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RESEARCH ARTICLE

MEDICATED CHEWING GUM: EMERGING TECHNIQUE IN ORAL DRUG DELIVERY

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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 conve-nient 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 supplementa-tion etc. Medicated chewing gums are prepared by using a water insoluble gum base with water soluble bulk portion. A medicated chewing gum (MCG) is solid, single-dose dosage form. It is prepared such that it can be chewed for a period of time; deliver the drug and which may contain one or more active pharmaceutical ingredients. Medicated chewing gum provides a wide range of advantages that helps to make it an excellent alternative over other chewable dosage forms. Medicated chewing gum (MCG) is a drug delivery system that consists of an active ingredient incorporated into a chewing gum and released by the mechanical action of chewing. A special *in-vitro* apparatus was designed and constructed for release testing of MCGs which is official in European Pharmacopoeia. It offers a highly convenient, patient-compliant way of dosing medications, particularly for people with swallowing difficulties such as children and the elderly.

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INTRODUCTION

The European Pharmacopoeia defines medicated chewing gum as ''solid, single-dose preparations with a base consisting mainly of gum that are intended to be chewed but not swallowed''. (Upendra Nagaich *et al*., 2010) These type drug delivery system is increases patient compliance, especially for geriatrics and pediatrics with swallowing disorders; moreover, the product can be taken anywhere without water or without liquid. (Swamy *et al*., 2012) Nowdays MCG is convenient drug delivery system which is appropriate for a wide range of active substances. (Fertin Pharma, 2015) The first patent for the production of chewing gum was filed in 1869 and was issued to Mr. W. F. Semple in Ohio under U. S. Patent No. 98,304. A MCG containing Acetyl Salicylic Acid was commercially introduced in 1928. In 1991, Chewing Gum was approved as a term for pharmaceutical dosage form by the commission of European Council. (Basani Gavaskar *et al*., 2011) chewing the drug contained in the gum is released into the saliva. The released drug has got two ways either it could be absorbed through the oral mucosa or may reach the stomach for GI absorption. In fact both these two ways may occur simultaneously.

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So, medicated chewing gums offer both local and sys-temic effect. Drug absorbed directly via the buccal membrane and The later is of special interest with respect to bio-availability, since it avoids metabolism of the drug in the gastrointestinal tract and the so called liver-first-pass effect. (Sabera Khatun and Kumar Bishwajit Sutradhar, 2012) Chewing gums are mobile drug delivery systems. Chewing gum usually consists of a gum core, which may or may not be coated. Chewing gum can be used as a convenient modified release drug delivery system. Medicated chewing gums are currently available for pain relief, smoking cessation, travel illness, and freshening of breath. In addition, a large number of chewing gum intended for prevention of caries, xerostomia alleviation and vitamin or mineral supplementation are currently available. (Sharma Narendra *et al*., 2013)

Advantages

1) Does not require water to swallow. 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,

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) Stomach does not suffer from direct contact with high concentrations of active principles, thus reducing the risk of intolerance of gastric mucosa,
10) Fraction of product reaching the stomach is conveyed by saliva delivered continuously and regularly
11) Aspirin, Dimenhydrinate and Caffeine shows faster absorption through MCG than tablets,
12) Stimulates flow of saliva in the mouth,
13) Neutralizes plaque acids that form in the mouth after eating fermentable carbohydrates,
14) Helps whiten teeth by reducing and preventing stains. (Ezhumalai *et al*., 2011; Jadhav and Mohite, 2014)

Composition of medicated chewing gum (Vasudha Lakshmi *et al*., 2014; Harnish Patel *et al*., 2014; Shashank Nayak *et al*., 2012; Nagasamy Venkatesh *et al*., 2014)

Gum base: Gum base is an inert and insoluble nonnutritive product used as a support for the edible and soluble of the medicated chewing gum such as sugar, glucose, poly oils and flavors.

Elastomer : It provide elasticity and cohesion to the chewing gum.

Active pharmaceutical drug- Purpose for pharmacological action.

Antioxidants: prevention of oxidation Ascorbic acid, tocopherol, and butyl hydroxytoluene

Emulisifier and Fats-provide soften the mixture and optimize chewabilty.

Monoglycerides, diglycerides and partly hardened vegetable and animal fat

Fillers - They provide the right texture for the gum base, improve chewability, and provide reasonable size of the gum lump with low dose drug. Magnesium and Calcium Carbonate, Ground Limestone, Magnesium and Aluminium Silicate, Clay, Alumina, Talc

Coloring agent–provide color to the preparation FD & C type dyes and lakes, fruit and vegetable extracts

Flavouring agent- Citrus oil, fruit essences, Peppermint oil, Spearmint oil, Mint oil, Clove oil.

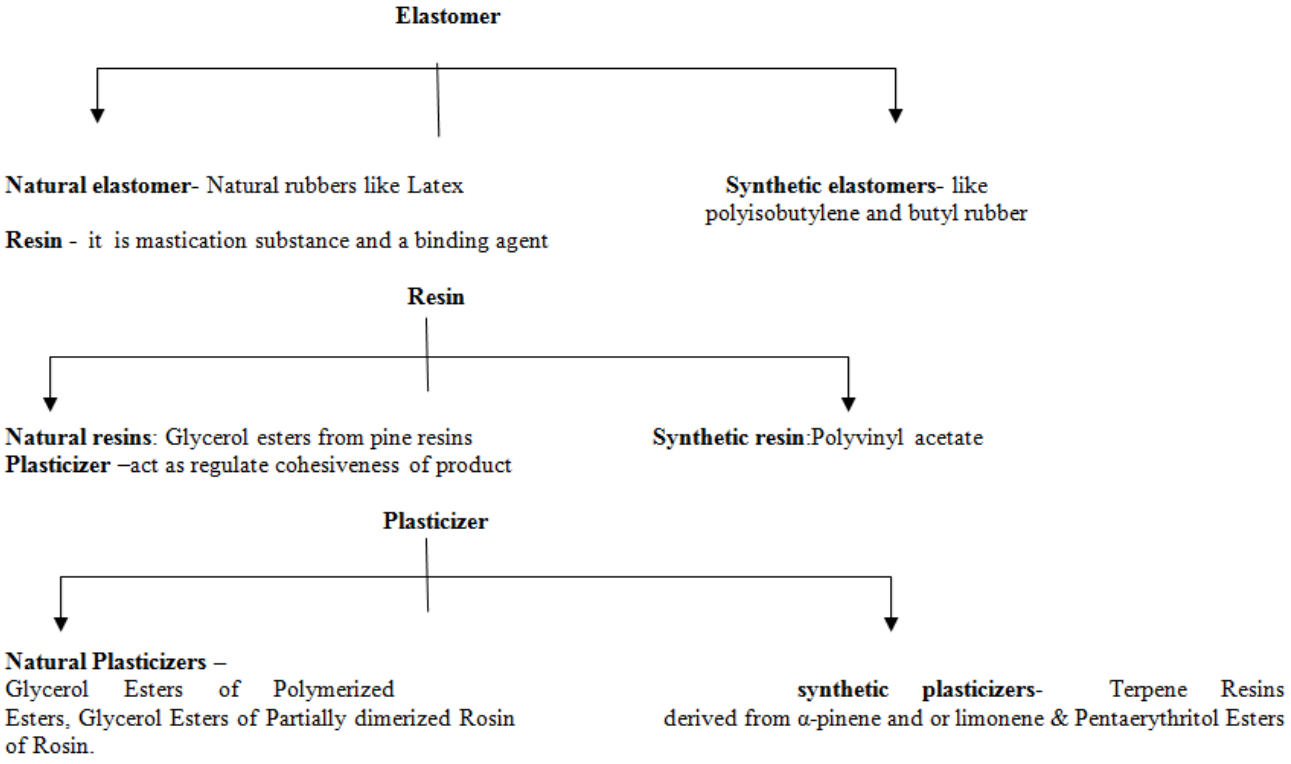
MANUFACTURING PROCESS (Kinjal R. Shah and Tejal, 2014; Naik Heema, 2010).

Conventional/Traditional Method

Gum base are melted in a planetary mixer with syrups, colorants and other excipients then the gum base pass through a series of rollers until a thin flat ribbon is formed. The gum is allowed to cool for 2 days.

Freezing, grinding and tabletting Method

The gum base cooled upto -15°C and Pregrinded in large fragments.Gring and anti caking agents are added.Blended with lubricant and sweetners and the granules are coated by using FBP. Antiadherents are added and granules are compressed.



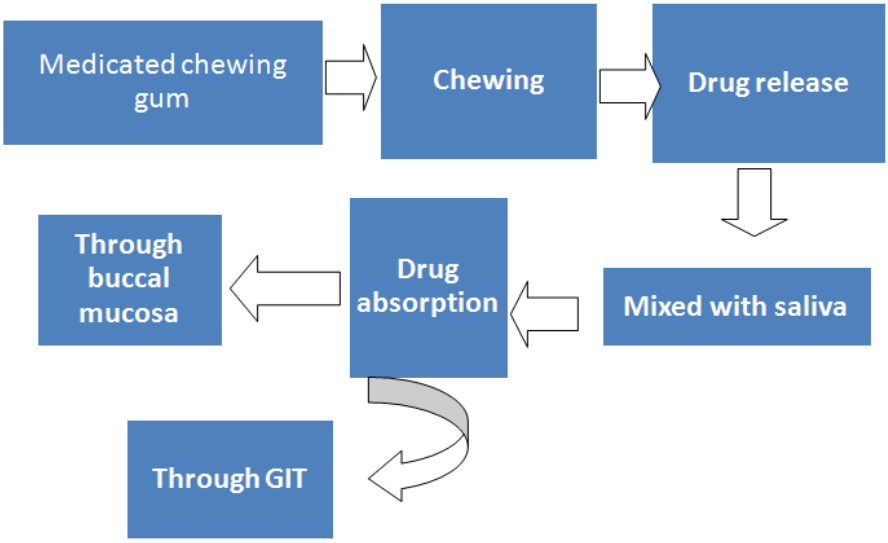
Direct compression Method

It is suitable when the directly compressible excipients are available. The limitations of melting & freezing can be overcome by the use of these. It is manufactured under CGMP conditions and complies with Food Chemicals Codex specifications as well as with FDA, so they can be considered as "Generally regarded as safe" (GRAS).

Some important formulation aspect (Savaliya pratik *et al.*, 2011)

- Increased amount of softners and emulsifiers in gum base fasten release whereas hard gum may retard.
- Solubilisation technique increases aqueous solubility of drugs that are poorly water soluble.

Mechanism (Abhilash Mund *et al.*, 2015)



Mechanism of Drug Transport (Prashant K. Pagare *et al.*, 2012)

Main pathways of drug transport across buccal mucosa follow simple ficksian diffusion. Passive diffusion occurs in accordance without the pH partition theory. Equation for drug flux is:

J = DKp/Δce
J = drug flux
D = diffusivity
Kp = partition coefficient
ΔCe = concentration gradient
h = diffusional path length

It shows (h) that the flux may be increased by decreasing the diffusional resistance of the membrane by making it more fluid, increasing the solubility of the drug in the saliva immediately adjacent to the epithelium or enhancing the lipophilicity through pro-drug modification.

Because of the barrier properties of the tight buccal mucosa, the rate limiting step is the movement of the drug molecules across the epithelium. Two pathways of permeation across the buccal mucosa are transcellular and paracellular.

The pathway of drug transport across oral mucosa may be studied using:

- Microscopic techniques using fluorescent dyes
- Autoradiography and
- Confocal laser scanning microscopic procedures.

- A solid system of lipophilic active ingredients bound to the cation exchange resin permits a sustained drug delivery system.
- Microencapsulation or agglomeration are the methods to modify and control the release of active ingredient.

Available Patent related to medicated chewing gum (http://worldwide.espacenet.com/searchResults?page=1 &ST=singleline &query=medicated+chewing+gum&locale=en_EP&D)

Stable medicated chewing gum comprising cyclodextrin inclusion complex	US2013022652
Medicated chewing gum delivery system for nicotine	MY124346
Medicated chewing gum	US2010209359
Medicated chewing gum and a process for preparation thereof	US5866179
Medicinal chewing gum that incorporates acetylsalicylic acid	JPH04312532
Pharmaceutical compositions for the treatment of aphtha and erosive lichen	GB981260
Laxative chewing gum	GB249816
Stable medicated chewing gum comprising antioxidant	WO2009006892
Medicated toothcleaning chewing gum	CN1181927

Optimum Properties of Drug (Mohan *et al.*, 2012)

Physicochemical Properties of Drug	Patient Related Factors
High Salivary Solubility	Non-toxic to oromucosa and salivary Ducts
pH independent solubility	Non-carcinogenic
	Should not cause tooth decay
Tasteless	Should not cause oromucosa and teeth
	staining
	Should not affect salivary flow rate

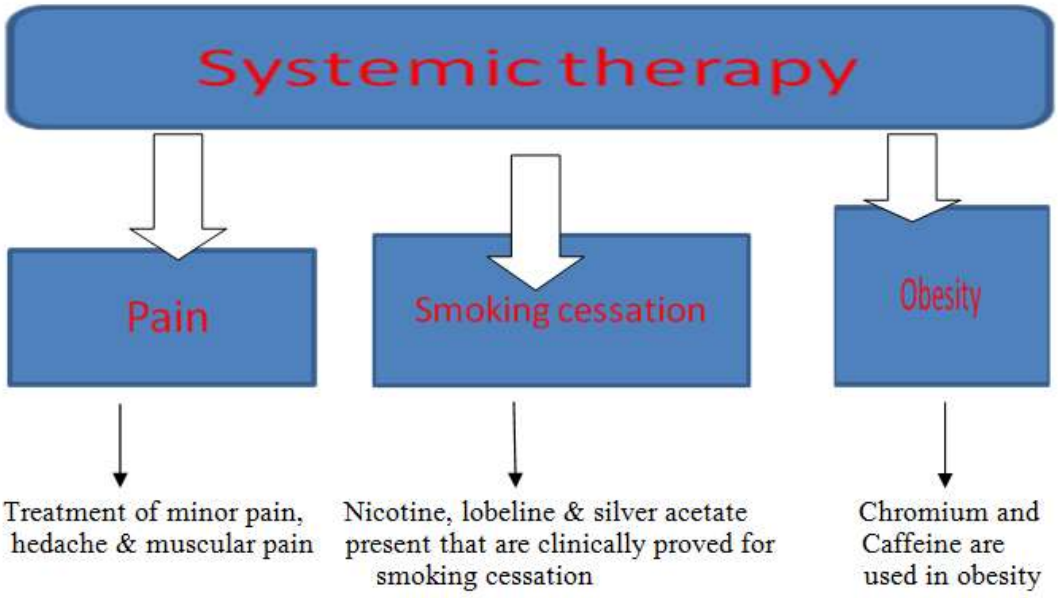
Formulation techniques for the preparation of sustained release Medicated chewing gum (Navya and N.Rama Rao, 2014)

1. Particle size of the drug
2. Drug-Ion exchange complex: Drug make a Complex with ion exchange resin show the release of drug slow from gum base.
3. Adsorption: Adsoprtion of a flavoring agents onto silica gel could reduce the release rate of drug from chewing gum.
4. Coating and embedding: Coating of drug with various coating agents like PVP, celluloses and Embedding a drug in hydrophobic matrix consisting of lecithin, synthetic waxes or mixtures was found to reduce the release rate of drug from chewing gum.

Application (Shahid Mohammed and Niranjan Babu, 2014; Tarun Garg and Amit K. Goyal, 2014)

Dental caries

Prevention and cure of oral disease are obvious targets for chewing gum formulations. It can control the release rate of active substances providing a prolonged local effect. It also re elevates plaque pH which lowers intensity and frequency of dental caries. Fluoride containing gums have been useful in preventing dental caries in children and in adults with xerostomia. Chlorhexidine chewing gum can be used to treat gingivitis, periodontitis, oral and pharyngeal infections.



Factors affecting drug release from chewing gum (Prabhanshu Vaishy *et al*., 2014)

• **Contact Time:** The local or systemic effect is dependent on contact time of MCG in oral mucosa. In the clinical trial studies chewing time of 30 minutes was considered close to ordinary use.

• **Physicochemical properties of drug:** Physicochemical proprty plays a very important role in release of drug from MCG. Ingredients soluble in saliva will be immediately released within few minutes whereas lipid soluble drugs are released first into the gum base and then released slowly.

• **Inter individual variability:** Chewing frequency and Chewing intensity which affect the drug release from MCG may vary from individuals. The *in-vitro* study prescribed in European Pharmacopoeia suggest 60 cycles per minute chewing rate for proper release of active ingredient.

• **Formulation factor:** Composition and amount of gum base affect rate of release of active ingredient. The increased lipid fraction of gum leads to the delayed release rate of drug

Future prospective

Medicated chewing gum is a advance form of the oral formulation and they develops a dramatic change in the patient suffering from the swallow able disorder and patient that are older in age. Medicated chewing gum are most popular among children and they easily take the drug like a chocolate, but apart from this medicated chewing gum is suffering from several incompatibility related problems and the most common is physical incompatibility. A lot of research is required on the Medicated chewing gum for the drugs that are suitable for the preparation of the Medicated chewing gum and not have physical incompatibility.

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