Chewing Gum:  
A Novel Approach for Drug Delivery

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INTRODUCTION

Chewing gum is a pleasure that almost everyone enjoys. In addition to its confectionery role, chewing gum also has a proven value as a delivery vehicle for pharmaceutical and nutraceutical ingredients.¹ It can be taken discreetly without water, and allows for local and systemic delivery. It can be employed for treatment of diseases of the oral cavity and throat, e.g. for caries prevention, or it can release drugs that can be absorbed through oral mucosa directly into the systemic circulation. In addition, drug that is not absorbed by the oral cavity membranes can be dissolved in the saliva before swallowing, thus leading to a more rapid onset of action.²

Chewing gum may be a particularly effective means for delivering and maintaining a sufficient antibacterial dose of KSL-W in the oral cavity. Because chewing gum is usually kept in the mouth much longer than rinses and toothpastes, the active agent included in a chewing gum formulation, if efficiently released into the saliva, could...
exhibit sustained and improved delivery in the mouth.3-5

Chewing gum possesses many advantages, which include, improved memory, reduction in symptoms of stress, helping to manage weight, and improvement in digestion and oral health.6 Chewing gum may not be suitable for children and geriatric patients. The chewing gum drug delivery possesses other advantages such as more patient compliance as compared to buccal and sublingual drug delivery systems. Recently, the chewing gum bases are widely used in controlled drug delivery systems.

STRUCTURE AND FUNCTION OF ORAL MUCOSA

A stratified, squamous epithelium lines the oral cavity. Three different types of oral mucosa can be identified, i.e., masticatory, lining, and specialized mucosa (Fig. 1).7 The masticatory mucosa covers the gingiva and hard palate. It comprises a keratinized epithelium strongly attached to underlying tissues by a collagenous connective tissue, and as such, is able to withstand the abrasion and shearing forces of the masticatory process. The lining mucosa covers all other areas except the dorsal surface of the tongue, and is covered by a nonkeratinized and hence more permeable epithelium.8 This mucosa is capable of elastic deformation, and stretches to accommodate speech and mastication requirements.

The epithelium in humans varies in thickness according to the region, e.g., floor of the mouth, 190 μm; hard palate, 310 μm; buccal, and 580 μm.9 A loose, elastic connective tissue attaches the lining mucosa to underlying structures. The specialized mucosa of the dorsum of the tongue is characteristic of both the masticatory and lining mucosa in that it consists of epithelium partly keratinized and partly nonkeratinized.

This epithelium is bound to the muscle of the tongue. The regional differences in morphology result in different permeability characteristics that have considerable influence on the design and sitting of drug delivery systems. The differentiation process that gives rise to the regional differences occurs as the keratinocytes migrate from the buccal layers to the epithelial surface. Within the basal layer the keratinocytes are cuboidal or columnar, with a surrounding plasma membrane and containing the usual intracellular organelles. A constant population of epithelial cells is maintained by the division of the basal keratinocytes at a rate equating to the desquamation of surface cells. Aging and disease can result in a loss of this balance, which can lead to a thickening (hypertrophy) or thinning (atrophy) of the epithelium. The media turnover time is slower for keratinized tissue, e.g., hard palate 24 days, than nonkeratinized, e.g., buccal mucosa 13 days.10 Also relevant to the development of drug delivery systems are the surface areas of the human mouth occupied by keratinized (50%) and nonkeratinized (30%) tissues. Percentages are expressed with reference to the total surface area of the mouth.11

In nonkeratinized epithelium, the morphological changes upon differentiation are less than for keratinized tissue. Also there is less accumulation of lipids and cytokeratins in the keratinocytes. Mature cells become larger and flatter, exhibiting a protein envelope, nuclei, and other organelles.

There is no tendency for aggregation of the cytokeratins as is evident in keratinized tissue and the glycogen content increases.
Desmosomes are still present between cells in the surface cell layer, where intercellular spaces are both wide and irregular. Membrane-coating granules appear as approximately 200-nm spheres in the prickle cell layers, which subsequently fuse with cell membranes to discharge their contents in the superficial cell layer. Some of the membrane-coating granules contain lamellae, which upon discharge may give rise to short stacks of lamellar lipid observed in the intercellular spaces in the outer layers of the epithelium. The majority, however, are amorphous.

Also present in the granules are hydrolytic enzymes and glycoconjugates, probably glycoproteins and glycolipids. Evidence suggests that the intercellular permeability barrier arises from the discharged contents of the membrane-coating granules.

**POTENTIAL ATTRIBUTES OF CHEWING GUM AS A DRUG DELIVERY SYSTEM**

CGDDs provide various new competitive advantages over conventional drug delivery systems. These include, fewer side effects due to avoidance of high plasma peak concentrations and the promotion of the controlled release of the drug. This avoids fast pass metabolism, sustaining the release of active substances that may deliberately prolong exposure, stimulating salivary secretion and thereby decreasing dryness in the mouth (xerostomia), fast onset of action because the active substances pass by the jugular veins directly to the systemic circulation, high bioavailability, pleasant taste, higher patient compliance due to its easy and discreet administration without water, readiness for use, high acceptance by children, and a topical effect in the oral cavity and in the throat.

**FORMULATION DEVELOPMENT APPROACHES WITH CGDDs**

Medicated chewing gum has a core consisting of the components given in Table 1. The core normally weighs approximately 1 g. A coating can then be applied to the gum either as a film of polymer, wax, or bulk sweetener or as a thicker layer of sugar/ sugar alcohol. The gum base consists of elastomers,

<table>
<thead>
<tr>
<th>Component</th>
<th>Examples</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Substances</td>
<td>Vitamins, Oral Contraceptives, Nicotine, Minerals, Analgesics, Antacids, Muscle Relaxants, Antihistamines, Decongestants, Anesthetics, Antitussives, Antibiotics, etc.</td>
<td>Max. approximately 50</td>
</tr>
<tr>
<td>Flavoring Agents</td>
<td>Citrus, Peppermint, Spearmint, Anise, Wintergreen Oil and Synthetic flavors</td>
<td>1–5</td>
</tr>
<tr>
<td>Sweetners</td>
<td>Sorbitol, Mannitol, Aspartane, Saccharin etc</td>
<td>30–75</td>
</tr>
<tr>
<td>Gum Base</td>
<td>Synthetic (Styrene Butadiene Rubber, Polyethylene and Polyvinyl Acetate) &amp; Natural (Smoked Rubber)</td>
<td>20–40</td>
</tr>
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<td>20–40</td>
</tr>
<tr>
<td>Coloring Agents</td>
<td>FD&amp;C Dyes</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Others</td>
<td>Plasticizers, Elastomers, Lipids (Soyabil), Emulsifiers (Lecithin), Fillers, Texture Agents (Talc), Coating and Binding Agents, Film Formers etc.</td>
<td>0.5-5</td>
</tr>
</tbody>
</table>

Table 1. Components of CGDDs
resins, fats, emulsifiers, fillers, and possibly antioxidants. There are a number of different commercially available gum bases, each with different characteristics. All gum bases are insoluble in saliva and it is the gum base that determines the basic characteristics of the product. The characteristics that will be influenced by the choice of gum base include texture, release, stability, and the processing. It is possible (but unusual) to manufacture chewing gum with both a larger and a smaller amount of gum base described in Table 1.19,20

**MANUFACTURING PROCESS OF CHEWING GUM**

The majority of gum delivery systems today are manufactured using conventional gum processes, and gum manufacturing technology is a barrier to market entry for many generic pharmaceutical companies, restricting competition. Furthermore, the heating process involved in conventional methods of production may limit the suitability of gum for the formulation of thermally labile drugs.

In general, chewing gum is manufactured by sequentially adding the ingredients to a commercially available mixer known in the art. After the ingredients have been thoroughly mixed, the gum mass is discharged from the mixer and shaped into the desired form such as extruding in to chunks or casting into pellets which are then coated or panned. The ingredients are mixed by first melting the gum base and adding to it the running mixer. The base may be melted in the mixer itself and other additives added at this time. The entire procedure takes from 5-15 min, but longer mixing time may be manufactured depending on the texture and function of gum base.21-23

**SCALE-UP PROBLEMS**

In the traditional manufacturing process using mixing and rolling, the majority of scale-up problems are related to the achievement of a proper texture and to obtaining the proper mass and dimensions of the cores. The problem is solved by choosing the mixer type and size in relation to the adjusting abilities of the full-scale equipment. During manufacturing process, chewing gum softens at temperatures above 30 °C. Hence during the coating process, high temperature can be a problem. If the temperature in the coating equipment is too high, it can result in deformation of the gum. It is therefore necessary to coat at a lower temperature.19

**EVALUATION OF CGDDs**

The absorption of active substances through the buccal mucosa can be examined by both in vitro and in vivo methods.

**In-vitro testing**

A number of devices to mimic the chewing action have been reported.26 In 2000, the European Pharmacopoeia published a monograph describing a suitable apparatus for studying the in vitro release of drug substances from chewing gums (Fig. 2 and Fig. 3).18,25,27

Likewise, a human TR146 cell culture
model has proven to be a good in vitro model for investigating permeability, permeability mechanisms, effects of chemical enhancers, and toxic effects. The machines are driven by air, and are set to a specific number and frequency of chews inside a water bath at 37 °C, similar to the temperature of saliva in a person’s mouth. Once the gum is “chewed,” the fluid is tested to see how much of the drug has been released. The results are used to evaluate effectiveness and to develop new gum products.

In vivo studies

Buccal absorption of active substances can also be tested by various in vivo methods. Beckett and Triggs introduced a mouth wash procedure in 1967, in which a buffered solution of the active substance is swirled in the oral cavity for a known period of time. Subsequently, the solution is expelled and the oral cavity is rinsed with buffer. The difference between the amount of active substance contained in the original solution and the amount recovered is assumed to be the amount of active substance absorbed from the oral cavity. Since the introduction of this method, it has been improved by various modifications. However, the main limitation lies in the fact that the method cannot account for storage of active substances in the mucosa.

Another in vivo method involves a perfusion chamber, which is adhered to the buccal mucosa of the test person. The absorbed amount of active substance perfused through the chamber is calculated as the decrease in active substance.

MECHANISM OF DRUG RELEASE THROUGH CHEWING GUM

Until recently, the release of substances from gum during mastication was studied using a panel of tasters and “chew out” studies. During mastication, the medication contained in gum is released into the saliva in the mouth, and is either absorbed through the buccal mucosa or swallowed and absorbed via the gastrointestinal tract. The need for, and value of, in vitro drug release testing is well established for a range of dosage forms. However, standard dissolution apparatus is not suitable for monitoring the release of drugs from gum, as mastication is essential in creating a new surface for drug release.

In 2000, the European Pharmacopoeia produced a monograph describing a suitable apparatus for studying the release of drugs from gum. Factors affecting the release of medication from chewing gum can be divided into three groups: the physicochemical properties of the drug, the gum’s properties, and chew-related factors such as chewing rate and frequency. For most pharmaceuticals, aqueous solubility of the drug will be a major factor affecting the release rate. For drugs to be released, the gum must be hydrated. The drugs can then dissolve and diffuse through the gum base under the action of chewing.

Patient-controlled delivery rates, achieved by varying chewing frequency, have contributed to the success of nicotine-containing gums and could also prove beneficial for applications such as analgesia, but may limit applicability for drugs with a narrow therapeutic index or prescribed pharmacokinetics. Guidance can be given regarding chewing condition, but factors such as the force of chewing and salivary flow will affect drug release and the fraction of the drug absorbed via the oral mucosa. Released drugs can be swallowed with the saliva, leading to multiple absorption sites and potentially variable pharmacokinetics.
**STABILITY**

The stability of chewing gum is comparable to that of most other solid delivery systems. Chewing gum normally contains little water (2–5%), and the water can be bound to other components in the product and is therefore not significantly reactive. The water activity (aw) in chewing gum is normally below 0.6 and typically 0.4–0.5. If the water content is very critical for the stability of a 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 also 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 an appropriate packaging. For very temperature-labile components, 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 a lower temperature to avoid this issue.

**REGULATORY ISSUES**

The first monograph on medicated chewing gum was published in the European Pharmacopoeia in 1998. Use of a solid, tasteless masticatory gum base and coating to protect from humidity and light, if necessary, is described. Being a single dose preparation, medicated chewing gum has to comply with tests for uniformity of content and uniformity of mass. In addition, the microbial quality has to be ensured.

Release testing is prescribed to control the bioavailability of the drug(s). In the year 2000, the first monograph on a principle chewing apparatus and a procedure for the determination of drug release from medicated chewing gum was published in the European Pharmacopoeia. Chewing gum must be chewed to release the drug(s) and it is accepted that a residual of the drug(s) may be left in the chewing gum after finishing chewing. Generally, a reproducible residual of a lipophilic drug will remain after chewing a gum at a constant rate for a predetermined period of time. In some cases, e.g., smoking cessation, one only chews the gum until the desired effect is obtained, hence the expelled gum will contain inter individual variations in the amount of residual drug.

**APPLICATIONS OF CGDDS**

**Dental Caries**

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 re-elevates plaque Ph, which lowers intensity and frequency of dental caries.

Fluoride containing gums have been useful in preventing dental caries in children and in adults with xerostomia. Chlorhexidine chewing gum can be used to treat gingivitis, periodontitis, oral and pharyngeal infections. It can also be used for inhibition of plaque growth. Chlorhexidine chewing gum offers numerous flexibility in its formulation as it can be used to control the bioavailability of the drug(s).

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Indication(s)</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicorette®</td>
<td>Nicotine</td>
<td>Smoking cessation</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Nicotinell®</td>
<td>Nicotine</td>
<td>Smoking cessation</td>
<td>Novartis Consumer Health</td>
</tr>
<tr>
<td>NiQuitin CQ®</td>
<td>Nicotine</td>
<td>Smoking cessation</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Fluorette®</td>
<td>Fluoride</td>
<td>Prevention of dental caries</td>
<td>Fertin Pharma A/S</td>
</tr>
<tr>
<td>Vitafo CHX®</td>
<td>Chlorhexidine</td>
<td>Treatment of gingivitis and plaque</td>
<td>Fertin Pharma A/S</td>
</tr>
<tr>
<td>Stay Alert®</td>
<td>Caffeine</td>
<td>Antibacterial</td>
<td>Stay Alert Safety Services, Inc</td>
</tr>
<tr>
<td>Travvell®</td>
<td>Dimenhydrinate</td>
<td>Motion sickness</td>
<td>Asta Medica</td>
</tr>
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</table>

**Table 2. Marketed Products of Chewing Gum**
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.35

**Systemic Therapy**

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

- **Pain**: Treatment of minor pains, headache, and muscular aches can be successfully accomplished.36
- **Smoking Cessation**: Chewing gum formulation containing nicotine, lobeline, and silver acetate have 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. The formulation nicorette® available as mint and classic with different flavor and dosage, released 90% of drug after 30 min chewing.37 The release rate was controlled by the rate and vigour of chewing. 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.
- **Obesity**: Active substances like chromium, guaran, and caffeine are proved to be efficient in treating obesity. Chromium is claimed to reduce craving for food due to an improved blood-glucose balance. Caffeine and guaran stimulate lipolysis and have a thermogenic effect (increased energy expenditure) and reduce feeling of hunger.38
- **Other Indications**: Xerostomia, allergy, motion sickness, acidity, cold and cough, diabetes, and anxiety are all indications for which chewing gum as drug delivery system could be beneficial.20 At present, there are various chewing gum drugs are available in the market, few of them are given in Table 2.

**SAFETY ASPECTS**

Chewing gum has several drawbacks as the drug released into saliva disappears rapidly from the oral cavity because of involuntary swallowing. The concentration of drug in the oral cavity always tends to decrease as a result of salivary dilution. Administration of such dosage form is restricted to short period of time because the presence of the delivery system in the oral cavity causes disturbance in drinking, eating and speaking.

Generally, it is currently perfectly safe to chew a gum. Previously, hard chewing gums have caused broken teeth. Extensive chewing for a long period of time may cause painful jaw muscles, and extensive use of sugar-alcohol-containing chewing gum may cause diarrhea. Long-term frequent chewing of gum has been reported to cause increased release of mercury vapor from dental amalgam fillings.23,24 However, medicated chewing gum does not normally require extensive chewing, or consumption to a great extent. Flavors, colors, etc may cause allergic reactions. Overdosing by use of chewing gum is unlikely, because a large amount of gum has to be chewed in a short period of time to achieve this. Swallowing pieces of medicated chewing gum will only cause minor release of the drug, because the drug can only be released from the gum base by active chewing. As a general rule, medicated chewing gum (like other medicines) should be kept out of reach of children. In addition, if required, drug delivery may be promptly terminated by removal of the gum.19

**FUTURE PROSPECTS OF CHEWING GUM AS A DRUG DELIVERY SYSTEM**

Chewing gum of the future will most likely be composed in a way so it can be removed from indoor and outdoor surfaces by conventional cleaning methods and technologies. It will disappear by means of nature’s own remedies, i.e., water, light, and bacteria. In the future, chewing gum as a drug delivery system will likely be forthcoming for the treatment of mouth and throat diseases, both of which require a long period of local drug release to the oral cavity. By using optimal...
release systems and a better utilization of flavors, more drugs will be successfully formulated in chewing gum in the future. 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. Now, however, 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.

As chewing gum is intended to be retained in the mouth for a long time, the issue of taste-masking remains an important factor in product development, as does the control of drug release from the gum base. The convenience and acceptability of chewing gums, combined with effective sweetening and taste masking, may lead to improved compliance. New gum base formulations that are compressible, digestible and potentially biodegradable will further extend applications for chewing gum, but the impact of these bases on drug release must be fully investigated. Drug entrapment and release is still being developed on a product-by-product basis.

Knowledge of the factors controlling release will facilitate rational design. Local delivery using chewing gum will continue to be developed, due to its convenience and its potential in maintaining effective drug concentrations at the site of action. Innovations in dental care may include chewing gum for sensitive teeth and for tobacco stain prevention. Preparations for the treatment of diseases in the oral cavity and throat are being investigated. There are opportunities for both the food and pharmaceutical industries to develop formulations for the delivery of nutraceuticals, while chewing gums containing probiotics or soluble fiber have been launched. Systemic buccal delivery with chewing gum – avoiding first-pass metabolism – combined with rapid onset of action make gum an attractive dosage form, as evidenced by nicotine replacement, and it has significant advantages for pediatric drug delivery.

Gum-based drug delivery for children Discreet administration, portability, and convenience are major reasons for using chewing gum to deliver drugs to children. Current and potential applications include:

- Oral hygiene and treatment of oral conditions
- Treatment of motion sickness, nausea, allergies and ADHD disorder
- Vitamin and mineral supplementation

**CONCLUSIONS**

Chewing gum is an excellent drug delivery system for self-medication, as it is convenient and can be administered discreetly without water. It offers several advantages compared to chewable tablets, lozenges and other related formulations hence in the coming years it is very likely that chewing gum will become a common drug delivery system.

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