Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Archives of Applied Science Research, 2010, 2 (2): 79-99
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-508X
CODEN (USA) AASRC9

Chewing gum as a drug delivery system

Farhad Mehta*, Raj K. Keservani, C. Karthikeyan and Piyush Trivedi

School of Pharmaceutical Sciences, Rajiv Gandhi Proudyogiki Vishwavidyalaya, Bhopal, (M.P.), India

---

Abstract

The potential of chewing gum as a drug delivery system together with different formulation principles and methods of assessment are discussed in this article. The release of a drug from chewing gum is dependent upon its water solubility. Water soluble substances are released rapidly and completely from chewing gum and methods are available which retard their release from chewing gum to provide an extended release profile. Slightly water-soluble drugs are released slowly and incompletely from chewing gum and require special formulation techniques to produce a satisfactory release profile. Studies evaluating the potential application of medicated and non-medicated chewing gum in the treatment of local diseases in the oral cavity are described. Specific examples of the use of chewing gum as a delivery system for dental health, smoking cessation and antifungal therapy are cited. Few drugs are suitable candidates for incorporation into chewing gum formulations for the intention of their systemic delivery. Know-how derived from the development and manufacture of already existing medicated and non-medicated chewing gum, supplemented with today's knowledge of the principles of pharmaceutical formulation, constitute the basis for the development of the medicinal chewing gum of tomorrow.

Key words: Buccal delivery, Increased release, Sustained release, Dental health, Oral candidiasis, Smoking cessation.

INTRODUCTION

Medicated chewing gum is solid, single-dose preparations that have to be chewed & not swallowed; chewing gums contain one or more active ingredient that is released by chewing. A medicated chewing gum is intended to be chewed for a certain period of time, required to deliver the dose, after which the remaining mass is discarded. During the chewing process the drug contained in the gum product is released from the mass into saliva & could be absorbed through the oral mucosa or swallowed reaching stomach for gastro-intestinal absorption.

Empiric findings had shown that people chewing gum was better at keeping awake and alert, and that gum chewing eased tension. The acceptance of this somewhat anecdotally understood effect

achieved a better scientific basis in the summer 2002 when L Wilkinson and co-workers published a study of 75 healthy volunteers who were led through a number of cognitive, recognition, and memory tests. The results provided the first evidence that the chewing of gum can improve episodic memory and working memory. [1] The anecdotal effect of chewing gum on weight loss has also been studied recently. In December 1999, The New England Journal of Medicine revealed that while chewing gum, energy expenditure increases from 58 kcal per hour to 70 kcal per hour – an increase of 19% (Fig 1). The conclusion was that if a person chewed gum during walking hours, this alone would mean a yearly weight loss of more than 5 kg. Though there are many other interesting anecdotal effects that result from gum chewing, such as the easing of blocked ears. [2]

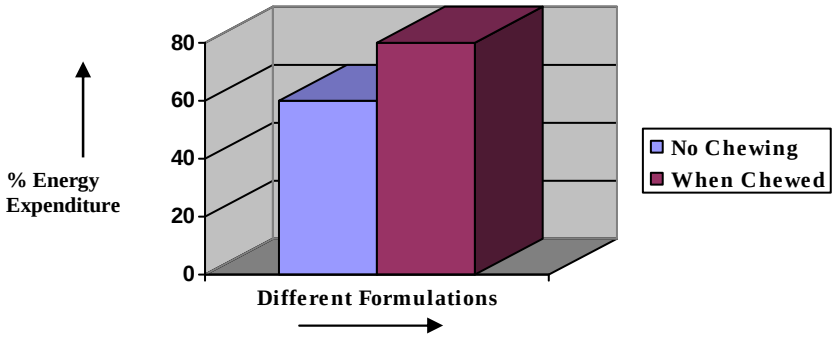

Fig 1. Effect of Chewing on Energy Expenditure

1. Chewing Gum as a Drug Delivery System

The advantages of utilizing a chewing gum drug delivery system are highlighted by T Imfeld in his 1999 review of gum chewing and oral health. There are two absorption pathways which are possible to introduce the active ingredient into the systemic circulation giving rise to a systemic effect. Drug absorbed directly via the buccal membrane avoids metabolism in the G.I tract & the first-pass effect of the liver; it might therefore be to administer a reduce dose in chewing gum compared to other oral delivery system. [3]

(A). Local effect

To obtain the optimal local effect to treat a health condition requires that the relevant active substance be available at a therapeutic level near or within the tissue being treated, regardless of the delivery system. For the treatment of oral cavity conditions, it is beneficial to achieve a therapeutic level of active substance in the saliva, and different formulations (e.g. oral gel, mouth rinse) have been created to meet this goal. Chewing gum is an ideal drug delivery system for this treatment area; the active substances are released as the gum is chewed, thus providing the potential for a high level of active substance to obtain local effect in the oral cavity. It is possible to design a chewing gum that releases active substances over a prolonged period. The “Oral health and caries prevention” and “Oral fungal infection” provide a more comprehensive review of the advantages of chewing gum drug delivery systems for the local treatment of oral health conditions.

(B). Systemic effect

Systemic effects of active substances released from chewing gum can be achieved in two ways: in the “traditional” way, by swallowing the active substance, or buccally via absorption through the oral mucosa. The latter is of special interest. As buccal absorption avoids first-pass hepatic metabolism of the active substance, it could provide better bioavailability. [3] Buccal absorption

may also lead to fast onset of the active substance as the vascular supply of the buccal mucosa is rich and lead directly into the systemic circulation. Chewing gum promotes buccal absorption by releasing active substances at carefully controlled rates, thus allowing for extended exposure in the oral cavity. There are several methods for examining buccal absorption; these methods are described by MR Rassing and co-workers. The buccal absorption of nicotine has been studied extensively and is, therefore, a good example of buccal absorption obtained when using chewing gum as a drug delivery system. [4,5]

A study of the pharmacokinetics of nicotine chewing gum indicated that some of the nicotine was not absorbed buccally, but was swallowed and underwent first-pass metabolism. It was estimated that approximately 80% of the nicotine released from the chewing gum was absorbed buccally. [6] Though the percentage swallowed was higher for a 4 mg than for a 2 mg formulation, the systemic dose achieved was only 50% higher after intake of a 4 mg formulation. (Fig 2) A similar result was found when administering nicotine in a sublingual tablet; incorrect use of the sublingual tablet, however, has shown to lead to variations in bioavailability. [7]

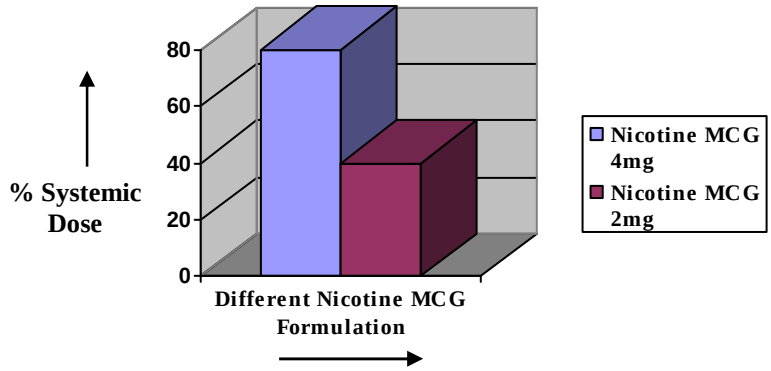

Fig 2. Effect of Different Nicotine MCG Formulation on % Systemic Dose

Different clinical studies of nicotine chewing gum have shown interpatient variations. The variations could be explained by differences in swallowing frequency, but could perhaps also be explained by the intensity with which the gum is chewed. Patient training and informational/instructional inserts that provide guidelines for proper chewing could significantly reduce this variability. Different delivery forms that facilitate buccal absorption have been compared in a study using a radiolabelled model substance. [8] The study looked at local kinetic parameters after administration of lozenges, chewing gum, and sublingual tablets. Six healthy males were included in this crossover study. The disappearance half-life from the oral cavity (*T1/2*) was longest for sublingual tablets, followed by chewing gums, and the shortest *T1/2* was seen for lozenges. The AUC values obtained from the activity-time curves in the oral cavity followed the same pattern: highest for sublingual tablets, followed by chewing gum, and lowest for lozenges all differences were statistically significant. The problem with regard to the right placing of the sublingual tablet and the resulting differences in bioavailability is an important factor for consideration while using sublingual tablet for drug delivery.

Similar studies have been carried out with other active substances. Some of these are mentioned in the above section. With any chewing gum formulation, part of the active substance will be swallowed with the saliva and absorbed through the GI tract. This process is comparable to absorption from conventional tablets. As the active substance released from chewing gum is dissolved in saliva, however, it is readily accessible for absorption, and the processes of disintegration and dissolution are bypassed.

2. Other Aspects of Chewing Gum

As suggested above, it is obvious that the length of time that patients chew becomes important when using chewing gum as a drug delivery system. In order to receive the full benefit from either buccal absorption or local effect, a certain concentration level in the oral cavity has to be maintained for a period of time. [9] The question is, therefore, what prescribed chewing duration will the typical patient accept; A study of 4,064 Americans between the ages of 12 and 55 answered this question to some degree. Participants were asked about their gum chewing habits, and results showed that mean chewing time was 36 minutes – a sufficient time to obtain local effect or buccal absorption of an active substance.

Patients generally do not experience differences among different equivalent brands while swallowing tablets. When they chew a piece of medical chewing gum, however, differences in flavor (a feature also inherent in liquids and chewable tablets), texture and stickiness are very apparent. A clinical trial comparing two different brands of nicotine chewing gum (Nicorette® and Nicotinell®) highlight the importance of these factors for patient preference. [10] In this randomized crossover study, twenty volunteers rated the two brands. The Nicotinell® brand was rated significantly better with respect to both rated properties: texture and stickiness. At the end of the two-week trial period, 90% of the participants preferred Nicotinell®. [11] When asked what product they would use if they had to start a nicotine replacement treatment tomorrow, again 90% answered Nicotinell®. (Fig 3) A comprehensive description of the development and design of medical chewing gum can be found in an overview by MR Rassing and co-workers and in the paper "Development of medical chewing gum". [12] The release of active substances can be controlled carefully through the specific formulation of the chewing gum; consequently, chewing gum can be developed to be bioequivalent to tablets or other formulation

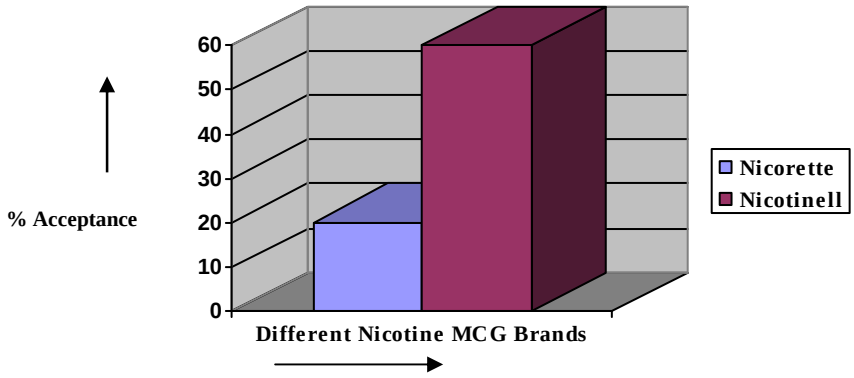

Fig 3. Effect of Different Nicotine MCG Brand on % Acceptance

3. Effect of Chewing Gum on the Gi Tract

(A). Effect on the oral cavity – stimulation of salivary flow

When chewing a piece of gum, not only are the mouth and breath refreshed, but salivary production increases as well. Numerous clinical trials have validated the beneficial effects that chewing gum has on the oral cavity. Articles by T Imfeld, WM Edgar, [13] and MR Rassing [14] have reviewed the beneficial effects of chewing gum on the oral cavity. All three researchers highlight that gum chewing stimulates salivary flow, effects dental health positively, and has a non-cariogenic effect through stimulation of salivary flow and increase in plaque pH. Though Imfeld, Edgar, and Rassing have each provided comprehensive reviews, results from some additional clinical trials are also noteworthy. Olsson [15] and co-workers asked elderly people (mean age of 66.7) with a chronic feeling of dry mouth to chew gum for 35 minutes. They collected samples of the participants' saliva prior to chewing and after 5, 15, and 30 minutes of

chewing. They found that gum chewing resulted in an increase in salivary secretion rate. A different study showed that chewing sugar free gum over a prolonged time period [16] (ten minutes every waking hour for two weeks) resulted in a functional increase in the output of stimulated saliva and an increase in the pH and buffer capacity of whole and parotid saliva, implying a reduction in plaque acidogenicity. (Fig 4).

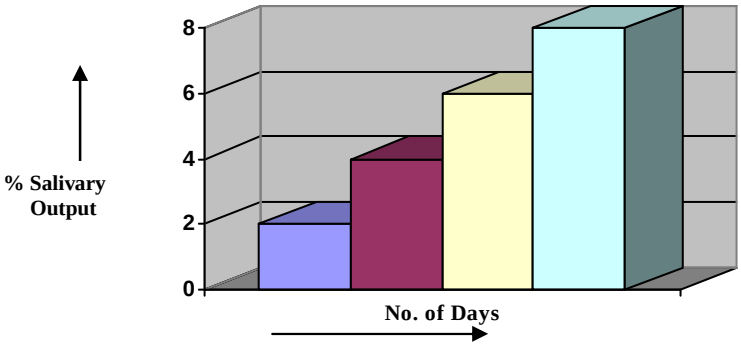

Fig 4. Effect of Chewing MCG on Salivary Output & pH for 14 days

These findings were further confirmed by F Odusola, [17] who reviewed the work carried out by the School of Dental and Oral Surgery at Columbia University, and by C Dawes and co-worker, [18] who found that the salivary flow was increased 10-12 times by chewing gum when compared to unstimulated flow rates. After 20 minutes of chewing, the flow rates were still 2.7 times higher than the unstimulated flow. (Fig 5). The latter study was conducted on healthy volunteers.

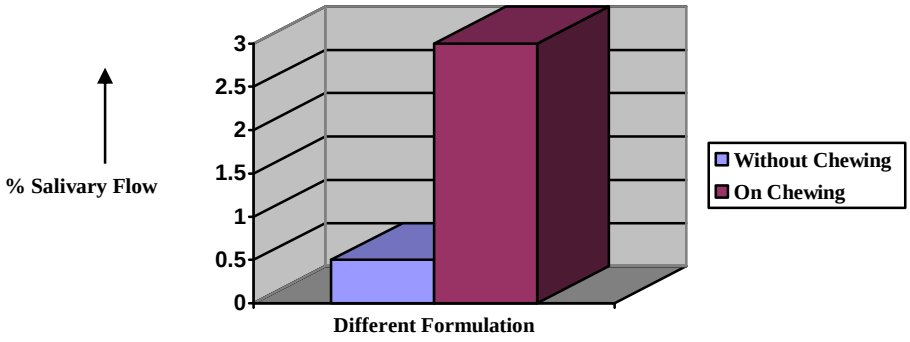

Fig 5. Effect on % Salivary Flow on chewing MCG

Another group studied the effect of chewing gum on salivary flow rates in healthy young students. [19] They found that daily gum chewing increased unstimulated salivary flow rates, especially in those with low salivary function. The increase in mean flow rate remained significantly higher even eight weeks after the treatment was stopped. H Risheim and co-worker [20] tested the stimulating effect of chewing gum and lozenges on salivary secretion in 18 rheumatic patients suffering from xerostomia. Nearly half of the patients (7) had xerostomia for more than ten years. The two treatments provided a slight effect on unstimulated salivary flow rates, however, one-third experienced good relief of their dry mouth symptoms. Another study compared tablets, mouth rinses, and lozenges containing substances with salivary stimulating properties and chewing gum. [21] The results from this study showed that gum chewing was as effective in stimulating salivary production as salivary stimulating substances (e.g. ascorbic acid, nicotinamide, and carboxymethylcellulose) in a tablet or lozenge formulation, and that chewing

gum was rated by patients as the best product. As the results of the above described studies show, the positive functional effects of chewing gum have been well established.

(B). Effect on esophagus and esophageal reflux

It is well understood that patients suffering from oesophageal reflux receive a beneficial effect from their own saliva. Not only does saliva protect against the acid-induced damage on the mucosa in the oesophagus, the bicarbonate in saliva also neutralizes acid and accelerates acid clearance time. As chewing gum increases salivary secretion, Jv Schönfeld and his group set out to investigate if chewing gum could have a beneficial effect on oesophageal reflux. [22] The study was designed to investigate the interrelation between exposure to acid in the oesophagus and salivary secretion. The clearance time after a bolus of acid (20 ml of 0.1 N hydrochloric acid) was measured in 10 healthy volunteers.

The study showed that prolonged chewing of gum base (which is colorless, tasteless, and non-caloric) significantly increased salivary flow and significantly shortened acid clearance time. Jv Schönfeld and his group [23,24] discuss that another group has reported on the effect of oral lozenges on acid clearance time. The results obtained with lozenges, however, were not as pronounced as those obtained with chewing gum by the Schönfeld group. Finally, Schönfeld and his group emphasized that it is very likely that the use of chewing gum will be even more beneficial than is seen in the study, as increased salivary secretion will induce more frequent swallowing and, therefore, faster clearance time; in the study, swallowing was done at a predetermined fixed rate.

Based on these results, a comparative study of chewing gum and postprandial walking in patients with gastro-oesophageal reflux (GERD) was carried out. Walking also has been described to have a beneficial effect on reflux. [25] In this study, patients suffering from GERD were asked to walk, sit, or chew gum for one hour after having eaten breakfast. The study also included a healthy control group. As expected in patients with GERD, sitting did not have any effect on acid contact time in the oesophagus. Walking was associated with a significant reduction in acid contact time, however, only as long as the patients were actually in motion. After the one hour of walking, acid contact time again followed the pattern seen in the sitting group (Fig 6).

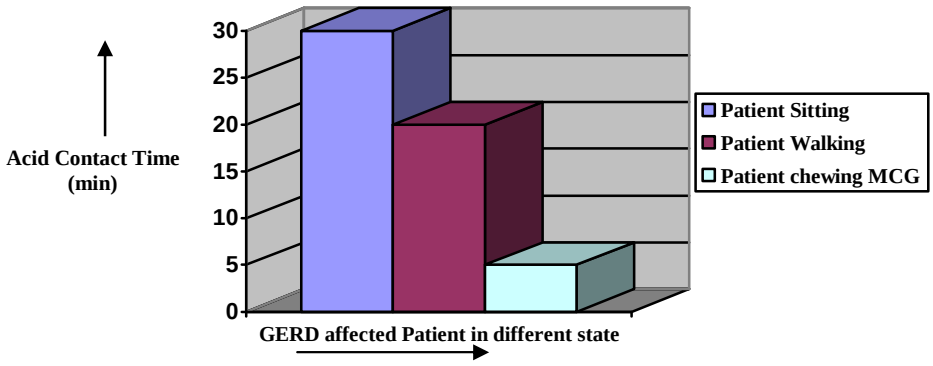

Fig 6. Effect of Acid Contact time on GERD affected patients

After one hour of chewing gum, not only there was a significant reduction in acid contact time, but reduction continued for 3 hours post-chewing. Chewing gum also had a better effect on the frequency of reflux episodes than walking did. The study concludes that gum chewing reduced acid contact time significantly in refluxers and control subjects for the entire postprandial period, and that the results from the study indicate that the duration of reflux inhibition provided by gum

chewing sufficient to counteract meal-induced reflux. The authors recommend that walking and gum chewing is part of the general measures in the non-pharmacological treatment of GERD.

In May 2001, a study comparing regular chewing gum to chewing gum containing bicarbonate in patients with laryngopharyngeal reflux. [26] The study showed that chewing gum substantially and significantly shifts the pH in the pharynx and in the oesophagus, and that bicarbonate chewing gum induced higher increases than regular chewing gum. The beneficial effect of chewing gum lasts more than twice as long as the actual gum chewing period, and the beneficial effects appear to last significantly longer than the buffering effect of an ordinary meal. The authors concluded that chewing gum appears to be a useful adjunctive in entire therapy.

Finally, results were presented in 2001 at the 66th Annual Scientific Meeting of the American College of Gastroenterology [27] and recently published, [28] show that calcium carbonate in a chewing gum formulation is superior to chewable tablets, even though the chewing gum dosage studied was lower than the chewable tablet dosage (600 mg or 900 mg calcium carbonate for chewing gum versus 1000 mg for the chewable tablet).That chewing gum has such a pronounced effect on reflux can be explained by the increase in salivary flow rates, salivary bicarbonate concentration, and the rate of swallowing. Another factor that could explain the effect of chewing gum on the treatment of reflux disorders could be the stimulation of GI motility. So far, it has only been proven that chewing gum has a stimulating effect on bowel motility. This was demonstrated in a study performed on patients undergoing elective laparoscopic colectomy. [29] The patients chewing gum had significantly shorter time to first postoperative flatus, postoperative defecation, and had a shorter postoperative hospitalization.

(C). Effect on gastric acid

As mentioned in “Effect on the oral cavity – stimulation of salivary flow”, it has been proven that chewing gum has a strong salivary stimulating effect. Is there a similar stimulating effect on the secretion of gastric acid; Is it safe for people with gastric ulcers to chew gum. The first study on the effect of chewing gum on gastric acid was represented by E.A Hansen in 1972. [30] Although this study was published over 30 years ago, the results remain interesting even today. In the study, 15 patients, 10 of whom had a duodenal ulcer, were asked to chew gum for 30 minutes. Aspirations from the stomach were performed every 15 minutes beginning one hour before the gum chewing commenced and ending one hour after. The result of this study showed that chewing gum has a weak stimulating effect on gastric acid secretion.

However, according to the authors, the increase in acid output does not result in any increase in acid concentration owing to the neutralization of acid by the salivary bicarbonate swallowed during chewing. Other studies had also reported similar findings. One study used a gamma camera to monitor healthy volunteers prior to and during gum chewing. [31] It found an initial decrease in intragastric pH; however, when the subject swallowed saliva, the pH began to rise. After 5 minutes, the pH was identical to the initial pH value. A larger study including 77 patients also found that chewing gum did not affect gastric content. [32] In this study, both volume and pH were measured: no differences were found between the groups whether they had chewed gum or not. Different lengths of chewing time did not result in pH differences. EA Hansen & co-workers concludes that “although chewing gum causes a stimulation of the gastric acid secretion, this increase is so small that it does not justify an advice against use of chewing gum in patients with duodenal ulcer or X-ray negative dyspepsia”.

4. Chewing Gum Containing Active Substances

The use of chewing gum as a delivery system for an active substance is not new. Between the two World Wars, the first chewing gum with an active substance became commercially available. The big breakthrough, however, had to wait until the launch of nicotine chewing gum for smoking cessation. That the breakthrough happens at this point in time is likely due to increased patient involvement in their own treatment and improved development and manufacturing processes for chewing gum.

Oral health and caries prevention

In 1997, I Itthagarun and co-worker reviewed the literature on chewing gum and oral health. They found that the use of sugar free chewing gum has been increasingly accepted as an adjunct to other oral products and has become a part of anti-caries prevention programmers. They suggest that "chewing gum not only acts as a salivary stimulant but may also be a useful vehicle for some agents such as fluoride, chlorhexidine, and calcium phosphate." Bacterial plaque is one of the major etiologic agents involved in the initiation and progression of dental caries, gingivitis, and periodontal diseases. Consequently, the control of plaque becomes an important factor in the preservation of oral health. Several studies have been performed with regard to chewing gum and oral health, some of which were mentioned in "Effect on the oral cavity – stimulation of salivary flow". A review of additional studies that focus on active substances delivered via chewing gum for the treatment and prevention of oral health problems follows. [33]

4. (A). Fluoride

Fluoride plays a major role in oral health and in the prevention of tooth decay, as it has the following effects: [34]

- Inhibition of demineralization
- Enhancement of remineralisation
- Inhibition of bacterial activity in dental plaque

Several studies have been conducted in which fluoride has been administered in a chewing gum formulation. J Ekstrand and co-workers [35] compared chewing gum containing 0.25 mg of fluoride with a placebo chewing gum in 20 healthy volunteers in a double-blind crossover study. The results from the study indicated that slightly elevated levels of fluoride in the saliva, achieved by repeated intake of fluoride gum for seven days, are sufficient to influence the acidogenicity of dental plaque. A similar study conducted at the same Swedish institute [36] concluded that chewing gum containing fluoride is a convenient and safe way to administer fluoride – it elevates fluoride concentration and, as a positive "side effect", stimulates salivary secretion. A larger study compared the salivary concentration of fluoride after intake of different fluoride tablets and fluoride chewing gum in 55 subjects (20 children age 10-12 years, 20 healthy adults, and 15 patients suffering from dry mouth). [37]

The main conclusion from the study was that the saliva clearance patterns and salivary stimulating effects of all the products were approximately the same. There were great variations among the subjects, however. Another study compared fluoride chewing gum with a sorbitol chewing gum and a control group, looking specifically at the remineralisation of root lesions. [38] It was shown that the frequent administration of low fluoride doses was able to produce high fluoride incorporation in root surfaces. In the conclusion, the authors indicated that the "findings present encouraging results in fluoride uptake and remineralization using fluoride chewing gum", and "it is also expected that patient compliance should be high since the chewing habit is generally accepted by many people."

Comparison between different methods of applying fluoride (e.g. lozenges, chewing gum, and mouth rinse) has also been carried out. [39] Toothpaste and mouth rinse increased the concentration of fluoride significantly more than lozenges and chewing gum. However, the authors pointed out in the discussion that the differences are small and not crucial for caries prevention efficacy. (Fig 7) Consequently, the most important issue is that the formulation be acceptable and convenient to the patient for regularly use. A multinational group [40] studied the safety of fluoride chewing gum by measuring the uptake of fluoride in humans after chewing fluoride chewing gum. Though there was a 1.7 fold increase in fluoride levels on plaque, the plasma fluoride levels were negligible indicating that fluoride chewing gum is safe.

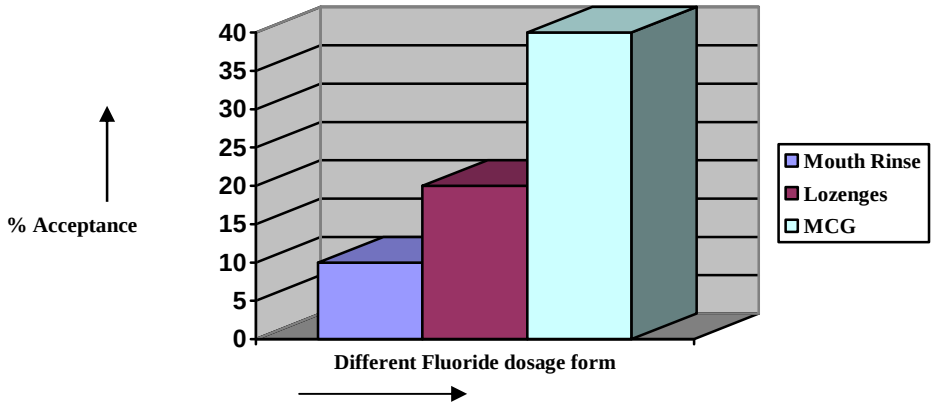

Fig 7. Effect of different Fluoride dosage form on patient acceptance

4. (B). Xylitol

Xylitol (a polyol sugar alcohol – also referred to as birch sugar because it can be produced from birch trees) is used frequently, especially in Finland, and has been used for oral health care. The regular use of xylitol chewing gum [41] leads to a reduction in the acidogenic potential of dental plaque, and studies [42-44] have shown that xylitol reduces enamel demineralization and inhibits caries. One study even claimed that xylitol is cariostatic and can reduce the risk of mother-child transmission of mutans streptococci. [45] This is an important factor in oral health, as the prevention of colonisation of mutans streptococci in early childhood has been shown to lead to the prevention of dental decay. That mother-child transmission of streptococci can be reduced was proven in another study that included 195 mothers with mutans streptococci. [46] The mothers in this study were randomized to either receive chewing gum containing xylitol, fluoride varnish, or chlorhexidine varnish. At age 5, the children of the mothers chewing xylitol had a reduction in dentinal caries of 70% when compared to the other treatment groups. Other long-term studies show that daily use of xylitol chewing gum by children significantly lowered their caries score, and that this decrease could still be seen five years after discontinuation of therapy. [47] The best result was achieved if xylitol chewing gum treatment was initiated at least one year prior to eruption of permanent teeth. [48]

Finally, a review of cariologic aspects of xylitol concluded that a daily intake of two to three pieces of xylitol chewing gum resulted in a defined reduction of caries [49]. Regular and prolonged use of xylitol chewing gum may have a caries-preventive effect. Other researchers have not been convinced of the beneficial effect of xylitol, however, and the above results have been questioned by some. [50]

4. (C). Urea

Studies have also been performed to test if chewing gum containing urea could have a caries-preventive effect. A study was carried out on schoolchildren in Madagascar. [51] The study

included 376 children who were asked to chew gum containing urea and 326 children of the same age in a control group that received no chewing gum. At the end of the three-year follow-up period, a positive effect on DMFS (**A numerical expression of caries prevalence that is obtained by calculating the number of decayed (D), missing (M), filled (F) surfaces (S).*) was seen on the children chewing gum containing urea as compared with the controls. Though this was not a significant difference, a statistically significant reduction of occlusal dental caries was seen in a subgroup of the gum-chewing children. It was concluded that "the present investigation indicated a positive clinical effect of using chewing gum", and "the use of such chewing gum may be considered a supplement to the control of occlusal dental caries in permanent teeth of young schoolchildren, particularly in developing countries with limited resources for formal oral health care."

In Lithuania, a similar study [52] was performed on 602 children. The children were given sorbitol/urea chewing gum, sorbitol chewing gum, xylitol chewing gum, control chewing gum, or no chewing gum. The children were monitored for three years. At the end of the trial period, there were significantly lower caries increments in the groups receiving sorbitol chewing gum, xylitol chewing gum and the control chewing gum than in the no chewing gum group. There was not a statistically significant difference between the control group and the group receiving sorbitol/urea chewing gum. The authors concluded that there is an indication that though caries cannot be further prevented by sweeteners or additives such as polyol and urea, they can be by merely chewing sugar free gum.

A study performed on Swedish adults [53] compared chewing gum containing urea with a placebo chewing gum with regard to formation of calculus. Little effect was seen, and the main conclusion was that three months of frequent use of sugar-free chewing gum – with or without urea – neither promotes nor inhibits calculus formation.

4. (D). Chlorhexidine

The anti-plaque effect of chlorhexidine has been extensively tested and documented in mouth rinse, toothpaste, and chewing gum. [54] A dose finding study proved that a daily dose of two pieces of 5 mg chlorhexidine in a chewing gum was as effective as mouth rinse in a daily dose of 40 mg. [55] Another study compared a daily dose of 40 mg chlorhexidine in a mouth rinse with a daily dose of 20 mg chlorhexidine in chewing gum [56] and found that similar benefits to oral hygiene and gingival health were achieved from both formulations.

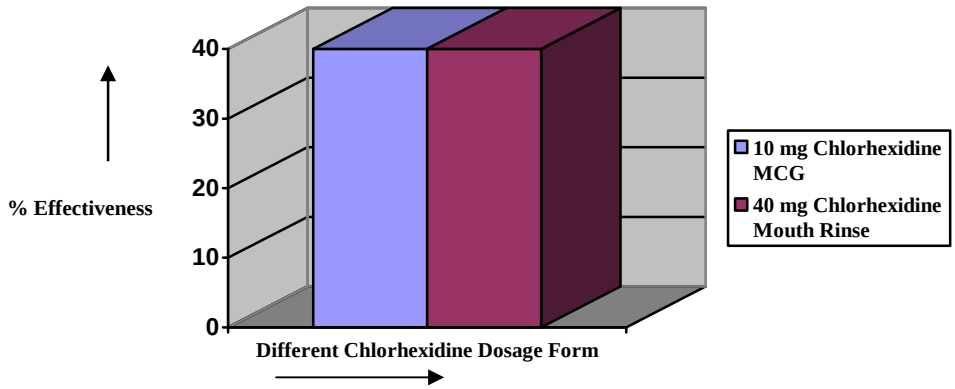

Fig 8. Effect of different Chlorhexidine dosage form on drug effectiveness

The study did show a difference; however, as it was proven that the chewing gum formulation resulted in significantly less stain intensity after 8 weeks. The beneficial effect on plaque and

gingivitis were confirmed by D Simons and co-workers. [57] Additionally, a double-blind crossover study [58] has proven that chlorhexidine chewing gum has a beneficial effect on plaque growth, [59] and that it has a significantly better effect on reduction of plaque than sorbitol or xylitol chewing gum.

That chlorhexidine chewing gum can be useful in elderly patients was proven in a study conducted in nursing homes in the UK. The study found a significant reduction in salivary levels of mutans streptococci, lactobacilli, and yeast after 14 days of treatment in elderly patients (mean age 79.5 +/- 7.7). [60]

Furthermore, the treatment was acceptable for the elderly, and they were especially satisfied with the beneficial effect on dry mouth. This study was followed by a study in the elderly class that ran for 12 months, [61-63] through which it was proven that chewing gum containing chlorhexidine was significantly better in reducing plaque and gingival indices than a plain piece of chewing gum (both chewing gum formulations had the same content of xylitol). The chlorhexidine chewing gum lowered denture debris status, reduced denture stomatitis by 91%, and reduced angular cheilitis prevalence by 75%.

4. (E). Vitamin C

A group from the Royal Danish School of Pharmacy [64] compared the excretion of ascorbic acid in urine after administration via chewing gum and chewable tablets. Six healthy volunteers were included. The study showed a higher recovery of vitamin C in the urine after administration of the chewing gum formulation when compared to the chewable tablet indicating a better bioavailability for the chewing gum formulation. Another study with vitamin C was performed in Sweden. [65] The aim of the study was to evaluate the effect of frequent use of a sugar free chewing gum containing vitamin C (60 mg) on calculus formation and other oral parameters. The study showed that frequent use of chewing gum containing vitamin C reduces not only calculus formation, but also gingival bleeding and plaque formation. The reductions were significant when compared to a group receiving no chewing gum. Though chewing gum without vitamin C also created reductions in the same study, these reductions were not significant.

4. (F). Zinc

Zinc in a chewing gum formulation has been compared to zinc in a mouth rinse formulation. [66] The study set out to examine whether zinc could be made available in the oral cavity and inhibit the production of volatile sulphur-containing compounds. The “morning breath” of 11 healthy subjects was tested. The mouth rinse and chewing gum had similar effects resulting in a 45% reduction in volatile sulphur-containing compounds.

4. (G). Other Active Substances

Zirconium silicate in a chewing gum formulation has been tested in 10-12 year old children. [67] It was shown that the chewing gum reduced plaque thickness and plaque areas compared to placebo chewing gum.

Another study tested chewing gum containing sodium bicarbonate and found that the presence of sodium bicarbonate in a chewing gum can supplement the salivary buffering system by causing a faster rise in pH and allowing the plaque pH to remain at an elevated level for at least 20 minutes following food intake. [68] It was concluded, therefore, that sodium bicarbonate may be useful in products designed to reduce the acidogenic challenge to the teeth following food digestion.

5. USES

5. 1. Oral Fungal Infection

As mentioned in "Local effect", chewing gum has advantages as a drug delivery system for active substances where a local effect is the object of treatment. Several studies have been performed regarding the possibility of obtaining a constant, prolonged level of active substance locally for the treatment of oral fungal infections. The release of metronidazole [69] from chewing gum was tested in an early study. It was possible to make a formulation that released 90% (+/- 16) of metronidazole within 15 minutes of chewing. A similar study was carried out with nystatin, [70] and good release results were obtained one of the formulations tested had a release of 95% (+/- 2.1).

Miconazole has also been formulated as chewing gum [71-72], and these formulations have been used in clinical trials. The first study [73] proved that a good correlation existed between the in-vivo and in-vitro release of miconazole from different chewing gum formulations. In another study [74] different formulations of chewing gum containing miconazole were used and, again, good correlation between in-vivo and in-vitro release was proven. A more interesting finding from the latter study is the result of a comparison between gel and chewing gum formulations: the same level of miconazole concentration was found in the saliva whether oral gel or chewing gum were used despite the fact that a dosage of 100 mg of miconazole was applied when using gel versus only 3.8 mg of miconazole when using chewing gum. Inspired by these findings, a pilot study [75] was performed. The study included 32 patients with chronic oral candidosis, 11 of which were HIV infected.

The patients were randomized to receive either 50 mg of miconazole in an oral gel or 3.6 mg miconazole in a chewing gum formulation. Both treatments were administered four times daily. All patients were successfully treated; after six weeks of treatment, there was no clinical evidence of infection in any of the patients. The authors concluded that the smaller dose of miconazole released from chewing gum is as efficient as a large dose released from gel. Moreover, patients considered the chewing gum to be a pleasant formulation. This pilot study was followed by a larger double-dummy, double-blind study that included 106 patients [76], and which compared placebo with miconazole gel (50 mg) and miconazole chewing gum (3.6 mg released). After six weeks of treatment, the cure rate for the patients treated with chewing gum was at east as high as the cure rate for patients treated with gel. (Fig 9). The treatment method preferred by the patients was the chewing gum. The main reason for preferring the chewing gum was that it was easier to use and fewer adverse events were experienced.

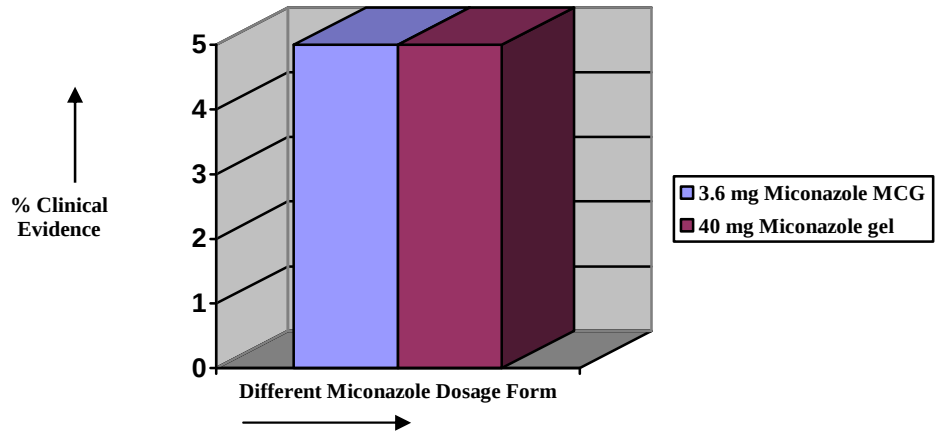

Fig 9. Effect of different Miconazole dosage form on % clinical evidence after infection

5.2. Smoking Cessation

The use of chewing gum as a drug delivery system in smoking cessation is well established and has become highly accepted by consumers. In 1983, nicotine chewing gum was first approved for smoking cessation, though the first clinical trials date back to the 1960s. [77] Prior to the launch of nicotine chewing gum, a chewing gum containing silver acetate was sold as a smoking cessation aid. The success of chewing gum in this treatment area may be explained by M J Peters and co-worker [78] "the process of their [the smokers'] use [of nicotine chewing gum] is a ritual that is in some ways analogous to smoking, and this may be an advantage."

5.3. Silver Acetate

Prior to the development of a chewing gum formulation, silver acetate had been used for decades as an aid in smoking cessation. [79] Silver acetate works by giving the tobacco smoke an unpleasant taste. In early trials with silver acetate, the protocol did not include other interventions aside from prescription of silver acetate. This is unlike many trials in smoking cessation today and could explain why only a modest effect was seen.

In comparison studies of chewing gum containing silver acetate, nicotine, and placebo [80-81], nicotine was found to provide a better success rate than silver acetate, while silver acetate was better than placebo. One study [82] did find silver acetate to be superior to nicotine, however, only in patients with a low weighted pack year consumption (*Weighted pack year consumption was defined as duration of smoking in years multiplied by number of cigarettes smoked per day multiplied by a coefficient and divided by 20.)*

5.4. Nicotine

The idea of nicotine replacement therapy was developed in the 1960s by Ferno and co-workers. They believed that nicotine was the chemical reinforcer of the smoking habit; therefore, nicotine alone, without any other components of cigarette smoke, may help reduce the craving for cigarettes observed after smoking cessation. Having failed in developing an aerosol dosage form, Ferno and co-workers developed a chewing gum formulation that allowed adequate absorption of nicotine through the buccal mucosa. A tablet formulation was not an option due to the extensive first-pass metabolism of nicotine in the liver. Researchers originally believed that nicotine chewing gum could provide the same nicotine level as obtained by smoking [83] however; studies have shown that this is not the case. Though nicotine is absorbed well through all body surfaces, the surface of the alveolar is vast; therefore, a better and faster absorption is seen after cigarette smoking than after chewing nicotine gum. [84]

The use of nicotine chewing gum is well-established as can be seen not only from current sales numbers, but also from the number of articles published. In August 2002, an update on a Cochrane review of nicotine replacement therapy [85] was published. A total of 110 trials/articles (including 35,600 participants) regarding nicotine replacement therapy in smoking cessation were found; of these, 53 included nicotine chewing gum.

The chewing gum used in the trials contained either 2 or 4 mg of nicotine. Of the 53 trials that included nicotine chewing gum, 51 had a placebo or non-nicotine arm. In all but 12 of the trials with chewing gum, the participants were followed for more than 12 months. After a follow-up period of 12 months, 18% of the smokers who had been in treatment with nicotine chewing gum were still abstinent; only 14% of smokers treated with a transdermal patch were abstinent after 12 months. Slightly higher figures were found for intranasal, inhaler, and sublingual tablet treatments. (Fig 10). The odds ratio for quitting smoking by using nicotine chewing gum (2 and 4 mg) was 1.74 (1.64-1.86) while self-help interventions alone only gave an odds ratio of 0.97-

1.1986. [86] The one trial that compared the different methods did not find any difference in abstinence after 12 weeks.

The Cochrane authors' conclusion was that nicotine replacement therapy is effective as part of a strategy to promote smoking cessation, though only minimal evidence is available for people who smoked fewer than 10-15 cigarettes per day. Furthermore, the Cochrane review found that if 2 mg nicotine chewing gum failed, 4 mg should be offered as effect could be anticipated.

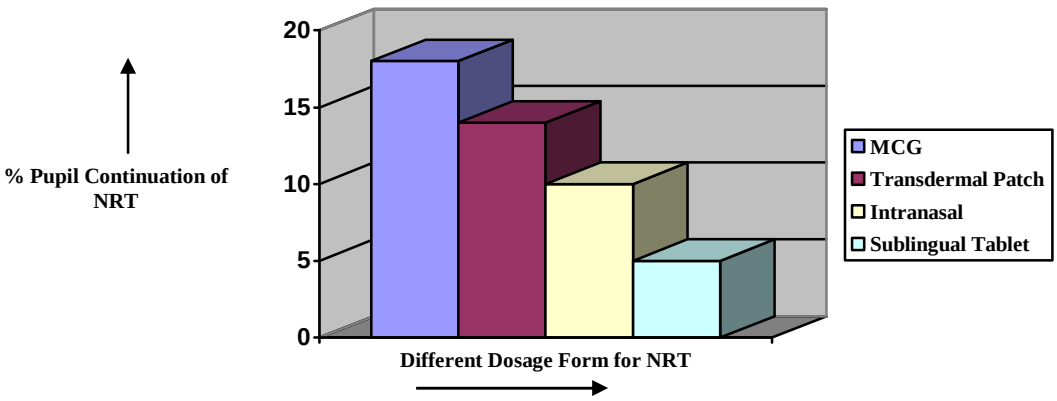

Fig 10. Effect of different dosage form for NRT on % pupil continuation of NRT

Other reviews/meta-analyses have been published. Several of these have concluded that nicotine chewing gum [87-88] is superior to placebo or no chewing gum. The positive results have been explained by the combination of an interaction between the pharmacological properties of chewing gum and the effectiveness of intensive treatment strategies. The conclusion of one review from 1995 was that, though nicotine dependency is difficult to treat, it can be done; the most effective pharmacologic options are nicotine chewing gum and nicotine patches, especially when in combination with behavioral interventions and counseling. In a 1999 literature review, it was found that by using nicotine replacement therapy, the long-term success rate can be doubled. The success rate increased with the level of adjunctive behavioral support. [89]

5.5. Obesity

Smoking could be described as an "oral habit." This expression could also be used to describe obesity. Therefore, a chewing gum drug delivery system should be an obvious choice in this treatment area – the oral habit is maintained by chewing gum with an active substance instead of eating food. Additionally, and as mentioned in the beginning of this paper, chewing gum creates a minor increase in energy expenditure.

At the obesity congress in Sao Paolo in August 2002, a group presented results from a trial [90-91] with a chewing gum formulation containing nicotine and caffeine. The study showed that nicotine had a thermogenic effect, and that this effect was enhanced by caffeine. Furthermore, the combination decreased feelings of hunger and increased satiety to a larger extent than nicotine alone. An article from this study has recently been accepted by The American Journal of Clinical Nutrition. [92] The randomized, double-blind, placebo-controlled, crossover study included 12 healthy males. Different combinations of nicotine (ranging from 0-2 mg) and caffeine (ranging from 0-100 mg caffeine) were tested.

5.6. Pain

The oldest medical chewing gum available is Aspergum®, a chewing gum containing ASA (aspirin or acetylsalicylic acid). Aspergum was tested and it was shown that the bioavailability

was lower in this chewing gum formulation than in tablets. [93] This is not surprising, as Aspergum® is an old product with low, insufficient release. Intensive research has been carried out in recent years to enhance the properties of chewing gum as a drug delivery system for active substances. Another, newer study with Aspergum® confirmed this finding. [94]

Furthermore, the latter study also showed that Tmax was shorter for the chewing gum formulation suggesting that there might be faster absorption from chewing gum. LL Christrup and co-workers [95] made fourteen different chewing gum formulations containing salicylamide and tested the release. The study showed that the content of gum base influenced the release rate of salicylamide: an increase in gum base content tended to lower the release rate. In this study, there was no correlation between the in-vivo and the in-vitro release results, possibly due to the small number (four) of in-vitro tests carried out. The same group also compared methadone in a tablet formulation to a chewing gum formulation. [96] Six male patients suffering from chronic pancreatitis and one male patient suffering from thyroid cancer received the methadone formulation using an open balanced crossover design.

5.7. Stimulating Activating Effect

It is a well-known fact that caffeine has stimulating effect. It could, therefore, be interesting to combine it with chewing gum's generally positive effect on memory. The ability of healthy volunteers to stay awake at night was tested in two different experiments. [97]

The first compared a gum-chewing group to a control group. The second experiment included nurses and technicians on night duty. As in the first experiment, a gum-chewing group was compared to a control group that did not chew gum. The conclusion of the study was that chewing of gum can alleviate the subjective feeling of sleepiness in persons exposed to night watch. The relief of sleepiness was significant after 15 minutes of standing up, but highly significant after 15 minutes of chewing.

Another study [98] compared a chewing gum formulation containing caffeine with a capsule formulation of caffeine. The study found that the rate of absorption was significantly faster from the chewing gum formulation indicating buccal absorption. The authors concluded that there may be an earlier onset of pharmacological effects of caffeine when delivered in a chewing gum formulation versus a capsule formulation. This is advantageous in situations where the rapid reversal of alertness and performance deficit resulting from sleep loss is desirable.

5.8 Treatment of Otitis Media

In March 1995, a group of Swedish doctors began a clinical trial [99] comparing chewing gum containing xylitol with a chewing gum containing sucrose for the prevention of acute otitis media in children. Included in this randomised, double-blind study were 306 day-care children. After 2 months of “treatment”, 20.8% of the children receiving the sucrose chewing gum had at least one episode of acute otitis media compared with only 12.1% of the children receiving xylitol. Furthermore, significantly fewer antimicrobials were prescribed in the xylitol group (18.5% versus 28.9% of the children).

The conclusion was that xylitol seems to have a preventive effect against acute otitis media. The same group of Swedish doctors [100] conducted another study of xylitol and otitis media. In this study, they included 857 day-care children and randomised them into five different treatment groups: syrup without xylitol (control), syrup with xylitol, chewing gum without xylitol (control), chewing gum with xylitol, and lozenges with xylitol. The children receiving xylitol

syrup or xylitol chewing gum showed statistically significant 30% and 40% decreases in otitis media respectively when compared to the control groups. A decrease of 20% was seen in the group treated with lozenges, which was not statistically significant. As in the previous study, there was a corresponding decrease in the usage of antimicrobials. This decrease was significant for both the chewing gum and syrup groups.

6. Acceptance of Chewing Gum in Treatment of Medical Conditions

There is no doubt that chewing gum has become firmly established in the smoking cessation market, and that it is highly accepted as a drug delivery system in this area. Questions remain, however. Will consumers accept chewing gum as a drug delivery system in other treatment areas; will chewing gum be acceptable to all age groups.

Acceptance of medical chewing gum in the elderly

The elderly segment of the population did not grow up with chewing gum. On the contrary, when chewing gum became commercially available, a significant portion of the population thought gum chewing in public to be ill-mannered. As the elderly population group consumes the larger part of the pharmaceuticals in most markets, their attitude towards using chewing gum as a drug delivery system is highly relevant. A clinical study has been performed with chewing gum in elderly patients. [103-104]

Among nine different nursing homes in the United Kingdom, 207 residents were asked to chew two pieces of chlorhexidine chewing gum twice daily for 7 days.

The mean age of the residents was 82.2. Though 37 of the residents were unable to chew the gum, the remaining 170 residents chewed for the entire 7-day period. At the end of the trial, 53.6% of the dentate residents and 40.9% of the edentate residents wished to continue the chewing gum treatment. The major benefits reported by the participating residents were reduction of mouth dryness (57.2%), and that their mouth felt healthy (45.1%). The one year follow up study mentioned earlier in the section “Chlorhexidine”, also with elderly residents in nursing homes, found that 84% of the patients wanted to continue using the chewing gum containing chlorhexidine after the 1 year trial period. A vast majority of participants (84%) said the chewing was easy, and 79% found that the chewing gum kept the mouth healthy.

This clinical trial demonstrated that medical chewing gum is acceptable to elderly people and even to edentulous populations.

General acceptance of medical chewing gum

Unfortunately, clinical trials to determine the acceptance of chewing gum as a drug delivery system have not been conducted in other age groups. However, as this information is highly relevant, Fertin Pharma initiated market research in 2001-2002. [105]

The objective of the market research was to disclose the end-user attitude toward chewing gum as a drug delivery system. The research was carried out in Denmark in 2001 and in Germany and the USA in 2002. The first part – the Danish part – was an omnibus telephone-based study; the second part – the German and American part – was an internet-based study.

The Danish Study

In the late summer of 2001, an omnibus study interviewing 501 people was carried out. The cohort was representative of the Danish population with regard to sex, age, social class, and occupation. The questions were general; no explanation of why chewing gum could be

interesting in medical treatment was given or any other descriptions of the concept. The first question was: imagine that it is possible to get various pharmaceutical products formulated as a piece of chewing gum instead of a tablet. Would you be interested in taking medicine in a chewing gum formulation? The respondents could choose between the following answers: very interested, interested, maybe interested, not interested, do not know.

Acceptance of chewing gum was rated by the research institute to be excellent. An average of 30% of the participants showing interest (very interested, interested or maybe interested) is regarded to be very good in an omnibus, unaided questionnaire. The younger population segments were most interested, but interest was also evident in the middle-aged population group.

Responding parents were asked if they would be interested in using a chewing gum formulation for medical treatment of their children, if a chewing gum formulation was available for treatment of motion sickness, for example. Again, a very positive response was achieved: 60% said that they would use the chewing gum formulation instead of a tablet formulation. In general, the research indicated a high interest in chewing gum formulations both for adults and for children.

The German and American Study

In the spring of 2002, Fertin Pharma carried out the international part of the planned survey; however, it was decided to make the research more comprehensive. Four different treatment areas were selected. These were allergy, pain, dyspepsia, and cough-and-cold. Germany and the USA were selected as representative countries. The survey included 9,000 respondents. One of the inclusion criteria was that the end-user (the respondent him/herself or the respondent's child under the age of 15) had to have used an OTC product for treatment of the complaint in question to participate in the survey. The survey showed a very high acceptance of chewing gum as a drug delivery system (Fig 1.12). In the survey, the end-users were given a description of properties for an active substance in a chewing gum formulation.

The properties perceived as most advantageous by the end-users were: fast onset of action (87-89%), convenience (75-81%), fresh and pleasant feeling of the mouth (71-78%, highest in dyspepsia), and accepted by children (60-67%, highest in cough-and-cold). The end-users were then asked if they would try a chewing gum formulation when it becomes available (Fig 1.13). Finally, they were asked if they would switch brands in order to get a chewing gum formulation (Fig 1.14). The conclusion that can be drawn from the survey is that there is a very high acceptance of chewing gum as a drug delivery system, and that the majority of the end-users would not only consider using an OTC product in a chewing gum formulation, but would even switch brands in order to get a chewing gum formulation.

Acceptance in people wearing orthodontic appliances

A study was performed to determine if chewing gum would be acceptable for people wearing orthodontic appliances. [106] Included were 25 orthodontic patients and 25 healthy controls with a mean age of 16 (range from 11-53 years of age). Participants were asked to chew two different chewing gum products after which they had to complete a questionnaire. The study showed that low-tack chewing gum was preferred by the patients; however, only five of the patients found an increase in discomfort when chewing gums. Furthermore, it was concluded that for orthodontic patients with fixed bonded or banded appliances, the use of chewing gum would seem to be of benefit in the prevention of early decay due to increased susceptibility to early carious lesions. This finding was confirmed by TM Graber and co-workers. [107]

CONCLUSION

For most drugs there are realistic possibilities of formulating them into a suitable chewing gum delivery system, although active agents with an extremely bitter taste would not be suitable candidates. Poorly water-soluble drugs require specialised formulation techniques to promote release, but these techniques are reasonably well developed. Dental health chewing gum for caries prevention has come to stay and the indications are that it will become more and more accepted. In oral diseases where a long release period is required, e.g., treatment of fungal diseases, chewing gum as a drug delivery system appears to have a future role. It is also predicted that patients with xerostomia will increasingly find chewing gum - and especially chewing gum which contains an active ingredient to prevent caries - to be attractive means of stimulating saliva.

Chewing gum for smoking cessation will also remain despite the fact that nicotine patches have grown in popularity lately. This is because the very act of chewing gum also provides a physical substitute for the smoking habit and thereby increases the possiblity of successfully quitting. Ingredients delivered in chewing gum to help reduce weight will, we believe, come and go like most other weight reducing supplements. For drugs treating diseases where a rapid onset of action is needed, such as transport sickness, nausea and headache, chewing gum may be a potentially viable delivery system.Although drugs are absorbed from the oral cavity directly into the systemic circulation the number of suitable drug candidates is small.

Finally, in the future, we may see drugs formulated into chewing gum in preference to other delivery systems to deliver drugs locally to the oral cavity. The reason is simple - that the chewing gum delivery system is convenient, easy to administer - anywhere, anytime - and is pleasantly tasting making it patient acceptable.

REFERENCES

[1] L. Wilkinson, A .Scholey, K .Wesnes, *Appetite.*, **2002**, 38, 235-236.
[2] J. Levine, P .Baukol, I .Pavlidis, *N. Engl. J. Med.*, **1999**, 241, 2100.
[3] T. Imfeld, *Crit. Rev .Oral .Biol. Med.*, **1999,** 10, 405-419.
[4] MR .Rassing., Specialized oral mucosal drug delivery systems, chewing gum. In: MJ . Rathbone: Oral Mucosal Drug Delivery; Marcel Dekker, **1996**, 319-357.
[5] M.R. Rassing, J. Jacobsen, H.M. Nielsen, Ellermann Carecom., **2002.**
[6] N.L. Benowitz, P .Jacob III, C. Savanapridi, *Clin. Pharmacol. Ther.*, **1987,** 41,467-473.
[7] L .Molander, E. Lunell, *Eur .J .Clin.Pharmacol.*, **2001,** 56, 813-819.
[8] L.L. Christrup, S.S. Davis, M .Frier, C.D. Melia, S.N. Rasmussen, N. Washington, I.R. Wilding, C. Andersen, *Int. J. Pharmaceuticals.*, **1990**, 66,169-174.
[9] R. Barabolak, K. Hoerman, B. Kroll, D .Record,*Dent. Oral. Epidemiol*., **1991**,19, 125- 126.
[10] M. Rasmussen, J.T. Jørgensen, J .Rømsing,*Clin. Drug. Invest.*, **1997,** 13, 5, 277-281.
[11] M.R Rassing, J. Jacobsen, Medicated Chewing gum, In, M.J Rathbone, J Hadgraft, MS Roberts, Modified-release drug delivery technology, Marcel Dekker, **2002**, 419-429.
[12] Fertin Pharma, Development of medical chewing gum, Ellermann Carecom, **2002.**
[13] W.M. Edgar,*Br. Dent. J.***, 1998,** 184, 1, 29-32.
[14] M.R. Rassing, *Advanced. Drug. Delivery. Reviews.*, **1994,** 13, 89-121.
[15] H. Olsson, C.J. Spak, T .Axéll, *Acta. Odontol. Scand.*, **1991,** 49, 273-279.
[16] M.W.J. Dodds, S.C .Hsieh, D.A .Johnson,*J .Dent. Res*., **1991,** 70, 12, 1474-1478.
[17] F .Odusola, *N.Y. State. Dent. J.*, **1991,** 4, 28-31.

[18] C .Dawes, L.M.D .Macpherson, *Caries. Res.*, **1992**, 26, 176-182.
[19] G.N. Jenkins, W.M. Edgar, *J. Dent Res*., **1989,** 68, 5, 786-790.
[20] H. Risheim, P. Arneberg, *Scand. J. Dent. Res.*, **1993,** 101, 40-43.
[21] M .Björnström, T. Axéll, D. Birkhed, *Swed. Dent. J*., **1990,** 14, 153- 161.
[22] Jv Schönfeld, M. Hector, D.F. Evans, D.L. Wingate, *Digestion*., 1997; 58; 111-114.
[23] J.F. Helm, W.J .Doods, D.R. Riedel, B.C .Teeter, W.L. Hogan, R.C. Arndorfer, *Gastroenterology*., **1987,** 85, 607-612.
[24] J.F. Helm, W.J. Dodds, L.R. Pelc, D.W .Palmer, W.J. Hogan, B.C Teeter,*N .Engl. J . Med*., **1984,** 310, 284-288.
[25] B. Avidan, A. Sonnenberg, T.G. Schnell, S.J Sontag, *Aliment. Pharmacol .Ther.*, **2001,** 15, 151-155.
[26] B.R. Smoak, J.A .Koufman, *Ann. Otol. Rhinol. Laryngol*, **2001,** 110, 1117-1119.
[27] K.L .Collings, S. Rodriguez -Stanley, M.G. Robinson, H. Proskin, P.B .Miner Jr, *Am. J. Gastroenterol.,* **2001,** 96, 9, suppl, S8.
[28] K.L. Collings, S. Rodriguez-Stanley, H.M. Proskin, M. Robinson, P.B. Miner Jr, *Aliment Pharmacol Ther*, **2002,** 16, 2029-2035.
[29] T. Asao, H. Kuwano, J-i .Nakamura, N. Morinaga, I .Hirayama, M. Ide,. *J. Am .Coll. Surg.*, **2002,** 195, 1, 30-32.
[30] E.A .Hansen, S.J .Rune, *Scand. J. Gastroent*., **1972,** 7,733-736.
[31] J.B.Lauritzen, L.Højgaard, A.Uhrenholdt, K.B. Lauritsen, F.Moesgaard, *Nuclear. Med .Commun* , **1985,** 6,229-233.
[32] S.A. Dubin, H.G. Jense, J.M. McCranie, V. Zubar, *Can .J. Anaesth.*, **1994,** 41, 603-606.
[33] A. Itthagarun, S. Wei, *J. Clin. Dent.*, **1997,** 8, 159-162.
[34] J.D. Featherstone, *Community Dent Oral Epidemiol*, **1999**, 27, 31-40.
[35] J. Ekstrand, D. Birkhed, L-E Lindgren, A .Oliveby, S. Edwardsson, G. Frostell, *Scand. J. Dent. Res.*, **1985,** 93, 309-314.
[36] A. Oliveby, J. Ekstrand, F. Lagerlöf,*Caries Res*, **1987,** 21,393-401.
[37] K. Sjögren, D. Birkhed, L.G. Persson, J.G. Norén,*Chang. Gung. Med. J.*, **1991**, 14, 174-185.
[38] L Seppä, S. Salmenkivi, H. Hausen, *Acta. Odontol. Scand.*, **1997,** 55, 84-87.
[39] F.N. Hattab, R.M. Green, K.M .Pang, Y.C. Mok, *Clin. Preventive. Dent.*, **1989,** 11, 6-11.
[40] O. Aguirre-Zero, D.T. Zero, H.M. Proskin, *Caries. Res.*, **1993**, 27, 55-59.
[41] J. Arends.*Caries Res*, **1984**, 18, 296-301.
[42] K.K. Mäkinen, *Int Dent J*, **1996,** 46, 22-34.
[43] J.M. Tanzer, *Int Dent J*, **1995,** 45, 1, 65-76.
[44] E. Söderling, *C. Res*, **2001,** 35, 173-177.
[45] P. Isokangas, E. Söderling, K .Pienihäkkinen, P. Alanen, *J. Dent. Res*, **2000,** 79, 1885-1889.
[46] P. Isokangas, *Caries. Res*.,**1993,** 27, 495-498.
[47] P.P. Hujoel, *J. Dent. Res*, **1999,** 78, 797-803.
[48] D .Birkhed, *Acta. Odontol. Scand*, **1994,** 52, 116-127.
[49] A.Aa. Scheie, O.B .Fejerskov,*Oral Diseases* ,**1998,** 4, 268-278.
[50] P.E. Petersen, N. Razanamihaja, *In. Dent. J.*, **1999,** 49, 226-230.
[51] V. Machiulskiene, B.Nyvad, V. Baelum, *Community. Dent. Oral. Epidemiol.*, **2001,** 29, 278-288.
[52] S .Fure, P. Lingström, D. Birkhed, *J. Dent. Re.s*, **1998,** 77, 1630-1637.
[53] A. Hugoson, G. Koch, S .Johansson,Consensus: Klorhexidin inom tandvarden. Lic Forlag, 1990.
[54] J..Ainamo, A. Nieminen, U. Westerlund, *J. Clin. Periodontol.*, **1990,** 17, 729-733.
[55] A.J. Smith, J. Moran, L.V. Dangler, R.S. Leight, M. Addy , *J .Clin. Periodontol.*, **1996,** 23, 19-23.
[56] D. Simons, D. Beighton, E.A.M. Kidd, F.I. Collier,*J. Clin. Periodontol.*, **1999,** 26, 388-391.

[57] G. Tellefsen, G. Larsen, R. Kaligithi, G.J. Zimmerman, U.M.E.Wikesjo, *J. Periodontol.*, **1996,** 67, 181-183.
[58] J. Ainamo, H. Etemadzadeh, *J. Clin. Periodontol.*, **1987,** 14, 524-527.
[59] D. Simons, E.A.M. Kidd, D. Beighton, B. Jones, *Caries. Res*., **1997,** 31, 91-96.
[60] D. Simons, S. Brailsford, E.A.M. Kidd, D. Beighton,*J. Clin. Periodontol.*, **2001,** 28, 1010-1015.
[61] D. Simons, S.R. Brailsford, E.A.M Kidd, D. Beighton, *J. Am. Geriatr. Soc*., **2002,** 50, 1348-1353.
[62] J.A. Ship, *J. Am. Geriatr. Soc*., **2002,** 50, 1454-1455.
[63] L.L. Christrup, S.N. Rasmussen, M.R. Rassing, *Farmaci. Sci. Ed* .,**1988,** 16, 44-47.
[64] P. Lindström, S. Fure, D. Birkhed, *J. Dent. Res.*, **2001**, 80, 599.
[65] S.M. Wåler, *Acta. Odontol. Scand.*, 1997, 55, 198-200.
[66] C.J. Kleber, M.S.Putt,*Compend. Contin. Educ. Dent.*, **1986**, 7, 9, 681-685.
[67] K. Ingarashi, I.K Lee, C.F. Schachtele, J. Dent. Res., **1988,** 67, 3, 531-535.
[68] E. Jensen, K.B. Lokind, M. Pedersen, M.R. Rassing, *Farmaci. Sci. Ed*, **1988,** 16, 94-97.
[69] T. Andersen, M. Gram-Hansen, M. Pedersen, M.R. Rassing, *Drug. Dev. Ind. Pharm.,* **1990**, 16, 1985-1994.
[70] M. Pedersen, M.R. Rassing, *Drug. Dev. Ind. Pharm*., **1990,** 16, 1, 55-74.
[71] J. Jacobsen, S. Bjerregaard, M. Pedersen, *Eur. J. Pharma. Biopharma.,* **1999,** 48, 217-224.
[72] M. Pedersen, M.R. Rassing, *Drug. Dev. Ind. Pharm*., **1990,** 16, 2015-2030.
[73] M. Pedersen, M.R. Rassing, *Drug. Dev. Ind. Pharm.*, **1991,** 17, 3, 411-420.
[74] J.L. Rindum, P. Holmstrup, M. Pedersen, M.R. Rassing, K. Stoltze, *Scand. J. Dent. Res.*, **1993,** 101, 386-390.
[75] H.L. Bastian, J. Rindum, H. Lindeberg,*Oral. Surg. Oral. Med. Oral. Pathol.*, Accepted.
[76] C.L. Nunn-Thompson, P.A. Simon, *Clin. Pharm.*, **1989,** 8, 710-720.
[77] M.J. Peters, L.C. Morgan, *Med. J. Australia.*, ***2002,*** 176, 486-490.
[78] R. Malcolm, H.S. Currey, M.A. Mitchell, J.E. Keil, *Chest.*, **1986,** 90, 107-111.
[79] E.J. Jensen, E. Schmidt, B. Pedersen, R. Dahl,*Thorax.*, **1990,** 45, 831-834.
[80] E.J. Jensen, E. Schmidt, B. Pedersen, R. Dahl, *Int. J. Addiction.*, **1991,** 26, 1223-1231.
[81] E.J. Jensen, E. Schmidt, B. Pedersen, R. Dahl,*Psychopharmacology.*, **1991,** 104, 470-474.
[82] E.L. Herod, *Compend. Contin. Edu.c Dent.*, **1989**, 10, 284-288.
[83] D.G. Haxby,*Am. J. Health-Syst. Pham.*, **1995**, 52, 265-281.
[84] C. Silagy, T. Lancaster, L. Stead, D. Mant, G. Fowler, *Cochrane. Database. Syst. Rev*. **2002,** 4, 1-98.
[85] T. Lancaster, L.F. Stead, *Cochrane. Database. Syst. Rev.*, **2002,** 4, 1-57.
[86] A. Cepeda-Benito, *J. Cons. Clin. Psychology.*, **1993,** 61, 5, 822-830.
[87] J.E. Rose,*Annu. Rev. Med*., **1996,** 47, 493-507.
[88] P. Tønnesen, *Monaldi. Arch. Chest. Dis.*, **1999,** 54, 6, 489-494.
[89] A. Jessen, S. Toubro, A. Astrup, *Int. J. Obesity* ,**2002,** 26, 97.
[90] A. Jessen, S. Toubro, *Int J Obesity* **2002**, 26; 158
[91] AB Jessen, S Toubro, A. Astrup *Am. J. Cl. Nutrition.*, submitted.
[92] D.W. Woodford, L.J. Lesko,*J Pharm Scie.*, **1981,** 70, 12, 1341-1343.
[93] E. Bousquet, S. Tirendi, F.P. Bonina, L. Montenegro, A. Bianchi, N. Ciampini, *Pharmazie.*, **1992,** 47, H8, 607-609.
[94] L.L. Christrup, M.R Rassing, *Farmaci Sci*, Ed **1988,** 16, 1-5.
[95] L.L. Christrup, H.R. Angelo, J. Bonde, F. Kristensen, S.N. Rasmussen,*Acta Pharm. Nord*, **1990,** 2, 83-88.
[96] D. Hodoba, *Sleep. Res. Online.*, **1999,** 2, 101-105.
[97] G.H. Kamimori, C.S. Karyekar, R. Otterstetter, D.S. Cox, T.J. Balkin, G.L. Belenky, N.D. Eddington,*Int. J. Pharmaceutics.*, **2002,** 234, 159-167.

[98] M. Uhari, T. Kontiokari, M. Koskela, M. Niemelä,*B.M.J* ,**1996,** 313, 1180-1184.
[99] M. Uhari, T. Kontiokari, M. Niemelä, *Pediatrics.*, **1998**, 102, 4. 879-884.
[100] G. Skofitsch, F. Lembeck, *Drug Res,* **1983,** 33, 1674-1676.
[101] L.L. Christrup, J. Bonde, S.N. Rasmussen, M.R. Rassing, *Acta. Pharm. Nord,* **1990,** 2, 371-376.
[102] D. Simons, P. Baker, D. Knott, S. Rush, T. Briggs, E.A.M Kidd, D. Beighton, *Br. Dent. J.*, **1999,** 187, 11, 612-615.
[103] D. Simons, P. Baker, D. Knott, S. Rush, T. Briggs, E.A.M Kidd, D. Beighton, *Br Dent. J.*, **1999,** 187, 11, 604.
[104] Data on file, *Fertin Pharma* **2002**.
[105] A. Gray, M.M. Ferguson, *Austr. Dent. J.*, **1996,** 41, 373-376.
[106] T.M. Graber, T.P. Muller, V.D. Bhatia, *Swed Dent J Suppl*, **1982,** 15, 41-5.