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RESEARCH ARTICLE

A mathematical model for calculating the shelf life of ascorbic acid solution under given conditions

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Abstract

The objective of this paper is to calculate the shelf life of ascorbic acid solution under given conditions by using a mathematical model. An antioxidant, sodium metabisulfite, was added to the ascorbic acid solution. The kinetic parameters of the degradation reaction of ascorbic acid and sodium metabisulfite, were investigated, respectively, and then a mathematical model was developed. According to the mathematical model, the calculated shelf lives of ascorbic acid solution were 783, 835, 873, and 885 days for specifications 2, 5, 10, and 20 mL, respectively. The results showed that the obtained mathematical model can be used to calculate the shelf life of ascorbic acid solution under given conditions.

Keywords: Reaction order, rate constant, dissolved oxygen, sodium metabisulfite, kinetic parameters, drug stability

Introduction

Drug stability refers to the capacity of a drug substance of product to remain within established specification of identity, strength quality, and purity in a specified period of time-shelf life. Estimation of product shelf life is done by two methods–estimate from data obtained under the same conditions as those that the final product is expected to withstand and estimate from tests conducted under accelerated conditions[1–5]. The 1987 Stability Guidelines state that "It is also suggested that the following conditions be evaluated in stability studies on solutions or suspensions of the bulk drug substances.... High oxygen atmosphere"[6]. This indicates that oxygen is one of the factors that affect the stability of drug, especially the drug solution.

Often, the effect of oxygen on the stability of oxygen-sensitive drug solution can be eliminated by the addition of antioxidants[7–9]. The kinetics of the oxidation of oxygen-sensitive drug can be affected by the availability of oxygen[10]. That is, the shelf life of oxygen-sensitive drug solution will be different for different specifications because the residual content of oxygen is different in different specification containers. Therefore, to estimate the shelf life of different specification drug solutions, retest is necessary. But this is time-consuming.

We think there is a mathematical equation by which the shelf life of oxygen-sensitive drug solution with different specifications can be calculated provided the kinetic parameters of drug and antioxidant were known. Thus we only need to obtain the kinetic parameters of drug and antioxidant, the shelf life of different specifications of drug solution can be calculated.

To validate our hypothesis, ascorbic acid and sodium metabisulfite were used as a model drug and a model antioxidant, respectively. The kinetic parameters of the degradation reactions of ascorbic acid under both anaerobic and aerobic conditions and sodium metabisulfite, were investigated, respectively, and then a mathematical model was developed. According to the obtained mathematical model, the shelf lives of different specifications of ascorbic acid solution were calculated. The significance of this work is that it made the estimation of shelf life of ascorbic acid solution under given conditions simple and time-saving.

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Materials and methods

Apparatus and reagents

An isothermal heating oven with high precision (The accuracy, precision, and reproducibility of temperature are ≤0.5°C in the range of room temperature to 100°C, self-made), two electromagnetic vibratory air pumps (HP-201, Zhejiang, China), a pH meter (Delta-320, Shanghai, China), and a Fortin type mercurial barometer (the accuracy is ±0.2 mmHg, Jiaxing, China) were used.

Ascorbic acid (Chengdu Tianhua Co. Ltd., it contains ≥99.7% of $C_6H_8O_6$), sodium metabisulfite (Tianjin Bodi Co. Ltd., it contains ≥96.0% of $Na_2S_2O_5$) were used. The other reagents were all analytical grade.

Methods

Preparation of 10% ascorbic acid solution

A 50 g quantity of ascorbic acid was dissolved in distilled water and 150 mg of Na_2-EDTA was added to avoid the effect of metal ion on the oxidation rate of ascorbic acid. The solution was adjusted with saturated NaOH to pH6.8 and then was diluted with distilled water to a total volume of 500 mL.

Preparation of 0.2% sodium metabisulfite solution

A 0.2 g quantity of sodium metabisulfite and 30 mg of Na_2-EDTA were dissolved in distilled water. The solution was adjusted with saturated NaOH to pH6.8 and then was diluted with distilled water to a total volume of 100 mL.

Preparation of mixed solution of 10% ascorbic acid and 0.2% sodium metabisulfite

A 50 g quantity of ascorbic acid, 0.15 g of Na_2-EDTA and 1.0 g of sodium metabisulfite were dissolved in distilled water. The solution was adjusted with saturated NaOH to pH6.8 and then was diluted with distilled water to a total volume of 500 mL.

Assays

Measurement of ascorbic acid

A 5 mL aliquot of ascorbic acid solution was placed in a 100 mL stoppered flask. Then 15 mL distilled water and 4 mL 0.6% diluted acetic acid were added, then titrated with 0.05865 mol l^{-1} iodine solution using starch as indicator. A blank titration was run under identical conditions.[11]

Measurement of sodium metabisulfite

A 10 mL aliquot of sodium metabisulfite solution was placed in a 100 mL stoppered flask. A 5 mL aliquot of 0.05865 mol·l^{-1} iodine solution and 1 mL hydrochloric acid were added. The flask was stoppered and kept in dark for 5 min. Then the sodium metabisulfite was titrated with 0.01746 mol·l^{-1} sodium thiosulphate using starch as indicator. A blank titration was run under identical conditions.

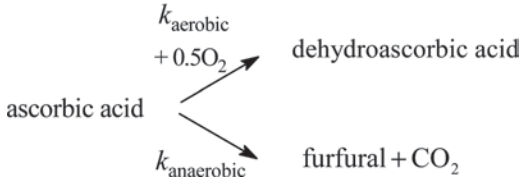
Measurement of ascorbic acid in the mixed solution

A 5 mL aliquot of sample solution was placed in a 100 mL stoppered flask. Then 20 mL distilled water and 2 mL acetone were added. The flask was stoppered and kept in dark for 5 min. Then 2 mL 0.6% of diluted acetic acid was added, and titrated with 0.05865 mol·l^{-1} iodine solution using starch as indicator. A blank titration was run under identical conditions.

Results and discussion

Determination of the degradation kinetic parameters of ascorbic acid

It is reported that the degradation of ascorbic acid follows a reaction network that consists of two parallel reactions, aerobic and anaerobic degradation[12,13]:



The degradation rate equation of ascorbic acid under anaerobic and aerobic conditions can be expressed as following, respectively:

$$\frac{d\Delta c_{A,anaerobic}}{dt} = k_{A,anaerobic} c_A^{\alpha} \quad (1)$$

$$\frac{d\Delta c_{A,aerobic}}{dt} = k_{A,aerobic} c_A^{\beta} c_{O_2,d}^{\gamma} \quad (2)$$

where $k_{A,anaerobic}$ and $k_{A,aerobic}$ are rate constants of ascorbic acid under anaerobic and aerobic conditions, respectively; $\Delta c_{A,anaerobic}$ and $\Delta c_{A,aerobic}$ are concentration drops of ascorbic acid under anaerobic and aerobic conditions, respectively; c_A and $c_{O_2,d}$ are the residual concentrations of ascorbic acid and the dissolved oxygen at time t, respectively; α is the reaction order with respect to ascorbic acid under anaerobic condition; β and γ are the reaction orders with respect to ascorbic acid and oxygen, respectively, under aerobic condition.

Determination of the reaction order (α) and rate constant ($k_{A,anaerobic,\ 25°C}$) for the anaerobic degradation of ascorbic acid

Since the anaerobic degradation rate of ascorbic acid is very slow at temperature 25°C, $k_{A,anaerobic,\ 25°C}$ was estimated based on the experimental data at temperatures 55, 65, 75 and 85°C. The ascorbic acid solution used in the experiment was the same as that mentioned in the section "Preparation of 10% ascorbic acid solution" except that the water used was previously boiled to remove O_2 and cooled to ambient temperature. The solution was fully filled into 10-mL glass bottles before the bottles were sealed. Then the bottles were incubated at temperatures 55, 65, 75, and 85°C, respectively, in a high precision isothermal heating oven. Three bottles were taken out of the oven at specific intervals of time, cooled, and the residual concentrations of the ascorbic acid were measured iodometrically. The results are listed in Table 1. By plotting c_A against t, straight lines were obtained as

Table 1. The residual concentrations of ascorbic acid under anaerobic condition at 55°C, 65°C, 75°C and 85°C.

55°C		65°C		75°C		85°C	
t/h	c/(mol·l^{-1})	t/h	c/(mol·l^{-1})	t/h	c/(mol·l^{-1})	t/h	c/(mol·l^{-1})
0	0.5655 ± 0.0007	0	0.5655 ± 0.0007	0	0.5655 ± 0.0007	0	0.5655 ± 0.0007
48.5	0.5619 ± 0.0018	24	0.5628 ± 0.0008	48	0.5286 ± 0.0018	24	0.5454 ± 0.0018
96	0.561 ± 0.0024	48.5	0.5606 ± 0.0027	82	0.5155 ± 0.0035	48.5	0.5236 ± 0.0018
145.5	0.5589 ± 0.0013	82.5	0.5537 ± 0.0024	143.5	0.4926 ± 0.0027	72.5	0.4933 ± 0.0010
203	0.5508 ± 0.0018	145.5	0.5417 ± 0.0014	178	0.4816 ± 0.0037	96	0.4694 ± 0.0018
288.5	0.5473 ± 0.0030	203	0.5314 ± 0.0015	202	0.4655 ± 0.0018	120	0.4364 ± 0.0024
384	0.5411 ± 0.0028	263.5	0.5187 ± 0.0019	239.5	0.4432 ± 0.0019	145.5	0.4118 ± 0.0036
419	0.5362 ± 0.0021	359.5	0.5126 ± 0.0013	289	0.4286 ± 0.0036	169.5	0.3922 ± 0.0058
528.5	0.5276 ± 0.0025	417	0.4975 ± 0.0024	311.5	0.4078 ± 0.0053	192.5	0.3651 ± 0.0035
672.5	0.5210 ± 0.0018	465	0.4851 ± 0.0013	359.5	0.4025 ± 0.0036	202.5	0.3560 ± 0.0054

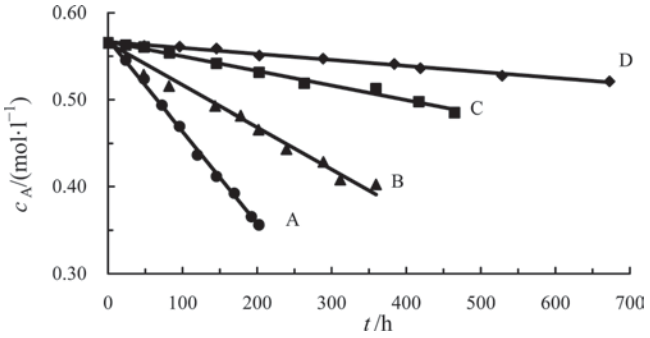


Figure 1. Relationship between c_A and t under anaerobic conditions at (A) 85°C, (B) 75°C, (C) 65°C and (D) 55°C.

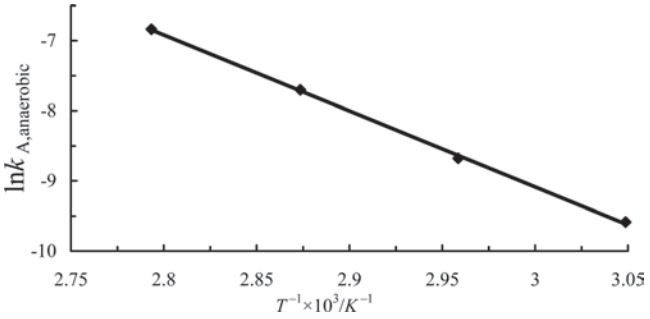


Figure 2. Relationship between $\ln k_{A,anaerobic}$ and T^{-1}.

shown in Figure 1, indicated that the anaerobic degradation is zero-order with respect to ascorbic acid, i.e. $\alpha = 0$. The rate constants at various temperatures were obtained from the slopes of the lines. By plotting $\ln k_{A,anaerobic}$ against $1/T$, a straight line with correlation coefficient $r = -0.9997$ was obtained, as shown in Figure 2 and the $k_{A,anaerobic,25°C} = 2.402 \times 10^{-6}$ (mol·l^{-1} h^{-1}) was extrapolated from the line.

Determination of the reaction order (β) with respect to ascorbic acid in aerobic degradation

To determine the value of β, dissolved oxygen concentration should be maintained constant during the reaction. Therefore, sufficient air was continually bubbled into the solution by an air pump. The experiment equipment is shown in Figure 3. It was reported that oxygen dissolution was much faster than its disappearance through the

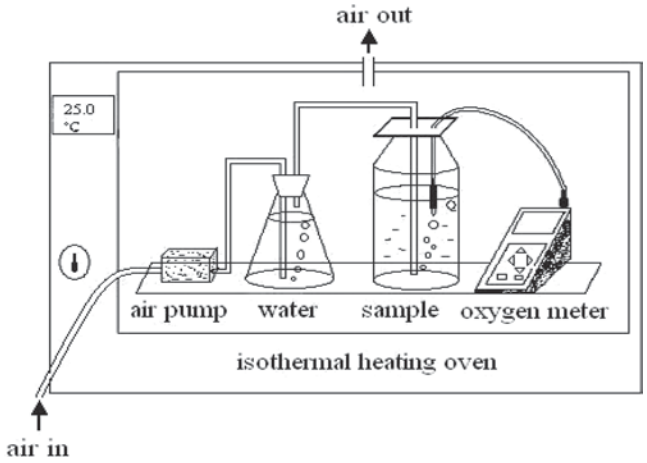


Figure 3. The assembly of the oxidative degradation and the oxygen meter.

reaction with ascorbic acid[14,15]. So was essentially constant throughout the reaction. Let

$$k_{A,apparent} = k_{A,aerobic} c_{O_2,d}^{\gamma} \quad (3)$$

Equation 1 can be rewritten as:

$$\frac{d\Delta c_{A,aerobic}}{dt} = k_{A,apparent} c_A^{\beta} \quad (4)$$

A 500 mL of 10% ascorbic acid solution was placed in a glass bottle and incubated at temperature 25°C in the high precision isothermal heating oven. Three exact volumes of 5 mL of the solution were taken out of the oven at intervals of time, and the residual concentration of the ascorbic acid was measured iodometrically. The results are listed in Table 2. Our experimental results showed that the amount of anaerobic degradation of ascorbic acid was about 0.1% of that of aerobic degradation. For simplicity we assume that anaerobic degradation was negligible compared to aerobic degradation under this condition. By plotting c_A against t, a straight line with the slope $k_{A,apparent} = 2.262 \times 10^{-3}$ and correlation coefficient $r = -0.9988$ was obtained, as shown in Figure 4, indicating that the oxidation reaction is zero-order with respect to ascorbic acid, i.e. $\beta = 0$.

Table 2. The residual concentrations of ascorbic acid under aerobic condition.

t/h	c_A/(mol·l^{-1})
0	0.5655 ± 0.0012
4	0.5582 ± 0.0016
9	0.5436 ± 0.0011
13	0.5351 ± 0.0021
18	0.5229 ± 0.0024
25.5	0.5041 ± 0.0022
33	0.4901 ± 0.0006
37.5	0.4840 ± 0.0016
42	0.4719 ± 0.0012
52	0.4475 ± 0.0006

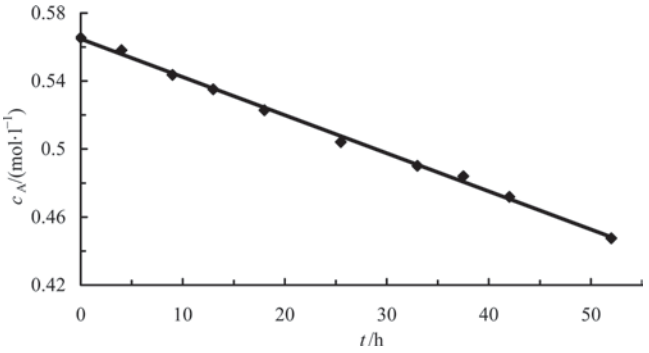


Figure 4. Relationship between c_A and t under aerobic condition.

Determination of the reaction order (γ) with respect to the dissolved oxygen in the ascorbic acid solution

To determine the reaction order with respect to the dissolved oxygen in the ascorbic acid solution, the concentration of the dissolved oxygen should not be maintained constant during the reaction. So the experiment was carried out in sealed ampoules. The concentration drop of ascorbic acid under aerobic condition is $\Delta c_{A,aerobic}$ within time t, and the concentration of oxygen consumed by ascorbic acid should be $(\Delta c_{A,aerobic})/2$ provided the molar ratio of ascorbic acid to molecular oxygen is 2:1[13]. Let n_{O_2} be the total number of moles of oxygen in the sealed ampoule at time t and n_{O_2} at initial time, respectively. So n_{O_2} is given by

$$n_{O_2} = n_{O_2,0} - \frac{1}{2} V_s \Delta c_{A,aerobic} \quad (5)$$

where V_s is the volume of solution in the sealed ampoule.

The n_{O_2} is also can be expressed as:

$$n_{O_2} = c_{O_2,d} V_s + c_{O_2,g} V_g \quad (6)$$

where c_{O_2g} is the concentration of gasiform oxygen and V_g is the volume of the headspace air in the ampoule.

Because oxygen dissolution was much faster than its disappearance through the reaction with ascorbic acid, there is equilibrium between the dissolved oxygen in the solution and the gasiform oxygen in the headspace

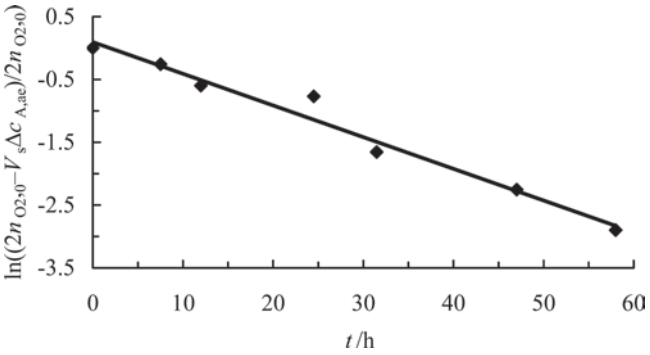


Figure 5. Relationship between $\ln\left(\left(2n_{O_2,0} - V_s \mathrm{D} c_{A,aerobic}\right)/2n_{O_2,0}\right)$ and t.

air. The ratio of $c_{O_2,d}$ to $c_{O_2,g}$ is a constant K according to Henry's law:

$$\frac{c_{O_2g}}{c_{O_2,d}} = K \quad (7)$$

The atmospheric pressure is about 720 mmHg, i.e. 0.9474 atm, measured by a Fortin type mercurial barometer in Chengdu. The concentration of dissolved oxygen $c_{O_2,d}$ is 2.58×10^{-4} mol·l^{-1} at 1 atm and should be 2.444×10^{-4} mol·l^{-1} at 0.9474 atm according to Henry's law. The calculated value of the concentration of gasiform oxygen $c_{O_2,g}$ is 8.135×10^{-3} mol·l^{-1} at 0.9474 atm according to the ideal-gas law: $pv = nRT$, and the value of K is 33.29 according to Equation 7.

Combining equations 5–7 yields:

$$c_{O_2,d} = \frac{n_{O_2,0} - \frac{1}{2}\Delta c_{A,aerobic} V_s}{V_s + K V_g} \quad (8)$$

Substituting Equation 8 and $\beta = 0$ into Equation 1 yields:

$$\frac{\mathrm{d}\Delta c_{A,aerobic}}{\mathrm{d}t} = k_{A,aerobic}\left(\frac{n_{O_2,0} - \frac{1}{2}\Delta c_{A,aerobic} V_s}{V_s + K V_g}\right)^{\gamma} \quad (9)$$

It was reported that the oxidation reaction was first order with respect to the concentration of oxygen in the ascorbic acid solution[12,16]. So substituting $\gamma = 1$ into Equation 9, after integrating yields:

$$\ln\left(\frac{2n_{O_2,0} - V_s \Delta c_{A,aerobic}}{2n_{O_2,0}}\right) = -\frac{k_{A,aerobic} V_s}{2\left(V_s + K V_g\right)} t \quad (10)$$

By plotting $\ln\left[\left(2n_{O_2,0} - V_s \Delta c_{A,aerobic}\right)/2n_{O_2,0}\right]$ against t, a straight line with correlation coefficient $r = -0.9911$ was obtained, as shown in Figure 5. For comparison, zero- and second-order oxidation reaction rate plots with correlation coefficients $r = -0.9301$ and $r = -0.9288$ were constructed for the experimental data, respectively. This

indicates that the experimental result is in good agreement with the reported one.

Determination of the kinetic parameters of oxidation reaction of sodium metabisulfite

The reaction equation of sodium metabisulfite with molecular oxygen can be expressed as[15]:

$$S_2O_5^{2-} + O_2 + H_2O \rightarrow 2SO_4^{2-} + 2H^+$$

The oxidation rate equation of sodium metabisulfite can be expressed as:

$$\frac{d\Delta c_B}{dt} = k_B c_B^{\delta} c_{O_2,d}^{\lambda} \quad (11)$$

where k_B is the rate constant for the oxidation of sodium metabisulfite; Δc_B and c_B are the concentration drop and residual concentrations of sodium metabisulfite, respectively; δ and λ are the reaction-order with respect to sodium metabisulfite and the dissolved oxygen, respectively.

Determination of δ, the reaction order of sodium metabisulfite

The same procedure that mentioned in the section "Determination of the reaction order (β) with respect to ascorbic acid in aerobic degradation" was applied to determine the value of δ. Let

$$k_{B,apparent} = k_B c_{O_2,d}^{\lambda} \quad (12)$$

Equation 11 can be rewritten as:

$$\frac{d\Delta c_B}{dt} = k_{B,apparent} c_B^{\delta} \quad (13)$$

A 500 mL of 0.2% sodium metabisulfite solution was placed in a glass bottle and incubated at temperature 25°C in the high precision isothermal heating oven. Three exact volumes of 10 mL of the solution were taken out of the oven after each incubation and the residual concentrations of the sodium metabisulfite were measured iodometrically. The results are listed in Table 3. By plotting c_B against t, a straight line with the slope $k_{B,apparent} = 1.118 \times 10^{-4}$ and correlation coefficient $r = -0.9956$ was obtained, as shown in Figure 6, indicating that the oxidation reaction is zero order with respect to sodium metabisulfite, i.e. $\delta = 0$.

Determination of λ, reaction order of dissolved oxygen in the sodium metabisulfite solution

The same procedure that mentioned in the section "Determination of the reaction order (α) with respect to the dissolved oxygen in the ascorbic acid solution" was applied to determine the value of λ. A 15 mL of 0.2% sodium metabisulfite solution was filled into 20-mL (labeled) ampoules and the ampoules were sealed. The headspace air in the ampoule was about 12 mL. Then the ampoules were incubated at temperature 25°C in the high precision isothermal heating oven. Three ampoules were taken out of the oven after each incubation and the residual concentrations of ascorbic acid were measured iodometrically. The results are listed in Table 4.

Table 3. The residual concentrations of sodium metabisulfite under aerobic condition.

t/h	$c \times 10^2$/(mol·l^{-1})
0	1.052 ± 0.0021
4	1.010 ± 0.0080
7.5	0.9612 ± 0.0044
9.5	0.9413 ± 0.0022
16	0.8482 ± 0.0038
20	0.8438 ± 0.0022
24	0.7973 ± 0.0038
28	0.7176 ± 0.0044
32	0.6821 ± 0.0044
40	0.6113 ± 0.0050

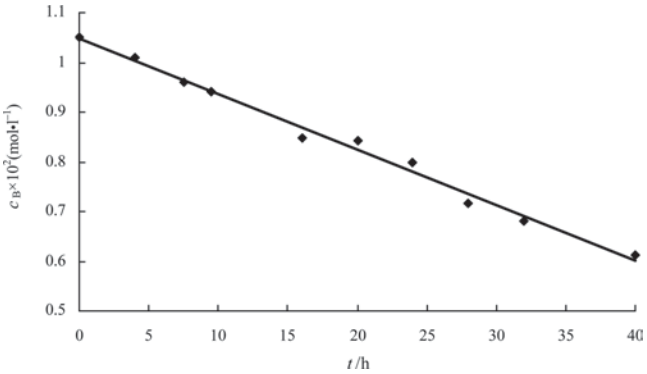


Figure 6. Relationship between c_B and t.

The concentration drop of sodium metabisulfite is Δc_B within time t, and the concentration of oxygen consumed by sodium metabisulfite should be Δc_B provided the molar ratio of sodium metabisulfite to molecular oxygen is 1:1[15]. Then n_{O_2} in the sodium metabisulfite solution can be expressed as:

$$n_{O_2} = n_{O_2,0} - \Delta c_B V_s \quad (14)$$

Combining equations 6, 7, 14 yields:

$$c_{O_2,d} = \frac{n_{O_2,0} - \Delta c_B V_s}{V_s + K V_g} \quad (15)$$

Substituting $\delta = 0$ and Equation 15 into Equation 11 yields:

$$\frac{d\Delta c_B}{dt} = k_B \left(\frac{n_{O_2,0} - \Delta c_B V_s}{V_s + K V_g} \right)^{\lambda} \quad (16)$$

Substituting $\lambda = 1$ into Equation 16, after integrating, the following equation can be obtained.

$$\ln\left(\frac{n_{O_2,0} - V_s \Delta c_B}{n_{O_2,0}} \right) = -\frac{k_B V_s}{V_s + K V_g} t \quad (17)$$

Table 4. The residual concentrations of sodium metabisulfite in sealed ampoules.

t/h	$c\times10^2$/(mol·l^{-1})
0	1.052 ± 0.0020
5	1.029 ± 0.0063
16	0.9925 ± 0.0021
26	0.9479 ± 0.0021
39.5	0.9224 ± 0.0064
48.5	0.8565 ± 0.0021
63	0.7999 ± 0.0014
78.5	0.8033 ± 0.0135
87.5	0.7545 ± 0.0093
111.5	0.7162 ± 0.0074

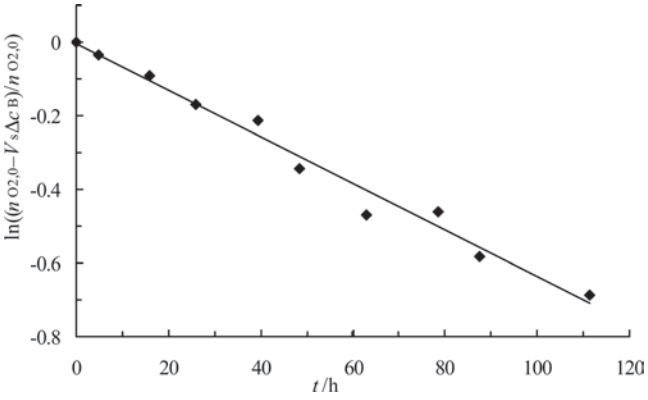


Figure 7. Relationship between $\ln\left(\left(n_{O_2,0}-V_s\Delta c_B\right)/n_{O_2,0}\right)$ t.

By plotting $\ln\left[\left(n_{O_2,0}-V_s\Delta c_B\right)/n_{O_2,0}\right]$ against t, a straight line with correlation coefficient $r=-0.9905$ was obtained, as shown in Figure 7. For comparison, zero- and second-order oxidation reaction rate plots with correlation coefficients $r=-0.9845$ and $r=-0.9888$ were constructed for the experimental data, respectively. This indicates that first-order reaction was appropriate with respect to the dissolved oxygen in the sodium metabisulfite solution, i.e. $\lambda=1$.

Rate equation for the degradation of ascorbic acid in the mixed solution of 10% ascorbic acid and 0.2% sodium metabisulfite

In the mixed solution of ascorbic acid and sodium metabisulfite, the total amount of oxygen consumed by both reductants is $\left(\frac{1}{2}\Delta c_{A,aerobic}+\Delta c_B\right)V_s$ within time t provided the two reductants consume oxygen simultaneously. Then n_{O_2} in the mixed solution can be expressed as:

$$n_{O_2}=n_{O_2,0}-\left(\frac{1}{2}\Delta c_{A,aerobic}+\Delta c_B\right)V_s \quad (18)$$

In the mixed solution the value of $c_{O_2,d}$ in Equation 1 is the same as that in Equation 11. Substituting $\beta=0$, $\gamma=1$ and $\delta=0$, $\lambda=1$ into Equation 1 and Equation 11, respectively. Then the expression of n_{O_2} can be obtained by substituting $\Delta c_B=(k_B\Delta c_A)/k_A$ into Equation 18.

$$n_{O_2}=\frac{2k_{A,aerobic}n_{O_2,0}-(k_{A,aerobic}+2k_B)\Delta c_{A,aerobic}V_s}{2k_{A,aerobic}} \quad (19)$$

Combining equations 6, 7, 19 yields:

$$c_{O_2,d}=\frac{2k_{A,aerobic}n_{O_2,0}-(k_{A,aerobic}+2k_B)V_s\Delta c_{A,aerobic}}{2k_{A,aerobic}(V_s+KV_g)} \quad (20)$$

Substituting Equation 20 and $\beta=0$ into Equation 1, after integrating yields:

$$\Delta c_{A,aerobic}=\frac{2k_{A,aerobic}n_{O_2,0}\left[1-\exp\left(\frac{-(k_{A,aerobic}+2k_B)V_s}{2(V_s+KV_g)}t\right)\right]}{V_s(k_{A,aerobic}+2k_B)} \quad (21)$$

The total concentration drop of ascorbic acid ($\Delta c_{A,total}$) is the sum of $\Delta c_{A,aerobic}$ and $\Delta c_{A,anaerobic}$. Substituting $\alpha=0$ into Equation 2 and after integrating, the expression of $\Delta c_{A,anaerobic}$ can be obtained and then combining it with Equation 21 yields:

$$\Delta c_{A,total}=\frac{2k_{A,aerobic}n_{O_2,0}\left[1-\exp\left(\frac{-(k_{A,aerobic}+2k_B)V_s}{2(V_s+KV_g)}t\right)\right]}{V_s(k_{A,aerobic}+2k_B)}+k_{A,anaerobic}t \quad (22)$$

Because it is difficult to obtain the inverse function $t=f(\Delta c_{A,total})$ of Equation 22, the shelf life of ascorbic acid under a given condition can be calculated according to Equation 22 by using successive approximation method.

Calculate the shelf life of ascorbic acid under given conditions

Shelf life is referred to as t_{90} when the lower specification limit of content is 90%. So $\Delta c_{A,total}$ can be calculated according to $\Delta c_{A,total}=\Delta c_{A,0}\times90\%$ (where $\Delta c_{A,0}$ is the concentration of ascorbic acid at initial time). Since $k_{A,aerobic}$, $k_{A,anaerobic}$ and k_B are constants and V_s, V_g and n_{O_2} can be calculated under a given condition. Therefore only t is unknown in Equation 22, and can be calculated substituting the values of $\Delta c_{A,total}$, $k_{A,aerobic}$, $k_{A,anaerobic}$, k_B, V_s, V_g and n_{O_2} into Equation 22.

There are 2, 5, 10, and 20 mL specifications ascorbic acid injection. If 2 mL mixed solution of 10% ascorbic acid and 0.2% sodium metabisulfite were filled into 2-mL ampoules, the headspace air is about 1.5 mL, and then the ampoules were sealed. The $n_{O_2}=1.269\times10^{-5}$ mol in the sealed ampoule according to equation 6. The $k_{A,aerobic}=9.255\,h^{-1}$ and $k_B=0.4574\,h^{-1}$ were obtained by substituting $c_{O_2,d}=2.444\times10^{-4}$, $\gamma=1$ and $\lambda=1$ into equations 3 and 12, respectively. Finally, the

Table 5. The relationship between shelf life and specification of ascorbic acid solution.

Specification (mL)	Shelf life (days)
2	783
5	835
10	873
20	885

calculated value of shelf life was 783 days by substituting $\Delta c_{A,total} = 0.0567$, 10% of the $c_{A,0}$, $k_{A,aerobic} = 9.255$ and $k_B = 0.4574$ into Equation 22.

Similarly, the shelf lives for 5 mL, 10 mL and 20 mL were listed in Table 5. The results showed that the shelf lives were different for different specifications of ascorbic acid injection.

The normally used method for the estimation of shelf life is under elevated temperatures. With temperature increasing, oxygen solubility in aqueous media decreased. The effect of oxygen on the degradation of oxygen sensitive drug will be decreased at elevated temperature. So the obtained rate constant of oxygen sensitive drug will be smaller than that of oxygen stable drug at elevated temperature. Therefore the extrapolated rate constant at 25°C will be decreased. However the aerobic degradation rate constant of ascorbic acid of this work was obtained at 25°C. Therefore the estimated shelf lives of ascorbic acid solution by using the normally used method will be longer than that by using the mathematical model. The shelf lives of ascorbic acid solution by using the mathematical model will be more precise.

Conclusion

The calculated values of shelf lives of ascorbic acid solution by the obtained mathematical model were 783, 835, 873, and 885 days for 2, 5, 10, and 20 mL specifications, respectively. This indicated that shelf lives of different specifications of ascorbic acid solution were different and shelf life under a given condition can be calculated, provided the kinetic parameters of ascorbic acid and antioxidant, were known. The significance of this work is: (i) it made the estimation of shelf life of ascorbic acid under given conditions simple and time-saving; (ii) it presented a method that construct a mathematical model. For other oxygen sensitive drug a similar mathematical model will be obtained by using this work presented method. If the drug only takes place aerobic degradation, the obtained mathematical model will be simpler than that this work obtained.

Declartion of interest

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