}a}{h}$$

Substituting A and B expressions into Eq. (14) gives:

$$C_A = \frac{C_{As}a(a+h)}{hr} - \frac{C_{As}a}{h} \tag{17}$$

But the flux of the solid material is defined in Eq. (11) as:

$$N_{Ar} = -D\frac{dC_A}{dr}$$

The first derivative of Eq. (17) with respect to r is

$$\frac{dC_A}{dr} = \frac{-C_{As}a(a+h)}{hr^2} \tag{18}$$

Combining Eq. (11) with Eq. (18) gives

$$N_{Ar} = \frac{DC_{As}a(a+h)}{hr^2} \tag{19}$$

The dissolution rate (DR) of the particle in units of (mass/time) is given by:

$$DR = \frac{4\pi DC_{As}a(a+h)}{h} \tag{20}$$

Appendix B

By applying the assumption that the flux of the solid particle is due to the contributions of diffusion and convection, N_{Ar} could be defined in terms of solute mass fraction as:

$$N_{Ar} = -D\frac{dC_A}{dr} + x_A N_{Ar} \tag{21}$$

Therefore,

$$N_{Ar} = -\frac{DC}{1-x_A}\frac{dx_A}{dr} \tag{22}$$

where C is bulk solution density. Substituting Eq. (22) into Eq. (8) gives:

$$\frac{d}{dr}\left(r^2\frac{1}{1-x_A}\frac{dx_A}{dr}\right) = 0 \tag{23}$$

Solving for x_A by separating the variables

$$\int \frac{d}{dr}\left(r^2\frac{1}{1-x_A}\frac{dx_A}{dr}\right) = 0 \tag{24}$$

Solving the integration gives

$$r^2\frac{1}{1-x_A}\frac{dx_A}{dr} = E \tag{25}$$

where E is an integration constant. Again solving the integration

$$\int \frac{1}{1-x_A}dx_A = \int \frac{E}{r^2}dr \tag{26}$$

Then,

$$-\ln(1-x_A) = \frac{-E}{r} + F \tag{27}$$

The integration constants E and F can be calculated by applying the following boundary conditions:

1. At the particle surface ($r = a$) benzocaine concentration equals to its saturation solubility (i.e. $x_A = x_{As}$).
2. At the diffusion film thickness ($r = a + h$) there is a sink condition (i.e. $x_A = 0$).

Applying the boundary conditions to Eq. (27) gives

$$-\ln(1-x_{As}) = -\frac{E}{a} + F \tag{28}$$

$$0 = -\frac{E}{a+h} + F \tag{29}$$

Solving Eq. (28) and Eq. (29) simultaneously gives:

$$E = \frac{\ln(1-x_{As})}{h}a(a+h) \text{ and } F = \frac{a\ln(1-x_{As})}{h}$$

Substituting E and F expressions into Eq. (27) gives:

$$-\ln(1-x_A) = -\frac{a(a+h)\ln(1-x_{As})}{hr} + \frac{a\ln(1-x_{As})}{h} \tag{30}$$

But the flux of the solid material is defined in Eq. (22) as

$$N_{Ar} = -\frac{DC}{1-x_A}\frac{dx_A}{dr}$$

The first derivative of Eq. (30) with respect to r is

$$\frac{1}{1-x_A}\frac{dx_A}{dr} = \frac{a(a+h)\ln(1-x_{As})}{hr^2} \tag{31}$$

Then,

$$\frac{dx_A}{dr} = \frac{a(a+h)(1-x_A)\ln(1-x_{As})}{hr^2} \tag{32}$$

Combining Eq. (22) with Eq. (32) gives:

$$N_{Ar} = -\frac{CDa(a+h)\ln(1-x_{As})}{hr^2} \tag{33}$$

The dissolution rate of the particle in units of (mass/time) is given by:

$$DR = \frac{-4\pi CDa(a+h)\ln(1-x_{As})}{h} \tag{34}$$

Eq. (34) describes the dissolution rate of spherical particle in which the convection has been taken into account. To the best of our knowledge, this equation has not been published elsewhere.

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