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Research Article

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Dissolution characteristics of anti-cancer drug Cytarabine

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ABSTRACT

Cytarabine is an effective drug for the treatment of leukemia. In this paper, the dissolution behavior of Cytarabine in normal saline and citric acid solution was studied using microcalorimetry in order to obtain integral and differential heat of solution. This study not only established the relation between the solute and heat, but also determined the kinetic equations of Cytarabine in normal saline and citric acid solution as well as the half-life, $\Delta_{sol}H_m$, $\Delta_{sol}G_m$ and $\Delta_{sol}S_m$. This work could provide experimental support for the clinical study of Cytarabine.

Keywords: thermodynamics; dynamics; Cytarabine; half-life

INTRODUCTION

Cytarabine (commercial name: Sai Desa), chemical name: 1-D-arabinofuranosyl-4 - amino -2 (1H) - pyrimidinone hydrochloride has the following chemical and physical properties: formula: $C_9H_{13}N_3O_5$ • HCL, molecular weight: 279.68, appearance: white or almost white crystalline powder, and solubility: soluble in water, ethanol and chloroform. [1,2] It is a glycoside compound formed by cytosine arabinose, and it is a competitive inhibitor of DNA polymerase which can inhibit the biosynthesis of DNA in vivo. Hence, it is an effective anti-tumor agent, especially for the treatment of leukemia[3-5].

Clinical studies of recent years show that the Ara is mainly used for the treatment of acute leukemia and acute myeloid leukemia, meanwhile it lymphoma, lung cancer, gastrointestinal cancer, head and neck cancer[6,7]. However, most of Ara's research focuses on the is also could be used for the treatment for malignant synthesis method, side effects, but few studies have been conducted to investigate the thermohydrodynamic kinetics of dissolution. Lacking of such fundamental theories would be difficult to understand the full effect of the drug[8].

The half-life is an important parameter for drug assessment. The half-life is usually determined using animal tests based on the pharmaco plasma by high-performance liquid chromatography (HPLC). This traditional approach is effective but complex, and it would be impacted by individual differences of samples which may decrease kinetic principles to measure the concentration of drug in the results accuracy. Therefore, in order to efficiently generate the reliable data, a simple approach is needed. In this study, we developed a new approach, namely microcalorimetry approach, to can be used to calculate the half-life of cytrarabine. This approach is reliable and easy to implement, and it can be used to learn about the distribution of a variety of systems and thermodynamic stability by study the thermodynamic functions and kinetic parameters of cytrarabine in saline and citric acid solution under 37 ℃. The results of ΔS in the dissolution process could provide solid theoretical reference for clinical trial implementation and understanding[9,10].

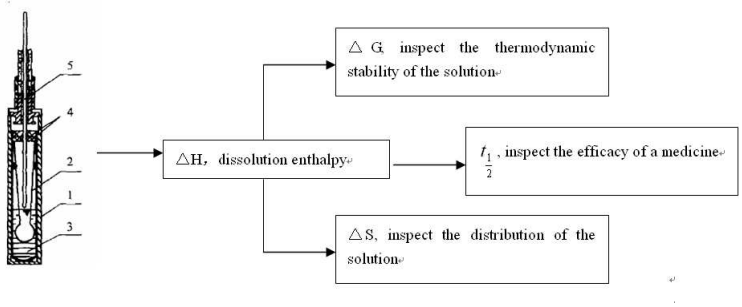
EXPERIMENTAL SECTION

1.1 *Materials*

Cytarabine (99%). Normal saline (medical purity). Electronic scale (Mianyang CAEP Thermal Analysis Instrument Company, China). The microcalorimeter was calibrated by Joule effect and its sensitivity was 64.22±0.04 μV·mW-1 at 309.65 K. The enthalpy of dissolution of KCl (spectrum purity) in distilled water (about 20 mg/2.00 g) measured at 298.15 K was 17.535 kJ·mol-1, which kJ·mol-1, which was consistent with the value 17.536 kJ·mol-1 reported in literature, and this can demonstrate that the was consistent with the value 17.536 kJ·mol-1 measurement of enthalpy in this work was reliable.

1.2 *Experimental Methods*

15.04 mg, 17.49 mg, 19.97 mg, 22.57 mg and 24.96mg cytarabine (grinded to fine powders and screened by 200-mesh sieve) were dissolved in the same volume (1.5 mL) saline solvent, respectively. The enthalpy change was detected by RD496-2000 Calvet Microcalorimeter. The whole process is given as follow:



RESULTS AND DISCUSSION

2.1 *Thermochemical behaviors of dissolution of Cytarabine*

The dissolution of cytarabine in saline and citric acid solution was endothermic process under 309.65 K. The heat flow curve is shown in Fig.1,2.

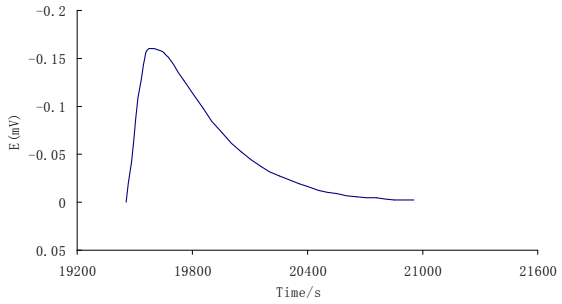


Fig.1 Thermal rate of the entire dissolution process of Cytarabine in Citric acid solution

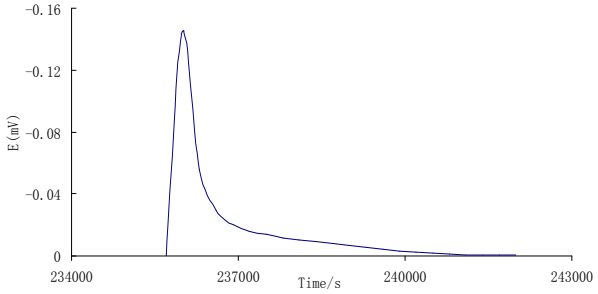


Fig.2 Thermal rate of the entire dissolution process of Cytarabine in normal saline

The enthalpies of different mass of cytarabine in 1.50 ml normal saline and citric acid are given in Table 1,2.

Table 1. The dissolution enthalpy of Cytarabine in normal saline

Sample mass/mg	n/(×10^{-3}mol)	Q/mJ	$\Delta_{so}H_m$/(J·mol^{-1})	r
15.04	0.0618	-1258.6	-20353	0.9993
17.49	0.0719	-1481.1	-20596	0.9994
19.97	0.0821	-1679.1	-20449	0.9994
22.57	0.0928	-1885.1	-20313	0.9995
24.96	0.1026	-2082.9	-20296	0.9998
Average			-20401	

Table 2. The dissolution enthalpy of Cytarabine in citric acid solution

Sample mass/mg	n/(×10^{-3}mol)	Q/mJ	$\Delta_{so}H_m$/(J·mol^{-1})	r
9.99	0.0411	-220.9	-5378	0.9995
14.99	0.0616	-335.8	-5448	0.9997
20.04	0.0824	-452.3	-5489	0.9994
25.04	0.1030	-551.7	-5359	0.9995
29.98	0.1233	-668.3	-5421	0.9997
Average			-5419	

1.2, the heat adsorption increases as the cytarabine quality increases, but the molar enthalpy remains constant, therefore the average of molar enthalpy calculated under different mass can be used as the infinite dilution molar enthalpy of cytarabine in saline or citric acid. Obviously, the relationship between different mass of cytarabine and thermal effect can be represented in Figure 3.4, and the molar enthalpy can be calculated as -5.408 kJ·mol^{-1} and -20.058 kJ·mol^{-1}, respectively.

Q = -5406.7n – 1.0577 (1)

Q = -20030n –29.766 (2)

2.2 ***Kinetic of dissolution process of Cytarabine***

Based on the experimental data (Tables 1, 2), the kinetic equation can be represented as (3)

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t}=kf(\alpha) \tag{3}$$

According to the cytarabine dissolution rate, a can be replaced by H_t/H_0 and the new equation is given in Eq.(4)

$$\ln[\frac{1}{H_0}(\frac{dH}{dt})_i]=\ln k+n\ln[1-(\frac{H_t}{H_0})_i] \qquad i=1,2,\cdots,L \tag{4}$$

The reaction rate constant *k* and the reaction order *n* can be calculated by H_t and H_0 at time *t*.

Based on the figure of Eq. (4), the slope and intercept can be calculated, and results generated from different n are given in table 3, where the slope is the reaction order n with intercept ln*k*.

Table 3 slope and intercept of different concentrations in normal saline

Sample amount/ mg	*n*	*k* / s^{-1}	r
19.97	1.1314	1.78×10^{-4}	0.9997
17.49	0.9676	2.15×10^{-4}	0.9998
24.96	1.1414	1.69×10^{-4}	0.9996
15.04	0.9452	1.76×10^{-4}	0.9997
22.57	0.9283	1.89×10^{-4}	0.9997
Average	1.0228	1.85×10^{-4}	

Table 4 slope and intercept of different concentrations in citric acid solution

Sample amount/ mg	*n*	*k* / s^{-1}	r
9.99	0.9675	2.66×10^{-4}	0.9999
14.99	0.8865	2.78×10^{-4}	0.9998
20.04	0.8406	2.35×10^{-4}	0.9999
25.04	0.8177	2.74×10^{-4}	0.9999
29.98	1.0406	2.27×10^{-4}	0.9998
Average	0.9146	2.56×10^{-4}	

Based on the data, the kinetic equation of cytosine arabinoside in saline at 309.65K can be calculated by Eq.(5) where the reaction order *n* is 1.02 and *k* is $10^{-1.85}$:

$$\frac{da}{dt} = 10^{-1.85}(1-a)^{1.02} \tag{5}$$

Based on Eq.(5), the dissolution can be regarded as a pseudo first order reaction, and the half-life of first-order reaction is given in Eq.(6)

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

The half-life of dissolution process of is $t_{\frac{1}{2}}$ = 62. 45min.With the same calculation, the half-life of dissolution in citrate solution is $t_{\frac{1}{2}}$ = 45.12min

2.3 *The dissolution process*

Based on the experimental data and calculated results, the $\Delta_{sol}S_m$ in dissolution process can be calculated by Eq. (7) [11]:

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

Equation (7) can be converted as (8):

$$\ln\frac{k \cdot h}{k_B \cdot T} = \frac{\Delta_{sol} S_m}{R} - \frac{\Delta_{sol} H_m}{R \cdot T} \tag{8}$$

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

Substituting k_B = 1.38×10^{-23} J K^{-1}, h = 6.626×10^{-34} J s^{-1}, $\Delta_{sol}H_m$ =-20.40 kJ mol^{-1} 、-5.419 kJ mol^{-1}into Eq.(8) and Eq.(9) , the $\Delta_{sol}S_m$ =-250.79 J·mol-1·K^{1}、-299.09J·mol-1·K^{1}。$\Delta_{sol}G_m$ =57.26 kJ mol^{-1} 、87.20 kJ mol^{-1} can be generated

2.4 *Energy changes in dissolution process*

The drug is generally divided into two physical state, i.e. solid and liquid. The problem of liquid-drug manufacturing is the solvent selection, which requires fully understand about the activation energy variation in dissolution process. Based on the Arrhenius equation (10):

$$\ln k = -\frac{E}{RT} + C \tag{10}$$

Based on Eq. (10), the activation energy of dissolution process can be calculated, and such information could be used to understand the dissolution process and determine the suitable solvent. For this study, the saline and lemon acid solution were used as the solvent, and the activation energy of cytarabine in citric acid and saline solution are calculated as E=28.24 kJ· mol^{-1} and 23.21 kJ·mol^{-1}, respectively.

CONCLUSION

1. The melting heat of cytarabine in saline and citric acid were -20.40 kJ·mol^{-1}and -5.42 kJ·mol^{-1}; the half-life were 62.45 min and 45.12 min that are consistent with the literature.
2. Dissolving entropy cytarabine in saline and citric acid solution were -250.792 J· k^{-1} mol^{-1} and -299.09 J·k^{-1}·mol^{-1}, the completely dissolved cytarabine in saline solution would be more stable.

3. The activation energy in DMSO, physiological saline and citric acid solution are 45.16 kJ·mol^{-1}, 28.45 kJ·mol^{-1} and 23.21 kJ·mol^{-1}, respectively. The dissolution behaviors of cytarabine in different solutions are different, e.g. chemical reaction was occurred in DMSO, and dispersion behavior was observed in saline and citric acid.

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