THE STICKY SOLUTION TO DRUG DELIVERY

It is widely used and often abused, but chewing gum is now being seen as a useful way of administering medication. Dr Barbara Conway outlines the benefits of chewing gum as a vehicle for drug delivery.

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Dr Barbara Conway is a senior lecturer at the Medicines Research Unit at Aston University in the UK. Her research interests include: the development of oral, ophthalmic and transdermal drug delivery systems; the design of modified release systems for drug delivery, including the use of mucoadhesives, fast-dissolving and chewing gum formulations; the enhancement of solubility and dissolution for poorly soluble drugs; the prediction of the properties of salts; and the development of in *vitro-in vivo* correlations.

Although medicinal chewing gums have been available since the late 1920s (Aspergum®, for example), it was only during the 1970s that the first gums containing nicotine were introduced and the potential of chewing gum as a dug delivery system was recognised.

The $12 billion gum market is currently growing at 3% annually, while sales of sugar-free gum are rising by 15% per annum. Chewing sugar-free gum has been shown to decrease dental decay by increasing plaque pH and stimulating saliva flow, while the chewing of xylitol-containing gums has been promoted as a public health prevention strategy.

Drug delivery

A drug released in the mouth from gum can act locally, it can be absorbed via the buccal mucosa or swallowed with saliva. Medicated gums can be used for the delivery of dental products in the mouth. Fluoride-containing gums, an alternative to mouthwashes and tablets, are available in a number of European countries (Fluogum® and Fluorette®, for example), while others are marketed for teeth whitening.

ADVANTAGES OF CHEWING GUM-BASED DRUG DELIVERY

- Convenient and discreet
- Widely acceptable
- Suitable for prolonged-release applications
- Suitable for local and systemic applications
- Fast acting

The potential of medicated chewing gums for the treatment of oral infections has been recognised, and gums containing chlorhexidine (Solo® and Vitaflo CHX®) are available for the treatment of gingivitis and plaque. Gums have also been produced that contain antifungal agents (such as nystatin and miconazole) or antibiotics, (penicillin and metronidazole) for the treatment of oral gingivitis. Functional chewing gums can be designed to appeal

to children that can improve their oral hygiene and provide them with minerals. It is claimed that Recaldent® in Trident® chewing gum for children strengthens the teeth by directly delivering calcium and phosphate.

The buccal mucosa is well-vascularised, and if a drug is absorbed buccally, then first-pass metabolism can be avoided and a faster onset of action is possible. Associated increases in bioavailability facilitate the use of lower doses and may reduce the incidence of gastric side-effects, a potential benefit of metformin gum that is currently under development.

Chewing gum is a highly convenient dosage form, as it can be administered without water. Although medicated gums are generally intended to be chewed for 10–30 minutes and can therefore be designed for sustained release, fast action can be achieved either from buccal absorption or by the active ingredient being dissolved in the saliva prior to swallowing. Aspirin, verapamil and caffeine-containing gums (Jol® varieties and Stay Alert®), have been shown to have a fast rate of absorption, while sustained blood levels can be maintained by repeated dosing.

Along with nicotine replacement patches, nicotine chewing gum for smoking cessation therapy has been a great success. In many countries, nicotine gum is available without a prescription, increasing its availability. Recent product variations have been launched with improved flavours, such as mint and fruit, rather than the original peppery flavouring – designed to reduce the unpleasant taste and burning sensation from nicotine – and flavoured, coated gums that are sweeter and easier to chew.

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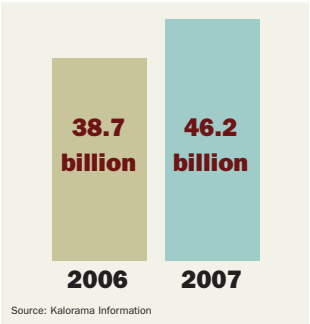
Other applications for chewing gum formulations include the delivery of antacids, such as calcium carbonate, and anti-emetics for travel sickness (such as Travel Gum®, available in some European countries).

The potential of gum in terms of fast onset of action, through buccal absorption and product development make it an attractive alternative delivery form for a range of other applications.

Pediatric medications

People who find it difficult to swallow tablets, such as children, can benefit from using chewing gum delivery systems. However, many products are unavailable in formulations suitable for paediatric administration and one consequence of this has been the production and administration of unlicensed formulations, often involving the manipulation of adult dosage forms.

Figure 1. Worldwide market for paediatric medications



Source: Kalorama Information

Fortunately, recent legislation and recommendations for the development of formulations designed for paediatric administration are expected to contribute to a 6.2% projected increase in sales of paediatric medicines (see Figure 1). The convenience and acceptability of chewing gum, the potential for buccal absorption and effective sweetening and taste masking make chewing gum an attractive dosage form for children. And there is considerable potential for developing child-specific over-the-counter healthcare, with fun shapes and formats that will increase compliance while maintaining parental confidence.

Manufacturing issues

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. As a result, directly compressible, free-flowing powdered gums have been developed to simplify the process (Pharmagum® and MedGumBase®). These powders can be blended with the active ingredient and compacted into a gum tablet using a conventional tablet press, simplifying the manufacture and facilitating inclusion of a wider range of drugs.

Drug release

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.

Future development

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.

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

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 fibre 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 paediatric drug delivery. **END**