Expert Opinion

The MediChew® technology platform

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A few decades ago, chewing gum was rarely considered when industry searched for an applicable delivery vehicle for an active pharmaceutical substance. Yet, the 1980s and 1990s saw gum become the most successful nicotine delivery form; unawareness changed to cautious scepticism, and today the merits of chewing gum drug delivery technologies are generally appreciated. MediChew® is the registered trademark of Fertin Pharma's medical chewing gum technology platform. Based on patent-protected technologies, it offers unique taste-masking possibilities and allows control of drug molecule release. Medical chewing gum products based on these technologies are specifically suitable for convenient administration on demand, for active substances providing a topical effect in the oral cavity and throat, and for systemic delivery of drug molecules that readily cross the oromucosal membranes.

Keywords: controlled release, drug delivery, medical chewing gum, medicated chewing gum, MediChew®, modified release

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1. Introduction

If possible, the oral route remains the preferred method of administrating drugs. The commercial potential of pharmaceutical delivery systems has facilitated the development of several new oral formulations competing on easy administration and fast onset of action. The competitive nature of the commercial environment demands patent-protected delivery technologies with clear and unique benefits, and new oral delivery forms are continually gaining market shares even if conventional tablets remain the main vehicle of administration.

For pharmaceutical companies, new delivery systems add value not only by providing product life cycle management opportunities but also by offering clinical advantages with regards to safety, efficacy and compliance.

The MediChew® technology [101,102] offers advantages unique to medical chewing gum: for active substances aimed at providing topical effect in tissues of the oral cavity and throat, chewing gum can be used to control the release and maintain therapeutic concentrations for prolonged periods. Chewing gum is also used for systemic delivery of active substances, which are either swallowed and absorbed through the gastrointestinal tract or absorbed through the oromucosal membranes. MediChew may be safer than many other dosage forms as extreme doses can be ingested only through extensive chewing. The active substance is released mainly during chewing and only part of the active substance will be released from the gum base if the gum is swallowed [1].

Another issue often disregarded by formulation scientists is the general perception of chewing gum as a delivery vehicle that does not signal illness. It has, therefore, gained widespread interest among companies marketing lifestyle drugs, and is currently the delivery form of choice for nicotine replacement therapy.

Finally, MediChew shares some advantages with oral disintegrating dosage forms: it allows discreet and convenient administration without the need for water, it is an attractive option for delivery of medication on demand, it is an obvious

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Table 1. Chewing gum core components.

Component	Quantity
Active pharmaceutical substance	< 30%
Gum base	20 – 75%
Bulk sweeteners	25 – 75%
Softeners	0 – 10%
Flavouring agents	1 – 5%

choice for children and there are clear advantages for patients having diffiulty swallowing tablets.

The main disadvantages are relatively high development costs and difficulties with taste masking of extremely bitter-tasting drugs.

2. The MediChew® technology platform

2.1 Composition of medical chewing gum

Medical chewing gum can be formulated in many different ways; the most common and most appropriate being a coated piece of chewing gum with a core weighing ~ 1 g. Typical components of a chewing gum core are shown in Table 1.

The coat can either be a sugar or a sugar-free dragée coat with bulk sweeteners, a film coat or just a thin wax polishing. The active substance is usually added to the core, but may also be located in the coating to achieve faster release. A characteristic component in all chewing gums is the gum base, which comprises a complex mixture of elastomers, plasticisers, texturisers, fillers and antioxidants. The main gum base components are shown in Table 2.

In an uncoated formulation, the gum base accounts for 20 – 75% weight/weight of the product. As a lipophilic component, the gum base is insoluble in saliva and it thus constitutes the residue left after the product is chewed.

2.2 Gum bases

The gum base consists of a heterogenic mixture of polymers with different functions in combination with an inorganic filler (Table 2). The composition of the gum base is adjusted to optimise the product with regard to texture, hydrophilicity and stability.

2.2.1 *Texture*

The texture is optimised by modifying the softening system and adjusting the molecular weight of elastomers and plasticisers, thereby achieving a product with the right softness/hardness, elasticity, tack to teeth, mouth feel, residue volume and other properties.

2.2.2 *Hydrophilicity*

Gum base hydrophilicity determines the release of active substances and flavours. Release is controlled by regulation of the type and quantity of plasticisers and texturisers. When release of lipophilic molecules is required, it is often necessary to add high hydrophilicity emulsifiers, which also requires an adjustment of the resin content in the gum base.

2.2.3 *Stability*

Gum bases contain no water and are thus stable systems with regards to microbiological contamination and hydrolytic reactions. They can be exposed to oxidation, which often makes it necessary to add antioxidants and to specify storage requirements [2]. Other factors critical to the reproduction of a gum base with the right specification include various stages in the manufacturing process.

2.3 Properties of a medical chewing gum

The most important points to consider for a medical chewing gum are taste, mouth feel and control of release of the active substance.

2.3.1 *Taste and mouth feel*

The formulation of a pleasant medical chewing gum is often difficult and depends on the taste and release properties of the active substance. Optimal masking of a bitter or acrid tasting drug often requires the modification of flavour by adjustment of both flavour components and sweeteners. Lyn Hughes (Rohm and Haas) suggests three different mechanistic approaches to improve product taste:

- modifying the taste
- changing the taste
- reducing the taste

The sensory experience changes during the mastication process and a fourth approach is therefore also relevant:

- matching the release of active substances and flavours

The mouth feel depends on the gum base used in the formulation, but also, to some extent, by the softeners and the sweeteners used.

2.3.1.1 *Modifying the taste*

The simplest approach is to mask the taste with pleasant tasting flavours. Professional tasters, specially trained in evaluating the taste of various active substances, monitor taste properties and other organoleptic data of the products during tests in order to establish objective measurements. Based on these tests, the formulation scientists adjust the final taste of the product.

2.3.1.2 *Changing the taste*

In some products it is possible to add taste inhibitors that reversibly inhibit certain tastes [3] and substances affecting the taste buds, thus reducing taste perceptions [103]. Different salt forms of the same drug molecule will not necessarily have the same taste, so if the better tasting form has a suitable pharmacokinetic profile, this approach is worth considering.

Table 2. Main gum base components.

Component	Quantity	Constituents	Characteristics
Elastomers	10 – 15%	Polyisobutylene, butyl rubber	Constitutes a matrix enhancing product elasticity. Its properties make the product return to its initial shape after deformation
Plasticiser	30 – 50%	Resins, polyvinylacetate	Regulates plasticity by keeping the product in shape after deformation
Texturiser	20 – 30%	Fat, microvax, lipophilic emulsifier	Causes the product to be softer (e.g., by controlling hydration and forming a water/oil emulsion)
Inorganic filler	0 – 35%	Calcium carbonate or talcum powder	Stabilises the product and eases the manufacturing process

However, regulatory status, toxicology and other relevant issues often restrict the choice.

2.3.1.3 *Reducing the taste*

One way of reducing the taste of drug molecules is to form cyclodextrine inclusion complexes [104]. However, this approach requires the size of the drug molecule to be small enough to fit into the cyclodextrin centre and, because inclusion complexes with cyclodextrins are quite bulky, the loading dose must be restricted. Alternatively, it is possible to encapsulate the active substance because the low water content in the gum base prevents leaching of pervious coatings [105]. In this case, the challenge lies in the particle size, which must be very small because the coating is crushed when chewed.

2.3.1.4 *Matching release of active substances and flavours*

The release rate of the drug changes with time during the chewing process, and the concentration in saliva is usually highest at the beginning of the chewing. It is, therefore, important to use a flavour and sweetener composition with a release matching the release of the drug. This can be obtained by using the methods explained in Section 2.3.2 [102].

2.3.2 *Controlled release*

It is possible to control the release of both lipophilic and hydrophilic active substances from a chewing gum formulation, and the gum can be designed to give either instant or sustained release. The release rate is determined both by the properties of the active substance and the formulation of the chewing gum. *In vitro* release of the active substances can be determined by the dissolution test method for medicated chewing gums established by Fertin Pharma [4]. Highly water-soluble drugs will be released in 5 – 15 min, whereas drugs with solubility < 1 g/100 g in water will have a slower or possibly incomplete release, as lipid-soluble drugs are dissolved in the lipophilic components of the gum base and are thereby slowly and incompletely released. An optimal formulation, therefore, requires release rate adjustment to obtain either slow release of readily water-soluble drugs or enhanced or more complete release of water-insoluble drugs.

2.3.2.1 *Slow release of water-soluble drugs*

Nicotine is a water-soluble drug. The nicotine release rate from chewing gum is decreased by formulating the gum with a relatively high percentage of gum base (~ 70%). The lipophilic part of the formulation is thus increased, which slows down the release of the drug. It is further reduced through binding of the nicotine to a weak acidic ion exchange resin [5]. Another way to reduce the release is to encapsulate the drug. One method comprises a hydrophobic coating of drug particles (e.g., coating with ethyl cellulose [6]). Other methods comprise granulation of the drug with hydrophobic components or mixing of the drug with a melted polymer [106].

2.3.2.2 *Enhanced release of water-insoluble drugs*

When the active substance is lipophilic it sticks to the gum base, which makes it necessary to enhance the release. This can be achieved either by adding a solubiliser (Figure 1) [6] or by adjusting the type and quantity of the gum base (Figure 2). The former technique may be problematic because solubilisers have a dissolving effect on the gum base and a special gum base is, therefore, required [101]. The above encapsulation technique may also be used to enhance the release of lipophilic drugs if a hydrophilic coating or granulating components are used. However, when the active substance is highly lipophilic, solubilising encapsulation techniques are required [107].

3. Clinical profile

3.1 Systemic effect

Active substances are released from medical chewing gum during chewing and are dissolved or dispersed in saliva. By controlling the release rate, extended exposure in the oral cavity can be obtained.

Active substances absorbed through the oromucosal membranes pass via the jugular veins directly into the systemic circulation. Owing to the rich vascular supply of the buccal mucosa, measurable concentrations of the active substance may be present in the blood after only a few minutes of

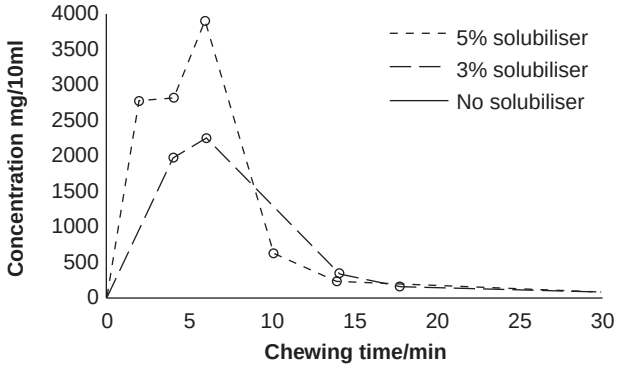

Figure 1. Modified release of lipophilic miconazole from chewing gum *in vitro*.

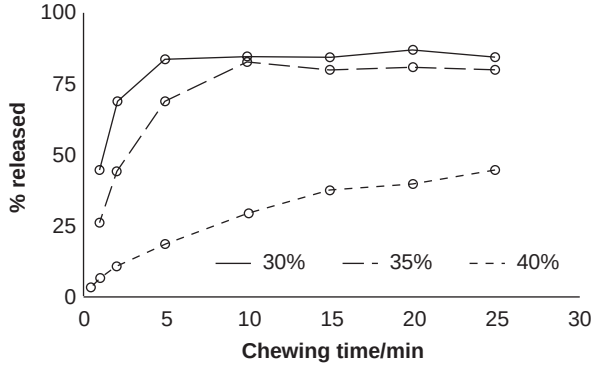

Figure 2. Release of methylene blue from MediChew® formulations with different quantity of gum base.

chewing, and fast onset of action is thus likely to be attained. Furthermore, hepatic first-pass metabolism and gastrointestinal tract degradation is avoided for substances absorbed through the oromucosal membranes, and bioavailability may, therefore, be increased. A fraction of the active substance will be swallowed with saliva and is accessible for absorption in the gastrointestinal tract. The distribution of oromucosal and gastrointestinal absorption varies depending on the physical and chemical properties of the active substance, the salivary flow rate and other such factors. Medical chewing gum may outperform conventional tablets in terms of fast absorption of the active substance, not only because of absorption through the oromucosal membranes but also because the active substance is dissolved in saliva when swallowed and is, therefore, readily accessible for absorption in the gastrointestinal tract.

3.2 Topical effect

Preventing or treating local conditions in the oral cavity requires that the active substance be available at therapeutic levels near or within the tissue being treated for a sufficient period of time. Chewing gum may outperform other topical drug delivery systems (e.g., oral gel, lozenges or mouth wash) as the release of active substances and maintenance of therapeutic concentrations can be controlled for longer periods. The deposition and clearance of a model substance, ^{99m}TcE-*N*-(*N*'-2,6-dimethylphenyl) carbamoylmethyl iminoacetic acid (HIDA), administered in sublingual tablets, chewing gum and lozenges were followed in the oral cavity/upper oesophagus by γ-scintigraphy [7]. The disappearance half-life and the area under the activity versus time curves showed a significant difference in the order sublingual tablets > chewing gum > lozenges, indicating that chewing gum is superior to lozenges as a delivery system for topically acting drugs.

3.3 Clinical experience with medical chewing gum

Nicotine chewing gum is by far the most well-known and well-documented medical chewing gum on the market. It was launched in the 1970s as an aid to smoking cessation and is now available in two strengths (2 and 4 mg) and in several flavours. Benowitz *et al.* [8] estimated that ~ 80% of the nicotine released from the chewing gum is absorbed through the oromucosal membranes. This is essential to the success of nicotine gum, as nicotine undergoes extensive first-pass metabolism (80%). A recent review confirms the efficacy of nicotine chewing gum in smoking cessation [9].

Acetylsalicylic acid chewing gum (Aspergum) was the first commercially available medical chewing gum. It was launched almost 80 years ago and is still among the pain relievers sold on the US market. Bousquet *et al.* [10] examined the relative bioavailability of acetylsalicylic acid in two chewing gum formulations (480 mg) compared with a conventional tablet formulation (500 mg) in 10 healthy male volunteers. The two chewing gum formulations had a significantly shorter time to maximum plasma concentration (T_{max}) than the tablet, possibly suggesting faster absorption from chewing gum. Bioavailability and maximum concentration (C_{max}) were lower for the chewing gum than for the tablet, which may be explained by incomplete release of acetylsalicylic acid from these specific formulations. Based on cumulative recovery of total salicylate in urine, Woodford and Lesko [11] found the relative bioavailability of Aspergum to be 70% compared with tablets. The chewed gum contained almost 38% of the administered dose, accounting for the remaining salicylate.

Dimenhydrinate chewing gum for the treatment of motion sickness is also commercially available. The bioavailability of dimenhydrinate from chewing gum and tablets was compared by Skofitsch and Lembeck [12]. They showed a slower rise in serum concentration for chewing gum than for tablets, but after 60 min the serum concentrations were comparable. Again, release of the active substance from chewing gum was not complete.

The rate of absorption and relative bioavailability of caffeine administered in chewing gum and capsules was recently examined [13]. T_{max} was 55 min for 200 mg caffeine

administered in chewing gum compared with 120 min for 200 mg caffeine capsules, thus indicating that the rate of absorption was significantly faster for chewing gum than for capsules. The absorption rate constant was also significantly higher. The area under the curve (AUC) and C_{max} were similar for both formulations.

Reportedly, a combination of nicotine and caffeine in chewing gum significantly increased the energy expenditure in healthy men [14]. Nicotine alone is known to have a thermogenic effect, which is enhanced by caffeine. Nicotine/caffeine doses of 0/0, 1/0, 2/0, 1/50, 2/50, 1/100 and 2/100 mg/mg were examined. Although there seemed to be a dose–response effect, the combination of nicotine 1 mg and caffeine 50 mg showed the most promising results as it had no adverse effects and still provided a high thermogenic response (7.9% increase compared with placebo). All combinations of nicotine and caffeine significantly decreased hunger feelings and increased satiety more than nicotine alone [15]. A nicotine/caffeine chewing gum may thus be useful in preventing weight gain after smoking cessation.

Christrup *et al.* [16] examined the bioavailability of the calcium blocker verapamil in chewing gum and tablets. Verapamil undergoes extensive first-pass metabolism and thus has a relatively low bioavailability following peroral administration. The AUC was slightly, but not significantly, higher after administration of chewing gum when compared with tablets. Verapamil could be measured in plasma 5 min after the administration of chewing gum and 15 min after the administration of tablets, indicating faster absorption from chewing gum. The AUC mean ratio of verapamil and its metabolite norverapamil was 0.8 after the administration of tablets and 1.5 after the administration of chewing gum. This difference was statistically significant and indicates that part of the verapamil was absorbed through the oromucosal membranes.

A similar study compared the bioavailability of methadone from chewing gum and tablets in seven patients with chronic pain [17]. Both the rate and extent of absorption were comparable for the two delivery forms.

The antifungal drug miconazole has been formulated in chewing gum to ensure a slow and prolonged release of the active substance for topical treatment in the mouth [18]. Clinical studies proved that miconazole chewing gum was at least as effective as miconazole gel, although only 3.6 mg of miconazole was released from chewing gum compared with a dose of 50 mg from the oral gel [19,20].

A number of other agents have been formulated in chewing gum to provide a topical effect in the oral cavity. These include fluoride [21-24] and chlorhexidine [25-31]. Chewing gum *per se* may also be beneficial (e.g., to patients suffering from xerostomia) as chewing gum increases the salivary flow [6]. Furthermore, clinical studies have shown that chewing gum has a beneficial effect on oesophageal reflux [32,33].

4. Conclusion

Medical chewing gum provides extended drug exposure in the oral cavity and throat. Drugs may either act topically or be absorbed through the oromucosal membranes and in the gastrointestinal tract to act systemically. Medical chewing gum based on the MediChew technology is successfully being deployed for systemic delivery of nicotine and local delivery of fluoride and chlorhexidine, for example.

Several new pharmaceutical products based on the MediChew technology platform will be available shortly.

5. Expert opinion

The increased need for new patient-friendly dosage forms with fast onset of action has paved the way for various oral dissolving/disintegrating technologies, and as chewing gum offers similar as well as additional benefits as a delivery vehicle for a wide range of pharmaceutical substances, medical chewing gum is likely to become more generally appreciated.

Clinical and commercial evidence indicates that the MediChew technology is superior as a delivery vehicle for active substances aimed at yielding topical effect in tissues of the oral cavity and the throat; for trans-oromucosal delivery of various absorbable active substances; and in treatment areas where the perception of chewing gum fits the product profile.

5.1 Topical treatment

Medical chewing gum is an obvious choice for topical delivery to the oral cavity and throat, and it has gained widespread acceptance for a range of lifestyle-related areas, mainly within general oral healthcare and fresh breath. The prophylactic use of fluoride chewing gum for dental care and chlorhexidine gum for disinfection and antiplaque treatments has been known for years. Compared with other delivery forms, such as lozenges and mouth wash, chewing gum may offer increased treatment efficacy as therapeutic concentrations may be achieved for a prolonged period in the oral cavity. Chewing gum was also found to be a successful delivery vehicle for antifungal treatment. Miconazole was investigated in a number of clinical studies [18-20], and it has been shown that a much lower drug dosage can provide an efficient therapeutic concentration in the mouth compared with oral gels. Medical chewing gum as a drug delivery system may, therefore, have fewer adverse effects than treatment with other delivery forms and may allow a more cost-efficient use of the active substance. Obviously, thorough drug release control is crucial to obtain the described benefits.

Topical treatment in the throat may also be a promising new area for medical chewing gum. Compared with other dosage forms such as lozenges, chewable tablets or syrups, chewing gum can provide prolonged and controlled drug

delivery. The extensive topical drug distribution is ensured by the mastication process.

5.2 Drug absorption

Drug absorption through the oromucosal membranes has a significant potential, especially in therapies that favour the avoidance of hepatic first-pass metabolism, fast onset of action and limitation of gastrointestinal adverse effects. The known drug delivery systems include medical chewing gum, lozenges, sublingual tablets, gels and various buccal adhesives. The oromucosal absorption of nicotine is the best demonstrated example and has become a major commercial success. To optimise oromucosal absorption, the release of the drug must be controlled and it must be provided in a chemical form that allows membrane passage.

5.3 Systemic effect

Drugs given for systemic effects are usually administered in tablets, but they could also be administered in a chewing gum formulation. For lipophilic drugs this would be an advantage because the chewing process will increase saliva flow, helping solubilise poorly soluble drugs *in situ*. In addition, xerostomia is a common adverse effect in a significant number of drugs. The increased saliva flow will counteract the patient's sensation of dry mouth and yield better product acceptance.

In the years to come, it is anticipated that medical chewing gum will become widely used in therapeutic areas such as cough and cold, allergies, migraine, pain relief and various lifestyle-related diseases.

People of the twenty first century are familiar with chewing gum and the past 30 years of nicotine replacement therapy has gradually helped to change the image of gum; making chewing gum widely accepted by the patient. Convenience and lifestyle play an increasingly important role in everyday life and the growing demand for easy, convenient and efficient delivery of medicine has made chewing gum an obvious candidate for the treatment of a wide range of diseases.

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