Chlorhexidine and the control of plaque and gingivitis

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Chapter 8

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General summary and discussion

The underlying idea of this thesis is to investigate the efficacy of CHX mouthrinses on supra-gingival plaque accumulation in order to control gingivitis, a disease entity that precedes periodontal breakdown. Related to efficacy, several aspects of CHX mouthrinses have been questioned.

The interaction between CHX and SLS: friend or enemy?

Chemical plaque control by the use of a CHX mouthrinse may be important in some patient populations. When mouthrinses are used as supplements to toothbrushing with dentifrice, they may have some adjunctive plaque inhibiting effect. Although there is evidence that a dentifrice does not primarily attribute to the “instant” mechanical plaque removal, toothbrushing with a dentifrice is traditionally recommended especially for the prevention of staining and application of chemotherapeutics such as fluorides (Paraskevas et al. 2005). A common ingredient of most dentifrices is the detergent SLS. From the existing literature, it is apparent that the activity of the cationic (+) CHX molecule as active ingredient of a CHX mouthrinse, is rapidly reduced in the presence of the anionic (-) agent SLS found within certain types of dentifrice (Barkvoll et al. 1989). The research presented in chapter 2, 3 and 4 intends to bring clarity in the anti-plaque efficacy of a CHX mouthrinse when used in combination with toothbrushing with an SLS-containing dentifrice.

Since it has been suggested that SLS and CHX may counteract in the oral cavity, dentists recommend their rinsing patients to use an SLS-free dentifrice, to postpone the rinsing 30 min to 2 hours after brushing with an SLS- containing dentifrice or to refrain from the use of dentifrice (Barkvoll et al. 1989). In order to comply with the professional advices, patients are forced either to look continuously at the clock or to purchase a non-SLS dentifrice. Therefore, these advices may have an impact on patient's compliance and consequently may influence the outcome of antimicrobial therapy. These professional advices, in use since 1989, are, however, based on research data derived from non-brushing/SLS-slurry investigations dating performed in the past and not from ordinary brushing/SLS-dentifrice studies. For this reason, the plaque inhibiting effect of a CHX mouthrinse under influence of toothbrushing with an SLS-containing dentifrice was studied in a series of three “SLS brushing/ CHX rinsing” interaction, studies that are described in chapter 2, 3 and 4.

In all three studies the same research model was used, considering one jaw as the “CHX rinsing-study jaw”, which received no mechanical plaque control, and the opposite jaw as
the “brushing-dentifrice/CHX” jaw, where toothbrushing was performed in combination with 
CHX-rinsing. Unlike what was expected, the results of the first SLS/CHX study (described 
in chapter 2) using a non-supervised cross-over design with 16 healthy volunteers rinsing 
with a 0.2% CHX rinse and brushing with an 1.5% SLS-containing dentifrice, did not show 
any significant difference in plaque inhibition between the CHX rinsing group and the SLS-
dentifrice/CHX group. It may be argued that this lack of an inhibiting effect might be due 
to a poor compliance of the panelists participating in the study. Consequently, a second, 
supervised, cross-over study with 35 volunteers using three different dentifrices, with and 
without SLS, was performed. In addition, the effect of inversed rinsing-brushing orders has 
also been examined but again, no significant difference was found between the groups. Since 
both cross-over studies contradicted the existing literature, a final third SLS/CHX study was 
performed, using a supervised parallel design where 120 volunteers were involved. One regi-
men consisted of rinsing with CHX alone. The second regimen consisted of rinsing with 0.2% 
CHX preceded by rinsing with an SLS-containing slurry, similar to the two earlier studies, 
while in the third regimen rinsing with 02% CHX was preceded by toothbrushing with an SLS-
containing in the “dentifrice” jaw. The anti-plaque efficacy of a 0.2% CHX rinse was not reduced 
when preceded by everyday tooth brushing with an SLS- containing dentifrice. However, when 
preceded by rinsing with an SLS-containing slurry, the anti-plaque efficacy of a 0.2% CHX 
rinse was reduced.

In summary, none of the three SLS/CHX interaction studies demonstrated a significant 
difference in amount of plaque accumulation during four days between the CHX alone regi-
men and the CHX/SLS regimens. Only when a 0.2% CHX rinse was preceded by rinsing with 
an SLS-containing slurry, the anti-plaque efficacy of CHX was reduced, which is in accordance 
to earlier conclusions. Based on the above mentioned results it was concluded that tooth-
brushing with an SLS-containing dentifrice under home-care conditions does not reduce the 
anti-plaque efficacy of a 0.2% CHX mouthrinse, irrespective whether the dentifrice was used 
before or after the rinse. The most likely explanation seems to be that ordinary oral hygiene 
procedures involve a toothbrush and dentifrice to brush the teeth after which the dentifrice 
foam is expectorated and the oral cavity is rinsed with water. Following such a procedure, 
the interaction between SLS and CHX is probably minimal because most of the effects of the 
dentifrice ingredients are eliminated (Sjögren & Birkhed 1994). Expectoration and rinsing with 
water clears the oral cavity of most residual SLS dentifrice. A low intra-oral SLS-concentration 
is considered as a likely explanation for the observed absence of an inhibition of the anti-
plaque effect of a CHX rinse in combination with an SLS-containing dentifrice. In case of a 0.2% CHX rinse preceded by rinsing with an SLS-containing slurry, the oral cavity was not cleared from SLS after rinsing with the aqueous dentifrice-slurry-solution. This would probably result in a much higher oral load of SLS compared to the SLS load of the brushing, expectorating the dentifrice foam and rinsing with water.

**The inclusion of alcohol in a CHX mouthrinse: the high of victory!**

As mentioned in the introduction of the present thesis, alcohol may play an important role in the formulation of a mouthrinse vehicle solution. A significant amount of alcohol, which may vary from around 7% to 27%, is added to mouthrinses to provide a soluble vehicle for distribution of the active ingredient and to improve some preservative power of the mouthrinse, the shelf life of the product and in some extend the pleasurable characteristics of mouthrinising (See Chapter 1).

However, alcohol may also have some more or less important disadvantages. It is a drying agent and appears to increase discomfort. The oral mucosa for instance may be sensitive to alcohol. Sometimes alcohol can also adversely affect the surface hardness and color stability of tooth-colored restorations. Other important issues that arise as a result of the presence of alcohol in mouthrinses is the systemic toxicity from swallowing, which could be a problem for children and alcohol addicts. Also the supposed co-carcinogenicity with smoking might lead to oral and pharyngeal cancers when actively imbibed. When correctly prescribed, the risk is probably minuscule, but this does not obviate the possible risk from self-prescription and chronic use of mouthrinses. Although the evidence of these side-effects is qualitatively poor and at present considered not to be the case or unproven, the inclusion of alcohol in mouthrinses remains a controversial topic, due to the possible health risk associated with long-term use of alcohol containing products. Primarily based on health reasons but also on social reasons, including religious objections and the potential for detecting alcohol in the breath, there is an increase in the demand for alcohol-free mouthrinses. Besides, the absence of alcohol in mouthrinses might cause fewer side-effects.

In terms of efficacy, the question arises whether the addition of alcohol to CHX mouthrinses is necessary. The answer to this question is brought forward in chapter 5 where the plaque inhibition of two commercially available CHX mouthrinses, with different concentration, quantity, composition (with and without alcohol) and rinsing time, was compared. 40 healthy volunteers were enrolled in the study. Results show that, twice daily rinsing for
30 seconds with 15 ml of an alcohol-free 0.12% CHX mouthrinse (Perio-Aid®) appears not to be significantly different in plaque inhibition capacity from twice daily rinsing for 60 seconds with 10 ml of an alcohol-containing 0.2% CHX mouthrinse (Corsodyl®). A 30-second rinsing time was equally effective to a 60 second rinsing time and confirms the studies of Keijser et al. (2003) and Van der Weijden et al. (2005). This equality is probably due to the fact that approximately 50% of the CHX was retained after the first 15 seconds of rinsing and approximately 75% within 30 seconds (Bonesvoll et al. 1974). More than the concentration, the dose of CHX seems also of considerable relevance to the efficacy of the mouthrinse formulations. Concentrations of 0.12% CHX appear as effective as 0.2% if the volume of the rinse is increased from 10 to 15 ml, giving an 18 mg dose on each occasion. However, the 0.12% CHX mouthrinse (Perio-Aid®) additionally contains 0.5% CPC. Existing evidence suggests that CPC mouthrinses, when used as adjuncts to oral hygiene, provide a small but significant additional benefit in reducing plaque accumulation and gingival inflammation (Haps et al. 2008). Therefore it could be possible that the addition of CPC may have compensated for a possible alcohol effect.

In contrast to other studies, (Quirynen et al. 2001, Keijser et al. 2003) from which was concluded that there was no significant difference in terms of taste perception, the study described in chapter 5 shows that the subjects appreciated the taste of the alcohol-free CHX solution more than the taste of the alcohol-containing CHX, but the after-taste of the alcohol-free rinse remained longer in the mouth. One can ask if it is the lower concentration, the absence of alcohol, the inclusion of CPC, the shorter rinsing time, or perhaps even a combination of these factors, which is responsible for the better appreciation of the taste of the 0.12% rinse. No explanation has been brought forward for the better after-taste of the 0.2% rinse. As the benefit of alcohol in a mouthrinse was not substantiated and the effect of a CHX mouthrinse on plaque inhibition is more dependent on the dose of the rinse (volume x concentration) than on the concentration, it could be of common interest to use 15 ml of an 0.12% alcohol-free CHX mouthrinse rinse (PerioAid®) instead of 10 ml of an alcohol-containing 0.2% CHX mouthrinse (Corsodyl®) in order to inhibit plaque and control gingival inflammation. Since the efficacy on plaque inhibition of both mouthrinses is the same, it can be concluded that, for reasons of taste perception, it is up to the patient to freely choose which mouthwash he or she prefers.

Besides efficacy, taste and social factors, some other aspects may be important with regard to mouthrinses. In the Netherlands, the “Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten Fagg http://www.fagg-afmps.be/nl stated that “Any substance
or combination of substances presented for treating or preventing disease in humans or any substances or combination of substances which can be used by humans to restore physiological functions, to correct or modify either a pharmacological, immunological or metabolic action, or to provide a diagnose, is defined as a drug”. This opens the discussion to what extend mouthrinses should be regarded as drugs. The alcohol-containing 0.2% mouthrinse (Corsodyl®), used as a control in the study described in chapter 5, has been designated as an effective anti-microbial mouthrinse in the prevention and the control of dental plaque, in the treatment of gingivitis simplex or gingvitis ulcerosa, stomatitis prothetica, oro-pharyngeal infections such as stomatitis aphtosa, candidiasis and as disinfectant during periodontal surgery. In accordance with these indications, Corsodyl® is considered a drug with the obligatory control by the FAGG authorities. This is in contradiction with the free use of the tested 0.12% alcohol-free mouthrinse (Perioaid®), which is classified as a cosmetic product. In contrast to cosmetic products, drugs must meet many conditions in order to be considered not only as an effective product but also as a safe product. This includes manufacturing, marketing, distribution, delivery, research, development, safety monitoring and advertising. In order to protect the drug from moisture, light and air, the packaging must meet all FAGG requirements and disclose the name of the product, the dose, the pharmacological form, the name of the company which brings the drug on the market, the license number, the lot number, the expiration date, the composition, the route of administration and if needed any special storage conditions. Also the shelf life and expiration date are strictly controlled. This implies that, although Corsodyl® may be a more expensive mouthrinse, it may still be considered as the golden standard, partly due to the high level of quality control.

The effect of a CHX-releasing toothbrush: a useful tool or a gadget?
Manufacturers try very hard to develop products that make oral hygiene procedures easier for consumers, sometimes at the request of the dental professional. Examples are a coating of CHX on the filaments of interdental brushes or adding antibacterial properties to toothbrushes to give them an antimicrobial function. The study presented in chapter 6 evaluates whether the effect of toothbrushing could be enhanced by the use of a CHX-releasing toothbrush. This prototype contains a template within the brush head which releases CHX when brought into contact with oral fluids. The delivery system may provide the benefits of reduced plaque and gingivitis beyond toothbrushing alone, whilst also diminishing the negative tooth staining side effects of traditional CHX therapy and enhancing users’ oral hygiene and compliance.
The purpose of this study was to test whether toothbrushing with a template test toothbrush with a slow release system of CHX is more effective in inhibiting plaque and gingival bleeding than brushing with the template control brush in conjunction with a CHX rinse served as positive control. A second objective was to assess the amount of stain on the teeth, being considered as a well-known side-effect of CHX, and last but not least, to detect the presence of oral tissue abnormalities. 150 healthy volunteers were enrolled in the study. After 6 weeks of use, no differences were detected compared to the control brush in oral tissue changes, nor a beneficial effect on plaque inhibition or an inhibition of staining could be demonstrated for the experimental CHX releasing toothbrush. Whilst researchers continue to search for the most convenient and clinically effective way of delivering additional chemical plaque control, the use of a 0.2% CHX mouthrinse (in combination with toothbrushing) remains the gold standard, despite the well-known tooth staining side effect.

The result of a systematic review of CHX mouthrinses: To rinse or not to rinse, that's the focussed question!

In chapter 7 the literature is evaluated a systematic way to assess the clinical effect of a CHX mouthrinse in gingivitis patients.

Archie Cochrane (1909-1988), a British epidemiologist and founder of the Cochrane Collaboration, advocated the use of randomized controlled trials as a means of informing healthcare practice of the current standard of knowledge with respect to therapy. In 1979, he stated that “it is surely a great criticism of our profession that we have not organized a critical summary, by specialty or sub-specialty adapted periodically, of all relevant randomized controlled trials”. His efforts proved to be successful and resulted in many “Cochrane” systematic reviews of high quality, which are published under the strict guidance of the Cochrane Collaboration. In a systematic review all studies on a topic are systematically identified, critically appraised and summarized with explicit and reproducible methods. The rationale behind this approach is that standardization, transparency of the methods used by the authors, and the acquisition of available studies meeting the required criteria, minimize the potential of bias.

In contrast to narrative reviews, systematic reviews are a more rigorous compilation of evidence from the literature simply because the search strategy for finding and summarizing studies is clearly defined. By designing a well-structured protocol, the systematic review process is more objective in its appraisal of quality and the reader should have a greater confidence in the conclusions of the review than other summaries of clinical evidence. Systematic reviews
of different formats providing substantial evidence relevant to health care have become widely used and gained an important place in aiding clinical decision making across all fields of medicine. Although dentistry has been a little slower to adopt this approach, many systematic reviews on dental topics are today a welcome addition to the dental literature. The literature relating to the use of CHX mouthrines as anti-plaque & anti-gingivitis agents is immense and many narrative reviews have been published. So far, a systematic review on the effect of a CHX mouthrinse on plaque, gingival inflammation and staining was however lacking and is presented in chapter 7.

The format of the present review is based on the criteria of a Cochrane Review. The PubMed-MEDLINE, EMBASE, and Cochrane-CENTRAL were searched up to April 2011. 1355 titles and abstracts provided 36 eligible publications in which CHX rinsing was combined with oral hygiene procedures. Not a single study in which only rinsing was performed without toothbrushing met the criteria of eligibility. In all the included studies rinsing with CHX was always combined with regular oral hygiene procedures. The fact that the majority of studies combined CHX rinsing with the use of an SLS-containing dentifrice and that the majority of these studies show a positive effect of CHX on plaque control, support the findings of the SLS-CHX interaction studies, presented in chapter 2, 3 and 4. One study reported about the difference in efficacy of a CHX with and without alcohol (Leyes Borrajo et al. 2002). In this study the alcohol-free rinse was as effective as the one containing alcohol in controlling plaque and gingivitis, which supports the results presented in chapter 5. As also stated in that same chapter, the data in the present review also show a significant reduction in plaque and gingivitis scores, in favour of a CHX rinse, irrespective of the concentration. No significant difference in the level of plaque, gingival inflammation or in the amount of stain was observed in this review whether the subjects rinsed for 30, 45 or 60 seconds with chlorhexidine, which also confirms the findings presented in chapter 5. It can be questioned how long the evaluation period has to be in order to be taken up in a systematic review of mouthrines. Because mouthrines are mostly prescribed for short periods and thus their efficacy over shorter periods is of interest, studies with an evaluation period of at least 4 weeks were considered as valuable. According to Gunsolley (2006), short-term studies of less than 2 weeks can be used only to investigate the anti-plaque effect of a chemical agent. Intermediate trials (2 to 8 weeks) can evaluate both the anti-plaque and anti-gingivitis efficacy of a product. However, the limitation of intermediate-length trials is that they may not reflect the efficacy and safety of the product nor patients’ compliance over a longer period of time. For this reason, the
American Dental Association (ADA, 2008) and the U.S. Food and Drug Administration (FDA 2012) require a long-term study period of 6 months in their approval of a chemical agent (http://www.Fda.gov). Products that contain chemotherapeutic agents must comply with the ADA “Acceptance Program Guidelines for Chemotherapeutic Products for Control of Gingivitis (1997)”. However, mainly because of the esthetic problem and the perturbation of the taste, most practitioners do not recommend long-term use of CHX as a mouthrinse. Given therefore that mouthrinses with and without oral hygiene are also used and prescribed for short periods, their efficacy over shorter periods remains also of interest. Concerning “adjunctive” devices for controlling plaque and gingivitis, the ADA demands an evaluation period of at least 4 weeks (see Acceptance Program Guidelines. Adjunctive Dental Therapies for the Reduction of Plaque and Gingivitis, March 2010). Consequently, in this review, for the evaluation of the anti-plaque and anti-gingivitis efficacy of a CHX rinse as an adjunct to regular oral hygiene, studies with an evaluation period of at least 4 weeks were included.

Data were extracted and a meta-analysis providing means and standard deviations for plaque and gingivitis were calculated, showing a significant weighted mean difference (WMD) for the Plaque Indices of Silness & Loe (1964) and Quigley & Hein (1962), for the Bleeding Index of Saxer & Mühlemann (1975) and for the Gingival Index (Löe & Silness 1963). In addition, a sub meta-analysis of studies with a low risk of the author’s estimated bias was performed for the Plaque Index of Quigley & Hein (1962) and for the Gingival Index (Löe & Silness 1963). All results were in favour of the CHX rinse compared to the control. There was no apparent difference between the results of meta-analysis and those of the sub meta-analysis of the low risk studies. Relative to the control the use of CHX attributed to a 33% reduction of plaque and a 26% reduction of gingivitis.

In the present review, no study could be included which met the eligibility criteria where only rinsing was performed without mechanical oral hygiene. In all the included studies rinsing with CHX was always combined with regular oral hygiene procedures. Toothbrushing with the use of a dentifrice was performed in 26 of the 30 studies. Only two studies specifically reported that no dentifrice was used (# 2,15), while in two remaining studies no information about the use of dentifrice was provided (# 10,13). The fact that the majority of studies combined CHX rinsing with the use of a dentifrice and that 25 out of 29 of these studies show a positive effect of CHX on plaque, is in itself surprising, since one of the most widely used detergents in dentifrice is sodium lauryl sulphate (SLS). In vitro SLS and CHX have been shown to act as antagonists (Bonesvoll 1977, Barkvoll et al.1988). Ever since the 1980’s it has been
recommended that the time between CHX rinsing and toothbrushing with an SLS-containing dentifrice should at least be 30 min, in order to avoid reduction in the anti-microbial effect of CHX. To optimise the efficacy of a CHX rinse, it has been suggested that toothbrushing with dentifrice should be suspended or toothbrushing should be performed with dentifrice formulations without antagonistic ingredients (Owens et al. 1997, Kohali et al. 2006). The results of this systematic review do not support the findings of these earlier studies. A likely explanation was provided by Van Strydonck et al. (2004a,b, 2006) who had previously questioned the effect of dentifrice in combination with normal toothbrushing. In a 4-day plaque accumulation model, they investigated the plaque-inhibition of a 0.2% CHX rinse in one jaw under the influence of toothbrushing with a 1.5% SLS-containing dentifrice in the opposite jaw. On the basis of their clinical results, it appeared that the anti-plaque efficacy of the 0.2% CHX mouthrinse was not reduced. Ordinary oral hygiene procedures involve a toothbrush and dentifrice to brush the teeth after which the dentifrice foam is expectorated and the oral cavity is rinsed with water. Following such a procedure, the interaction between CHX and SLS is probably minimal because most of the effects of the dentifrice ingredients are eliminated (Sjögren & Birkhed 1994). Expectoration and rinsing with water clears the oral cavity of most residual SLS dentifrice. A low intra-oral SLS-concentration is considered to be responsible for the observed absence of reduction in plaque inhibition when using a CHX rinse in combination with a dentifrice (Van Strydonck et al.2004a,b).

This review has limitations. Most importantly it is restricted to gingivitis patients. The various indications for the use of a CHX rinse have been stated by the Federal Food & Drug Administration (FDA 2012). These indications are: the use of CHX between dental visits as part of a professional programme for the treatment of gingivitis as characterised by redness and swelling of the gingivae including gingival bleeding upon probing, or the use in patients with adult periodontitis to reduce pocket depth. The present review focussed on gingivitis patients. This focus is particularly relevant because long-term gingivitis increases the risk of loss of attachment, and the prevention of gingival inflammation might reduce the prevalence of mild to moderate periodontitis (Lang et al. 2009). Although established destructive periodontitis with pocket formation and subgingival plaque seems to be unaffected by CHX (Gjermo 1977), a CHX mouthrinse could be used in the treatment of chronic periodontitis patients as an adjunct to scaling and root planing procedures to control supra-gingival plaque (Feres et al. 2009), during a supportive periodontal care programme for non-compliant periodontitis patients (Escribano et al. 2010), or for supra-gingival plaque control when conventional oral
hygiene is not possible, for instance following oral periodontal surgery (Duss et al. 2010, Newman & Addy 1978). Due to the large body of evidence presented in this review, these alternative indications were not addressed and may become part of future projects.

A great effort has been made to address the quality assessment. Each article was assessed according to 17 quality criteria (see appendix S2). However, only 7 out of the 17 items were used to assess the potential risk of bias. The reason for using only a limited number is that, by applying all 17 items, none of the studies would have had an acceptable risk of bias, which in turn would result in an over-estimation of the potential risk of bias. On the other hand the reader should have insight in all aspects that could affect bias and weigh the outcome of the systematic review against the interpretation of the risk of bias. With the exception of allocation concealment, these 7 items represent the Cochrane Handbook criteria for judging ‘risk of bias’ (Higgins & Green 2009).

Allocation concealment is the one aspect of bias protection shown to have a great impact on bias (Pildal et al. 2007). Where a trial has unclear methods, e.g. for allocation concealment, it should be at best of moderate risk of bias. Therefore, looking at the included studies from this perspective there are only 3 studies with a low risk (# 1,12,16). For the appraisal of study quality (Table 6), allocation concealment was not considered as an item to estimate the risk of bias. Although the authors recognize that this is an important issue, they are also aware that reporting on allocation concealment in the dental literature has not been a critical item up until the recent past. Therefore, including this item would result in an overestimation of the risk of bias not reflecting study conduct but rather study report. It is, however, emphasized that for future studies researchers should provide information on this aspect, which is also an item on the CONSORT-statement (Schulz et al. 2010). On the other hand, a recent study has provided an interesting new insight (Kaptchuk et al. 2010). It assessed in a 3 week randomized controlled trial the effect of an open label placebo to no treatment on irritable bowel syndrome (IBS). The results show that even though the participants were fully aware that they were given placebo tablets still a significant improvement of the IBS symptoms was observed as compared to no treatment. Consequently, the absence of allocation concealment in the study did not prevent a placebo-effect.

In conclusion, when a CHX mouthrinse is used in addition to oral hygiene procedures, a significant reduction in the plaque and gingivitis scores can be achieved in gingivitis patients. However, since staining remains an obstacle to the generalized use of CHX, rinsing with CHX
as an adjunct to toothbrushing may only be indicated when mechanical plaque control is compromised or difficult.

The present systematic review is part of a series of reviews that have addressed the efficacy of various chemical agents in oral health care products for gingivitis patients. These include the use of Triclosan (Hioe 2005), Stannous-Fluoride (Paraskevas 2006), Essential Oils (Stoeken et al. 2007), Cetylpiridinium Chloride (Haps et al. 2008), Hexetidine (Afenich et al. 2010), and Hydrogen Peroxide (Hossainian et al. 2011). Addy et al (2007) evaluated on a systematic matter the effect of Delmopinol. With respect to plaque, Stoeken et al. (2007) using the same Quigley & Hein plaque index (1962) as in the present review, showed that the WMD for Listerine (Essential Oils) on plaque was 0.83 (95% 0.53-1.13). In the light of these results, one could conclude that the effect on plaque and gingivitis as established for CHX 0.67 (95%CI: 0.82-0.52) and Listerine in mouthrinses so far is the largest. However, for Listerine and CHX, the test for heterogeneity was statistically significant, which urges the reader to be careful with the exact measure of the outcome. If heterogeneity is observed in a meta-analysis, it reflects different behaviours of the study populations to the study product, differences in study designs and in all other factors that may influence the outcomes. Consequently, the reader must take caution in using the WMD as the exact measure for the effect. On the other hand, the confidence intervals of the two weighted mean differences for both chemotherapeutics do overlap. This indicates that the effect probably lies in the same range. A recent systematic review (Van Leeuwen et al. 2011) is in support of this supposition and demonstrates that in long-term use, the standardized formulation of essential oils mouthwash is not different from a chlorhexidine mouthwash with respect to parameters of gingival inflammation. However, with respect to plaque scores, chlorhexidine provided better results.

In conclusion, the work presented in this thesis clearly shows that the anti-plaque and anti-gingivitis preventive action of chlorhexidine is the gold standard among oral antimicrobial preventive agents.
Conclusions

The SLS/CHX interaction studies show that the anti-plaque activity of 0.2% CHX mouth-rinse is not reduced when immediately preceded or followed by toothbrushing with an SLS-containing dentifrice. The advice of using a dentifrice without SLS or inserting an interval of minimal 30 minutes between brushing with an SLS-containing dentifrice and rinsing with CHX is no longer applicable.

The addition of alcohol in the mouthrinse vehicle solution does not appear to be necessary. If the dose (volume x concentration) and the rinsing time are respected, the efficacy on plaque inhibition and gingival inflammation of an alcohol-free mouthrinse (Perio-aid) and an alcohol-containing mouthrinse (Corsodyl®) is comparable. Based on efficacy and taste perception, patients could freely choose which mouthwash they prefer. However, Corsodyl is registered as a drug and therefore subjected to a high level of control by authorities, which may favour its use.

In order to inhibit plaque accumulation and control gingivitis, there is no beneficial effect for twice daily brushing with a CHX-releasing toothbrush compared to brushing with an ordinary toothbrush. Brushing with the CHX-releasing toothbrush is also less efficient than brushing with an ordinary toothbrush followed by rinsing with 0.2% CHX.

In case of rinsing with CHX before or after toothbrushing during 30 seconds, an additional reduction of 33% for plaque and 26% for gingivitis has been determined. This additional effect may be less than what is generally expected by the dental practitioners.

No data are available providing any evidence for the beneficial effect of a CHX rinse used alone as a monotherapy. Further research should focus on the development or improvement of a mouthrinse with enhanced anti-plaque effect and anti-gingivitis properties when used alone, while minimizing the well-known side-effects, especially the brown staining.