Medicated chewing gums – An Overview

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ABSTRACT

Now-a-days, there is increased interest on the formulation of oral delivery systems the reason behind this the ease of administration offered by oral route. Besides its ease, oral route offers a variety of advantages over others. Medicated chewing gum is one the technological advancement in the field of oral drug delivery systems. In recent years, chewing gums gained increased acceptability among the patients because of its advantages like local and systemic effects, avoidance of first pass metabolism, fast action with fewer side-effects etc. Chewing gums provide feasibility of removing the chewed mass from the oral cavity at times needed without any invasive means. Medicated chewing gums uses a gum base into which other additives like elastomers, plasticizers, softeners, fillers, colors, flavors, sweeteners and ofcourse an active drug are incorporated. They provide a beautiful means of self-medication and can be administered anytime, anywhere without need of water. Drug release from the chewing gums is directly proportional to the extent we chew the gum mass in the oral cavity. Thus, in near future we may find various drugs formulated in the form of chewing gums. The current review presents a brief idea on the history, advantages, composition, manufacturing and evaluation of medicated chewing gums.

Keywords: Chewing gum, Gum base, Plasticizers, Elastomers, Mucosa, Saliva.

INTRODUCTION

Chewing gum is a pleasure that almost all people use it the world wide. These are used as a convenient modified release drug delivery system. Chewing gums usually contain gum core, which is either coated or not coated. Commercially available medicated chewing gums are used for pain relief, smoking cessation, travel illness and freshening of mouth. In recent years, they are considered as friendly oral mucosal drug delivery system. [1] When compared to other routes of administration, oral route is very convenient for patients due to various advantages.

Medicated chewing gums are solid single dose preparations that have to be chewed but not
swallowed. They contain one or more active ingredients that are released by chewing. Basis for introducing medicated chewing gums in today’s market is to provide the release of drug substances directly into bloodstream faster than pills.

Medicated chewing gums are intended to be chewed for a certain period of time, required to deliver dose, after which remaining mass is discarded. During chewing process drug contained in a gum is released into saliva, and could be absorbed through oral mucosal or swallowed reaching stomach for GI absorption.

Chewing gums contain water soluble and water insoluble portions. Water soluble portions include plasticizers, elastomers, fillers and mineral adjuvants. Water insoluble portion includes sweeteners, antioxidants, softeners, bulking agents and emulsifiers. Chewing gums are now extensively used as drug delivery agents for many components in order to treat oral and throat infections. Particularly, for children this is very convenient method of administration when compared to tablets, liquids. Nowadays, chewing gums must meet the high quality standards as tablets. In particular, anecdotal effect of chewing gum on weight loss must also be studied [1,2].

HISTORY

Homosapiens use different natural resources for survival like shrub, herb, plant, trees and utilized them in the form of food, wood, medicine, shelter etc. Ancient people know how to use plant parts. For example, before invention of tooth brush they used Azadirachta indica (neem) to clean their teeth and for its antibacterial action. In the same way, chewing gums today are used as they provide antimicrobial actions and prevent dental caries. In the recent trend, researchers for drug loaded chewing gum and smoke session chewing gum.

Chewing gum has been used since centuries by mayanIndians chewed tree resin form sapodilla tree to clear their mouth and fresher their teeth. These medicated chewing has been used since world war-II due to shortage of natural gum bases, due to enhanced development of systemic gum bases that are used now a days. Chewing gums has old and long history in 50 AD, Greek sweetened to breathe and clean their teeth by Mastic resin from bark of mastic tree.

The first chewing gum was marketed in 1948 in USA i.e. State of Maine pure spruce gum. Aspergum is the first chewing gum launched in 1928 for analgesic activity. Dimenhydrinate is another commercially available chewing gum for motion sickness. First patent was issue to DR. W.F Semple who was a dentist of ohio in 1869. In 1999 December new England journal of medicine, reveals that chewing gums increases energy from 58k.cal hour to 70 k.cal per hour. [3,4]

ADVANTAGES OF CHEWING GUM

Chewing gums provide the following advantages
1. Chewing gums have pleasant taste.
2. High availability.
3. GI suffers less from effect of excipients.
5. Fewer side effects.
6. High acceptance of children.
7. Easy administration without water.
8. Excellent for acute medication.
10. To help reduce food cravings.
11. Treatment complete at any time.
12. No first pass metabolism.
13. Both systemic and local delivery.
15. Provide relief from stress.

STRUCTURE AND FUNCTIONS OF ORAL MUCOSA

Oral mucosa is consisting of three different types of cells they are
1. Masticatory mucosa
2. Lining mucosa
3. Specialized mucosa

Masticatory mucosa withstand abrasion and shearing forces of Masticatory process. Lining mucosa cover no keratinized tissue. Mucosa has capable of elastic deformation, stretches to speech. Epithelium of humans varies in thickness
according to region .regional difference in morphology result in different permeability characters these influence on design of drug delivery system .Aging and disease condition result in loss of this balance .This cause thinking (atrophia) thickening ( hypertrophic)of Epithelium .human tissue contain keratinized and non keratinized tissues .Turn over time is slow for keratinized tissue .example: hard palate 24 days than non keratinized tissue and also there is accumulation of liquids fluids lipids cytokeratin’s are less in keratinocytes and glycogen content is also more in keratinocytes.

![Fig. no.1 Distribution of masticatory, lining and specialized mucosa in buccal cavity](image)

**CHEWING GUM AND SALIVA**

Chewing gum has powerful defense mechanism in body saliva. Saliva is important to oral health and it is protector of oral cavity, chewing gum is increases the saliva without drugs .Increasing saliva in mouth is accomplished by stimulation of flavors 'and GI actions of chewing .saliva has three protective mechanisms they are:

- Ca+ and k+ ions produce remineralization of dental caries lesions ,saliva contain antibacterial agents
- Dilutes and washes away food particles.
- Bicarbonate neutralizes and buffers plague acids [6, 7, 8].

**Definition of medicated chewing gum**

Chewing gum is a solid dosing medicinal form with a base consisting mainly of gum, which is intended for chewing .It contains one or more active ingredients that are released during chewing by providing local or systemic action after absorption through buccal mucosa and gastrointestinal tract.

**Uses of medicated chewing gum**

- Chewing gums are used to improve
  - oral health
  - Digestion process
  - Memory functions
- Help in managing body weight
- Help in reducing symptoms like nausea and vomiting.
- Play a vital role in the treatment of gingivitis, throat and oral infections, acidic problems,
xerostamia, pharyngeal infections, travelines and motion sickness

✔ Used in smoking cessation.

**Composition of chewing gum**

Basic raw material for all chewing gum is natural gum chicle which is obtained from sapodilla tree. Chicle is very expensive so we use synthetic material like polyvinyl acetate gum base. Chewing gum has two parts: water soluble portions, water insoluble portions.

**Gum base**

Chewing gum is insoluble and inert non nutritive product used to soluble of chewing gum. Atypical gum base consisting of formula: sweeteners (30-60%), elastomers (10%), gum bases (20-90%), softeners (5-35%), fillers (4-50%), and flavoring agents (2-5%), preservatives (0.1%).

**Plasticizers**

Plasticizers incorporated into gum base for variety of desirable consistency and texture properties. Plasticizers such as stearic acid, potassium stearate acetylated mono glyceride, paraffin waxes, oleic acid, vegetable oils.

**Elastomers**

These are obtained as natural and synthetic rubbers. Gum base contain elastomers solvents to softening gum base component. Elastomers are terpene resins such as polymers of glycerol, methyl esters of resins. Synthetic elastomers such as bufadiene, polyethylene mixtures, nontoxic vinyl polymers such as polyvinyl alcohol. Elastomers used amount of 5-75% by weight of gum base.

**Adjuvants**

Talc, calcium carbonate others are used. Mineral adjuvants are magnesium carbonate, calcium carbonate, aluminum hydroxide, aluminum silicate calcium phosphate used as fillers.

**Antioxidants**

These are used to prevent oxidation reaction such as propyl gallate, butylated hydroxy toluene.

**Sweeteners**

- Sweeteners available
- Water soluble sweetening agents
- Water soluble artificial agents
- Protein based sweeteners
- Dipeptide based sweeteners.

Example are sorbitol, mannitol, aspartate, sucrose and sodium saccharin salts, calcium saccharin salts.

**Coloring agents**

These are incorporated into gum base as 6% weight of gum base composition. Coloring agents include pigments, titanium dioxide, food colours and dyes suitable for food drug and cosmetic applications.

**Flavouring agents**

These are essential oils, synthetic flavors, such as citrus oil, fruit essences, peppermint oil, winter green oil, spearmint oil, anise oil. [9, 10]

**MANUFACTURING METHODS**

Manufacturing of chewing gum can be prepared by different methods they are classified in the following:

- Direct compression method
- Conventional / traditional method (melting)
- Freezing, grinding & tableting method

**Direct Compression Method**

A new technology is developed for preparation of chewing gums is direct compression method. The direct compression method used for overcome limiting of melting and freezing methods. SPI pharma developed the Pharma gum it is a compactable gum system. Pharma gum is a mixture of sugars with a chewing gum base. It regarded as a safe (Gras). Pharmagum exists in three forms i.e. S, M & C forms. Pharmagum S has less gum base when compared with pharmagum M. Pharma gum “M” contain mannitol & gum base. Pharma gum’s” contain sorbitol & gum base. Formulation prepared by pharmagum S & M is similar to tablet appearance. Chewing gums prepared by using direct compression method is 10 times crumbled and harder, when applying of pressure they release drug faster than conventional methods. When compared with traditional method formulation prepared by pharma gum S, M, and C it enables formulators to utilize gum delivery system quickly and more cost effectively.
In this method, first prepare formulation before tableting by adding granulating agents, sweet, emulsifiers, antioxidants etc…

In this first step is dry mixture of gum base, granulating agent then add all active ingredients to formulation then directly compressing chewing gum into tablets

**Conventional/traditional method**

Preparation of chewing gum by using traditional method has 2 types there are
- Conventional fusion method
- Conventional fusion mixing technique

First step is melt and soften the gum base at 60°C and place this mixture in kettle mixture it contain blades soften the base, then sugar, sweet, glycerin, taste agents are added to gum base, after at 40°C flavor agents are added, followed by cooling and rolling is done, after that rolled chewing gum is cut into pieces of desired shapes and sizes.

Second type of conventional method is if sugar contain chewing gum is needed, corn syrup is added to mixer, then powdered sugar is gradually added, after that plasticizers and sweet added, due to volatile nature of flavoring agents there are added at the end of preparation. Mixing is continued until it forms homogenous mass, at least 8 minutes mixing is continued.

After formation of matrix preparation, mixing it well, gum base add to chamber all at once. The particles are heated and mixed before adding all other ingredients to gum base, in this mixing continue 10 to 20 minutes, then gum is cooled up to 48hrs. Finally gum cut into desired shapes.

Difference between the conventional (fusion) method sweet and other ingredients added to molten gum base, but in conventional (fusion) method mixing technique, sweet matrix is first formed, then gum base as pellets are added.

**COOLING, GRINDING AND TABLETING METHOD**

**Cooling and grinding**

In this added the gum base with flavors, sweet corn syrups, flavoring agents colorant and then cool it by keeping in it refrigerator by freezer apparatus at temperature -15°C, after it crushed it with cutter to form minute particles, then after it they minute particles are heat to a temperature to make them adhere to each other and form uniform and consistent texture with low specific gravity.

Coolants such as carbon dioxide (-15°C) and liquid nitrogen hydro carbon is preferred in some times chewing mixture composition, precipitated silica and solid carbon dioxide is ground in a mill grinder. In first step, then addition carbon dioxide and silica are add to ground composition and further ground in second step for prevention of sticking to grinding apparatus we added phosphate and alkaline earth metal phosphate.

**Tableting Method**

After coolant remove from powder, powder mix with binders, coating agents, lubricants sweet etc… all this are compactable with chewing gum base in a small mill blender. Next use “ fluidized bed reactor “ for formation of powder into granules and coating of powder/ granules with coating agents, this prevent agglomeration process.

Then granules mixed with anti adherents like talc. Then in “ V “ type blender mixture is blended, screened and compressed by punching machine by maintaining proper temperature [11,12].

**FACTORS AFFECTING RELEASE OF ACTIVE INGREDIENTS**

There are several factors affecting release of active ingredients of medicated chewing gum are:

**Environmental factors**

- **Salivary glands**
  Drug is placed either adjacent to salivary glands or over a duct because results excessive wash out of drug it cause difficult to achieve high local drug concentration.

- **Saliva**
  Saliva contains pH 6.5-7.5 and 99% of water. Salivary flow rate increase cause secretion of watery saliva, salivary pH is important for passive diffusion of unionized drug.
Chewing rate and chewing time

Chewing rate also effect the drug release, average chewing rate is 60 chews / min. Chewing time also effects rate of drug release chewing time is 20-30min.

Contact Time

Local and systemic effect depending on chewing gum contact time in oral cavity . chewing time 30 min consider as close to ordinary use in clinical trials.

Formulation factors

Amount of gum base and composition also affects the rate of release of drug . fraction of gum increases release rate decrease.

Membrane factors

Permeability and thickness difference affect rate and extent of drug release. Absorption membrane thickness, lymph drainage, enzyme content also affect rate of drug release.

Inter Individual variability

Drug release from medicated chewing gum is vary from person to person . Invitro study done by European pharmacopoeia suggest 60 cycles per minute chewing rate for release of drug property [13].

EVALUATION PARAMETERS

Product performance Test

There are two tests are performed to check drug characters they are product quality performance tests. USP containing individual monographs with product quality test for nicotine polacrilex and nicotine polacrilex gum. pH. eur. adopted monographs on chewing gum and those monographs describe apparatus for dissertation testing of chewing gum.

Invitro drug release Test

Official MCG Chewing gum apparatus

These apparatus consist of pair of horizontal pistons and chewing chamber supply with vertical piston working alternative to horizontal pistons that ensure gum always positioned in correct place during mastication process and the temperature of chamber maintained at 37°C – 0.5°C. Also adjust volume of medium, twisting movement, distance between jaws. European pharmacopoeia recommends 20ml of buffer in chewing chamber of 40ml and chewing rate is 60 strokes per minute. By using European pharmacopoeia several studies have been carry out, results indicate and reproducible.

Unofficial chewing single module apparatus

To study dissolution characters of mcg unofficial apparatus are used and these are designed by wennergren. This apparatus contain temperature control reservoir for dissolution medium and two pistons. Upper jaw has flat surface and it is paraller to central part of lower surface. It contain small bowl with flat bottoms. This bowl is used to prevent sliding of chewing gum during mastication. During one cycle of chewing, one piston on each side shift towards to each other. When these two pistons get together chewing gum presses between them. For carrying of drug release test quantity of chewing gum place in the 20ml of dissolution medium and maintain the temperature 37°C, twisting and pressing forces are transmitted to gum by the pistons at chew rate 60strokes per minute. At 3, 5, 10 minutes intravels samples are collected and analyse for percentage drug release.

INVIVO CHEW-OUT STUDIES

Release of drug in saliva

Minimum of four human volunteers are selected (to female and two male). Volunteers are instructed to clean their teeth by water and allowed chewing gum for 15mins, so that its maximum release has taken, after 2, 4, 6, 8, 10, 12, 14, 15, mits samples of saliva are taken. Sample can be diluted with solvent and absorbance is analyzed by analytical method.

Urinary excretion profile of medicated chewing gum

In this also minimum of four human volunteers are selected for formulations studies. This method useful only to those drugs which are excrete through urine. Instructed volunteers that they are don’t take any medicine last 48 hrs. They are fasted overnight and emptied their bladder. Samples are collected after administration of chewing gum at intervals of 1, 2, 3, 4, 6, 8, 10, 11, 12, 24 hrs. Volunteers are asked to drink water at every 30 minutes and urine samples are analysed.
**Buccal absorption Test**

Healthy human volunteers are selected and fixed volume of drug solution of known concentration at different pH values of 7.5, 7.8, 8 in oral cavities for 15 minutes and then expelled out. Sample is analysed for drug content and back calculated for buccal absorption [14, 15].

**CONCLUSION**

It can be concluded that the chewing gum used as carrier for many drugs, where extended local action and release desired. They can be used as taste masking of certain drugs and produced systemic and buccal effects in oral cavity. Chewing gum not only offer clinical benefits also used as efficient drug delivery system and protect against acids and enzymes, low first pass metabolism, however there new and old appraisal action, prove our statement as it can be seeing that they are treatment for pain, smoking, motions skinness decay.

Scientists and researchers should also considered new formulation for chewing gum for increase variations of chewing gum due to patient’s different styles and providing release pattern for chewing gum containing drugs.

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