Medicated Chewing Gum: A Novel Drug Delivery System

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ABSTRACT

In the recent years scientific and technological advancements have been made in the research and development of oral drug delivery systems. The reasons that the oral route achieved such popularity may be primarily due to its ease of administration. Chewing gum is one of the very popular oral confectionary products. It is a potentially useful means of administering drugs either locally or systematically via the oral cavity. The medicated chewing gum has through the recent years gained increasing acceptance as a drug delivery system. Chewing gum known as gum base (insoluble gum base resin) contains elastomers, emulsifiers, fillers, waxes, antioxidants, softeners, sweeteners, food colorings, flavoring agents, and in case of medical chewing gum, active substances. It offers various advantages over conventional drug delivery systems. Unlike chewable tablets, medicated chewing gums are not supposed to be swallowed and may be removed from the site of application without resorting to invasive means. Moreover medicated chewing gums require the active and continuous masticatory activities for activation and continuation of drug release. An In-vitro apparatus was specially designed and constructed for release testing of medicated chewing gums. Medicated chewing gums are excellent mobile drug delivery systems for self-medication as it is convenient and can be administered discretely without water.

Keywords: Oral drug delivery, chewing gum, patient compliance, mobile drug delivery system, mouth diseases.

INTRODUCTION

Now-a-days most of the drugs are formulated into various solid dosage forms including the most popular ones like Tablets, capsules etc. and semi-solid dosage forms such as creams, ointments, gels etc. Chewing gum is being used worldwide since ancient times after man experienced the pleasure of chewing a variety of substance. It can be used as a convenient modified release drug delivery system. Chewing gum has been used for centuries to clean the mouth and freshen the breath (Jacobsen et al., 2004). One thousand years ago the Mayan Indians chewed the tree resin (Chicle) from the sapodilla tree to clean their teeth and freshen their breath.
The first commercial chewing gum “State of Maine pure spruce gum” was marketed in 1948 in the U.S.A. The first patent was filed in 1869 (Conway et al., 2003). The gum was intended as dentifrices but it has never been marketed. The first Medicated chewing gum “Aspergum” was launched in 1928. This chewing gum is still available and contains acetylsalicylic acid. Another commercially available medicated chewing gum is dimenhydrinate– containing chewing gum for motion sickness. However, chewing gum did not gain acceptance as a reliable drug delivery system until 1978, when nicotine chewing gum became available. In 1991, Chewing Gum was approved as a term for pharmaceutical dosage form by the commission of European Council. Moreover, there is need of reformulation of existing drug into New Drug Delivery Systems (NDDS) to extend or protect product patents thereby delaying, reducing or avoiding generic erosion at patent expiry.

Today improved technology and extended know how have made it possible to develop and manufacture medicated chewing gum with pre-defined properties. MCG is one of them. Owing to new social and behavioral trends in the past modern age, such as the growing consumer health awareness and increasing attention to safety products, chewing gum has been known for a new image and potential. Chewing gum today is gaining consideration as a vehicle or a drug delivery system to administer active principles that can improve health and nutrition.

Definition
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.

Why Use Chewing Gum As A Drug Delivery System?
Chewing gum provides new competitive advantages over conventional drug delivery system:
- Fast onset of action and high bioavailability
- Pleasant taste
- Higher compliance (easy and discreet administration without water)
- Ready for use
- High acceptance by children (Lamb et al., 1993)

Fewer side effects
Low dosage gives high efficacy as hepatic first pass metabolism is avoided. The controlled release rate also reduces the risk of side effects, as high plasma peak concentrations are avoided.

Systemic effect
Active substances can be absorbed through the buccal mucosa and/or through the GI tract when saliva is swallowed. Once the active substance is present in the blood, systemic affect can be obtained (Lamb et al., 1993).

Fast onset of action
Fast onset of systemic effect is seen for active substances absorbed through the buccal mucosa, as the active substances pass by the jugular veins directly to the systemic circulation.

Local effect
Chewing gum is an obvious drug delivery system for local treatment of diseases in the oral cavity and in the throat, as sustaining the release of active substances may deliberately prolong exposure.

Effect on dry mouth (xerostomia)
Dry mouth is a side effect of many types of medicament (e.g. antidepressants) and it is also part of the symptomatology of several diseases (e.g. sjogren’s syndrome-an autoimmune disorder characterized by lymphocytic infiltration of the salivary and lacrimal glands) (Sjögren et al., 2002). Chewing gum stimulates salivary secretion thereby decreasing dryness in the mouth.

Anatomy And Physiology Of The Oral Mucosa
(Rhodus et al., 1991; Rathbone et al., 1996; Squier et al., 1996)

The oral mucosa can be subdivided into two general regions, the outer vestibule and oral cavity. Microscopically the oral mucosa consists of three main layers:
- The oral epithelium;
- The lamina propria;
- The sub mucosa.
The oral epithelium

The epithelium of mouth consists of stratified, squamous epithelium, which can be keratinized or non-keratinized. Keratinized epithelium is dehydrated, mechanically tough and chemically resistant. It is found in oral cavity subject to mechanical stress such as mucosa of gingival and hard palate (roof of mouth). Non-keratinized epithelium is relatively flexible and is found in areas such as the soft palate, the floor of mouth, the lips and the cheeks. The epithelium of the oral cavity is supported by the basement membrane, which separates the epithelium from the underlying connective tissue layer (the lamina propria). Oral epithelium broadly similar to stratified squamous epithelia found elsewhere in the body, for example the skin, in that cells are produce by mitosis in the basal layer of the epithelium and these proliferating cells push existing cells towards the surface. The phase of this process are represented in four morphological layers:

- Basal layer;
- Prickle cell layer;
- Intermediate layer;
- Superficial layer: Structural changes that occur during this upward transit, from basal to superficial layer, include the cells becoming
- Larger in size;
- More flattened: the cuboidal cells of the basal layer are more polygonal shape in prickle cell layer, become slightly flattened in the intermediate layer and more flattened in the superficial layer.
- More proteinaceous: increasing amount of protein are found in the cells (for both keratinized and non-keratinized epithelium) toward the epithelial surface, in the form of protein monofilaments;
- Less viable: there is an absence of organelles in superficial cells, indicates that these cells are no longer viable.

The lamina propria

The lamina propria contains a sheet of connective tissue containing collagen elastic fiber and cellular components in hydrated ground substance. It also carries blood capillaries and nerve fibers that serves the mucosa. It is through the blood vessels in the lamina propria that drug moieties can gain the entry in systemic circulation.

The salivary glands

Saliva is a hypotonic, watery secretion containing variable amount of mucus, enzyme, antibodies and inorganic ions. The surface of mucus membrane is constantly washed.
by a stream of about 0.5 to 2L of saliva daily produce in the salivary gland the chief secretion is supplied by three pairs of glands, the parotid, the sub maxillary, and the sublingual glands.

The presence of saliva in mouth is important for two main reasons:
- Drug permeation across moist membranes occurs much more readily than across non mucous membranes; compared to drug absorption across the GI track and skin,
- Drug are commonly administered to mouth in clinical setting in solid dosage form. The drug must therefore first dissolve in saliva before it can be absorbed across the oral mucosa; that is the drug cannot be absorbed directly from the tablet.

**MERITS OF THE MCG (PHARMACOLOGICAL)**

The active component absorbed at the oral level avoids the enterohepatic circulation and the associated metabolism (Conway et al., 2003). The product is rapidly released from the gum after a short period of mastication; some absorption takes place directly through the oral mucosa depending upon the active ingredient. Importantly, not being swallowed, the gum does not reach the stomach, which means that the GIT suffers less from the excipients and the iatrogenic effects. (observed with some galenical form) (Conway et al., 2003).

Moreover the stomach does not suffer from direct contact with high concentration of the active principle, thus reducing the risk of intolerance of the gastric mucosa (Conway et al., 2003). The fraction of the product reaching the stomach is conveyed by the saliva and delivered continuously and regularly.

- Others:
- Relaxes and eases tension.
- Freshens the breath.
- Decreases ear discomfort when flying.
- Satisfies snack craving.
- Cleans teeth after meals.
- It’s fun.

**DEMERITS OF THE MCG (PHARMACOLOGICAL)**

If you chew gum on a regular basis, please consider the following:

Chewing gum causes unnecessary wear and tear of the cartilage that acts as a shock absorber in the jaw joints. Once damaged this area can create pain and discomfort for lifetime (Weil et al., 1978).

You use eight different facial muscles to chew. Unnecessary chewing can create chronic tightness in 2 of these muscles located close to the temples. This can put pressure on the nerves contributing to chronic intermittent headaches (Weil et al., 1978).

You have six salivary glands located throughout mouth that are stimulated to produce and release saliva whenever you chew. Producing a steady stream of saliva for chewing gum is a waste of energy and resources that otherwise could be used for essential metabolic activities.

Most of the chewing gums are sweetened with aspartame: long use causes cancer, diabetes, neurological disorder and birth defects.

Flavor color etc. may cause allergic reaction.

Long term frequent use causes increase release of mercury vapor from dental amalgam filling. However medicated chewing gums do not normally require extensive chewing or consumption to a great extent.

**MERITS OF THE MCG (OVER OTHER DOSAGE FORMS)**

- Dose not requires water to swallow. Hence can be taken anywhere (Morjaria et al., 2004).
- Advantageous for patients having difficulty in swallowing.
- Excellent for acute medication (Conway et al., 2003).
- Counteracts dry mouth, prevents candidiasis and caries.
- Highly acceptable by children (Morjaria et al., 2004).
- Avooids First Pass Metabolism and thus increases the bioavailability of drugs (Conway et al., 2003).
- Fast onset due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation (Conway et al., 2003).
- Gum does not reach the stomach. Hence G.I.T. suffers less from the effects of excipients.
- Stomach does not suffer from direct contact with high concentrations of active principles, thus reducing the risk of intolerance of gastric mucosa (Conway et al., 2003).
- 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.

**DEMERITS OF THE MCG (OVER OTHER DOSAGE FORMS)**

- 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 (Jacobsen et al., 2004).
- Sorbitol present in MCG formulation may cause flatulence, diarrhoea.
- Additives in gum like flavouring agent, Cinnamon can cause Ulcers in oral cavity and Licorice cause Hypertension.
- Chlorhexidine oromucosal application is limited to short term use because of its unpleasant taste and staining properties to teeth and tongue.
Chewing gum have been shown to adhere to different degrees to enamel dentures and fillers.

Prolong chewing on gum may result in pain in facial muscles and earache in children.

**Mechanism of Drug Transport** (Rathbone et al., 1996; Squier et al., 1996)

During the chewing process, most of the medications contained within the drug product are released into the saliva and are either absorbed through buccal mucosa or swallowed or absorbed through GIT.

Major pathways of drug transport across buccal mucosa follow simple fickian diffusion. Passive diffusion occurs in accordance without the pH partition theory. Some carrier mediated transport also observed. Equation for drug flux is:

\[ J = \frac{DKp}{\Delta C_e} \]

Where,
- \( J \) = drug flux
- \( D \) = diffusivity
- \( Kp \) = partition coefficient
- \( \Delta C_e \) = concentration gradient
- \( h \) = diffusional path length

It shows (h) that the flux may be increased by decreasing the diffusional resistance of the membrane by making it more fluid, increasing the solubility of the drug in the saliva immediately adjacent to the epithelium or enhancing the lipophilicity through pro-drug modification. Because of the barrier properties of the tight buccal mucosa, the rate limiting step is the movement of the drug molecules across the epithelium.

Two pathways of permeation across the buccal mucosa are transcellular and paracellular. Permeability coefficient typically ranges from \( 1 \times 10^{-5} \) to \( 2 \times 10^{-10} \) cm/s. The pathway of drug transport across oral mucosa may be studied using:

- Microscopic techniques using fluorescent dyes
- Autoradiography and
- Confocal laser scanning microscopic procedures.

**Factors Affecting Mucosal Drug Delivery** (Rathbone et al., 1996; Rider et al., 1992; Rindum et al., 1993; Rowe et al., 2003)

**Membrane factor**

Regional difference in both permeability and thickness affect both the rate and the extent of drug reaching the systemic circulation. Keratinisation and composition also affect systemic mucosal delivery. Additional factors such as absorptive membrane thickness, blood supply, blood/lymph drainage, cell renewal rate, and enzyme content will also govern the rate and extent of drug absorption.

**Environmental factor**

**Saliva**

It is composed of water 99% and pH of 6.5 to 7.5 depending on the flow rate and location. And increase in the salivary flow rate leads to the secretion of watery saliva. Stimulated saliva secretion affects the film thickness and aids in the easy migration of the test compounds. Salivary pH is also important for the passive diffusion of the unionized drug.

**Salivary glands**

Drug delivery system should be placed either over a duct or adjacent to the salivary duct because it may result in excessive washout of drug or rapid dissolution of the system making it difficult to achieve high local drug concentration.

**Chewing time and chewing rate**

Time should be around 20 to 30 min. the rate of chewing also affects the drug release. The average chewing rate is about 60 chews/min.

**Aqueous solubility of the drug**

Release of the water soluble drug (solubility > 1:10) about 75% or more during 5 mins of chewing and 90% or more during 15 mins of chewing at a rate of 60 chews per min. Drug with the aqueous solubility between 1:10 and 1:300 demonstrate upto 60% release during ten minutes of chewing and between 60% and 90% when the gum is chewed for 15 mins. The release of the drug which is only slightly water soluble can only be expected to be small i.e. less than 5% even if the gum is chewed for 30 mins.

**% of drug**

The release of fluoride from a chewing gum (1g) containing 0.1 mg and 1mg NaF (aqueous solubility 1:25) has been compared. The percentage of the drug retained in the gum for two formulations are similar. Indeed the percentage released for 0.1 mg and 1mg fluoride are very similar after 8 mins. at 75% and 80% respectively.

**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 (European Pharmacopoeia. Strasbourg, 2004).

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 (European Pharmacopoeia. Strasbourg, 2004).

CONCEPT OF FORMULATION DEVELOPMENT

(Abelson et al., 1990; Chistrup et al., 1990; Pedersen et al., 1990; Rindum et al., 1993)

A piece of chewing gum usually consists of gum core, which may or may not be coated.

The core is composed of an insoluble gum base resin, elastomers, emulsifiers, fillers, waxes, antioxidants and softeners, sweeteners, flavoring agents, and in case of medical chewing gum, active substances. The water content of chewing gum is very low and no preservative is needed. The gum base determines the basic characteristics of the product, e.g. the texture: is soft or hard to chew? Does it crumble? Does it stick to the teeth? The gum base also determines the release profile of active substances and changing the gum base composition may therefore change the release profile.

Increased Release

Many drugs used today are lipophilic in nature; these are partially soluble in the gum bases. Consequently they exhibit a slow release rate from the chewing gum and only small percentage of the total amount of the drug incorporated is released even after prolonged chewing time. For such drugs following correction is required:

Addition of a buffering agent

Folic acid is beneficial for gingivitis. Three different chewing gum formulations of slightly water soluble B vitamin, folic acid (5mg/piece)
- Contain NaHCO₃ (11mg/piece)
- Contain both NaHCO₃ and Na₂CO₃ (5.5mg and 6.9mg/piece)
- No buffering agent

Both in vivo and in vitro activity was carried out and it was found that the release of drug is higher, in a and b as compared to c and release profile from a and b formulation is satisfactory for its intended purpose.

Coating with and hydrophilic gum

Nystatin, slightly water soluble finely divided particles coated with Arabic gum. When uncoated the drug was incorporated into chewing gum at 4% release observed and this amount increased to 24% when coated drug was incorporated into gum.

Solubilising agent

The affect of addition various solubilising agents to a chewing gum formulation on the release rate has been studied for different drug. In a study with nystatin, non ionic surfactant Cremophor RH40, Tween 60 and Panadan AB90 were added.

The drug release was observed to increase with factor of 50-70 with upto 95%. While opposite effects were observed during the study of metronidazole and propanolol HCL with glycerol and span 20. It is conclude that by testing the addition of different solubilising agents to the chewing gum, it will often be possible to find an agent that substantially increases the release.

Solid dispersion

For miconazole some carriers were studied including PEG, PVP, Xylitol and carbamide. Because of the solid dispersion release rate increased to a large extent over the first few minutes of mastication.

Sustained release of the drug

The sustained release of the drug can be achieved by one of the following methods:

Particle size of the drug

Reduction of particle size of an incorporated ingredient might be valuable approach to retard the release of the drug from chewing gum.

Drug-Ion exchange complex

Nicotine is liquid with boiling point 247°C, basic in nature with pKa 3.12 and 8.02 and freely soluble. When incorporated into ordinary gum composition, its release occur rapidly but undesirable for its clinical use which requires smoking substitute that should be uniform and last for at least 20 mins.

The cation exchanger used in the marketed nicorette chewing gum is amberliteIRP 64, a weak acidic methacrylic acid polymer and nicotine complex product is referred to nicotine polacrilex.

Coating and embedding

Different coating principles and different coating agents such as PVP and cellulose compounds have been used in order to a prolonged release of flavor and sweetener from chewing gum. Embedding a drug in hydrophobic matrix consisting of lecithin, synthetic waxes or mixtures there of reduced release rate of drug from chewing gum.
**Adsorption**

A flavor was adsorbed into silica gel which as then dispersed throughout a thermoplastic material such as cellulose-2-hydroxy propyl-ether. The release rate reduced from 35% to 20% during 20 mins of mastication.

**Requirement of drug**

**Molecular size**

Molecular wt. less than 100 dalton are rapidly transported through buccal mucosa.

**Lipid solubility**

For non-ionisable compound as lipophilicity rises, the drug permeability typically increases. To maximize absorption rate, a drug should be available in the salivary film at its solubility limit.

**Ionization**

For ionisable drugs maximum permeation occurs at the pH at which ionization is least.

**Rate of drug absorption**

For Transcellular route is pH dependant. Such dependency results from membrane/aqueous partition coefficient for an ionisable drug is pH dependant.

**COMPONENTS OF THE MCG**

Chewing gum is a mixture of natural or synthetic gums and resins, sweetened with sugar, corn syrup, artificial sweeteners and may also contain colouring agents and flavour. 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 polyvinylacetate and similar polymers can be used as gum base.

Typically Chewing Gum comprises two parts

- Water insoluble chewable gum base portion (Zyck et al., 2003)
- Water-soluble bulk portion (Zyck et al., 2003)

**Water insoluble gum base generally comprises of**

(Conway et al., 2003; Zyck et al., 2003)

**Elastomers (40-70% by wt. of gum base).**

Elastomer provides elasticity and controls gummy texture. Natural elastomer: Natural rubbers like Latex or Natural gums such as Jelutong, Lechi Caspi, Perillo, and Chicle.

**Plastisizers (3-20% by wt. of gum base).**

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

Natural Plastisizers include Natural rosin esters like Glycerol Esters or Partially hydrogenated Rosin, Glycerol Esters of Polymerized Esters, Glycerol Esters of Partially dimerized Rosin & Pentaerythritol Esters of Rosin. Synthetic Plastisizers include Terpene Resins derived from α-pinene and/or d-limonene.

**Fillers or Texturizers (2-60% by wt. of gum base).**

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 Aluminum Silicate, Clay, Alumina, Talc, Titanium Oxide & Mono/ di/ tri Calcium Phosphate.

**Water soluble portions comprises of**

Softeners 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**

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

**Sweeteners (50-65% of gum base composition)**

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, Galactose, Corn Syrup. 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, Glycerhizin, Dihydrochalcones.

**Bulking agents**

These are used if low calorie gum is desired. Examples of low caliber bulking agents include Polydextrose, Oligofructose, Inulin, Fructooligosaccharides, Guar gum 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 colour or a thick layer of sugar or sugar alcohol.

MANUFACTURE OF THE MCG

Different methods employed for the manufacturing of CG can be broadly classified into three main classes namely:

- Conventional/traditional Method (Melting).
- Freezing, grinding and tabletting Method.
- Direct Compression Method

Conventional/traditional Method (Melting) (Athanikar et al., 2001)

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 (Cherukuri et al., 1988)
- Elevated temperature used in melting restricts the use of this method for thermo labile drugs.
- Melting and mixing of highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult.
- Lack of precise form, shape or weight of dosage form.
- Technology not so easily adaptable to incorporate the stringent manufacturing conditions required for production of pharmaceutical products.
- 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 (Athanikar et al., 2001; Mochizuki et al., 1976)

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

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 is around -15°C or lower. Amongst the various coolants like liquid nitrogen, hydrocarbon slush use of solid carbon dioxide is preferred as it can give temperatures as low as -78.5°C, it sublimes readily on warming the mixture, is not absorbed by the chewing gum composition, does not interact adversely with the processing apparatus and does not leave behind any residue which may be undesirable or potentially hazardous. The refrigerated composition is then crushed or ground to obtain minute fragments of finely ground pieces of the composition. Alternatively, the steps of cooling the chewing gum composition can be combined into a single step. As an example, cooling the grinding apparatus itself which can be done by contacting the grinding apparatus with a coolant or by placing the grinding apparatus in a cooling jacket of liquid nitrogen or other cold liquid. 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 keep 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. The same process can be made multiple by adding incorporating additional carbon dioxide and/or precipitated silica at each step. Certain additives can be added to the chewing gum composition to facilitate cooling, grinding and to achieve desired properties of chewing gum. These include use of anti-caking agent and grinding agent.

**Use of anti-caking agent**

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.

**Use of grinding agents**

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 molten 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. They also tend to remain in the composition and final chewing gum tablet and thus may be problematic for therapeutic and safety point of view. After the composition is ground to a powder, the coolant can be removed by allowing the coolant to evaporate. Alternatively it has been found that such a powdered mass when warmed to room temperature from the refrigerated state, they become cross linked or self adhere together to form an integrated body which incorporates minute air bubbles in the texture between the particles. 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, 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.

**Limitation**

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**

(Atanikar et al., 2001; Mochizuki et al., 1976)

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) & or 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 have shown that use of Pharmagum in formulation showed a faster release rate. Formulations made with Pharmagum® M & S are similar to tablet in appearance. Gums formed using compressible formulation are 10 times harder and crumble when pressure is applied resulting in faster release than conventional methods. Use of Pharmagum S, M and C enables formulators to utilize a gum delivery system quickly & more cost effectively than by traditional methods. A novel drug delivery system creates additional patient benefits that will add
new competitive advantages for a drug and, thus, conserve or increase revenue. Chewing gum as drug delivery system holds tremendous potential not only in smoking cessation and oral health care arenas but also in other indications.

STABILITY OF THE MCG

The stability of chewing gum is comparable to most of other solid delivery systems. Chewing gum normally contains little water (2-5%) and the water can be bound to the other components in the product and is therefore not very reactive. The water activity (Aw) in chewing gum normally below 0.6 and typically (0.4-0.5) if water content is very critical for stability of the drug, the chewing gum can be manufactured without water (less than 0.2). This will, however, often make the product hygroscopic and affect the texture. The low water content inhibits microbial growth in the chewing gum during storage. Antioxidants are normally added with the gum base. Furthermore, the product can be protected against oxidation by a sealed coat and by appropriate packaging. For every temperature component, e.g. enzymes, the process temperature of 50-60°C during mixing may create a stability problem. It is however, possible to operate the process at lower temperature to avoid this issue (European Pharmacopoeia).

QUALITY CONTROL OF THE MCG

Medicated chewing gum complies with the requirements of the third edition of European pharmacopoeia (European Pharmacopoeia).

Uniformity of content

Unless otherwise prescribed or justified and authorized, medicated chewing gum with content of 2 mg or less than 2 percent of total mass comply with test A for uniformity of content of single dose preparation. If the preparation contains more than one active substance, the requirements applies only to those active substances, which corresponds to the above condition.

Uniformity of mass

Uncoated medicated chewing gum and, unless otherwise justified and authorized, coated medicated chewing comply with the test for uniformity of mass of single dose preparations. If the test uniformity of content is prescribed for all the active substances, the test for uniformity of mass is not required.

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 special dosage forms, including medicated chewing gums (Siewert et al., 2003; Moller et al., 1999; Yang et al., 2004). 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. The performance tests, however, must be able to detect the influence of critical manufacturing variables, discriminate between different degrees of product performance, and to some extent, describe the biopharmaceutical quality of finished products. The scope, purpose, and importance of release test have been discussed previously (Shah et al., 2006).

Besides the product quality tests, the drug release tests can provide useful information about the characteristics of the product itself, which includes but is not limited to the influence of the composition of the gum and other excipients on drug release, a main tool required primarily during product screening and development, and to some extent the product performance in vivo.

Drug Release Testing Methodology

Ph. Eur. has adopted an apparatus to determine the release rate from chewing gum formulations (European Pharmacopoeia. General Monograph 2.9.25, 2008). 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 (European Pharmacopoeia. General Monograph 2.9.25, 2008). 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 mechanism and kinetics of drug release from chewing gums have not yet been completely understood due to the complexity of the formulation itself. 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 (European Pharmacopoeia. Suppl. General Chapter 2.9.25, 2000). Figure 5 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. If necessary, 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. (European Pharmacopoeia. General Monograph 2.9.25, 2000, 2005, 2008). Several studies (Yang et al., 2004; Jensen et al., 1988; Christrup et al., 1986; Christrup et al., 1988; Faraj et al., 2007; Pedersen et al., 1990; Pedersen et al., 1991) 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, Non compendial—Wennnergren

One of the non compendial apparatus commercially available was designed by Wennnergren (Kvist et al., 1999). The
schematic representation of the Wennergren chewing apparatus is shown in Figure 6.

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. (Kvist et al., 1999). The influences of different operational parameters of the chewing gum apparatus on drug release have been carefully investigated (Kvist et al., 2000).

General Comments about Apparatus I and Apparatus II

Both the apparatus described have been well studied and reported in the literature (Yang et al., 2004; Jensen et al., 1988; Christrup et al., 1986; Christrup et al., 1988). 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 testing of medicated chewing gums both in quality control as well as in product development. To some extent relevance to in vivo behavior has been demonstrated using both the apparatus (Kvist et al., 1999; Christrup et al., 1986) which suggests their usefulness in the quality control and product development environments.

Fig. 5: Apparatus I Chewing Gum Apparatus Compendial – Ph. Eur.
Table 1: Worldwide marketed Medicated Chewing Gums.

| 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       |
| Trawell      | Dimenhydrinate   | Travel illness               | Italy, Switzerland              |
| Superpep     | Dimenhydrinate   | Travel illness               | Germany, Switzerland            |
| Chooz        | Calcium Carbonate| Stomach & neutralization     | USA                             |
| Endykay Vit.C| Vitamin C        | General Health               | Middle East, UK                 |
| Stamil Vit.C | Vitamin C        | General Health               | Australia                       |
| Source Vit.C | Vitamin C        | General Health               | Australia                       |
| Brain        | DHA & CCE        | Enhanced brain activity      | Japan                           |
| Stay Alert   | Caffeine         | Alertness                    | USA                             |
| Café Coffee  | Caffeine         | Alertness                    | Japan                           |
| Buzz Gum     | Guarana          | Alertness                    | United Kingdom                  |
| Go Gum       | Guarana          | Alertness                    | Australia                       |
| Chrona Slim  | CR               | Diet                         | USA                             |
| Fluorette    | Fluoride         | Cariostatic                  | USA                             |
| Vitaflo CHX  | Chlorhexidine    | Preventing tooth decay       | USA                             |
| Travvel      | Dimenhydrinate   | Motion sickness              | USA, Australia                   |
| V6           | Xylitol          | Prevention of treatment of dental caries | United Kingdom                  |

Table 2: Vitamins, minerals and Herbal Medicines.

| Formulation                                                                 | Main Indications                                      |
|---------------------------------------------------------------------------|-------------------------------------------------------|
| 1) Calcium 500mg + CCP 100mg (Calcium Casein Peptide)                      | Calcium Supplement                                    |
| 2) Chamomile (Matricaria) 25 or 100mg                                      | Mild Sedative                                         |
| 3) Coffee enriched with 150 mg caffeine                                    | Energiser, to increase intellectual performance       |
| 4) Ether 500 mg (Guar Galactomannan)                                       | Guar dietary fiber supplement, slimming agent         |
| 5) Ginger 50 or 100 or 150 mg                                             | Gastric stimulant, natural anti-emetic                |
| 6) Magnesium and potassium aspartate 325 mg                                | Magnesium and potassium deficiency (sport gum)        |
| 7) Multivitamins (Betacarotene, Vit C, B1, B2, B6, B12, Folic acid)       | Vitamin Supplement                                    |
| 8) Passion Flower + Camomile + Hawthorn + Linden tree                      | Natural anti-stress-sedative-antalgic                 |
| 9) Perilla dry extract 27 mg                                               | Natural anti-allergic                                  |
| 10) Zinc 12 mg                                                            | Enzyme cofactor                                       |
APPLICATIONS OF THE MCG

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. Oral diseases are prevented or cured with MCG. MCGs can be used for systemic effect in conditions like vitamin C deficiency, pain & fever, alertness, motion sickness, smoking cessation, as well as for local effect in conditions like plaque acid neutralization, fresh breath, dental caries, antiplaque, fungal, and bacterial infections. Prevention and cure of oral diseases is a prime target for chewing gum formulations.

Local Therapy
(Dalai et al., 1999; Ferno et al., 1974; Dodds et al., 1991)

Chewing gum 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 large 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 (Pedersen et al., 1990; Rindum et al., 1993) Clinical trials involving patients with oral candidiasis have shown that miconazole chewing gum is at least as sufficient as miconazole oral gel in the treatment of fungal infections in the mouth. A miconazole chewing gum is yet to be launched (Pedersen et al., 1990; Rindum et al., 1993)

Systemic therapy

Chewing gum can be used in treatment of minor pains, headache and muscular aches. Chewing gum formulation containing nicotine (Nemeth et al., 1988) and Lobeline have been clinically tested as aids to smoking cessation. 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. Xerostomia, Allergy, Motion sickness, Acidity, Cold and Cough, Diabetes, Anxiety, etc are all indications for which chewing gum is a means of drug delivery. Medicated chewing gum is used to counteract dental caries by stimulation of saliva secretion. Non-mediated chewing gums increases plaque pH, stimulates saliva flow and decrease decay.

FUTURE TRENDS

Chewing gum is no longer seen simply as confectionary. It 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 diseases was surgical procedure but now more and more diseases can be treated with Novel Drug Delivery Systems. Generally, it takes time for a new drug delivery system to establish itself in the market and gain acceptance by patients, however chewing gum is believed to manifest its position as a convenient and advantageous drug delivery system as it meets the high quality standards of pharmaceutical industry and can be formulated to obtain different release profiles of active substances. 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. Dental health chewing gum is here to stay, as is medicated gum for smoking cessation and travel sickness. A bright future for a preparation with a long history.

Chromium (Pittler et al., 2003; Martin et al., 2006)

Insulin’s little helper is the mineral chromium picolinate, which makes your body’s cells more sensitive to the effects of
insulin. Numerous studies have shown that taking chromium picolinate supplements can curb excessive levels of insulin and make insulin receptors more responsive to its effects. By way of analogy, chromium picolinate helps to reset your body is insulin and blood sugar thermostat. Without the peaks and troughs of high and low blood sugar and the subsequent craving to increase blood sugar levels, you no longer have the instinctual urge to consume high carbohydrate diet.

In 2005, researchers put chromium to the test by giving 113 carbohydrate cravers either daily chromium picolinate supplements or placebo pills for eight weeks. At the end of the study, the participants receiving chromium picolinate (but not the placebo) had almost totally overcome their frequent sugar cravings. What's more, they also had lower overall daily food intake, meaning that they didn't compensate for their sugar cravings by eating more from other food groups. The dosage of chromium picolinate used in this study was 600 mcg per day (3 x 200 mcg tablets per day).

CONCLUSION

For most drugs there are realistic possibilities of formulating them into a suitable chewing gum delivery system, although active agents with an extremely bitter taste 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. 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. 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. Finally, in the future, we may see drugs formulated into chewing gum in preference to other delivery systems to deliver drugs locally to the oral cavity. The reason is simple - that the chewing gum delivery system is convenient, easy to administer anywhere, anytime and its pleasant taste improves patient compliance.

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