



REVIEW ARTICLE



Medicated chewing gum: An unconventional drug delivery system

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ABSTRACT

Medicated chewing gum has a history for about a century. Now-a-days it is considered to be a potential and convenient modified release drug delivery system which can be used in pain relief medication, smoking cessation, travel illness, freshening of breath, prevention of dental caries, alleviation of xerostomia, vitamin or mineral supplementation etc. Medicated chewing gums are prepared by using a water insoluble gum base with water soluble bulk portion. This formulation offers both local and systemic effects and has a range of advantages over conventional oral solid dosage forms. USP currently has no *in vitro* release testing apparatus for the evaluation and determination of drug release from the prepared chewing gums. But European Pharmacopoeia adopted a compendial apparatus to do so. Medicated chewing has drawn attention to the researchers as potential drug delivery system and it could be a commercial success in near future.

Key Words: pharmaceutical chewing gum, gum base, oral mucosal drug delivery, buccal membrane, apparatus.

INTRODUCTION

The first medicated chewing gum was introduced in the USA in 1924 with the brand name Aspergum® (Imfeld, 1999). But history suggests that chewing of non-food items for the purpose of pleasure is as old as ancient Egyptian, Mayan civilizations. In 1848, the first commercial chewing gum named State of Maine Pure Spruce Gum appeared in the market whereas the first patent was issued to Dr. W.F. Semple who was a dentist at Ohio in 1869. Many people chew gum partly due to the belief that it increases aspects of mental performance, including concentration (Wilkinson *et al.*, 2002). In a study published by Al-Haboubi *et al.* in 2010 concluded that regular use of sugar-free chewing gum is associated with certain clinical and self-perceived benefits in older people living in the community. Scholey *et al.* 2009 found that the chewing of gum was associated with a small overall increase in performance on a battery of cognitive tests. Other studies indicate that chewing gum offers a range of benefits (Onyper *et al.*, 2011) like verbal working

memory (Hirano *et al.*, 2008; Zoladz and Raudenbush, 2005), free recall (Baker *et al.*, 2004; Johnson & Miles, 2008), attention (Smith, 2010; Tucha *et al.*, 2004; Tucha & Simpson, 2011), as well as performance on reaction time measures (Sakamoto *et al.*, 2009; Smith, 2010).

As chewing gums are taken orally and oral route of drug delivery is the most preferred route amongst the patient and clinicians due to various advantages it offers (Shojaei, 1998), in recent years chewing gums are considered to be friendly oral mucosal drug delivery systems (Surana, 2010). Chewing gum has been used to deliver therapeutic agents such as nicotine for smoking cessation therapy (Batra *et al.*, 2005; Moore *et al.*, 2008). A medicated chewing gum is solid, single-dose preparation that is intended to be chewed for a certain period of time, deliver the drug and which may contain one or more than one active pharmaceutical ingredient (Mehta *et al.*, 2010). Chewing gums are not swallowed and the remaining mass after chewing is discarded. During chewing the drug contained in the gum is released into the saliva. The released drug has got two fates; either it could be absorbed through the oral mucosa or may reach the stomach for GI absorption. In fact both these two fates may occur simultaneously. So, medicated chewing gums offer both local and systemic effect. This drug delivery system offers two

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Table 1: Limitations of conventional/traditional method and freezing, grinding & tableting method of chewing gum preparation (Heema and Stuti, 2010).

Manufacturing method	Limitation
Conventional/ traditional method	Manufacturing of thermolabile may become challenging as elevated temperature is required during melting; If the gum is highly viscous, accurate dosing is not possible; Lack of precise form, shape, weight of dosage form; Grinding and compression: difficult to formulate chewing gum as tablets due to high moisture content.
Freezing, grinding and tableting method	High-tech, expensive equipments are required; Careful monitoring of humidity during manufacturing process becomes a challenge.

absorption pathways. Drug absorbed directly via the buccal membrane avoids metabolism in the gastrointestinal tract and thus the chance of first pass effect of the liver. As a result drug formulation as medicated chewing gum may require reduced dose compared to other oral drug delivery systems.

This review will focus on different aspects of medicated chewing gum including advantages of the dosage form over other oral solid dosage forms, manufacturing methods, methods for evaluation, therapeutic applications.

BENEFITS

Medicated chewing gums offer a range of advantages as identified by the classic review work of Imfeld in 1999. The advantages may be summarized as below:

- Chewing gum can be used without water, at any time, and everywhere.
- As the incorporated therapeutic agents are protected from oxygen, light, and water, product stability is good.
- Chewing gum can produce both local effects in the mouth (local delivery) and systemic effects after the active agents have been swallowed or (preferably) after they have been absorbed through the oral mucosa. The later is of special interest with respect to bioavailability, since it avoids metabolism of the drug in the gastrointestinal tract and the so called liver-first-pass effect, because oral veins drain into the vena cava.

The other benefits that chewing gum may offer as a pharmaceutical dosage form are (Rassing, 1996; Surana, 2010; Heema and Stuti, 2010):

1. Fast/rapid onset of action
2. High bioavailability
3. Pleasant taste
4. Ready for use
5. High acceptance by children and for patients who find swallowing tablets difficult
6. Fewer side effects
7. Effect on dry mouth (xerostomia)
8. Product distinctiveness from a marketing perspective
9. Excellent for acute medication
10. Aspirin, Dimenhydrinate and Caffeine shows faster absorption through MCG than tablets.

MANUFACTURING AND EVALUATION

Medicated chewing gums can be manufactured by various techniques and methods. There are three major manufacturing methods available for medicated chewing gum formulation; 1) Conventional/traditional method (melting) (Athanikar and Gubler, 2001), 2) freezing, grinding and tableting method (Athanikar and Gubler, 2001; Keizo and Fumio, 1976) and 3) direct compression method (Heema and Stuti, 2010). Chewing gum prepared by using directly compressible chewing gum excipients like PharmaGum S, M and C offers formulation of a chewing gum which delivers drug more quickly and can be prepared in a more cost effective manner. The other two methods have got some limitations as described in Table 1.

Table 2: Components required for medicated chewing gum formulation.

Component	Function	Example
Water insoluble gum base		
Elastomers	Provides elasticity and controls gummy texture	Natural (chicle gum, nispero, rosadinha, jelutong, periollo, lechi-capsi, sorva etc.) and synthetic rubbers (butadiene, styrene copolymers, polyisobutylene, polyethylene mixtures, polyvinyl alcohol etc.)
Elastomer solvents	Softening the elastomer base component	Terpinene resins (polymers of alpha-pinene or beta-pinene), modified resins or gums (hydrogenated, dimerized or polymerized resins)
Plastisizers	To obtain a variety of desirable textures and consistency properties	Lanolin, palmitic acid, oleic acid, stearic acid, glyceryl triacetate, propylene glycol monostearate, glycerine, natural and synthetic waxes, hydrogenated vegetable oils, paraffin waxes, fatty waxes, sorbital monostearate, propylene glycol
Fillers or texturizers or mineral adjuvant	Provide texture, improve chewability, provide reasonable size of the gum lump with low dose drug	Calcium carbonate, magnesium carbonate, aluminum hydroxide, talc, aluminum silicate
Water soluble portions		
Softeners and emulsifiers	These are added to the chewing gum in order to optimize the chewability and mouth feel of the gum	Glycerin, lecithin, tallow, hydrogenated tallow, mono/ di/ tri glycerides
Colorants and whiteners	Gives the formulation soothing color and improves acceptability of the formulation	Titanium dioxide, natural food colors and dyes suitable for food, drug and cosmetic applications
Sweeteners	To provide the desired sweetness of the product	Water soluble sweetening agents (xylose, ribulose, glucose, mannose, galactose, sucrose, fructose, maltose, monellin, sugar alcohols like sorbitol, mannitol etc.), water soluble artificial sweeteners (sodium or calcium saccharin salts, cyclamate salts etc.), dipeptide based sweeteners (aspartame, alitame etc.), naturally occurring water soluble sweeteners, chlorinated derivatives of ordinary sugar (sucralose), protein based sweeteners (thaumatin I and II)
Antioxidants	Prevents any possible microbial growth	Butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate
Flavoring agents	To enhance consumer acceptability	Essential oils (citrus oil, fruit essences, peppermint oil, spearmint oil, mint oil, clove oil and oil of wintergreen) and synthetic or artificial flavors
Bulking agents	Used if low calorie gum is desired	Polydextrose, oligofructose, inulin, fructooligosaccharides, guar gum hydrolysate, indigestible dextrin
Compression adjuvant	To ease the compression process	Silicon dioxide, magnesium stearate, calcium stearate, talc

Composition

The most important material in chewing gum formulation apart from the active ingredient is the gum base which is an inert and insoluble no-nutritive

component. The other materials may be grouped as water soluble bulk portion (Zyck *et al.*, 2003). Table 2 summarizes the basic components required for the manufacturing of medicated chewing gum with

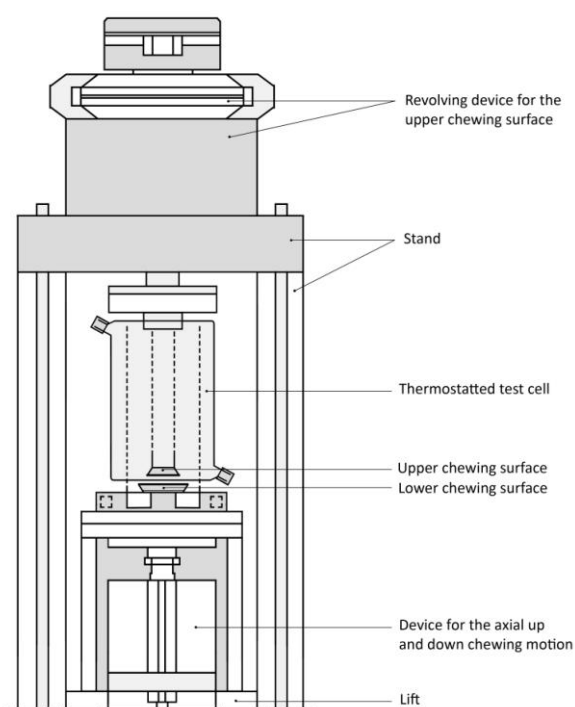


Figure 1: Schematic diagram of chewing apparatus for *in vitro* drug release study from medicated chewing gum (adopted from Gajendran *et al.*, 2008).

their function and suitable examples (Bhise and Jagirdar, 2005; Heema and Stuti, 2010).

Evaluation

Product quality tests for medicated chewing gums are described by Gajendran *et al.* (2008) according to European Pharmacopoeia. The tests include assay, identification and uniformity of dosage units, content, and mass. In addition to product quality tests several additional tests are done which are specific to the product and these tests ensure that the finished product is of quality as desired by the manufacturer. The tests generally include: texture analysis, product feel and consistency, evaluation of flavors and sweeteners, tests for coatings, impurities, water content, degradation products, residual solvents, etc. As USP does not contain a compendial apparatus for performance testing of medicated chewing gums in many cases product performance data are generated by apparatus developed by the drug product manufacturers and is not contained in the public monograph.

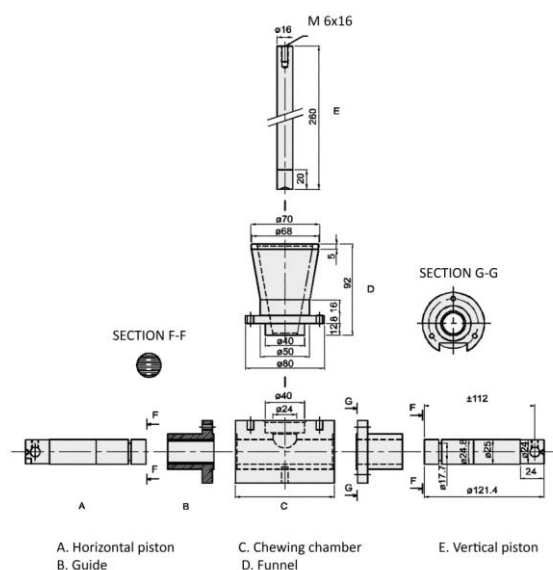


Figure 2: Schematic diagram of single-module chewing apparatus for *in vitro* drug release study from medicated chewing gum (adopted from Gajendran *et al.*, 2008).

To study *in vitro* drug release from the medicated chewing gum European Pharmacopoeia adopted an apparatus; Apparatus I. Chewing Gum Apparatus, Compendial-Ph. Eur in 2000 (European Directorate for the Quality of Medicines, Council of Europe, European Pharmacopoeia, 2000). Apparatus II, Alternative Chewing Gum Apparatus, Noncompendial-Wennergren is one of the noncompendial apparatus commercially available which was designed by Wennergren (Kvist *et al.*, 1999). Schematic diagram of apparatus for determination of drug release and single-module chewing apparatus (apparatus II) for *in vitro* drug releases study of medicated chewing gum are presented in Figure 1 and Figure 2 respectively.

THERAPEUTIC APPLICATION

Medicated chewing gums are used in various therapeutic purposes. A brief list of the therapeutic uses of medicated chewing gums is given in Table 3.

CONCLUSION

Medicated chewing gums could be a great way of delivering drug to the body either for local or systemic effect. The preparation procedure is easy and the dosage form is convenient to use, has got great

Table 3: Therapeutic uses of medicated chewing gums.

Therapeutic use	Specific example	Reference
Oral antifungal	Econazole Nystatine Miconazole	Jacobsen <i>et al.</i> , 1999 Andersen <i>et al.</i> , 1990 Pedersen and Rassing, 1990a; Jacobsen <i>et al.</i> , 1999; Pedersen and Rassing, 1990b; Pedersen and Rassing, 1991; Rindum <i>et al.</i> , 1993; Bastian <i>et al.</i> , 2004
Smoking cessation	Nicotine Silver acetate	Jensen <i>et al.</i> , 1990; Jensen <i>et al.</i> , 1991; Peters and Morgan, 2002; Morjaria <i>et al.</i> , 2004 Malcolm <i>et al.</i> , 1986; Jensen <i>et al.</i> , 1990; Jensen <i>et al.</i> , 1991
Pain relievers	Aspirin Methadone	Bousquet <i>et al.</i> , 1992; Christrup and Rassing, 1988 Hodoba, 1999
CNS stimulation, improvement of memory	Caffeine	Kamimori <i>et al.</i> , 2002
Treatment of otitis media	Xylitol	Uhari <i>et al.</i> , 1998; Skofitsch and Lembeck, 1983
Treatment of dental carries	Chlorhexidine	Imfeld, 2006
Treatment of vitamin C deficiency		Christrup <i>et al.</i> , 1988; Heema and Stuti, 2010
Treatment and management of motion sickness	Dimenhydrinate	Seibel <i>et al.</i> , 2002
Acid neutralization	Antacid	Bhise and Jahagirdar, 2005

patient compliance. The mouth freshening effect also adds some advantages. But quality testing procedures are not still well developed. The USP does not have any official method of *in vitro* drug release study. So evaluation of the prepared chewing gums is one of the major challenges.

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