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ORIGINAL CONTRIBUTION

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# The release of cephanone in CTAB/$n$-$C_5H_{11}OH$/$H_2O$ system

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**Abstract** Controlled release of cephanone from hexadecyltrimethylammonium bromide (CTAB) micelles and CTAB/$n$-$C_5H_{11}OH$/$H_2O$ microemulsions was studied. The results showed that the release rate of cephanone was reduced in CTAB micelles and CTAB/$n$-$C_5H_{11}OH$/$H_2O$ microemulsions, because of the solubilization of cephanone in micelles and microemulsions. The release of cephanone from CTAB micelles and CTAB/$n$-$C_5H_{11}OH$/$H_2O$ microemulsions was characterized by Fickian diffusion and non-Fickian diffusion.

**Keywords** Cephanone · CTAB · Micelles · Microemulsions · Controlled release

## Introduction

The controlled release of drug is to control the release rate of drug in the human body, enhance the drug utilization ratio, and treat a certain illness by preparing the drug to a certain medicament form with other substance as drug carrier or media [1–4]. There are four kinds of controlled release systems: diffusion, chemistry, solvolytic and magnetism-controlled release systems [2–4]. Diffusion controlled release system, the most widely used system, is superior to the other systems in preparation and application of drugs. Surfactant aggregations such as micelles and microemulsions have been well applied in the field of pharmaceuticals as drug-controlled release system due to their thermodynamical stability and high solubilization amount [5–12]. The release of drugs in micelle and microemulsion system is a diffusion-controlled release [13–15].

Cephanone, a kind of $\beta$-lactam compound, has been widely applied in medicine. But the concentration of cephanone in the body cannot be maintained in the effective range due to its high release rate [16, 17]. In the present paper, the release of cephanone in CTAB/$n$-$C_5H_{11}OH$/$H_2O$ system was studied in order to decrease the release rate and enhance the drug availability.

## Experiments

### Materials

Hexadecyltrimethylammonium bromide (CTAB, Aldrich, 99 + %), $n$-pentanol ($n$-$C_5H_{11}OH$, Aldrich, 99 + %), pyrene (Aldrich, 99 + %), cephanone (The Pharmaceutical Factory of ChongQing, 1,000,000 units) were used as received. Water that was used was distilled twice. The chemical structures of CTAB and cephanone molecule are shown in Fig. 1.

### Determination of release of cephanone

Uv–vis spectra of samples were measured by UV–vis absorption spectroscopy (UV-2501PC, Shimazu Co. Japan). The standard curve of cephanone aqueous could be obtained from the relationship between the absorbance A and cephanone concentration, and then the apparent molar absorption coefficient ε was obtained from the slope of line.

Two milliliters of sample of CTAB/cephanone (aq) or CTAB/$n$-$C_5H_{11}OH$/cephanone(aq) was introduced into a dialysis membrane bag (width is 44 mm, dialysis molecular weight < 15000) as drug donor, and the bag

was placed in 10-ml phosphate buffer solution (pH = 6.86) as release media (receiver). The aqueous solution was withdrawn from the release media for the determination of UV spectra at 254 nm at the predetermined time intervals. The curve of release rate for cephanone could be obtained from the relationship between cumulative release amount and time $t$.

### Measurement of distribution coefficient $K_D$

The distribution coefficient $K_D$ of cephanone between the micellar phase and the aqueous phase could be determined according to the measurment of UV absorbance at 254 nm.

### Measurement of micropolarity in micelles or microemulsions

The stable-state fluorescent spectra were measured by using pyrene as probe, with the excitation wavelength being 338 nm and the emission wavelength being 384 nm, respectively (RF-5301PC, Shimazu Co. Japan). The intensity ratios of the first peak (near 373 nm) to the third peak (near 384 nm) ($I_1/I_3$) of fluorescent spectra could show the micropolarity of the microenvironment where pyrene existed, and the location of cephanone in the micelles could be determined by the value of $I_1/I_3$ [18]. The pyrene concentration was $1.0\times10^{-6}$ mol $l^{-1}$ .

All above experiments were carried out at 37 ± 0.1°C.

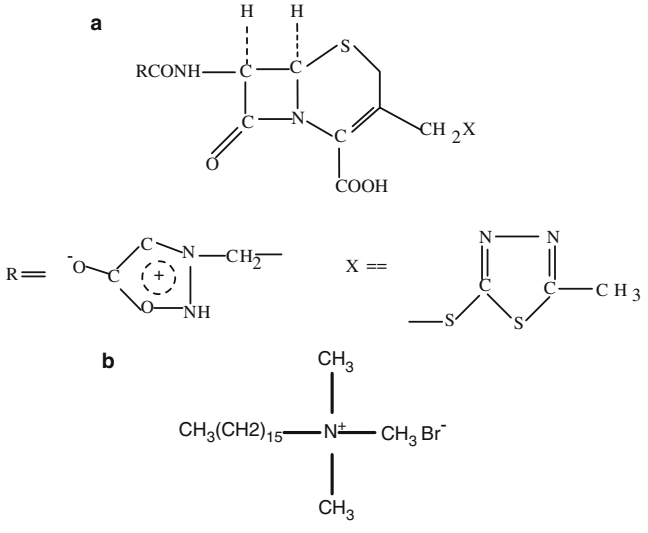


**Fig. 1** The molecular structures of CTAB and cephanone. **a** cephanone, **b** CTAB

## Results and discussion

### Release of cephanone in CTAB micelles

It can been seen from Fig. 2 that the relationship between absorbance A and cephanone concentration c was linear in the cephanone concentration range of 0 ~ $4.5\times10^{-3}$ mol $l^{-1}$ . The maximum cephanone concentration is $3.04\times10^{-3}$ mol $l^{-1}$ in the present study. So the cephanone concentration can be quantified by Fig. 2.

Figure 3 shows that the release rate of cephanone can be reduced in CTAB micelles and decreases with the increase of CTAB content.

In CTAB micelles, cephanone molecules not only locate in water continuous phase but also locate in the palisade of CTAB micelles because of the interaction between the $COO^-$ group of cephanone and the amino group of CTAB molecule. The release of cephanone in CTAB micelles can be divided into two parts:

1. The diffusion of cephanone from aqueous phase to the receiver through the membrane. The diffusion rate is related to the size of the molecule.
2. The diffusion of drug is from micelles to aqueous phase, which is a rate-limiting step, because cephanone molecules must overcome the palisade barrier of micellar palisade.

Obviously, the location of cephanone in the micellar palisade makes the diffusion of cephanone decrease so

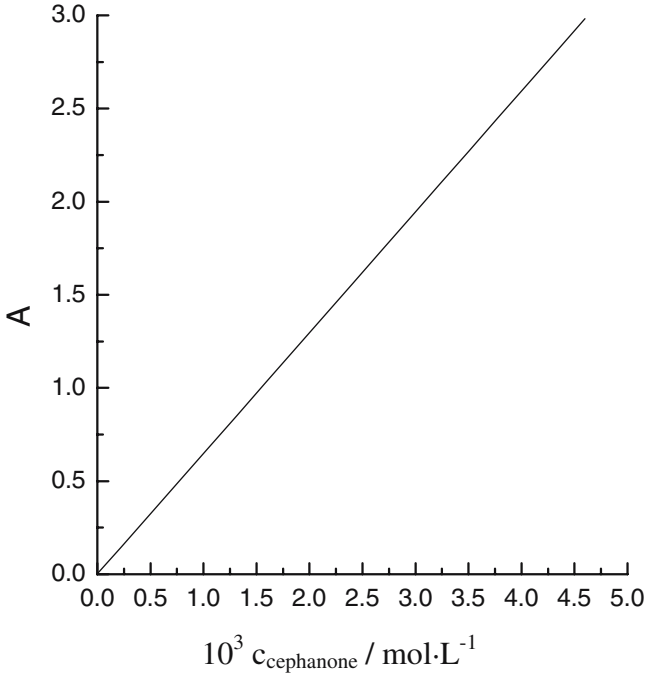


**Fig. 2** Standard curve of cephanone

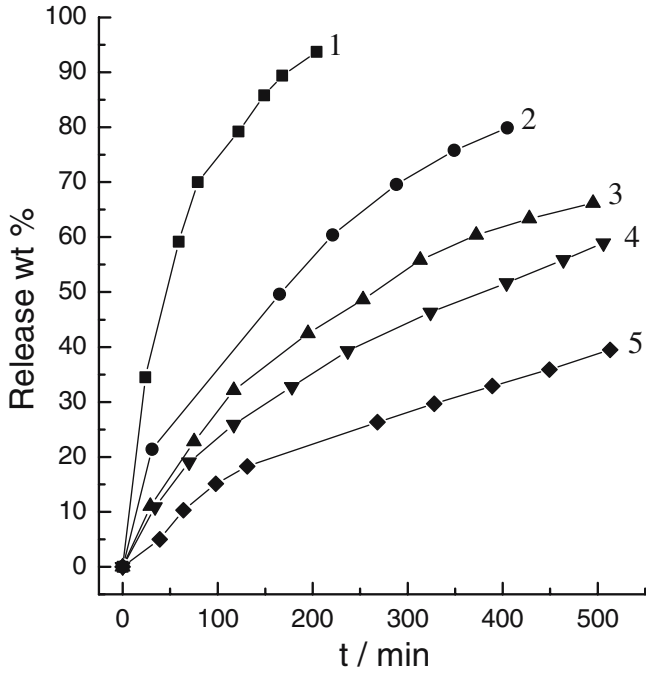


**Fig. 3** The effects of CTAB content on the release rate of cephanone in CTAB micelle. CTAB content: *1* 0%, *2* 0.5%, *3* 1.0%, *4* 2.0%, *5* 3.0%

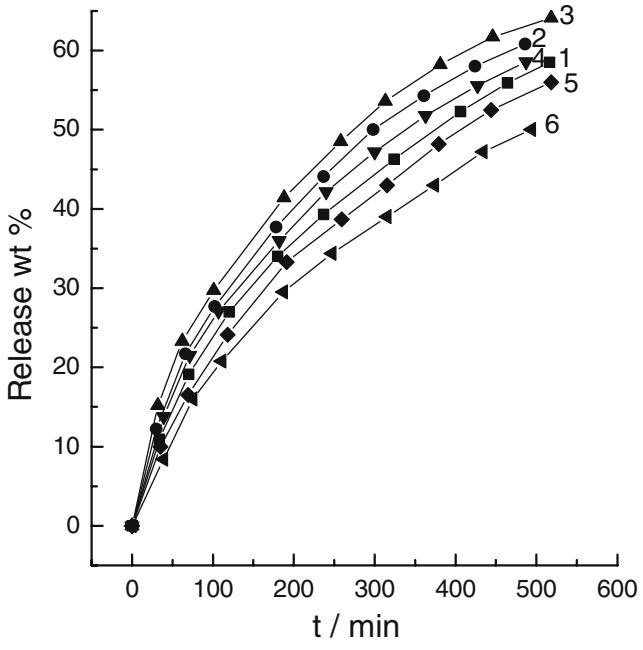


**Fig. 4** The effects of $n$-$C_5H_{11}OH$ content on the release rate of cephanone in the O/W microemulsion. Weight ratio of CTAB: $H_2O$ is 2:98. $n$-$C_5H_{11}OH$ content: *1* 0%, *2* 0.5%, *3* 1.0%, *4* 1.5%, *5* 2.0%, *6* 3.0%

that the release rate of cephanone decreases. Further, the number of micelles increases with the increase of CTAB content, which makes the amount of cephanone located in the CTAB micelles increase and the diffusion rate decrease. So does the release rate of cephanone. Although the electrostatic interactions between $CTA^+$ and membrane and the permeation of CTAB monomers can affect the release of cephanone, the reduction of 3.3% of CTAB concentration in the permeation tests, performed from 3% of CTAB aqueous solution in the dialysis membrane bag for 2 h, shows that it is insignificant.

## Release of cephanone in CTAB/$n$-$C_5H_{11}OH$/$H_2O$ O/W microemulsion

Figure 4 shows that the release rate of cephanone first increases and then decreases with the increase of $n$-$C_5H_{11}OH$ content in the CTAB/$n$-$C_5H_{11}OH$/$H_2O$ O/W microemulsions.

$n$-$C_5H_{11}OH$ mainly locates in the water continuous phase when the $n$-$C_5H_{11}OH$ content is very low. Thus, the interaction among cephanone, $n$-$C_5H_{11}OH$ and $H_2O$ increases the distribution of cephanone in the water, and also increases the release rate of cephanone. When the $n$-$C_5H_{11}OH$ content is more than 1.0%, $n$-$C_5H_{11}OH$ mainly acts as a cosurfactant to participate in the formation of the microemulsion droplets, which increases the size of micelles. So the amount of cephanone located in the interphase of microemulsion droplets increases, and the diffusion rate of cephanone and the release rate decreases.

The location of $n$-$C_5H_{11}OH$ into the micelles can be confirmed by the effect of $n$-$C_5H_{11}OH$ on the micropolarity ($I_1/I_3$) of the microenvironment where pyrene exists. Figure 5 shows that $I_1/I_3$ value changes slightly with the increasing $n$-$C_5H_{11}OH$ content when the content of $n$-$C_5H_{11}OH$ is less than 1.1% and decreases suddenly when the content of $n$-$C_5H_{11}OH$ is more than 1.1%. The results show that $n$-$C_5H_{11}OH$ mainly locates in the water continuous phase in the former case, so the effects of $n$-$C_5H_{11}OH$ on $I_1/I_3$ value is slight, and $n$-$C_5H_{11}OH$ mainly locates in the palisade of the micelles in the later case, which makes pyrene transfer to the inside of the palisade of the micelles and the $I_1/I_3$ value decreases.

Further, the interactions between pentanol and cephanone by hydrogen bonds, which cause $n$-$C_5H_{11}OH$ transfer to the inside of the palisade of microemulsion droplets [19], make microemulsions steady and the diffusion of $n$-$C_5H_{11}OH$ to the receiver difficult.

Figure 6 is the curve of release rate of cephanone versus CTAB content in the CTAB/$n$-$C_5H_{11}OH$/$H_2O$ O/W microemulsions at a constant weight ratio of $n$-$C_5H_{11}OH$ to $H_2O$. It can be seen that the release rate of cephanone decreases with the increasing CTAB content. Obviously, the number of O/W microemulsion droplets

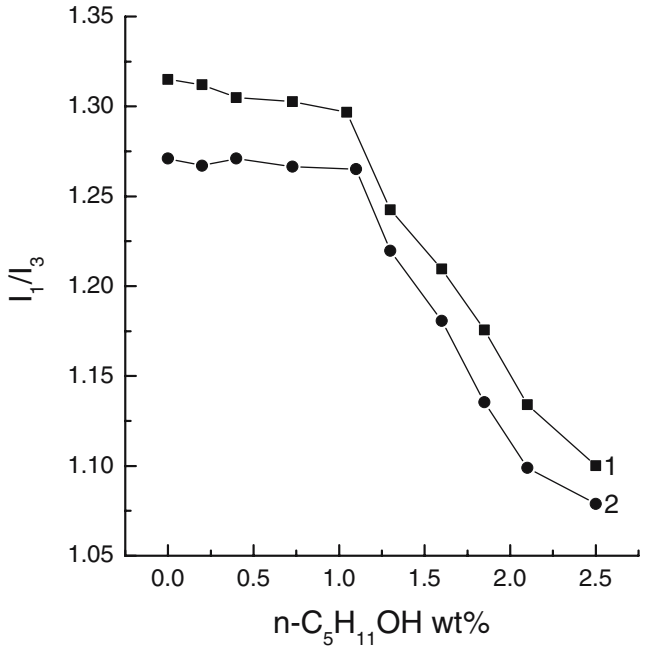


**Fig. 5** Micropolarity $I_1/I_3$ value versus $n$-$C_5OH_{11}OH$ content. Weight ratio of CTAB: $H_2O$ is 2:98. Cephanone content: *1* 0.0%, *2* 0.5%

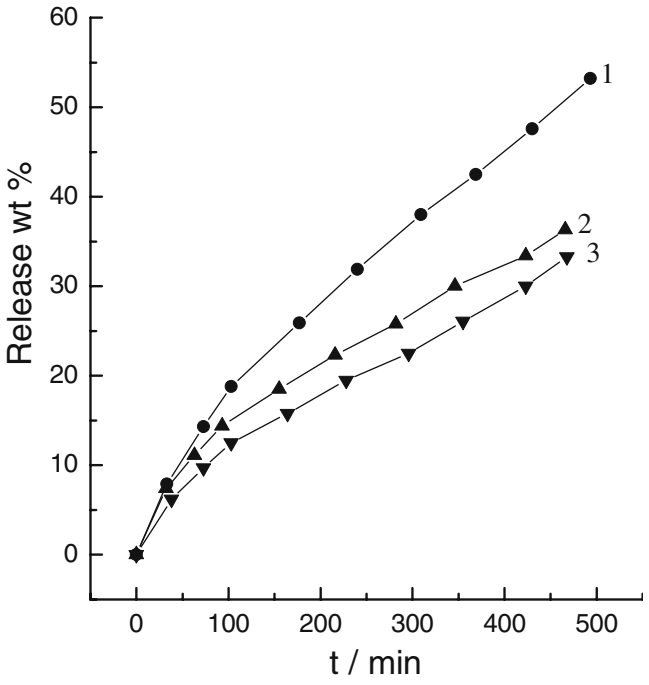


**Fig. 7** The effects of $n$-$C_5H_{11}OH$ content on the release rate of cephanone in the W/O microemulsion. Weight ratio of CTAB: $H_2O$ is 50:50. $n$-$C_5H_{11}OH$ content: *1* 85.0%, *2* 90.0%, *3* 93.0%

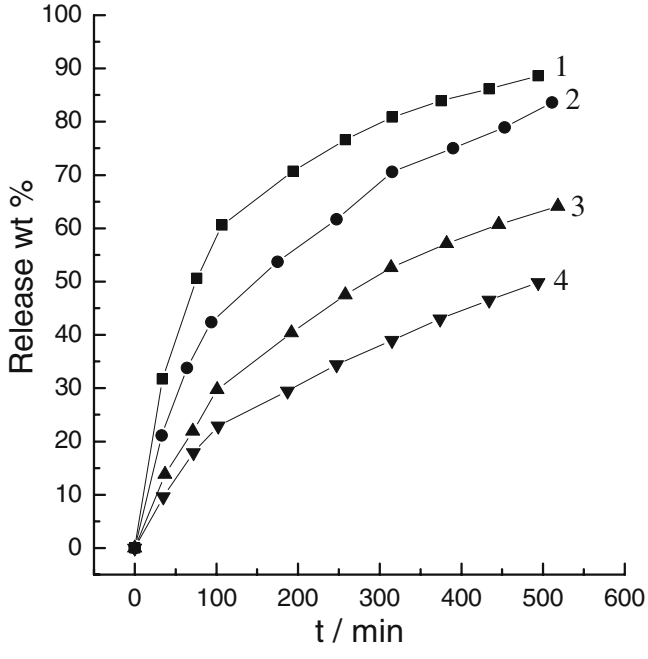


**Fig. 6** The effects of CTAB content on the release rate of cephanone in the O/W microemulsion. Weight ratio of $n$-$C_5H_{11}OH$: $H_2O$ is 1:99. CTAB content: *1* 0.5%, *2* 1.0%, *3* 2.0%, *4* 3.0%

increases with the increase of CTAB content, which increases the solubilization amount of cephanone in the O/W microemulsion droplets. Thus, the release rate of cephanone decreases. Meanwhile, the amount of cephanone and CTAB complex in the water continuous phase increases with the increasing CTAB content. Therefore, the diffusion rate of cephanone and the release rate decreases.

## Release of cephanone in CTAB/$n$-$C_5H_{11}OH$/$H_2O$ W/O microemulsion

In the W/O microemulsion system, $n$-$C_5H_{11}OH$ is not only a cosurfactant but also mainly acts as a continuous phase. Thus, the diffusion barrier of cephanone from micellar palisade to oil continuous phase and then to the receiver increases with the increasing $n$-$C_5H_{11}OH$ content, and the release rate decreases (Fig.7).

Figure 8 shows that the release rate decreases with the increasing CTAB content in the CTAB/$n$-$C_5H_{11}OH$/$H_2O$ W/O microemulsions at a constant weight ratio of $n$-$C_5H_{11}OH$ to $H_2O$. Obviously, the amount of cephanone solubilizated in the water core of W/O microemulsion increases with the increase of CTAB content. Thus, the release rate of cephanone decreases.

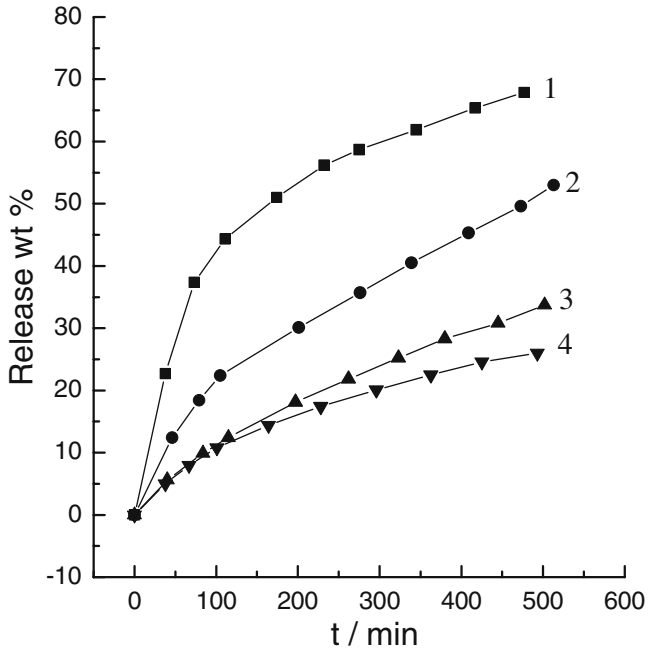


**Fig. 8** The effects of CTAB content on the release rate of cephanone in the W/O microemulsion. Weight ratio of $H_2O$:*n*-$C_5H_{11}OH$ is 5:95. CTAB content: *1* 0.5%, *2* 1.0%, *3* 2.0%, *4* 3.0%

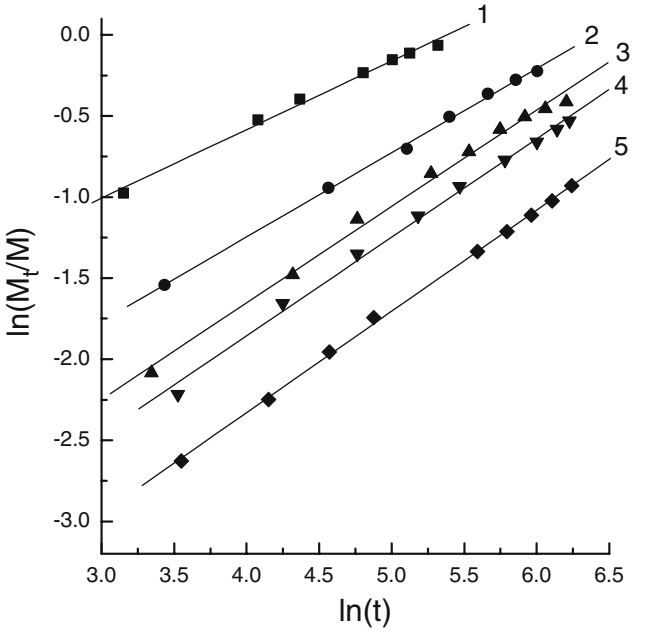


**Fig. 9** The relationship between $\ln(M_t/M)$ and lnt in the CTAB micelle system. CTAB content: *1* 0%, *2* 0.5%, *3* 1.0%, *4* 2.0%, *5*3.0%

## The kinetics of release of cephanone

To analyze the mechanism of release of the cephanone, the release of kinetic parameters were calculated using the following equation [20]:

$$\frac{M_t}{M} = k \cdot t^n, \tag{1}$$

where $M_t/M$ is the fraction of drug that has been released at time $t$, $k$ is a kinetic constant and $n$ is an exponent related to the mechanism of drug release. $k$ and $n$ can be calculated from intercept and slope of the straight line in Fig. 9. The release of drug occurs quickly as $k$ increases. An $n$ value of 0.5 indicates Fickian diffusion, n = 1 corresponds to zero-order release kinetics, and $0.5 < n < 1$ indicates a non-Fickian release model [21].

As clearly seen from Table 1, $k$ values in the CTAB micelle or CTAB/*n*-$C_5H_{11}OH/H_2O$ microemulsion are much lower than that in the water system. It indicates that CTAB micelle or CTAB/*n*-$C_5H_{11}OH/H_2O$ microemulsion system can control the release of cephanone, which is in accord with the above discussion (see Table 1). The $n$ value in the water is 0.49, which exhibits a Fickian-diffusion release. However, $n$ value is 0.52 when CTAB content is 0.5%, which approximately shows a Fickian-diffusion release. Then, $n$ value increases with the CTAB content. It shows that the diffusion model of release of cephanone in the CTAB micelles transformed from Fickian-diffusion to non-Fickian diffusion with the increasing CTAB content. Similarly, $n$ value is greater than 0.5 and smaller than 1 ($0.5 < n < 1$) in the CTAB/*n*-$C_5H_{11}OH/H_2O$ microemulsion system, which indicates that the release of cephanone in the CTAB/*n*-$C_5H_{11}OH/H_2O$ microemulsion system is a non-Fickian release. It is obvious that the release of cephanone must overcome the palisade barrier because of the solubilization of cephanone in the palisade of CTAB micelle or in CTAB/*n*-$C_5H_{11}OH/H_2O$ microemulsion.

## Solubilization of cephanone in the micelles and microemulsions

The solubilization Gibbs free energies $\Delta G$ of cephanone in micelles or microemulsions can be calculated from the formula $\Delta G = -RTln\ K_D$, where, $K_D$, the distribution coefficient of cephanone between micellar phase and water phase (continuous phase for O/W and water core for W/O) can be defined as follows [22, 23]:

$$\frac{1}{E_\psi - E_W} = \frac{1}{K_D(E_m - E_W)} \times \frac{1}{C_D} + \frac{1}{E_m - E_W}, \tag{2}$$

where $C_D$ is the concentration of surfactant, $E_\psi$ is the apparent molar absorption coefficient of cephanone at a certain wavelength. $E_w$, $E_m$ is the apparent molar absorption coefficient of cephanone in water phase(continuous phase for O/W and water core for W/O) and in micellar phase, respectively. The distribu-

**Table 1** The kinetic constant $k$ and exponent $n$ of cephanone release in different systems

| $W_{CTAB}$ (%) | $10^2$ $k$ | $n$ |
|---|---|---|
| (a) Micelle | | |
| 0.0 | 10.30 | 0.49 |
| 0.5 | 3.60 | 0.52 |
| 1.0 | 1.77 | 0.57 |
| 2.0 | 1.48 | 0.59 |
| 3.0 | 0.79 | 0.62 |

| $W_{CTAB}/W_{H_2O} = 2/98$ | | | $W_n - C_5H_{11}OH/W_{H_2O} = 1/99$ | | |
|---|---|---|---|---|---|
| $W_{n-C_5H_{11}OH}$ (%) | $10^2$ $k$ | $n$ | $W_{CTAB}$ (%) | $10^2$ $k$ | $n$ |
| (b) CTAB/$n$-$C_5H_{11}OH/H_2O$ O/W microemulsion | | | | | |
| 0.0 | 1.57 | 0.58 | 0.5 | 4.60 | 0.52 |
| 0.5 | 2.11 | 0.56 | 1.0 | 2.97 | 0.55 |
| 1.0 | 2.39 | 0.54 | 2.0 | 2.33 | 0.56 |
| 1.5 | 2.14 | 0.55 | 3.0 | 1.32 | 0.60 |
| 2.0 | 1.27 | 0.61 | — | — | — |
| 3.0 | 1.03 | 0.63 | — | — | — |

| $W_{CTAB}/W_{H_2O} = 50/50$ | | | $W_{H_2O}/W_{n-C_5H_{11}OH} = 5/95$ | | |
|---|---|---|---|---|---|
| $W_{n-C_5H_{11}OH}$ (%) | $10^2$ $k$ | n | $W_{CTAB}$% | $10^2$ $k$ | n |
| (c) CTAB/$n$-$C_5H_{11}OH/H_2O$ W/O microemulsion | | | | | |
| 85.0 | 1.29 | 0.57 | 0.5 | 3.04 | 0.54 |
| 90.0 | 0.99 | 0.59 | 1.0 | 1.46 | 0.57 |
| 93.0 | 0.60 | 0.64 | 2.0 | 0.67 | 0.63 |
| — | — | — | 3.0 | 0.49 | 0.65 |

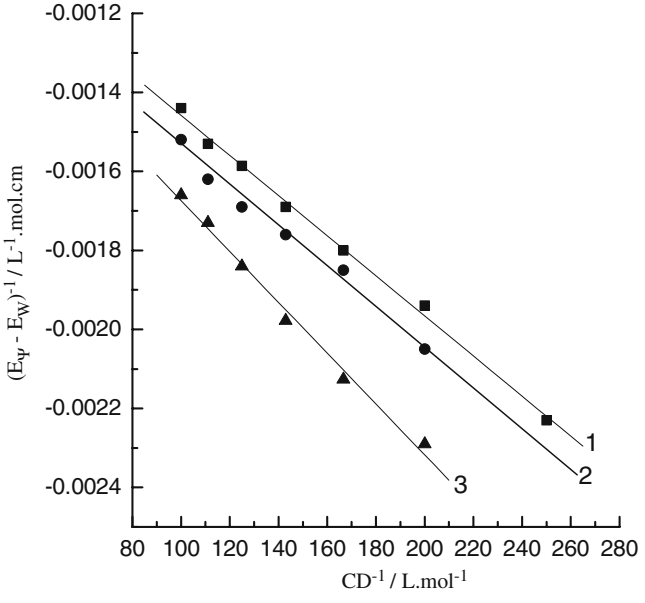


**Fig. 10** The curves of $(E_\Psi\text{-}E_w)^{-1}$ versus $C_D^{-1}$ . Cephanone concentration is $3.0\times10^{-3}$ mol $l^{-1}$ Media: *1* micelles; *2* O/W microemulsions; *3*W/O microemulsions

**Table 2** The distribution coefficients $K_D$ and the Gibbs free energies $\Delta G$ of cephanone between the CTAB micelle and the aqueous phase

| Media | $10^{-2}$ $K_D$ | $\Delta G$ (kJ mol$^{-1}$) |
|---|---|---|
| Micelles | 1.87 | −13.47 |
| O/W | 2.12 | −13.83 |
| W/O | 1.64 | −13.14 |

tion coefficient $K_D$ can be calculated from the slope and intercept of line in Fig. 10.

Table 2 shows that both the solubilization Gibbs free energies $\Delta G$ of cephanone in micelles and microemulsions (including O/W and W/O) are negative. The results illustrate that cephanone can be spontaneously solubilized in the micelles and microemulsions.

## Conclusions

The release rate of cephanone can be controlled in CTAB micelles and CTAB/$n$-$C_5H_{11}OH/H_2O$ microemulsions. The release rate decreases with the increase of

CTAB content, but first increases and then decreases with the increase of $n$-$C_5H_{11}OH$ content. The phenomenon is likely due to cephanone that can be solubilized spontaneously in CTAB micelles and CTAB/$n$-$C_5H_{11}OH/H_2O$ microemulsions.

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