

## Therapeutic Chewing Gums: Review

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### ABSTRACT

Chewing gums are mobile drug delivery systems. It is a potentially useful means of administering drugs either locally or systemically via, the oral cavity. The medicated chewing gum has through the years gained increasing acceptance as a drug delivery system. Several ingredients are now incorporated in medicated chewing gum, e.g. Fluoride for prophylaxis of dental caries, chlorhexidine as local disinfectant, nicotine for smoking cessation, aspirin as an analgesic, and caffeine as a stay alert preparation. MCGs are solid, single dose preparations with a base consisting mainly of gums that are intended to be chewed but not swallowed. They contain one or more active substances which are released by chewing and are intended to be used for local treatment of mouth diseases or systemic delivery after absorption through the buccal mucosa.

**Key words:** Chewing gums, medicated, oral, smoking.

### INTRODUCTION

The chewing of non-food items for pleasure has a long history (Cloys et al., 1992). Tree resins were chewed by the ancient Egyptians, the Mayan Indians, and the early American Indians. The first commercial chewing gum, State of Maine Pure Spruce Gum, appeared in 1848. 1 The first medicated chewing gum was introduced in the USA in 1924 with the brand name Aspergum®. 2 But history suggests that chewing of non-food items for the purpose of pleasure is as old as ancient Egyptian, Mayan civilizations. In 1848, the first commercial chewing gum named State of Maine Pure Spruce Gum appeared in the market whereas the first patent was issued to Dr. W.F. Semple who was a dentist at Ohio in 1869. Many people chew gum partly due to the belief that it increases aspects of mental performance, including concentration. 3 As chewing gums are taken orally and oral route of drug delivery is the most preferred route amongst the patient and clinicians due to various advantages it offers. 4

In recent years chewing gums are considered to be friendly oral mucosal drug delivery systems. 5 Chewing gum has been used to deliver therapeutic agents such as nicotine for smoking cessation therapy (Batra et al., 2005; Moore et al., 2008). 6 7 A medicated chewing gum is solid, single-dose preparation that is intended to be chewed for a certain period of time, deliver the drug and which may contain one or more than one active pharmaceutical ingredient (Mehta et al., 2010). 8

During chewing the drug contained in the gum is released into the saliva. The released drug has got two fates; either it could be absorbed through the oral mucosa or may reach the stomach for GI absorption. In fact both these two fates may occur simultaneously. So, medicated chewing gums offer both local and systemic effect. This drug delivery system offers two absorption pathways. Drug absorbed directly via the buccal membrane avoids metabolism in the gastrointestinal tract and thus the chance of first pass effect of the liver. As a result drug formulation as medicated chewing gum

may require reduced dose compared to other oral drug delivery systems.

### Composition

The most important material in chewing gum formulation apart from the active ingredient is the gum base which is an inert and insoluble non-nutritive component. The other materials may be grouped as water soluble bulk portion (Zycket *et al.*, 2003)<sup>9</sup>. Table 1 summarizes the basic components required for the manufacturing of medicated chewing gum with their function and suitable examples (Bhise and Ja-hagirdar, 2005; Heema and Stuti, 2010)<sup>10,11</sup>.

### Benefits

Medicated chewing gums offer a range of advantages as identified by the classic review work of Imfeld in 1999.<sup>2</sup> The advantages may be summarized as below:

- Chewing gum can be used without water, at any time, and everywhere.
- As the incorporated therapeutic agents are protected from oxygen, light, and water, product stability is good.
- Chewing gum can produce both local effects in the mouth (local delivery) and systemic effects after the active agents have been swallowed or (preferably) after they have been absorbed through the oral mucosa. The latter is of special interest with respect to bio-availability, since it avoids metabolism of the drug in the gastrointestinal tract and the so called liver-first-pass effect, because oral veins drain into the vena cava.

The other benefits that chewing gum may offer as a pharmaceutical dosage form are (Heema and Stuti, 2010, Rassing, 1996; Su-rana, 2010);<sup>11,12,13</sup>:

1. Fast/rapid onset of action.
2. High bioavailability.
3. Pleasant taste.
4. Ready for use .
5. High acceptance by children and for patients who find swallowing tablets difficult .6. Fewer side effects.
7. Effect on dry mouth (xerostomia).
8. Product distinctiveness from a marketing

pers-pective.

9. Excellent for acute medication.

### Sugar-Free Chewing Gums

The main ingredients of a modern day chewing gum is a combination of powered cane or beet sugar (50-65%) chewing gum base (18-30%) corn syrup (12-20%) colour and flavouring agents (1-2%) and softeners (0.3–3%).

Importantly more than half of its ingredients are sugar. The sugar used in sugared gum is sucrose, fructose and or hydrogenated glucose. In sugar-free gums sugar substitutes are used. The term sugar-free may be misleading.

The sugar substitutes commonly used may be bulk sweeteners like sorbitol, mannitol or xylitol or intense sweeteners like aspartame. <sup>14</sup>

These polyols have all been certified as safe for teeth by appropriate plaque pH testing; thus, while their inherent sweetness helps to stimulate saliva, their rate of metabolism and acid production by the oral (plaque) bacteria is slow and does not cause an effective drop in the plaque pH, so the net effect is an increase in the plaque pH. There has been considerable research to test whether certain polyols show superior efficacy.

One specific example is xylitol, a five-carbon polyol sugar, the most widely used sugar substitute in chewing gum which cannot be metabolised by the acid-forming bacteria in the dental plaque. Although in theory this should confer some advantage for xylitol as a sweetening agent, clinical data confirming the superior efficacy of xylitol over other polyols in chewing gum for prevention of plaque, . There is still an uncertainty about the nature of the effect of xylitol in caries. One view is that it merely replaces sucrose with a non-metabolised substance and thus prevents acid production by *Streptococci mutans*, which thrives best on sucrose. On this basis xylitol can be described as a non-cariogenic, but not anticariogenic.

Sorbitol and mannitol are polyols that are metabolised by oral bacteria so slowly that any acid produced is simultaneously neutralised; hence they

are considered noncariogenic. 15 Aspartame invitro as well as in rats have shown their ability to reduce adherent plaque formed by *Streptococci mutans* and considered as non cariogenic as well as anticariogenic, 16,17.

#### **Fluoride-containing chewing gum**

Fluoride-containing chewing gum was proposed early as an alternative to fluoride mouth rinses and tablets for persons with rampant caries and for children living in areas with a fluoride concentration of the drinking water below 0.7 mg F- per liter and no salt fluoridation. Fluoride is readily released from chewing gum. After 10 min of mastication, from 80 to 94% is dissolved in oral fluid (Duckworth and Emslie, 1961). The effect of fluoride-containing chewing gum on the remineralization of artificial caries lesions worn *in situ* has been investigated. In a larger (N=15) *in situ* remineralisation study, which also specifically excluded use of fluoride dentifrice, failed to show an overall difference in remineralisation parameters between fluoride-containing and placebo gums. 18

#### **Chlorhexidine containing chewing gums**

The proven efficacy and the advantages of CHX-containing chewing gum over CHX rinses—i.e., less bitter taste, better oral distribution, less staining, longer oral presence, and convenience of intake—clearly make CHX-containing chewing gum a valid choice for persons with a high caries activity, especially for oligosialic (hyposalivary) and xerostomic people. CHX-containing gum is further indicated for patients undergoing periodontal therapy, e.g., in initial therapy following scaling and in the maintenance phase, when oral hygiene proves insufficient. CHX gum should also be chewed by persons temporarily unable to perform mechanical oral hygiene for whatever reason. A number of studies of chlorhexidine (CHX) gum and plaque/gingivitis have been undertaken, and most have demonstrated significant plaque- and gingivitis-reducing effects of the CHX gums. 19, 20 However, as described earlier, there may be regulatory and consumer acceptance issues with marketing a chewing gum with a strong antimicrobial agent, especially one where there is a known taste issue. Therefore, CHX gums may be indicated for high caries patients only.

#### **Carbamide in chewing gum**

Carbamide helps to neutralise plaque pH more effectively than regular sugar-free gum, although the clinical research findings on the addition of this ingredient to chewing gum are equivocal. Some studies showed that Carbamide-containing gums helped to neutralise plaque pH more effectively than placebo gum, 21, 22. While others found no differences in terms of either plaque pH response after sugar challenge or extent of remineralisation in subjects who chewed either urea or placebo gums for four weeks. 18, 23

#### **Mineral salts in chewing gum**

Calcium and phosphate supplementation of the diet was assumed to increase the buffering potential and to decrease the demineralisation capacity of plaque at the site of the cariogenic challenge (Nizel and Harris, 1964).

Casein Phospho Peptide Amorphous Calcium Phosphate (CPP-ACP), a milk product that can strengthen teeth and help prevent dental caries was introduced in 1999. A systematic review with meta-analysis concluded that chewing gum containing CPP-ACP had remineralising potential on short term use and caries preventing potential on long term use. 24 CPP has a remarkable ability to stabilise calcium phosphosyl residues by forming clusters, localises ACP in dental plaque which buffers the free calcium and phosphate ion activities, thereby helping to maintain a state of super saturation with respect to tooth depressing demineralisation and enhancing remineralisation.

The clinical evidence for a superior demineralising/anti-caries effect of casein-calcium conjugates, such as CPP-ACP, has previously been reviewed. 25-27 Based on these reviews there is still no scientific consensus that CPP-ACP provides superior remineralisation benefits in a chewing gum delivery system, and the published *in situ* chewing gum studies have for the most part relied on a methodology that has been criticised. 26 Therefore, while CPP-ACP shows promise as a demineralising agent in topical pastes, creams and rinses, 25, 27 its efficacy in chewing gum requires confirmation by independent research groups. 26

Component	Function	Example
<b>Water insoluble gum base</b>		
Elastomers	Water insoluble gum base Provides elasticity and controls gummy texture	Water insoluble gum base Natural (chicle gum, nispero, rosadinha, jelutong, periollo, lechi-capsi, sorva etc.) and synthetic rub-bers (butadiene, styrene copolymers, polyisobutylene, polyethylene mixtures, polyvinyl alcohol etc.)
Elastomer solvents	Softening the elastomer base component	Terpinene resins (polymers of alpha-pinene or beta-pinene), modified resins or gums (hydrogenated, dimerized or polymerized resins)
Plastisizers	To obtain a variety of desirable textures and consistency proper-ties	Lanolin, palmitic acid, oleic acid, stearic acid, gly-ceryl triacetate, propylene glycol monostearate, glycerine, natural and synthetic waxes, hydroge-nated vegetable oils, paraffin waxes, fatty waxes, sorbitalmonostearate, propylene glycol
Fillers or texturizers or mineral adjuvant	Provide texture, improve chewa-bility, provide reasonable size of the gum lump with low dose drug	Calcium carbonate, magnesium carbonate, alumi-num hydroxide, talc, aluminum silicate
<b>Water soluble portions</b>		
Softners and emulsifiers	These are added to the chewing gum in order to optimize the chewability and mouth feel of the gum	Glycerin, lecithin, tallow, hydrogenated tallow, mono/ di/ tri glycerides
Colorants and whiteners	Gives the formulation soothing color and improves acceptability of the formulation	Titanium dioxide, natural food colors and dyes suit-able for food, drug and cosmetic applications
Sweeteners	To provide the desired sweetness of the product	Water soluble sweetening agents (xylose, ribulose, glucose, mannose, galactose, sucrose, fructose, mal-tose, monellin, sugar alcohols like sorbitol, mannitol etc.), water soluble artificial sweeteners (sodium or calcium saccharin salts, cyclamate salts etc.), di-peptide based sweeteners (aspartame, alitame etc.),

Antioxidants	Prevents any possible microbial growth	naturally occurring water soluble sweeteners, chlorinated derivatives of ordinary sugar (sucralose), protein based sweeteners (thaumatin I and II) Butylatedhydroxytoluene, butylatedhydroxyanisole, propyl gallate
Flavoring agents	To enhance consumer acceptability	Essential oils (citrus oil, fruit essences, peppermint oil, spearmint oil, mint oil, clove oil and oil of wintergreen) and synthetic or artificial flavors
Bulking agents	Used if low calorie gum is desired	Polydextrose, oligofructose, inulin, fructooligosaccharides, guar gum hydrolysate, indigestible dextrin
Compression adjuvant	To ease the compression process	Silicon dioxide, magnesium stearate, calcium stearate, talc

### Probiotic in chewing gums

Probiotic therapy has the potential to provide oral health benefits, through modulation or suppression of oral pathogens, although chewing gum studies are rare, and few of these have determined an end point directly relevant to caries. One such study measured salivary counts of lactobacilli and *S. mutans* in subjects who consumed probiotic gum, xylitol gum, xylitol gum with probiotic, or placebo for three weeks. While both probiotic and xylitol gum groups showed significant reductions in *S. mutans* scores, the combination of probiotics and xylitol had no effect, suggesting a negative interaction between the two. In an *in vivo* study, chewing sugar-free probiotic gum may reduce the risk of developing white spot lesions and gingival inflammation in susceptible orthodontic patients. The use of probiotic strains for caries prevention showed promising results even if only few studies have demonstrated clear clinical outcomes. Therefore, the scientific evidence is still poor. A continuous regular almost daily intake is

probably required; this maybe a compliance aspect to be considered. However, for all products effective in caries prevention (*i.e.*, fluoride and chlorhexidine) a frequent intake is required, so a possible way of administration could be to insert probiotic in other daily preventive products like toothpaste, chewing gums.

### CONCLUSIONS

Chewing gum not only offers clinical benefits but also is an attractive, discrete and efficient drug delivery system. A few decades ago, the only treatment for some disease was surgical procedure but now more and more disease can be treated with Novel Drug Delivery Systems. Generally, it takes time for a new drug delivery system to establish itself in the market and gain acceptance by patients, however chewing gum is believed to manifest its position as a convenient and advantageous drug delivery system.

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