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A review on: medicated chewing gum

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Abstract

Chewing gums are the type of mobile drug delivery systems. It is useful by means of administering drugs either locally or systemically through, the oral cavity. The treated chewing gum has through the times gained adding acceptance as a medicine delivery system. As compare to that chewable tablets treated epoxies aren't supposed to be swallowed and it can be removed from the point of operation without resort to invasive means and treated biting gum. MCG is solid, single cure medication. The end of this review is to gives an overview of gum composition, manufacturing process, and characterization. Due to the failure of studies concerning the evaluation of the mechanical parcels of MCGs, lesser effect was placed on the available performance tests and procedures for the estimation of their mechanical and textural parcels. It can be used either for original (mucosal) treatment of mouth complaint or for systemic (transmucosal) delivery by direct intra oral immersion through the buccal mucosa.

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Introduction [2,3,56]

There is a long history of chewing on objects that aren't food for enjoyment (Cloys et al., 1992). The early American Indians, Mayan Indians, and ancient Egyptians all chewed tree resin. In 1848, State of Maine Pure Spruce Gum the first chewing gum used in commerce—was found. MCG is regarded as a vehicle or a method of drug administration for the introduction of active ingredients that can enhance nutrition and health. The newest method, MCG, has applications in nutraceuticals, over-the-counter treatments, and pharmaceuticals. Generally speaking, chewing gums fall into one of four categories: (I) sugar chewing gums, (II) sugar-free chewing gums, (III) coated chewing gums, and (IV) pharmaceutical or medicated chewing gums (MCGs). In accordance with the European Pharmacopoeia and the recommendations for pharmaceutical. Medicated chewing gums are described by the European Pharmacopoeia and in addition to the 1991 recommendations for pharmaceutical dosage forms made by the Committee for Medicinal Products for Human Use (CPMP), which defined them as "solid single dose preparations with a base including primarily of gum that are used to be chewed but not to be swallowed, providing a slow steady release of the medicine contained." The medication in the gum is released into the saliva while you chew. The released medication has two possible outcomes: it may enter the stomach for gastrointestinal absorption or it may be absorbed through the mouth mucosa. The effect of chewing gum in promoting healthy teeth has been described in numerous scientific research. Most nations have made chewing gum a popular habit. Since ancient times, chewing gum has been used to clean the mouth. Due to the success of the nicotine chewing gum in the 1980s, MCGs are currently the preferred method of nicotine replacement treatment. The great level of acceptability of this new method of medication delivery

can be attributed to advanced technology, extensive chewing gum knowledge, and the inclusion of medicated chewing gum in the European Pharmacopoeia in 1998. There are two absorption routes offered by this drug delivery technology. Drug absorption across the buccal membrane prevents GIT metabolism and, thus, the risk of liver first pass effects. The gum base that incorporates drugs is known as medicated chewing gum (MCG). [56]

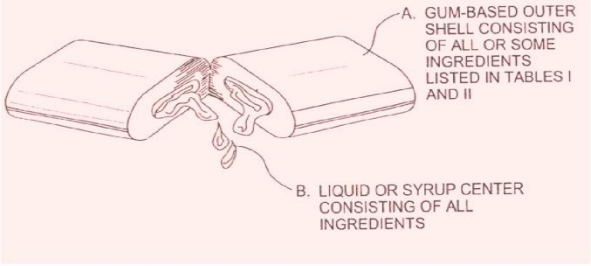


Figure 1 Schematic diagram of drug release from a chewing gum

4. Evolution Of Medicated Chewing Gum

Table: 1 – History of Medicated Chewing Gum (Lakshmi et al., 2014)

Year of Invention	Inventor	Invention
1848	John Curtis	Commertial Chewing Gum
1860	Jhon Cogan	Flavored Chewing Gum
1869	William Finely Simple	Commertial Chewing Gum Patent
1870	Thomas Admas	Modern Chewing Gum
1871	Thomas Admas	Patent for chewing gum manufacturing machinery
1880	William White	Flavored chewing gum
1880	Henry Fleer and Frank Fleer	Chiclet and Blibber –Bubber gum
1888	Thomas Admas	Tutti-Frutii
1891-1893	Wringley	Lotta, Vassar, Juicy fruit and Spearmint gum
1914	William Wringly and Henry Fleer	Wringleys Doublemint gum and Clove chewing gum
1928	Walter Diemer	Double Bubble
1928	Frank M. Dillard and William C. Nalle	Medicated chewing gum
1960	Petrulis	Sugar free chewing gum
1980	OveFerno	Nicorrete
2000-2015	-	Synthetic gum bases
2015-2020	-	Biodegradable medicated sugar free chewing gum

5.Need of Medicated Chewing Gum as a drug delivery system[60]

Chewing gum provides new competitive advantages over conventional drug delivery system:

Fig2 - Medicated Chewing Gum as a Drug Delivery System

6. Composition of Medicated Chewing Gum [16, 17, 19, 27]

Chewing gum is a mixture of natural or synthetic gum and resin, sweetened with sugar, corn syrup, and artificial sweeteners, and may also contain colors and flavors. The basic raw material for all CGs is Chicle natural gum, obtained from the sapodilla plant. Chicle is expensive and often difficult to find, so other natural or synthetic gums such as polyvinyl acetate and similar polymers can be used as gum substrates. Basically, chewing gum consists of two parts:

6.1.Water insoluble gum base – Plasticizer, Elastomers, Elastomeric solvents, Fillers

Ingredients Water insoluble gum base	Function	Example
Plasticizers	To obtain a variety of desirable textures and consistency proper-ties	Lanolin, palmitic acid, oleic acid, stearic acid, glyceryl triacetate, propylene glycol monostearate, glycerine, natural and synthetic waxes, hydrogenated vegetable oils, paraffin waxes, fatty waxes, sorbitol monostearate, propylene glycol
Elastomers	Provides elasticity and controls gummy texture	Natural- chicle gum, nispero, rosadinha, jelutong, periollo, lechicapsi, sorva etc.) Synthetic rubbers- (butadiene, styrene, polyisobutylene, polyethylene mixtures, polyvinyl alcohol etc.)
Elastomeric solvents	Softening the elastomeric base component	Terpinene resins (polymers of alpha-pinene or betapinene), modified resins or gums (hydrogenated, dimerized or polymerized resins)
Fillers or texturizers or mineral adjuvant	Provide texture, improve chew ability, provide reasonable size of the gum lump with low dose drug	Calcium carbonate, magnesium carbonate, aluminum hydroxide, talc, aluminum silicate.

6.2.Water soluble gum base- Sweetners, Antioxidants, Softner and emulsifier, Colorants and whiteners, Flavouring agents, Bulking agent, Compression adjunt

Ingredients Water soluble gum base	Function	Example
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.), Di-peptide 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	Butylated hydroxytoluene,

	microbial growth	butylated hydroxyanisole, propyl gallate
Softeners and emulsifiers	These are added to the chewing gum in order to optimize the chew ability 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
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, fructooligo saccharides, guargum hydrolysate, indigestible dextrin
Compression adjuvant	To ease the compression process	Silicon dioxide, magnesium stearate, calcium stearate, talc

Table 2: Difference between natural gum base and conventional gum base

Natural gum base	Conventional gum base
Biodegradable	Non-biodegradable
Manufactured from plant source	Manufactured from petro-chemicals
Not harmful to the human and environment	Harmful to human and earth
Difficult in mass production due to limited secretion of tree latex	Ease of mass production with smooth texture
No artificial sweeteners	Contains artificial sweeteners
Does not require cost for disposal and cleaning of environment	High cost of disposal and cleaning the environment
Product cost is high	Product cost is les
Required high manpower for collection of sap	No sap required
Very few products available in the market	Enormous products are available in the market

7. Advantages of MCG[4,5]

Medicated chewing gums have a range of advantages . The advantages are summarized as further:

1.Chewing gum can be used without water, at any time, and everywhere.

2. MCG reduced the risk of overdosing while its swallowing.

3. High acceptance by children and teenagers .

4. Good stability against light, oxygen, and moisture.

5. As the incorporated therapeutic agents are protected from oxygen, light, and water, product stability is good.

6. Dental Caries: Prevention and treatment of oral diseases are common goals of chewing gum formulations. It can control the release rate of active ingredients by providing a sustained topical effect.

7. Systemic Therapy: : (a) You can also successfully treat pain such as mild pain, headache, and muscle pain. (b) Quit Smoking - Chewing gum formulations containing nicotine, lobeline, and silver acetate have been clinically tested as smoking cessation aids.The other benefits of chewing gum may offer as a pharmaceutical dosage form are as…

1. Fast or 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. Advantageous for patients with difficulty in swallowing tablets

8. Disadvantages of MCG [20,22] : MCG some limitations;

- Effect of chewing speed and pattern on drug release Drug release from MCGs is strongly influenced by how the patient chews the MCG formulation. H. A chewing rate of 1 chew per second resulted in significantly higher nicotine release from Nicorette gum than all chewing rates.
- Absorption site variation due to salivary dilution and involuntary swallowing Especially for transmucosal administration, the reduction of drug concentration in the oral cavity as a result of salivary dilution is a major obstacle to oral drug delivery. Drugs released into saliva can be quickly eliminated from the oral cavity by unconsciously swallowing saliva in a state in which the drug is dispersed and dissolved, reducing the possibility of drug absorption through the oral mucosa. Compared to other conventional systemic oral mucosal drug delivery systems (slimming solutions or tablets, fast-dissolving tablets and buccal dissolving films), MCG has a longer retention and contact time on the oral mucosa, and the drug inside is gradually released upon chewing. disappears to A composition that is released into the saliva.
- MCG has allergic reactions to artificial sweetners.
- Stomach irritation, gastric ulcer through continuous swallowing of saliva and flatulence may also occurs due to presence of sorbitol in some formulations.
- Chances to getting chocked by swallowing gum under-aged children.

9. Processes of MCG Manufacturing :

There are mainly Three methods of manufacturing of mcg as further:

1. Traditional or Conventional (melting) Method
2. Direct Compression
3. Grinding, Freezing, Tableting Method

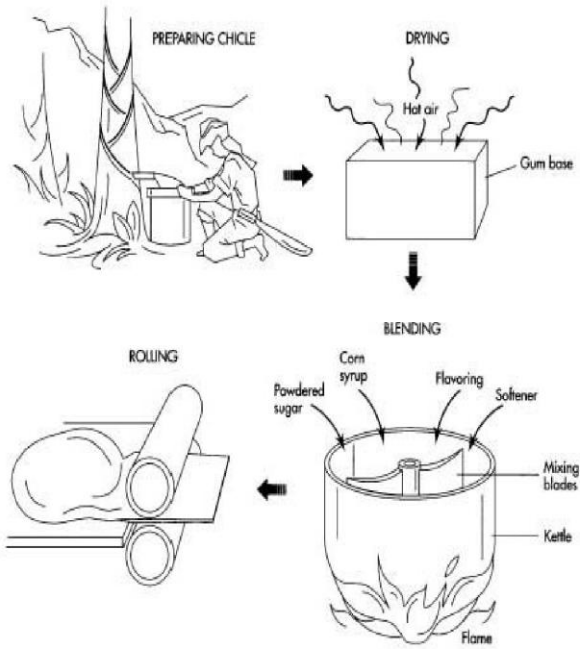
This can be reviewed as follows:

9.1.Traditional / Conventioal Method[42,58]

The traditional method involves first cutting the bark of the sapodilla tree to collect the chicle and cooking it over an open flame to evaporate excess moisture. When it looks like chunky toffee, it is stuffed into wooden molds, made into blocks, dried with hot air, and melted and softened. Then place it in a kettle blender and add the corn syrup, active ingredients, bulking agents, sweeteners (powdered sugar) and other excipients such as fruity flavors, one at a time.[42] Roll the chewing gum into a thin, wide ribbon. During this processing time, a light coating of finely powdered sugar is added to prevent the gum from sticking. Then refrigerate the gum for 2 days. This will allow the gum to cure properly. Finally, cut the chewing gum to your preferred size.

Fig 3: Methods of preparation of MCG

9.2.Direct Compression Method[10]



The direct compression process uses a processed compressible gum substance, most often in powder form, to produce chewing gum tablets. For example, Health in Gum refers to a group of free-flowing, directly compressible gum-like substances developed by Cafosa Gum SAU. These directly compressible co-processed gum bases contain high proportions of inert soft thermoplastic elastomers, blends of polyols (sorbitol/xylitol/mannitol), sugars, plasticizers and anti-caking agents. When compressed, Health in Gum becomes a compact that looks similar to a pharmaceutical pill. They are harder and more fragile than the medicated gum produced by Medicated Chewing Gum 2913 by conventional methods. They also have other effects on API release. Nicotine gum made with the direct compression method has a faster release rate than Nicorette made with the conventional

method. Health in Gum currently comes in three varieties: HiG PWD-01, HiG PWD-03 and HiG PWD04, containing 25, 35 and 30% gum base respectively. They have a lower moisture content, which increases the shelf life of the integrated active molecules.

9.3.Freezing, Grinding and Tabletting Method:

9.3.1.Freezing/Cooling and Tableting Method[22,24]

The MCG composition is cooled to a temperature at which it will be sufficiently brittle and will remain brittle throughout the grinding step without sticking to the grinding equipment. The temperature required for cooling is determined in part by the composition of the GC and is easily determined by observing the properties of the cooled gum composition. Most of the time, the temperature of the mixture being cooled is around -15°C or lower. The cooled composition is then ground or ground to obtain finely ground flakes of the composition. For more extensive cooling, the gum composition may be pre-cooled prior to cooling to refrigeration temperature.

Anti-caking agents, such as precipitated silicon dioxide, may be mixed with the gum preparation and solid carbon dioxide prior to grinding. This will prevent agglomeration of the gum particles that are then ground. To prevent gum from sticking to the mill, 2 to 8% by weight of a grinding aid such as alkali metal phosphate, alkaline earth metal phosphate or maltodextrin can be added.

9.3.2.Tabletting Method[10]

Once the coolant will be removed from the dough, the powder can be mixed with other ingredients such as binders, lubricants, coatings and sweeteners, etc. All are compatible with gum base components in a suitable mixer such as a sigma grinder or high shear mixer. . Alternatively, a fluidized bed reactor (FBR) can also be used. The use of FBR is beneficial because it partially restructures the powder into granules, as well as coats the powder particles or granules with a coating, thereby minimizing unwanted particle agglomeration. Therefore, the resulting granules can be mixed with anti-adhesive agents such as talc. This mixture can be mixed in a V-type mixer, screened and spread for compaction. Compression can be done by any of the conventional methods such as punching. This requires equipment that is different from conventional pelletizing equipment and requires careful monitoring of moisture during pelleting.

Table 3: Limitations of Conventional/ traditional method and Freezing, grinding and tableting method: (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.

10.Factors affecting release of active ingredient from MCG:

10.1.Physiochemical Properties[11]

Properties of the active ingredient such as molecular weight, ionized or non-ionized form, lipophilicity or hydrophilicity, stability to salivary enzymes (amylases), and solubility in saliva plays an important role in drug release from the MCG and in the absorption of the active substance. drug through the oral mucosa. The water solubility of the API is the most important factor in the release of a gum preparation, i.e. the release of a water-soluble drug (water solubility >1:10), in general, about 75 % or more for 5 minutes chewing and 90% or more for 15 minutes of chewing at a rate of 60 chews per minute. Drugs with a water solubility of 1:10 to 1:300 showed a release of up to 60% within 10 minutes of chewing and a release of 50 to 90% after 15 minutes of chewing.

10.2.Person-to-person variability[15]

One of the reasons MCG is under-explored is because of therapeutic uncertainties related to how the drug is administered. H. Mechanical chewing movements of the patient. The therapeutic effect of chewing gum depends on the force with which you chew. Results vary from person to person, as chewing force, chewing frequency, and chewing time vary from person to person. Balaborak et al. Used as a self-report questionnaire technique to determine chewing time (in minutes). The average chewing time per gum was 36 minutes, so they suggested that when designing clinical trials, chewing times of 30 minutes should be used if results are to be extrapolated to normal gum use.

10.3. Formulation Related Factors [16,17]

The composition, amount, and type of chewing base, solubilizers, and plasticizers can also affect the release rate of active ingredients from MCG [16]. For example, the release of miconazole is inadequate when incorporated directly into chewing gum. In vitro release studies using his chewing machine and in vivo studies using healthy adult volunteers showed that solid dispersions of miconazole-PEG 6000 (1:4 ratio) in chewing gum formulations showed higher than pure miconazole It has been shown to affect the release rate. This happened because PEG 6000 increases the water solubility of miconazole. Addition of lecithin to miconazole-PEG chewing gum formulations significantly increased both the release rate and release time of miconazole in vitro and in vivo [16]. One study examined the effect of gum base on drug release using salicylamide as a representative. When salicylamide was incorporated into chewing gum with a relatively high proportion of gum base, the release of gum base was significantly lower at 25.6% compared to chewing gum with less gum base, namely 52.0%.

11. Some categories of diseases and related drugs that can be used in MCG formulation can be tabulated as follows:

Table 4: Categories and Related Drugs for MCG-

Category	Drugs
Cardiovascular [Antihyperrtensive]	Telmisartan, Verapamil
Antifungal	Flucanazole
Peridontal Gum Disease	Chlorhexidine
Antiemetic Agents	Dolasetron, Domperidon, Ondensetrol
Antimicrobial	Chlorhexidine, Chitosan, Xylitol
Gingival Inflammation	Polyol MCG
Oral Candidiasis	Nystatin
Antiulcer	Terminalia, Chebula, Ocimum, Sactum
Motion Sickness	Dimenhydrinate
Antitussive	Noscapine
Pain, Fever [Antipyretic]	Aspirin
Vitamin C Difficiency	Ascorbic Acid [Vit.C]
Smoking Cessation	Silver Acetate

12.Evaluation Parameters for MCG[30,31,10]

12.1.Test for Uniformity of Content- Unless otherwise specified or justified and permitted, medicated chewing gum containing less than 2 mg or 2% of the total mass of the chewing gum meets this test.

12.2.Uniformity of mass – Uncoated medicated chewing gums and, unless otherwise justified and permitted, coated medicated chewing gums have passed the unit dose formulation mass uniformity test.

12.3.Dissolution test of residual medicated chewing gum- In this experiment, gums will be tested by a group of volunteers to validate the drug release process from the drug delivery system.

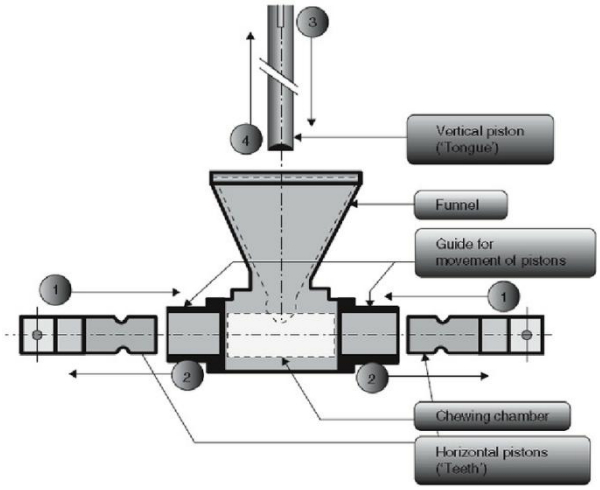


Fig 4: Dissolution apparatus

12.4.Stability study- This is done by storing 10g of gum base in a bottle at 30°C/65% RH. It complies with WHO guidelines on chewing gum duration and aging and can be reviewed after 6 months.

12.5.Chew out study – The initiation stages of chewing studies include various parameters such as softness, sweetness, slipperiness, cooling effect, texture, firmness and smoothness.

12.6.Structural analysis of MCG- A visual inspection is performed on various MCG formulations. Structural properties of the gum base were determined from studying its moisture absorption, relative humidity, solubility, and understanding color. Formulations are physically evaluated for parameters such as weight change, appearance, cohesiveness, hardness and plasticity.

12.7.Hardness/Plasticity - Due to the lack of reported procedures, we chose to use a Monsanto-type hardness tester to determine the hardness of all MCG formulations. [10]

Hardness or Plasticity is determined by using Monsanto Type Hardness Tester.

12.8. Stickiness- The MCG was placed on a flat surface and impacted with a 250g cylindrical hammer for 10 minutes. The number of hits is about 30 times per minute. After 10 minutes clumping was observed and reported on the hammered surface..[10]

12.9.In-vitro drug release from MCG Unofficial single-module chewing apparatus[30] - One of the unofficial devices for performing MCG dissolution tests was designed by Wenergren. The device consists of two pistons and a temperature-controlled reservoir for the dissolution medium. The upper jaw has a plane parallel to the central part of the lower surface.

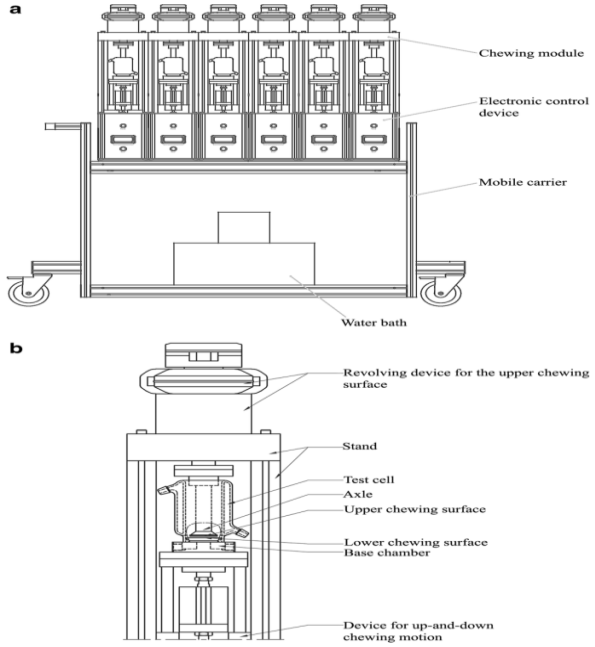


Fig 5 – Unofficial single-module chewing apparatus

13.Table 4: Therapeutic Appications of MCG[15]

Therapeutic use	Specific example	Marketed products
Smoking cessation	Nicotine	Nicorette
Pain relives	Aspirin	Alka seltzer
CNS stimulation, Improvement of memory	Caffein	Stay alert
Treatment of dental carries	Chlorhexidine	Advanced+
Treatment of oddities	Xylitol	Spray
Treatment and management of motion sickness	Dimenhydrinate	Travvell
Acid neutralization	Antacid	Chooz

14.Table6: Commercially available medical chewing gums and their trademarks[57]

Trade Mark	Active Substance	Aim
Aspargum	Aspirin	Pain relief
Nicorette	Nicotine	Smoking cessation
Chooz	Calcium carbonate	Stomatch acid neutralization
Stay alert	Caffeine	Alertness
Brain	DHA And CCE	Enhanced brain activity
Fluorette	Fluoride	Cariostatic
Trawel	Dimenhydrinate	Motion Sickness
Nicotinelle	Nicotine	Smoking cessation
Endekey	Vitamin C	General health

15.Saftey Aspects [10,20]

Chewing gum appears to have a lower risk of accidental or abuse overdose than flavored chewable tablets [10]. In general, chewing gum today is completely safe. Hard chewing gum used to lead to broken teeth.Excessive chewing for a long time hurts the jaw muscles and excessive consumption of chewing gum containing sugar alcohols can cause diarrhea.Chewing gum frequently for a long period of time has been reported to increase the release of mercury vapor from dental amalgam fillings. However, medicated chewing gums usually do not need to be chewed or consumed in large amounts. Flavors, colorings, etc. can cause allergic reactions. Chewing gum overdose is rare because you have to chew a lot of gum in a short amount of time. As a general rule, medicated chewing gum (like other medicines) should be kept out of reach of children.

16.Future Prospects[10]

Future of chewing gum will screen all the scientists` efforts for the improvement of chewing gum as a contemporary-day drug shipping device and development of chewing gum manufacturing technology. In the destiny, different tries could be visible to formulate greater capsules the usage of chewing gum as a drug shipping device. Treatment of fungal sicknesses, prevention of caries and different dental fitness issues, smoking cessation, etc., are not unusualplace fitness paintings of MCGs. But remineralization of teeth, bloodless relief, power enhancing, anti-nausea and such a lot of new benefits of this novel drug shipping device are going to play an critical function thru destiny studies. MCGs are

admissible options of chewable or preferred drugs and oral disintegrated dosage forms.MCG is Long lasting flavored, stuffed gums, timed-release, and different new MCGs formulated for sicknesses that preceding shipping structures had been used for, are cutting-edge merchandise to be visible withinside the destiny as a brand new type of chewing gum that is made biodegradable and may be dissolve in round 1 month.. Chewing gum now no longer most effective gives scientific blessings however is also an attractive, discrete and green drug shipping device. [10]

The possibility of oral administration of MCG, rapid onset of action, and the potential for expanding product lines make MCG an attractive delivery route. Reformulations of existing products are necessary for patent protection, additional patient benefits, and revenue protection.[10]

Summary

Medicated chewing gum is a unit-dose solid formulation with a base consisting primarily of gum that is intended to be chewed but not swallowed. Today, improved technology and expanded know-how enable the development and production of medicated chewing gums with predefined properties. MCGs containing acetylsalicylic acid (Aspergum) are effective in treating mild acute pain, headaches, and muscle aches. MCGs with methadone, on the other hand, are more effective for acute severe pain. Fast-acting chewing gum formulations provide rapid pain relief and are suitable for treating acute pain.

Supporting both local and systemic delivery simultaneously, protecting against acids and enzymes, low first-pass metabolism, enhancing alertness and cognitive function, excellent stability, and taste-masking chewing gum as a novel drug delivery. Certain drugs and many others, according to benefits. It can be concluded that chewing gum will become more accessible to patients and markets in the coming years [59].

Medicated chewing gums have an advantage over other traditional dosage forms because they have a faster onset of action and offer an excellent opportunity to deliver metabolically labile drugs. Problems such as high first-pass metabolism and drug degradation in the gastrointestinal environment can be circumvented by administering drugs via the oral route.

It has a more rapid onset of action than oral administration, but treatment can be discontinued if necessary. This drug delivery is suitable for administration to patients who are poorly adaptable to oral therapy.

18. Conclusion [10, 57]

The technology to bring chewing gum to market and provide healthcare systems as a reliable alternative to different types of pills is not yet perfected or fully understood. There is still a lot of information and knowledge to explore regarding chewing gum manufacturing. Fortunately, however, this procedure is permissible to proceed. Nicotine patches are becoming more and more popular these days, but chewing gum for quitting smoking will continue to be. Chewing gum itself is also a physical substitute for the smoking habit, to increase the chances of successful quitting [10]. Scientists and researchers should consider new chewing gum formulations to increase chewing gum variations for different patient styles and to provide appropriate release patterns of chewing gum and drugs. Although chewing gum as a drug delivery system is currently only widely accepted within the context of smoking cessation and oral health, there is significant and growing interest in this mode of drug delivery for a variety of other indications. In the next few years, new formulations will be introduced and chewing gum will become a more widely used drug delivery system [57].

19. Conflict of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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