Study on the Stability of Salicin in the Dissolution Process

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Salicin's dissolution behaviour in saline solution were studied by a micro-calorimetric method. The measured integral and differential heat of solution ($\Delta_{sol}H_m$ and $\Delta_{dif}H_m$)were used to build equations of the solute and the heat, so that dissolution thermodynamic equations $\Delta_{sol}H_m$, $\Delta_{sol}G_m$ and $\Delta_{sol}S_m$ were achieved. The current study provides theoretical bases for clinical applications of salicin.

Key Words: Salicin, Thermodynamic, Kinetics, Saline solution.

INTRODUCTION

Salicin, is widely found in the bark and leaves of Salix and Populus, especially in willow[1]. It has a high medicinal value[2], especially has a good effect on the antipyretic, analgesic[3] and rheumatoid arthritis[4], *etc.* However, the literatures have carried out only from the extraction[5], medicinal mechanism and the precursor compounds[6]. Its thermodynamics were rarely reported. Therefore, we studied the process of salicin dissolved in saline solution using micro-calorimetry. This method was used to investigate the dissolution thermal change of drugs in variety solvents. We can understand the distribution and the thermodynamic stability of this system from $\Delta_{sol}S_m$ of the dissolution process. Thus, it has an important significance to enhance the quality of medicines and the clinical by studying its thermodynamic functions, determine the kinetic parameters.

EXPERIMENTAL

Salicin samples with various masses were measured and dissolved in 1.50 mL of 0.9 % saline under the atmospheric pressure and at certain temperatures. The RD496-2000 micro-calorimeter was used to monitor thermodynamic enthalpy changes. 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 g) measured at 298.15 K was 17.535 kJ mol^{-1}, which was in an accordance with the literature value 17.536 kJ mol^{-1} [7], showing that the device of measuring the enthalpy used in this work was reliable.

RESULTS AND DISCUSSION

Thermodynamic dissolution behaviour of salicin in saline. Based on the method given in experimental section, the disso-

lution curve of salicin in saline solution under the atmospheric pressure at 298.15 K were shown in Fig. 1.
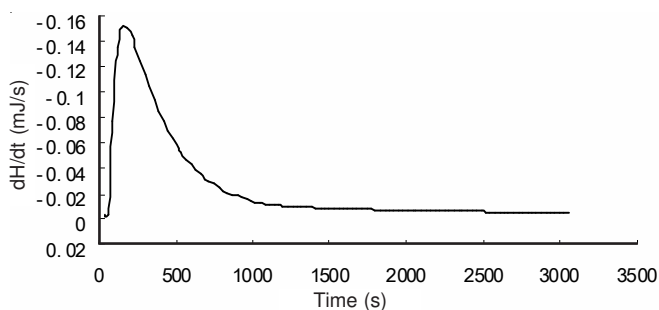

Fig. 1. Heating rate (dH/dt) of the entire dissolution process of salicin in 1.50 mL normal saline

For the discussion convenience, the released heats during these dissolution processes were listed in Table-1.

TABLE-1
DISSOLUTION ENTHALPY OF SALICIN
IN 1.50 mL SALINE SOLUTION

m/mg	n/10^{3}mol	Q/J	ΔH/kJ mol^{-1}
11.20	0.039	-0.52	-13.29
16.60	0.058	-0.80	-13.80
25.39	0.089	-1.20	-13.53
26.59	0.093	-1.25	-13.46
32.58	0.114	-1.45	-12.74
40.49	0.141	-1.82	-12.87
Average			-13.28 ± 0.4

Table-1 shows that the increasing mass of salicin led to increasing released heats, but kept the molar enthalpy ($\Delta_{sol}H_m$) constant. So the average of molar enthalpies from different

masses, which is -13.28 kJ mol^{-1} can be considered as the molar enthalpy ($\Delta_{sol}H_m$) in the infinitely diluted saline solution at 298.15 K[8].

The heat effect *vs* the amount of the substance relationships of salicin in normal saline is shown in Fig. 2.
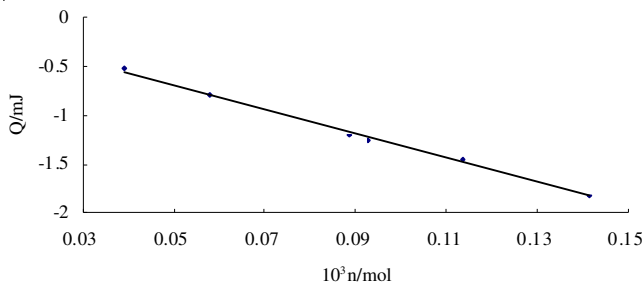

Fig. 2.   Linear relationship between the heat effect (Q) and the amount of the salicin (n)

The linear equation for the normal saline is as follows:

$$Q = -12.482n - 0.0627 \quad r = 0.9981 \tag{1}$$

where, r is correlation coefficient.

The differential enthalpy ($\Delta_{dif}H_m$) is obtained from the eqn. (1). So the differential enthalpy of salicin in normal saline is about -12.54 kJ mol^{-1}.

Kinetic of dissolution process of salicin in normal saline: Table-2 shows the original data in dissolution process of salicin in saline solution, the kinetic equation eqn. (2)[9] describing the dissolution of salicin in saline solution is chosen as the model function to describe the dissolution rate.

$$\frac{d\alpha}{dt} = kf(\alpha) \tag{2}$$

and then substituting $\alpha = \dfrac{H_t}{H_0}$ into the eqn. (2) and then get a logarithmic converter:

$$\ln\left[\frac{1}{H_0}\left(\frac{dH}{dt}\right)_i\right] = \ln k + n\ln\left[1 - \left(\frac{H_t}{H_0}\right)_i\right] \quad i = 1,2,......,L \tag{3}$$

In these equations, α is the conversion degree; f(α) is the kinetic function; H_t represents the heat at time of t; H_0 is the heat of the whole process; k is the rate of salicin dissolved in saline solution and n is the reaction order, L is the counting number. By substituting the data taken from Table-2, (dH/dt)$_i$,(H/H$_\infty$)$_i$, H$_\infty$, i = 1, 2, …, L, into the kinetic eqn. (3), the obtained values of n and lnk are listed in Table-3.

Substituting the values of n and k in Table-3 into eqn. (2), we can get that the kinetics equation of the dissolution process is $\dfrac{d\alpha}{dt} = 10^{-3.61}(1-\alpha)^{1.74}$.

Calculation of thermodynamic functions: Thermodynamic relation is shown as:

$$\Delta G_{\neq} = -RT\ln k^{\neq}$$

$$k = \frac{RT}{Nh}k^{\neq}$$

and then

$$\Delta G_{\neq}^{\theta} = RT\ln[\frac{RT}{Nhk}]$$

$$k = \frac{RT}{Nh}e^{-\Delta G_{\neq}^{\theta}/RT} = \frac{RT}{Nh}e^{(T\Delta S_{\neq}^{\theta}-\Delta H_{\neq}^{\theta})/RT} = \frac{RT}{Nh}e^{\Delta S_{\neq}^{\theta}/R}e^{-\Delta H_{\neq}^{\theta}/RT}$$

then,

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

$$\ln\frac{k \cdot h}{k_B \cdot T} = \frac{\Delta_{sol}S_m}{R} - \frac{\Delta_{sol}H_m}{RT} \tag{4}$$

Substituting k = 10$^{-3.61}$ s^{-1}, k$_B$ = 1.38 × 10^{-23} J·K^{-1}, h = 6.626 × 10^{-34} Js^{-1}, R = 8.314 J mol^{-1} K^{-1}, $\Delta_{sol}H_m$ = -13.28 kJ mol^{-1}, T = 298.15 K into eqn. (4), so $\Delta_{sol}S_m$ = -358.45 J mol^{-1} K^{-1}.

Under the isothermal conditions, the dynamic equation is

$$\Delta_{sol}G_m = \Delta_{sol}H_m - T \cdot \Delta_{sol}S_m \tag{5}$$

So the free energy is calculated, which is 93.59 kJ mol^{-1}.

TABLE-2
ORIGINAL DATA OF SALICIN IN 1.50 mL NORMAL SALINE

m/mg	t/s	dH/dt (mJ s^{-1})	H$_t$/mJ	H$_t$/H$_0$	H$_\infty$/kJ mol^{-1}
11.2	0	-0.041	-75.5	0.146	-13.29
	30	-0.039	-94.4	0.183	
	60	-0.037	-112.5	0.218	
	90	-0.035	-129.7	0.251	
	120	-0.033	-145.8	0.282	
	150	-0.031	-160.8	0.311	
	180	-0.029	-174.8	0.339	
	210	-0.027	-187.9	0.364	
	240	-0.025	-200.1	0.388	
	270	-0.024	-211.5	0.410	
	300	-0.022	-222.3	0.431	
	330	-0.021	-232.4	0.450	
	360	-0.020	-242.0	0.469	
	390	-0.019	-251.1	0.486	
	420	-0.018	-259.7	0.503	
	450	-0.017	-267.9	0.519	
16.6	0	-0.082	-390.0	0.488	-13.80
	40	-0.070	-438.2	0.548	
	80	-0.061	-479.2	0.600	
	120	-0.051	-514.8	0.644	
	160	-0.045	-545.0	0.682	
	200	-0.038	-571.2	0.715	
	240	-0.033	-593.4	0.743	
	280	-0.028	-612.3	0.766	
	320	-0.024	-628.7	0.787	
	360	-0.021	-642.9	0.805	
	400	-0.018	-655.0	0.820	
	440	-0.016	-665.5	0.833	
	480	-0.014	-675.0	0.845	
25.39	0	-0.114	-470.7	0.394	-13.53
	30	-0.104	-522.2	0.437	
	60	-0.094	-559.0	0.467	
	90	-0.085	-601.3	0.503	
	120	-0.077	-639.5	0.535	
	150	-0.069	-674.1	0.564	
	180	-0.063	-705.3	0.590	
	210	-0.057	-733.6	0.613	
	240	-0.052	-759.2	0.635	
	270	-0.047	-782.5	0.654	
	300	-0.043	-803.7	0.672	

m/mg	t/s	dH/dt(mJ s⁻¹)	H_t/mJ	H_t/H_0	H_∞/kJ mol⁻¹
	330	-0.039	-823.0	0.688	
	360	-0.036	-840.7	0.703	
	390	-0.033	-856.7	0.716	
	420	-0.030	-871.4	0.729	
	450	-0.027	-884.8	0.740	
	480	-0.025	-897.1	0.750	
26.59	0	-0.138	-430.4	0.345	-13.46
	40	-0.123	-492.9	0.396	
	80	-0.109	-546.0	0.438	
	120	-0.095	-610.2	0.490	
	160	-0.083	-666.4	0.535	
	200	-0.072	-715.4	0.574	
	240	-0.063	-768.1	0.616	
	280	-0.055	-795.3	0.638	
	320	-0.048	-827.8	0.664	
	360	-0.042	-856.2	0.687	
	400	-0.037	-881.2	0.707	
	440	-0.033	-903.3	0.725	
	480	-0.029	-922.9	0.741	
	520	-0.026	-940.4	0.755	
32.58	0	-0.182	-295.0	0.203	-12.74
	40	-0.170	-366.3	0.252	
	80	-0.152	-448.0	0.308	
	120	-0.134	-538.4	0.370	
	160	-0.117	-607.6	0.418	
	200	-0.101	-676.4	0.465	
	240	-0.088	-735.9	0.506	
	280	-0.075	-787.3	0.541	
	320	-0.065	-841.5	0.579	
	360	-0.056	-879.4	0.605	
	400	-0.048	-922.1	0.634	
	440	-0.041	-960.3	0.660	
	480	-0.036	-984.6	0.677	
40.49	0	-0.156	-997.0	0.549	-12.87
	40	-0.136	-1089.0	0.600	
	80	-0.117	-1168.7	0.644	
	120	-0.102	-1237.6	0.682	
	160	-0.088	-1297.2	0.715	
	200	-0.076	-1348.7	0.743	
	240	-0.066	-1393.2	0.768	
	280	-0.057	-1431.8	0.789	
	320	-0.049	-1465.3	0.807	
	360	-0.043	-1494.3	0.823	
	400	-0.037	-1519.4	0.837	
	440	-0.032	-1541.0	0.849	
	480	-0.027	-1559.6	0.859	

TABLE-3
n AND ln *k* OF SALICIN IN SALINE SOLUTION
(0.9 %) AT 298.15 K

m/mg	n	ln k/s⁻¹	r
11.20	1.57	-9.17	0.9969
16.60	1.51	-8.11	0.9943
25.39	1.85	-8.25	0.9913
26.59	1.96	-8.11	0.9942
32.58	1.80	-8.49	0.9927
40.49	1.72	-7.80	0.9923
Average	1.74	-8.32	

Conclusion

The calorimetric method has been successfully used to achieve salicin's $\Delta_{sol}H_m$, $\Delta_{sol}S_m$, $\Delta_{sol}G_m$, and thermal dynamic equation of the dissolution process. All of these information provide evidence for clinical applications of this medicine. From the results it can be observed that the concentration of salicin have little impact to the enthalpies. Thus, the average value of $\Delta_{sol}H_m$ can represent the molar enthalpy, which is -13.28 kJ mol⁻¹.

The kinetic equation of the dissolution process of salicin in saline solution at 298.15 K is $\frac{d\alpha}{dt} = 10^{-3.61}(1-a)^{1.74}$, the rate constant k = 10⁻³·⁶¹ s⁻¹.

The dissolution of salicin in saline solution is of an endothermic process. The molar enthalpy ($\Delta_{sol}H_m$) is -13.28 kJ mol⁻¹ and $\Delta_{sol}S_m$ is -358.45 J mol⁻¹ K⁻¹. The negative value of entropy of activation indicates that the dissolution of salicin in saline solution get a more ordered system.

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