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A PROLONGED-RELEASE FLUORIDE TABLET

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ABSTRACT

A prolonged-release tablet of sodium fluoride was prepared by dispersing the sodium fluoride in a waxy matrix. The prolonged release in 6 human subjects was demonstrated by urinary data.

INTRODUCTION

For children in regions in which the drinking water is not fluoridated it is generally recognized that the daily administration of a conventional tablet containing 1 mg of fluoride ion significantly reduces the incidence of dental caries. The total intake of fluoride by persons ingesting one tablet daily and by those drinking water containing 1 ppm of fluoride ion is approximately the same; however, better protection from caries is attained by the consumption of fluoridated water (1-3).

After the administration of a conventional fluoride tablet a soluble fluoride is rapidly absorbed from the gastrointestinal tract, and there is a rapid increase in the concentration of fluoride ion in the blood. The concentration in the blood then decreases rapidly as the fluoride ion is excreted selectively by the kidneys. If the concentration of the fluoride ion in the blood could be sustained, a greater proportion would appear in the gingival fluid and saliva. In response to a suggestion from the Department of Pedodontics of the University of Iowa, the feasibility of preparing a prolonged-release sodium fluoride tablet was investigated. If a prolonged-release tablet of sodium fluoride were designed to immediately release part of the fluoride in the oral cavity before being swallowed, and gradually after being swallowed release the remainder in the gastrointestinal tract over several hours, it would provide in the mouth continuous concentrations of clinical significance.

EXPERIMENTAL

Preparation of Prolonged-Release Tablet. After compressing several preliminary formulations containing 1.0 mg of fluoride ion per tablet and studying their in vitro dissolution patterns, the following formulation was selected for evaluation:

	Milligrams Per Tablet
Hydrogenated castor oil[1]	120.0
Glyceryl monostearate[2]	120.0
Mannitol[3]	50.0
Sodium fluoride[4]	2.2
Microcrystalline cellulose[5]	168.8
Corn starch[6]	31.2
Gelatin[7]	10.0
Magnesium stearate[8]	5.0

The sodium fluoride was suspended in a waxy matrix by adding sodium fluoride and mannitol to fused mixture of hydrogenated castor oil and glyceryl monstearate and stirring unitl the mass congealed. The mass was passed through a mill[9] fitted with a 12-mesh screen, and a 16/20-mesh size fraction was separated by a sonic sifter. The 16/20-mesh size fraction was granulated with an aqueous 10% gelatin solution, and the wet granulation was dried in an oven at 50°C for 6 hours. The dried granulation was blended with microcrystalline cellulose, corn starch and magnesium stearate. The blend was compressed using a 1.27 cm punch and die set to a Stokes hardness of 5^{+}_{-} 1 kg.

Dissolution Profile. The in vitro dissolution profile was

obtained using the U.S.P. dissolution apparatus rotated at 100 rpm with 900 ml of distilled water at 37°C in a one-liter plastic beaker covered with a plastic lid (4). Samples were withdrawn, and the volume of the dissolution medium was maintained constant by the addition of the same volume of water.

The samples were analyzed for fluoride by the U.S.P. method (5) using a fluoride ion combination electrode[9] coupled to a digital pH meter[10]. A sample was withdrawn by pipet, placed in volumetric flask, and adjusted to 100 ml with TBS [500 ml of 1.0 M tris (hydroxymethyl) aminomethane solution[11] and 403 ml of 1.0 N hydrochloric acid diluted to 1 L]. This solution was transferred to a plastic beaker containing a plastic coated stirring bar. The potential of the solution was measured when it did not fluctuate more than 0.4 millivots within an interval of 5 minutes. The concentration of fluoride was determined by multiplying the value obtained from a standard curve by the dilution factor. Corrections were made to compensate for the fluoride removed in previous samples. The precent of fluoride dissolved was calculated and plotted against time as shown in Figure 1.

Protocol for Urinary Recovery. Six health male volunteers were used in a cross-over study to compare the urinary

excretion from 20 mg of fluoride ion administered as a solution and as prolonged-release tablets. Diet was not restricted, but the subjects were instructed to drink only distilled water for 48 hours before and for the 24 hours after ingestion of the fluoride. The subjects were instructed to empty their bladders before administration of the fluoride and to collect and measure the volume of urine at intervals of 2 hours from the zero to the sixteenth hour and to collect and pool the urine samples from the sixteenth to the twenty-fourth hour. The method used for the analysis of the fluoride ion in the urine specimens was similar to that used by Hall et al. (6) and Cernik (7).

RESULTS AND DISCUSSION

The dissolution profile shown in Figure 1 is indicative of a prolonged-release pattern. Twenty percent of the fluoride ion was dissolved at 5 minutes; this suggested that if the tablet were held in the mouth for a short time a significant amount of fluoride would be released to exert local action on the tooth enamel. The remainder of the fluoride was released over a 4-hour period and would presumably be available for absorption to provide a prolonged blood concentration.

In order to select the proper protocol for conducting the urine excretion study a solution of sodium fluoride was

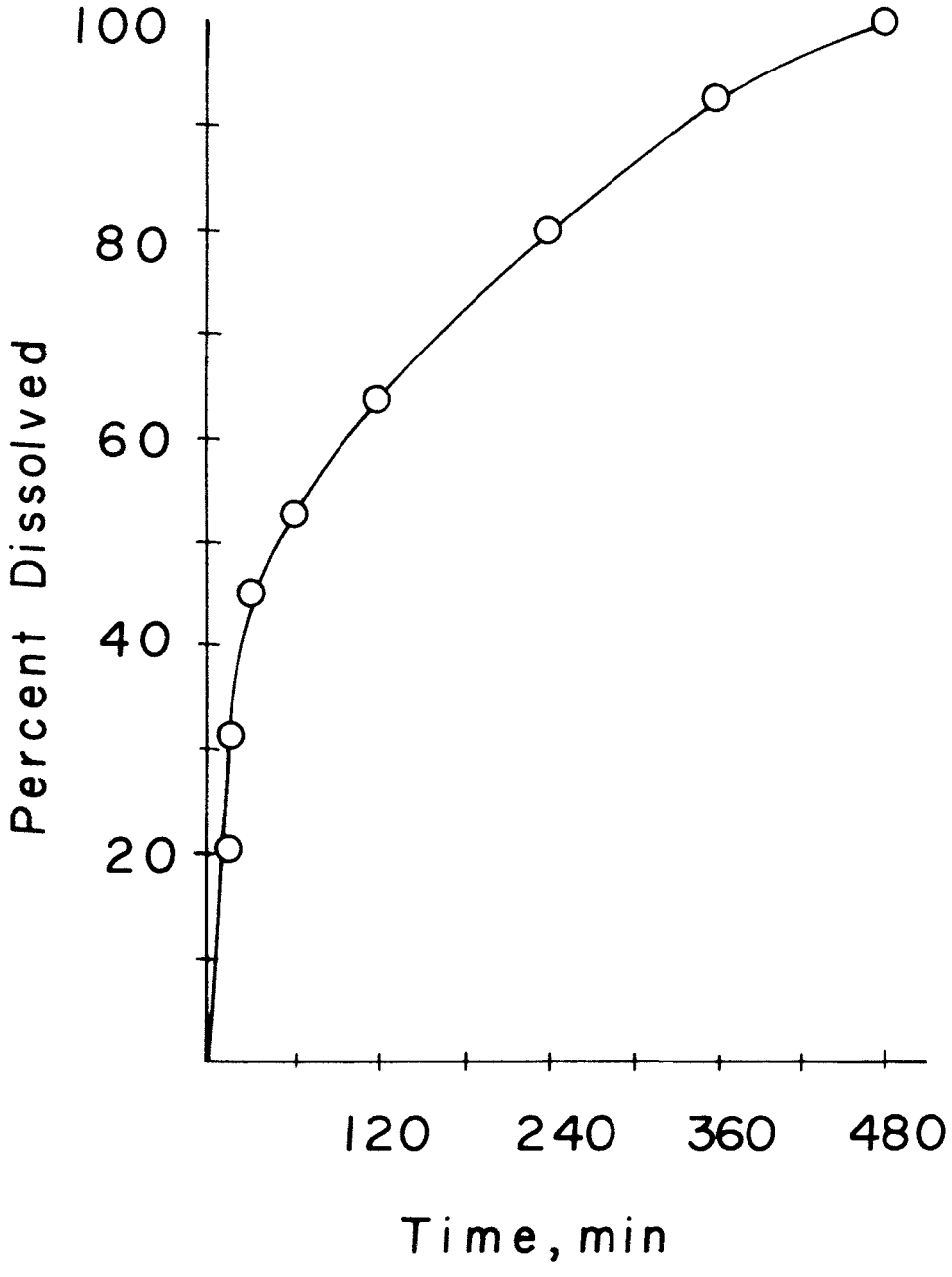

FIGURE 1

Dissolution profile in water at 37°C of a prolonged-release tablet

administered to 2 subjects, and urine was collected for 48 hours. By means of a plot of the percent of excretable fluoride against time (8,9), the half life for excretion in the urine was found to be 7.8 and 9.8 hours. Thus, the use of a collection interval of 2 hours for 16 hours was adequate for evaluation.

The milligrams of fluoride ion excreted in intervals of 2 hours from the solution and from the prolonged-release tablets are shown for the 6 subjects in Table 1.

In all subjects the maximum excretion of fluoride after the ingestion of the solution occurred at 2 hours, and the amounts excreted subsequently decreased exponentially. The amount of fluoride excreted after the administration of the prolonged-release tablets was less at 2 hours than that excreted from the solution. Thus, the release from the tablet matrix was delayed. The amount of fluoride ion excreted from the prolonged-release tablets from the second to the tenth hour tended to be a constant value.

The mean rate ($\pm$ SE) of excretion of fluoride ion for 6 subjects is given in Figure 2. Figure 3 shows the mean cumulative milligrams ($\pm$ SE) of fluoride ion excreted by the 6 subjects as a function of ime. The rate of excretion (0.6 mg per hour as represented by the slope) is constant during the first 8 hours. Since a constant rate of excretion

TABLE 1

Comparison of Fluoride Ion Escreted in the Urine of Six Subjects After the Administration of 20 mg of Fluoride in Solution and as Sustained-Release Tablets

Hr	Solution		Sustained-Release Tablets	
	Mg	Cumulative mg	Mg	Cumulative mg
		Subject A		
2	3.86	3.86	1.40	1.40
4	3.05	6.91	1.81	3.21
6	1.80	8.71	1.79	5.00
8	1.75	10.46	1.61	6.61
10	1.89	12.35	1.89	8.50
12	1.54	13.89	1.21	9.71
14	1.10	14.99	1.20	10.91
16	0.56	15.55	0.89	11.80
24	1.59	17.14	1.38	13.18
48	2.13	19.27	1.05	14.23
		Subject B		
2	1.38	1.38	0.91	0.91
4	1.23	2.61	0.90	1.81
6	0.81	3.42	0.73	2.54
8	0.95	4.37	1.21	3.75
10	0.37	4.74	0.55	4.30
12	0.94	5.68	0.34	4.64
14	0.92	6.60	0.76	5.40
16	0.66	7.26	0.61	6.01
24	1.22	8.48	1.86	7.87
48	1.62	10.10	3.32	11.19

TABLE 1 (Continued)

Hr	Solution		Sustained-Release Tablets	
	Mg	Cumulative mg	Mg	Cumulative mg
		Subject C		
2	2.89	2.89	1.53	1.53
4	2.45	5.34	-	-
4.25	-	-	1.63	3.16
6	2.02	7.36	1.18	4.34
8	1.11	8.47	-	-
8.7	-	-	1.02	5.36
10	0.73	9.20	0.65	6.01
12	0.43	9.63	0.84	6.85
14	0.44	10.07	0.47	7.32
16	0.41	10.48	-	-
17.7	-	-	0.68	8.00
24	0.78	11.26	0.87	8.87
		Subject D		
2	2.29	2.29	1.44	1.44
4	1.58	3.87	1.16	2.60
6	1.50	5.37	1.12	3.72
8	1.69	7.06	1.29	5.01
10	1.01	8.07	1.00	6.01
12	0.95	9.02	0.77	6.78
14	0.93	9.95	0.65	7.43
16	0.60	10.55	0.40	7.83
24	1.31	11.86	0.74	8.57

TABLE 1 (Continued)

Hr	Solution		Sustained-Release Tablets	
	Mg	Cumulative mg	Mg	Cumulative mg
		Subject E		
2	2.53	2.53	0.61	0.61
4	1.36	3.89	0.92	1.53
6	1.33	5.22	0.87	2.40
8	1.51	6.73	1.07	3.47
10	0.96	7.69	1.21	4.68
12	1.19	8.88	0.83	5.51
14	0.67	9.55	0.59	6.10
16	0.27	9.82	0.23	6.33
24	0.68	10.50	0.75	7.08
		Subject F		
2	3.21	3.21	1.59	1.59
4	1.88	5.09	1.63	3.22
6	1.47	6.56	0.95	4.17
8	0.72	7.28	0.73	4.90
10	0.95	8.23	0.26	5.16
12	0.79	9.02	0.39	5.55
14	-	-	0.31	5.86
14.5	0.69	9.71	-	-
16	-	-	0.31	6.17
24	1.46	11.17	0.60	6.77

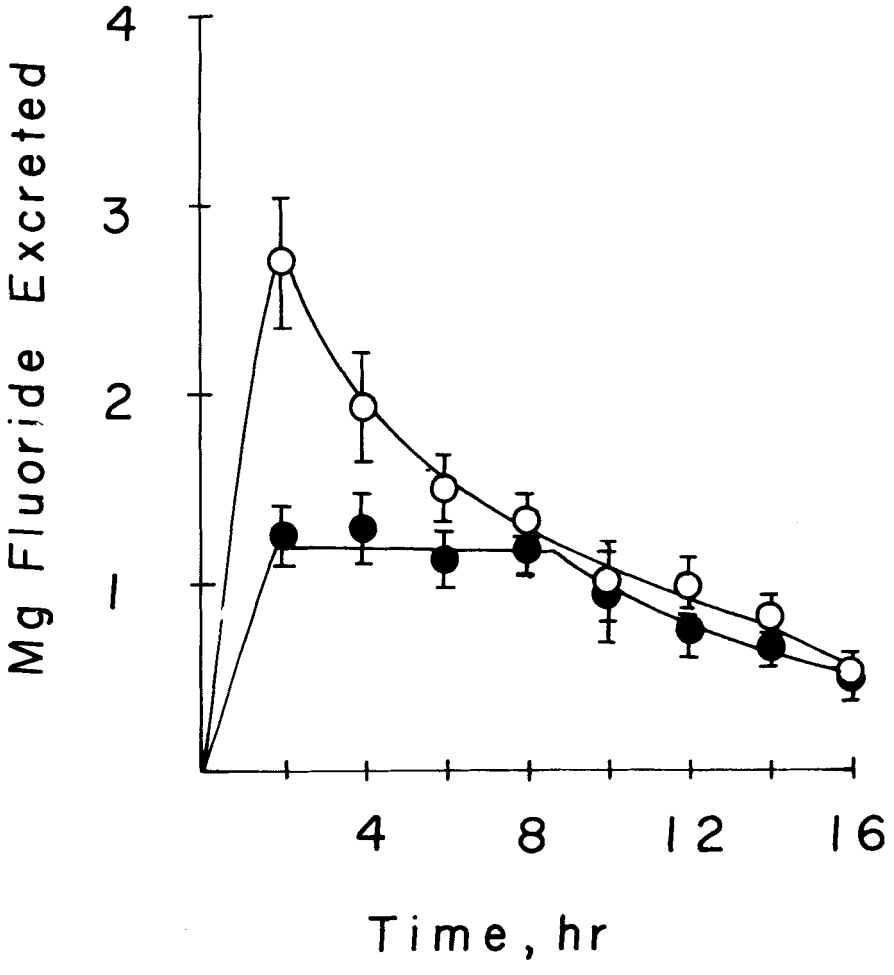

FIGURE 2

Mean amount of fluoride ion excreted in the urine per two-hour interval for 6 subjects following ingestion of 20 mg of fluoride ion in solution and 20 mg of fluoride ion in prolonged-release tablets. Vertical bars represent the standard error. Key: ○, solution; and ●, prolonged release tablets.

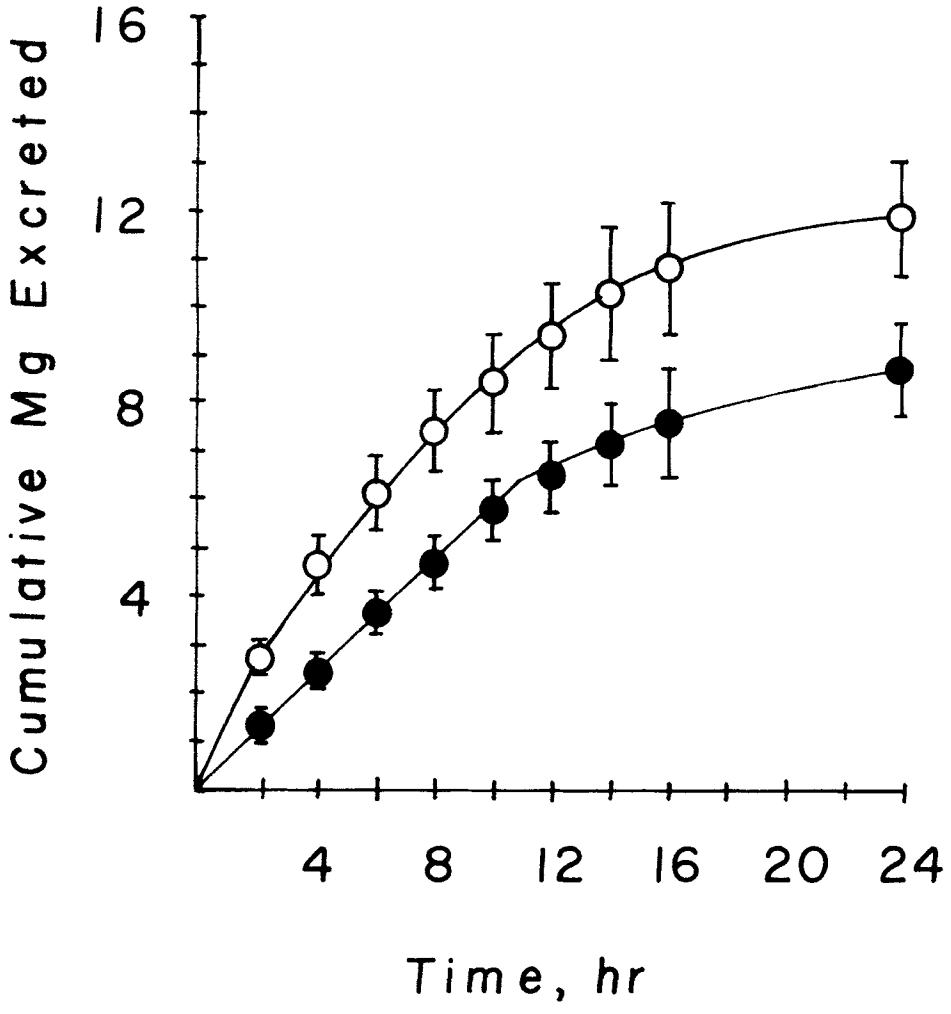

FIGURE 3

Mean cumulative amount of fluoride ion excreted in the urine for 6 subjects following ingestion of 20 mg of fluoride ion in solution and 20 mg of fluoride ion in prolonged-release tablets. Vertical bars represent the standard error. Key: ○, solution; and ●, prolonged-release tablets.

is a characteristic of a prolonged-release dosage form, this preliminary study based on urinary excretion data demonstrates that it is feasible to prepare a prolonged-release tablet that will release some fluoride ion in the mouth and after swallowing the remainder will be adsorbed over an 8 hour period from the gastorintestinal tract.

FOOTNOTES

1 Castorwax, Baker Castor Oil Company, Bayonne, N.J.

2 N.F., Fisher Scientific Company, Pittsburgh, Pa.

3 U.S.P., Mallinckrodt Chemical Works, St. Louis, Mo.

4 U.S.P., J.T. Baker Co., Phillipsburgh, N.J.

5 N.F., Avicel PH 101, FMC Corporation, Marcus Hook, Pa.

6 U.S.P., Fisher Scientific Company, Pittsburgh, Pa.

7 U.S.P., Type B, Fisher Scientific Company, Pittsburgh, Pa.

8 U.S.P., Mallinckrodt Chemical Works, St. Louis, Mo.

9 Homoloid model JT, Fitzpatrick Co., Elmhurst, Ill.

10 Orion model 96-09, Orion Research Inc., Cambridge, Mass.

11 Orion model 801A, Orion Research Inc., Cambridge, Mass.

12 Fisher Scientific Company, Pittsburgh, Pa.

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