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Medicated Chewing Gum- A Novel Drug Delivery System: An Updated Review

Ritesh Kumar*[1], Pavitra Solanki[2] and Amrish Chandra[3]

[1]Dr. K. N. Modi Institute of Pharmaceutical Education & Research, Modinagar, Uttar Pradesh, India
[2]Sanjay College of Pharmacy, Mathura, Uttar Pradesh, India
[3]Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh, India

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Address for Correspondence
Asst. Prof., Dr. K. N. Modi Institute of Pharmaceutical Education & Research Modinagar- 201204, Uttar Pradesh, India.

Tel. +91-8755170024.
E-mail: ritesh_pharma@rediffmail.com

ABSTRACT

Chewing gums are mobile drug delivery systems. Unlike chewable tablets medicated gums are not supposed to be swallowed and may be removed from the site of application without resort to invasive means and medicated chewing gum MCG is solid, single dose preparation. As for as patient convenience is concerned it is discrete and easy administration without water promotes higher compliance. Since it can be taken anywhere, a chewing gum formulation is an excellent choice for acute medication. The advantages for children and for patients who find swallowing tablets difficult are obvious. The medicated chewing gums 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. This concept is supported by statements that chewing sugar free gum can help reduce the risk of dental caries (cavities). The objective of this systematic study is to appraise existing evidence concerning a possible therapeutic effect of sugar-free chewing gum for patients. MCG represents the newest system with potential uses in pharmaceuticals, over the counter medicines and nutraceuticals.

Keywords: Chewing gums, Mobile drug delivery system, Dental caries, Mouth diseases, Saliva.

INTRODUCTION

Medicated Chewing Gum (MCG) is a novel drug delivery system containing masticatory gum base with pharmacologically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. MCG is considered as vehicle or a drug delivery system to administer active

principles that can improve health and nutrition. MCG represents the newest system with potential uses in pharmaceuticals, over the counter medicines and nutraceuticals[1]. The drugs intended to act in oral cavity often have low water/saliva solubility and chewing gum constitute a valuable delivery system for such drugs. Medicated chewing gum is a solid or semisolid dosage form which consists of one or more active ingredient (water soluble or insoluble) incorporated in water insoluble base. Many scientific studies have explored the role of chewing gum in promoting healthy teeth. Gum chewing is a common habit in many countries[2]. Chewing gum has been used for centuries to clean the mouth and freshen the breath. A MCG containing Acetyl Salicylic Acid was commercially introduced in 1928[3]. In 1991, Chewing gum was approved as a term for pharmaceutical dosage form by the commission of European Council. Approximately £80 to 100 million, 55% of it being sugar free gum. Seventy-nine percent of the chewing gums sold in Switzerland are sugar-free, 70% of the consumers are teenagers, and girls chew more gum than boys. Chewing gum was initially sweetened with sugar, which contributed to dental caries. Today, however, more than 50% of chewing gum sold in Europe is sweetened with sugar substitutes (polyols). Clinical evidence shows that sugar substituted chewing gum does not lead to caries, because the polyols do not lead to a clinically relevant production of metabolic acids in dental plaque. The objective of this systematic literature review is to appraise existing evidence concerning a possible therapeutic/ anti-carcinogenic effect of sugar-free chewing gum for patients. MCG represents the newest system with potential uses in pharmaceuticals, over the counter medicines and nutraceuticals[4,5]. A devoted gum chewer can confidently transverse the globe with the assurance that his/her masticatory needs will be met. These are some of the international terms which identify chewing gum (e.g. goma de mascara in Argentina; kaugummi in Austria; le chewing gum in France; ellk in Arabian area; tskles in Greece; gamu in Japan, tyggegummi in Norway and heung how chu in Taiwan). So it can be considered as an international habit among all countries of the world (except in some countries and in some religious communities where gum chewing is still considered as bad manners or even forbidden e.g. Singapore & UAE).

In 1987, gum products accounted for 550 million dollars in sales in the USA. Chewing gum provides new competitive advantages over conventional 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.

US market accounts for approx. 50% of world market for medicated chewing gums.

The medicated chewing gum consists of active ingredient in the core or on the surface of it.

History of Medicated Chewing Gum

One thousand years ago, the Mayan Indians chewed tree resin from the sapodilla tree in order to clean their teeth and freshen the breath[6,7]. Shortage of natural gum bases during World War II enhanced development of the synthetic gum bases that are used today.

The first patent for the production of chewing gum was filed in 1869 and was issued to Mr. W. F. Semple in Ohio under U. S. Patent No. 98,304. The first medical chewing gum, Aspergum®, was launched in 1928[8,9]. This chewing gum contains the analgesic substance acetylsalicylic acid

known from Aspirin® tablets. Chewing gum did not gain acceptance as a reliable drug delivery system until 1978, when nicotine chewing gum became available. Another commercially available medical chewing gum is dimenhydrinate-containing chewing gum for motion sickness.

Chewing gum has an old and long history, in 50 AD; the Greeks sweetened their breath and cleansed their teeth by using mastiche, a resin from the bark of mastic tree. (The English word "masticate" is derived from the root word mastiche) At the beginning of its history this product was not so much accepted by the public. Spruce gum, which was manufactured in 1848, became the first chewing gum product to be manufactured commercially Called "STATE OF MAINEPURE SPRUCE GUM." However, its use was eventually replaced by paraffin, which is still being chewed in some areas.

The first patent for chewing gum, U.S. number 98,304 was filed on December 28, 1869 by Dr. William F. Sample, a dentist from Mount Vernon, Ohio. This product, consisting of liquorice and rubber dissolved in alcohol and naphtha, was initially intended to be used as a dentifrice. In 1891, William Wrigley Jr., arrived in Chicago with $32 in cash with a desire to market his special variety of soap. Eventually, he switched from soap to baking powder sales and offered chewing gum premiums to merchants who became his customers. By 1892, when the premiums had become more popular than the baking powder, Wrigley launched his first chewing gum products, LOTTA and VASSAR. A year later, he developed JUICY FRUIT, and shortly thereafter, WRIGLEY's SPEARMINT gum. Sugarless gum made its debut in the early 1950s, generally used sorbital as a sugar substitute. The first brand to be marketed was HARVEY's followed by TRIDENT and CAREFREE. In 1975, the Wm. Wrigley Jr. Company introduced the arrival of a new chewing gum product, FREEDENT, designed especially for denture wearers, which did not stick to most dentures as ordinary gums.

Merits of Medicated Chewing Gum[9-11]

- Does not require water to swallow. Hence it can be taken anywhere.
- Advantageous for patients having difficulty in swallowing.
- Excellent for acute medication.
- Counteracts dry mouth, prevents candidiasis and caries.
- Highly acceptable by children[10].
- Avoids first pass metabolism and thus increases the bioavailability of drugs.
- Fast onset of action due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation.
- Stomach does not suffer from direct contact with high concentrations of active principles, thus reducing the risk of intolerance of gastric mucosa[11].
- Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly. Duration of action is increased.
- Aspirin, Dimenhydrinate and Caffeine shows faster absorption through MCG than tablets.
- Stimulates flow of saliva in the mouth.
- Neutralizes plaque acids that form in the mouth after eating fermentable carbohydrates.
- Helps whiten teeth by reducing and preventing stains[11].

Demerits of Medicated Chewing Gum[12-16]

- Risk of over dosage with MCG compared with chewable tablets or lozenges that can be consumed in a considerable number and within much shorter period of time.
- Sorbitol present in MCG formulation may cause flatulence and diarrhoea.

- Additives in gum like flavouring agent, Cinnamon can cause ulcers in oral cavity and liqorice cause hypertension.
- Chlorhexidine oromucosal application is limited to short term use because of its unpleasant taste and staining properties to teeth and tongue.
- Prolong chewing on gum may result in pain in facial muscles.

Problems Occurred During Manufacturing of Chewing Gums[17]

- Generally the chewing gum will jam the grinding machine, sticking to blades, screens and other surfaces if the moisture level is not controlled.
- Another problem associated with the above methods is that the gum base is heated to a fluid mass to facilitate mixing of other ingredients. Such elevated. Temperatures can cause degradation of heat sensitive compounds, including active agents and flavors.
- In manufacturing of chewing gum, sometimes organic solvents are used to dissolve the active agents. It is difficult to eliminate these organic solvents from the final product and may present certain health risks if even trace amounts remain in the final dosage forms.
- Water can also be utilized in gum preparations, but it is difficult to eliminate at low temperature. Heating the gum mass to eliminate water is not advisable because the gum will then become stickier, which makes handling difficult and. Interferes with large-scale production.

Chewing Gum and Saliva[18]

Chewing gum stimulates one of the most powerful defense mechanisms in the body–saliva. Saliva is vital to good oral health. Saliva has three main protective (anti-caries) functions:

(1) Dilutes and washes away food debris;

(2) The bicarbonate neutralizes and buffers plaque acids;

(3) The calcium and phosphate ions contribute to remineralization of early dental caries lesions. Saliva also contains antibacterial agents.

Saliva alone is a powerful protector of the oral cavity and chewing gum is an efficient and pleasant way to increase saliva without drugs. Increasing saliva in the mouth is accomplished by the stimulation of flavors and the gustatory action of chewing.

Taste and Texture[19]

To succeed in the market, the chewing gum formulation must have a pleasant taste and texture. Most active substances have an unpleasant, bitter or metallic taste. Since the active substance will be released in the oral cavity and remain there for a longer period of time than in the case with ordinary delivery forms (usual chewing time is 10 to 20 minutes), unique expertise in taste definition, taste masking and taste modification are essential for the success of a medical chewing gum product. The release profile of the flavours and sweeteners, therefore, is usually designed to follow the release profile of the active substance.

Composition of Medicated Chewing Gum[20]

Chewing gum is a mixture of natural or synthetic gums and resins, sweetened with sugar, corn syrup, artificial sweeteners and may also contain coloring agents and flavor. The basic raw material for all CG is natural gum Chicle, obtained from the sapodilla tree. Chicle is very expensive and difficult to procure therefore other natural gum or synthetic materials like polyvinyl acetate and similar polymers can be used as gum base. Typically Chewing Gum comprises two parts viz.

Water Insoluble Gum Base Generally Comprises Elastomers, Resins, Fats, Oils, and Inorganic Fillers

Elastomers

Elastomer provides elasticity and controls gummy texture. Natural elastomer which is a natural rubber like Latex or Natural gum such as Jelutong, Lechi Caspi, Puerile, Chicle.

Plasticizers

Which are used to regulate cohesiveness of product and are divided into Natural and Synthetic.

Natural Plasticizers - Natural resin esters like Glycerol esters or partially hydrogenated resin, Polymerized glycerol esters, Glycerol esters of partially dimerized resin & Pentaerythritol esters of resin.

Synthetic Plasticizers - Terpene resins derived from α-pinene and/or d-limonene.

Fillers or Texturizers

Provide texture, improve chewability and provide reasonable size of the gum lump with low dose drug. Commonly used fillers are Magnesium and Calcium Carbonate, Ground Limestone, Magnesium and Aluminium Silicate, Clay, Alumina, Talc, Titanium Oxide & Mono/ Di/ Ttri Calcium Phosphate.

Water Soluble Portions Contain Bulk Sweeteners, High intensity Sweeteners, Flavouring agents, Softners, Emulsifiers, Colours and Antioxidants

Softners and Emulsifiers

These are added to the chewing gum in order to optimize the chewability and mouth feel of the gum. Softners include Glycerin, Lecithin, Tallow, Hydrogenated Tallow, Mono/ Di/ Tri-Glycerides, Fatty acids like Stearic acid, Palmitic acid, Oleic acid and Linoleic acid.

Colourants and Whiteners

It may include FD & C type dyes and lakes, fruit and vegetable extracts, Titanium Dioxide.

Sweeteners

These are of two types, Aqueous and Bulk. Aqueous Sweeteners can be used as softners to blend the ingredients and retain moisture. These include Sorbitol, Hydrogenated Starch Hydrolysates and Corn Syrups. Corn syrup keeps gum fresh and flexible.

Bulk Sweeteners include Sugar and Sugarless components. Sugar components include Saccharides like Sucrose, Dextrose, Maltose, Dextrin, Fructose and Galactose.

Sugarless components include sugar alcohols such as Sorbitol, Manitol, 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, Glycyrrhizin, Dihydrochalcones.

Bulking Agents

These are used if low calorie gum is desired. Examples of low calorie bulking agents include Polydextrose, Oligofructose, Inulin, Guargum hydrolysate, Indigestible Dextrin.

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 Component

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. MCG consists 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 colours or a thick layer of sugar or sugar alcohol. The optimal properties of active ingredient in MCG are shown below in table1[21].

MANUFACTURING PROCESSES

Different methods employed for the manufacturing of chewing gum can be broadly classified into three main classes namely.

1. Conventional/traditional Method (Melting).
2. Freezing, grinding and tabletting Method
3. Direct Compression Method.

Conventional / Traditional Method[22]

Components of gum base are softened or melted and placed in a kettle mixer to which sweeteners, syrups, active ingredients and other excipients are added at a definite time. The gum is then sent through a series of rollers that form into a thin, wide ribbon. During this process, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to enhance the flavour. In a carefully controlled room, the gum is cooled for up to 48 hours. This allows the gum to set properly. Finally the gum is cut to the desired size and cooled at a carefully controlled temperature and humidity.

Limitations[23]

1). Elevated temperature used in melting restricts the use of this method for thermolabile drugs.
2). Melting and mixing of highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult.
3). Lack of precise form, shape or weight of dosage form.
4). Technology not so easily adaptable to incorporate the stringent manufacturing conditions required for production of pharmaceutical products.
5). Such a chewing gum composition is difficult to form into chewing gum tablets because of their moisture content (2-8%). If attempted to grind and tablet such a composition would jam the grinding machine, stick to blades, screens adhere to .punches and would be difficult to compress.

Cooling, Grinding and Tabletting Method

This method has been developed with an attempt to lower the moisture content and alleviate the problems mentioned in conventional method.

Cooling and Grinding[22,24]

The CG 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 temperature required for cooling is determined in part by the composition of the CG and is easily determined empirically by observing the properties of the cooled chewing gum composition. Generally the temperatures of the refrigerated mixture are around -15ºC or lower. The refrigerated composition is then crushed or ground to obtain minute fragments of finely ground pieces of the composition. For more efficient cooling, the chewing gum composition can be pre cooled prior to cooling to the refrigeration temperature. Sometimes a mixture of chewing

gum composition, solid carbon dioxide and precipitated silica is ground in a mill grinder in a first grinding step. Additional solid carbon dioxide and silica are added to the ground composition, and the composition is further ground in a second grinding step. This two step grinding process advantageously keeps the chewing gum composition at a very low temperature. The presence of solid carbon dioxide also serves to enhance the efficiency of the grinding process.

An anti-caking agent such as precipitated silicon dioxide can be mixed with chewing gum composition and solid carbon dioxide prior to grinding. This helps to prevent agglomeration of the subsequently ground chewing gum particles.

To prevent the gum from sticking to the grinding apparatus, 2-8% by weight of grinding aid such as alkaline metal phosphate, an alkaline earth metal phosphate or malto dextrin can be incorporated. However practical use of these substances is limited because these substances are highly alkaline and hence would be incompatible with acidic ionisable therapeutic agents. This provides a chewing gum product that is light and gives a soft chewing impression when chewed.

Tabletting

Once the coolant has been removed from the powder, the powder can be mixed with other ingredients such as binders, lubricants, coating agents and sweeteners etc, all of which are compatible with the components of the chewing gum base in a suitable blender such as sigma mill or a high shear mixer. Alternatively a Fluidized Bed Reactor (FBR) can 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 antiadherents 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.

It requires equipment other than conventional tabletting equipment and requires careful monitoring of humidity during the tabletting process.

Use of Directly Compressible Chewing Gum Excipients[26]

The manufacturing process can be accelerated if a directly compressible chewing gum excipient is available. The limitations of melting & freezing can be overcome by the use of these. PHARMAGUM® is one such compactable gum system developed by SPI Pharma. Pharmagum is a mixture of polyol(s) and sugars with a chewing gum base. It is available as directly compressible powder, free flowing powder which can be compacted into a gum tablet using conventional tablet press thus enabling rapid and low cost development of a gum delivery system. It is manufactured under CGMP conditions and complies with Food Chemicals Codex specifications as well as with FDA, so they can be considered as "Generally regarded as safe" (GRAS).

Pharmagum® is available in three forms namely S, M and C. Pharmagum® M has 50% greater gum base compared to Pharmagum®S. Pharmagum®S consists primarily of gumbase and sorbitol. Pharmagum®M contains gumbase, mannitol & Isomalt. Release of nicotine from directly compressible nicotine gum formulations and from Nicorette® prepared by conventional methods has shown that use of Pharmagum in formulation showed a faster release rate. Formulations made with Pharmagum® M & S are similar to tablet in appearance. Use of Pharmagum S, M and C enables formulators to utilize a gum delivery system quickly & more cost effectively than by traditional methods.

Factors Affecting Release of Active Ingredient

Contact Time

The local or systemic effect is dependent on time of contact of MCG in oral cavity. In clinical trial chewing time of 30 minutes was considered close to ordinary use.

Physicochemical Properties of Active Ingredient

Physicochemical properties of active ingredient plays very important role in release of drug from MCG. 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.

Inter Individual Variability

The chewing frequency and chewing intensity which affect the drug release from MCG 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[25].

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.

Some Important Formulation Aspect

- Increased amount of softeners and emulsifiers in gum base fasten release whereas hard gum may retard[6,27].
- Cyclodextrin complexation or solubilisation technique increases aqueous solubility of drugs that are poorly water soluble[28,29].
- A solid system of lipophilic active ingredients bound to the cation exchange resin permits a sustained drug delivery system.
- Microencapsulation or agglomerations are the methods to modify and control the release of active ingredient[30,31].

Scientific Rationale for *in vitro* Drug Release Determination

Currently, the USP monograph for nicotine polacrilex gums does not contain a drug release test. Recently, much effort has been spent describing the *in vitro* release kinetics of specialdosage forms, including medicated chewing gums [32,33]. Due to the complexity of the release mechanisms involved, researchers proposed minimal requirements for experimental settings with respect to the site of release and absorption. Besides the product quality tests, the drug release tests can provide useful information about the characteristics of the product, a main tool required primarily during product screening and development, and to some extent the product performance *in vivo*[34].

Drug Release Testing Methodology

Ph. Eur. has adopted an apparatus to determine the release rate from chewing gum formulations. The basic principle is a simple masticatory movement employed to simulate the chewing action on a piece of gum placed in a small chewing chamber containing a known volume of buffer solution at a given temperature[35]. The drug release rate is influenced by the chewing rate and angle, which provides the necessary shear force to expose new gum surfaces and is a requisite for further drug release. The transition from the inactive gum to the active dosage form is influenced by-

- Mechanical forces
- Temperature
- Wettability and water permeation.

As a general rule under sink conditions, the rate at which the drug is released is directly proportional to the chewing frequency and aqueous solubility of

drug substance and is indirectly proportional to the mass of the gum base.

Apparatus I. Chewing Gum Apparatus, Compendial-Ph. Eur

The chewing apparatus for medicated chewing gum was adopted by Ph. Eur. in 2000[36]. Figure 1 shows the construction of the apparatus. The chewing apparatus comprises 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 the gum stays in the right place between chews. The working procedure of this chewing apparatus is described in Ph. Eur[36,37] several studies have been carried out using the Ph. Eur. apparatus, and the results indicate the methodology is rugged and reproducible.

Apparatus II. Alternative Chewing Gum Apparatus, Noncompendial-Wennergren

One of the noncompendial apparatus commercially available was designed by Wennergren[38]. 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*[38,39].

Characterization of Medicated Chewing Gum

Physical Evaluation of Medicated Chewing Gum

All Medicated Chewing Gum formulations were visually inspected; various physical properties of gum base were studied on basis of their solubility studies, relative humidity, color and moisture absorption[40]. Following parameters were studied:

Weight Variation

Weight variation of all formulation was done by method described in experimental work. Weight of ten chewing gum was taken in one batch, then average weight is calculated from that standard deviation is calculated.

Physical Evaluation of Medicated Chewing Gum

All formulation prepared by above procedure were physically evaluated for following parameters, Appearance, Color, Stickness, Hardness, Weight variation and Plasticity.

Hardness/Plasticity

Due to absence of any reported method, it was decided to use the Monsanto type hardness tester for determination of hardness of all MCG formulations.

Stickiness

MCG placed on plane surface, 250gm cylindrical hammer collide on to it for period of ten minutes .The frequency of hammering was about 30 per minute. After 10 minutes, sticking of mass to hammered surface was observed and reported.

Chew Out Study

Chew out study protocol was formulated based on input from Fertin Pharma Pvt. Ltd. Denmark, one of the world largest manufactures of medicated chewing

gum. Denmark. Initial phase of chew out study included various parameters like texture, elasticity, smoothness, crankiness, softness, cheesiness, sweetness, cooling effect, hardness, juiciness & lubricating feel[41].

In vitro Drug Release Based On

- Change in twisting angle of upper mastication jaw from ($5^0 – 30^0$).
- Change in distance b/w upper & lower masticating Jaw from (1-2 mm).
- Change in chewing frequency of lower masticating Jaw from (20 strokes/minute to 120 strokes/ minute).
- Change in temperature from (30^0C – 40 ^{0}C).

The chewing gum was inserted between the pistons on to the lower chewing surface. The chewing procedure consisted of up and down stroke of lower masticating surface combined with twisting movement of upper masticating surface, thereby masticating the chewing gum and consequently agitating the test medium. The optimized chewing frequency employed in the study was 60±2 strokes per minute. At predominant time interval aliquot of the artificial saliva, were removed and assayed for drug content by UV spectrophotometric analysis. The release medium was replaced with fresh artificial saliva after each sample was taken[42,43].

Stability Study of Synthetic Gum Base

Store 10 gm of synthetic gum base in bottle at 30°C ± 2°C/65% RH ± 5% RH (According to WHO guideline for stability) for a period of six months. After six months, examine the gum for signs of ageing and physical deformalities[44].

Therapeutic Uses of MCG

The use of sugar free gum to counteract dental caries by stimulation of saliva secretion has led to a more widespread use and acceptance of gums. It has been proved that chewing nonmedicated chewing gums increases plaque pH stimulates saliva flow and decrease decay[45,46]. MCGs containing Chlorhexidine for treatment of gingivitis and plaque has been available. The use of MCG in the treatment of oral infections has also been reported[47]. The active ingredient is released from the MCG and sufficient concentration is achieved in the oral cavity to prevent or treat local conditions of oral cavity. MCG is also useful delivery system for agents intended for systemic delivery. Drug that is released from gum within oral cavity can be absorbed via buccal mucosa. The MCGs can also be used as an alternative tool to buccal and sublingual tablets which are intended to act systemically because active ingredient is released more uniformly and cover greater area of absorption in oral cavity. MCGs for systemic effect in conditions like vitamin C deficiency[48], pain & fever[49], alertness[50], motion sickness[51], smoking cessation[52], as well as for local effect in the conditions like plaque acid neutralization[53], fresh breath[46], disinfection[54], anti-caries[55], antiplaque[56], antifungal[57], antibacterial[58] are available.

SAFETY ASPECTS

Difference commercial chewing gums have been shown to adhere to different degree to dentures, fillers and crowns. Over chewing causes painful jaw muscles. Chewing gum appears to offer a smaller risk of overdosing by mistake or misuse than flavored chewable tablets. Medicated chewing gums should, like other medicaments, be kept out of reach of children and it would be wise to advice people prone to allergic responses to check the flavoring and sweetening agents included in the chewing gum formulations[46].

FUTURE TRENDS

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.

Chewable Birth Control Will Be Available Soon

Women will have another birth control option next year - chewable pills. Next spring, Warner Chilcott Inc. will start marketing its spearmint-flavored Ovcon 35, a chewable birth control drug approved by the Food and Drug Administration[59,60].

APPLICATIONS

Dental Caries[61,62]

Prevention and cure of oral disease are obvious targets for chewing gum formulations. It can control the release rate of active substances providing a prolonged local effect. It also reelevates 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.

Systemic Therapy

Chewing gum as a drug delivery system is beneficial to a number of indications, some of which are discussed below:

(a) Pain-Treatment of minor pains, headache, muscular aches can be successfully accomplished.

(b) Smoking Cessation-Chewing gum formulation containing nicotine, lobeline and silver acetate has been clinically tested as aids to smoking cessation.

Nicotine is a natural alkaloid occurring in the leaves of tobacco plant. It is a.therapeutic agent intended to help smokers break the psychological habit of smoking by reducing the nicotine withdrawal symptoms normally experienced when smoking is stopped. Thus the patient can control the drug intake to match his needs. Increasing the pH of the medium in which it is dissolved can enhance nicotine absorption.

(c) 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 guarantee stimulate lipolysis and have a thermogenic effect (increased energy expenditure) and reduce feeling of hunger.

(d) Other indications- xerostomia, Allergy, Motion sickness, Acidity, Cold and Cough, Diabetes, Anxiety etc are all indications for which chewing gum as drug delivery system could be beneficial.

CONCLUSION

Chewing gum is an excellent drug delivery system for self medication, as it is convenient and can be administered discretely without water. It offers several advantages compared to chewable tablets, lozenges and other related formulations. Hence in forth coming years it will become a much more common and popular drug delivery system. The potential of MCG for buccal delivery, fast onset of action and the opportunity for product-line extension makes it an attractive delivery form. Reformulation of an existing product is required for patent protection, additional patient benefits and conservation of revenues.

Chewing gum for smoking cessation will also remain despite the fact that nicotine patches have grown in popularity lately. This is because the very act of chewing gum also provides a physical substitute for the smoking

habit and thereby increases the possibility of successful quitting.

REFERENCES

1. Lee WW. Chewing gum as a delivery vehicle for pharmaceutical and nutraceutical substances. *Pharm Tech Online* 2001; 2: 1-11.
2. Edgar W, Geddes D. Chewing gum and dental health - A review. *Br Dent J* 1990; 168:173-177.
3. Conway B. Chewing gum as a drug delivery system. The Drug Delivery Companies Report Autumn/Winter; 2003: 33-35.
4. Patel PV, Desai TR, Dedakiya AS, Bandhiya HM. Medicated chewing gum: A review. *IJUPLS* 2011; 1(1): 111-128.
5. Biswal PK and Kumar A. An Updated Review on Medicated Chewing Gum. *IJAPBC* 2013; 2(2): 351-59.
6. Jacobsen J, Christrup LL, Jensen NH. Medicated chewing gum. *Am J Drug Deliv* 2004; 2: 75-88.
7. Cloys L, Christen A, Christen J. The development & history of chewing gum. *Bulletin of the History of Dentistry* 1992; 40: 57-65.
8. Owens, L. Gumtech to Produce Aspergum and Chooz for Schering-Plough Health Care Products. Business Wire 1998.
9. Khanekar P, Mhatre S, Momin M. Medicated Chewing Gum: *A Potential Drug Delivery System. IJPFR* 2012; 2(4): 64-75.
10. Morjaria Y, Irwin WJ, Barnett PX, Chanvv RS, Conway BR. *In vitro* Release of nicotine from chewing gum formulations. *Dissolution Technologies* 2004; 12-15.
11. Naik H, Gupta S. Medicated Chewing Gums- Updated Review. *IJPRD* 2011; 2 (8): 66-76.
12. Jacobsen J, Christrup LL, Jensen NH. Medicated chewing gum: Pros and Cons. *Am J Drug Deliv* 2004; 2 (2): 75-88.
13. Goldberg LD, Ditchek NT. Chewing gum diarrhea, *Am J Dig Dis* 1978; 23(6): 568-62.
14. Addy M, Roberts WR. Comparison of the bis biguanide antiseptics alexidine and chlorhexidine II. Clinical and *in vitro* staining properties. *J Clin. Periodontol* 1981; 8(3):220-30.
15. Munksgaard EC, Nolte J, Kristensen K. Adherence of chewing gum to dental restorative materials. *Am J Dent* 1995; 8(3): 137-139.
16. Weil AT. Coca leaf as a therapeutic agent. *Am J Drug Alcohol Abuse* 1978; 5(1): 75-86.
17. Martin R. Chewing gum. *BMJ* 1985; 290:1232-1236.
18. Edgar WM, Dawes C, O'Mullane D. Saliva and oral health: An essential overview for the health professional. 3rd ed., British Dental Association Publication, London; 2004.
19. Sharma NS, Arjariya PA, Jat RC, Fiza F, Sharma G, Rathore SA, Tiwari R. An overview on medicated chewing gum and its applications. *IJPFR* 2013; 4(3); 3158-73.
20. Zyck DJ, Greenberg MJ, Barkla DG, Marske SW, Schnell PG, Mazzone P.. Method of making coated chewing gum products containing various antacids. *US Patent* 2003; 6: 635-45.
21. Kahtani D. Chewing gum: trick or treat. *SDJ* 1999; 11(1): 27-34.
22. Athanikar NK, Gubler SA. Process for manufacturing a pharmaceutical chewing gum. *US Patent* 2001; 6: 322-828.
23. Subraman CR, Kirshnayya B. Tableted chewing gum composition and method of preparation. *US Patent* 1988; 4: 753-805.

24. Keizo M, Yokomichi FY. Process for the preparation of chewing gum. *US Patent* 1976; 4:321.
25. European Pharmacopoeia. Strasbourg: European directorate for the quality of medicines. Chewing gums: Medicated. 5th ed. 2004: 260, 601.
26. Shah KR, Mehta TA. Medicated chewing gum- A mobile oral drug delivery system. *Int. J. Pharm Tech Res.* 2014; 6(1): 35-48 .
27. Lieberman HA, Lachman L, Schwartz JB., Pharmaceutical Dosage Forms: Tablets. II ed., Lippincott Willians & Wilkins, New York; 1990, 1: 367-415.
28. Barabolak R, Hoerman K, Kroll N. Chewing gum profiles. US Population. *Community Dent Oral Epidemiol* 1999; 19: 125-26.
29. Jacobsen J, Bjerregaard S, Pedersen M. Cyclodextrin inclusion complexes of antimycotics intended to act in the oral cavity- drug super saturation, toxicity on TR146 cells and release from a delivery system. *Eur J Pharm Biopharm* 1999; 48 (3): 217-24.
30. Gudas VV, Reed MA, Schnell PG, Tyrpin HT, Russell MP, Witkewitz DL. Method of controlling release of caffeine in chewing gum. *US Patent* 1998; 6: 165, 516.
31. Yang RK. Encapsulation composition for use with chewing gum and edible products. *US Patent* 1988; 4: 740,376.
32. Siewert M, Dressman JB, Brown C, Shah VP. AAPS guidelines for dissolution *in vitro* release testing of novel special dosage forms. *Dissolution Technol* 2003; 2: 6–15.
33. Yang X, Wang G, Zhang X. Release kinetics of catechins from chewing gum. *J Pharm Sci* 2004; 93(2): 293–99.
34. Shah VP, Derdzinski K, Ewing G. A performance test for topical and transdermal dosage forms. *Pharm Forum* 2006; 32(5): 1586–89.
35. 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): 405–11.
36. 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.
37. 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; 3116–17.
38. 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.
39. 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): 405–11.
40. Vries ME, Bodde HE, Verhoef JC, Junginger HE, *Crit Rev Ther Drug Carr Sys*, 1991.
41. Mochizuki K, Yokomichi F. Process for preparation of chewing gum. *US Patent 1976;* 000321.
42. Subraman R, John M, Jack E, Edward J, Carlos D, Gitchell Joe. *Medicated chewing gum delivery system for nicotine*, *US Patent* 2002; 6344222.
43. Amir.H; Shojaei; Bret.Berner; Xiaoling.Li. *Pharma Res* 1998; 15(8): 1182-88.
44. Hughes, Lyn, Buccal, Dissolution of active substances 2003; US 2003; 0087457.

45. Lieberman HA, Lachman L, Schwartz JB, II edition, Pharmaceutical Dosage Forms, Tablets. 2nd ed., 1990, 1, 367-415.
46. Imfeld T. Chewing gum-facts and fiction: a review of gum-chewing and oral health. *Crit Rev Oral Biol Med* 1999; 10(3): 405-19.
47. Pedersen M, Rassing MR. Miconazole chewing gum as a drug delivery system. *Drug Dev Ind Pharm* 1991; 17(3): 411-20.
48. Christrup LL, Rasmussen SN, Rassing MR.: Chewing gum as a drug delivery system. Farmaci. Sci Ed 1988; 16: 44-47.
49. Woodford DW, Lesko LJ. Relative bioavailability of aspirin gum. *J Pharm Sci* 1981; 70(12): 1341-43.
50. Tyrpin HT, Russell MP, Witkewitz DL, Johnson SS, Ream RL, Corriveau CL. Caffeine coated chewing gum product and process of making. US Patent: 6, 444, 241; 2002.
51. Seibel K, Schaffler K, Reitmeir P, Golly I.: A randomised, placebo-controlled study comparing two formulations of dimenhydrinate with respect to efficacy in motion sickness and sedation. *Arzneimittel forschung* 2002; 52(7): 529-36.
52. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2001; (3): 146.
53. Finn SB, Jamison HC. The effect of a dicalcium phosphate chewing gum on caries incidence in children: 30-month results. *J Am Dent Assoc* 1967; 74(5): 987-95.
54. Smith AJ, Moran J, Dangler LV, Leight RS, Addy M. The efficacy of an anti-gingivitis chewing gum. *J Clin Periodontol 1996*; 23(1): 19-23.
55. Oliveby A, Ekstrand J, Lagerlof F. Effect of salivary flow rate on salivary fluoride clearance after use of a fluoride-containing chewing gum. *Caries Res* 1987; 21(5): 393-401.
56. Etemadzadeh H. Plaque-growth inhibiting effect of chewing gum containing urea hydrogen peroxide. *J Clin Periodontol* 1991**;** 18(5): 337-40.
57. Pedersen M, Rassing MR. Miconazole and miconazole nitrate chewing gum as drug delivery system– a practical application of solid dispersion technique. *Drug Dev Ind Pharm 1990*; 16(1): 55-74.
58. Wertalik F, Bonorden R. Salivary levels of antibiotics from use of neomycin-gramicidin chewing troches. *J Pharm Sci* 1968; 57(3): 530-31.
59. Smith A. Health Note, the Post-Standard (Syracuse, NY) Nov. 24 2003.
60. Chilcott W. Contraceptive Technology Update on Feb 1 2004.
61. 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; 70:1474-78.
62. Barabolak R, Hoerman K, Kroll N, Record D. Chewing gum Profiles in U.S. Population. *Commun. Dent. Oral Epidemiol* 1991; 19: 125.
63. http://www.patentgenius.com/patent.html.
64. Ezhumalai K, Ilavarasan P, Rajalakshmi A N, Sathiyaraj U., Murali Mugundhan R. Medicated chewing gum- A novel drug delivery technique for systemic and targeted drug delivery. *IJPT* 2011, 3 (1): 725-744.

Table 1. Optimal properties of drug

Physicochemical Properties of Drug	High Salivary Solubility
	pH independent solubility
	Tasteless
Patient Related Factors	Non-toxic to oromucosa and salivary ducts
	Non-carcinogenic
	Should not cause tooth decay
	Should not cause oromucosa and teeth staining
	Should not affect salivary flow rate

Table 2. Us patents on medicated chewing gum[63]

Match	Document	Document Title
1.	6537525	Medicated Chewing-Gum
2.	5879699	Medication Chewing Dentifrices
3.	6344222	Medicated chewing gum delivery system for nicotine
4.	1396641	Medicated chewing-gum
5.	5866179	Medicated Chewing Gum and a Process for Preparation Thereof

Table 3. Medicated chewing gum sold worldwide[64]

Trade Mark	Active Substance	Aim	Commercially Available
Aspergum	Aspirin	Pain relief	North America
Nicorette	Nicotine	Smoking cessation	Worldwide
Nicotinelle	Nicotine	Smoking cessation	Western Europe, Australia, New Zealand
Trawell	Dimenhydrinate	Travel illness	Italy, Switzerland,
Superpep	Dimenhydrinate	Travel illness	Germany, Switzerland
Chooz	Calcium carbonate	Stomach acid neutralization	USA
Endekay Vitamin C	Vitamin C	General health	Middle East, United Kingdom
Source Vitamin C	Vitamin C	General health	Australia
Brain	DHA & CCE	Enhanced brain activity	Japan
Stay Alert	Caffeine	Alertness	USA
Cafe Coffee	Caffeine	Alertness	Japan
Buzz Gum	Guarana	Alertness	United Kingdom
Go Gum	Guarana	Alertness	Australia
Chroma Slim	CR	Diet	USA
Fluorette	Fluoride	Cariostatic	USA
Vitaflo CHX	Chlorhexidine	Preventing Tooth decay	USA
Travvel	Dimenhydrinate	Motion sickness	USA, Australia

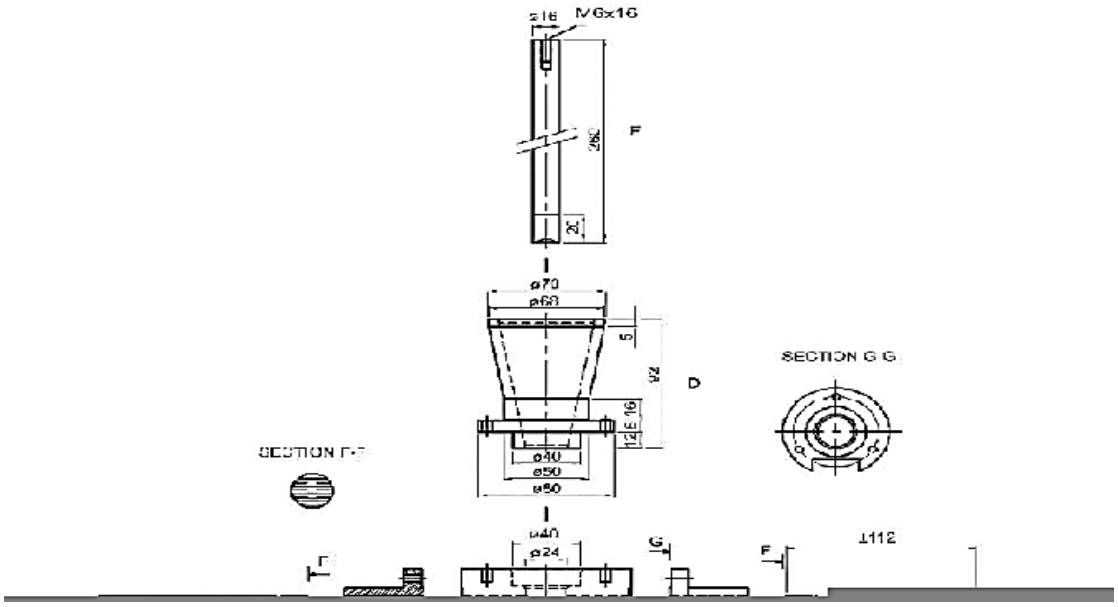

Figure 1. Apparatus for the determination of drug release from medicated chewing gum[35]

A- Horizontal Piston, B- Chewing Chamber, C- Vertical Piston, D- Guide, E- Fennel

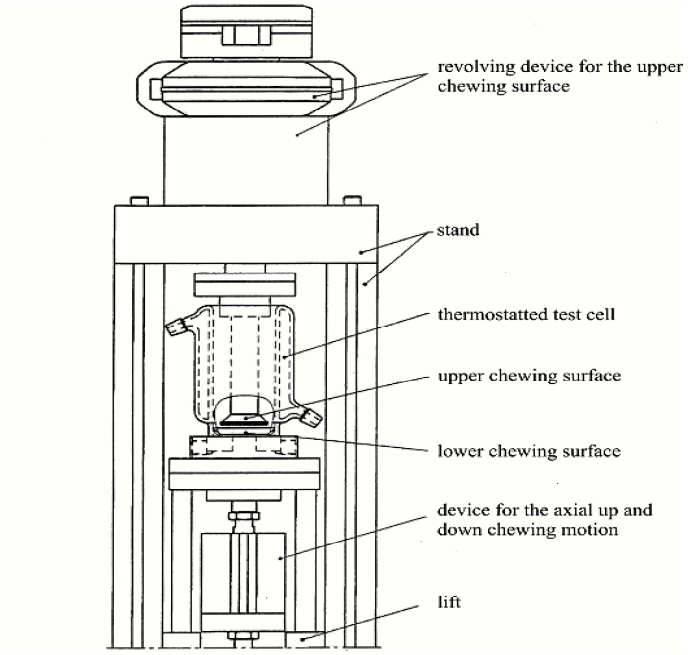

Figure 2. Single-module chewing apparatus from Wennergren[39]