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International Journal of Pharmaceutics 222 (2001) 91–99

international journal of pharmaceutics

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# Stabilization of minodronic acid in aqueous solution for parenteral formulation

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Received 7 February 2001; received in revised form 3 April 2001; accepted 18 April 2001

**Abstract**

The composition, concentration, and buffer pH of potential minodronic acid formulations were evaluated for their drug stability and for their tendency to generate particles after storage for up to 4 weeks at 60°C. The results indicate that citrate and tartrate buffers maintain drug stability and inhibit the formation of particles. The stability of minodronic acid in these solutions increased slightly as the buffer concentration increased, exhibiting less particle formation than in other buffers. Since citrate buffer was considered the most promising stabilizer for minodronic acid, the pH-stability relationship in 100 mM citrate with pH ranging from 3 to 7 was evaluated during storage for 4 weeks at 60°C. The results demonstrate that solution pH of 3–5 result in optimal stability of minodronic acid with no formation of precipitates. A white precipitate was observed in citrate-containing sample solutions with pH of 6 and 7. Analysis of the isolated precipitate provided support for the hypothesis that the precipitate is a complex between minodronic acid and aluminum ions apparently leached from the glass of the ampoules. 

*Keywords:* Minodronic acid; Parenteral formulation; Stability; Precipitate; Complex; Aluminum ion

## 1. Introduction

Drug products must remain stable for a sufficient time period to cover supply and use of the finished products following their manufacture. Consequently, much effort is expended on researching drug formulations to insure the stability not only of the drug, but of the formulation itself. It is especially important for parenteral formulations that no visible particulate matter is generated during storage.

Minodronic acid hydrate, [1-hydroxy-2-(imidazo[1,2-*a*]pyridin-3-yl)ethylidene]bisphosphonic

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0378-5173/01/$ - see front matter 
PII: S0378-5173(01)00704-9

acid monohydrate, is a new bisphosphonate which is expected to prove clinically useful in the treatment of osteoporosis and hypercalcemia. In animal studies, this compound inhibits bone resorption with 100-fold greater potency than pamidronate (Kudo et al., 1992), and has ten times greater efficacy than incadronate disodium, disodium cycloheptylaminomethylenediphosphonate monohydrate (Kudo et al., 1990, 1992). For clinical trials now underway, both intravenous as well as oral formulations of minodronic acid are being tested.

The aim of this study was to test and find components that stabilize minodronic acid in solution and to evaluate the feasibility of a parenteral formulation. To achieve this goal, the effects of several buffers, their concentrations and pH were tested. In addition, a precipitate generated during these tests was analyzed to determine the potential causes of minodronic acid instability as well as the cause of precipitate formation.

## 2. Materials and methods

### 2.1. Materials

Minodronic acid hydrate was synthesized by Yamanouchi Pharmaceutical Co., Ltd. Ascorbic acid (pharmaceutical grade) was purchased from Takeda Chemical Industries, Ltd. (Osaka, Japan); glycine and citric acid monohydrate (analytical grade) were from Wako Pure Chemicals Industries, Ltd. (Osaka, Japan); succinic acid (analytical grade) was from Nacalai Tesque, Inc. (Kyoto, Japan); acetic acid and tartaric acid (analytical grade) were from Kanto Chemical Co. (Tokyo, Japan); lactic acid (analytical grade) was from Nippon Rika Co., Ltd. (Tokyo, Japan); maleic acid (analytical grade) was from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). All other reagents were analytical grade chemicals. Flint glass ampoules with a 2-ml capacity were obtained from Japan Glass Industry Co., Ltd. (Tokyo, Japan).

### 2.2. General procedure for preparation of minodronic acid solutions

Table 1 shows the seven buffer systems tested. First, the necessary amount of ingredients required to make any given final buffer was dissolved in distilled water at $\approx 85\%$ of the final volume. Sufficient minodronic acid hydrate was added to the buffer solutions to yield the desired concentration for each test. A 1 N sodium hydroxide solution was used to adjust the pH of

Table 1
Percentage of minodronic acid remaining in each 100 mM buffer tested after storage at 60°C

| Buffer | Initial pH | Time | | | |
|---|---|---|---|---|---|
| | | Initial | 1 week | 2 weeks | 4 weeks |
| Glycine–HCl | 3.0 | 100 | 99.1 | 98.2 | 78.1 |
| | 5.1 | 100 | 98.6 | 97.3 | 95.5 |
| Citrate | 3.0 | 100 | 100.1 | 100.6 | 99.5 |
| | 5.0 | 100 | 100.7 | 100.0 | 101.8 |
| Succinate | 3.1 | 100 | 101.3 | 95.7 | 82.4 |
| | 5.0 | 100 | 99.0 | 93.9 | 94.4 |
| Acetate | 3.1 | 100 | 100.1 | 90.7 | 74.8 |
| | 5.0 | 100 | 97.8 | 95.0 | 88.5 |
| Tartrate | 3.0 | 100 | 99.8 | 100.1 | 93.4 |
| | 5.0 | 100 | 99.1 | 97.7 | 95.7 |
| Lactate | 3.1 | 100 | 100.5 | 100.6 | 86.0 |
| | 4.4 | 100 | 99.9 | 99.0 | 93.9 |
| Maleate | 3.1 | 100 | 101.0 | 98.5 | 87.3 |
| | 5.0 | 100 | 99.0 | 87.7 | 80.1 |

Each value represents the mean of two measurements.

the solutions to the desired value. The minodronic acid solutions were brought to final volume with water and filter sterilized through a 0.2 μm filter. The formulations were filled into clean 2-ml flint glass ampoules, hermetically sealed, and sterilized in an autoclave at 115°C for 30 min.

### 2.3. Stability evaluation

The ampoules were stored in a temperature-controlled incubator. At appropriate time intervals, ampoules were withdrawn and cooled to ambient temperature to test remaining minodronic acid content of, and particulate matter in, each solution.

First, to investigate the effect of buffer compositions on the stability, seven buffers were chosen consisting of excipients usually used for parenteral formulations and evaluated for their ability to stabilize minodronic acid in solution (Table 1). To facilitate comparisons of buffer effects, their concentrations were fixed at 100 mM, which was considered a sufficient concentration to display their buffering capacity. The concentration of minodronic acid was set at $\approx$ 0.5 mg $ml^{-1}$. Samples were stored at 60°C for up to 4 weeks.

Next, the effect of drug and buffer concentrations on the stability of minodronic acid formulations was examined in detail using minodronic acid concentrations of 0.1–2.4 mg $ml^{-1}$ and citrate concentrations of 1–10 mM. Tartrate buffer, the second choice, was also evaluated. In this experiment, pH 5 was chosen for the stability evaluation. Samples were stored at 60°C for up to 4 weeks.

Finally, the pH-stability relationship of minodronic acid solution was examined using formulations of 0.5 mg $ml^{-1}$ minodronic acid in 100 mM citrate buffer with pH ranging from 3 to 7. Samples were evaluated after storage for 4 weeks at 60°C.

### 2.4. Isolation of precipitate observed in ampoules

The white precipitate observed in some ampoules was removed from solution by centrifugation in an L-70 ultracentrifuge at $100\,000 \times g$ for 20 min (Beckman Instruments, Inc., Palo Alto, CA). After removal, the precipitate was rinsed with distilled water, and vacuum dried in preparation for analysis.

### 2.5. pH measurement

The pH of minodronic acid solutions was measured using an HM-26S pH meter (TOA Electronics Ltd., Tokyo, Japan) or the equivalent.

### 2.6. Particle counting

The number of particles in minodronic acid solutions was determined with a HIAC/ROYCO Model 4100 particle counter, a Model 3000 syringe controller, an HRLD-150 sensor (Pacific Scientific, Menlo Park, CA) and a DPU-411 Type II thermal printer (Seiko Instruments Inc., Chiba, Japan). A sample collection probe was inserted directly into each open ampoule, and the solution within was drawn into the HIAC system and analyzed. The tare volume, the amount of solution allowed to flow through the sensor before the actual sample volume, was 0.5 ml, and the sample volume was 1 ml.

### 2.7. High performance liquid chromatography

High performance liquid chromatography (HPLC) was performed to measure minodronic acid stability. A Shimazu chromatographic system was used; it comprised an LC 9A pump, an SIL 6A autosampler, an SPD UV detector, and a C-R4A integrator (Shimazu, Kyoto, Japan) or the equivalent. Chromatography was conducted using a Develosil ODS-5 column (150 × 4.6 ID mm, 5 μm; Nomura Chemical, Tokyo, Japan). The column temperature was maintained at 25°C. The sample volume was 10 μl, and minodronic acid was detected by its absorbance at 226 nm. The flow rate was 1.2 ml $min^{-1}$.

The mobile phase consisted of a 5:95 (v/v) methanol–10 mM sodium pyrophosphate solution containing 1 mM tetra-*n*-butylammonium

phosphate; the solution was adjusted to pH 7.6 with orthophosphoric acid. The mobile phase was filtered and degassed before use.

### 2.8. Physical analysis of minodronic acid and the precipitate

Analysis of minodronic acid hydrate and the precipitate was conducted as follows: $^1$H-NMR spectra of samples dissolved in $D_2O$ containing $K_2CO_3$ were measured with a JNM-ALPHA500 spectrometer (JEOL Ltd., Tokyo, Japan); TSP-$d_4$ (3-(trimethylsilyl)propionic-2,2,3,3-$d_4$ acid, sodium salt) was used as an internal standard. Samples of both minodronic acid hydrate and the precipitate were dissolved separately in $D_2O$ by addition of $K_2CO_3$, although an excess amount of $K_2CO_3$ was required to dissolve the precipitate. Infrared spectra were measured with a 1600 Series FTIR spectrometer (Perkin–Elmer, Norwalk, CT) using the potassium bromide disk method.

### 2.9. Thermal gravimetric analysis and differential scanning calorimetry

Thermal gravimetric analysis and differential scanning calorimetry (TGA/DSC) curves of minodronic acid hydrate and the precipitate were measured using an 8085 E1 differential scanning calorimetric balance (Rigaku Corporation, Tokyo, Japan) in flowing nitrogen at a heating rate of 10°C per minute.

### 2.10. Scanning electron microscopy–energy dispersive X-ray analysis

Scanning electron microscopy–energy dispersive X-ray (SEM/EDX) analysis was performed using a JEOL analytical system (JEOL Ltd., Tokyo, Japan). The precipitate was carbon-film-coated with a JEC-550 twin coater. These samples were examined with a JSM-5400 scanning microscope to select a suitable object for EDX analysis. The conditions for SEM were as follows: 15 kV electron beam potential, a 20 mm working distance, and a back-scattered electron detector. EDX analysis was performed with a JED-2001 EDX microanalyzer to identify the partial elemental content of the precipitate. A 20 kV electron beam was used to probe the sample, and a SiLi detector was used to detect the X-rays generated by the sample.

## 3. Results and discussion

### 3.1. Effect of buffer compositions on the stability of minodronic acid in solution

Initially, the pH values of each formulation were relatively stable for 4 weeks, with the exception of the lactate buffer, which initially shifted from 5 to 4.4 due to the hydrolysis of some of the lactate to lactic acid during autoclave sterilization.

Comparison of minodronic acid stability in buffered formulations revealed that stability of minodronic acid was acceptable in all buffers except acetate and maleate (Table 1). Buffers that retained more than 90% of the initial minodronic acid amount after storage for 4 weeks were the pH 5 glycine–HCl and succinate buffers, and the pH 4.4 lactate buffer, and both the pH 3 and 5 citrate and tartrate buffers.

However, larger amounts of particles were detected in the pH 5 formulations compared with the pH 3 formulations. Among the buffers which retained more than 90% of the initial minodronic acid amount, the number of particles increased drastically in glycine–HCl and succinate buffers. In contrast, citrate and tartrate buffers inhibited particle formation at pH 3 and 5 (Table 2).

These results indicate the citrate and tartrate buffers are good stabilizers for minodronic acid. Comparison of stability data from citrate and tartrate buffers indicates that citrate buffer stabilizes minodronic acid in solution better than tartrate buffer; the citrate buffer formulation retained almost 100% of the initial minodronic acid amount after storage for 4 weeks at 60°C. In contrast, tartrate buffers showed a slight decrease in the amount of minodronic acid after storage. Therefore, it is concluded that the citrate buffer is the best choice to stabilize minodronic acid in solution.

Table 2
The number of particles (≥2 μm) generated in each 100 mM buffer tested after storage at 60°C

| Buffer | Initial pH | Time | | | |
|---|---|---|---|---|---|
| | | Initial | 1 week | 2 weeks | 4 weeks |
| Glycine–HCl | 3.0 | − | + | + | ++ |
| | 5.1 | ++ | ++ | +++ | +++ |
| Citrate | 3.0 | − | − | − | − |
| | 5.0 | − | − | − | − |
| Succinate | 3.1 | − | − | + | ++ |
| | 5.0 | ++ | +++ | +++ | +++ |
| Acetate | 3.1 | − | + | + | + |
| | 5.0 | ++ | +++ | +++ | ++ |
| Tartrate | 3.0 | − | − | − | − |
| | 5.0 | − | − | − | − |
| Lactate | 3.1 | − | − | − | + |
| | 4.4 | + | ++ | ++ | ++ |
| Maleate | 3.1 | − | − | + | ++ |
| | 5.0 | ++ | +++ | +++ | +++ |

The symbols indicate particle counts per milliliter as follows: − (0–99), + (100–999), ++ (1000–9999), +++ (≥1000).

Table 3
Effect of minodronic acid and buffer concentrations on percentage of minodronic acid remaining after storage at 60°C

| Buffer | Minodronic acid concentration (mg ml$^{-1}$) | Buffer concentration (mM) | Time | | | |
|---|---|---|---|---|---|---|
| | | | Initial | 1 week | 2 weeks | 4 weeks |
| Citrate | 0.1 | 1 | 100 | 99.3 | 103.7 | 99.2 |
| | | 5 | 100 | 98.0 | 103.1 | 98.1 |
| | | 10 | 100 | 99.2 | 101.0 | 98.0 |
| | 0.5 | 1 | 100 | 101.3 | 104.2 | 99.7 |
| | | 5 | 100 | 103.7 | 105.9 | 100.8 |
| | | 10 | 100 | 103.2 | 103.9 | 100.7 |
| | | 100 | 100 | 100.7 | 100.0 | 101.8 |
| | 2.4 | 1 | 100 | 100.8 | 104.8 | 100.6 |
| | | 5 | 100 | 102.8 | 106.7 | 100.3 |
| | | 10 | 100 | 101.0 | 104.5 | 99.9 |
| Tartrate | 0.5 | 1 | 100 | 98.8 | 100.5 | 96.7 |
| | | 5 | 100 | 99.1 | 102.0 | 98.0 |
| | | 10 | 100 | 101.3 | 101.0 | 98.4 |
| | | 100 | 100 | 99.1 | 97.7 | 95.7 |

Each value represents the mean of two measurements.

### *3.2. Effect of drug and buffer concentrations on the stability of minodronic acid solution*

The pH values of each formulation were almost the same at all buffer concentrations except the 1 mM, in which a slight increase by $\approx 0.3$ units was observed during storage.

Table 3 lists the effect of minodronic acid and buffer concentrations on the stability of minodronic acid after storage at 60°C. Stability of minodronic acid was acceptable throughout the test period in both buffer solutions. In compari-son, minodronic acid was more stable in all citrate buffers tested. Table 4 displays the inhibitory

Table 4
Effect of minodronic acid and buffer concentrations on particle (≥2 μm) generation after storage at 60°C

| Buffer | Minodronic acid concentration (mg ml$^{-1}$) | Buffer concentration (mM) | Time | | | |
|---|---|---|---|---|---|---|
| | | | Initial | 1 week | 2 weeks | 4 weeks |
| Citrate | 0.1 | 1 | NT | NT | − | − |
| | | 5 | NT | NT | − | − |
| | | 10 | NT | NT | − | − |
| | 0.5 | 1 | NT | NT | + | ++ |
| | | 5 | NT | NT | + | ++ |
| | | 10 | NT | NT | − | − |
| | | 100 | − | − | − | − |
| | 2.4 | 1 | NT | NT | +++ | +++ |
| | | 5 | NT | NT | ++ | +++ |
| | | 10 | NT | NT | + | ++ |
| Tartrate | 0.5 | 1 | NT | NT | − | + |
| | | 5 | NT | NT | − | − |
| | | 10 | NT | NT | − | − |
| | | 100 | − | − | − | − |

The symbols indicate particle counts per milliliter as follows: − (0–99), + (100–999), ++ (1000–9999), +++ (≥1000). NT – not tested.

effect of buffers on particle generation. The results indicate that particle generation is suppressed either by increasing concentrations of citrate buffer or decreasing concentrations of minodronic acid. Comparison of results from citrate and tartrate buffers containing 0.5 mg ml$^{-1}$ of minodronic acid (Table 4) indicates that 1 and 5 mM tartrate solutions inhibit particle generation much more effectively than 1 and 5 mM citrate solutions. However, 10 and 100 mM citrate concentrations inhibit particle generation to the same extent as tartrate (Table 4). Consequently, an optimization is required between the stabilizing effect on minodronic acid and the inhibitory effect on particle generation. Therefore, formulations containing a minodronic acid concentration of 0.5 mg ml$^{-1}$ and a citrate concentration of 10–100 mM are thought to be the best in both preserving stability and preventing particle formulation.

### 3.3. pH-stability relationship in citrate solution

As shown in Table 5, minodronic acid was stable over the whole range of pH tested. However, visual inspection under a white light source that emits an illuminance of 1000 lux revealed precipitates in all the ampoules of the pH 6 and 7 formulations. As a parenteral liquid formulation, formulations that forms precipitates are not acceptable. Therefore, a pH of 3–5 is considered optimal in terms of overall stability of minodronic acid.

### 3.4. Investigation of the potential cause of minodronic acid instability in solution

To investigate the potential cause of minodronic acid instability in solution, the precip-

Table 5
The stability of minodronic acid in 100 mM citrate buffers after storage for 4 weeks at 60°C

| pH | Minodronic acid remaining (%) | Appearance |
|---|---|---|
| 3 | 98.7 | Clear and colorless |
| 4 | 99.8 | Clear and colorless |
| 5 | 99.8 | Clear and colorless |
| 6 | 98.2 | White precipitate |
| 7 | 100.6 | White precipitate |

Each value represents the mean of two measurements.

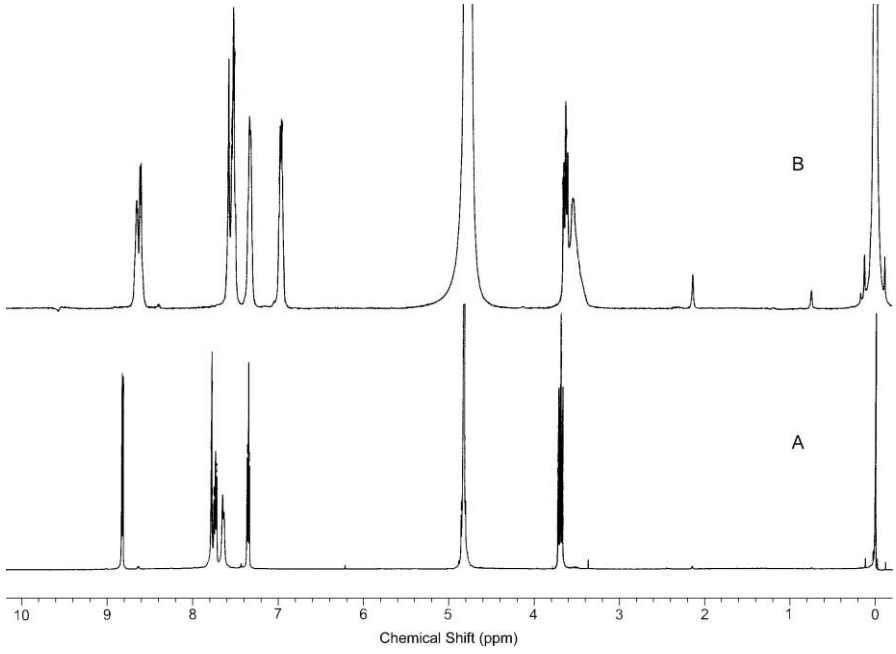


Fig. 1. $^{1}$H-NMR spectra of (A) minodronic acid hydrate and (B) the precipitate filtered from the unstable citrate buffer formulation.

itate removed from the pH 7 citrate buffer formulation was analyzed.

SEM/EDX was used to obtain the partial elemental content information on the precipitate. The results revealed that in addition to C, O, Na, and P, which are obviously derived from the ingredients of the formulation, the precipitate also contains aluminum; this result was quite unexpected. One possible source of the aluminum ions is thought to be the glass ampoule itself, because glass containers are composed of 1–5% aluminum (Hoiberg, 1989). Aluminum ions leach from glass containers during sterilization by autoclave or during storage (Hoiberg, 1989; Pavanetto et al., 1989). Additionally, it is well known that bisphosphonates form complexes with metal ions (Claessens and van der Linden, 1984; Lamson et al., 1984). Thus, the elemental analysis provides support for the hypothesis that minodronic acid forms an insoluble complex with aluminum ions leached from the ampoule and precipitates.

To determine whether minodronic acid is contained in the precipitate, an $^{1}$H-NMR spectrum of the precipitate was compared to a spectrum of an authentic sample of minodronic acid hydrate. The similarity of the signal patterns in both spectra clearly demonstrate that the chemical structure of minodronic acid is maintained in the precipitate (Fig. 1). Second, comparison of IR spectra from the precipitate and minodronic acid hydrate revealed that the precipitate exhibits the same two characteristic peaks, one at $\approx 1660$ cm$^{-1}$ and the other at 1530 cm$^{-1}$, as minodronic acid hydrate does (Fig. 2). These peaks are attributable to $\nu$(C=C) and $\nu$(C=N) of the heterocyclic imidazopyridine group. IR spectra also support the existence of imidazopyridine structure in the precipitate, as the $^{1}$H-NMR spectra do. Finally, TGA/DSC revealed that the precipitate exhibits no endothermal peak, but minodronic acid hydrate has one endothermic peak with the weight loss at $\approx 155$°C, corresponding to the elimination of water of crystallization (Figs. 3 and 4). A

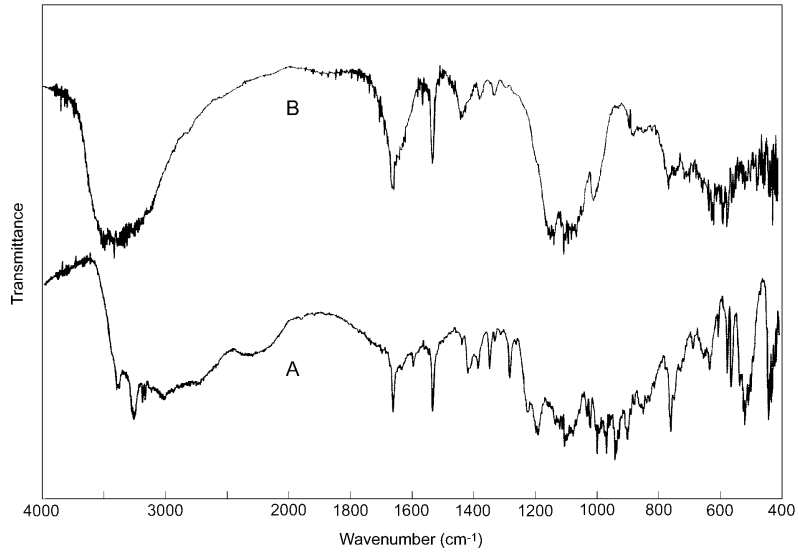


Fig. 2. FTIR spectra of (A) minodronic acid hydrate and (B) the precipitate filtered from the unstable citrate buffer formulation.

significant difference in the exothermic peak between the precipitate and minodronic acid hydrate was observed. One possible cause of this peak shift might be the presence of aluminum ions in the precipitate. Taken together, the results of $^{1}$H-NMR, IR, and TGA/DSC analyses indicate that the precipitate contains intact minodronic acid that does not have any water of crystallization (minodronic acid anhydrous).

Consequently, a series of observation provides support for the hypothesis that minodronic acid forms a complex with aluminum ions leached from the ampoule, which then precipitates. However, additional research is needed to clarify the details of the complex formation and its structure. Additionally, and perhaps unexpectedly, more precipitate was generated in formulations with higher pH. This might be attributed to the dissociation state of the minodronic acid phosphate groups. The higher the pH is, the greater the degree of dissociation of these phosphate groups. This may contribute to facilitating complex formation between minodronic acid molecules and aluminum cations. Furthermore, assuming the minodronic acid content loss observed in these formulations is a result of aluminum ions leaching from the glass of the ampoules, it is reasonable to conclude that citrate, a relatively strong chelating agent among the excipients tested (Hasegawa et al., 1982a,b,c,d,e), stabilized minodronic acid by scavenging aluminum ions from the solution, thus preventing the loss of minodronic acid from solution.

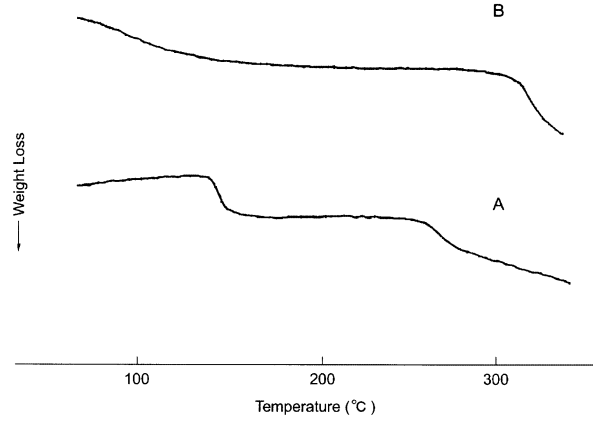


Fig. 3. TGA curves of (A) minodronic acid hydrate and (B) the precipitate filtered from the unstable citrate buffer formulation.

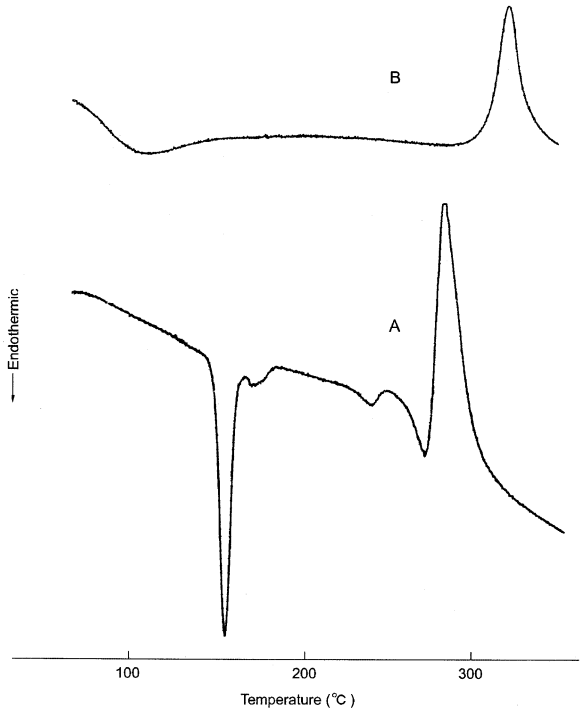


Fig. 4. DSC curves of (A) minodronic acid hydrate and (B) the precipitate filtered from the unstable citrate buffer formulation.

## 4. Conclusions

Preliminary formulation studies for a minodronic acid injectable indicate that 10 mM or higher citrate buffers with pH ranging from 3 to 5 optimize drug stability; these solutions retain almost 100% of the initial minodronic acid amount after the test storage period and prevent particle formation. The white precipitate observed in citrate-containing solutions with pH of 6 and 7 was isolated and analyzed by SEM/EDX, NMR, IR, and TGA/DSC. Analysis of the isolated precipitate provided support for the hypothesis that the precipitate is a complex between minodronic acid and aluminum ions apparently leached from the glass of the ampoules.

## Acknowledgements

The authors thank Mr Steven E. Johnson for editing this manuscript.

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