Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(12):114-117

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Dissolution behavior of clofarabine in dimethyl sulfoxide

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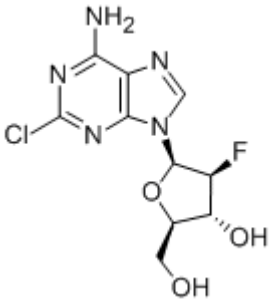
ABSTRACT

The enthalpies of dissolution for clofarabine in dimethyl sulfoxide (DMSO) were studied. Differential enthalpies and molar enthalpies were determined, so that we can set up the observations that describe the heat effect of each process and the amount of the substance. So we can know the process of dissolution is pseudo first order reaction on the basis of the dynamics equation. The half-life period, the molar enthalpy $\Delta_{sol}H_m$=5.913 kJ·mol^{-1}, the molar Gibbs free energy $\Delta_{sol}G_m$=97.61 kJ·mol^{-1}, the molar entropy is $\Delta_{sol}S_m$= -296.09 J·mol^{-1}·K^{-1}.

Key words: Microcalorimeter; Thermodynamics; Kinetics; clofarabine; DMSO

INTRODUCTION

Clofarabine was developed by Genzyme corporation, it is a new type of purine nucleotides anticancer drugs [1-2]. Especially, it plays an irreplaceable role in the treatment of acute lymphoblastic leukemia in recent years [3]. Clofarabine is white crystalline power and its structure as follow:



Because clofarabine with special effect for some cancer, so it obtains increasing attention from chemists and medical practitioners. In recent years, there are a lot of clofarabine researches, which mainly focus on the anticancer mechanism, clinical trials, side effects etc [4-6]. While the dissolution properties of clofarabine, especially in the aspects of dissolution kinetic equation and thermodynamic parameters have rarely been reported.

It is widely believed that a drug's half-life is an important parameter characterizing its efficacy. However, it is currently measured via in vivo animal pharmacokinetic experiments, in which the half-life of a few drugs using high performance liquid chromatography to detect its concentration change in animal bloods based on pharmacokinetic principles. This method was accurate and effective for living system but the operating procedure was complex and its results produced a great deviation, Therefore, an easy and reliable method is highly desirable for measuring drug's half-life. In this article, the thermodynamic parameters and kinetic equation for the dissolution of clofarabine in DMSO was measured at the normal human body temperature by microcalorimetry. This method is not only reliable but also possesses the advantage of easy operation [7-8]. In particular, because the entropy of

dissolution was achieved, the order of degree (distribution states) as well as the thermodynamic stability of systems can also be deduced. This study could provide a theoretical reference for the clinical applications of clofarabine.

EXPERIMENTAL SECTION

Material

Clofarabine (99.9%, Shanghai Ziyi Reagent Corporation), dimethyl sulfoxide (DMSO) (analytical grade).

Equipment and conditions

The experiment was performed using a C80CSEVOL microcalorimeter (Setaram Company, France), the microcalorimeter was calibrated by the Joule effect, and its sensitivity was (64.62±0.04) μV mW^{-1} at 309.65K. The enthalpy of dissolution of KCl (spectrum purity) in distilled water (about 20 mg/2.000 g) measured at 278.15K was 17.535 $kJ \cdot mol^{-1}$, which was in excellent accordance with the literature value of 17.545$kJ \cdot mol^{-1}$, proving that the device for measuring the enthalpy used in this study was reliable. Electronic balance (AB135-S).

Experimental Methods

The certain amounts of clofarabine(9.99 mg、20.43mg、24.99 mg、30.08 mg、34.94 mg) were dissolved in 1.50 ml of dimethyl sulfoxide (DMSO) at 309.65 K under atmospheric pressure, respectively. The enthalpy change during the process of dissolution was detected by the C80CSEVOL microcalorimeter.

RESULTS AND DISCUSSION

Thermodynamics Behavior of Dissolution of clofarabine in DMSO

The dissolution of clofarabine in dimethyl sulfoxide at 309.65 K is exothermic process. It can be seen from Fig.1.

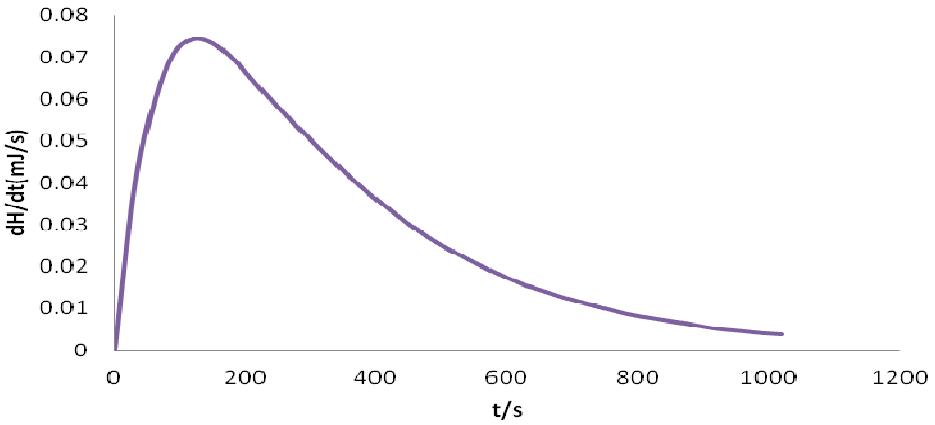


Fig. 1 The dissolution process curve of clofarabine in 1.50 ml DMSO

Table 1 shows the experimental data obtained from the typical thermogram curve of the dissolution with different masses of clofarabine in 1.50 ml dimethyl sulfoxide.

Table 1 The dissolution enthalpy of clofarabine in 1.50 ml DMSO

Sample amount(mg)	$n/10^{-3}$mol	Q/mJ	$\Delta_{sol}H_m$/kJ·mol^{-1}
9.99	0.03290	196.3	5.967
20.43	0.06727	406.4	6.041
24.99	0.08229	482.7	5.866
30.08	0.09905	577.9	5.834
34.94	0.11506	673.9	5.857
Average			5.913

n is the amount of clofarabine, Q is the heat effect of the process and $\Delta_{sol}H_m$ is the molar enthalpy

We can see from Table 1, the concentration of the solvent has little impact on the values of the molar enthalpy ($\Delta_{sol}H_m$) at 309.65 K. So the average value of $\Delta_{sol}H_m$ can represent the molar enthalpy of infinitely dilute solution at 309.65 K.

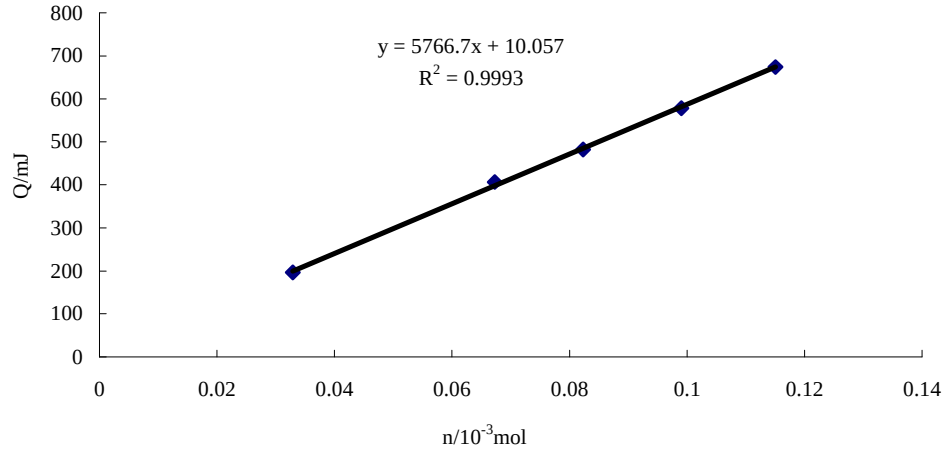


Fig .2 Relationship between the amount of clofarabine (n) dissolved in DMSO and the heat Q

Liner curve (Fig.2) was generated from the released heats (Q) and sample masses, and the corresponding liner equation is shown as Eq.1:

Q= 5766.8n+ 10.055 r=0.9996 (1)

The above equation shows that the mass of clofarabine and heat Q have very good liner relationships, so the calculated molar enthalpy change from Eq.1 was measured, and its value is 5.78 $kJ{\cdot}mol^{-1}$.

Kinetics of Dissolution process of clofarabine in DMSO

The dissolution rates of clofarabine in dimethyl sulfoxide can be described by Eqs.2 and 3, then substituting (3) into (2), we get Eq.4.

$$da/dt = kf(a) \quad (2)$$

$$f(\alpha) = (1-\alpha)^n \quad (3)$$

$$\frac{d\alpha}{dt} = k(1-\alpha)^n \quad (4)$$

Substituting $\alpha = \frac{H_t}{H_0}$ into Eq.4. After achieving a logarithmic converter:

$$\ln[\frac{1}{H_0}(\frac{dH_t}{dt})_i] = \ln k + n\ln[1-(\frac{H_t}{H_0})_i] \quad i = 1,2,\cdots,L \quad (5)$$

In these equations, α is the conversion degree; $f(\alpha)$ is the kinetic function; H_t represents the heat at time t; H_0 is the heat of the whole process; k is the rate at which clofarabine is dissolved in dimethyl sulfoxide; n is the reaction order, and L is the counting index. The obtained values of n and lnk are listed in Table 2.

Table 2 The reaction series n and lnk of clofarabine dissolved in1.50 ml dimethyl sulfoxide at 309.65 K

m/mg	*n*	Ln*k*/s^{-1}	R^2
9.99	0.6641	-8.202	0.9997
20.43	0.7547	-8.5629	0.9995
24.99	0.8466	-8.4527	0.9998
30.08	0.8525	-8.5579	0.9996
34.94	0.7963	-8.3051	0.9998
Average	0.7828	-8.4161	

The kinetic equation of the dissolution process of clofarabine in DMSO is $\frac{d\alpha}{dt} = 10^{-3.66} \times (1-\alpha)^{0.78}$

The kinetic equation is similar to quasi-first order reaction of the dissolution process. So the half life period can be calculated with Eq.4, which was 52.3 min.

$$t_{\frac{1}{2}} = \frac{\ln 2}{k} \tag{6}$$

$t_{\frac{1}{2}}$ =52.3 min

According to these experimental data and calculated results, the thermodynamic and kinetic parameters of the dissolution process were obtained through the Eq.7.

$$\ln \frac{k}{T} = (\frac{\Delta S_m^\theta}{R} + \ln \frac{k_B}{h}) - \frac{\Delta H_m^\theta}{RT} \tag{7}$$

Equation 7 can be changed into the following expression:

$$\ln \frac{kh}{k_B T} = \frac{\Delta_{sol} S_m}{R} - \frac{\Delta_{sol} H_m}{RT} \tag{8}$$

Substituting T=309.65 K, R=8.314J·mol^{-1}·k^{-1}, h=6.626×10^{-34}J·s^{-1},k_B=1.38×10^{-23}J·K^{-1} , And the value of k and $\triangle_{sol}H_m$ of doxifluridine in different solvents into Eq.(11) ,we can get the values of $\triangle_{sol}S_m$, and thus $\triangle_{sol}S_m$ =-296.09 J·mol^{-1}·k^{-1} .After putting $\triangle_{sol}S_m$ and $\triangle_{sol}H_m$ into the follow formula:

$$\triangle_{sol}G_m = \triangle_{sol}H_m - T\triangle_{sol}S_m \tag{9}$$

We can obtain $\triangle_{sol}G_m$ =97.61kJ·mol^{-1}.

CONCLUSION

The molar enthalpy of clofarabine in dimethyl sulfoxide was measured with the C80CSEVOL microcalorimeter at 309.65K under atmospheric pressure. From the results it can be observed that the concentration of clofarabine has little impact on the enthalpies. So we can conclude that the average value of $\triangle_{sol}H_m$ can represent the molar enthalpy which is 5.913 kJ·mol^{-1}; The kinetic equation of the dissolution process of clofarabine in DMSO at 309.65K is $\frac{d\alpha}{dt} = 10^{-3.66} \times (1-\alpha)^{0.78}$, it is a quasi-first order reaction, the rate constant is k=10$^{-3.66}$ s^{-1}, so the half-life is $t_{1/2}$=48.4min; The dissolution of clofarabine in the solution of DMSO is an exothermic process. The $\triangle_{sol}G_m$ is 97.61 kJ·mol^{-1} and $\triangle_{sol}S_m$ is -296.09 J·mol^{-1}·k^{-1}. According to the negative value of entropy of activation indicates that the dissolution of clofarabine in DMSO solution get a more ordered system. Thereby the study provides a strong reference for the clinical application of the drug.

Acknowledgements
This work was supported by Natural Science Foundation of Shaanxi Province (Grant No.2012Jm2019) and the Key Laboratory of Shaanxi Province (Grant No.12JS006).

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