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Medicated cheewing gum: A modernized system for delivering bioactive compounds

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Abstract
Medicated chewing gum soft cohesive enjoyable confectionery in nature which is fill with bioactive compound are chew then it release bioactive substance which is heal the traget site. Production of chewing gum in global chewing quickly increase Application of chewing gum are increasing as compared to other dosage form. After gum base throw away, it is not biodegradable therefore it causes harm to environment.

Keywords: Medicated cheewing, enjoyable, biodegradable

Introduction

Human beings have been chewing gum like substances from ancient time, but chewing gum as such has a relative short history. In 1869 the first patent for chewing gum was taken out by a dentist, Dr. William F. Semple from Mount Vernon, Ohio under U.S. Patent No. 98,304. He deemed that chewing gum is not only a tasty confectionery but also had a potential role as a dentifrice [1]. People of every society have chewed varieties of gum and gum like substances (resins and waxes) for thousands of year. Medicated chewing gum is not different from it, but it is the gum base incorporated drug (s) [2]. A recent national consumer survey revealed that around 56% of U.S. households consume chewing gums with an annual consumption rate of 160 to 180 sticks per person [3]. Global consumption of Functional Chewing Gum rises up from 186780.4 MT in 2012 [41] to 217675.4 MT in 2016, with an average annual growth rate of 3.90%. The reason causes this increase is the growing demand for the Functional Chewing Gum products, which is the result of the growing needs of downstream industry. The worldwide market for Functional Chewing Gum is expected to grow at a CAGR of roughly 2.5% over the next five years, will reach 3530 million US$ in 2024, from 3050 million US$ in 2019, according to a new GIR (Global Info Research) study [4].

Chewing gums are mainly classified into four classes

1. Sugar chewing gums
2. Sugar-free chewing gums
3. Coated chewing gums, and
4. Pharmaceutical or Medicated chewing gums (MCGs) [5].

Medicated chewing gum (MCG) is a novel drug delivery system containing gum base with active pharmaceutical ingredient intended for local treatment of mouth diseases or systemic absorption through oral mucosa [6]. Medicated chewing gum is defined by the European Pharmacopoeia and the guidelines for pharmaceutical dosage forms issued in 1991 by the committee for Medicinal Product for Human Use (CPMP) as “solid single dose preparations with a base consisting mainly of gum that are intended to be chewed but not to be swallowed, providing a slow steady release of the medicine contained” [7]. The first MCG product ‘Aspergum’ containing acetylsalicylic acid as active ingredient for headache was introduced in 1928 [8]. Many scientific literatures have been reported on the use of medicated chewing gums containing various drugs, such as dextromethorphan hydrobromide, nicotine, aspirin, miconazole, cetirizine, dimenhydrinate hydrochloride, caffeine, and nystatin to prevent oral cavity, aid with smoke cessation, treat motion sickness, treat oral fungal infections and relieve pain [9-16].

Superior technology and comprehensive knowledge of chewing gum, with the addition of medicated chewing gum in the European Pharmacopoeia in 1998, have added a high acceptance for this recent system of drug delivery [2]. Recently medicated chewing gums meets the same superior quality of standards as tablets as per current Good manufacturing practices (cGMP) guidelines and also it can be easily formulated to obtain a different release rates of the drugs, which enables distinct patient group targeting. Particularly in children, medicated chewing gum may be more favored method of drug administration compared to tablets or liquids preparations.

Advantages of medicated chewing gums

1. Increased rate of effectiveness as compared to other oral dosage form.
2. Local as well as systemic effect can be achieved.
3. Removal of gum at any time; therefore termination of drug delivery.
4. Does not require water to swallow. Hence it can be taken anywhere.
5. Advantageous for the patients having difficulty in swallowing.
6. Protection of the susceptible drugs contained from chemical or enzymatic attack in gastrointestinal tract.
7. Stomach does not suffer from direct contact with high concentration of active ingredients, thus reducing the risk of intolerance to gastric mucosa.
8. Avoids first pass metabolism and thus increases the bioavailability of drugs.
9. Stimulates the flow of saliva in mouth.
10. Good stability against light, oxygen and moisture.
11. Improve work performance and cognitive functions.
12. Helps to reduce food cravings.

Disadvantages of medicated chewing gums

1. Prolong chewing on gum may result in pain in facial muscles.
2. Sorbitol present in medicated chewing gum formulation may cause flatulence and diarrhoea.
3. Allergic reaction to artificial sweeteners.
4. Different release profiles because of chewing style differences.
5. Teeth decay through being coated by sugar.
6. Additives in gum like flavoring agent, cinnamon can cause ulcers in oral cavity and licorice cause hypertension.
7. Variability in absorption site owing to salivary dilution and involuntary swallowing.

Table 1: Commercially available medicated chewing gum products [2, 3, 6]

Name	Therapeutic agent	Therapeutic aim	Commercial Availability
Nicorette	Nicotine	Smoking Cessation	Worldwide
Nicotinell	Nicotine	Smoking Cessation	Worldwide
Aspergum	Aspirin	Pain Relief	USA
Stay Alert	Caffeine	Alertness	USA
Café Coffee	Caffeine	Alertness	Japan
Buzz Gum	Guarana	Alertness	UK
Go Gum	Guarana	Alertness	Australia
Travell	Dimenhydrinate	Motion Sickness	Italy, Switzerland
Chooz	Calcium Carbonate	Heart Burn	USA
Stamil Vitamin C	Vitamin C	Nutrition	Australia
Endekay Vitamin C	Vitamin C	Nutrition	UK, Middle East
Fluorette	Fluoride	Cariostatic	USA
Vitaflo CHX	Chlorhexidine	Dental Hygiene	USA
Superpep	Dimenhydrinate	Motion Sickness	Germany, Switzerland

Composition of medicated chewing gums

Chewing gums are generally made by combining two phases. The first phase is a continuous water soluble phase that contains the ingredients like sweeteners, flavoring agent, coloring agent, bulking agent, antioxidant and API, and the second phase is a discontinuous water insoluble phase which mainly contains the gum base, which is the most important component of the formulation to give the chewing gum a rubbery like structure [2]. The gum base is usually present in an amount of 5-60%, by weight of the final chewing gum [17]. It also contains the ingredient, such as fillers, softeners, and texturizer. The factors that affect on the drug release of the chewing gum are illustrated in fig.1.

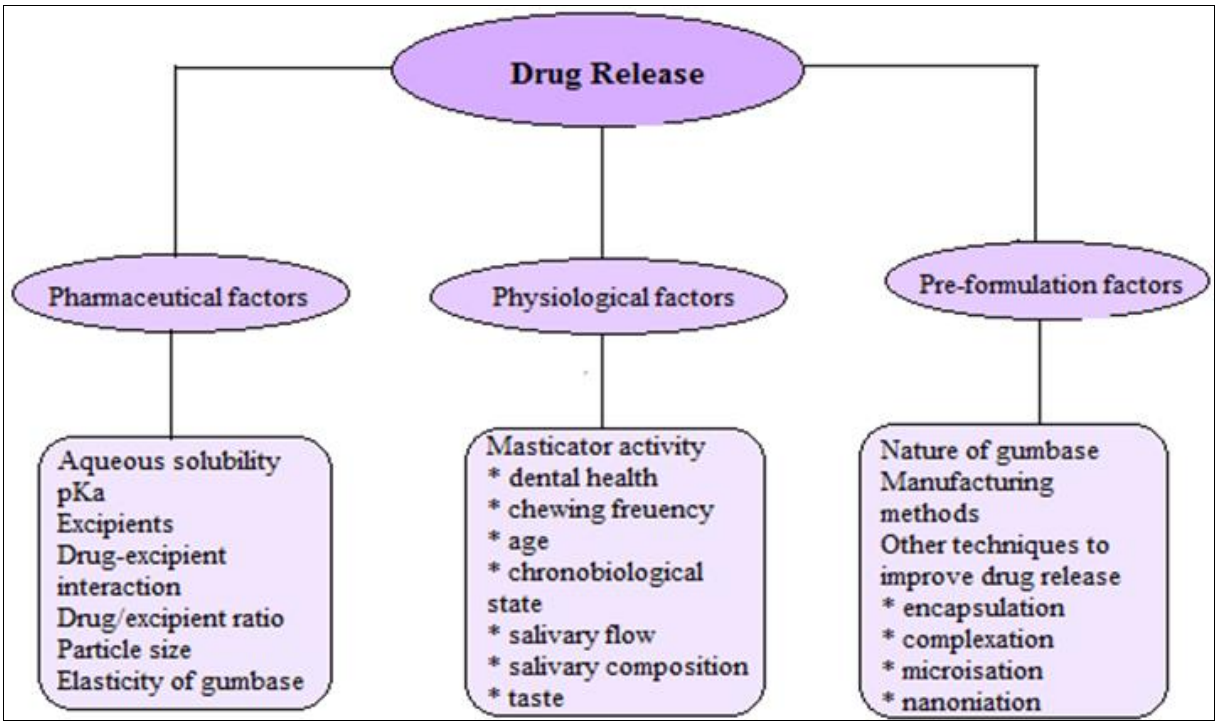

Fig 1: Factors affecting drug release from chewing gum formulations

Water soluble phase (Non-masticatory phase)

In water soluble phase ingredients such as sweetening agent, flavoring agent, coloring agent, bulking agents, antioxidants and active pharmaceutical ingredient.

Sweeteners

Sweeteners are the most important component of chewing gums and approximately 50-60% is its composition [20]. There are two types of sweeteners that are used in chewing

gum formulation, the first one is aqueous sweeteners and the other is bulk sweeteners.

Aqueous sweeteners
These sweeteners have softening and and moisture retention effect, it includes hydrogenated starch hydrolysates, sorbitol and corn syrups. Corn syrups have more ability to keep gum fresh and flexible [21].

Bulk sweeteners
These are further classified into nutritive and non-nutritive sweeteners. Sugar and sugar alcohols are each considered nutritive sweeteners. Sugars that are mainly used are; sucrose, dextrose, maltose, maltodextrin, fructose and galactose and are used at between 2 and 15%. The high intensity artificial sweeteners such as saccharin, aspartame, neotame, acesulfame potassium and sucralose are considered as non-nutritive sweeteners [2]. The amount of high intensity sweetener used in chewing gum composition is between 0.001 and 5.0%, most preferably in amounts from 0.05 to 1.00% to the final weight of chewing gum composition.

Flavoring agent
Flavoring agents are added to improve the flavor in chewing gum, which can overcome the bitterness of the drug. There are several natural and artificial flavors that can be described to possess similar taste masking effects. Some popular flavorants used in pharmaceuticals are; honey, berry, vanilla, coffee, chocolate, mint, peach, orange, lemon, lime, grape, melon, wintergreen, apricot etc. [22]. The amount of flavoring agent used is normally a matter of preference subject to the set range and factors such as the individual flavor, the type of bulking agent or carriers used, and the strength of flavor desired. The flavors may be supplemented by menthol as appropriate. Menthol is used as a flavoring adjuvant from 0.01 to 1.0% [2].

Coloring agent
In the US, FD&C number (which generally indicate that the FDA has approved the artificial coal tar dye colorant for use in foods, drugs and cosmetics) are given to approved synthetic food dyes that do not exist in nature, whereas in the European Union, E numbers are used for all the additives, both synthetic and natural, which are approved in food application. In US, seven coal tar dyes are permitted as far 2007 [23]. Artificial dyes are hazardous so natural colorants obtained from plant and animal sources have become more popular. The extracts obtained from plants such as chlorophyll-green, annatto-yellow, curcumin-yellow, saffron yellow and also the animal extracts such as cochineal red are incorporated to enhance a pleasing appearance or hide the colors of drug or excipient in the final product. Titanium dioxide and magnesium oxide are also included to provide whiteness to final product.
Bulking agent: These are used to produce required bulk of chewing gum when potent drug or low-dose drug is to be incorporated.

Active pharmaceutical ingredient
In medicated chewing gum API may be present in core or coat or in both. The final dosage form may have up to 30% w/w drug content. The release of drugs from chewing gums depends on their physiochemical properties which are illustrated in figure 1. Drugs that are slightly water soluble are released slower and incompletely as compared to water soluble drugs. So, special techniques and ingredients are required to produce a suitable release profile. Drugs that are suitable for inclusion in chewing gums should have acceptable taste, smaller particle size (<100μm), low molecular weight, unionized, stable against salivary enzyme, nontoxic to the oral mucosa, and do not cause tooth decay and staining [24].

Water insoluble phase (Primary phase/ Masticatory phase)
The water insoluble phase mainly consists of the gum base, plasticizer, elastomers, elastomer solvents (resins) and fillers.

Gum base
The fundamental raw material for chewing gum is natural gum Chicle, obtained from the Sapodilla tree, a member of the Sapotaceae, which is botanically known as *Manilkara Zapota* (L.) van Royen [2]. Chemically, chicle is composed of polyterpenes that have thousands of C_5H_8 isoprene (2-methyl-1,3-butadiene) subunits. Chicle is very costly and also not easy to obtain and manipulate when desired properties such as adherence and consistency that is needed, so currently it is not used.
Gum bases currently used are mostly from synthetic origin. They are very complex and contain a variety of specialized ingredients to maintain the desired performance. The exact composition of synthetic gum base is not available in the literature. Some patent reveals that many compounds are incorporated in the um base to provide the characteristic functionality [25]. The chewing gum made from synthetic origin consists of elastomer (10-40%), polyvinyl acetate (15-45%), plasticizer (20-30%), waxes (0-10%), elastomer solvent (2-18%), emulsifier (2-10%), and fillers (0-70%) [2].
Biodegradable gum bases: The vast intake of chewing gum has led to an environmental pollution due to its nonbiodegradable nature. So, efforts have been made to move towards greener approach and develop a biodegradable gum base. Corn zein is used as an alternative biodegradable molecule for gum base [26]. Wheat prolamin called gliadin is also used as a natural gum base having good chewiness. It is extracted from wheat flour using 70% aqueous ethanol [27].

Plasticizer
Plasticizers are small molecules that promote flexibility in gum base resulting in desirable texture and consistent properties [3]. They are also used to regulate cohesiveness of product and are divided into natural plasticizer and synthetic plasticizer.

Natural plasticizer
Natural resin esters like glycerol esters or partially hydrogenated resin, polymerized glycerol esters, glycerol esters of partially dimerized resin and pentaerythritol ester of resin.
Synthetic plasticizer - Terpene resin derived from α-pinene or d-limonene [6].
The plasticizers which are mostly preferred include, but are not limited to, triacetin, glycerin, propylene glycol, lecithin, and food grade organic solvents [18]. In spite not widely used, it has been shown that low molecular weight

polyethylene glycols, such as PEG 200, 300, 400 could also be used as plasticizers to develop non-sticky chewing gums made of proteinaceous material such as zein [19].

Elastomers

Elastomers are the important constituent of synthetic gum base. They are non-nutritive substance having visoelasticity that is important for textural and masticatory properties of gum [28]. The quantity of elastomer in gums is very important parameter to give them proper elasticity. The gums made from low quantity of elastomer lack elasticity whereas, high concentrations give them tough and rubbery like structure [29]. Common elastomers are styrene-butadiene (SBR) and polyisobutylene (PIB) rubbers. Although PIB is very costly, it is more widely used than SBR. SBR lacks the desired properties for making soft gums [30].

Elastomeric solvents

Elastomeric solvents or the resins are used to soften the elastomer. They provide elasticity, softening effect, and cohesion to the gum base components [31]. Gum bases with high plasticity are rigid and tough. Resins such as polymers of alpha-pinene or beta-pinene, methyl, glycerol, or pentaerythritol esters of resins are commonly used. Natural rosin esters such as partially hydrogenated rosin, pentaerythritol esters of rosin are also used. The excessive use of resins causes stickiness of the gum to the dental surface, low quantity results in unacceptable chewing characteristic [29].

Fillers

Fillers are used as texture modifier and bulking agent when low dose of drug is incorporated. Commonly used fillers are magnesium and calcium carbonates, ground limestone, magnesium and aluminium silicate, clay, alumina, talc, titanium oxide and mono/di/tri calcium phosphate. These agents provide better chewability by reducing tackiness of the gum base to the teeth. It is also used to lower the overall cost of producing chewing gums [32].

Table 2: Excipients used in medicated chewing gum formulation

Category	General range	Common examples
Sweetening agent	50-60%	Sugars (sucrose, dextrose, glucose), sugar alcohols (sorbitol, mannitol), saccharin, aspartame.
Flavoring agent	0.01-1.0%	Natural and artificial volatile oils
Coloring agent	0.1%	FD&C approved colors.
Bulking agent	Up to sufficient quantity	Insulin, polydextrose, oligofructose, indigestible dextrin.
Plasticizer/Softening agent	0.5-15%	Triacetin, glycerin, propylene glycol, lecithin, stearic acid.
Elastomer	15-45%	Styrene-butadiene (SBR) and polyisobutylene (PIB) rubbers.
Elastomeric solvent	45-70%	Polymers of alpha-pinene or beta-pinene, methyl, glycerol, or pentaerythritol esters of resins
Fillers	Up to 60%	Magnesium and calcium carbonates, ground limestone, magnesium and aluminium silicate, clay, alumina, talc.
Antioxidants	0.02% of gum base	Propyl gallate, butylated hydroxy toluene, butylated hydroxy anisole.
Opacifiers	0.5-2.0%	Magnesium oxide, titanium dioxide.

Manufacturing of MCG

Medicated Chewing Gums can be manufactured under GMP guidelines by one of the three methods;

a. Traditional/Conventional method
b. Cooling, Grinding and Tableting method
c. Direct compression method

A. Traditional/Conventional method

The specify amount of gum base is place in dry kettle and melted It at 120°c for softning of gum base. After this second phase ingredients such as syrup and sweeteners is added and mix it for 4 minute. The remaining Ingredients which is said to be third face ingredients are mix for 1 to 10 minutes with the help of blades in kettle. The mixture of the gums passes through series of roller which convert the bulk mass in to soft and thin shit of ribon then find sugar added during rolled process for inhancement of flavour and avoiding stiking of gum mixture to the machine. finally It is cool for 48 hars and cut into desired shape an coating is aply to produce coated cheewing gums [33].

B. Freezing grinding and tableting mothod

This method is use two reduce moisture content in the product and provide longer shelflife. In all three stages, in first stage involve cooling. Mixture cool at 50 °c or by using liquid nitrogen or solid CO2. It does not absorb by gum composition and not leave any residue. Also other method of cooling in which grijding apparatus is cooled by place in coolent in cooling jacket so initially ingredients are precooled for efficiant Cooling. In seconds stage remaining Ingreedient are added to gum base sillica (and anty caking) and solid CO2 whose partially added during 1st stage of grending process. After cooling and grinding, the gum composition converted into finly ground particles. Many grinding agent such as alkaline metals phosphate, alkaline earth metals phosphate are added during preparation to avoid stiking but they are incompatible with acidic medicinal agent due to their alkalinity. After this grounded particles dry for removal of coolent. Then the gum base athere and form bubble of air in a gum particle which provide light and soft impretion, when it get cheewed. alAfter removal of coolent other ingredienant such as coating agent, lubricant, and sweetness are added. This all ingredients uniformly grinded with mixture of chewing gum by using Sigma miling. During stage 3 tableting is done by compresing punch and then pack [33].

C. Direct compretion method

In these method at low temperature grinding agent such as sorbitol is added in gum base. Then lubricant, active ingredient, sweeter are added [34]. Lubricant such as stearic acid, magnesium stearatdle is add. Later it is compress into tablet an packing appropriate packeging material. Machanisms of transpot of active substance- active substance are releases in saliva during the process of

chewing it and it get absorb through saliva or through GIT. Simple fickin diffusion is use to calculate transfort of active substance approse buccal mucosa [35]. eqn for the drug flux is

$Jx=Dz\ Ep/\Delta c$

Where Jx = drug flux

Dz= Diffusivity of substance

Ep= partition coefficient

Δc= concentration gredience.

This eqn show transport of active ingredient through buccal mucosa. By converting active compound into more fluidy and also it can increase diffusivity by reducing diffusional resistance of membrane [36].

Evaluation test medicated chewing gums

1. *In-vitro* test

There are two types of apparatus used for chewing gum assessment Approved by the European Pharmacopoeia (for the Quality of Medicines And others, 2008). After accumulate the dissolution medium or saliva From the apparatus at different time interval subjected to spectrophotometric analysis for determining the percentage of drug release from The gummy mass, the absorbance was directly proportional to the concentration of drug release (Chaudhary and Shahiwala, 2010) [37]. The type One apparatus is compendial chewing gum apparatus that determines the Chewing rate at which maximum release takes place. It consists of a Chewing chamber, two horizontal and one vertical piston or tongue operated in opposite direction which stop the sliding of gum from the chamber during chewing. Two horizontal pistons are spin in opposite direction in their own axis at the end of the chew to obtain utmost chewing (Faraj *et al*., 2007). The type two apparatus is non compendial chewing gum apparatus design by Wennergren, 1928 and is commercially available. It consists of the upper surface jaw and lower surface jawcombined reciprocaly in which the chewing activity takes place by shearing. This configuration supply the adequate mastication and agitation of the testing medium. The flat surface the upper jaw is located parallelly to the central part of the lower surface. The lower flat bottom surface jaw accommodate small brim mounted at an angle of 45° which acts as small bowl to prevent the gum sliding during mastication. When these two surfaces contact each other, the pressing and twisting action created will allow to leave the active material from gummy mass into dissolution medium or artificial saliva

2. *In-vivo* studies

In-vivo studies for the drug release are performed with trained panelists Based on time-intensity level to study about how much active ingredients are released in the saliva and how they are absorbed or through oral mucosa or if swallowed, and how much are absorbed through of the GI-tract (Maggi *et al*., 2005). Salivation test is are conducted with the Minimum four volunteers. They should rinse their mouth thoroughly with distilled water before starting the test and allowed to chew gum for the 15 minutes. After chewing, saliva from the each volunteer were collected At different intervals and diluted with suitable solvent. The diluted Saliva samples were the further analyzed by HPLC or spectrophotometer (Rajitha *et al*., 2015). Dissolution test is carried out by the allowing the parparticipants/volunteers to chew the gum at certain period of the time. After Chewing, the residual gums were the collected from the each volunteer then cut Into the small pieces, frozen, and ground to fine powder. Then the total weight Minus the residual weight later chewing is used to calculate the amount of Active substances released from gum (Pratik *et al*., 2011). Urinary excretion test is only applicable for active compounds excreted through Urine. Minimum 4 volunteers were selected and strictly instructed before tests not take any medicine about 48 hours and to fast overnight. Then Their urine samples were collected from zero hour to several hours at the Particular interval. At every 30 min interval volunteers are asked To drink water. A suitable analytical method used test to collected Urine samples from the each volunteers (Ingole *et al*., 2012). Another important *in-vivo* test are the buccal absorption test. Goat buccal Mucosa was used to test the permeability of active substances across the Mucosa. It was located in the middle of the donor and a receiver compartment Of the Franz diffusion cell. Buffer solution, usually a phosphate buffer With pH 6.8 was filled in the donor compartment & buffer solution of blood (phosphate buffer with pH 7.4) was filled in the receiver compartment for simulating oral conditions. Chewing gum was allowed to Be chewed for 15 minutes and after chewing the released compounds were Collected in the donor cell and it was allowed to permeate through the Buccal mucosa for 30 min. The samples were collected and examine by (UV-spectrophotometer at range 284 nm) at every 5 min interval from the Receiver compartment. The test used to the determine the total content of Functional compounds permeated through buccal mucosa (Chaudhary and Shahiwala, 2010) [37].

3. Texture analysis

It is used to the determine the quality of gum and is carried out by both Subjective and objective methods. Subjective test is analyzed by the sensory panelist with the suitable sensory method. Textural properties such as the Hardness, gumminess, adhesiveness, chewiness and cohesiveness are determined by deformation curve obtained from the texture profile analyzer. Compression probe is used to the analyze the textural properties of the chewing Gum.

Applications of MCG for delivery of active compounds

1. Dental caries

When carbamide is added to chewing gums, ureolytic activity is induced when urease enzyme is present in the mouth. This results in ureolysis products (NH3 and CO2) that exacerbate caries. -a preventive measure

(2000) Machiulskiene *et al*. Prior investigations have turned up saliva, salivary sediment, dental plaque, and calculus with ureolytic activity. Chewing gum with urea raises the amounts of free lysine and arginine in people without caries. By combining urea with sodium bicarbonate solution, plaque pH can be raised more effectively. Chewing gum containing carbamide is highly advised for persons with chronic renal failure, high levels of oral caries, tooth erosions, hyposali- vary, xerostomia, anorexia nervosa, and bulimia. V6®, Dirol®, and Endekay are a few brands of chewing gum using carbamide as an ingredient.

2. Saliva stimulation

Fluoride chewing gum was developed as a replacement for fluoride tablets provided with fluoridated water or salt for high-risk populations in the early 1960s. Chewing gum with fluoride can be a ve-

Vehicles for fluoride compounds' delayed release. Fluoride's ability to dissolve quickly in aqueous solution, such as saliva, promotes salivary flow and keeps fluoride levels in saliva longer. It encourages remineralization, removes toxic compounds, and raises the pH of the saliva and the plaque (Tubert-Jeannin *et al*., 2011). The fluorides that are more frequently employed in fluoride chewing gums are NaF, Na2FPO3, SNF2, and amino fluorides. According to Buzalaf *et al*. (2012) [41], fluoride-deficient youngsters with enamel erosion, high caries, and dry mouth might benefit from eating gum with fluoride.

3. Calculus formation

Calculus formation refers to the calcification and hardening of oral biofilm as a result of the development of calcium phosphate mineral salts. Salivary calcium phosphate saturation and biofilm pH are crucial factors.

In the development of calculi (Jin and Yip, 2002) [42]. Regularly eating sugar-free chewing gum raises the pH of the biofilm, which leads to salivary calcium phosphate saturation, which encourages the production of calculi (Lingström *et al*., 2005) [43]. Active substances that keep the calcium phosphate deposits in oral biofilm in place prevent calculus development. Chewing gums containing vitamin C showed a reduction in supra-gingival calculus formation over a three-month period when consumed at least five times per day (Lingström *et al*., 2005) [43]. This is because vitamin C has an acidic nature that inhibits calcium phosphate deposits.

The superficial enamel layers of teeth absorb chromogens from food, beverages, or smoking, resulting in extrinsic tooth stain that alters the appearance of white teeth that are a sign of oral health. Routinely chewing sugar-free

4. Extrinsic tooth stain

Increased salivation and a significant impact on removing chromogen-induced extrinsic teeth stains were both demonstrated by chewing gum many times daily for more than four weeks (Milleman *et al*., 2014) [44]. When chewing two tablets three times a day for more than six weeks, sugar-free chewing gums containing any of the active ingredients, such as sodium hexa-metaphosphate and polyphosphates, improve the removal and prevention of extrinsic tooth stain (Porciani *et al*., 2010). However, because polyphosphates absorb highly negative charged, they make stain prevention more challenging.

5. Reduction of halitosis

The production of volatile sulphur compounds (VSCs), which include hydrogen sulphide and methyl-mercaptan, is caused by anaerobic gram-negative bacteria that cling to the tongue or are linked to periodontitis.

Halitosis, for example (Boches *et al*., 2000). Sugar-free chewing gums have been shown to lower the production of VSCs and produce fresher breath (Rösing *et al*., 2009). Regularly chewing sugar-free gum with active ingredients decreases halitosis by interacting with VSCs or the responsible bacteria. When these gums were chewed, especially zinc, which has a strong affinity to bond with allyl isothiocyanate, there were less VSCs than with control gums (Tian *et al*., 2013). The addition of magnolia bark extract in VSCs is the mechanism through which the guilty bacteria are targeted.

6. Neutralization of biofilm pH

Saliva's capacity to act as a buffer and keep the level of acidity in oral biofilm constant allowed for the intra-oral equilibrium between enamel demineralization and remineralization to be maintained. HCO3 bicarbonate

Is a salivary buffering agent that lowers the pH of oral biofilm. It can also be accomplished by adding carbamide (NH2)2CO or urea since urease is produced by oral bacteria, which causes urea to be hydrolyzed and converted into ammonia, creating an alkaline environment (Polland *et al*., 2003). Additionally, EFSA acknowledged that chewing sugar-free chewing gums other than those containing xylitol increases the pH of the biofilm and increases salivation, which strengthens the enamel's resistance to acid challenges (Dodds *et al*., 2012; on Dietetic Products and (NDA), 2010). The addition of bicarbonates also improved the saliva's ability to buffer.

7. Plaque formation

A powerful bacteriostatic and antiseptic, chlorohexidine is a bisiguanide. Prior to recently, it was utilised in mouthwashes to treat periodontitis, plaque development, and Oral cavity infections and gingivitis (James *et al*., 2017). Chewing gums containing chlorhexidine have superior plaque-reduction capabilities compared to sugar-free gums (xylitol & sorbitol). Chlorohexidine chewing gums provide several advantages over chlorohexidine mouth rinses, including a less bitter taste, better oral distribution, a longer oral presence, and convenience of ingestion. By reducing plaque buildup and micrococcus levels while chewing xylitol gums with chlorohexidine therapeutic agent, pathogen suppression activity is maintained and long-term caries activity is prevented (Hildebrandt and Sparks, 2000).

Conclusion

Mostly cheewingum can be use because of their slow and continuous releasing property which give local As well as systemic effect. However main problem releted to cheewing gum is its degradability. It is not Biodegradable and causes harm two environment.so we avoid use of synthetic gum base and protect Over environment. This review article provide information two prepare degredabale gum to solve this Problem.

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