Effect of Cyclodextrins and Polymers on Triclosan Availability and Substantivity in Toothpastes in Vivo

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Abstract □ The aqueous solubility of triclosan is only about 10 μg/mL. This very low solubility can hamper its biological activity in the oral cavity, which could explain the mixed clinical results obtained from triclosan toothpaste trials. Triclosan availability in a silica-based toothpaste was improved through cyclodextrin solubilization. The triclosan in vivo availability was optimized through a series of phase-solubility studies and triclosan release studies. It was found that in toothpastes, natural β-cyclodextrin (βCD) was just as good a solubilizer as the more water-soluble βCD derivatives. Furthermore, the amount of cyclodextrin could be reduced by as much as 60% through the addition of a small amount of carboxymethylcellulose (CMC), without affecting triclosan release from the toothpaste. Optimally, cyclodextrins resulted in an almost 3-fold enhancement of triclosan availability compared to an identical toothpaste containing no cyclodextrin. In vivo studies in humans showed that replacing triclosan with triclosan/βCD in the toothpaste resulted in only moderate improvement in triclosan substantivity. However, replacing triclosan with triclosan/βCD/CMC complex resulted in significant improvement in triclosan substantivity. Furthermore, the in vivo studies showed that replacing free triclosan with triclosan/βCD/CMC complex resulted in an almost 3-fold increase in initial triclosan concentration in saliva after brushing and about 2-fold increase in duration of activity.

Introduction

Addition of antibacterial agents to oral care products is an effective way for preventing bacterial plaque formation on tooth surfaces and consequent formation of gingivitis.[1−3] However, the antiplaque activity of an antibacterial agent is not solely related to in vitro antimicrobial activity. Other factors, such as the availability of the antibacterial agent in the oral product and its substantivity in the mouth (i.e., the magnitude and duration of antibacterial effect in saliva) appear to be important parameters.[3,4] The release rate of the antibacterial agent from the oral care product into the aqueous salvia and consequent partition of the agent into the lipophilic intraoral sites can be a crucial factor for effective plaque inhibitation. Furthermore, the concentration of the antimicrobial agent in saliva must be above the minimal inhibitory concentration to exert a bacteriostatic effect. Thus, to ensure a bacteriostatic concentration, the antibacterial agent must be soluble in the aqueous saliva and, at the same time, the agent must be lipophilic to be able to partition from salvia into the lipophilic intraoral sites. Cationic antibacterial agents which exhibit prolonged substantivity in the mouth, such as chlorhexidine, are among the most effective antiplaque agents available. However, their incompatibility with anionic surfactants, staining of teeth and disturbances of taste have limited their usage in oral care products.

Triclosan (Figure 1) is a lipophilic, water-insoluble antibacterial agent which is commonly added to toothpastes, and other oral care products, as a dental antiplaque agent. In general, the availability and substantivity of triclosan is significantly less than those of chlorhexidine and, thus, triclosan is a less effective antiplaque agent than chlorhexidine.[5] However, formulations which improve the availability and/or substantivity, such as triclosan containing liposomes[6] and triclosan/copolymer dentifrice,[7] can significantly improve the antiplaque effect. It has been shown that good delivery of an antiplaque agent, such as triclosan, requires a highly optimized formulation.[8]

Cyclodextrins are cyclic oligosaccharides with a lipophilic central cavity and hydrophilic outer surface. Cyclodextrins are able to form complexes with lipophilic water-insoluble compounds by taking up the compound, or more frequently some lipophilic moiety of the compound, into the cavity. No covalent bonds are formed or broken during the complex formation, and free (i.e., unbound) molecules are in equilibrium with molecules bound in the complex.[9,10] Cyclodextrins increase the delivery of lipophilic, water-insoluble drugs into biological membranes by increasing the drug availability at the hydrated surface of the membrane.[11] The most common natural cyclodextrins are α-cyclodextrin (αCD), β-cyclodextrin (βCD), and γ-cyclodextrin (γCD), which consist of six, seven, and eight glucopyranose units, respectively. These natural cyclodextrins, in particular βCD, and their complexes have limited aqueous solubility. Therefore, numerous water-soluble cyclodextrin derivatives have been synthesized. The complexation efficacy of cyclodextrins is rather low and, thus, relatively large amounts of cyclodextrins are frequently needed to solubilize small amounts of a lipophilic, water-insoluble compound. It is possible to enhance both the aqueous solubility of the complexes and the complexation efficacy by adding small amounts of a water-soluble polymer to the aqueous complexation media.[12] The bioavailability of lipophilic drugs in aqueous cyclodextrin solutions is, in general, improved by addition of the polymers. The purpose of this study was to enhance the availability and substantivity of triclosan through cyclodextrin complexation.

Materials and Methods

Materials—Triclosan was purchased from Ciba-Geigy (Greensboro, NC). β-Cyclodextrin (βCD), γ-cyclodextrin (γCD), and randomly methylated β-cyclodextrin (RMβCD), with a degree of substitution of 1.8, were purchased from Wacker-Chemie (Munich, Germany). α-Cyclodextrin (αCD) was obtained from Nihon Shokuhin Kato Co. (Tokyo, Japan) and 2-hydroxypropyl-β-cyclodextrin

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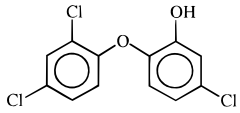

Figure 1—The structure of triclosan, mol wt 289.54, pK_a 7.9.

(HPβCD), with a degree of substitution 2.9, from Janssen Biotech N.V. (Olen, Belgium). Maltosyl β-cyclodextrin (MβCD) was kindly donated by Ensuiko Sugar Refining Co. (Yokohama, Japan) and sulfobutyl ether β-cyclodextrin sodium salt (SBEβCD) by CyDex Inc. (Overland Park, KS). Hydroxypropyl methylcellulose Ph.Eur.'97 (HPMC) was purchased from Mecobenzon (Copenhagen, Denmark), and poly(vinylpyrrolidone) (PVP) of molecular weight 40 000 and carboxymethylcellulose sodium salt (CMC), low viscosity, from Sigma Chemical Co. (St. Louis, MO). All other chemicals used in this study were of reagent or analytical grade and obtained from commercial sources.

The silica-based dentifrice used throughout this study consisted of hydrated silica, sorbitol, glycerine, water, sodium lauryl sulfate, tetrapotassium and tetrasodium pyrophosphate, carbomer, poly(ethylene glycol), sodium phosphate, sodium saccharine, sodium fluoride, and xanthan gum.

Solubility Determinations—An excess amount of triclosan was added to each of the aqueous unbuffered cyclodextrin solutions. The pH of the solutions was between 5 and 6. The solutions were then heated in an autoclave in sealed vials to 121 °C for 20 min. After cooling to room temperature (22−23 °C), a small amount of solid triclosan was added to each vial to promote triclosan precipitation. Then the suspensions were allowed to equilibrate for 5 days at room temperature. After equilibration was attained, an aliquot of each suspension was filtered through a 0.45 μm membrane filter, diluted with the mobile phase, and analyzed by HPLC. Each experiment was performed three times, and the results are presented as the mean ± standard deviation (SD).

Preparation of the Dry Triclosan/βCD Complex Powder—The dry complex was prepared by heating a suspension of triclosan and βCD in an aqueous 0.5% (w/v) CMC solution, or an aqueous solution containing from 0.0 to 1.0% CMC, in an autoclave for 40 min. This was followed by equilibration, at room temperature (22−23 °C) for at least 3 days, and lyophilization.

Preparation of Triclosan/Cyclodextrin-Containing Toothpaste—Cyclodextrin solutions were made by dissolving suitable amount of cyclodextrin (the amount was calculated from the phase-solubility studies) in water or the aqueous polymer solutions. Solutions containing lower and higher cyclodextrin concentrations were also made, altogether 10 different solutions/suspensions for each cyclodextrin derivative. An appropriate amount of triclosan was then added to each solution, and these were heated (120−140 °C) in an autoclave for 40 min. The solutions were allowed to equilibrate for 2 days. A triclosan/cyclodextrin solution/suspension (7.255 g) was then mixed thoroughly with 42.745 g of the silica-based dentifrice resulting in 50 g of toothpaste containing 0.28% (w/w) triclosan. Alternatively, an appropriate amount of lyophilized triclosan/βCD was mixed with 42.705 g of the silica-based dentifrice and water added ad 50 g. After mixing, the samples were allowed to equilibrate for at least 1 day before the triclosan availability was evaluated.

Triclosan Availability Evaluations—The effect of the triclosan/cyclodextrin complex on the permeability of triclosan through a semipermeable cellophane membrane molecular weight cutoff 6 000−8 000 (Spectra/Pore, Fisher Scientific, Pittsburgh, PA) was investigated. The membrane was placed in a Franz diffusion cell (Vangard International Inc., Neptune, NJ) containing 12 mL of an aqueous isotonic pH 7.4 phosphate buffer solution containing 5% (w/v) HPβCD (to solubilize triclosan) and additional 2% (w/v) sodium chloride (to obtain isotonicity with the toothpaste) as a receptor phase. The donor phase consisted of 3 mL of the toothpaste which was applied to the membrane surface (area 3.14 cm^2). The triclosan concentration in the toothpaste was 0.28% (w/w). The assembled diffusion cells were kept at room temperature (about 23 °C), and samples (30 μL) were removed from the donor phase and analyzed by HPLC. The triclosan flux was obtained by plotting the amount of triclosan which went through the membrane against time. The results presented are the means of two experiments.

Table 1—Triclosan Solubility in Aqueous 5.0% (w/v) Cyclodextrin Solution (mean ± SD, n = 3) with or without 0.20% (w/v) Polymer[a]

cyclodextrin and polymer	solubility of triclosan (mg/mL)
αCD in water (no polymer)	0.32 ± 0.00
αCD in aqueous PVP solution	0.29 ± 0.00
αCD in aqueous CMC solution	0.43 ± 0.00
αCD in aqueous HPMC solution	0.44 ± 0.00
βCD* in water (no polymer)	0.09 ± 0.00
βCD* in aqueous PVP solution	0.07 ± 0.01
βCD* in aqueous CMC solution	0.09 ± 0.00
βCD* in aqueous HPMC solution	0.21 ± 0.01**
HPβCD in water (no polymer)	1.75 ± 0.03
HPβCD in aqueous PVP solution	1.60 ± 0.02
HPβCD in aqueous CMC solution	1.78 ± 0.01
HPβCD in aqueous HPMC solution	1.42 ± 0.02
MβCD in water (no polymer)	0.65 ± 0.01
MβCD in aqueous HPMC solution	0.98 ± 0.00
RMβCD in water (no polymer)	1.39 ± 0.02
RMβCD in aqueous PVP solution	1.37 ± 0.02
RMβCD in aqueous CMC solution	1.52 ± 0.02
RMβCD in aqueous HPMC solution	3.70 ± 0.08
SBEβCD in water (no polymer)	2.14 ± 0.03
SBEβCD in aqueous PVP solution	2.07 ± 0.06
SBEβCD in aqueous CMC solution	2.15 ± 0.01
SBEβCD in aqueous HPMC solution	2.22 ± 0.06

[a] *The solubility of βCD in water is 1.85% (w/v). βCD formed a 5% (w/v) suspension before addition of triclosan. **The water-soluble polymers can increase the aqueous solubility of βCD and its complexes.

Triclosan Substantivity Evaluations—Six healthy volunteers (5 males and 1 female), who were not either pregnant, receiving antimicrobial therapy, or had dental disease, were recruited for this part of the study. Sampling was separated by at least 2 days, and all the volunteers used a nontriclosan toothpaste throughout the study, with at least a two-day wash-out period prior to commencing the study. Participants were not allowed to brush their teeth for at least 2 h prior to the test occasion.

For each product evaluation, each participant gave an initial saliva sample prior to brushing with the sample toothpaste, to confirm the absence of triclosan. Each brushed for 1 min with 1.5 g of the test toothpaste and then rinsed the mouth with 20 mL of deionized water. Unstimulated saliva samples were then taken at 10, 20, and 60 min postbrushing. The saliva was weighed into 10 mL volumetric flasks, 4 mL of methanol and 2 mL of the HPLC mobile phase were added, and the sample was mixed and made to volume with methanol. Finally, the sample was filtered through a 0.45 μm membrane filter and analyzed by HPLC.

HPLC Analysis of Triclosan—The quantitative determination of triclosan was performed on a high performance liquid chromatographic (HPLC) component system from Merck Hitachi (Dramstadt, Germany), consisting of a pump (model no. L-6200A) operated at 1.5 mL/min, autosampler (model no. L-7200) with injection volume adjusted to 20 μL, LiChrosorb RP-18 (125/4 mm, 5 μm) column, UV/vis detector (model no. L-4200) operated at 283 nm, and an integrator (model no. D-2500). The mobile phase consisted of acetonitrile and 40 mM aqueous pH 3.0 disodium hydrogen phosphate (50:50). A standard curve was determined for each run.

Results

Cyclodextrin Solubilization of Triclosan—In the preliminary studies all the cyclodextrins tested, except the natural γCD, formed water-soluble complexes with triclosan. However, αCD had much less solubilizing effect than the βCDs and, thus, only the natural βCD and its derivatives were studied further (Table 1). The natural βCD and its triclosan complex have very limited solubility in water. The βCD derivatives, i.e., RMβCD, SBEβCD, HPβCD, and MβCD, formed water-soluble complexes with triclosan, and, frequently, addition of a water-soluble polymer increased the solubilizing effect of the cyclodextrin. All the βCD derivatives formed linear phase−solubility

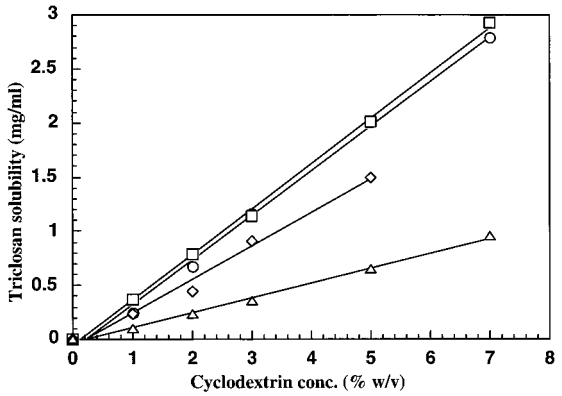

Figure 2—The phase-solubility diagrams of triclosan in aqueous cyclodextrin solutions at 22 °C. HPβCD (○), SBEβCD sodium salt (□), RMβCD (◇), and MβCD (Δ).

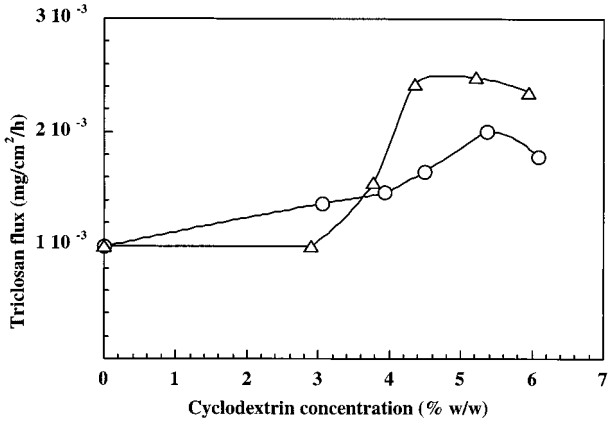

Figure 3—The triclosan flux from a toothpaste as a function of cyclodextrin concentration, RMβCD without polymer (○), RMβCD containing 0.2% HPMC (Δ). The initial triclosan concentration in the toothpaste was 0.28% (w/w).

diagrams, indicating that one cyclodextrin molecule forms a complex with one triclosan molecule (i.e., 1:1 complexes)[13] (Figure 2). The amount of cyclodextrin needed to solubilize triclosan in the toothpaste formulations was estimated from these and comparable phase−solubility diagrams.

Evaluation of Triclosan Availability in Toothpaste Formulations—On the basis of previous investigations, it can be assumed that the triclosan availability in the toothpaste formulations will be at its maximum when just enough cyclodextrin is used to solubilize triclosan in the toothpaste. Addition of too much or too little cyclodextrin will result in less than optimum triclosan availability.[11,12] The approximate amounts of the various cyclodextrins needed to dissolve 0.28% (w/w) triclosan in the toothpaste formulations was estimated from phase−solubility diagrams of triclosan in aqueous cyclodextrin solutions. Since the various constituents of the toothpaste formulation will interfere with the complexation, final adjustments of the cyclodextrin concentrations had to be based on the rate of triclosan release from the triclosan/cyclodextrin-containing toothpastes. Figure 3 shows a representative release profile observed as the flux of triclosan from the toothpaste through a semipermeable cellophane membrane. The maximum triclosan flux and the optimum cyclodextrin concentration from toothpastes containing 0.28% (w/w) triclosan and the various cyclodextrins is shown in Table 2. Optimally, the cyclodextrins resulted in 2- to 3-fold flux enhancement compared to toothpaste containing no cyclodextrin, i.e., addition of triclosan/cyclodextrin complexes to the toothpaste formulations resulted in 2- to 3-fold enhancement of the triclosan availability. Surprisingly, although βCD and its triclosan complex have limited

Table 2—The Flux of Triclosan from the Toothpastes at Optimum Cyclodextrin Concentration[a]

cyclodextrin	cyclodextrin concn (% w/w)	flux (mg/cm²/h)	flux ratio[b]
αCD	7.30	1.91×10^{-3}	1.9
αCD with PVP	7.30	1.50×10^{-3}	1.5
βCD	7.30	2.10×10^{-3}	2.1
βCD with CMC	3.00	2.20×10^{-3}	2.2
HPβCD	4.64	2.27×10^{-3}	2.3
HPβCD with PVP	6.09	2.26×10^{-3}	2.3
SBEβCD	6.09	0.57×10^{-3}	0.6
SBEβCD with PVP	4.64	1.31×10^{-3}	1.3
RMβCD	5.37	2.01×10^{-3}	2.0
RMβCD with CMC	5.22	2.48×10^{-3}	2.5

[a] The triclosan concentration in the toothpastes was in all cases 0.28% (w/v). In some cases 0.20% (w/v) polymer was added during the triclosan/cyclodextrin complex formation. The flux was determined at 22 to 23 °C. [b] The flux divided by the triclosan flux obtained from a toothpaste containing no cyclodextrin (0.99×10^{-3} mg/cm²/h).

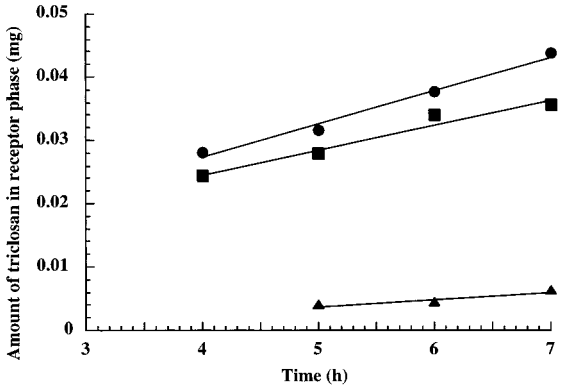

Figure 4—Representative figure which shows the release of triclosan from toothpastes containing no βCD or CMC (▲), triclosan/βCD complex (■), or triclosan/βCD/CMC complex (●) through a semipermeable cellophane membrane at 22 to 23 °C. The triclosan concentration toothpaste was kept constant at 0.28% (w/w). The βCD concentration in the toothpaste was 3.0% (w/w) when it was present in the toothpaste. When CMC was present, the CMC concentration was kept at 0.50% (w/v) during the preparation of the triclosan/βCD/CMC complex.

solubility in pure water, addition of triclosan/βCD complexes to the toothpaste resulted in significant enhancement of the triclosan availability. Furthermore, addition of CMC reduced significantly the amount of βCD needed to enhance the triclosan availability.

The effect of βCD concentration on the flux of triclosan from toothpaste formulations was investigated. During preparation of the dry triclosan/βCD complex powder, the CMC concentration was kept constant at 0.50% (w/v), but the βCD concentration was varied. The dry complex powder was then mixed into the toothpaste resulting in 0.28% (w/w) triclosan concentration in the final toothpaste formulation. The triclosan availability in the toothpaste was evaluated by determining the triclosan flux from the toothpaste through a semipermeable cellophane membrane (Figure 4). As can be seen in Figure 5 the optimum βCD concentration was 3% (w/v). Then the optimum polymer concentration was determined. Triclosan/βCD complexes were prepared in aqueous solutions containing from 0.00 to 1.00% (w/v) CMC. The βCD concentration and the triclosan concentration were kept constant in the final toothpaste formulation, at 3.0% (w/w) and 0.28% (w/w), respectively (Figure 6). Maximum triclosan flux (i.e., maximum triclosan availability) was obtained when the CMC concentration during preparation of the triclosan/βCD complex was between 0.10 and 0.20% (w/v). No further

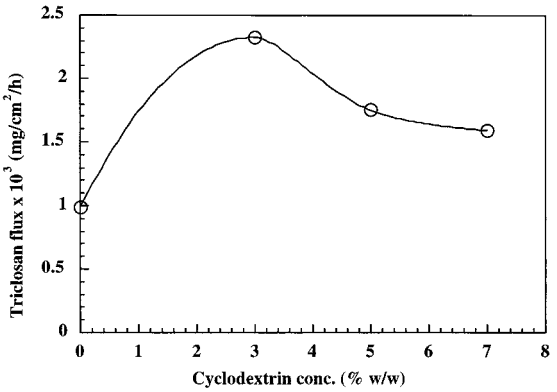

Figure 5—The effect of βCD concentration in the toothpaste formulation of the flux of triclosan through a semipermeable cellophane membrane at 22 to 23 °C. The triclosan concentration was kept constant at 0.28% (w/w), and CMC concentration was kept at 0.50% (w/v) during the preparation of the triclosan/βCD complex.

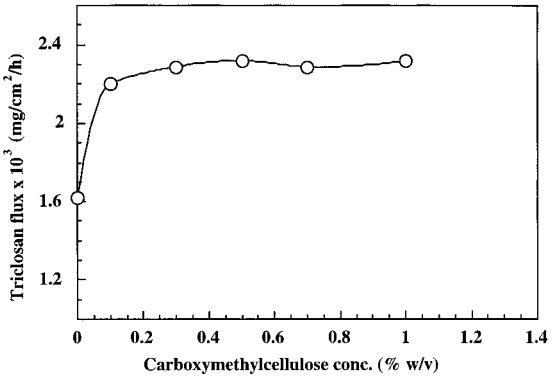

Figure 6—The effect of CMC concentration during preparation of the complex on the flux of triclosan from the toothpaste through a semipermeable cellophane membrane at 22 to 23 °C. The triclosan concentration was kept constant at 0.28% (w/v), and the βCD concentration was kept constant at 3.0% (w/v) in the toothpaste.

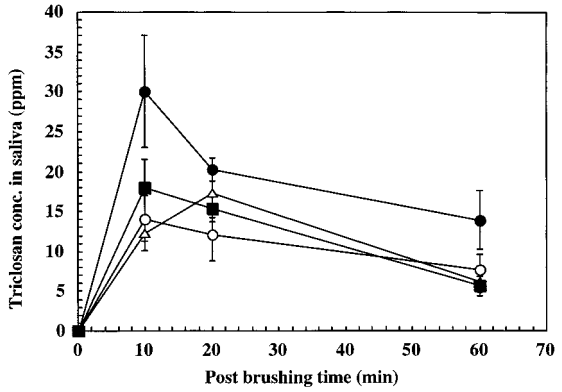

Figure 7—The triclosan concentration in saliva (mean ± SEM, $n = 6$) at various times after brushing with toothpaste containing free triclosan (no cyclodextrin or polymer complex) (○), triclosan/βCD complex without polymer (■), triclosan/HPβCD complex without polymer (Δ), and triclosan/βCD/CMC complex (●).

increase in the triclosan flux was observed from complexes prepared at higher CMC concentrations.

Triclosan Substantivity Evaluations—Figure 7 shows the effect of cyclodextrin complexation of the triclosan saliva concentration time profile after brushing with toothpastes containing four different triclosan formulations. The area under the curves (AUC) from 0 to 60 min gives a rough estimate of how much triclosan is initially retained in the mouth after brushing. Replacing triclosan by triclosan/βCD complex or triclosan/HPβCD complex results in about 10% increase in AUC, indicating only minor improvement of the triclosan retention in the mouth. This was partly due to somewhat shorter duration, i.e., faster triclosan clearance, after brushing with the triclosan/cyclodextrin-containing toothpastes. However, replacing triclosan by triclosan/βCD/CMC complex resulted in about 80% increase in the AUC. Furthermore, the duration of the antibacterial effect was improved significantly upon replacing triclosan with the triclosan/βCD/CMC complex. Thus, formulation of triclosan in the toothpaste as a triclosan/βCD/CMC complex improves significantly the substantivity of triclosan in the mouth. The minimum inhibitory concentration (MIC) of triclosan versus a variety of oral bacteria is $\leq$10 ppm.[8,14]

Discussion

Through cyclodextrin complexation it is possible to increase the aqueous solubility of lipophilic, water-insoluble drugs, and other lipophilic compounds, without changing their molecular structure. That is, the cyclodextrins do not affect their intrinsic abilities to permeate into lipophilic biological membranes or interact with pharmacological receptors. The cyclodextrin molecules are relatively large (molecular weight ranging from almost 1000 to over 1500), with a hydrated outer surface, and under normal conditions, cyclodextrin molecules will only permeate biological membranes with considerable difficulty.[15,16] It is thought that cyclodextrins act as true carriers by keeping hydrophobic molecules in solution and delivering them to the surface of a lipophilic biological membrane, e.g., the oral mucosa, where they partition into the membrane.[11,16,17] The relatively lipophilic membrane has low affinity for the hydrophilic cyclodextrin molecules, and therefore they remain in the aqueous membrane exterior, e.g., the aqueous mucus layer or saliva. However, simply adding cyclodextrins to aqueous dentifrice formulations will not automatically result in enhanced triclosan penetration through the aqueous mucus layer into the lipophilic mucosa. Frequently, formation of cyclodextrin complexes results in decreased availability of an antibacterial agent.[16] Addition of small amounts of water-soluble polymers to aqueous cyclodextrin solution and heating increase the cyclodextrin complexation of lipophilic, water-insoluble compounds. The polymers do not only increase the complexation but also increase the availability of the compound in the cyclodextrin-containing formulation.[12,18] Furthermore, in the present formulation, addition of the ionized CMC prevented the formation of association colloids, resulting in clear triclosan cyclodextrin solutions. It is well-known that the polymers, such as carbohydrates, form complexes with mono- and oligosaccharides as well as with numerous other compounds.[19] Such interactions will influence the physicochemical properties of both the polymers and the saccharides. For example, carbohydrates are known to enhance the solubilizing abilities of surfactants.[12] In this present study the polymers enhanced the triclosan release rate from cyclodextrins (Figure 4) and the triclosan retention in the buccal area (Figure 7). Macromolecules, such as CMC, and their complexes are washed more slowly from biological surfaces than comparable smaller molecules. This could explain, at least partly, the enhanced triclosan retention observed when the simple triclosan/βCD complex in the toothpaste is replaced by the triclosan/βCD/CMC complex.

The availability of triclosan in the silica-based toothpaste formulation was optimized through a series of solubility studies in aqueous cyclodextrin solutions as well as through a series of triclosan release studies from the toothpaste through a cellophane membrane. Cyclodextrin formed 1:1

complexes with βCD and its derivatives. The availability of triclosan (i.e., the triclosan release rate) was improved significantly in the toothpaste formulation although the triclosan/βCD complex has limited solubility in pure aqueous solutions. This enhanced availability could be due to the solubilizing effects of the surfactants used in the formulation. Through addition of the water-soluble polymer CMC, it was possible to reduce the amount of βCD in the formulation by as much as 60% without affecting the triclosan availability (i.e., the release rate from the toothpaste). The result was a silica-based toothpaste containing 0.28% (w/w) triclosan and only 3.0% (w/w) βCD, or only 30−50 mg of βCD per brushing.

It has been suggested that the salivary concentration decline of an agent, such as triclosan, after using a dentifrice containing the agent follows first-order kinetics which can be described by the following equation:[20−22]

$$C_t = C_0 e^{-(Ft/V)} \qquad \text{(eq 1)}$$

where C_t is the concentration of the agent at time t, C_0 is the initial concentration of the agent (i.e., the concentration at t equal to zero), F is the saliva flow rate, and V is the volume of saliva in the mouth. Other investigators have fitted triclosan salivary elimination to a two-phase model (i.e., a two-compartment open model):[2,8]

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(eq 2)}$$

where the initial concentration of dissolved triclosan is the sum of A and B (i.e., $C_0 = A + B$), and α and β are hybrid first-order rate constants for the distribution phase and elimination phase, respectively. The distribution phase represents the rapid initial decline in the salivary triclosan concentration due to simultaneous (a) adsorption and absorption of the lipophilic triclosan to and into the oral mucosa, plaque, and other intraoral sites, and (b) triclosan elimination with saliva as described by eq 1. The elimination phase represents the somewhat slower decline in the salivary triclosan concentration after equilibrium has been reached between triclosan in saliva and triclosan in the various intraoral sites. According to both models, high initial concentration of triclosan dissolved in saliva should result in high oral substantivity. However, it has been shown that the concentration of triclosan at the site of biological action (i.e., in the oral mucosa or plaque) is more relevant to clinical activity than the salivary concentration profiles.[4] Triclosan must be in a hydrophilic, water-soluble form to be able to penetrate the aqueous mucous layer to the surface of the mucosa (and other intraoral sites), but at the same time triclosan must be in a lipophilic form to be able to partition into mucosa and its sites of action. High initial salivary concentration of available (i.e., dissolved) triclosan (or more precisely, high triclosan activity) will enhance triclosan delivery to the various oral triclosan reservoirs and its sites of action.

Formulating triclosan as a water-soluble triclosan/βCD/CMC complex resulted in high initial triclosan concentration and a high oral triclosan substantivity. At 10 min the triclosan salivary concentration was determined to be 13 ppm when the toothpaste contained free triclosan (i.e., without cyclodextrin), which is comparable to reported triclosan salivary levels after brushing with other triclosan-containing dentifrices[8] but at the same time point the triclosan concentration was 30.0 ppm when the toothpaste contained the triclosan/βCD/CMC complex. The profile could be fitted to a two-phase model with a short distribution phase ($t_{1/2} \approx 0.3$ h) and extended elimination phase ($t_{1/2}$ between 1 and 2 h). The duration of activity, based on MIC of 10 ppm, was extended from about 0.7 h (free triclosan) to about 1.5 h (triclosan/βCD/CMC complex). Thus, replacing free triclosan with the triclosan/βCD/CMC complex resulted in almost 3-fold increase in C_0 and about 2-fold increase in the duration of activity.

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