



Medicated chewing gum: modern approach to improve mucosal drug delivery system- a review

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ABSTRACT

In current years technological advancements have been made in the research and development of oral drug delivery systems. 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 sickness, freshening of breath, avert of dental caries, mitigation of xerostomia, vitamin or mineral companion etc. Medicated chewing gums are solid, single dose making with a base consisting mainly of gums that are intended to be chewed but not swallowed. It is a potentially valuable means of administering drugs either locally or systematically via, the oral cavity. Chewing gum known as gum base (insoluble gum base resin) contains elastomer, emulsifiers, fillers, waxes, antioxidants, softeners, sweeteners, food colorings, add to flavor agents, and in case of medicated chewing gum, active contents. An In-vitro apparatus was specially designed and constructed for release testing of medicated chewing gums.

Keywords: Oral drug release, medicated chewing gum, patient, sickness, xerostomia.

INTRODUCTION:

It is well known fact that the right drug delivery system is critical to the success of a pharmaceutical product. Now-a-days most of the pharmacological active agents or drugs are formulated into various solid dosage forms including the most popular ones like capsules, tablets etc. and semi-solid dosage forms such as creams, ointments, gels etc. and also formulated into variety of dosage forms like capsules, tablets, inhalers, injectables, ointments etc considering pharmacokinetic and pharmacodynamic parameters, physicochemical properties, and biopharmaceutical aspects of drugs. MCG represents the newest system with potential uses in pharmaceuticals, over the counter medicines and nutraceuticals¹. The drugs intended to act in oral cavity often have low water/saliva solubility and chewing gum constitute a valuable delivery system for such drugs.² The use of MCG is feasible in local treatment of diseases of oral cavity as well as treatment of systemic conditions.³ Oral route is the most preferred route amongst the patient and clinicians due to various advantages it offers. One reason is that the oral route achieves such popularity may be in part attributed to its ease of administration.⁴ Medicated chewing gum (MCG) is the gum base incorporating drug(s) which may or may not be coated. The water content of chewing gum is extremely low and requires no preservatives. MCGs are definite by the European Pharmacopoeia and the guidelines for

pharmaceutical dosage forms issued in 1991 by the Committee for Medicinal Products for Human Use (CPMP) as 'solid single dose preparations with a base consisting mainly of gum that are intended to be chewed but not to be swallowed, providing a slow steady release of the drug contained¹.

MERIT OF MCGs:^{6, 17-21, 26}

- Does not need water to swallow. Therefore can be taken anyplace.
- Ready for use.
- Valuable for patients having difficulty in swallowing.
- Excellent for acute medication.
- Counteracts dry mouth- throughout stimulation of the salivary secretion thereby preventing Candidacies and caries.
- Highly acceptable by children.
- Avoid first pass metabolism and therefore increases the bioavailability of drugs.
- Due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation thus results are the Rapid onset of action.
- Gum does not make contact with to stomach. Hence G.I.T. suffers less from the effects of excipient.
- Stomach does not suffer from direct contact with high concentrations of active principles, therefore reducing the risk of intolerance of gastric mucosa.

- Product's parts reaching the stomach is conveyed by saliva delivered continuously and regularly. Duration of action is increased.

DEMERIT OF MCGs:^{6, 21-26}

- 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.⁴
- In the MCG formulation present of Sorbitol may cause flatulence, diarrhea.

- Additives in gum like flavoring agent, etc., Liquorice can cause Hypertension and Cinnamon can cause Ulcers in oral cavity.

- Chlorhexidine oromucosal is limited function to short term use because of its unpleasant taste and staining properties to teeth and tongue.

FORMULATION, PREPRATION AND EVALUATION OF MCGs.:

TABLE 1: Composition of gum base and their function with examples.^{2, 5, 34}

COMPONENT	FUNCTION	PROPORTIONIZED	EXAMPLE
WATER INSOLUBLE CHEWABLE GUM BASE PORTION³⁴			
Elastomer Natural elastomer	Provides elasticity and controls gummy texture	45.0% to 70.0%, (with elastomer solvents) by weight of the gum base.	Natural rubbers similar to Latex or Natural gums such as <i>Chicle, Lechi</i> .
Synthetic elastomer			Butadiene, isobutylene etc.
Elastomer solvent	Softening the elastomer base component		Terpinene resins
Plasticizers a.)Natural plasticizers	to obtain a variety of desirable textures and consistency properties	(3-20)% by wt. of gum base	Natural rosin esters similar to Glycerol, Polymerized Esters,
Synthetic plasticizers			Derived from α -pinene.
Fillers and texturizers or mineral adjuvant	Improve chewability, Provide texture, and provide reasonable size of the gum lump with low dose drug	2-60 % by wt. of gum base	Magnesium carbonate, Calcium carbonate, talc, alumi-num hydroxide
WATER-SOLUBLE BULK PORTION³⁴			
Softners and emulsifiers	These are added to the CG in order to optimize the chewability and feel of the gum.	<0.1%	lecithin, hydrogenated tallow, mono/di/ tri glycerides Glycerin, tallow,
Colorants and whitners	Gives the formulation soothing color and improves acceptability of the formulation	<0.1%	Titanium dioxide, natural food colors and dyes suitable for cosmetic applications, drug, and food.
Sweetners Water-soluble sweetening agents	To provide the desired sweetness of the product	Upto 60%	Galactose, xylose, mannose, glucose,
Water-soluble artificial sweeteners			sodium saccharin salts and cyclamate
Dipeptide based sweeteners			Alitame, Aspartame,
Water-soluble sweeteners			Sucralose

Protein based sweeteners			Thaumaococcus-danielli.
Bulking agent	Used if low calorie gum is desired	0.01-1%	Oligof-ructose, Polydextrose, guar gum hydrolysate
Flavouring agent	To enhance consumer acceptability	0.01-1%	Essential oils (fruit essences, citrus oil,
Antioxidants	Prevents any possible microbial growth	0.02%	Propyl gallate, butylated hydroxyani-sole.
Compression adjuvants: Glidant, Adherent, Lubricant	To ease the compression process	0.2-1%	Talc, magnesium stearate, calcium stearate, Silicon dioxide.
Active ingredient	To achieve the pharmacological effect of the ingredient	0.5-30 % of final gum weight	Drug

MANUFACTURE OF THE MCG:^{2, 35}

Different methods employed for the manufacturing of Chewing gum can be broadly classified into three main classes namely-

- Conventional/ traditional Method (Melting),
- Freezing, grinding and tableting Method,
- Direct Compression Method

CONVENTIONAL/ TRADITIONAL METHOD (MELTING):³⁶

Components of gum base are softened or melted and placed in a kettle mixer to which active ingredients,

syrops, sweeteners, and other excipient are added at a definite time. After that the gum is sent through a series of rollers that form into a thin, wide ribbon. During this procedure, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to enhance the flavor. Within a carefully controlled room, the gum is cooled (for up to 48 hours). This permits the gum to place accurately. At last the gum is cut into the appropriate and suitable size and cooled at a carefully controlled temperature and humidity.

FREEZING, GRINDING AND TABLETING METHOD:^{2, 5}

Table 3: Steps of chewing gum manufacturing by freezing, grinding and tableting.

FREEZING	GRINDING	TABLETTING
Gum base is cooled to a temperature at which the composition is sufficiently brittle and would remain brittle. The temperature of the refrigerated mixture is generally around- 15°C or lower. Various coolants like liquid nitrogen, hydrocarbon slush use of solid carbon dioxide are preferred.	A composition of chewing gum mixture, solid carbon dioxide and precipitate of silica is ground in a mill grinder To prevent the gum from sticking to the grinding apparatus, 2 to 8% by weight of grinding aid such as alkaline metal phosphate, altodextrin or an alkaline earth metal phosphate can be incorporated.	Once the coolant has been removed from the powder, the powder can be mix with additional ingredients such as binders, lubricants, coating agents and sweetners The granules accordingly obtained can be mixed with antiadherents like talc Compression must be carried out by conventional process like punching.

DIRECT COMPRESSION METHOD:^{36, 38}

EVALUATION/ STABILITY OF MCGs:²

IN-VITRO DRUG RELEASE TESTING METHODOLOGY:⁵

It has been commercially reported that the drug release from MGCs as per the specification given in European Pharmacopoeia and is determined by applying a mechanical kneading procedure to a piece of gum placed

in a small chewing chamber containing a known volume of buffer solution.

SCIENTIFIC RATIONALE FOR IN VITRO DRUG RELEASE DETERMINATION:

APPARATUS I: Compendia chewing gum apparatus-European Pharmacopoeia:^{2, 5, 45}

Adopted by Ph. Eur. in 2000 (Figure 4). The chewing apparatus include a chewing chamber, two horizontal pistons, and a third vertical piston (tongue). The vertical piston work alternatively with the two horizontal pistons and makes sure the gum stays in the right place between chews. If essential, it is feasible to construct the machine so that at the end of the chew the horizontal pistons rotate around their own axes in opposite directions to each other to obtain maximum chewing. The working process of this chewing apparatus is explained in Ph. Eur. (European Pharmacopoeia). General monographs 2.9.25, 2000, 2005, 2008). Numerous studies have been carried out using the Ph. Eur. apparatus, and the outcome indicates the methodology is rugged and reproducible.

APPARATUS II -Noncompendial chewing gum apparatus-Wennergren:^{2, 5, 45}

One of the non compendial apparatus commercially available was designed by Wennergren (Kvist et al, 1999) (Figure 5). The chewing process consists of reciprocations of the lower surface in combination with a shearing (twisting) movement of the upper surface that provides mastication of the chewing gum and at the same time

adequate agitation of the test medium. The flat surface of upper jaw is parallel to the central part of the lower surface. The small brim of the lower surface is angled upwards (45 degrees) so that the lower surface functions as a small bowl with a flat bottom. This bowl prevents the chewing gum during mastication from sliding. The influences of different operational parameters of the chewing gum apparatus on drug release have been carefully investigated.

In vivo 'chew-out' studies:^{26, 46.}

The in vivo release of active ingredient from chewing gum during mastication can be studied by recruiting a panel of sufficient numbers of tasters and scheduled chew-out studies. For the period of the chewing procedure the drug contained within the MCG is released in the saliva and then it is either absorbed through oral mucosa or, if swallowed, it is absorbed throughout the gastrointestinal tract.

- a. Release of drug in saliva:
- b. Dissolution test of residual medicated chewing gum:
- c. Urinary excretion profile of medicated chewing gum:
- d. Buccal absorption test:

APPLICATIONS:^{6, 41, 47-50}

Table 4: List of marketed MCGs^{2, 5}

Therapeutic effect	Active pharmaceutical ingredient	Trade name	Commercially Available
Local therapy			
The Cariostatic re-elevates plaque pH which lowers intensity and frequency of dental caries	Fluoride	Fluorette	USA
For Dental hygiene and tooth whitening	Calcium as a tri calcium phosphate	Orbit white	
		Happydent white	
		Trident white	
		Recaldent	
Antibacterial agent – preventing tooth decay & to treat periodontitis, pharyngeal Infections, oral and gingivitis.	Chlorhexidine	Vitaflo CHX	USA
		Advanced +	
		HEXIT	
Systemic therapy			
Pain relief- in treatment of minor pains, headache and muscular aches	Aspirin	Aspergum	North America
Smoking cessation	Nicotine	Nicorette	Worldwide
		Nicotinelle	Western Europe,
		NiQuitin CQ	Australia
Neutralization & Stomach	Calcium carbonate	Chooz	USA
General health	Vitamin C	Endykay	Middle East, Uk
		Stamil	Australia

		Source	Australia
Enhanced brain activity	CCE & DHA	Brain	Japan
Alertness and lipolysis and have a thermogenic effect (increased energy expenditure) and reduce feeling of hunger	Caffeine	Stay alert	USA
		Café coffee	Japan
	Guaran	Buzz gum	United Kingdom
		Go gum	Australia
Diet	CR	Chroma slim	USA
Reduces the symptoms associated with stress, anxiety and depression	Extracts of Jujube Fruit Calcium carbonate, Passion Flower.	Zoft stress gum	
Symptomatic relief from postmenopausal syndrome	Extracts of Dong Quai Root, Black Cohosh Root, Damiana Leaf, Mexican Wild Yam Root	Zoft menopause gum	
Appetite suppressant for weight loss	Extracts of Hoodia gordonni -- nature's calcium channel blocker	Slim n trim Chew away gum	
Increases male sexual desire and Performance	Extracts of Ginkgo Biloba Leaf	Zoft virility gum	

FUTURE OPPORTUNITIES:²⁶

Chewing gum not only offers clinical benefits but also is an efficient, discrete, mobile and attractive drug delivery system. Generally it takes time for a novel drug delivery system to establish itself in the market and gain acceptance and popularity by the patients, though chewing gum is supposed 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. The MCG has potential for rapid onset of action, buccal delivery, and the opportunity for product. The cause is easy that the chewing gum delivery system is easy to administer anytime, anywhere, convenient, suitable and its pleasant taste increases the patient compliance and product acceptability. From these reasons, the preparation of MCG has a bright future.

CONCLUSION:

MCGs are most suitable, self medicated, convenient, easily administered without water and very patient compliant. Thus, it can be concluded that the chewing gum can be use, as a carrier for extensive categories of drugs where extended release and the local action is desired. A chewing gum formulation must have a

pleasant taste and texture. A large amount of active substances have a bitter, unpleasant, or metallic taste. (Chewing time is 10–20 minute). Poorly water-soluble drugs require specialized formulation techniques to encourage release, and these techniques are practically well developed. Dental health medicated chewing gum for caries treatment or prevention has come to stay and the indications are that it will be accepted widely in future.

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