Catalytic protection of stannous ion by ascorbic acid in diphosphonic acids solutions

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Abstract The protective ability of ascorbic acid (Vc) on stannous ion and the influence of light irradiation on the stability of stannous ion in diphosphonate medium at pH=5 have been examined in order to attain minimal loss of stannous ion during the production of lyophilized radiopharmaceutical kits. The sum of stannous ion and Vc was determined with iodometric method. It was shown that the protective ability of Vc was still strong at Vc concentration much lower than that of stannous ion and the illumination by fluorescent lamp was unfavorable to the stability of stannous ion. The change of pH in the range 3~9 did not affect the action of Vc significantly.

Keywords Stability of stannous ion, Bone imaging kits, Ascorbic acid, Light irradiation

1 Introduction

Stannous ion is widely used as reductant for labeling metastable technetium in the field of nuclear medicine since early seventies[1], but it is very unstable due to the aerobic oxidation. This unstablility directly affects the labeling of technetium.[2] Although the stability of stannous ion has been extensively studied in inorganic acid solution, it is far from clear in the kit solution before lyophilization.

$SnCl_2$-HCl system is extensively studied, for stannous ion is often deliveried in the form of $SnCl_2$ or $SnCl_2 \cdot 2H_2O$ and the solution has to be acidic to avoid hydrolysis. The following factors are critical to the aerobic oxidation of stannous ion. (a) Irradiation by ultra-violet light strongly accelerates the aerobic oxidation.[3] (b) The reaction rate directly varies with the partial pressure of oxygen or the amount of dissolved oxygen.[4] (c) The reaction proceeds faster at higher concentration of stannous chloride, and the rate increases fast in low concentration range.[4] (e) High temperature (above 15°C) accelerates the reaction.[5] (f) A large number of substances are inhibitors for the aerobic oxidation of stannous ion[5~7], some of them do not change completely. (g) The oxidation rate increases with the concentration of HCl.[4] It is considered that the aerobic oxidation is a chain reaction and the active species to be oxidized is $HSnCl_3$. Kodina *et al*[8] reexamined the aerobic oxidation of stannous ion in $SnCl_2$-HCl system on the practical purpose.[8] What they are interested in is not the concentration of stannous ions but the percentage of them remained. Stannous ion is more stable at higher concentration and in more concentrated HCl medium.

The results from $SnCl_2$-HCl system help to prepare $SnCl_2$ stock solution in practical use for minimal loss of stannous ions. For kit preparation, the formulated solution containing stannous chloride, pharmaceutical ligand, and other ingredients will stand a long duration for filtration and dividing. So far, the behavior of stannous ion is not thoroughly studied in these particular system, although it has been known that various pharmaceutial ligands affect the stability of stannous ion[9] and antioxidants can also inhibit the oxidation in kits.[10] In this paper, we focus on diphosphonate system. Because the concentration and pH of the diphosphonate solution are already fixed in the optimum particular formulated kits, the amount of ascorbic acid (Vc) and light irradiation are mainly examined to choose good conditions for the preparation of these bone imaging kits.

2 Experimental

2.1 Materials

All common laboratory chemicals were reagent grade and were used without further purification. MDP($CH_2(PO_3H_2)_2$) and $SnCl_2 \cdot 2H_2O$ were purchased from

Manuscript received date: 1997-12-08

SIGMA and Aldrich, respectively. HEDP ($CH_3C(OH)(PO_3)_2HNa_3$) was prepared according to literature method. The structure and purity were confirmed by ^{1}HNMR and elemental analysis. The stock solution of I_2 (0.04975 mol/L)-KI(0.25 mol/L) for iodometric titration was standardized with 0.05 mol/L standard potassium dichromate solution. The standardization was achieved by titrating the same 0.05 mol/L $SnCl_2$ in 1 mol/L nitrogen-purged HCl solution with both I_2-KI and $K_2Cr_2O_7$ solutions, separately.

2.2 Methods

The sum of the concentrations of stannous ion and Vc was determined with ten times diluted I_2-KI standard solution by a microburette. The pH of the diphosphonate medium solution was finally adjusted to 5.00±0.10 with 1 mol/L NaOH and 1 mol/L HCl and monitored by an acidmeter.

To detect the influence of the amounts of Vc added, a series of seven 10 ml diphosphonate solutions (5.00 mg/ml) were formulated at pH=5.00, containing 0.00~10.00 mg $SnCl_2·2H_2O$ and 10.00~0.00 mg Vc. The mass ratios of $SnCl_2·2H_2O$ to Vc were 10/0, 9/1, 7/3, 5/5, 3/7, 1/9, 0/10, respectively. The diphosphonates used were HEDP, MDP and PYP ($O(PO_3)_2Na_4·10H_2O$). 1.00 ml samples were taken out from each solution at different time and were titrated by ten times diluted standard I_2-KI.

The influence of pH in the solution was examined with the solution of $SnCl_2·2H_2O$/Vc (7:3) as an example in the pH range 3~9. The amount of I_2-KI consumed was recorded versus time. The diphosphonate used was HEDP.

To observe the influence of light irradiation, the following experiment was carried out during night at a laboratory lightened by two 40 W fluorescent lamps on the ceiling. 25.00 ml HEDP (10.00 mg/ml), 5.00 ml $SnCl_2·2H_2O$ in 3 mol/L HCl solution (10.00 mg/ml), 15 ml deionized water were mixed and then adjusted to pH= 5.00 and diluted to 50 ml. Two 10.00 ml solutions were put into two 50 ml volumetric flasks, respectively. One of them was first wrapped with aluminum sheets, then with black paper, and a black paper cylinder cap on the neck. The consumption of I_2-KI solution for 1.00 ml sample were obtained immediately after the solution was made and 10.5 h later.

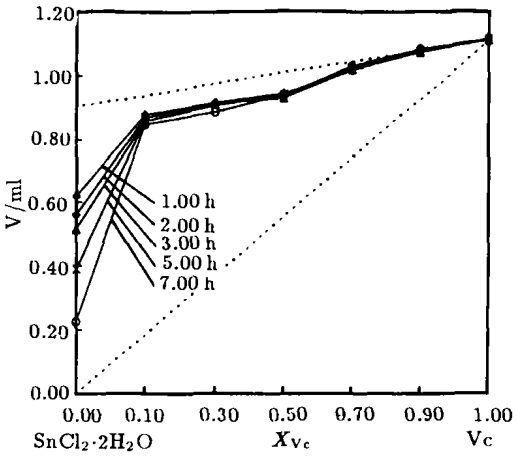

Fig.1 Influence of amount of Vc on the aerobic oxidation of stannous ion. V: Volume of ten times diluted standard I_2-KI solution consumed per ml sample. X_{Vc}: mass fraction of Vc in the sum (10 mg) of Vc and $SnCl_2·H_2O$ in 10 ml solutions containing 50.0 mg HEDP at pH=5

3 Results and Discussion

3.1 Influence of the amount of Vc and pH

The influence of the $SnCl_2·2H_2O$/Vc ratio on the aerobic oxidation of stannous ion in HEDP solution at pH=5.00 is shown in Fig.1, where the upper dash line corresponds to the theoretical consumption volumes of 10 times diluted I_2-KI stock solution per 1 ml sample for Sn^{2+} and Vc together, and the lower dash line to the theoretical consumption per 1 ml sample for Vc only. It can be concluded from Fig.1 that Vc is stable in the experimental conditions, so the initial drop of the experimental points from the upper dash line can be ascribed to the oxidation of stannous ion. For the later decrease in the consumption volume of I_2-KI is very slow, the initial drop may result from the aerobic oxidation before complete mixing of Vc and Sn^{2+} solution. The protective ability of Vc for stannous ion is excellent even at the 1/9 ratio of Vc to $SnCl_2·2H_2O$. The mole ratio at this point is 7.0 ($n_{Sn^{2+}}$ versus n_{Vc}). From the above facts it can be concluded that the protective effect of Vc results from neither its complexation with the stannous ion nor its preferential consumption of dissolved air oxygen. This conclusion is consis-

tent with the observation for other system.[5~7] The results in Fig.1 are obtained from one performance. Reproducible data are often not obtained from the repetition of the same experiment. The main reason is that the consumed rate of stannous ion in the solution without Vc and the initial drop of other solutions containing both Vc and Sn^{2+} are changing from one performance to another. This indicates that some uncontrolled factors, such as light irradiation, may affect the aerobic oxidation of stannous ion.

When HEDP is replaced by MDP or PYP, the results are very similar. The pH of the solution does not result in obvious difference in the decreasing rate of stannous ion within the pH range 3~9 for mole ratio 3/7 ($Vc/SnCl_2 \cdot 2H_2O$) solution as shown in Table 1, which means the pH adjustment can not be responsible to the initial drop mentioned above.

Table 1 Influence of pH on the stability of stannous ion*

	pH						
t/h	2.97	4.00	4.93	5.99	6.98	7.92	9.09
1.0	0.900	0.910	0.930	0.945	0.930	0.945	0.925
2.0	0.915	0.905	0.920	0.935	0.930	0.925	0.900
3.0	0.905	0.885	0.915	0.920	0.925	0.925	0.860
4.0	0.895	0.875	0.885	0.910	0.915	0.910	0.840
5.0	0.890	0.860	0.860	0.895	0.915	0.905	0.815

*The data mean the volume of ten times diluted standard I_2-KI consumed per ml sample

3.2 Influence of light irradiation

Light is an important factor to make the stannous ion oxidized, as shown in Table 2. Because of no Vc added, the consumption of I_2-KI is directly corresponding to the concentration of stannous ion remained. It was reported that the aerobic oxidation of stannous ion proceeded through a chain mechanism[3,5~7] and ultra-violet irradiation strongly accelerates the aerobic oxidation of $SnCl_2$ in $SnCl_2$-HCl system.[3] Our results show that light irradiation is still effective in the diphosphonate medium at pH=5.00 although the stannous ions are complexed with the diphosphonates. It was found that daylight has little influence on the reaction. This is consistent with the observation of Haring *et al.*[5] The effect of fluorescent lamp may be caused by the ultra-violet part in its spectrum. Which kind of particles is excited and responsible to the acceleration of the aerobic oxidation is still unknown. It was assumed that $HSnCl_3$ and H_2SnCl_4 were the active agents.[3] Alternatively, it was found that Vc could inhibit photodynamic effects in biological system, which shows Vc is a singlet-oxygen quencher.[11]

Table 2 The consumed volume (ml) of $I_2(9.95\times10^{-3}$/mol/L)-KI(0.025 mol/L) at different times

Time/h	0.0	10.5
Wrapped	0.830	0.600
Unwrapped	0.830	0.315

4 Conclusion

In HEDP, MDP, PYP solution at pH=5.00, the protective effect of Vc retains even at the concentration much lower than that of stannous ion, which confirms the catalytic action of Vc. This result indicates that there is a wide range selection for the amount of Vc. The change of pH from 3 to 9 does not affect the protective ability of Vc significantly. The illumination by fluorescent lamp in the sterile chamber is unfavorable to the kit preparation.

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