e-ISSN:2320-7949
p-ISSN:2322-0090
RESEARCH AND REVIEWS: JOURNAL OF DENTAL SCIENCES

Medicated Chewing Gum: An Overview.

Vasudha Lakshmi S, Hemant K S Yadav*, Mahesh KP, Abhay Raizaday, Navya Manne, Ayaz A, and BV Nagavarma N.

Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Mysore, Karnataka – 570015, India.
Department of Oral Medicine and Radiology, JSS dental college, JSS University, Mysore, Karnataka – 570015, India.

Review Article

Received: 27/01/2014
Revised: 18/02/2014
Accepted: 04/03/2014

*For Correspondence

Dept. of Pharmaceutics
JSS College of Pharmacy,
JSS University
S.S Nagar, Mysore-570 015
Tel: +91-9886112637;
Fax: 0821-2548359

Keywords: Chewing Gum, Dental Caries, DDS, medicaments.

ABSTRACT

Oral drug delivery system has been area of interest for researcher and scientist to explore it to the extreme potential in drug delivery system in past few years. The researchers are focusing on this drug delivery because of ease of administration and comfort offered by this route to patient. Hence drug delivery can be achieved by incorporating medicament in Chewing gum (CG) base because oral mucosa is highly vascular in nature resulting in rapid absorption of the drug into the systemic circulation. Chewing gum is a combination of a water-immiscible phase, known as gum base (insoluble gum base resin), emulsifiers, elastomers, fillers, antioxidants, softeners, sweeteners, food colourings, flavouring agents, waxes and in case of medicated chewing gum there is an incorporation of active substances in the formulation for getting the desired therapeutic effect. Due to sweet and refreshing taste of chewing gum it can be used as drug delivery system (DDS). CG can be used in prevention of dental caries, prevent the dryness of mouth and help in maintaining oral hygiene. Therefore it can be concluded that oral drug delivery can make treatment more patient friendly, can be taken without water and reduce the cost of manufacturing compared to convention DDS.

INTRODUCTION

Homo sapiens use different kind of natural resources for its survival. Plants, tress, herb and shrub were utilised in the form of food, wood, medicine, shelter etc. During the ancient time human knew how to use the different parts of plant for its beneficiary proposes.

Before the invention of tooth brush human are using Azadirachta indica (neem) branches to clean their teeth because of it antibacterial, cleaning activity [1]. In today era CG is used as a substitute for brushing and it is contains xylitol which prevents the dental carries which is now getting attracting of researcher to make drug loaded chewing gum and smoking cessation CG etc. So the CG has proven its potential as DDS vehicle [2].

There are countless application of chewing gum because it prevent the mouth from getting dry, prevent the dental carries, freshen the breath, increases the salivation, exercise the jaw muscle, some people uses CG during working because it helps them to focus on their work[3]. There are lot of patent given for the remarkable work done on it but the first patent was given to Mr W. F. Semple in Ohio under U. S. Patent No. 98,304 in 1869 for the production of chewing gum. The first commercially Acetyl Salicylic Acid containing medicated chewing gum was introduced in year 1928[4]. People chew gum for a variety of reasons includes modulating mental status, for example to concentrate more on a particular topic and sometime people used to have CG after meal to improve the digestion by increasing in saliva secretion and to help relieve mental stress.

One study was conducted to see the effect of chewing gum on person mood and performance in 1930s by scientist called Hollingworth[6].Hollingworth*et al* has studied the effect of candy coated chicle (the sap from the sapodilla tree) on the person mood and work performance. Several controlled laboratory studies have identified that chewing gum can improve memory [7-9]. Another study reported the effects of CG saying that the chewing gum affects the attention but not memory [13]. While there is evidence of cortical activation during chewing a gum [14]. Any

relationship to cognitive processing is not clear at present. Certainly the exact mechanisms underpinning any cognition-enhancing effects have been the subject of speculation but remain to be elucidated [15-18].

Medicated chewing gum is solid, single-dose preparations that have to be chewed and not swallowed; chewing gums contain one or more active ingredient that is released by chewing by the action of saliva which diffuses out the active ingredient from the gum matrix. It also could be defined as both solid and semi-solid preparations based on the art of manufacturing, i. e using conventional melting procedures or direct compression of tailored gum base powder.

In December 1999, The New England Journal of Medicine [19] revealed that chewing gum, energy expenditure increases from 58 kcal per hour to 70 kcal per hour – an increase of 11%. The water content of chewing gum is very low and no preservatives are needed. The gum base determines the basic characteristics of the product e.g. the texture. The gum base also determines the release profile of active substances, and changing the gum base composition may therefore change the release profile from the gum matrix.

Chitin and chitosan are versatile and they are promising biomaterials in pharmaceuticals. The deacetylated chitin derivative is a more useful and interesting bioactive polymer. Despite its biodegradability, chitin has many amino side groups in its structure, which offer much opportunity of chemical modifications, forming a large variety of useful derivatives.

BODY

Advantages of chewing gum[20-22]

- Fast/rapid onset of action: - Due to chewing effect the gum is masticated resulting in immediate release of active ingredient.
- High bioavailability: - Drug gets directly absorbed from the oral mucosa, preventing the degradation of drug from gastric pH of stomach.
- Pleasant taste: - addition of sweeting agent and colouring agent enhances the organoleptic characteristic of the formulation.
- Easy for administration without water promotes higher patient compliance.
- Ready for use.
- High acceptance by children and for patients who find swallowing tablets difficult are obvious.
- Fewer side effects.
- Systemic effect.
- Local effect.
- Reduce dry mouth (xerostomia).
- Product distinctiveness from a marketing perspective.
- People find relaxation and comfort in the simple act of chewing gum.
- It relieves muscular and nervous tension.
- Ease to carry and transport.
- Lesser cost of manufacturing comparing to conventional DDS.
- Treat Halitosis.

Health benefits of chewing gum

- Chewing gum improves memory.
- Chewing gum reduces symptoms of stress.
- Chewing gum helps to manage weight.
- Chewing gum improves digestion.
- Chewing gum improves oral health.
- Chewing gum improves oral Hygiene and prevent oral bad smell.
- Chewing gum helps in quitting smoking (Nicotine Chewing Gum)
- Treat Halitosis.

Different types of Chewing Gum

Chewing gum is gaining its market because of its lot of application, so manufacturer are making it in many shape, size (cube shape, ball shape, oval shape and also in strips) flavour (mint flavour, strawberry, orange, mango etc) and there is no standard size and shape for CG. Chewing gum basically contain water-insoluble phase i.e. gum base with a water-soluble phase of sweeteners, flavouring and food colouring and active pharmaceutical ingredient.

e-ISSN:2320-7949
p-ISSN:2322-0090

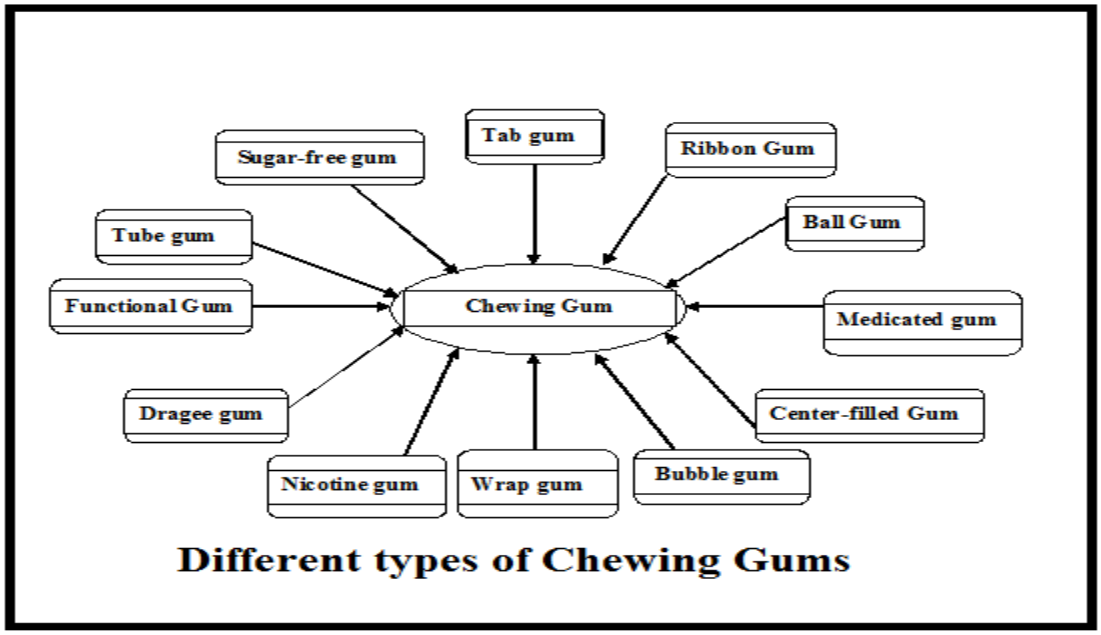

Diagram 1: Different types of Chewing Gum.

Bubble gum - Bubble gum have a property of blowing bubbles because film-forming characteristics of the gum base.

Sugar-free gum –It was formulated for diabetic patient so instead of sugar, sugar-free gum has artificial sweeteners to provide the taste to the CG.

Ball Gum – The name suggest it is in ball shape and it has gain most popularity among all age of people.

Centre-filled Gum – Centre-filled gum in its centre has a soft mass, usually filled with some tasty liquid to increase its organolaptic properties.

Stick gum - Stick gum is a thin, flat, slab of gum usually in rectangular shape.

Ribbon Gum -Ribbon gum is like the stick gum, it is longer, coiled up in a cylindrical container, and the consumer tears off a piece of the size he wants.

Tab gum – Tab gum is shorter than stick gum and also thicker.

Tube gum -Tube gum or spaghetti gum comes in a tube and the gum inside the tube is a very soft bubble gum.

Dragee gum – Dragee gum has the most popular format for chewing gum, dragee gum is a pillow-shaped coated pellet, often packed in blister packs.

Wrap gum – Wrap gum and cut gum is usually in the form of a chunk, cube or cylindrical shape, depending on the machine that wraps it.

Functional Gum - Functional gum is chewing gum that has a practical function attached to it, like chewing gum with vitamins and minerals or something else to the body.

Medicated gum – Medicated gum is a chewing gum with a purpose to introduce medicated substances into blood stream faster than pills.

Nicotine gum – Nicotine chewing gum is designed for people who are trying to quit smoking. Nicotine is the main active ingredient in this type of chewing gum and it helps the smoker, because it releases nicotine which minimise the reoccurrence episode of having cigarette.

Several types of chewing gum are designed for different purpose like CG preventing dental carries, smoking cessation, gums causing whitening of teeth, energy gum, herbal gum, vitamin gum etc.

e-ISSN:2320-7949
p-ISSN:2322-0090

Composition of chewing gum

Chewing gum base should be free of non-silica fibres and consists of high molecular weight poly isobutylene and powered lecithin.

Materials

The most important material required in formulating any type of CG is the gum base. Other ingredients which are required in formulating a chewing gum are: -flavouring agents, sweetening agents and aromatics.

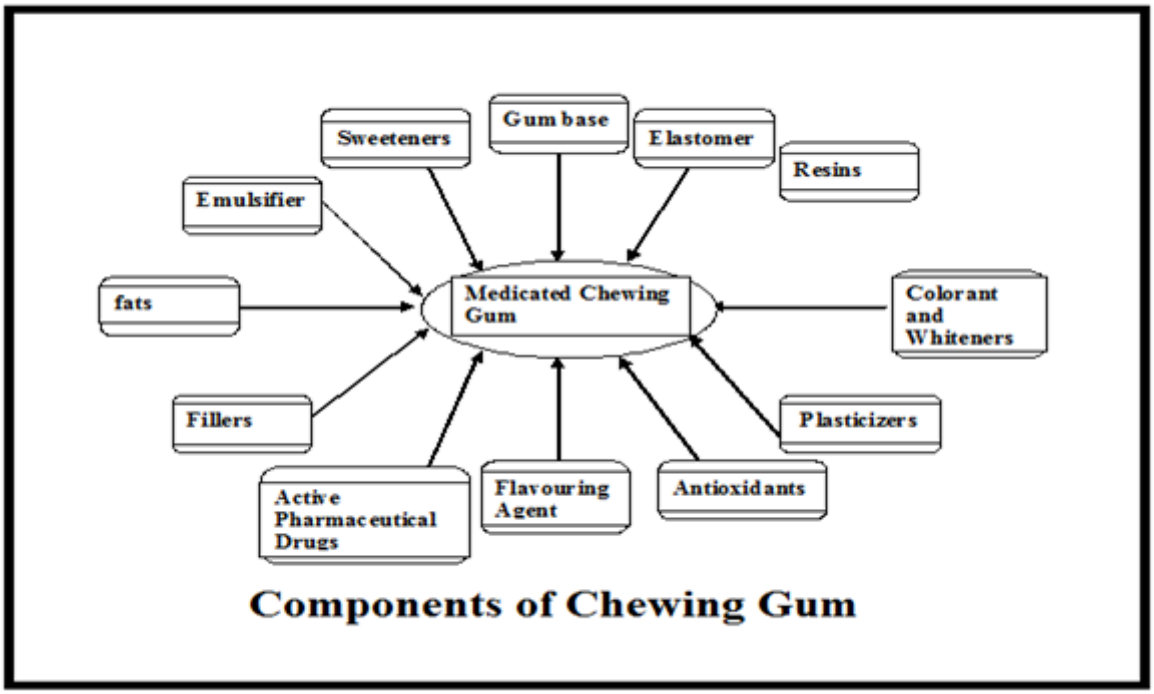

Diagram 2: Components of Chewing Gum.

Elastomers: CG has a typical property of elasticity and cohesion which is provided by the addition of elastomers.There are two types of elastomers i.e. natural and synthetic. Natural rubbers like Latex or Natural gums such as Jelutong, Lechi Caspi, Perillo, Chicle and synthetic elastomers like polyisobutylene and butyl rubber are generally used in the preparation of CG.

Resins: The main property which a resins gives to final preparation are; -firstly, as mastication substance and other as binding agent between elastomers and fillers. Resin are also responsible for providing the balance between the elasticity and plasticity examples of natural resins are Glycerol esters from pine resins and synthetic resin like polyvinyl acetate which caused prevention of adhering of CG to teeth (detackifier) and also it help CG to get into pieces when it is chewed.

Emulsifiers and Fats: The reason of addition of these ingredients in the formulation is that it softens the mixture and gives required chew during mastication. Example for these agents include: -Monoglycerides, diglycerides and partly hardened vegetable and animal fat are used.

Plasticizers: To regulate cohesiveness of formulation, natural and synthetic plasticizers are used. Natural Plasticizers include Natural rosin esters like Glycerol Esters or partially hydrogenated Rosin, Glycerol Esters of Polymerized Esters, Glycerol Esters of Partially dimerized Rosin & Penta erythritol Esters of Rosin. Synthetic Plasticizers include Terpene Resins derived from a-pinene and/or d-limonene.

Antioxidants: To prevent the oxidation of gum base, flavours and other composite present in the CG. These agents can be incorporated in the formulation. Agents commonly used are Ascorbic acid, tocopherol, butylhdroxytoluene.

Fillers: For giving a proper texture to gum base Talc, calcium carbonate can be used .

Colorants and Whiteners: May include FD & C type dyes, fruit and vegetable extracts, Titanium Dioxide.

Sweeteners: Sweeting agents include Saccharides like Fructose, Dextrose, Sucrose, Maltose, Dextrin, Galactose, and Corn Syrup. Sugarless Components include sugar alcohols such as Sorbitol, Mannitol, Xylitol, hydrogenated starch hydrolysate. High intensity artificial sweeteners can also be included to provide longer lasting sweetness and flavour perception e.g. Sucralose, Aspartame, salt of Acesulfame, Alitame, Saccharin, Glycerrhizin, Dihydrochalcones. Aqueous Sweeteners can also be used as softeners to blend the ingredients and retain moisture in the preparation for this purpose sorbitol, hydrogenated starch hydrolysates and corn syrups can be used. Corn syrup keeps gum fresh and flexible.

Flavouring Agents: A variety of flavouring agents are used to improve flavour in chewing gum includes essential oils, such as Citrus oil, fruit essences, Peppermint oil, Spearmint oil, Mint oil, Clove oil & Oil of Wintergreen. Artificial flavouring agents can also be used.

Active Pharmaceutical Drugs: In medicated chewing gum active pharmacological agent may be present in core or coat or in both. The proportion of which may vary from 0.5-30% of final gum weight. A small, unionized, lipophilic and enzymatically stable active agent is likely to be absorbed more readily. A saliva soluble ingredient will be completely released within 10-15 minutes of chewing whereas lipid soluble ingredient will dissolve in the gum base and thereafter be slowly and completely absorbed. Medicated chewing gums consist of masticatory gum core that may be coated. The core is composed of an aqueous insoluble gum base which can be mixed with Sweeteners and Flavours. The coating can be applied as a film of polymers, waxes, sweeteners, flavours and colour or a thick layer of sugar or sugar alcohol [23,24].

Medicament used in medicated Chewing gum

Chlorhexidine

The main cause for causing dental caries, periodontal disease and gingivitis is irregular brushing will result in the formation of thin film of bacteria well as known as Dental plaque. It was early known that the chronic gingivitis is caused by microorganism which is result of poor oral hygiene and if left untreated it results in the periodontitis [25-27]. Due to the relationship between oral microorganisms and caries as well as periodontal diseases, the dentist's has shown their interest in the topical use of antimicrobial agents. Hence dentist use Chemical therapy as a first line of treatment rather than going for mechanical therapy.

The first chemical entity which show antimicrobial activity against microorganism that causes dental plaque formation was Chlorhexidine (CHX)[28]. The main limitation of CHX is that it does not show its antibacterial activity against systemic infection hence it indicates that CHX is only applicable for oral and topical use.

CHX chemical composition is cationic chlorophenylbisbiguanide antiseptic. Bisbiguanides are the primary second-generation antiplaque agents exhibiting considerable substantively and very broad antibacterial properties. CHX is a strong base and at physiologic pH is a large dicationic molecule [1,6-di(4-chlorophenyl-diguanido) hexane] with two positive charges distributed over the nitrogen atoms on either side of the hexamethylene bridge[29, 30]. By virtue of its positive charge, CHX has the ability to bind to negatively charged surfaces such as the bacterial cell wall.[31].

Due to cationic nature of the CHX its get uniformly distribute within the mouth because the mucosal surface of mouth is negatively charged resulting in the antibacteriostaticaction of the drug [32]. The substantively of CHX is given by the fact that once adsorbed to intraoral surfaces it gets only slowly displaced by calcium ions from saliva. The dicationic nature making CHX extremely interactive with anions is not only relevant to its efficacy, safety, but also to local side effects and difficulties with the product formulation.

CHX is available as digluconate, acetate or hydrochloride salt. Digluconate and acetate salts are water soluble, CHX hydrochloride is weakly soluble in water. CHX, developed by Imperial Chemical Industries, GB, after intensive investigations of the biological properties of polybiguanide compounds was first marketed as an antiseptic for skin wounds in 1953. It has undergone extensive laboratory testing.

In general medicine CHX shows the following application: Skin disinfection, surgical hand disinfection, hygienic hand disinfection, preoperative whole-body disinfection, urology (irrigant, lubricant and antiseptic), obstetrics and gynaecology (irrigant and antiseptic), nasal cavity and throat, wounds and burns.

In dental medicine, CHX was initially used for pre-surgical disinfection of the mouth and in endodontology. Plaque inhibition by CHX was already investigated in 1962[33] but the first controlled clinical study was performed by LÖE & SCHIOTT (1970). This study showed that rinsing for 60 sec, twice per day with 10 ml of a 0.2% (20 mg dose) CHX gluconate solution inhibited plaque re-growth in the absence of normal tooth cleaning. Numerous studies have

followed such that CHX is one of the best investigated compounds in dentistry and to date still remains the gold standard to which other antiplaque and antigingivitis agents are compared [34-36]. For purposes of dental medicine, CHX is marketed and routinely used in various galenic forms such as mouthrinse, toothpaste, spray, gel, varnish and pastille or lozenge.

Fluoride

Fluoride plays a major role in oral health and in the prevention of tooth decay, as it has the following effects [37]:

- Inhibition of demineralization
- Enhancement of remineralisation
- And bacterial activity in dental plaque is inhibited

Several research works has been conducted to see the effect of fluoride in the chewing gum formulation. One study was conducted by JEkstrand and co-workers[38] to see the effect of fluoride when incorporated inside the dummy chewing gum and given to 20 healthy volunteers in a double-blind crossover study.

Several studies have been conducted in which fluorides have been administered in a chewing gum formulation. J Ekstrand and co-workers[38] 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 research was conducted at the same Swedish institute[39] 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)[40].

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 [41]. It was shown that high fluoride incorporation in the root surfaces can be achieved by frequent administration of low fluoride. In the conclusion, the authors indicated that the "findings present encouraging results in fluoride uptake and remineralisation 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." And another study was done regarding the Comparison between different methods of applying fluoride (e.g. lozenges, chewing gum, and mouth rinse) has also been carried out [42]. 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. Consequently, the most important issue is that the formulation should be acceptable and convenient to the patient for regular use. A multinational group [43] 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.

Xylitol

Xylitol (a polyol sugar alcohol – also referred to as birch sugar because it can be produced from birch trees) is used frequently for oral health care, especially in Finland. The regular use of xylitol chewing gum [44] leads to a reduction in the acidogenic potential of dental plaque, and studies [45-47] 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[48]. This is an important factor in oral health, as the prevention of colonisation of mutans streptococci in early childhood has been shown leading to the prevention of dental decay. In another study it was proven that mother-child transmission of streptococci can be reduced that was done on 195 mothers with mutansstreptococci[49]. 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 dental caries of 70% when compared to the other treatment groups. Other long term studies show that even after the discontinuation of therapy there is a significantly decrease in the dental caries score [50]. The best result was achieved if xylitol chewing gum treatment was initiated at least one year prior to eruption of permanent teeth [51]. Finally, a review of cariologic aspects of xylitol concluded that a daily intake of two or three pieces of xylitol chewing gum resulted in a defined reduction of caries [52].

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 school children in Madagascar[53]. 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 school children, particularly in developing countries with limited resources for formal oral health care."

In Lithuania, a similar study [54] 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 prevented by chewing sugar free gum.

Vitamin C

A group from the Royal Danish School of Pharmacy [55] 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[56]. 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.

Zinc

Zinc in a chewing gum formulation has been compared to zinc in a mouth rinse formulation [57]. The study was 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.

Mechanism of drug release

Drug release from the CG happen when the CG is chewed for a specific period of time resulting in mixing of drug with that of saliva. This causes the release of drug from the medicated chewing drug and absorption of drug can happen from the oral mucosa which are rich with blood supply or the content can be swallowed reaching the stomach for gastro-intestinal absorption and after that the gum as be spitted out from the mouth. So therefore there are two possible pathway by which a drug of choice can reach the blood circulation, firstly absorption through the buccal membrane which prevent the drug from getting metabolised in the gastrointestinal tract and first pass metabolism of the liver. This causes the administration of reduced dose than compared to other oral delivery system into the chewing gum and secondly, the drug should get mixed with saliva and pass through GIT to get absorbed through stomach wall.

Procedure for preparing chewing gum

Three types of manufacturing processes are available for the production of chewing gum.

Melting method or conventional production process

In this method firstly the gum base is melted in the jacketed mixer. When the gum base is in liquid form, then the drug and other ingredient are added to the melted gum base in a regular time interval, with flavour added at last. Then the mixture is cooled and rolled into big sheet. These sheets are cut into small pieces to get finished CG. As CG is also a dosage form hence all the GMP guideline has to be followed which were establish by regulatory bodies.

e-ISSN:2320-7949
p-ISSN:2322-0090

Disadvantage of conventional production process

The main disadvantage of this process is the thermal instability of many active ingredients (vitamins, vegetable extract etc.) Precludes traditional chewing gum production methods because the temperature profiles, associated with this type of production, may reach 90°C.

Cooling, Grinding and Tableting Method

This method has been developed with an attempt to lower the moisture content and alleviate the problems faced in conventional method. The Chewing Gum composition (base) is cooled to a temperature at which the composition is sufficiently brittle and would remain brittle during the subsequent grinding step without adhesion to the grinding apparatus. The cooling temperature required for this process is determined by the composition of the Chewing Gum and is easily determined empirically by observing the properties of the cooled chewing gum composition. Generally the temperature of the refrigerated mixture is around -15^{o}C or lower. Therefore, solid carbon dioxide is used as coolant amongst the various coolants like liquid nitrogen, hydrocarbon slush because it can give temperatures as low as -78.5°C. The solid carbon dioxide sublimes readily on warming the mixture and is not absorbed by the chewing gum composition, because of these properties solid carbon dioxide does not hamper any processing apparatus. To obtain the minute fragment of the refrigerated composition, the composition is crushed.

On the other hand, cooling of the chewing gum composition can be combined into a single step. The grinding apparatus itself is cooled by keeping the grinding apparatus in contact with a coolant or by placing the grinding apparatus in a cooling jacket of liquid nitrogen or other cold liquid. The chewing gum composition should be pre- cooled to the refrigeration temperature, for more efficient cooling.

In a first step of grinding, in a mill grinder, mixture of chewing gum composition, solid carbon dioxide and precipitated silica is ground. Moreover add some more quantity of solid carbon dioxide and silica to the ground composition. It is further ground in a second grinding step. This two-step grinding process keeps the chewing gum composition at a very low temperature. Efficiency of the grinding process is enhanced by the presence of solid carbon dioxide. Addition of carbon dioxide and/or precipitated silica at each step in same process can enhance the process efficiency.

Addition of certain additives to the chewing gum composition can facilitate cooling, grinding and can help in achieving desired properties of chewing gum. Some of the example are use of anti-caking agent and grinding agent.

After the removal of the coolant from the mixture, the composition is mixed with other ingredients which are compatible with the chewing gum base such as binders, coating agents, lubricants, sweeteners, etc, in a suitable blender such as sigma mill or a high shear mixer.

Alternatively a Fluidized Bed Reactor (FBR) can also be used. The use of FBR is advantageous as it partially rebuilds the powder into granules, as well as coats the powder particles or granules with a coating agent thereby minimizing undesirable particle agglomeration. The granules so obtained can be mixed with anti-adherents like talc. The mixture can be blended in a V type blender, screened & staged for compression. Compression can be carried out by any conventional process like punching.

Cooling, Grinding and Tableting Method thus overcomes the limitations of Conventional technique. However, it requires equipment other than conventional tableting equipment thus making it an expensive process as compared to Conventional process. Similar to the Conventional process even this process requires careful monitoring of humidity during the tableting process [60,61].

Direct compression process

In Directly compressible technique free flowing powdered gums have been developed which contains mixtures of polyols and/or sugars with gum base. Such obtained gum base can be compacted in to a tablet form using a conventional tablet press. The finally obtained chewing gums are harder than their counter parts and texture analysis shows that they crumble under applied pressure.

These chewing gums include higher levels of active ingredients than traditional extruded gums. Low temperature protects sensitive bioactivity and phytochemical components, moreover lower moisture content also improves shelf life of active molecules. Release is faster than from the conventional gums.

e-ISSN:2320-7949
p-ISSN:2322-0090

Disadvantage of direct compression technique

The main disadvantage is its sticking effect to the punches of the tableting equipment. This effect is due to the adhesive nature of the gum which is the main component of the formulation. For this reason, the procedure becomes difficult and needs slower production speed and cooling operations to prevent the tableting machine damage. The tableting tools are kept at temperatures below 18°C. It should be noted that the temperature should not be so low as to interfere with the handling of the medicated gums and the tableting process. Thus, the temperature should be above 10 -12 °C[62].

Apparatus for testing medicated chewing gum

In vitro dissolution and drug release testing of tablets and capsules are well established and apparatuses and standardized methods are described in the pharmacopoeias. However, these methods are not suitable for studying the release of active substances from chewing gums, since there is a continuous mastication is needed for release of the drug. The release of drug substances from chewing gums have sometimes been quantified by chew-out studies where volunteers chew a gum for a certain time period and the gum is then analysed for the remaining amount of active substance[63,64]. This approach has some obvious disadvantages since it is difficult to standardize and more than one gum is needed to obtain a full release profile. Some in vitro dissolution chewing apparatuses have been described but no international standards have so far been set for controlled release tests of medicated chewing gums [65-68]. Pharmacopoeial guidelines state that in general, solid oral dosage forms in which absorption of the drug is essential for the therapeutic effect should be tested for in vitro drug release in order to guarantee the biopharmaceutical quality of the product. The increasing interest in chewing gums as drug delivery vehicles therefore calls for development of robust *in vitro* drug release equipment and standardized test methods also for gums.

We here describe an apparatus developed for *in vitro* dissolution of drug substances from medicated chewing gums. Specifically, important characteristics governing the release of the active substance to the test medium are discussed. Release profiles of drug substances from some commercially available products are also presented [69,70].

Apparatus–I chewing Gum Apparatus, Compendial—Ph. Eur.

The chewing apparatus for medicated chewing gum was adopted by Ph. Eur. in 2000.(2) Figure 1 shows the construction of the apparatus. The chewing apparatus comprises of a chewing chamber, two horizontal pistons, and a third vertical piston (tongue). The vertical piston operates alternatively with the two horizontal pistons and makes sure that the gum stays in the right place between chews. It is feasible to construct the machine so that at the end of the chew the horizontal pistons rotate around their own axes in opposite directions to each other to obtain maximum chewing. The working procedure of this chewing apparatus is described in Ph. Eur[71, 72]. Several studies [69,73-79] have been carried out using the Ph. Eur. apparatus, and the results indicate the methodology is rugged and reproducible.

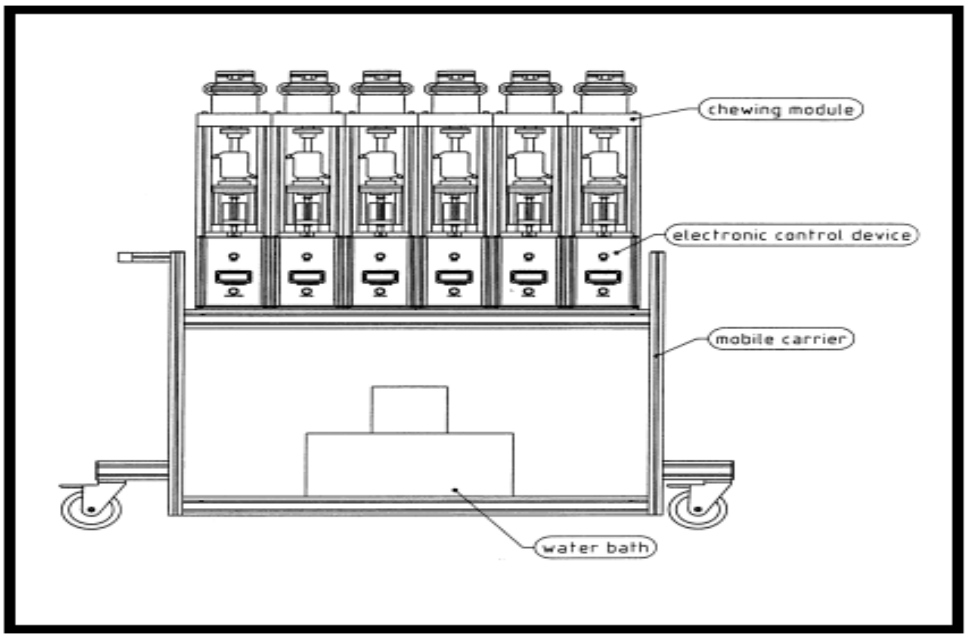

Figure 1: Technical drawing of chewing gum apparatus for testing drug release[66]

e-ISSN:2320-7949
p-ISSN:2322-0090

Apparatus -II. Alternative Chewing Gum Apparatus, Noncompendial—Wennergren

One of the non-compendial apparatus commercially available was designed by Wennergren[79]. The schematic representation of the Wennergren chewing apparatus is shown in Figure 2. The chewing procedure consists of reciprocations of the lower surface in combination with a shearing (twisting) movement of the upper surface that provides mastication of the chewing gum and at the same time adequate agitation of the test medium. The upper jaw has a flat surface that is parallel to the central part of the lower surface. The small brim of the lower surface is angled upwards (45 degrees) so that the lower surface functions as a small bowl with a flat bottom. This bowl prevents the chewing gum from sliding during mastication. Investigations of the performance of the chewing apparatus with multiple drug products were published by Wennergren et al[79]. The influences of different operational parameters of the chewing gum apparatus on drug release have been carefully investigated[80].

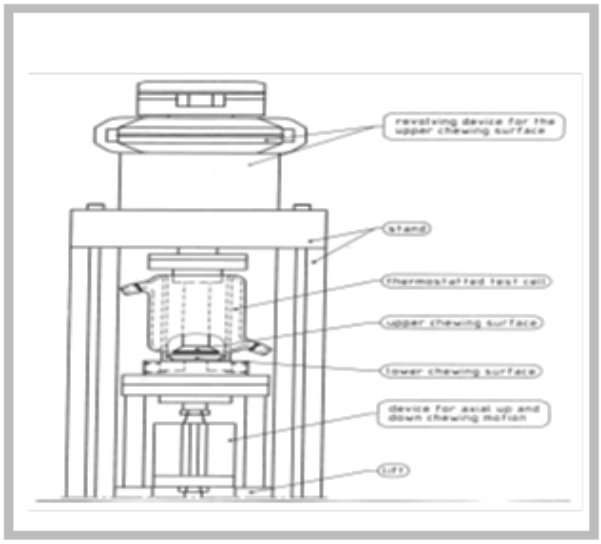

Figure 2: Apparatus for testing the release of drug from chewing gum [66]

In-vitro Apparatus

An apparatus was specially designed and constructed for studying the release pattern of drug from the medicated chewing gums. The ability of the instrument to adjust settings such as temperature, chewing frequency, chewing time, volume of test medium, distance between the jaws and twisting angle increases the versatility of the apparatus. Selecting the test medium is also an important parameter. Each sample was kneaded mechanically in separate test chambers and the drug release was followed by sampling and HPLC analysis. Formulations prepared from different gum were tested and the obtained results demonstrate satisfactory release curves for a variety of formulations and active ingredients. The tested gum formulations include xylitol, nicotine, meclizine, and dimenhydrinate. The apparatus proved to be suitable not only in product control of commercial batches but also a useful tool in the research and development of medicated chewing gum formulations [79-82].

General Comments about Apparatus I and Apparatus II

Both the apparatus described have been well studied and reported in the literature [73-75,79-83]. The results show that the apparatus can provide strong mechanical forces that influence drug release and can prove to be a useful tool for drug release.

In-vitro testing

The absorption of active substances through the buccal mucosa can be examined by both *in vitro* and *in vivo* methods. The most common method utilizes chamber where excised buccal mucosa (either from human or animal) is placed as a barrier between two chambers. The active substances transported across the mucosa can be measured by withdrawal of samples from each chamber. Oral cavity made up of Porcine is recommended, as it is morphologically similar to human oral cavity[84]. Likewise, a human TR146 cell culture model has proven a good *in-vitro* model for investigating permeability, permeability mechanisms, effects of chemical enhancers, and toxic effects [85-87].

e-ISSN:2320-7949
p-ISSN:2322-0090

Factors affecting release of active ingredient from Chewing gum

Contact Time

The local or systemic effect is dependent on time of contact of Medicated Chewing Gum in oral cavity. In clinical trial chewing time of 30 minutes was considered close to ordinary use. The average chewing rate is about 60 chews per minute.

Physicochemical properties of active ingredient

A physicochemical property of active ingredient plays a very important role in release of drug from Medicated Chewing Gum. The saliva soluble ingredients will be immediately released within few minutes whereas lipid soluble drugs are released first into the gum base and then released slowly. Release of water soluble drug (aqueous solubility greater than 1:10) is, in general, about 75% or more during 5 min of chewing and 90% or more during 15 min of chewing at rate of 60 chews per minute. Drugs with aqueous solubility between 1:10 and 1:300 demonstrate up to 60% release during 10 minutes of chewing and between 50 to 90% when the gum is chewed for 15 min. The release of the drug, which is only slightly water-soluble, can only be expected to be small (less than 5%) even if the gum is chewed for 30 min.

Inter individual variability

The chewing frequency and chewing intensity which affect the drug release from Medicated Chewing Gum may vary from person to person. In-vitro study prescribed by European Pharmacopoeia suggest 60 cycles per minute chewing rate for proper release of active ingredient.

Formulation factor

Composition and amount of gum base affect rate of release of active ingredient. If lipophilic fraction of gum is increased, the release rate is decreased [19] the influence of gum base mass on drug release has been investigated using salicylamide as model drug. When salicylamide was incorporated into a chewing gum, which contained a relatively large percentage of gum bases, the release after 30 min. of chewing was significantly lower (25.6%) compared to a gum in which less gum base was present (52%)[88,89)].

Applications:[83, 89, 90-97]

Dental caries

- Prevention and cure of oral disease are targets for chewing gum formulations.
- It can control the release rate of active substances providing a prolonged local effect.
- It also re-elevates plaque pH which lowers intensity and frequency of dental caries.
- Fluoride containing gums have been useful in preventing dental caries in children and in adults with xerostomia.
- Chlorhexidine chewing gum can be used to treat gingivitis, periodontitis, oral and pharyngeal
- Infections.
- It can also be used for inhibition of plaque growth.
- Chlorhexidine chewing gum offers numerous flexibility in its formulation as it gives less staining of the teeth and is distributed evenly in the oral cavity.
- The bitter taste of chlorhexidine can be masked quite well in a chewing gum formulation.

Systemic therapy

- **Pain**- chewing gum can be used in treatment of minor pains, headache and muscular aches.
- **Smoking cessation**- Chewing gum formulation containing nicotine and lobeline have been clinically tested as aids to smoking cessation.
- **Obesity**- Active substances like chromium, guaran and caffeine are proved to be efficient in treating obesity. Chromium is claimed to reduce craving for food due to an improved blood-glucose balance. Caffeine and guaran stimulate lipolysis and have a thermogenic effect (increased energy expenditure) and reduce feeling of hunger.
- **Other indications**- Xerostomia, Allergy, Motion sickness, Acidity, Cold and Cough, Diabetes, Anxiety, etc.

e-ISSN:2320-7949
p-ISSN:2322-0090

Future Trends

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 may not be suitable candidates. Poorly water-soluble drugs require specialized formulation techniques to promote release, and these techniques are reasonably well developed. Dental health chewing gum for caries prevention has come to stay and the indications are that it will be accepted widely in future. Although, it has a good potential to become a convenient alternative approach to improve patient compliance, it still remains as a field to be explored to the fullest.

Chewing gum not only offers clinical benefits but also an attractive, discrete and efficient drug delivery system. Nowadays 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 and popularity by the patients, however chewing gum is believed to manifest its position as a convenient and advantageous drug delivery system as it meets the high quality standards of pharmaceutical industry and can be formulated to obtain different release profiles of active substances. Finally, in the future, we may see that more and more 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 its pleasant taste increases the product acceptability and patient compliance.

REFERENCES

1. Morjaria Y, Irwin WJ, Barnett PX. In Vitro Release of Nicotine fromChewing Gum Formulations. Dissolution Technologies. 2004 May:12-15.
2. http://www.fertin.com.
3. Conway B. Chewing Gum as a Drug Delivery System. The Drug Delivery Companies Report. 2003: 33-35.
4. US Patent. 2001; 6,322,828.
5. Jacobsen J, Christrup LL, Jensen NH. Medicated Chewing Gum. Am J Drug Deliv. 2004;2 (2):75-88.
6. Hollingworth HL. Chewing as a technique of relaxation Science. 1939;90:385–7.
7. Baker JR, Bezance JB, Zellaby E. Chewing gum can produce on text dependent effects upon memory. Appetite. 2004;43(207):10.
8. Stephens R, Tunney RJ. Role of glucose in chewing gum-related facilitation of cognitive function. Appetite .2004;43:211–3.
9. Wilkinson L, Scholey A, Wesnes K. Chewing gum selectively improves aspects of memory in healthy volunteers. Appetite. 2002;38:235–6.
10. Johnson AJ, Miles C. Evidence against memorial facilitation and context-dependent memory effects through the chewing of gum. Appetite. 2007;48:394–6.
11. JohnsonAJ, Miles C. Chewing gumand context-dependentmemory: the independent roles of chewing gum and mint flavour. Br J Psychol. 2008;99:293–306.
12. Miles C, Johnson A. Chewing gum and context-dependent memory effects: a reexamination. Appetite. 2007;48:154–8.
13. Tucha O, Mecklinger L, Maier K, Hammerl M, LangeKW. Chewing gum differentially affects aspects of attention in healthy subjects. Appetite. 2004;42:327–9.
14. Takada T, Miyamoto T. A fronto-parietal network for chewing of gum: a study on human subjects with functional magnetic resonance imaging. NeurosciLett. 2004;360:137.
15. Scholey A. Chewing gum and cognitive performance: A case of a functional food with function but no food. Appetite. 2004;43:215–6.
16. Scholey A. Further issues regarding the possible modulation of cognitive function by the chewing of gum: Response to Stephens and Tunney (2004) and Tucha(2004). Appetite. 2004;43:221–3.
17. Stephens R, Tunney RJ. How does chewing gum affect cognitivefunction.Appetite. 2004;43:217–8.
18. Tucha O, Mecklinger L, Hammerl M, LangeKW. Effects of gum chewing on memory and attention. Appetite. 2004;43:219–20.
19. http:www.fertin.com/fileadmin/pdf/Doc_on_MCWG_booklet.pdf.-reference
20. Chien YW. Novel Drug Delivery Systems, 2nd edition, Revised and expanded, Marcel Dekker, New York. 1992; 139.
21. Lieberman HA, Lachman L, Schwartz JB. Pharmaceutical Dosage Forms: Tablets, Vol-I, IInd edition. 1990; 367-415.
22. Rassing MR. Specialized oral mucosal drug delivery systems: Chewing gums. In: Rathbone, M.J. (Ed.), Oral Muccosal Drug Delivery, Marcel Dekker, New York, 1996; 319-57.
23. Zyck D.J., Greenberg; M.J., Barkalow D.G., Marske S. W., Schnell P. G., Mazzone P.: Method of making coated chewing gum products containing various antacids. US Patent. 2003; 6,645,535.
24. Nilima T, Karishma P. A review on medicated chewing gum as a novel drug delivery system.Journal of Pharmacy Research .2011; 4(3): 848-851.
25. Ash MM, Gitlin BN, Smith NA. Correlation between plaque and gingivitis. J Periodontol.1964; 35: 424–429.
26. Loe H, Theilade E, Jensen SB: Experimental gingivitis in man. J Periodontol.1965; 36: 177–187.

27. Theilade E, Wright WH, Jensen SB, Loe H. Experimental gingivitis in man. II. A longitudinal clinical and bacteriological investigation. J Periodont Res. 1966; 1: 1–13.
28. Loe H, SChiott CR. The effect of mouthrinses and topical application of chlorhexidine on the development of dental plaque and gingivitis in man. J Periodont Res.1970; 5: 79–83.
29. Jones CG. Chlorhexidine: Is it still the gold standard, Periodontology. 2000;15: 55–62.
30. Albert A, Sargeant EP. Ionization Constants of Acids and Bases. Methuen, London, 1962; 173.
31. Koontongkaew S, Jitpukdeebodintra S. Interaction of chlorhexidine with cytoplasmic membranes of Streptococcus mutans GS-5. Caries Res. 1995; 29: 413–417.
32. Loesche WJ. Chemotherapy of dental plaque infections. Oral Sci Rev.1976; 9: 65–107.
33. Schroeder HE. Formation and Inhibition of Dental Calculus. Hans Huber, Berlin. 1969:145–172.
34. Gjermo P. Chlorhexidine and related compounds. J Dent Res. 1989; 68: 1602–1608.
35. Addy M, Moran J, Wade W. Chemical plaque control in the prevention of gingivitis and periodontitis. In: Lang N P, Karring T, (Eds.) Proceedings of the 1st European Workshop on Periodontology. Quintessence, London. 1994; pg 244–257.
36. Moshrefi A. Chlorhexidine. J West SocPeriodontol/Periodontal Abstract. 2002; 50: 5–9. Process for the preparation of chewing gum.1976: US Patent 4,000,321.
37. Featherstone JD.Prevention and reversal of dental caries: role of low level fluoride.Community Dent Oral Epidemiol.1999; 27, 31-40.
38. Ekstrand J, Birkhed D, Lindgren LE, Oliveby A, Edwardsson S, FrostelG.Effect of repeated intake of a sugar free fluoride-containing chewing gum on acidogenicity and microbial composition of dental plaque.ScandJ.Dent. Res. 1985;93:309-314.
39. Oliveby A, Ekstrand J, LagerlöfF.Effect of Salivary Flow Rate on Salivary Fluoride Clearance after Use of a Fluoride-Containing Chewing Gum.Caries Res.1987;21:393-401.
40. Sjogren K, Birkhed D, Persson LG, Noren JG. Salivary fluoride clearance after a single intake of fluoride tablets and chewing gums in children, adults, and dry mouth patients. Scand J Dent Res. 1993; 101: 274-278
41. Seppa L, Salmenkivi S, HausenH.Salivary fluoride concentration in adults after different fluoride procedures.Acta. Odontol. Scand.1997;55: 84-87.
42. Hattab FN, Green RM, Pang KM, MokYC.Effect of fluoride-containing chewing gum on remineralization of carious lesions and on fluoride uptake in man.Clin. Preventive. Dent.1989;11: 6-11.
43. Aguirre ZO, Zero DT, ProskinHM.Effect of Chewing Xylitol Chewing Gum on Salivary Flow Rate and the Acidogenic Potential of Dental Plaque.Caries. Res.1993; 27: 55-59.
44. ArendsJ.Influence of Xylitol on Demineralization of Enamel.Caries Res.1984; 18: 296-301.
45. MakinenKK.Conclusion and review of the “Michigan xylitol program” (1986-1995) for the prevention of dental caries.Int Dent J.1996;46: 22-34.
46. TanzerM.Xylitol chewing gum and dental caries.Int Dent J.1995;45- 1: 65-76.
47. SoderlingE,Influence of maternal xylitol consumption on mother-child transmission of mutans streptococci: 6-year follow-up.C. Res.2001;35: 173-177.
48. Isokangas P, Soderling E, Pienihakkinen K, AlanenP.Occurance of dental decay in children after maternal consumption of xylitol chewing gum a follow-up from 0-5years of age J. Dent. Res.2000;79:1885-1889.
49. IsokangasP.Long-term effect of xylitol chewing gum in the prevention of dental caries: a follow-up 5 years after termination of a prevention program. Caries. Res.1993;27: 495-498.
50. HujoelPP.The optimum time to initiate habitual xylitol gum-chewing for obtaining long-term caries prevention.J Dent Res.1999; 78: 797-803.
51. Birkhed D, ActaOS.Cariologic aspects of xylitol and its use in chewing gum: a review.1994;52: 116-127.
52. FejerskovOB.OralDiseases,Xylitol in caries prevention: what is the evidence for clinical efficacy.1998;4: 268-278.
53. Petersen PE, Kaka M. Oral health status of children and adults in the Republic of Niger, Africa. Int Dent J. 1999; 49:159-64.
54. Fure S, Lingström P, Birkhed D. Effect of Three Months' Frequent Use of Sugar-free Chewing Gum with and without Urea on Calculus Formation.J. Dent. Res.1998;77: 1630-1637.
55. Kamal RA, Radhika J, Chetan S. The antimicrobial potential of ten often used mouthwashes against four dental caries pathogens.LicForlag. 2010; 3(1): 15-2.
56. WalerSM.The effect of zinc-containing chewing gum on volatile sulfur-containing compounds in the oral cavity.Acta. Odontol. Scand.1997; 55: 198-200.
57. Kleber CJ, PuttMS.Chewing gum as a drug delivery system,Compend. Contin. Educ. Dent. 1986; 7(9): 681-685.
58. Mochizuki K, Yokomichi F. Process for the preparation of chewing gum, US Patent 1976; 4,000,321.
59. MingK,XiGC, KeX, Hyun JP. Antimicrobial properties of chitosan and mode of action: A state of the art review. International Journal of Food Microbiology. 2010;144,51–63.
60. Babak A, Ali AM, Soozan B, Sepideh S, Afsaneh R. Salvadora Persica extract chewing gum and gingival health: Improvement of gingivaland probe-bleeding index. Complementary Therapies in Clinical Practice. 2010;16,121–123.

61. RunwalAV ,PotnisVV, Lone KD. Medicated Chewing Gums - A Novel Option. Pharmaceutical Reviews e-journal. 2008; 6(3).
62. Athanikar NK, Mochizuki K, Yokomichi FGSA.Process for manufacturing a pharmaceutical chewing gum. US Patent 2001; 6,322,828.
63. Woodford DW, Lesko LJ. Relative bioavailability of aspirin gum. J. Pharm. Sci. 1981; 70, 1341–1343.
64. Nemeth CR, Benowitz NL, Robinson N, Henningfield ZE. Nicotine gum: Chew rate, subjective effects and plasma nicotine. Pharm. Biochem. Beh. 1988; 29: 747–751.
65. Kleber CJ, Schimmele RG, Putt MS, Muhler JC. A mastication device designed for evaluation of chewing gums. J. Dent. Res. 1981; 60: 109.
66. Christrup LL, Moller N. Chewing gum as a drug delivery system I. *In vitro* simulation of human mastication and influence of formulation upon the release rate of a water soluble drug. Arch. Pharm. Chem. Sci. Ed. 1986; 14: 30–36.
67. Liljewall LR. Methods and apparatus for mechanical processing of a sample and a member of such an apparatus. PCT Patent WO .1989; 89:05970.
68. Liljewall.R. Methods and apparatus for mechanical processing of a sample and a member of such an apparatus. United States Patent. 1992; 5 087 424.
69. Rider JN. Development and Evaluation of a novel dissolution apparatus for medicated chewing gum products. Pharm. Res. 1992; 9: 255–259.
70. Morjaria Y, Irwin WJ, Barnett PX, Chan RS, Conway BR. *In Vitro*release of Nicotine from chewing gum formulations. Dissolution Technologies. 2004; May: 12-15.
71. Yang X, Wang G, Zhang X. Release kinetics of catechins from chewing gum. J Pharm Sci. 2004;93(2): 293–299.
72. European Directorate for the Quality of Medicines, Council of Europe, European Pharmacopoeia. Suppl. General Chapter 2.9.25: Chewing Gum, Medicated Release from. 3rd Ed. Strasbourg, France; European Directorate for the Quality of Medicines, Council of Europe. 2000; 104.
73. European Directorate for the Quality of Medicines, Council of Europe. European Pharmacopoeia. Suppl. 5.2. General Monograph 2.9.25: Dissolution Test for Medicated Chewing Gums. 5th Ed. Strasbourg, France. 2005; 3116–3117.
74. Jensen E, Lokind KB, Pedersen M, Rassing MR. Chewing gum as a drug delivery system influence of additives upon the rate of drug release of metronidazole and propranolol hydrochloride from chewing gum. FarmaciSci Ed. 1988; 16: 94–97.
75. Christrup LL, Moeller N. Chewing gum as a drug delivery system I- *in vitro* simulation of human mastication and influence of formulation upon the release of a water–soluble drug. Arch Pharm ChemSci Ed. 1986; 14:30–36.
76. Christrup LL, Rassing MR. Chewing gum as a drug delivery system- influence of the formulation upon the rate of release of salicylamide. FarmaciSci Ed. 1988;16:1–5.
77. FarajJA, Dorati R, Schoubben A. Development of a peptide- containing chewing gum as a sustained release antiplaque antimicrobial delivery system. AAPS PharmSciTech.2007; 8(1): 26.
78. Pedersen M, Rassing MR. Miconazole and miconazolenitrate chewing gum as drug delivery systems: a practical approach of solid dispersion technique. Drug DevInd Pharm.1990; 16(1): 55–74.
79. Pedersen M, Rassing MR. Miconazole chewing gum as a drug delivery system test of release promoting additives. Drug DevInd Pharm. 1991; 17(3): 411–420.
80. Kvist C, Andersson SB, Fors S, Wennergren B, Berglund J. Apparatus for studying *in vitro* drug release from medicated chewing gums. Int J Pharm. 1999; 189(1): 57–65.
81. Kvist LC, Andersson SB, Berglund J, Wennergren B, Fors SM. Equipment for drug release testing of medicated chewing gums. J Pharm Biomed Anal. 2000: 22(3): 405–411.
82. Andersen T, Gram-Hansen M, Pedersen M, Rassing MR. Chewing gum as a drug delivery system for nystatin - influence of solubilizing agents upon the release of water insoluble drugs. Drug DevInd Pharm. 1990; 16(13): 1985–1994.
83. Jensen LN, Christrup LL, Menger N, Bundgaard H. Chewing gum and lozenges as delivery systems for noscapine. Acta Pharm Nord. 1991; 3(4): 219–222.
84. Rassing M, Chewing gum as a drug delivery system.Adv Drug Delivery Rev, 1994; 13: 89- 121.
85. Nielsen HM, Ph.D. thesis, HCØ Tryk, Copenhagen, DK. (2000). 86. Catharina Kvist , Sven BorjeAndersson, Susan Fors, BoWennergren, Johan Berglund, Apparatus for studying *in vitro* drug release from medicated chewing gums-International Journal of Pharmaceutics 1999; 189: 57–65.
86. Goldberg LD, Ditchek NT. Chewing gum diarrhea. Am J Dig Dis. 1978; 23(6): 568.
87. Morjaria Y, Irwin WJ, Barnett PX, Chan RS and Conway BR: *In Vitro* Release of Nicotine from Chewing Gum Formulations. Dissolution Technologies, 2004; May: 12-15.
88. RassingMRSpecialized oral mucosal drug delivery systems: Chewing gums. In: Rathbone, M.J. (Ed.), Oral Muccosal Drug Delivery, Marcel Dekker, New York, 1996; 319-57.
89. LameyPJ,LewisMAO.BuccalSubligual Delivery of Drugs in Routes of Administration, London. 1990; 30-47.
90. International Journal of Pharmaceutical Sciences Review and Research,. Article 012 ISSN 0976 – 044X. 2010; Volume 4, Issue 2, September – October, Page 68.
91. Dalai K. Chewinggum: trick or treat, The Saudi Dental J. 1999; Vol. 11(1): 27-34.

92. Dodds M, Hiesh S, Johnson D, The effect of increased mastication by daily gum chewing on salivary gland output & dental plaque acidogenicity, J Dent Res.1991; 70: 1474-1478.
93. Ferno OB, and Ohlsson CBI, Buffered smoking substitute compositions, U.S. Patent. 1974; 3,845,217.
94. Lichtneckert S, Lundgren C. and Ferno O, Chewable smoking substitute composition, U.S. Patent 1975;3,901,248.
95. European Pharmacopoeia, Strasbourg: European Directorate for the Quality of Medicines, Chewing Gums: Medicated, 5th edition, 260 & 601, 2004.
96. Dodds MWJ, Hsieh SC, Johnson DA. The effect on increased mastication by daily gum chewing on salivary gland output and dental plaque acidogenicity, J. Dent. Res. 1991; 70, 1474–1478.
97. Nozaki Y, KakumotM,Ohta M, Yukimastu M. A New Transmucosal Therapeutic System: An Over View of Formulation Development and *In-Vitro/In-Vivo*Clinical Performance, Drug Development Ind. Pharm.1993; 19, 221.