ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 45 (1998) 101–111

European Journal of Pharmaceutics and Biopharmaceutics

Review article

Current status in oral fluoride pharmacokinetics and implications for the prophylaxis against dental caries

N. Vivien Castioni[a,*], P.C. Baehni[a], R. Gurny[b]

[a]*School of Dental Medicine, University of Geneva, Geneva, Switzerland*
[b]*School of Pharmacy, University of Geneva, Geneva, Switzerland*

Received 3 December 1996; accepted 2 May 1997

Abstract

Fluoride plays a central role in the prevention of dental caries. There is evidence that its effect is mainly topical and that continuous presence of fluoride ions in low concentration at the plaque/enamel interface is essential. The present paper reviews the most important aspects of fluoride kinetics in the oral cavity and discusses their implications on preventive approaches to dental caries. As a continuous presence of fluoride ions in saliva is important for an optimum prophylactic effect, new formulations capable of delivering low levels of fluoride over prolonged periods of time have been developed. These systems consist either of intra-oral devices, or of restorative materials into which fluoride has been incorporated. Among all the preparations investigated, bioadhesive tablets and membrane-controlled reservoirs are the most promising. © 1998 Elsevier Science B.V.

Keywords: Fluoride; Controlled delivery systems; Dental caries; Fluoride kinetics; Salivary fluoride concentrations; Local drug delivery

1. Introduction

Dental caries is an infectious disease in which there is an interplay between different factors: teeth, bacteria that inhabit the oral cavity and substrates such as carbohydrates [1]. Essentially, the pathogenic process is due to specific acidogenic microorganisms at the tooth surface (dental plaque) that produce high concentrations of organic acids from dietary carbohydrates which, in turn, cause demineralization of enamel and dentin. Obviously, many secondary factors influence the rate of progression of the disease. The main strategies to prevent dental caries include the use of fluorides, of antiseptic agents, oral hygiene, reduced carbohydrate intake and consumption of non- or hypo-acidogenic food products.

The importance of fluoride in the prevention of dental caries was discovered through observations made in naturally fluoridated water areas. When the first fluoridation programs were started [2,3], about 50 years ago, the cariostatic effect of fluoride was attributed to the incorporation of the ion into the enamel during tooth development or by topical enrichment. It was presumed that fluoride reduced enamel solubility and therefore increased the resistance to caries [4–6]. Since then, numerous studies have shown the effectiveness of fluoride either contained in water or salt or in topical dental products such as toothpastes [7–9]. According to today's concept, the major effect of fluoride is post-eruptive [10,11]. When topically applied, fluoride present in the oral fluid environment, even in low concentration, can prevent demineralization as well as promote remineralization of incipient lesions under acidic conditions [12–16]. Most experts agree now that pre-eruptive incorporation is of limited importance [9,17,18]. At sufficiently high concentrations, fluoride also inhibits bacterial growth and reduces the

* Corresponding author. School of Dental Medicine, Faculty of Medicine, University of Geneva, 19, rue Barthelemy-Menn, CH-1211 Geneva 4, Switzerland. Tel.: +41 22 3829175; fax: +41 22 7811297;
e-mail: nathalie.viviencastioni@medecine.unige.ch

PII S0939-6411(97)00083-0

rate of acid production by cariogenic microorganisms [10].

The present paper reviews some important aspects of fluoride pharmacokinetics in oral cavity. These considerations have important implications for developing optimum prophylactic measures and products. In the second part of the review, some new approaches for preventing dental caries based on current knowledge concerning fluoride cariostatic mechanisms are discussed.

2. Kinetics of fluoride in the oral cavity

2.1. General considerations

The clearance of a substance introduced in the oral cavity is mainly achieved via saliva. However, many parameters may affect the process (Table 1). These factors are important and have to be considered when preventive agents are applied to the oral cavity. Under normal physiological conditions, without fluoride supplement, salivary fluoride concentrations were usually found to be very low, ranging from 0.01 to 0.04 ppm, depending on the authors [19,20]. When using fluoride, high initial concentrations can be observed, followed by a rapid decrease. Fig. 1 represents the interrelationships between the various components which play a role in the retention and clearance of the fluoride ion.

2.2. Salivary fluoride concentrations after various application modes

According to the majority of the studies involving common home-used topical fluoride products such as dentifrices or mouthrinses, salivary fluoride clearance is a biphasic elimination process, regardless of the formulation and application conditions [21–24]. A typical profile of salivary fluoride concentrations versus time is presented in Fig. 2. The initial rapid decrease in fluoride results most likely from swallowing and secretion of saliva, whereas the slower

Table 1

Parameters influencing the clearance of a product introduced in the oral cavity

Physiological and/or anatomical parameters
Salivary flow rate [29,46]
Swallowing frequency [31]
Residual volume of saliva [31,45]
Anatomical position of the salivary glands [46]
Anatomical factors (space between teeth, tongue position, etc.) [29,46]
Oral muscular movements [31]
Factors related to the product and its administration
Dose and concentration of the product [26]
Duration and frequency of the administration [26]
Association between products and/or buccal substrates [31]
Dilution (drinking habits, rinsing, etc.) [26,29,30]
Time of administration (day or night, proximity of a meal, etc.) [29]

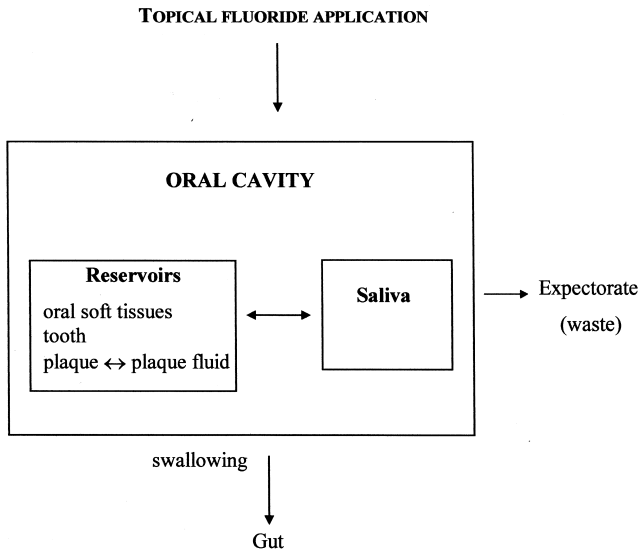

Fig. 1. Illustration of the inter-relationships between the various components involved in fluoride retention.

second phase reflects the release of fluoride that was initially stored in the oral cavity at the time of application. Such retention sites, or 'oral reservoirs', are mainly associated with the soft tissues, plaque and teeth (Fig. 1) [22,23,25–27]. With tablets, chewing gum and concentrated fluoride preparations, salivary clearance has to be considered as a multiexponential process, due to additional phenomena.

The concentrations of fluoride found in saliva after a single topical application have been investigated in many studies. The main representative papers are listed in Table 2. Some general trends may be deduced from these data. The first observation is that professionally applied products, containing high fluoride concentrations, lead to higher salivary levels as compared to self-applied preparations with a lower fluoride content. Varnishes generally give the highest concentrations followed by gels, rinses and finally dentifrices. Initial fluoride concentrations are of importance as they have a direct influence upon the clearance process. Indeed, highest initial levels correspond to a prolonged retention time and a longer clearance process. On the average, fluoride concentrations return to baseline within 1 or 2 h after

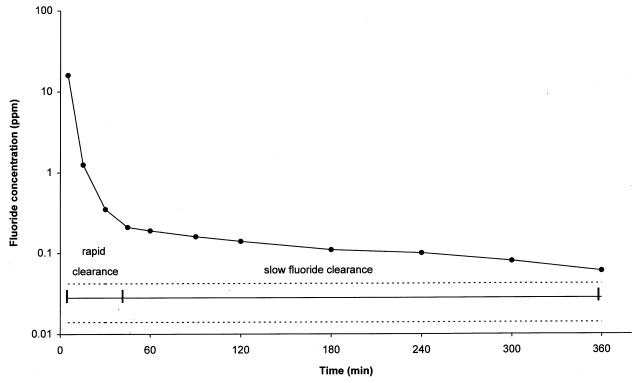

Fig. 2. Mean salivary fluoride concentrations ($n = 2$) after use of 250 ppm F^- rinse [N. Vivien Castioni, P. Baehni, R. Gurny, unpublished data].

Table 2

Reported salivary fluoride concentrations after single topical fluoride applications

Formulation	F^- source	Concentration (ppm F^-)	Salivary F^- at 30 min (μM)	Observation period	References
Dentifrice					
Colgate®	MFP[a]	1000	<25	24 h	[63]
Acta®	NaF	1000	<30	24 h	[63]
Crest®	NaF	1100	31	2 h	[29,31]
Crest Regular®	NaF	1500	n.a.	45 min	[30]
n.a.	MFP	1000	n.a.	3 h	[22,24,41]
		1500	4–9		
		2500	n.a.		
Rinse					
Fluorigard®	NaF	226	53/60	2 h/8 h/24 h	[29,31,46]
n.a.	NaF	226	27	48 h	[64]
		900	150/110/318	1 h/72 h/24 h	[63–65]
n.a.	NaF	250	~50	3 h	[23]
		830	100–110		
		2500	100–110		
Gel					
Alpha Gel®		9000	468	120 h	[64]
Thera-Flur®	NaF	5000	424	24 h	[29,46]
Tablet					
n.a.	NaF	0.25 mg	<50	1 h/24 h	[20,63]
Chewable tablet					
Gostrimant®	NaF	0.21 mg	<53	1 h/24 h	[20,63]
Chewing gum					
Fluomin®	NaF	0.25 mg	<20	1 h/24 h	[20,63]
Varnish					
Duraphat®	NaF	22600	1683	120 h	[64]

[a]Sodium monofluorophosphate (Na_2FPO_3).
n.a., not available.

using a dentifrice or a mouthrinse, 2–24 h after the use of gels or concentrated rinses, and over 24 h after applying varnishes and other topical products with very high fluoride concentrations [19,28]. The different profiles of salivary fluoride levels obtained with low and high-concentrated products are shown in Fig. 3.

Fluoride clearance is known to be more rapid after using a dentifrice than after a mouthrinse, with the same dose, and this results mainly from the extensive water rinse after brushing [24,29–31]. Duckworth, for example, showed that the clearance rate increases with increasing volume, frequency and duration of water rinses [24]. Mechanical stimulation of the salivary flow due to brushing action is probably also of importance [31].

It is interesting to note that the retention of fluoride in the oral cavity depends more on the concentration of fluoride rather than the applied dose. Duckworth and Stewart [23] have suggested that application of a given fluoride dose in a small volume but at high concentration increases efficacy: fluoride clearance is then reduced without the risk of adverse effects as a result of casual ingestion of a high dose.

Zéro et al. [29] reported that the time of application (day-

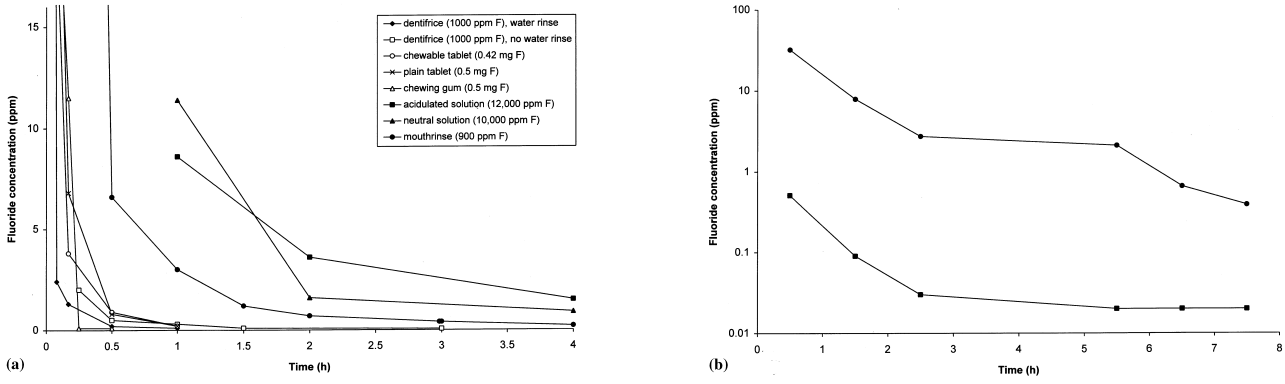

Fig. 3. (a) Salivary fluoride concentrations after various topical fluoride treatments. (Adapted from Ref. [63]). (b) Salivary fluoride concentrations after a varnish treatment (Duraphat®; ●) and a mouthrinse (0.05% NaF; ■). (Adapted from Ref. [64]).

time vs. night-time) is another important variable which can considerably influence fluoride levels in the mouth. Night-time fluoride application usually results in prolonged retention because of a reduced salivary flow as well as the absence of food and beverage intake.

It is worth mentioning that even if salivary fluoride levels vary widely according to the dose applied, the caries reduction obtained after various topical applications appears to be similar, suggesting that daily use of low fluoride products is at least as beneficial as treatments with highly-concentrated preparations applied at more broadly spaced intervals of time. In fact, the fluoride ion has to be present at the site during the development of the lesion to efficiently prevent caries. Both fluoride regimens mentioned above may provide fluoride ions during an acid attack, i.e. during the cariogenic stage. Daily use of low fluoride doses, either through home-used products or water and salt fluoridation, will both enrich the oral cavity with F^- ions. In the case of highly concentrated preparations, precipitate of calcium fluoride is usually formed during application which redissolves slowly when the pH drops, thus providing a source of fluoride ions.

2.3. Fluoride distribution in the mouth after topical application

2.3.1. Fluoride distribution in the different sites of the oral cavity

During the last 10 years, several studies have clearly shown that the pattern of fluoride distribution and clearance after topical application varied considerably from site to site in the mouth [32–34]. Weatherell et al. [33] and Primosch et al. [34] demonstrated that there is little saliva mixing between the different regions in the oral cavity. The authors also noticed that fluoride tended to be preferentially retained in the maxillary labial vestibule. Actually, each site appears to be characterized by its own rate of retention and clearance. This is probably due to the anatomical disposition of salivary ducts, to the rate of salivary secretion, and to other individual variations. It was suggested that the rapid clearance from the posterior regions of the labial vestibule is associated with the flow from the parotid, whereas secretions from the sublingual and submandibular glands as well as the act of swallowing play a role in the clearance from the entire lower labial sulcus [33]. This site-specific variability in oral fluoride concentrations is illustrated in Fig. 4.

2.3.2. Fluoride concentration in various tissues

Beside saliva, fluoride concentrations after topical application have been analyzed in samples from tooth surfaces, plaque or soft tissues. As for the site-specific variability, these observations are certainly relevant to the anti-caries effect of the fluoride ion since local concentrations are important.

Enamel surface. Assuming that more fluoride in the enamel would provide a greater anti-caries protection, measurements of fluoride in enamel have been undertaken by many authors. However, most of these studies failed to clearly demonstrate an inverse relationship between fluoride enamel content and caries prevalence [15,35,36].

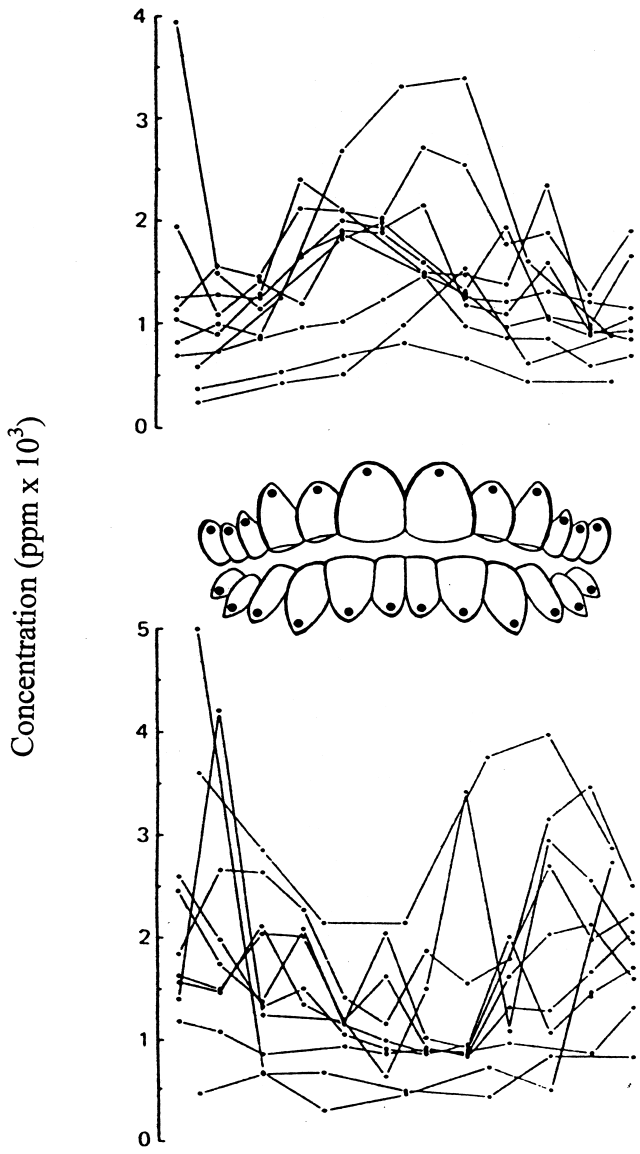

Fig. 4. Concentrations of fluoride taken up by dentin particles (indicated by the black spots on the diagram) mounted on dental splints after a 1000 ppm (20 ml) fluoride rinse (from Weatherell et al. [32], reproduced with permission of S. Karger AG, Basel).

Today we know that fluoride incorporated into the enamel mineral during tooth development has little effect on the caries process. However, fluoride incorporated post-eruptively, during the demineralization-remineralization process is of major importance [17]. Fluoride enhances remineralization providing thus a mineral which will be more resistant to subsequent acid attack than natural apatite-like material.

Plaque. Since recent developments in fluoride analysis, especially the advent of specific micro-electrodes, several investigators have assessed fluoride concentrations in dental

Table 3
Plaque fluoride concentrations (wet weight basis) recorded after various topical fluoride treatments

Fluoride product	ppm F^-	Plaque concentration (ppm F^-)		F in water (ppm F^-)	References
		Baseline	Regular use		
Dentifrice	1000	1.46	1.76–1.91	0.027	[39]
	1500		1.93–2.21		
	2500		2.36–2.54		
Dentifrice	1500	1.41	1.92	0.026	[40]
		4.34	5.28	0.16	
		6.96	8.57	1.0	
Rinse	100	1.2	~1.4	0.027	[38]
	250		~2.4		
	1000		3.3		
Placebo dentifrice		8.5	n.a.	0.9	[29]
Dentifrice	1100	9.8	n.a.		
Rinse	226	12.8	n.a.		
Gel	5000	8.0	n.a.		

n.a., not available.

plaque (Table 3). This information is of interest as fluoride values are determined in material collected near the site of the caries process. Likewise, fluoride concentration in plaque fluid could at least be as relevant as plaque fluoride to the anti-caries effect [35].

Total plaque fluoride data reported in the literature vary considerably but are usually within the range of 2–10 mg F^-/kg on a wet weight basis [37]. Higher values are obtained in areas with fluoridated water as well as after regular use of topical fluoride-containing products [22,29, 37–40].

Although higher than those of saliva, the concentration of fluoride in plaque generally follow the same pattern. Thus, Zéro et al. [29] showed a parallel evolution of fluoride levels in pooled plaque samples and whole saliva after home-use of topical fluorides application; they also showed that the highest fluoride concentrations in plaque and saliva were obtained after using fluoride gel, followed by fluoride rinse and dentifrice. Duckworth et al. [22,38] also reported a direct dose–response relationship between saliva and plaque fluoride after using different fluoride-containing mouthwashes and dentifrices. Furthermore, an inverse relationship was shown between plaque fluoride levels and 3-year caries increments [41]. These results support the assumption of an association between oral fluoride levels and caries, and suggest that oral fluoride measurements could be valuable in estimating the anti-caries potential of various fluoride regimens.

Mucosa. Some studies assessed fluoride uptake and clearance from oral mucosa, known to be a part of the oral fluoride reservoirs [25,27]. Jacobson et al. [27] showed that baseline fluoride mucosal levels were high (7–15 ppm) and that they did not significantly vary from site to site. After rinsing with a fluoridated mouthwash, mucosal samples presented elevated fluoride concentrations which declined with a $t_{1/2}$ of 45–60 min. According to the authors, the considerable difference between salivary and mucosal baseline levels may reflect a prolonged fluoride clearance from the oral soft tissues and suggests that these tissues could play a significant role in the kinetics of oral fluoride clearance. Fig. 5 shows the different rates of clearance between the saliva and mucosa, thereby revealing that mucosa can act as a potential fluoride reservoir in the oral cavity.

Zéro et al. [25] evaluated fluoride retention by oral soft tissues by comparing salivary concentrations in edentulous and fully dentate subjects. Contrary to Jacobson et al. [27], the authors found considerable differences in fluoride values among the various soft tissue sites. They also observed a correlation between concentrations in whole saliva and tissue levels after topical applications. The edentulous subjects presented somewhat higher salivary fluoride concentrations during the 24-h experimental period, thus showing the major role of the oral soft tissues in fluoride retention. High affinity for teeth and plaque may have contributed to the initial clearance of fluoride from saliva in the dentate subjects.

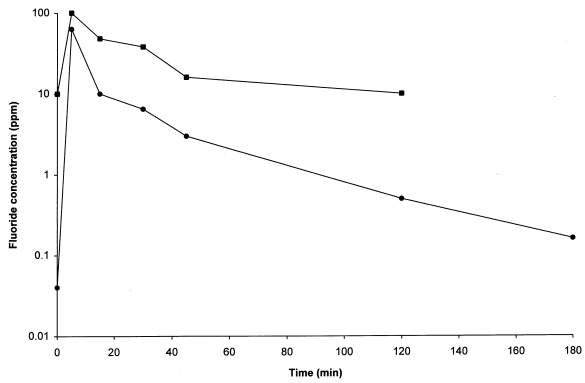

Fig. 5. Salivary (●) and buccal mucosal (■) fluoride concentrations after mouthrinsing (adapted from Ref. [27]).

2.4. Fluoride concentrations after long-term treatment

Most of the studies on salivary fluoride kinetics were limited to the concentrations obtained after single topical application. However, the situation differs drastically when using fluoride on a regular basis. Equilibrium studies were therefore undertaken in order to monitor changes in fluoride concentrations during prolonged use of dentifrices [22] and mouthrinses [38]. In accordance with the oral fluoride reservoir concept, the baseline level itself was found to be elevated during regular applications of topical fluoride. Duckworth et al. [22,38] reported that salivary levels took approximately 2 weeks to reach equilibrium after a change in the daily habits, thus giving evidence that fluoride is stored in the oral cavity. Previous studies had already shown that salivary fluoride concentrations rose significantly with increasing fluoride content of drinking water [40,42,43]. Moreover, Bruun and Thylstrup [42] found the mean DMF-S (decayed, missing, filled tooth surfaces) to be inversely related to whole saliva fluoride. Basal fluoride levels in plaque usually appear to be in good agreement with the corresponding salivary fluoride values and reflect as well long-term fluoride regimen [22,38]. Duckworth et al. [41] not only demonstrated a dose–response relationship between saliva and plaque fluoride concentrations after long-term use of dentifrices, but also showed an inverse correlation between fluoride, saliva and plaque levels, and the caries increment observed during a period of 3 years.

The influence of oral care habits on caries prevalence and incidence clearly illustrates the importance of a prolonged exposure to fluoride. Chesters et al. [44] demonstrated that brushing frequency and rinsing method after brushing were directly related to caries increment. Twice-a-day brushers and non-beaker rinsers had lower caries increment than less frequent brushers or than subjects using beakers for rinsing.

The following points summarize the present knowledge on the long-term fluoride concentration in the oral environment:

- In the absence of topical fluoride, salivary fluoride concentration is about two-thirds of the plasma levels [19]
- For a given regimen of daily fluoride, baseline level in saliva is usually constant [19]
- When a change in fluoride use occurs, a new equilibrium is reached after a 2-week period [38]

Consequently, none of the fluoride supplement, either systemic or topical, is able to produce a permanent elevation of oral fluoride concentration. Therefore, in order to achieve its optimum caries preventive effect, a regular topical fluoride supply is essential. As discussed by Axelsson [18], plaque control, either mechanical or chemical, is also of major importance for caries prevention. If plaque control is mandatory as an essential anti-caries measure, rational use of fluorides is the unquestionable complement to maintain dental caries progression as low as possible throughout the world.

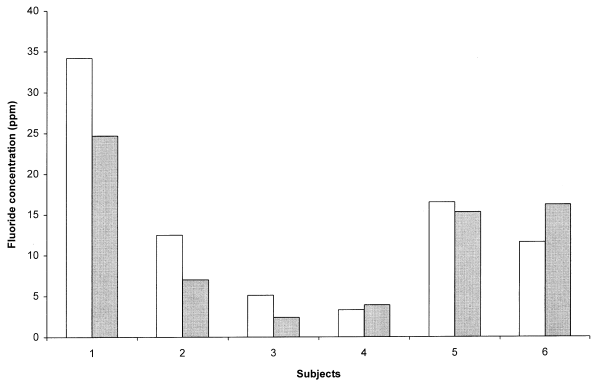

Fig. 6. Duplicate salivary fluoride concentrations 5 min after a mouthrinse (Mentadent® C sensitive, 250 ppm F^-) in six subjects, at 1-week interval [N. Vivien Castioni, P. Baehni, R. Gurny, unpublished data].

2.5. Individual variability

As discussed above, several local factors are involved in the kinetics of fluoride retention in the mouth. In addition, due to individual characteristics, e.g. salivary flow, swallowing frequency, diet, or bucco-dental hygiene, a great variability has been shown to occur between subjects and, for a given subject, from day to day [33,45].

Fig. 6 shows the salivary concentrations of fluoride, determined in duplicate on six volunteers, 5 min after mouthrinsing. As previously reported [33], individual fluctuations from 1 day to another are far less important than those observed between two subjects. In some pathological situations, such as xerostomia, the inter-subject variability may be increased to a greater extent. As a result of the low salivary flow rate, xerostomic patients generally show prolonged oral fluoride retention compared to healthy subjects [46]. This situation may be favourable for these patients, with very low salivary flow rate and usually high caries risk, as they will benefit more topical fluoride products. A simple and rapid prophylactic measure such as mouthrinses could then be used as successfully as more complicated and time-consuming procedures, e.g. applying gels in trays. In recommending mouthrinses instead of gels, patient compliance should also be improved.

3. New delivery systems

In light of our present knowledge, the use of fluoride and its role as a topical prophylactic agent in the caries process should be reconsidered. Guidelines for more rational use of fluorides should be revised based on the above-mentioned data [18,47]. In recent years, due to the widespread availability of fluoride sources and consequently a too high fluoride intake during tooth development, the prevalence of dental fluorosis in children has increased. Therefore, there

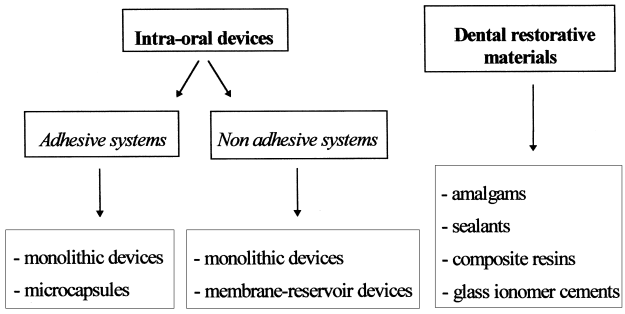

Fig. 7. Site-specific and sustained-release therapeutic systems for oral fluoride.

is a need to adapt fluoride preventive regimen and to reduce systemic fluoride in order to avoid enamel opacities. Recently, several dental associations have revised their guidelines for appropriate use of fluoride products [48–51]. It is important to stress that there is not one single fluoride program: fluoride should be used according to individual or population needs, mainly based on caries risk, oral hygiene status, dietary habits, living conditions, and actual caries prevalence and incidence [18,52].

In this context, and according to the need of individual prophylaxis, new formulations aimed at delivering low levels of fluoride over prolonged period of time were developed. Besides, in controlling the drug release to a certain extent, such devices should be able to reduce inter-individual variations.

Fig. 7 illustrates the different approaches investigated. Two major directions have been chosen, either to develop new intra-oral devices solely intended to deliver fluoride over a prolonged period, with or without rate control, or to incorporate fluoride into restorative materials. Although not directly useful for caries prevention on a large scale, the second approach presents some interest since it takes advantage of a restorative treatment to implement prophylactic measures in someone who needs them.

3.1. Intra-oral devices

Intra-oral devices are commonly classified according to the nature of the dosage form, and in particular to the mode of release of the fluoride or to the mode of retention of the device in the oral cavity; this second aspect can be mediated by including bioadhesive polymers in the device or by adding external adhesive materials.

Essentially three types of intra-oral devices releasing slowly fluoride have been developed: monolithic devices (bioadhesive or not), bioadhesive microcapsules, and membrane-reservoir devices (without adhesive properties). Examples of bioadhesive devices and other monolithic systems are given in Table 4. They include bioadhesive tablets, bioadhesive microcapsules designed to be sprayed on the teeth surface, and nonadhesive films that can be used for coating both orthodontic plates and chewing gums, or sealed on removable partial dentures.

These devices certainly represent an interesting concept in the current tendency to provide specific and optimized caries prophylaxis, however they still need improvement. Moreover, clinical studies will also have to assess their efficacy as well as patient compliance. At this time, mucoadhesive tablets appear to have the best potential. However, a compromise remains to be found between adhesive properties, biocompatibility, and adequate release profile. In vivo studies have shown that, depending on the polymer, some tablets present good mucoadhesive properties without adverse effects such as irritation, discomfort or bad taste [53–55]. These promising tablets were left in place for at least 8 h, and were able to release fluoride in concentrations high enough for a protective effect against dental caries. Although the release period with other devices such orthodontic plates is of great interest (from days to months), the number of patients likely to benefit from such prophylactic devices is very limited.

Membrane-controlled fluoride reservoirs are the most

Table 4
Bioadhesive and other monolithic devices intended for intra-oral slow-release of fluoride

System	Vehicle[a]	F^- (dose)	Type of study (release time)	References
Adhesive devices				
Microcapsule	EC + guar gum	NaF n.a.	In vitro	[66]
Tablet	Carbopol + HPMC	NaF, amines-F (0.1 mg)	In vitro	[67]
	Carbopol, HPMC, PEG, NaCMC, modified starch	NaF (0.1 mg)	In vivo (24 h; 8 h)	[53,55]
	PEG	NaF (0.1 mg)	In vivo (8 h)	[54]
Others				
Film	Cellulose	CaF_2 (1 mg)	In vivo (48 h)	[68]
Orthodontic plate	EC (+PEG)	NaF (0.06–0.5 mg/day)	In vitro (4 months)	[69]
	EC	NaF (5 mg)	In vivo (5 days)	[70]
Chewing gum	Silicone	NaF (0.06–0.5 mg/day)	In vitro (4 months)	[69]

[a]EC, ethylcellulose; HPMC, hydroxypropylmethylcellulose; PEG, polyethylene glycol; NaCMC, sodium carboxymethylcellulose; Carbopol®, polyacrylic acid.
n.a., not available.

Table 5

Representative in vivo studies carried out over the last 20 years

Study	Duration	Daily F^- dosage (mg)	References
Cowsar et al. (1976)	6 months	0.2–1	[56]
Mirth et al. (1982)	30 days	1.0	[71]
Mirth et al. (1983)	6 months	0.15	[72]
Mirth et al. (1985)	35 days	0.15–0.2	[73]
Corpron et al. (1986)	40 days	0.4	[74]
Shern et al. (1987)	30 days	0.5	[75]
Kula et al. (1987)	26 weeks	0.1	[76]
Cain et al. (1994)	7–50 days	0.07/0.23	[57]

extensively tested sustained-release devices for intra-oral use. Since their development by Cowsar et al. [56] in 1976, a large number of in vitro and in vivo studies have been carried out using similar devices (Table 5). Generally, the system consists of a core matrix containing NaF and a copolymer of hydroxyethyl and methyl methacrylate (50:50). The core is surrounded by a copolymer membrane of the same type (30:70) designed to control the rate of fluoride release. Such reservoir devices are able to deliver fluoride in the oral cavity at a constant rate, varying from 0.035 to 2 mg/day. The fluoride delivery period can also be made to vary considerably, from a few days to several months. Such a duration of fluoride release is of particular interest considering that the mean delivery period for bioadhesive tablets previously mentioned seldom exceeds 8 h.

Membrane-controlled reservoir-type devices offer several advantages. They may be designed in different sizes and forms and can present various fluoride delivery rates. Besides, their retention in the mouth may be achieve either using an appliance or directly by fixing the device on a tooth surface with resins or sealants. This large range of possibilities makes them adaptable to almost any situation. Some mucosal irritation and loss of the device during the experimental period have been reported, thus indicating that further improvements in manufacture and in retention are needed [57]. Furthermore, it should be stressed that such systems, which have to be placed by a dental health personnel, would apply mainly to patients with high risks of caries such as xerostomic people, handicapped persons, immunodeficient patients, and patients wearing orthodontic appliances.

3.2. Restorative materials

Rawls [58] reviewed the different dental systems capable of releasing therapeutic agents, including the sustained delivery of fluoride. The systems were divided in three categories as shown in Table 6. Mixtures of water-soluble agents generally show burst effects and a short-lived release; they also require frequent applications [59]. Dispersions of agents of very low water solubility such as glass ionomer cements appear promising according to recent studies [60,61]: beside their intrinsic property of releasing fluoride, they can take up fluoride from the surrounding medium for subsequent release. Moreover, a complete retention of the cement does not appear to be necessary for caries prevention [60]. Matrix-bound agents consisting of fluoride ion-exchange monomers bounded to a matrix represent the third category. In such a system, the fluoride ion is released by a chemical reaction, generally a hydrolysis, and diffuses out of the matrix. A clinical trial using an acrylic ion-exchange salt in a bracket bonding adhesive demonstrated a 90% reduction in the number of demineralized zones [58]. In a recent paper, Toumba et al. [59] reviewed studies on fluoride controlled-release systems, including dental materials. Systems such as amalgams, cements, fissure sealants and composite resins were also reported to be capable of releasing fluoride.

These fluoride releasing reconstructive materials may be of great interest in some cases, particularly in root and recurrent caries restorations as well as for the fixation of orthodontic appliances. However, they cannot be consid-

Table 6

Fluoride releasing restorative materials [58]

Type of material	Source of F^-	Comment
Mixtures of water-soluble agents		
Amalgam	SnF_2	Structure vulnerable to environmental degradation
Composite resin	NaF	
Sealant	NaF	
Dispersions of agents of very low water solubility		
Silicate cement	Leachable glasses	Structural stability preserved
Glass ionomer material	Leachable glasses	
Composite resin	YbF_3, NaF encapsulated	
	Leachable glass	
Matrix-bound agents		
Bis-GMA-type acrylic resin	Amine BF_3 Lewis salt	Structural integrity maintained
Light-cured sealant	Amine BF_3 Lewis salt	
	Amine HF salt	
	Methacryloyl fluoride	
Composite resin	Amine HF salt	

ered as an universal measure for the prevention of dental caries. They represent an additional support to treatment and reinforce preventive procedures.

4. Conclusions

During the last 20 years, great progress has been made in understanding the caries process. The mode of action of fluoride as a prophylactic agent is also better understood. As a consequence, efforts have been made to find approaches more adapted to recent findings for the prevention of dental caries.

It is well accepted today that the efficacy of fluoride against dental caries is mainly due to its topical effect. Only slightly elevated concentrations in the medium surrounding the tooth are necessary, provided that they can be maintained.

Nowadays, a large number of topical fluoride products are available on the market. They have played an important role in the decrease of caries prevalence worldwide. However, such products have not yet been optimized. Indeed, the currently home-used preparations, containing low concentrations of the fluoride ion, give only short-term salivary fluoride increase. Even if they provide the regular F^- ion supply needed, they cannot maintain high level enough to protect the teeth all day long, between two applications. Alternatively, professionally applied products with high concentrations can sustain elevated fluoride levels for several days. However, they are used only once or twice a year and cannot either insure a permanent cariostatic effect. Thus, none of the topical fluoride product currently on the market is sufficient by itself, especially in the presence of a high cariogenic challenge. This conclusion, already discussed in previous papers [18,62], emphasizes the importance of other prophylactic measures, mainly plaque control and reduction of sugar intake. Apart from these effective preventive approaches, it has been suggested that additional support could be obtained if sustained-release fluoride products were developed. These new delivery systems, although not yet currently applicable in clinical practice, have shown interesting results with continuous elevated salivary fluoride concentrations. Some of them, especially bioadhesive tablets, are currently clinically tested and should be helpful for patients with high risk of caries.

References

[1] G. Nikiforuk, The concept of prevention. An introduction, in: G. Nikiforuk (Ed.), Understanding Dental Caries. 2. Prevention. Basic and Clinical Aspects, Karger, Basel, 1985, pp. 1–12.

[2] H.T. Dean, Fluorine in dental caries control, Postgrad. Med. 5 (1949) 361–367.

[3] H.T. Dean, Fluoridation: mass control for dental caries. The adjustment of the fluoride concentration of the public water supply should markedly reduce the dental caries problem, Am. J. Nurs. 52 (1952) 210–212.

[4] T.M. Marthaler, Caries-inhibiting effect of fluoride tablets, Helv. Odont. Acta 13 (1969) 1–13.

[5] B.G. Bibby, F. Brudevold, The external action of fluorides and other agents on the teeth in the prevention of dental decay. Anonymous Fluoridation as a public health measure, American Association for the Advancement of Sciences, Washington, DC, 1954, pp. 148–178.

[6] J.E. McKee, A rational approach to fluoridation, J. Am. Water Works Assoc. 45 (1953) 376–386.

[7] J.A. Hargreaves, Water fluoridation and fluoride supplementation: considerations for the future, J. Dent. Res. 69 (1990) 765–770.

[8] H.S. Horowitz, The future of water fluoridation and other systemic fluorides, J. Dent. Res. 69 (1990) 760–764.

[9] A. Thylstrup, Clinical evidence of the role of pre-eruptive fluoride in caries prevention, J. Dent. Res. 69 (1990) 742–750.

[10] H.C. Margolis, E.C. Moreno, Physicochemical perspectives on the cariostatic mechanisms of systemic and topical fluorides, J. Dent. Res. 69 (1990) 606–613.

[11] T. Koulourides, P. Phantumvanit, E.C. Munksgaard, T. Housch, An intraoral model used for studies of fluoride incorporation in enamel, J. Oral Pathol. 3 (1974) 185–196.

[12] J.M. Ten Cate, P.P.E. Duijsters, Influence of fluoride in solution on tooth demineralization. II. Microradiographic data, Caries Res. 17 (1983) 513–519.

[13] M.J. Larsen, Chemical events during tooth dissolution, J. Dent. Res. 69 (1990) 575–580.

[14] J.D.B. Featherstone, D.T. Zéro, Laboratory and human studies to elucidate the mechanism of action of fluoride-containing dentifrices, in: G. Embery, G. Rölla (Eds.), Clinical and Biological Aspects of Dentifrices, Oxford University Press, New York, 1992, pp. 41–50.

[15] J. Arends, J. Christoffersen, Nature and role of loosely bound fluoride in dental caries, J. Dent. Res. 69 (1990) 601–605.

[16] R.P. Shellis, R.M. Duckworth, Studies on the cariostatic mechanisms of fluoride, Int. Dent. J. 44 (1994) 263–273.

[17] O. Fejerskov, B.H. Clarkson, Dynamics of caries lesion formation, in: O. Fejerskov, J. Ekstrand, B.A. Burt (Eds.), Fluoride in Dentistry, Munksgaard Textbook, Copenhagen, 1996, pp. 187–206.

[18] P. Axelsson, Current role of pharmaceuticals in prevention of caries and periodontal disease, Int. Dent. J. 43 (1993) 473–482.

[19] C. Dawes, J.A. Weatherell, Kinetics of fluoride in the oral fluids, J. Dent. Res. 69 (1990) 638–644.

[20] C. Bruun, H. Givskov, Fluoride concentrations in saliva in relation to chewing of various supplementary fluoride preparations, Scand. J. Dent. Res. 87 (1979) 1–6.

[21] J. Afflito, R. Schmid, A. Esposito, R. Toddywala, A. Gaffar, Fluoride availability in human saliva after dentifrice use: correlation with anticaries effects in rats, J. Dent. Res. 71 (1992) 841–845.

[22] R.M. Duckworth, S.N. Morgan, Oral fluoride retention after use of fluoride dentifrices, Caries Res. 25 (1991) 123–129.

[23] R.M. Duckworth, D. Stewart, Effect of mouthwashes of variable NaF concentration but constant NaF content on oral fluoride retention, Caries Res. 28 (1994) 43–47.

[24] R.M. Duckworth, D.T.M. Knoop, K.W. Stephen, Effect of mouthrinsing after toothbrushing with a fluoride dentifrice on human salivary fluoride levels, Caries Res. 25 (1991) 287–291.

[25] D.T. Zéro, R.F. Raubertas, A.M. Pedersen, J. Fu, A.L. Hayes, J.D.B. Featherstone, Studies of fluoride retention by oral soft tissues after the application of home-use topical fluorides, J. Dent. Res. 71 (1992) 1546–1552.

[26] R.M. Duckworth, S.N. Morgan, G.S. Ingram, D.J. Page, Oral fluoride reservoirs and their relationship to anticaries efficacy, in: G. Embery, G. Rölla (Eds.), Clinical and Biological Aspects of Dentifrices, Oxford University Press, New York, 1992, pp. 91–104.

[27] A.P.M. Jacobson, K.W. Stephen, R. Strang, Fluoride uptake and clearance from the buccal mucosa following mouthrinsing, Caries Res. 26 (1992) 56–58.

[28] G.K. Stookey, Critical evaluation of the composition and use of topical fluorides, J. Dent. Res. 69 (1990) 805–812.

[29] D.T. Zéro, R.F. Raubertas, J. Fu, A.M. Pedersen, A.L. Hayes, J.D.B. Featherstone, Fluoride concentrations in plaque, whole saliva, and ductal saliva after application of home-use topical fluorides, J. Dent. Res. 71 (1992) 1768–1775.
[30] K. Sjögren, D. Birkhed, Effect of various post-brushing activities on salivary fluoride concentration after toothbrushing with a sodium fluoride dentifrice, Caries Res. 28 (1994) 127–131.
[31] D.T. Zéro, J. Fu, M.A. Espeland, J.D.B. Featherstone, Comparison of fluoride concentrations in unstimulated whole saliva following the use of a fluoride dentifrice and a fluoride rinse, J. Dent. Res. 67 (1988) 1257–1262.
[32] J.A. Weatherell, M. Strong, J.P. Ralph, C. Robinson, Availability of fluoride at different sites in the buccal sulcus, Caries Res. 22 (1988) 129–133.
[33] J.A. Weatherell, M. Strong, C. Robinson, J.P. Ralph, Fluoride distribution in the mouth after fluoride rinsing, Caries Res. 20 (1986) 111–119.
[34] R.E. Primosch, J.A. Weatherell, M. Strong, Distribution and retention of salivary fluoride from a sodium fluoride tablet following various intra-oral dissolution methods, J. Dent. Res. 65 (1986) 1001–1005.
[35] R.M. Duckworth, R.J. Gilbert, Intra-oral models to assess cariogenicity: Evaluation of oral fluoride and pH, J. Dent. Res. 71 (1992) 934–944.
[36] O. Fejerskov, A. Thylstrup, M.J. Larsen, Rational use of fluorides in caries prevention. A concept based on possible cariostatic mechanisms, Acta Odontol. Scand. 39 (1981) 241–249.
[37] A. Tatevossian, Fluoride in dental plaque and its effects, J. Dent. Res. 69 (1990) 645–652.
[38] R.M. Duckworth, S.N. Morgan, A.M. Murray, Fluoride in saliva and plaque following use of fluoride-containing mouthwashes, J. Dent. Res. 66 (1987) 1730–1734.
[39] R.M. Duckworth, S.N. Morgan, C.K. Burchell, Fluoride in plaque following use of dentifrices containing sodium monofluorophosphate, J. Dent. Res. 68 (1989) 130–133.
[40] W.M. Edgar, G.S. Ingram, S.N. Morgan, Fluoride in saliva and plaque in relation to fluoride in drinking water and in dentifrice, in: G. Embery, G. Rölla (Eds.), Clinical and Biological Aspects of Dentifrices, Oxford University Press, New York, 1992, pp. 157–163.
[41] R.M. Duckworth, S.N. Morgan, R.J. Gilbert, Oral fluoride measurements for estimation of the anti-caries efficacy of fluoride treatments, J. Dent. Res. 71 (1992) 836–840.
[42] C. Bruun, A. Thylstrup, Fluoride in whole saliva and dental caries experience in areas with high or low concentrations of fluoride in the drinking water, Caries Res. 18 (1984) 450–456.
[43] A. Oliveby, S. Twetman, J. Ekstrand, Diurnal fluoride concentration in whole saliva in children living in a high- and a low-fluoride area, Caries Res. 24 (1990) 44–47.
[44] R.K. Chesters, E. Huntington, C.K. Burchell, K.W. Stephen, Effect of oral care habits on caries in adolescents, Caries Res. 26 (1992) 299–304.
[45] F. Lagerlöf, A. Oliveby, J. Ekstrand, Physiological factors influencing salivary clearance of sugar and fluoride, J. Dent. Res. 66 (1987) 430–435.
[46] R.J. Billings, C. Meyerowitz, J.D.B. Featherstone, M.A. Espeland, J. Fu, L.F. Cooper, H.M. Proskin, Retention of topical fluoride in the mouths of xerostomic subjects, Caries Res. 22 (1988) 306–310.
[47] D.G. Pendrys, Risk of fluorosis in a fluoridated population. Implications for the dentist and hygienist, J. Am. Dent. Assoc. 126 (1995) 1617–1624.
[48] American Dietetic Association, Position of the American Dietetic Association: the impact of fluoride on dental health, J. Am. Diet. Assoc. 94 (1994) 1428–1431.
[49] D.W. Lewis, A.I. Ismail, Periodic health examination, 1995 update. II. Prevention of dental caries, Can. Med. Assoc. J. 152 (1995) 836–846.
[50] R.D. Holt, J.H. Nunn, W.P. Rock, J. Page, British Society of Paediatric Dentistry: a policy document on fluoride dietary supplements and fluoride toothpastes for children, Int. J. Ped. Dent. 6 (1996) 139–142.
[51] Report of a WHO Expert Committee on oral health status and fluoride use. Fluorides and oral health, WHO Technical Report Series No. 846, WHO, Geneva, 1994.
[52] O. Fejerskov, Strategies in the design of preventive programs, Adv. Dent. Res. 9 (1995) 82–88.
[53] P. Bottenberg, R. Cleymaet, C. De Muynck, J.P. Remon, D. Coomans, Y. Michotte, D. Slop, Development and testing of bioadhesive, fluoride- containing slow-release tablets for oral use, J. Pharm. Pharmacol. 43 (1991) 457–464.
[54] P. Bottenberg, R. Cleymaet, C. De Muynck, J.P. Remon, D. Coomans, D. Slop, Comparison of salivary fluoride concentrations after administration of a bioadhesive slow-release tablet and a conventional fluoride tablet, J. Pharm. Pharmacol. 44 (1992) 684–686.
[55] P. Bottenberg, Effiziente Fluoriddarreichung durch Schleimhauthafttabletten mit verzögerter Freisetzung, Oralprophylaxe 13 (1991) 148–152.
[56] D.R. Cowsar, O.R. Tarwater, A.C. Tanquary, Controlled release of fluoride from hydrogels for dental applications, Am. Chem. Soc. Symp. Ser. 31 (1976) 180–197.
[57] B.E. Cain, R.E. Corpron, C.L. Fee, D.S. Strachan, C.J. Kowalski, Dose related remineralization using intraoral fluoride-releasing devices in situ, Caries Res. 28 (1994) 284–290.
[58] H.R. Rawls, Preventive dental materials: sustained delivery of fluoride and other therapeutic agents, Adv. Dent. Res. 5 (1991) 50–55.
[59] K.J. Toumba, M.E.J. Curzon, Slow-release fluoride, Caries Res. 27 (1993) 43–46.
[60] P. Arrow, P.J. Riordan, Retention and caries preventive effects of a GIC and a resin-based fissure sealant, Community Dent. Oral Epidemiol. 23 (1995) 282–285.
[61] S.L. Creanor, W.P. Saunders, L.M.C. Carruthers, R. Strang, R.H. Foye, Effect of extrinsic fluoride concentration on the uptake and release of fluoride from two glass ionomer cements, Caries Res. 29 (1995) 424–426.
[62] B. Krasse, The caries decline: is the effect of fluoride toothpaste overrated?, Eur. J. Oral Sci. 104 (1996) 426–429.
[63] C. Bruun, D. Lambrou, M.J. Larsen, O. Fejerskov, A. Thylstrup, Floride in mixed human saliva after different topical fluoride treatments and possible relation to caries inhibition, Community Dent. Oral Epidemiol. 10 (1982) 124–129.
[64] U. Heintze, L.G. Petersson, Accumulation and clearance of fluoride in human mixed saliva after different topical fluoride treatments, Swed. Dent. J. 3 (1979) 141–148.
[65] G.L. Vogel, C.M. Carey, J. Ekstrand, Distribution of fluoride in saliva and plaque fluid after a 0.048 mol/l NaF rinse, J. Dent. Res. 71 (1992) 1553–1557.
[66] D. Williams, P.M. Meier, P. Gron, C.J. Hitchcock, T.J. Mullins, W.H. Bowen, Cariostatic microcapsules for aerosol delivery, J. Pedod. 6 (1982) 218–228.
[67] P. Bottenberg, J. Herman, D. Coomans, C. De Muynck, J.P. Remon, D. Slop, Y. Michotte, Bioadhesion of fluoride containing slow-release tablets on porcine oral mucosa in vitro, STP Pharma 5 (1989) 863–866.
[68] L.J. Abrahams, M. Yonese, W.I. Higuchi, J.L. Fox, G.T. Charbeneau, In vivo remineralization using a sustained topical fluoride delivery system, J. Dent. Res. 59 (1980) 583–587.
[69] M. Friedman, Fluoride prolonged release preparations for topical use, J. Dent. Res. 59 (1980) 1392–1397.
[70] D. Harary, M. Friedman, Enhancement of fluoride concentration in saliva after topical application of fluoride sustained-release dosage form on orthodontic plates, J. Pharm. Sci. 73 (1984) 135–136.
[71] D.B. Mirth, R.J. Shern, C.G. Emilson, D.D. Adderly, S.-H. Li, I.M. Gomez, W.H. Bowen, Clinical evaluation of an intraoral device for the controlled release of fluoride, J. Am. Dent. Assoc. 105 (1982) 791–797.

[72] D.B. Mirth, D.D. Adderly, S.M. Amsbaugh, E. Monell-Torrens, S.-H. Li, W.H. Bowen, Inhibition of experimental dental caries using an intraoral fluoride-releasing device, J. Am. Dent. Assoc. 107 (1983) 55–58.

[73] D.B. Mirth, D.D. Adderly, E. Monell-Torrens, S.M. Amsbaugh, S.-H. Li, W.H. Bowen, Comparison of the cariostatic effect of topically and systemically administered controlled-release fluoride in the rat, Caries Res. 19 (1985) 466–474.

[74] R.E. Corpron, J.W. Clark, A. Tsai, F.G. More, D.F. Merrill, C.J. Kowalski, T.R. Tice, C.E. Rowe, Intraoral effects of a fluoride-releasing device on acid-softened enamel, J. Am. Dent. Assoc. 113 (1986) 383–388.

[75] R.J. Shern, D.B. Mirth, C.G. Emilson, D.D. Adderly, B.H. Bowen, Evaluation of an intraoral controlled release delivery system for fluoride in primates, Community Dent. Oral Epidemiol. 15 (1987) 113–116.

[76] K. Kula, T. Kula, W. Davidson, E. Parker, Pharmacological evaluation of an intra-oral fluoride-releasing device in adolescents, J. Dent. Res. 66 (1987) 1538–1542.