INSTABILITY OF SODIUM MONOFLUOROPHOSPHATE IN EFFERVESCENT TABLETS
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SUMMARY: Sodium monofluorophosphate (MFP, CAS 10163-15-2), widely used as an anti-caries agent and in the prevention or treatment of osteoporosis, is sensitive to moisture and acid. This research presents results of a study of the stability of MFP in tablets from four different pharmaceutical laboratories. With an initial water content of 2.9 to 4.0%, the pH of water solutions of three brands of non-effervescent tablets after disaggregation in water ranged from 5.2 to 7.4. The shelf half-life of these tablets ranged from 24 to 233 months. By contrast, effervescent tablets provided conditions that increased the instability of MFP: they produced the lowest pH (4.4) when dissolved in water and had the greatest water content (7% of tablet initial weight). They also had the shortest half-life (4.5 months). Kept in their original containers, effervescent tablets lost their total fluoride content at the rate of 41.0±8.9 µg F⁻/tablet/day (p<0.01), with half of this loss occurring as hydrofluoric acid at a rate 21±0.3 µg F⁻/tablet/day (p<0.01).

Keywords: Effervescent MFP tablets; Sodium monofluorophosphate, MFP; Stability of MFP tablets.

INTRODUCTION

Sodium fluoride (NaF, CAS 7681-49-4) and sodium monofluorophosphate (MFP, CAS 10163-15-2) are used as anti-caries agents in toothpastes, topical agents, and mouth rinses. 1 Both compounds produce ionic fluoride, which blocks glycolysis 2 and exchanges with the hydroxyl group of the hydroxyapatite crystal of enamel. 3 As a result, oral bacteria might produce lesser amounts of acidic compounds, and enamel hydroxyapatite, partially converted into fluorapatite, might become more insoluble. These effects are not only dependent on fluoride concentration but also on calcium and phosphate content of the saliva and diet. Consequently, the effect of fluoride in dental health is still a controversial issue. 4

NaF and MFP are also used alone or in combination with calcium, 5 vitamin D, 6 and estrogens 7 in the treatment of idiopathic and postmenopausal osteoporosis. 8-10 When administered chronically in adequate doses, fluoride has a mitogenic effect on osteoblasts that produces significant increases in bone mass. 11 As suggested by clinical trials, the strength and quality of bone formed under fluoride therapy are not always correlated with bone mineral density. 5,10

Some years ago, we reported that even in dry and dark conditions, MFP tablets, unless prepared by a dry method, undergo slow spontaneous hydrolysis liberating ionic fluoride. 12 In this paper we provide evidence that acidic compounds present in effervescent MFP tablets cause decomposition of MFP. Not only is the rate of hydrolysis increased but also the amount of fluorine present is reduced by volatilization as hydrofluoric acid. These results can be extended to other acid-sensitive compounds that generate a volatile product.
MATERIALS AND METHODS

Tablets: Four brands of MFP tablets, all produced in Argentina, were investigated in this work (Table 1). Tablets 1-3 are sold enclosed in plastic blisters; tablet 4 is marketed in aluminium containers with a desiccant.

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Composition</th>
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<tbody>
<tr>
<td>1</td>
<td>5 mg fluorine as glutamine MFP + 150 mg of Ca as gluconate and citrate</td>
</tr>
<tr>
<td>2</td>
<td>5 mg fluorine as glutamine MFP + 150 mg of Ca as citrate tetrahydrate</td>
</tr>
<tr>
<td>3</td>
<td>7.5 mg of fluorine as sodium MFP + 250 mg of calcium carbonate</td>
</tr>
<tr>
<td>4</td>
<td>13.2 mg of fluorine as sodium MFP + 1250 mg Ca carbonate + citric acid (effervescent type)</td>
</tr>
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Fluoride, MFP, and water content measurements: Fluoride concentrations were measured with an ion-selective electrode (94-09 Orion Research Inc., Orion Research Inc, Cambridge MA, USA). Electrodes were assembled as described by Hallsworth et al. to measure 20-50 µL. MFP was measured as described previously. After dissolution of the tablet in distilled water, the concentration of ionic fluoride was measured in an aliquot of the clear solution. A similar aliquot mixed with one tenth of its volume of rat intestinal alkaline phosphatase. After hydrolysis, the fluoride concentration was measured with the ion selective electrode. The difference between the two measurements was taken as the MFP concentration in the solution. For determination of their water content, tablets were placed in an oven at 110°C until the weight was constant. The water content of tablets is expressed as the % of reduction of initial weight.

pH of spontaneous disaggregation in water: Four tablets were dropped into 100 mL of distilled water at room temperature with stirring. The pH of the resulting solution after 15 min was measured with a combination glass electrode.

Stability of MFP in tablets: The contents of fluoride and MFP were measured weekly in tablets of the same batch for 43 weeks. Tablets were kept in their original containers. On the day of analyses, one tablet from each brand was dissolved in distilled water and treated immediately as stated above.

The MFP content of the tablets decayed as a single exponential function of time (t):

\[ \text{MFP} = \text{MFP}_0 \cdot \exp(-kt) \]

where \( \text{MFP}_0 \) stands for the initial amount of MFP. The half-life of MFP was calculated as \( \ln 2/k \), where \( k \) is the hydrolysis constant of MFP.

Measurement of fluoride loss in two selected brands of tablets: Since the total fluorine content of the #4 effervescent tablets decreased with time, presumably by volatilization as hydrofluoric acid, the rate of this phenomenon was measured with these tablets and compared with the #3 non-effervescent tablets prepared by a dry method.

A weighed fraction of each tablet was placed in a 1.5-mL Eppendorf tube. A small polyethylene tube containing 0.1 mL of 1.65 M NaOH was fixed inside the Eppendorf tube as described elsewhere. The container was capped and stored at room temperature for 15 days to allow isothermal distillation of HF into the alkali trap. Sixty tubes per brand were prepared at the beginning of the experiment.
Every day, the Eppendorf tubes from each series were opened. Glacial acetic acid (20 µL) was added to the small polyethylene tube to attain pH 4.5–5.0 in the solution. The amount of fluoride in the solution in the tube was measured with the fluoride selective electrode as described above. The amount of fluoride recovered in the alkali trap was used to calculate the rate of fluorine spontaneously lost from the tablet and expressed as µg of fluorine/tablet/day.

**Statistical Methods:** Nonlinear regression was employed to evaluate the exponential function.16 When more than two media were compared, one-way analysis of variance (ANOVA) and the multiple comparison test of Newman-Keuls were employed. Differences were considered significant when p<0.01.

**RESULTS**

Along with other measurements, Table 2 displays the pH values measured after dissolution of the four brands of tablets in distilled water. All solutions differed significantly in their pH (ANOVA, p<0.001). Among the different brands, the stability of MFP in the tablets over a period of 43 weeks, measured as the half-life, differed significantly (ANOVA, p<0.0001).

The half-life of MFP as a function of pH followed a simple exponential function:

\[ \text{Half-life} = 0.02633 \times \exp(1.228 \times \text{pH}). \]

Between pH 4.4 and 7.4, the half-life doubled in value when the pH increased by 0.56 units. Even though the MFP contents of tablets decreased following an exponential function of time, the total fluorine content of tablets (that of fluoride + MFP) remained constant throughout the experiment except for tablet 4. These results are shown in table 2 as the slope of the linear regression of total fluorine content as a function of time.

Table 2 also displays the slopes of the regression of fluoride lost from the tablet as a function of time for tablets 3 and 4.

**DISCUSSION**

Based on short-term experiments,17 and probably because of the low sensitivity of the method to detect small amounts of fluoride produced by hydrolysis, MFP has been assumed to be a stable drug. The rate of hydrolysis of MFP is negligible if the pH of the solution is above 4. Unless special precautions are taken in their preparation, however, the water content of MFP tablets may not be negligible. Moreover, the hygroscopic character of tablet components adversely affects the stability of the drug. Thus an acidic medium within the tablet accelerates the rate of hydrolysis during storage and decreases shelf life. Strong acidic conditions
within the tablet release fluoride as hydrofluoric acid that escapes from the tablet causing a reduction of total fluorine content.

REFERENCES

16 Graph Pad Prism 2.0. GraphPad Software, San Diego, CA USA. 1994.