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LONG TERM STABILITY OF SODIUM MONOFLUOROPHOSPHATE

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ABSTRACT

This paper reports data on the long term stability of the phosphorus-fluorine bond of sodium monofluorophosphate (MFP). Spontaneous hydrolysis of the drug in bulk form follows first order kinetics. Chemical stability, expressed as its $t_{1/2}$, was found to differ with different MFP preparations ($t_{1/2}$ = 35 to 114 months). Chemical stability of MFP in tablets appears dependent upon the method employed in their preparation. The long term stability of aqueous solutions is affected, as expected, by pH and temperature.

INTRODUCTION

Fluoride alone or in combination with other drugs is used in the therapy of idiopathic and postmenopausal osteoporosis. Sodium fluoride or sodium monofluorophosphate (MFP) are the salts more commonly employed [1-4]. MFP is receiving increased attention because compared with sodium fluoride it has better gastric acceptability and it is compatible with calcium salts, an almost obligatory complement of the therapy.

The absence of information on the long term chemical stability of MFP in the USP XXII [5] and other reference manuals may induce the false notion that MFP is a stable drug. This paper reports data on the long term chemical stability of MFP (bulk form, in tablets mixed with calcium carbonate and in aqueous solutions).

MATERIAL AND METHODS

In the past three years, MFP was obtained from several suppliers. MFP and fluoride (present either as excess reagent or the product of spontaneous hydrolysis) were measured with a technique published elsewhere [6], much simpler than that described in [5] and suitable for the measurement of submicromolar amounts of this drug present in microliter volumes. The procedure involves two fluoride measurements: before (i) and after (ii) enzymatic hydrolysis with alkaline phosphatase. i) Two hundred microliters of MFP solution (5-50mM) were mixed with 20 microliters of 2 M citrate buffer pH 5.5. Aliquots of 5 and 100 mM sodium fluoride standard solutions were processed likewise. The fluoride concentration of the MFP solution was calculated by interpolation between standards. ii) Two hundred microliters of MFP solution were mixed with 20 microliters of 5 M $CO_3^=/HCO_3^-$ buffer pH 9.7, and 20 microliters of alkaline phosphatase solution (activity = 0.2-0.3 micromoles MFP hydrolyzed/min/mg of proteins) and left for 45 minutes at 20° C. Fluoride standards were processed likewise. Twenty microliters of 2M citrate buffer pH 5.5 where then added to all tubes. Total fluoride concentration was calculated by interpolation between standards. The difference between fluoride content before and after enzymatic hydrolysis measured the MFP content.

The MFP content of five different lots of the drug were determined simultaneously as indicated in USP XXII [5] and by the enzymatic procedure described above.

Fluoride was measured with an ion-specific electrode (Orion Research 94-09). Electrodes were assembled as indicated by Hallsworth et al.[7] to measure small volume samples (50-100 microliters). A millivoltimeter with a gain setting x10 was employed in this work [8].

The stability of the drug in bulk form was monitored measuring fluoride and MFP in aqueous solutions of the drug (5-50 mM), prepared at monthly intervals, for 6-9 months.

The stability of MFP in tablets containing 0.35 millimoles of the drug and 6 millimoles of calcium carbonate were investigated as follows. At monthly intervals five tablets were selected at random. Each tablet was disintegrated in 30 ml of distilled water using an Ultraturrax homogenizer (30 seconds, 20000 rpm). The resulting suspensions were centrifuged at 3000 rpm for 10 minutes. Fluoride and MFP were then measured in the clear

supernatant [6]. Calcium did not interfere; the low solubility of calcium carbonate produced a molar F/Ca ratio greater than 100/1 in the supernatant.

The long term stability of aqueous solutions of MFP was also investigated. The rate of hydrolysis was determined at 20°C with 5 mM solutions adjusted to pH 2.4, 7.0 and 9.7. The effect of temperature was measured with 5 mM, pH 7.0 MFP solution kept at -20°C, 4°C, 20°C or 37°C.

RESULTS

Table 1 displays the results of a series of analysis of the MFP content of different lots of the drug, assayed simultaneously with the techniques described in [5] and [6]. Differences between paired measurements (1.7±1.1%, mean ± SEM) are not significant (P>0.05).

The drug, kept in closed containers at room temperature, hydrolyze spontaneously following first order kinetics which allows to define its chemical stability as its $t_{1/2}$. Long term stability of MFP showed a wide range of values. Three lots (#1720, #1864 and #8590) gave half lives of 114, 35 and 80 months, respectively. A sample of unknown origin, containing 75% of the theoretical amount of MFP had a $t_{1/2}$ of 3.3 months.

In tablets produced with the "wet granulation method" (MFP lot #8590) the drug hydrolyzed rapidly ($t_{1/2}$ = 1.4 months). When the procedure was improved (Adolcas ™, Casasco SAIC, Argentina) tablets had an acceptable stability ($t_{1/2}$ = 44 months).

Aqueous solutions of MFP hydrolyze following zero order kinetics, according to:

$$[MFP] = [MFP_0] - k.t$$

where [MFP] stands for the concentration of MFP at time t, $[MFP_0]$ is the initial concentration of MFP and k is a constant that measures the rate of hydrolysis. For 5 mM solutions adjusted to pH 2.4, 7.0 and 9.7, the rates of hydrolysis were 91.7±0.31, 14.3±1.2 and 0.58±0.11 micromoles/L.day, respectively. The rate of hydrolysis of a 5 mM MFP solution, pH 7.0, increased with temperature. At -20°C, 4°C, 20°C and 37°C the rates of hydrolysis were 6.1±0.1, 11.1±0.7, 15.4±0.2 and 128±13.1 micromoles/L.day.

Table 1. MFP Content (% of Theoretical Content) of Five Lots of the Drug, Assessed According to USP XXII and the Technique Described in Reference [6].

MFP lot #	Date	USP XXII	Technique Ref. [6]
1709	Sept'90	94.0	95.5
1720	Sept'90	93.0	91.0
1864	May'91	92.3	91.3
2860	Jan'92	96.4	94.0
8590	Feb'92	97.2	92.0

COMMENTS

The development of a simple method [6] applicable to the measurement of submicromolar amounts of MFP in microliter volumes of test solutions was instrumental to facilitate the study of long term stability of MFP. The proposed technique gives results comparable to those obtained with that stated in USP XXII (Table 1), indicating that enzymatic hydrolysis is as complete as acid hydrolysis.

The data reported in this paper indicate that the long term stability of MFP varies from lot to lot, due to as yet unknown causes. Lack of quality control of MFP employed in published reports may explain their discordant findings. Two studies have reported that MFP is about one half as toxic as sodium fluoride [10,11] while two others [12,13] did not detect such difference. If sodium fluoride is more toxic than MFP, partial hydrolysis of the latter should greatly affect its LD_{50} value.

Based on short term experiments, Setnikar and Arigoni [9] have stated that water solutions of MFP are stable between pH 2 to 13. Though long term instability of MFP solutions were to be expected, quantitative characterization is of some practical importance. When laboratory animals receive MFP in their water supply, these solutions should be renewed weekly.

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