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Short Communication

The determination of alendronate sodium in tablets by inductively coupled plasma (ICP)

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1. Introduction

Alendronate sodium (4-amino-1-hydroxybutylidene)bisphosphonic acid monosodium salt trihydrate, the structure of which is shown in Fig. 1, is an aminobisphosphonate which is under study as a therapeutic agent for osteoporosis and Paget's disease. Because alendronate sodium has no chromophore, previously described methods have required lengthy sample preparation techniques with either pre- or post-column derivatization for quantitation [1,2]. Conductivity and indirect UV detection methods have also been reported [3–5]. The present work describes a rapid, accurate, and precise method for quantitation of alendronate sodium in tablets (Fig. 2). Alendronate sodium is determined directly by dissolving samples and standards in water, and analyzing by ICP for phosphorus content. ICP has been used in other studies to directly and indirectly quantitate drugs [6–8]. ICP has also been used to quantitate another bis-phosphonate (etidronate disodium) following ion chromatographic separation [9]. This technique was demonstrated to be successful for direct alendronate sodium quantitation and yielded results comparable to those obtained by more complex derivatization procedures.

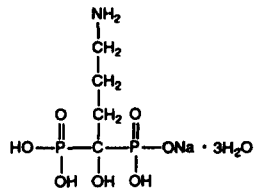

Fig. 1. Structure of alendronate sodium.

2. Experimental

2.1. Chemicals and reagents

Alendronate sodium bulk drug, active tablets, and placebo tablets were obtained through Merck Research Laboratories. All solutions were prepared in distilled, deionized water.

2.2. Instrumentation and conditions

The instrument used for analysis was a Spectro Model M Sequential ICP spectrometer. The wavelength used to detect phosphorus was 178.3 nm. A fixed quartz torch was used with 1.2 kW power. A concentric K-type nebulizer was utilized with a Scott-type spray chamber. Argon gas was used for purging. The sample flow rate was 2 ml min^{-1} with an integration time of 3 s on the peak used.

2.3. Preparation of linearity solutions

Solutions were prepared in water to demonstrate the linearity of alendronate sodium from 10 to 400% of the method concentration

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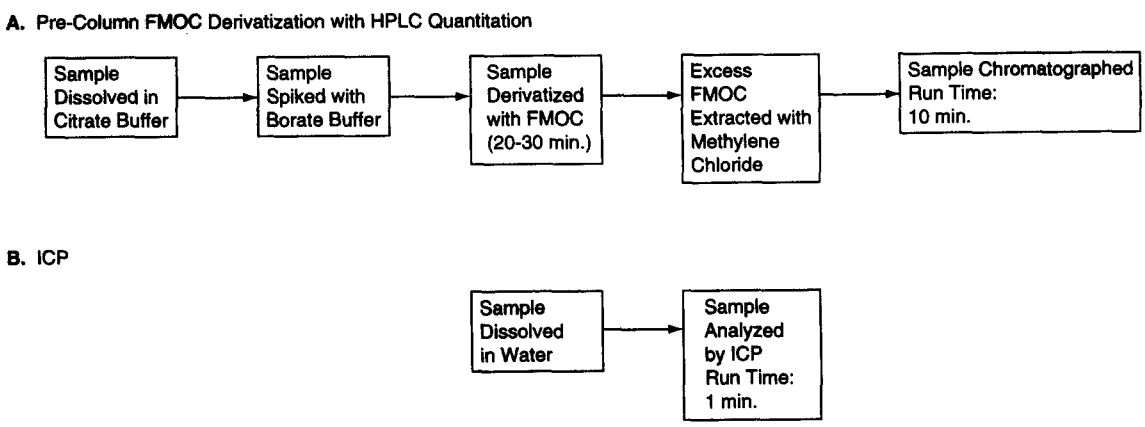

Fig. 2. Comparison of ICP technique to current FMOC HPLC technique.

(0.031 mg ml^{-1} as the sodium salt trihydrate). A stock solution was prepared by weighing 57.66 mg of alendronate sodium as the sodium salt trihydrate into a 500 ml volumetric flask, dissolving in water, and diluting to volume with water. Aliquots of the stock solution were taken and further diluted with water to give six working standard solutions with the following concentrations of alendronate sodium as the sodium salt trihydrate: 0.115, 0.057, 0.029, 0.012, 0.0035, and 0.0017 mg ml^{-1}. Each solution was analyzed in triplicate using the conditions described.

2.4. Preparation of alendronate sodium standard

The alendronate sodium standards used to determine the precision of analytical determination and tablet assays were prepared by weighing 40.03 and 39.99 mg, respectively, of alendronate as the sodium salt trihydrate into 50 ml volumetric flasks. The drug was dissolved and diluted with 50 ml of water. Two ml aliquots of each stock standard were further diluted to 50 ml with water to obtain the working standards.

2.5. Preparation of alendronate sodium tablet samples

Method A. 40 mg alendronate free acid equivalent tablet samples

Ten 40 mg alendronate free acid equivalent tablets (1.000 mg of alendronate sodium trihydrate is equivalent to 0.767 mg of alendronate free acid) were placed in each of six 1000 ml volumetric flasks. The tablets were dispersed in 500 ml of water by mechanically shaking for 30 min and sonicating for 5 min. The solutions were diluted to volume with water and mixed well. A 6 ml aliquot of the stock sample solution was further diluted to 100 ml with water to obtain the working sample solution.

Method B. 2.5 mg alendronate free acid equivalent tablet samples

Ten 2.5 mg alendronate free acid equivalent tablets were placed in each of six 1000 ml volumetric flasks. The tablets were dispersed in 500 ml of water by mechanically shaking for 30 min and sonicating for 5 min. The solutions were diluted to volume with water and mixed well. This was the working sample solution.

3. Results and discussion

3.1. Method validation

Linearity

The linearity of emission intensity for alen-

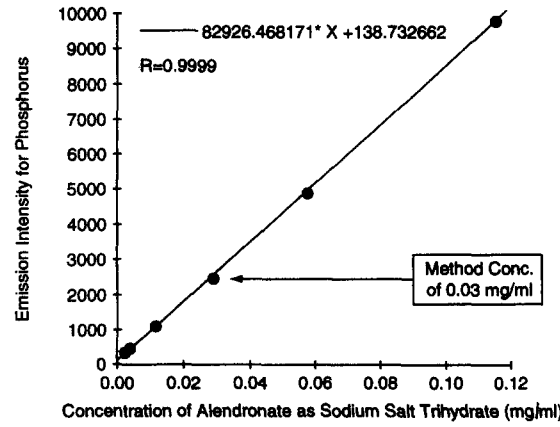

Fig. 3. Linearity of alendronate sodium by ICP.

Table 1
Precision of analytical determination for alendronate sodium standard 0.03 mg ml^{-1} as sodium salt trihydrate

Determination	Emission intensity [a]
1	2536
2	2538
3	2538
4	2666
5	2535
6	2553
7	2490
8	2526
9	2484
10	2524
Mean	2539
RSD	1.95%

[a] Corrected for blank.

Table 2
Alendronate sodium precision determination on 40 mg and 2.5 mg free acid equivalent tablets by ICP [a]

Tablets	Determination	mg alendronate per tablet
40 mg[b]	1	41.25
	2	40.59
	3	40.79
	4	40.79
	5	40.27
	6	40.97
	Mean	40.78
	RSD	0.82%
2.5 mg[c]	1	2.58
	2	2.53
	3	2.58
	4	2.60
	5	2.56
	6	2.47
	Mean	2.55
	RSD	1.85%

[a] 10 tablets used for each determination to eliminate variability of individual tablets; assay concentration = 0.03 mg ml^{-1}.
[b] Mean LC assay result = 40.34 mg per tablet [1].
[c] Mean LC assay result = 2.49 mg per tablet [1].

dronate sodium over a concentration range of 10–400% of the method concentration was evaluated. Emission intensity versus concentration for alendronate sodium was linear from 0.0017 to 0.115 mg ml^{-1} (Fig. 3), with a correlation coefficient of 0.9999. The precision of the triplicate analyses performed across the concentration analyzed was good, with RSDs of less than 2.0% obtained at all levels.

Precision

The precision of the analytical determination was ascertained by assaying an alendronate sodium standard solution 10 times (0.031 mg ml^{-1} as the sodium salt trihydrate). Good precision was obtained with an RSD of 1.95% (Table 1).

The precision of the method was determined by performing six composite assays each for the 40 mg and 2.5 mg tablets. Ten tablets were used for each determination to eliminate the variability of individual tablets. The results (Table 2) indicate good precision with average assay values of 40.78 mg per tablet (RSD = 0.82%) and 2.55 mg per tablet (RSD = 1.85%) for the 40 mg and 2.5 mg tablets, respectively.

Accuracy

The accuracy of the ICP method was determined by comparing the assay results obtained by ICP with those obtained by the HPLC method, utilizing pre-column derivatization with 9-fluorenylmethyl chloroformate (FMOC) [1]. Good correlation was obtained (Table 2).

4. Conclusions

A radid, precise, and accurate method was developed and validated for the quantitation of alendronate sodium in tablets. The method is suitable for content uniformity and potency assays; however, it does not indicate stability since it is specific to phosphorus and not to alendronate sodium. The method involves a rapid sample and standard preparation in water. No further manipulations or derivatizations are required prior to analysis. The method is linear over a broad range of concentrations, has good precision and gives results comparable to those obtained by HPLC following FMOC derivatization.

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