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Review On Medicated Chewing Gum Of Disulfiram As A Drug

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ABSTRACT:

The recent years scientific and technological advancements have been made in the research and development of oral drug delivery systems. The reasons that the oral route achieved such popularity may be primarily due to its ease of administration. Chewing gum is one of the very popular oral confectionary products. It is a potentially useful means of administering drugs either locally or systematically via, the oral cavity. The medicated chewing gum has through the recent years gained increasing acceptance as a drug delivery system. Chewing gum known as gum base (insoluble gum base resin) contains elastomers, emulsifiers, fillers, waxes, antioxidants, softeners, sweeteners, food colorings, flavoring agents, and in case of medical chewing gum, active substances. It offers various advantages over conventional drug delivery systems. Unlike chewable tablets, medicated chewing gums are not supposed to be swallowed and may be removed from the site of application without resorting to invasive means.[2] 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:

Medicated chewing gum, Oral drug delivery, Patient compliance, Mobile drug delivery system, Mouth diseases.

INTRODUCTION:

Definition: The Medicated Chewing Gum (MCG) is a novel drug delivery system containing masticatory gum base with pharmacologically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa.

Chewing gums are a worldwide consumable confectionery product that can be chewed for pleasure without being swallowed. It has a rubbery texture and is composed of various ingredients such as gum base, sugar, polyols, flavoring agent, acidulates, coloring agents, high intensity sweeteners and different additives. Chewing gums were ranked third in the overall confectionary market, after chocolates and candies.[9]

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 / mineral supplementation are currently available. One thousand years ago the Mayan Indians chewed tree resin from the sapodilla tree in order to clean their teeth and freshen their breath. Shortage of natural gum bases during World War II enhanced development of the synthetic gum bases that are used today.[8]

Anatomy and Physiology of oral mucosa:

The oral mucosa is the mucous membrane lining the inside of the mouth the oral mucosa can be subdivided in to two general regions, the outer vestibule and oral cavity. Microscopically the oral mucosa consists of three main layers:

A. Oral epithelium

B. Lamina propria

C. Sub mucosa

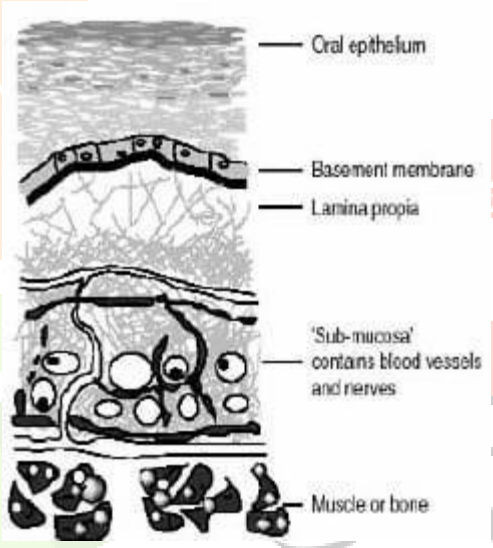


Figure 1: Generalized structure of mucosa

A. Oral epithelium:

The underlying tissue from the environment is get separated by the oral mucosal epithelium. Oral epithelium consists of two layers, the surface stratified squamous epithelium and deeper lamina propria. The squamous epithelium, which may be either keratinized or nonkeratinized, keratinized epithelium is dehydrated, mechanically in areas such as the soft palate, the floor of mouth, the lips and the cheeks tough and chemically resistant. And the Nonkeratinized epithelium is relatively flexible & The epithelium of the oral cavity is supported by the basement membrane. The membrane separates the epithelium from the underlying connectivetissue layer. This process is represented in four morphological layers.[39]

- Basal layer
- Prickle cell layer
- Intermediate layer

- Superficial layer

B. Lamina propria:

The lamina propria is a thin layer of connective tissue that forms part of the moist linings known as mucous membranes or mucosa, which line various tubes in the body, such as the respiratory tract, the gastrointestinal tract, and the urogenital tract. It is also consisting of blood capillaries and nerve fibres which serves the mucosa.[40]

C. Sub mucosa:

A sub mucosa may or may not be present deep to the dense layer of the lamina propria; depending on the region of the oral cavity. The sub mucosa usually contains loose connective tissue and also adipose connective tissue or salivary glands and overlying bone or muscle within the oral cavity. Saliva is a hypotonic, watery secretion containing variable amount of mucus, enzyme, antibodies and inorganic ions. The surface of mucus membrane is constantly washed by a stream of about 0.5 to 2L of saliva daily produce in the salivary gland the chief secretion is supplied by three pairs of glands i.e., the parotid, the sub maxillary and the sublingual glands.[40]

Functions of oral cavity:

- It helps in chewing, mastication and mixing of food stuff.
- It is helps to lubricate the food material and bolus.
- To identify the ingested material by taste buds of tongue.
- To initiate the carbohydrate and fat metabolism.
- As a portal for intake of food material and water

Methods to increase drug delivery via buccal route:

1. Absorption enhancers:

Absorption enhancers have exhibited their efficacy in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates. These may act by several methods, such as increasing the fluidity of the cell membrane, extracting inter/intracellular lipids, altering cellular proteins or altering surface mucin. The most common absorption enhancers are fatty acids, bile salts and surfactants such as sodium dodecyl sulphate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-identified dextran's across a tissue culture model of the buccal epithelium while Glyceryl monooleates were reported to enhance peptide absorption by a cotransport mechanism.[41]

Sr. no.	Permeation Enhancers	Sr. no.	Permeation Enhancers
1	2,3-Lauryl ether	14	Phosphatidylcholine

2	Aprotinin	15	Polyoxyethylene
3	Azone	16	Polysorbate 80
4	Benzalkonium chloride	17	Polyoxyethylene
5	Cetylpyridinium chloride	18	Phosphatidylcholine
6	Cetyltrimethyl ammonium bromide	19	Sodium EDTA
7	Cyclodextrin	20	Sodium glycocholate
8	Dextran Sulfate	21	Sodium glycodeoxycholate
9	Glycol	22	Sodium lauryl sulfate
10	Lauric acid	23	Sodium salicylate
11	Lauric acid/Propylene	24	Sodium taurocholate
12	Lysophosphatidylcholine	25	Sodium taurodeoxycholate
13	Menthol	26	sulfoxides

2. Prodrugsvir:

Hussain et al delivered opioid agonists and antagonists in acrimony prodrug forms and then found that the drug demonstrated low bioavailability as prodrug. Nalbuphine and naloxone bitter drugs when administered to dogs via the buccal mucosa, the caused excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in prodrug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds, which is generally 5% or less.[42]

3. pH:

Shojaei et al assessed absorptivity of acyclovir at pH ranges of 3.3 to 8.8, and in the presence of the absorption enhancer, sodium glycocholate. The in vitro permeability of acyclovir was found to be pH dependent with an increase in flux and permeability coefficient at both pH extremes (pH 3.3 and 8.8), as compared to the mid-range values (pH 4.1, 5.8, and 7.0).[43]

4. Patch design:

Several in vitro studies have been conducted regarding on the type and amount of backing materials and the drug release profile and it showed that both are interrelated. Also, the drug release pattern was different between single-layered and multi-layered patches.[44]

Advantages of medicated chewing gums:[14,15]

1. Increased rate of effectiveness rather than other oral delivery systems.
2. Removal of gum at any time; therefore, termination of drug delivery.
3. Reduced risk of overdosing while it's whole swallowed.
4. Requiring no water to drink.
5. Protection of the susceptible drugs contained from chemical or enzymatic attack in

gastrointestinal (GI) tract.

6. Both systemic and local drug delivery.
7. High acceptance by children and teenagers.
8. Low first-pass effect so reduced dose is formulated in chewing gum compared to other oral delivery systems.
9. Good for rapid delivery.
10. Fewer side effects.
11. Reduced risk of intolerance to gastric mucosa.
12. Good stability against light, oxygen, and moisture.
13. Annihilation of xerostomia and help tasting and swallowing in people with dry mouth.
14. Reduced pains and difficulties in swallowing following tonsillectomy.
15. Improving work performance and cognitive function.[17]
16. Fast bowel recovery after GI surgery.[20]
17. Reduced hypoglycemic shocks in people taking antidiabetic drugs.[20]
18. Stimulating alertness through increased blood flow to brain.[18]
19. Help reduce food cravings.[18]

Disadvantages of medicated chewing gums

1. 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.[33]
2. Sorbitol present in MCG formulation may cause flatulence and diarrhea.
3. Additives in gum like flavoring agent, Cinnamon can cause ulcers in oral cavity and liqorice cause hypertension. [34]
4. Chlorhexidine or mucosal application is limited to short term use because of its unpleasant taste and staining properties to teeth and tongue.[35]
5. Chewing gum has been shown to adhere to different degrees to enamel dentures and fillers.[36]
6. Prolong chewing on gum may result in pain in facial muscles.[37]

MANUFACTURING PROCESSES:

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

1. Conventional/traditional Method (Melting).
2. Freezing, grinding and tabletting Method
3. Direct Compression Method.[5]

Conventional / Traditional Method:

Components of gum base are softened or melted and placed in a kettle mixer to which sweeteners, syrups, active ingredients and other excipients are added at a definite time. The gum is then sent through a series of rollers that form into a thin, wide ribbon. During this process, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to enhance the flavour. In a carefully controlled room, the gum is cooled for up to 48 hours. This allows the gum to set properly. Finally, the gum is cut to the desired size and cooled at a carefully controlled temperature and humidity. [26]

Limitations:

1). Elevated temperature used in melting restricts the use of this method for thermolabile drugs.

2). Melting and mixing of highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult.

3). Lack of precise form, shape or weight of dosage form.

4). Technology not so easily adaptable to incorporate the stringent manufacturing conditions required for production of pharmaceutical products.

5). Such a chewing gum composition is difficult to form into chewing gum tablets because of their moisture content (2-8%). If attempted to grind and tablet such a composition would jam the grinding machine, stick to blades, screens adhere to. punches and would be difficult to compress.[27]

Cooling, Grinding and Tableting Method:

This method has been developed with an attempt to lower the moisture content and alleviate the problems mentioned in conventional method.

Cooling and Grinding:

The CG composition (base) is cooled to a temperature at which the composition is sufficiently brittle and would remain brittle during the subsequent grinding step without adhesion to the grinding apparatus. The temperature required for cooling is determined in part by the composition of the CG and is easily determined empirically by observing the properties of the cooled chewing gum composition. Generally the temperatures of the refrigerated mixture are around -15ºC or lower. The refrigerated composition is then crushed or ground to obtain minute fragments of finely ground pieces of the composition. For more efficient cooling, the chewing gum composition can be pre cooled prior to cooling to the refrigeration temperature.

Sometimes a mixture of chewing gum composition, solid carbon dioxide and precipitated silicais ground in a mill grinder in a first grinding step. Additional solid carbon dioxide and silica are added to the ground composition, and the composition is further ground in a second grinding step. This two step grinding process advantageously keeps the chewing gum composition at a very low temperature. The presence of solid carbon dioxide also serves to enhance the efficiency of the grinding process.

An anti-caking agent such as precipitated silicon dioxide can be mixed with chewing gum composition and solid carbon dioxide prior to grinding. This helps to prevent agglomeration of the subsequently ground chewing gum particles.

To prevent the gum from sticking to the grinding apparatus, 2-8% by weight of grinding aid such as alkaline metal phosphate, an alkaline earth metal phosphate or malto dextrin can be incorporated. However practical use of these substances is limited because these substances are highly alkaline and hence would be incompatible with acidic ionizable therapeutic agents. This provides a chewing gum product that is light and gives a soft chewing impression when chewed.[26,28]

Tabletting:

Once the coolant has been removed from the powder, the powder can be mixed with other ingredients such as binders, lubricants, coating agents and sweeteners etc., all of which are compatible with the components of the chewing gum base in a suitable blender such as sigma mill or a high shear mixer. Alternatively, a Fluidized Bed Reactor (FBR) can be used. The use of FBR is advantageous as it partially rebuilds the powder into granules, as well as coats the powder particles or granules with a coating agent thereby minimizing undesirable particle agglomeration. The granules so obtained can be mixed with ant adherents like talc. The mixture can be blended in a V type blender, screened & staged for compression. Compression can be carried out by any conventional process like punching.

It requires equipment other than conventional tabletting equipment and requires careful monitoring of humidity during the tabletting process.

Use of Directly Compressible Chewing Gum Excipients:

The manufacturing process can be accelerated if a directly compressible chewing gum excipient is available. The limitations of melting & freezing can be overcome by the use of these. PHARMAGUM® is one such compactable gum system developed by SPI Pharma. Pharma gum is a mixture of polyol(s) and sugars with a chewing gum base. It is available as directly compressible powder, free flowing powder which can be compacted into a gum tablet using conventional tablet press thus enabling rapid and low-cost development of a gum delivery system. 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).

Pharmagum® is available in three forms namely S, M and C. Pharmagum® M has 50% greater gum base compared to Pharmagum®S. Pharmagum® S consists primarily of gumbase and sorbitol. Pharmagum®M contains gumbase, mannitol & Isomalt. Release of nicotine from

directly compressible nicotine gum formulations and from Nicorette® prepared by conventional methods has shown that use of Pharmagum in formulation showed a faster release rate. Formulations made with Pharmagum® M & S are similar to tablet in appearance. Use of Pharmagum S, M and C enables formulators to utilize a gum delivery system quickly & morecost effectively than by traditional methods.[29]

Types of Chewing Gum:

1.Cut and wrap:

The gum bases for this type of line need a certain elasticity to withstand the stretching that takes place in the cooling tunnel. Chewing gum formulation should be softer than other chewing gum, due to the bigger size of the piece which is achieved by adding more liquids in the formula (glucose and sweeteners)

Figure 2: Cut and Wrap

2.Stick and tabes chewing gum:

Gum bases for laminated product should have the necessary plasticity to allow them to be shaped by the rolls and after the curing time, become hard enough to be wrapped properly. Laminated chewing gum usually have higher gum base percentage than cut and wrap gum. Besides that, the glucose contents need to be adjusted to afford the necessary hardness for the packaging process while maintaining sufficient elasticity to ensure that the pieces do not breakwhen bent.

Figure 3: Stick and tabes chewing gum

3.Pellets/pillows:

Similar to sticks, chewing gum is shaped in pellet form. Gum bases for laminated product should have the necessary plasticity to allow them to be shaped by the rolls and after the curing time, becomes hard enough to withstand the cooling process.

Figure 4: Pellets/pillows

4.Hollow balls:

Gum bases for revolutionary products must have certain elasticity (less than cut and wrap product) and have the necessary plasticity to maintain their shape and prevent leaks (if filled). Once the center is cured, it must be hard enough to withstand the coating process.

Figure 5: Hollow balls

5.Liquid filled gums:

Gum bases for stamped chewing gum should have special characteristics:

- Sufficient elasticity to withstand the equalizing steps where the stretching takes place.

- Correct plasticity to quickly adopt the shaped produced by the dies of the forming machine. The chewing gum should have a gum base percentage range that allows for good formation and a good seal. A deficiency or excess in the gum base content will lead to productdeformation.

Figure 6: Liquid filled gums

Gum filled candy:

All bubble gum bases can usually be used for this type of product, however due to high temperature of the candy, gum bases with lower viscosities may be more difficult to work with because they can become liquid.

Figure 7: Gum filled candy

6.Compressed chewing gum:

They are made of a powder ready to be compressed for functional and pharmaceuticalindustries.[3]

Figure 8: Compressed chewing gum

Factors Affecting Release of Active Ingredient

1. **Contact Time:** The local or systemic effect is dependent on time of contact of MCG in oral cavity. In clinical trial, chewing time of 30 min was considered close to ordinary use

2. **Physicochemical properties of active ingredient**: Physicochemical properties of active ingredient plays very important role in release of drug from MCG. The saliva soluble ingredients will be immediately released within few minutes, whereas lipid soluble drugs are released first into the gum base and then released slowly

3. **Inter individual variability:** The chewing frequency and chewing intensity that affect the drug release from MCG may vary from person to person. In-vitro study prescribed by European Pharmacopoeia suggests 60 cycles per minute chewing rate for proper release of active ingredient

4. **Formulation factor:** Composition and amount of gum base affect rate of release of active ingredient. If lipophilic fraction of gum is increased, the release rate is decreased.[11]

Methods:

Composition of Medicated Chewing Gum:

Gum base

This is the nonnutritive part of medicated chewing gum which does not dissolve while chewing. Usually, the gum base forms about 40% but can be up to 65%, and includes a complex mixture, insoluble in saliva, comprising mainly of elastomer, plasticizers, waxes,lipids, and emulsifiers.

Ingredient	Weight (%)	Example
Elastomer	10	Styrene-butadiene rubber
Plasticizer	30	Rosin esters
Texture agent/filler	35	Calcium carbonate
Wax	15	Paraffin wax
Lipid	7	Soya oil
Emulsifier	3	Lecithin
Miscellaneous	1	Colorant, antioxidant

1. Elastomers

These are polymers with high elongation properties and elasticity. They provide elasticity and controls gummy texture. Examples include natural rubbers like latex or natural gums such as Jelutong, Lechi-caspi, Perillo, Chile gum, Niger gutta, Nispero, etc.

Artificial elastomers such as polyisobutylene, isobutylene, isoprene copolymer, styrene- butadiene copolymer, polyvinyl acetate, etc. have also been used.

2. Plasticizers

Plasticizers are used to regulate the cohesiveness of the product. It promotes gum texture by applying plasticity and reducing brittleness. It also softens the elastomers.

Plasticizers of both natural and synthetic origin have been used in the manufacture of chewing gum. Examples include natural rosin esters like glycerol esters of partially dimerized rosin, glycerol esters of partially hydrogenated rosin, glycerol esters of polymerized esters, and pentaerythritol esters of rosin. Synthetic materials which are used as plasticizers include terpene resins derived from α-pinene and/or d-limonene.

3. Texture agents/ fillers

These include talc, calcium and magnesium carbonate, ground limestone, aluminum and magnesium silicate, alumina, clay, titanium oxide, and mono/ di/ tri-calcium phosphate. They provide texture, improve chewing ability, and provide reasonable size of the gum lump with low dose drug. They also facilitate blending and other processing stages.

Lipid and Wax

The lipid and the waxes melt in the mouth to provide a cooling, lubricating feeling. The base may be wax free.

4. Softeners and Emulsifiers.

These are added to MCG in order to optimize the chewability and mouth feel of the gum. Softeners used in the manufacture of medicated chewing gum include tallow, hydrogenated tallow, glycerine, lecithin, mono/ di/ triglycerides, fatty acids like oleic acid, stearic acid, linoleic acid, and palmitic acid.

5. Antioxidants

Antioxidants such as ascorbic acid, tocopherol, butylated hydroxyanisole, butylated hydroxytoluene, propyl gallate and mixtures thereof, may be added to inhibit oxidation.

6. Flavoring agents

These are used to improve flavor in medicated chewing gums. Examples include essential oils, such as citrus oil, fruit essences, spearmint oil, mint oil, peppermint oil, clove oil, anise oil, and oil of Wintergreen. Synthetic flavors can also be used.

7. Sweeteners

Sweeteners provide the desired sweetness of the product. Water-soluble sweetening agents e.g., sorbitol, hydrogenated starch, corn syrups, help to retain moisture and freshness of the finished product. They also act as a plasticizer or softening and binding agents.

High-intensity synthetic sweeteners can also be added to provide longer lasting sweetness and flavour perception. They produce lower calorie due to the partial absorbance in the intestine. Examples include sucralose, aspartame, alitame, saccharin, glycyrrhizin, dihydrochalcones etc.

8. Coloring agents

Colorants are added to improve the color of the formulation. Examples include FD & C type dyes and lakes, fruit and vegetable extracts, titanium dioxide.

9. Anti-tack agents

These are included in MCG to prevent self-adhesiveness also known as blocking in materials which have a tendency to stick together (e.g., rubbers). It also reduces fragmentation of the gum and prevents it from attaching to the teeth during mastication. Examples include α- cellulose and vegetable proteins.

Anti-caking agents

Anti-caking agents (e.g., precipitated silicon dioxide, solid carbon dioxide) are used to prevent caking and lump formation. These materials improve flow properties and rehydration and help for good packaging. They also help extend shelf life and detract dispersibility.

A typical chewing gum formulation is shown in the table below.

Ingredients	**Sugar gum**	**Sugar-free gum**
Gum base	19.4	25.0
Corn syrup	19.8	–
Sorbitol, 70 %	–	15.0
Sugar	59.7	–
Glycerin	0.5	6.5
Sorbitol	–	52.3
Flavor	0.6	1.2

DRUG PROFILE:

Disulfiram is an alcohol antagonist drug.

Chemical Name: bis(diethyl thiocarbamoyl) disulfide.

Structural Formula: [45]

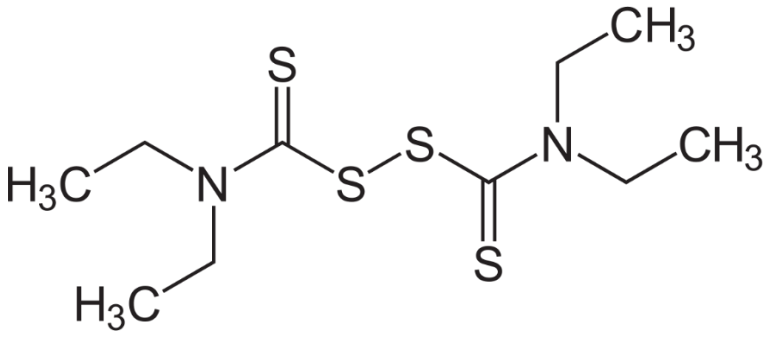
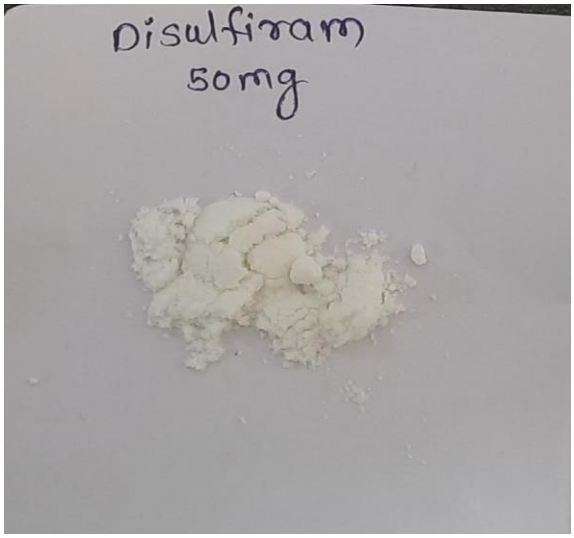


Figure 9: Structure of Disulfiram
Molecular Formula: $C_{10}H_{20}N_2S_4$
Molecular Weight: 296.54

Disulfiram occurs as a white to off-white, odorless, and almost tasteless powder, soluble in water to the extent of about 20 mg in 100 mL, and in alcohol to the extent of about 3.8 g in100 mL.

Disulfiram is a medication used to support the treatment of chronic alcoholism by producing an acute sensitivity to ethanol (drinking alcohol). Disulfiram works by inhibiting the enzyme aldehyde dehydrogenase, causing many of the effects of a hangover to be felt immediately following alcohol consumption. Disulfiram plus alcohol, even small amounts, produces flushing, throbbing in the head and neck, a throbbing headache, respiratory difficulty, nausea, copious vomiting, sweating, thirst, chest pain, palpitation, dyspnea, hyperventilation, fast heart rate, low blood pressure, fainting, marked uneasiness, weakness, vertigo, blurred vision, and confusion. In severe reactions there may be respiratory depression, cardiovascular collapse, abnormal heart rhythms, heart attack, acute congestive heart failure, unconsciousness, convulsions, and death.[14]

Fig 10: Disulfiram Drug



In the body, alcohol is converted to acetaldehyde, which is then broken down by acetaldehyde dehydrogenase. When the dehydrogenase enzyme is inhibited, acetaldehyde builds up, causing unpleasant side effects. Disulfiram should be used in conjunction with counseling and support.

MECHANISM OF ACTION OF DISULFIRAM:

Ethanol undergoes metabolism in the liver initially by alcohol dehydrogenase (ADH) forming acetaldehyde; this is removed from the body primarily by oxidation into acetate by acetaldehyde dehydrogenase (ALDH), which finally enters the citric acid cycle.

Disulfiram acts by inhibiting the enzyme ALDH via its metabolite S-methyl N, N-diethyl- dithio-carbamate-sulphoxide, leading to accumulation of acetaldehyde in blood. This gives rise to various manifestations of disulfiram-alcohol reaction (DER).

Since the inhibition of ALDH by disulfiram is irreversible, the DER will get terminated only after production of new ALDH once disulfiram is stopped.

The new ALDH takes about a week's time to be produced. Hence patients should be advised to take alcohol only after 2 weeks of stopping disulfiram. In addition to this, disulfiram also acts on the dopaminergic system, both disulfiram and its metabolite carbon disulfide leading to inhibition of dopamine beta-hydroxylase (DBH) that leads to increase in the levels of dopa-mine.

This may give rise to several neuropsychiatric manifestations such as delirium, paranoia, impairment of memory, ataxia, dysarthria and frontal lobe release signs.

Besides this action, disulfiram is also known to inhibit dopamine beta-hydroxylase leading to an increase in dopamine concentrations but decreased norepinephrine in the brain. This may suggest an anti-craving role of disulfiram in alcohol dependence.

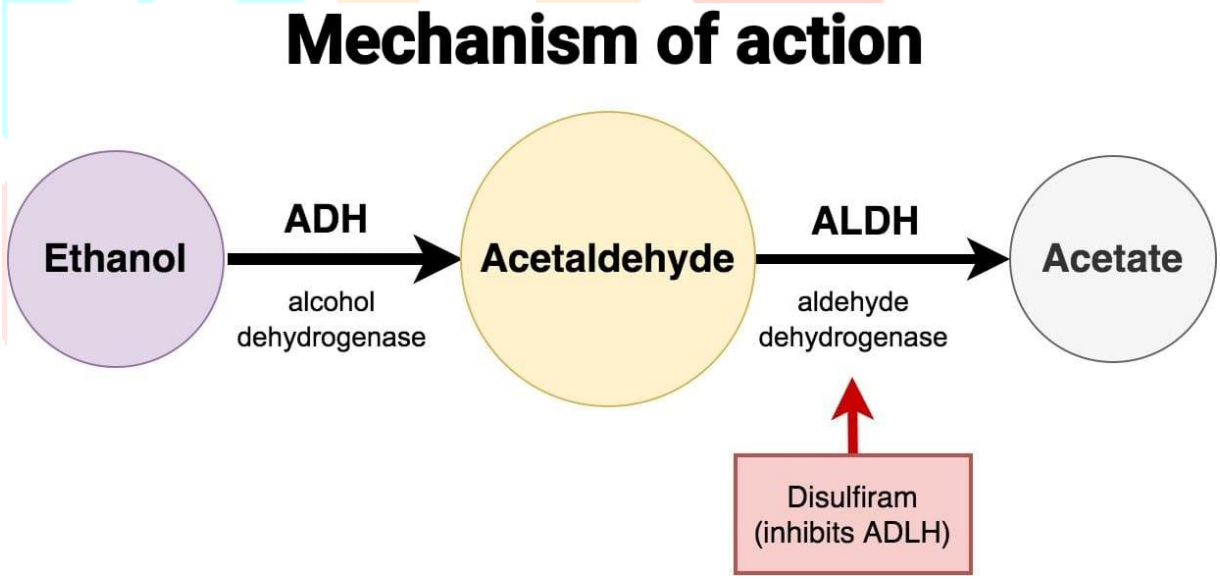


Figure 11: Mechanism of action

Pre formulations Studies of Drug:

Organoleptic Properties: The samples of Disulfiram was identified for colour, odour and taste which were found to be same as that of standard parameters.

PARAMETER	RESULT
Colour	White
Odour	Characteristics odour
Taste	Metallic Taste

Table 2: Organoleptic Properties

Melting Range: The melting point of Disulfiram was found to be 69-72 ºC and compare with reference i.e., 71ºC the drug was found to be in the pure form.

Solubility Studies: The solubility of the drug sample was determined by accurately weight 10 mg of Disulfiram was added in 6 test tubes and was added in aqueous and non-aqueous solvents and solution was kept for 24 hrs. and then samples were analyzed by U.V visible spectrophotometry and were found to be soluble in non-polar and were found to be insoluble in polar solvents.

Table 3: Solubility Profile of Disulfiram

SOLVENT	SOLUBILITY
Water	Insoluble
Methanol	Very Soluble
Ethanol	Sparingly Soluble
Chloroform	Soluble
Ether	Soluble

UV-Visible Spectrophotometric Studies:

Table 4: Absorbance of Disulfiram in Methanol

CONCENTRATION	ABSORBTION
0.2	0.2233
0.4	0.364
0.6	0.526
0.8	0.5994
1.0	0.7272

Evaluation of MGCs

1. **Uniformity of content**: Unless otherwise prescribed or justified and authorized, MGCs with a content of active ingredient less than 2 mg or less than 2 per cent of the total mass comply with test A for uniformity of content of single-dose preparations. If the preparation contains more than one active substance, the requirement applies only to those active substances whichcorrespond to the above conditions.

2. **Uniformity of mass**: Uncoated MGCs and, unless otherwise justified and authorized, coated medicated chewing gums comply with the test for uniformity of mass of single-dose preparations. If the test for uniformity of content is prescribed for all the active substances, the test for uniformity of mass is not required.

3. **In-vitro drug release**: It has been reported commercially that the drug release from MGCs as per the specification given in European Pharmacopoeia and determined by applying a mechanical kneading procedure to a piece of gum placed in a chewing chamber containing a known volume of buffer solution.

4. **In vivo chew out study**: The volunteers are asked to chew the drug delivery device for a certain period of time and to assess the remaining quantity of active substance in the residual gum. In this way, the gums are really chewed and the formulation is subjected not only to the mechanical stresses of an artificial machine but also it undergoes all the phenomena involved in this process (increase of salivary secretion, saliva pH variation, swallowing and absorption by the oral mucosa, etc.) which can strongly influence the performance of the dosage form as well as the amount and rate of drug release. Optimized formulation with good consistency can be selected for their lease of drug in the saliva. Minimum four human volunteers can be selected (two male and two female). should rinse their mouth with distilled water allowed to chewing the medicated chewing gum for 15 minutes, for maximum release has to be taken Sample of saliva are taken after 2, 4, 6, 8, 10, 12, 14 and 15 minutes. samples are diluted in required solvent and absorbance is measured using suitable analytical method.

5. **Dissolution test of residual MGCs**: In this experiment, gums are tested by a panel of volunteers to verify the drug release process from the drug delivery system. Each volunteer chews one sample of the tableted gum for different time periods (1, 5, 10 and 15 minutes). The residual gums are cut into small pieces frozen and then ground till obtaining a fine powder The residual drug content is determined by using suitable analytical method. The amount of drug released during mastication is calculated by subtracting the

amount of residual active ingredient present in the gum from the total content, where as pharmacokinetics can be determined from withdrawn blood samples at specific time intervals. The prerequisites of human volunteers, person-to-person variability in the chewing pattern, chewing frequencies, composition of individual salivary fluid and flow rate of saliva are a few limitations of chew-out studies.

6. Urinary excretion profile: Only applicable to drugs which are excreted via urine. minimum four healthy human volunteer are selected for the study. Volunteers are strictly instructed that they should not take any medicine in the last 48 hours. They are fasted overnight, and emptied their bladder in the volumetric flask. Sample collection starts from blank of zero hour urine. Then sample collection is done on 15 minutes, 1, 2, 3, 4, 6, 7, 8, 10, 11, 12 and 24 hour intervals after administration of medicated chewing gum. volunteers should drink water at regular intervals of 30 minutes. urine samples are analyzed by suitable analytical methods.

7. Buccal absorption test: Human volunteer swirled fixed volume of drug solution of known concentration at different pH value of 1.2, 5, 6, 6.5, 7, 7.5, 7.8, 8.0, in the oral cavity for 15minutes and then expelled out. saliva is analyzed for drug content and back calculated for buccal absorption.

8. Texture analysis: Texture studies by instrument Instrumental texture analysis is mainly concerned with the evaluation of mechanical characteristics where the mcg is subjected to a controlled force from which a deformation curve of its response is generated. For evaluating texture properties of MCG, a "compression" probe was used in this deformation method by using the texture analyzer. Squashing solid and self-supporting samples enabled a number of textural properties to be evaluated, including hardness (peak force that results from a sample being compressed to a given distance, time, or % of deformation) and adhesiveness (stickiness- related to how an MCG adheres to the inside of the mouth surfaces during chewing). It is recommended to use a compression probe with a greater surface area than that of the sample being tested, so a compression platen probe of 50 mm ø was used. During evaluation, a constant force should be applied on the surface of self-supporting MCG and upon fracture it should be withdrawn. Through which, a deformation curve can recorded and interpreted.[12]

FUTURE SCOPE:

Manufacturing natural gum bases instead of synthetic gum bases with new pharmaceutical compound, flavor's, healthy, and innovative gum hold a good opportunity for the confectionarymarket.

This review is an eyeopener to introduce a zero- waste technology for chewing gum manufacturers. Hence, innovative or modern gum base should be developed from natural source which can withstand in mouth during the chewing process and get digested in the intestine by colonic microorganisms after chewing and swallowing.[9]

Medical chewing gum meets the high-quality standards of the pharmaceutical industry and can be formulated to obtain different release profiles of active substances, thus enabling distinct patient group targeting.

A few decades ago, the only treatment for some diseases was surgical procedures (e.g., gastric ulcers); however, today more and more diseases are treated by medication.

This trend is likely to continue as sophisticated research methods allow the development of medication for an increasing number of diseases. At the same time, there is a demand for efficient and convenient drug delivery systems.

In general, it takes time for a new drug delivery system to establish itself on the market and gain acceptance by both professionals and patients.

Health encloses in gum suitable attract the patient and provide added value to the customer as well as differentiating market trend set.

Medicated chewing gum is a valid alternative to standard, chewable or orally disintegrating tablet presentations.

There are also some scopes for chewing gum for research in the treatment of amnesia, Alzheimer and memory defects.

No solid evidence is available that chewing gums increases aspects of mental performance, but there are some experiments and running clinical trials that shows practicing gum can improve episodic memory, working memory, and mood and also act as stress relief.

CONCLUSION:

Medicated chewing gums could be a great way of delivering drug to the body either for local or systemic effect. The preparation procedure is easy and the dosage form is convenient to use, has got great patient compliance. The mouth freshening effect also adds some advantages. But quality testing procedures are not still well developed. The USP does not have any official method of in vitro drug release study. So, evaluation of the prepared chewing gums is one of the major challenges.

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