



A REVIEW: MULTICOMPONENT MEDICATED HERBAL CHEWING GUM

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Abstract

Chewing gum is a mobile drug delivery system. It is potentially use for administrating drugs either locally or systematically via, the oral cavity. Herbal chewing gum has through the year gained increased acceptance as a drug delivery system. Several ingredients are no win corporate in herbal chewing gum. The aim of this study was to formulate herbal chewing gum using neem stem, yastimadhu, cinnamon oil and to prove its antibacterial property effectively at low dosage. Because cinnamon oil is a greater antibacterial agent against the Streptococcus mutans that causes too thd eacy. The herbal chewing gum of cinnamon oil is prepared using different concentration sofcinnamon oil and yastimadhu & various other active extract constituents from Neem. Medicated chewing gum as a modern drug delivery by introducing the history, advantages and disadvantages, methods of manufacturing, composition differences, evaluation tests and examples of varieties of medicated chewing gums. Acceptance of medicated chewing gum has been augmented through years. The advantages and therapeutic benefits of chewing gum support its development as we can see new formulations with new drugs contained have been produced from past and are going to find a place in market by formulation of new medicated chewing gums. Potential applications of medicated chewing gums are highly widespread as they will be recognized in future. Nowadays standards for qualifying chewing gums are the same as tablets. Patient-centered studies include medicated chewing gums as a delivery system too which creates compliance for patients.

Keywords: Oral drug delivery, medicated chewing gum, patient compliance.

INTRODUCTION

Chewing gum has been used for centuries to clean the mouth as well as breath. In the present work non, toxic natural food graded gum base has been used in the formulation of herbal chewing gum (HCG) containing antimicrobial agent Neem (Nimbidin). The aim of this work was to formulate, prepare and evaluate herbal antimicrobial chewing gum of Neem extract. Different excipients such as Honey, Sugar, Colouring and flavouring agents were used for the preparation. Medicated chewing gum is a solid or semisolid dosage form which consists of one or more active ingredient (water soluble or insoluble) incorporated in water insoluble base. Many scientific studies have explored the role of chewing gum in promoting healthy teeth. As for as patient convenience is concerned it is discrete and easy administration without water promotes higher compliance. Since it can be taken anywhere, a chewing gum formulation is an excellent choice for acute medication. The advantages for children and for patients who find swallowing tablets difficult are obvious. Chewing gum is a naturally occurring or synthetically fabricated resin or gum commonly sweetened and flavored by a wide range of ingredients (Haahr *et al.*, 2004). In the past, natural plant-based gums, such as Chicle and Jeltong-pontianak alone or in combination were known as the basic matrix of chewing gums (Abbasi, Rahimi, & Azizi, 2009). Exploiting these natural ingredients is limited as a result of difficulty of extraction and high cost of the end product. Accordingly, some natural gums and synthetic polymers were suggested as substitutes. Chewing gums are generally produced by water-soluble and water-insoluble components. The water-insoluble part is composed of elastomers to generate elasticity and to support the gummy texture; plasticizers to keep the gum cohesiveness;

filling and texturizing ingredients to strength the texture and gum chewability (Haahr *et al.*, 2004). On the other hand, the water-soluble part is composed of emulsifiers to create mouthfeel, colorants to provide a suitable eye appeal of the product, whitening agents to make tooth bright; and sweetening agents to retain moisture and to generate soft texture. On the basis of the process and the target, different ingredients, including bioactive compounds, pharmaceuticals, and nutraceutical compounds, may be loaded within the chewing gum, allowing their applications in several fields, not only in the food sector but also in the biomedical ones, as testified by the development and diffusion of medicated chewing gums (MCGs). In this framework, the present chapter is aimed to provide a complete overview about the main ingredients usually encapsulated within the chewing gum and the related main application, focalizing the attention of Mgs.

History of Medicated Chewing Gum

One thousand years ago, the Mayan Indians chewed tree resin from the sapodilla tree in order to clean their teeth and freshen the breath. Shortage of natural gum bases during World War II enhanced development of the synthetic gum bases that are used today. 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. The first medical chewing gum, Aspergum®, was launched in 1928. This chewing gum contains the analgesic substance acetylsalicylic acid known from Aspirin® tablets. Chewing gum did not gain acceptance as a reliable drug delivery system until 1978, when nicotine chewing gum became available. Another commercially available medical chewing gum is dimenhydrinate-containing chewing gum for motion sickness. Spruce gum, which was manufactured in 1848, became the first chewing gum product to be manufactured commercially Called "state of manicure spruce gum."

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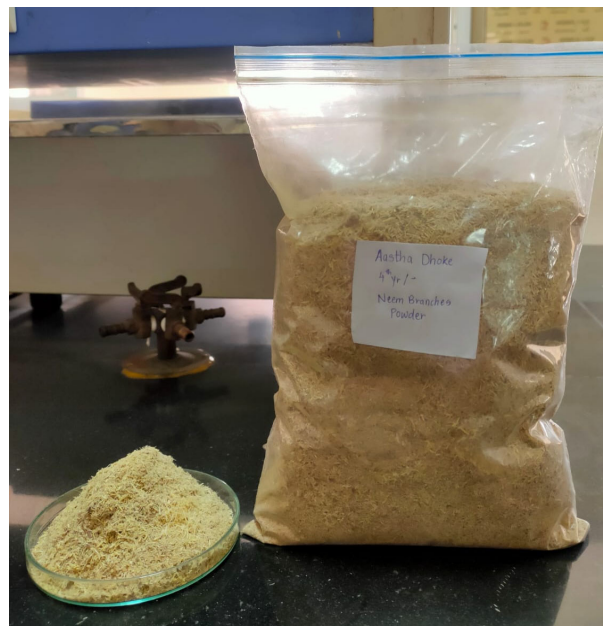
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Clinical evidence shows that sugar substituted chewing gum does not lead to caries, because the polyols do not lead to a clinically relevant production of metabolic acids in dental plaque. The objective of this systematic literature review is to appraise existing evidence concerning a possible therapeutic/anti-carcinogenic effect of sugar-free chewing gum for patients. MCG represents the newest system with potential uses in pharmaceuticals, over the counter medicines and nutraceuticals^(10,11). Unlike chewable tablets medicated gums are not supposed to be swallowed and may be removed from the site of application without resort to invasive means and MCGs are solid, single dose preparations. As for as patient convenience is concerned it is discrete and easy administration without water promotes higher compliance. Since it can be taken anywhere, a chewing gum formulation is an excellent choice for acute medication. The advantages for children and for patients who find swallowing tablets difficult are obvious. This product, consisting of liquorice and rubber dissolved in alcohol and naphtha, was initially intended to be used as a dentifrice. In 1891, William Wrigley Jr., arrived in Chicago with \$32 in cash with a desire to market his special variety of soap. Eventually, he switched from soap to baking powder sales and offered chewing gum premiums to merchants who became his customers. By 1892, when the premiums had become more popular than the baking powder, Wrigley launched his first chewing gum products, LOTTA and VASSAR. A year later, he developed JUICY FRUIT, and shortly thereafter, WRIGLEY's SPEARMINT gum. Sugarless gum made its debut in the early 1950s, generally used sorbitol as a sugar substitute. The first brand to be marketed was HARVEY's followed by TRIDENT and CAREFREE. In 1975, the Wm. Wrigley Jr. Company introduced the arrival of a new chewing gum product, FREEDENT, designed especially for denture wearers, which did not stick to most dentures as ordinary gums.

PROFILE OF DRUGS

NEEM

Neem is antimicrobial agent used for management of tooth decay. In mouth, Neem gets readily adsorbed to negatively charged area, including mucosa and pellicle coated teeth. *Azadirachta indica*, also known as Neem and Indian Lilac is a tree in the mahogany family Meliaceae. It is one two species in the genus *Azadirachta* and is native to India and the Indian subcontinent including Nepal, Pakistan, Bangladesh, and Sri Lanka.



It typically is grown in tropical and semi-tropical regions. Neem trees now also grow in islands located in the southern part of Iran. Its fruits and seeds are the source of neem oil. All parts of Neem tree used as antihelmintic, anti-fungal, anti-diabetic, antibacterial, antiviral, contraceptive and sedative. Neem tree is used in many medicinal treatment like skin diseases, healthy hair, improve liver function, detoxify the blood, pest and disease control, fever reduction, dental treatment, cough, asthma, ulcers, piles, intestinal worms, urinary diseases etc.

Yastimadhu

Glycyrrhiza glabra commonly known as Yashtimadhu which has been used in various systems of medicine viz Ayurvedic, Allopathic and other traditional systems of medicine. It is mainly used for the treatment of peptic ulcer, hepatitis C, and pulmonary and skin diseases, although clinical and experimental studies suggest that it has several other useful pharmacological properties such as anti-inflammatory, antiviral, antimicrobial, antioxidative, anticancer, immunomodulatory, hepatoprotective and cardio protective activities. Licorice a sweet in taste. It is used as a sweetening agent. Soothes your stomach. Licorice root is used to soothe gastrointestinal problems. This is due to the anti-inflammatory and immune-boosting properties of glycyrrhizic acid. It reduces stress, assist cancer treatment, protect the skin and teeth. It is also used in Chewing gums, chocolate candy, cigarette and chewing tobacco. In India the plant is grown in areas with the subtropical climate and receiving annual rainfall about 0cm or less.

The plant is grown in the month of March i.e. Autumn Season in the third or fourth year of cultivation. There are several variations and species of the licorice root sold in World's Market. *Glycyrrhiza* has demulcent and expectorant properties. Liquid extract used in treatment of peptic ulcer. Added to beer to form stable and enhanced foaminess. Ammoniated *Glycyrrhiza* is employed as a flavouring agent in beverages, pharmaceuticals and confectionery. *Glycyrrhetic acid* is employed in dermatology formulations for its remarkable anti-inflammatory properties.



Honey

Synonyms: Madhu, honey purified, mel.

Biological source: It is a secretion which is deposited in honey comb by bees, *Apis mellifera*, *Apis dorsata* and other species of bees.

Family: Apidae

Geographical source: In Africa, New Zealand, California and in India.

Honey consists chiefly of a mixture of dextrose and levulose (70-80%) and water (14-20%). It contains sucrose (1.2-4.5%), Dextrin (0.06-1.25%), volatile oil, pollen grains, enzymes, Vitamins, Amino acids, Proteins, Coloring matters, etc. Honey is used as a nutritive, Demulcent, Mild laxative, it is used as an important component of lozenges and cough mixtures, it is a sweetening agent, antiseptic and bactericidal. This is also used as a vehicle in Ayurvedic and Unani preparations, as a pill recipient. Recently, it is used in the preparation of creams, lotions, soft drinks and candies. Honey is an aqueous solution of glucose [35%], fructose [45%], sucrose [2%]. The constituents are maltose, gum, traces of succinic acid, acetic acid, dextrin, matters, enzymes [Invertase, Diastase, Inulase] and vitamins.

1. Protein and pollen grain from various flowers are found in honey.
2. Honey is a saturated solution of sugar, on keeping it crystallizes. The crystallized dextrose is called granulated honey.



Active Pharmaceutical Ingredient

Cinnamon oil shows a greater antibacterial activity against *Streptococcus mutans*, the nasty bug that causes most tooth

decay. But cinnamon oil irritates the mouth tissue. It is used as an antibacterial, astringent, antiseptic, immunostimulant, detoxifying agent, carminative, analgesic, antifungal, antidepressant, boost brain function, mouth freshener, pain relief, toothache, reduces ulcer, soothes sore throat, treats headache. e.g., Cinnamon oil.

Sweeteners

Bulk Polyol Sweeteners are responsible for initial sweetness, whereas intensive sweeteners are intended for prolonging the sweetness effect. Intensive Sweeteners are often encapsulated to delay the release of flavor. The most important among these are that added sugar in chewing gum acts as a sweetener, preservative, texture modifier, fermentation substrate, flavoring and coloring agent, bulking agent. e.g., sugar.

Formula of herbal chewing gum

Sr.No.	Ingredients	Batch 1	Batch 2	Batch 3
1	Gum base	1gm	1gm	1gm
2	Yastimadhu	0.015gm	0.020gm	0.025gm
3	Cinnamon oil	0.1gm	0.15gm	0.2gm
4	Honey	1gm	1gm	1gm
5	Sugar	q.s.	q.s.	q.s.
6	Elaychi	q.s.	q.s.	q.s.

*Note: Quantities per chewing gum

Phytochemistry of yastimadhu

In the last years, the chemical constituents of liquorice have been extensively investigated by different authors. Nevertheless, few studies were carried out on the nutritional composition of liquorice, liquorice is a source of proteins, amino acids, polysaccharides and simple sugars, mineral salts (such as calcium, phosphorus, sodium, potassium, iron, magnesium, silicon, selenium, manganese, zinc, and copper), pectins, resins, starches, sterols, and gums. Oestrogens, tannins, phytosterols (sitosterol and stigmasterol), coumarins, vitamins (B1, B2, B3, B5, E, and C), and glycosides have been reported. A large number of biological compounds have also been isolated, mostly triterpenes, saponins (responsible for the sweet taste), and flavonoids. The liquorice saponins are present as glucuronides, whereas the aglycones are present as oleananes. The triterpene saponins are the major characteristic constituents of liquorice, being responsible for the sweet taste. The contents of these compounds may vary significantly due to geographic sources, harvesting, and processing, affecting the therapeutic effects of liquorice. The main constituent of roots is glycyrrhizin, a triterpenoid saponin that is almost 50 times sweeter than sucrose, being the primary active ingredient. Glycyrrhizin represents about 10% of the liquorice root dry weight, being a mixture of potassium, calcium, and magnesium salts of glycyrrhizin acid that varies between 2% and 25%. After oral administration, glycyrrhizin is metabolized to 18-glycyrrhetic acid 3-O-mono-glucuronide and glycyrrhetic acid by intestinal bacteria. The yellow colour of liquorice is due to the flavonoid content. The flavonoids identified belong to different classes, including flavanones, flavones, flavanols, chalcones, isoflavones, and isoflavanones.

Phytochemistry of NEM

Like neem leaves, neem bark also contains a number of phytochemicals having different therapeutic value. It is very effective against many skin diseases. Neem bark is said to be cool, bitter, astringent and helpful to cough, fever, loss of appetite, worm disease, skin disorders, excessive thirst, and

diabetes in literature. Gastroesophageal and gastroduodenal ulcers may be treated with neem bark extract. Phenols, sterols, triterpenes, and saponins abundant in the bark extract. Bark also yields a number of phenolic diterpenoids, c-secomeliacins and limonoides. The glycosides in neem bark aqueous extract have antiulcer and antisecretory properties. Neem bark yields gum and tannins, which are utilised in tanning, tainting, and other processes.



Evaluation and parameters

Stickiness The formulated herbal chewing gum was placed on plane surface. A mass of 250gm was hammered on it up to 10min, after 10min, sticking of mass to hammered surface was observed.

Weight Variation Test Chewing gum from each batch were individually weighted on analytical balance. The average weight and standard deviation were calculated which was found in acceptable unit.

Plasticity/Hardness The hardness of chewing gum was determined by Monsanto hardness tester and the average hardness and standard deviation were reported.

Percentage Drug Content One gram of formulation taken in mortar, to this about 20ml of 6.8 phosphate buffer was added and triturate. This was transferred to conical flask. About 30ml of 6.8 phosphate buffer was added to this and shaken well for about 3 hours using orbital shaking incubator at 100rpm. Then was filtered and the filtrate was made up to make with the same buffer solution. Suitable dilutions were made, and the drug concentration was determined by measuring the absorbance at 279nm.

In Vitro Drug Release Studies In vitro drug release testing apparatus for chewing gum, was a self-fabricated apparatus which was a modification of disintegration apparatus. Here rigid basket rack assembly is supporting 6 cylindrical glass tube was replaced with the detachable stainless still road fitted with a Teflon bead assembly is supporting 6 cylindrical glass tube was replaced with the detachable stainless still road fitted with a Teflon bead which moves up and down vertically at 50 cycles per min. in the glass cylinder of 900ml capacity. Length of stainless still road can be adjusted by the adjusting screw which is positioned at the top of the stainless still road and is also used to fix the road to the disintegration apparatus. The base of glass cylinder was made up of Teflon. The temperature was maintained at 37 ± 5 . About 1 gm of formulation was placed in a glass tube between the Teflon bead and Teflon base to this about 900 ml of PH 6.8 phosphate buffer was added.

5ml of sample was withdrawn and replaced with 5ml of fresh PH 6.8 phosphate buffer at intervals (0, 2, 4, 6, 8, 10, 12 and 14min.) absorbance was recorded by ultraviolet spectrophotometer at 279nm. And % of drug released was determined as a function of time.

EXTRACTION METHODS

Maceration

In this process, the coarsely powdered crude drug is placed in a stoppered container with the solvent and allowed to stand at room temperature for a period of at least 3 days with frequent agitation until the soluble matter has dissolved. The mixture then is strained, the marc [the damp solid material] is pressed, and the combined liquids are clarified by filtration or decantation after standing.



Ultrasound sonication

The procedure involves the use of ultrasound with frequencies ranging 20 kHz to 2000kHz. This increases the permeability of cell walls and produces cavitation. The process is useful in some cases, like extraction of herbal chewing gum, its large-scale application is limited due to the higher costs.



Vacuum pump filtration

The vacuum filtration apparatus is used to easily filter out of solid, liquid and gases from the solution with the help of a vacuum pump. To the negative pressure at the outlet of the filter and use it as the driving force of filtration. Vacuum and pressure filtration is used for sample preparation in chemistry, environmental analysis. It is to separate a solid product from a liquid mixture or solvent. Filtration is also a stage of purification. The apparatus is often used to purify a liquid.



Freeze drying

Freeze drying also called lyophilization. It is process in which material is freeze then high-pressure vacuum is applied to sublimate the water in the form of vapour. Process was first applied to food products after the second world war. Based on sublimation, where water passes directly from solid state [ice] to the vapour state without passing through the liquid state. Material to be dried is first frozen and then subjected under a high vacuum to heat ;frozen liquid sublimates leaving only solid, dried components.

Steps in freeze Drying

1. Pretreatment
2. Freezing
3. Primary Drying
4. Secondary Drying

Pretreatment: Method of treating the product prior to freezing including concentrating the product, formulation revision, decreasing a high- vapour- pressure solvent, or increasing the surface area.

Freezing: The product is frozen .The provides a necessary condition for low temperature drying, freezing temperature are between -50 C and -80 C.

Primary Drying: Pressure is lowered, and enough heat is supplied to the material for the ice to sublime. This phase may be slow because, if too much heat is added, the material's structure could be altered.

Secondary Drying: To remove unfrozen water molecules, since the ice was removed in the primary drying phase. In this the temperature is raised higher than in the primary drying phase, to break any physicochemical interactions that have formed between then water molecules and the frozen material.



Conclusion

Chewing gum during the workday was associated with higher productivity and fewer cognitive problems, raised cortisol levels in the morning, and did not affect heart rate. According to the results of research among presented at pharmaceutical market MCG is dominated dental due to their range. This medicinal form is an alternative for patients who have difficulty swallowing exercise, or for children who are not able to swallow the medicine.

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