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MEDICATED CHEWING GUM AS DRUG DELIVERY SYSTEMS

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ABSTRACT:
Now-a-days medicated chewing gums are considered to be a potential and convenient modified release drug delivery system, owing to scientific and technological advancements made in the research and development of oral drug delivery systems. It offers a highly convenient patient-compliant way of dosing medications that unlike chewable tablets are not supposed to be swallowed and may be removed from the oral cavity without resorting to invasive means. Moreover medicated chewing gums require the active and continuous masticatory activities for activation of drug release. It has drawn attention to the researchers as potential drug delivery systems and it could be a commercial success in the near future.

Keywords: Medicated chewing gum, oral mucosa, gum base, dental caries, smoking cessation.

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INTRODUCTION

A novel drug delivery system creates additional patient benefits that will add new competitive advantages for a drug and thus increase revenue. Oral route is the most preferred route because of its ease in administration[1]. The intra oral route is one of the more preferred routes of the drug administration as it is convenient and, with certain drugs, may provide a more rapid onset of action. Chewing Gum (CG) has proven value as a delivery vehicle for pharmaceutical and nutraceutical ingredients[2, 3]. A basic design of a typical chewing gum is shown in Figure 1.

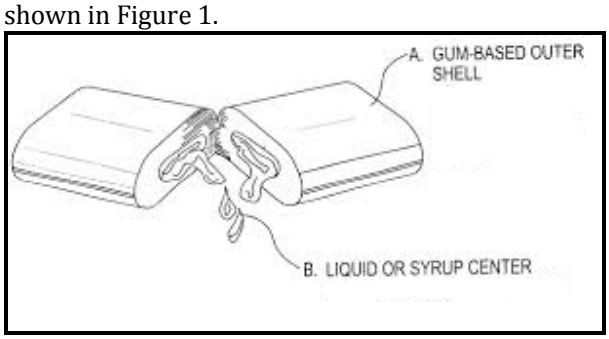

Fig. 1: Medicated Chewing Gum

Definition

The latin term for medicated chewing gums (MCG) is *Masticabilia gummis medicate*. These 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.

Advantages[4-7]

1) Does not require water to swallow and hence can be taken anywhere.
2) Advantageous for patients having difficulty in swallowing.
3) Excellent for acute medication.
4) Counteracts dry mouth, prevents candidiasis and caries.
5) Highly acceptable by children.
6) Avoids first pass metabolism and thus increases the bioavailability of drugs. Duration of action is increased.
7) Fast onset due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation.

8) Gum does not reach the stomach. Hence G.I.T. suffers less from the effects of excipients.
9) Neutralizes plaque acids that form in the mouth and prevents stains.

Disadvantages[8-11]

1. 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.
2. Sorbitol present in MCG formulation may cause flatulence, diarrhoea.
3. Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers.
4. Prolonged chewing of gum may result in pain in facial muscles and ear ache in children.

ANATOMY AND PHYSIOLOGY OF THE ORAL MUCOSA[12-14]

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 generalized structure of oral mucosa is shown in Figure 2.

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 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).

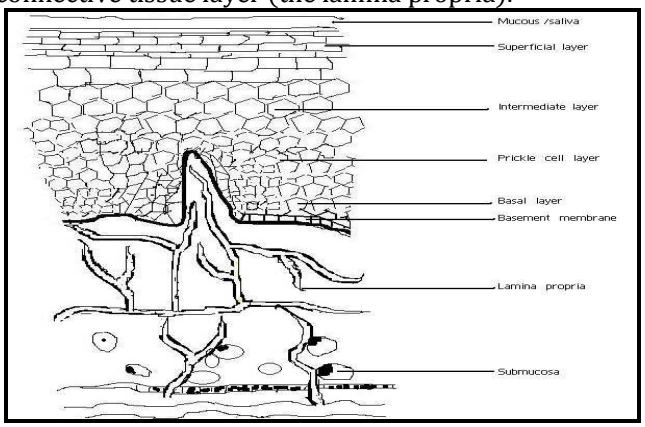

Fig. 2: Generalized Structure of Oral Mucosa

The lamina propria

The lamina propria contains a sheet of connective tissue containing collagen elastic fiber and cellular components in hydrated ground substance. 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.

MECHANISM OF DRUG TRANSPORT[12, 14]

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 in accordance with the pH partition theory. The equation for drug flux is:

$$J = -D\frac{dC_m}{dx}$$

Where,
J = flux of the drug across a membrane in the direction of decreasing concentration,
D = Diffusion coefficient of the drug, and
dCm /dx = Change in the concentration of the drug in the membrane.
Two pathways of permeation across the buccal mucosa are transcellular and paracellular, as shown in Figure 3.

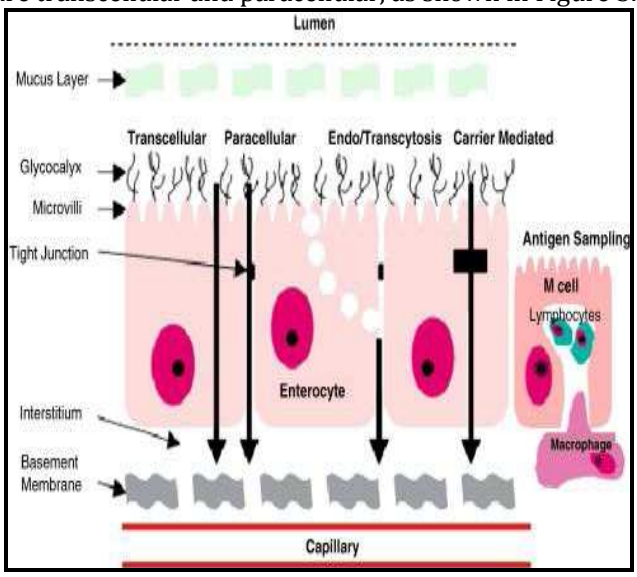

Fig. 3: Routes and Mechanisms for drug transport across Epithelia.

FACTORS AFFECTING MUCOSAL DRUG DELIVERY[15-17]

1. Membrane factor

Regional difference in both permeability and thickness affect the rate and extent of drug reaching the systemic circulation. Additional factors such as absorptive membrane thickness, blood supply, blood/lymph drainage, cell renewal rate, and enzyme content are equally involved.

2. Saliva

Saliva is composed of water 99% and pH of 6.5 to 7.5. 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.

3. Chewing time and chewing rate

Time should be around 20 to 30 min. The average chewing rate is about 60 chews/min.

4. Aqueous solubility of the drug

Release of the water soluble drug is 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.

5. Percentage of drug

The release of fluoride from a chewing gum (1 g) 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.

6. 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.

7. Physicochemical properties of active ingredient

It 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.

8. 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 drug.

9. Formulation factor

Composition and amount of gum base affect rate of release of active ingredient. If lipophilicity fraction of gum is increased, the release rate is decreased.

COMPOSITION OF MEDICATED CHEWING GUMS

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[18, 19].

1. Gum Base

Gum base is the non-nutritive, non-digestible, water-insoluble masticatory delivery system used to carry sweeteners, flavors and any other desired substances in chewing gum and bubble gum. It provides all the basic textural and masticatory properties of gum. The exact composition of gum bases consists of ingredients from the following categories mentioned below[19].

2. Elastomers

These include natural and synthetic rubbers. The gum base composition may contain conventional elastomer solvents to aid in softening the elastomer base component. Such elastomer solvents may comprise terpinene resins such as polymers of alpha-pinene or beta-pinene, glycerol or pentaerythritol esters of resins or modified resins and gums, such as hydrogenated, dimerized or polymerized resins or mixtures. The elastomer solvents may be employed in amounts from 5.0% to 75.0%, by weight of the gum base, and preferably from 45.0% to 70.0%, by weight of the gum base[19, 20]. Synthetic elastomers such as butadiene, styrene copolymers, polyisobutylene, isobutylene isoprene copolymers, polyethylene mixtures, and polyvinyl alcohol are widely used bases.

3. Plasticizers

These include waxes, vegetable oils, glycerides. Plasticizers or softeners such as lanolin, palmitic acid, oleic acid, stearic acid, sodium stearate, potassium stearate, glyceryl triacetate, glyceryl lecithin, glyceryl monostearate, propylene glycol monostearate, acetylated monoglyceride, glycerine, natural and synthetic waxes, hydrogenated vegetable oils, polyurethane waxes, paraffin waxes, microcrystalline waxes, sorbital monostearate, propylene glycol, may be incorporated.

4. Adjuvants

Mineral adjuvants such as calcium carbonate, magnesium carbonate, aluminum hydroxide, aluminum

silicate, talc, tricalcium phosphate, dicalcium phosphate serve as fillers and textural agents.

5. Antioxidants

An anti- oxidant such as butylated hydroxytoluene, butylated hydroxyanisole and propyl gallate may be included as antioxidants.

6. Compression adjuvants

Suitable compression adjuvant such as silicon dioxide, magnesium stearate, calcium stearate and talc can be used in medicated chewing gum for ease of compression. If oil lubricants are used, it is preferred to be 0.4% to 1% by weight of the tableted chewing gum composition. The amount of glidant present in the tableted chewing gum composition is from 0.5% to 5% by weight of the tableted chewing gum composition. Antiadherents function to prevent tablet granulations from sticking to the faces of the punches and the die walls, and prevent adherence of chewing gum granules from adhering to one another, a phenomenon known as blocking. The preferred antiadherents are fumed silica and talc[18].

7. Sweeteners

a) Water-soluble sweetening agents:

Xylose, ribulose, glucose, mannose, galactose, fructose, sucrose, sucralose, maltose, invert sugar partially hydrolyzed starch, dihyrochalcones, monellin, steviosides, glycyrrhizin and sugar alcohols such as sorbitol, mannitol, hydrogenated starch hydrolysates.

b) Water-soluble artificial sweeteners:

Soluble saccharin salts, i.e. sodium or calcium saccharin salts, cyclamate salts.

c) Dipeptide based sweeteners:

L-Aspartic acid derived sweeteners such as Aspartame, Alitame, methyl esters of L-aspartyl-L phyenylglycerine and L-aspartyl 2,5-dihyrophenylglycine, L-aspartyl 2,5-dihydro-L phenylalanine - L aspartyl - L (1-cyclohexen) alanine are commonly used.

d) Protein based sweeteners:

It is obtained from Thaumaoccous danielli (Thaumatin I and II).

8. Coloring Agents

The coloring agents include pigments, which may be incorporated in amounts up to about 6% by weight of the gum composition; titanium dioxide may be incorporated in amounts up to about 2%. The colorants may also include natural food colors and dyes suitable for food drug and cosmetic applications[19].

9. Flavouring Agents

Flavoring agents suitable for use are essential oils and synthetic flavors such as citrus oils, fruit essences, peppermint oil, spearmint oil, clove oil wintergreen oil, and anise oil.

10. 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.

The optimal properties of active ingredient in MCG are shown in Table 1[20]

Table 1: Optimal Properties of Drug

Physicochemical properties of drug	High salivary solubility pH independent solubility Tasteless
Patient related factors	Non - toxic to oral mucosa and salivary ducts Non - carcinogenic Should not cause tooth decay Should not cause staining of oral mucosa and teeth Should not affect salivary flow rate

METHODS OF PREPARATION

Different methods employed for the manufacturing of Medicated Chewing Gum[21], can be classified into three main classes:

1. Conventional Method.
2. Cooling, grinding and tabletting Method.
3. Direct Compression Method

1. Conventional/ traditional Method (melting)

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 forms into a thin, wide ribbon as depicted in Figure 4. 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 flavor. 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

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. This technology is 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[22].

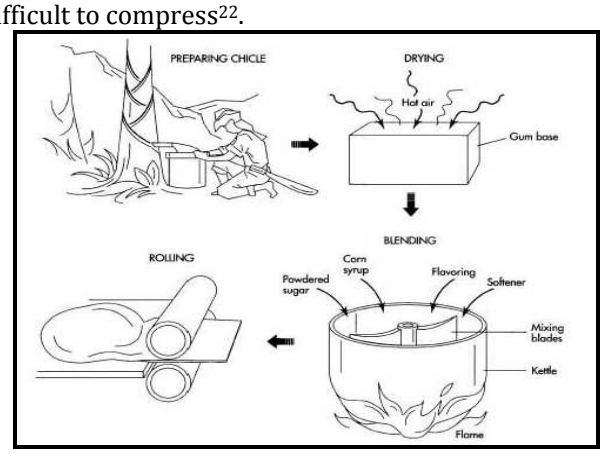

Fig. 4: Conventional Manufacture of a Medicated Chewing Gum.

2. Cooling, Grinding and Tabletting Method (thermoliable)

This method has been developed with an attempt to lower the moisture content and alleviate the problems faced in conventional method. The 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. Generally the temperature of the refrigerated mixture is around -15^{0}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^{0}C. The solid carbon dioxide sublimes readily on warming the mixture and is not absorbed by the chewing gum composition. The refrigerated composition is then crushed or ground to obtain minute fragments of finely ground pieces of the composition[21, 22]. Certain additives such as anti-caking and grinding agents can be added to the chewing gum composition to facilitate cooling, grinding and to achieve desired properties of chewing gum.

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.

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 maltodextrin can be incorporated[23].

3. Direct Compression Chewing Gum

SPI Pharma has developed a compatible gum system known as Pharmagum. Pharmagum is a mixture of polyols and of sugar with gum base. Pharmagum® S consists primarily of gum base and sorbitol. Pharmagum® M contains gum base, Mannitol and Isomalt. These are free Flowing powders, which are directly compressible. Direct compression chewing gum can be directly compressed on a traditional tabletting machine, thus enabling rapid and low cost development of a gum delivery system[22, 23].

EVALUATION OF MCGs

Product quality tests for medicated chewing gums are described by Gajendran *et al.* according to European Pharmacopoeia[24,25]. The tests include assay, identification and uniformity of dosage units, content, and mass. Other tests include: texture analysis, product feel and consistency, evaluation of flavors and sweeteners, tests for coatings, impurities, water content, degradation products, residual solvents, etc.

To study *in vitro* drug release from the medicated chewing gum, European Pharmacopoeia adopted an apparatus - Apparatus I. Chewing Gum Apparatus, Compendial-Ph. Eur. (Figure 5) in 2000. Apparatus II, Alternative Chewing Gum Apparatus, Non-compendial-Wennergren (Figure 6) is one of the non-compendial apparatus commercially available which was designed by Wennergren[26].

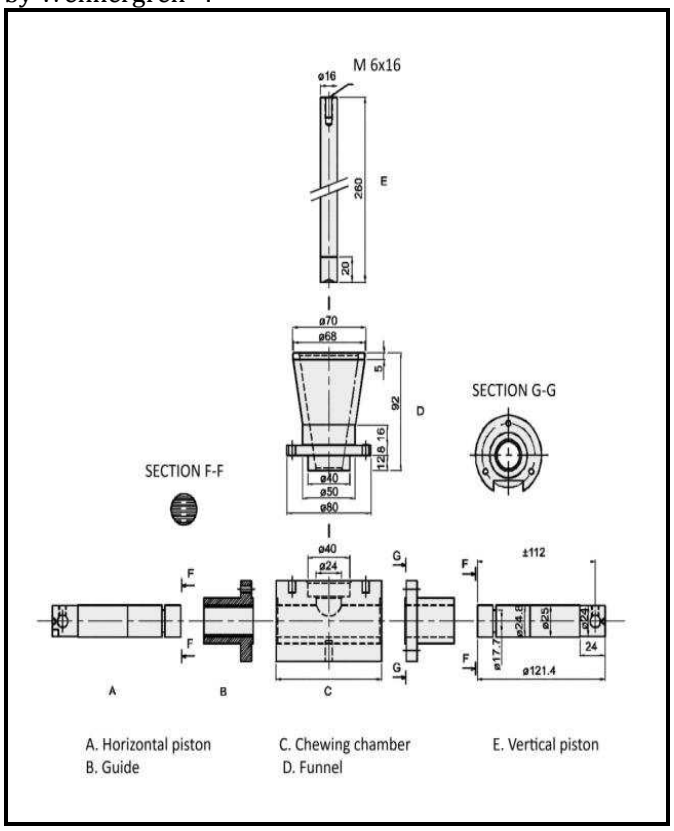

Fig. 5: Apparatus I Chewing Gum Apparatus Compendial - Ph. Eur.

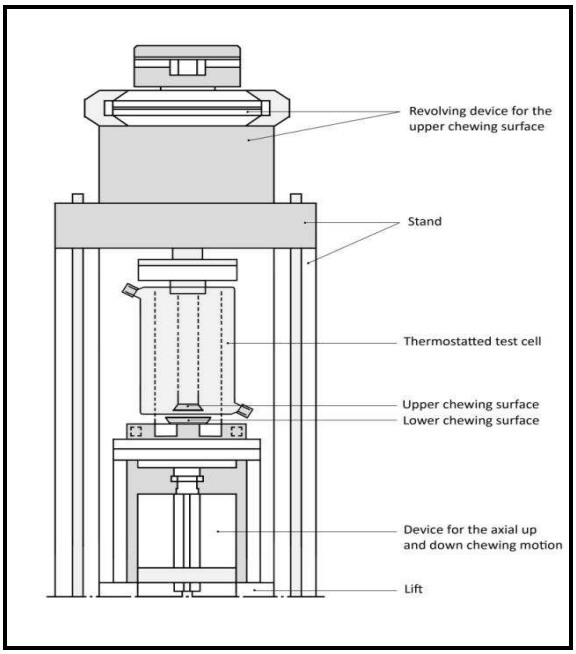

Fig. 6: Apparatus II Chewing Gum Apparatus Non-Compendial – Wennergren

APPLICATIONS OF MEDICATED GUMS[27-31]

1. **Dental caries**

a. Prevention and cure of oral disease are targets for chewing gum formulations.

b. Fluoride containing gums have been useful in preventing dental caries in children and in adults with xerostomia.

c. Chlorhexidine chewing gum can be used to treat gingivitis, periodontitis, oral and pharyngeal infections.

2. **Systemic therapy**

a) Pain - Chewing gum can be used in treatment of minor pains, headache and muscular aches.

b) Smoking cessation - Chewing gum formulation containing nicotine and lobeline have been clinically tested as aids to smoking cessation.

c) 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.

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.

Table 2 shows some of the important commercially available medicated chewing gums with their use[32].

Table 2: Some important commercially available medicated chewing gums and their trademarks

Trade Mark (™)	Active Substance	Aim
Aspergum	Aspirin	Pain relief
Nicorette	Nicotine	Smoking cessation
Chooz	Calcium carbonate	Stomach acid neutralization
Stay Alert	Caffeine	Alertness
Brain	DHA and CCE	Enhanced brain activity
Fluorette	Fluoride	Cariostatic
Trawel	Dimenhydrinate	Motion sickness
Nicotinelle	Nicotine	Smoking cessation
Endekay	Vitamin C	General health

STABILITY ISSUES OF MEDICATED CHEWING GUMS

The stability of chewing gum is comparable to that of most other solid delivery systems. Chewing gum normally contains little water (2.5%). If the water content is very critical for the stability of drug, the chewing gum can be manufactured without water (less 0.2%). This will however, often make the product hygroscopic and will affect the texture. The low water content also inhibits microbial growth in the chewing gum during storage. Furthermore, the product can be protected against oxidation by a sealed coat and by an appropriate packing[33-35].

CONCLUSION

A 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 is the case with ordinary delivery forms, unique expertise in taste definition, taste masking, and taste modification are essential to the success of a medical chewing gum product. Though chewing gum as a drug delivery system has currently gained wide acceptance only within smoking cessation and oral healthcare, vast interest in this mode of drug delivery for a wide variety of other indications exists and continues to grow. In the coming years, new formulations will enter the market and chewing gum will become a much more common drug delivery system.

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