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Review on Medicated Chewing Gum of Diasulfiram

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Abstract: *Since ancient times, chewing gum has been used to refresh breath and clean the mouth. In 1869, the first chewing gum patent was submitted, and in 1928, the first medicated chewing gum was released into the market. The European Pharmacopoeia described the intended use of medicinal chewing gum in 1991 as either systemic distribution following absorption from the gastrointestinal tract or buccal mucosa, or as local treatment of oral disorders. The heart of medicated chewing gum is masticatory gum covered in a layer of polymers, waxes, sugar, sweeteners, flavors, or colors. The coating, the core, or both may contain the pharmacologically active component. The mucosa's state, the duration of contact, and the active ingredient's physicochemical characteristics all affect how much is absorbed through the mucosa. The most probable substance to be absorbed is a tiny, enzymatically stable, un-ionized lipophilic molecule dissolved in saliva. In terms of local actions, medicated chewing gum can have positive results that may even outperform lozenges. While a lipid-soluble substance will dissolve in the gum base and then be released gradually and incompletely, a saliva-soluble ingredient will be released nearly entirely within 10 to 15 minutes of chewing.as Mastication increases salivary flow, and the active substance (based on its properties) dissolves in the saliva before being eaten and then absorbed systemically. As a medicine delivery method, medicated chewing gum has grown in popularity over time. Medicated chewing gum now contains a number of ingredients, such as fluoride to prevent dental cavities, chlorhexidine to disinfect the area, nicotine to help people quit smoking, aspirin (acetylsalicylic acid) to relieve pain, dimenhydrinate to prevent motion sickness, and caffeine to help people stay alert. The usage of medicinal chewing gum may be beneficial for a variety of other illnesses and ailments. When opposed to oral liquids or tablets, chewing gum may be a preferred way of medicine delivery for children in particular. Chewing gum with medication can be used to treat systemic disorders as well as diseases of the oral cavity locally..*

Keywords: Mastication

I. INTRODUCTION

Disulfiram was initially synthesized in 1881 by the German scientist M. Grodzki, although his discovery was not widely accepted at the time of his Berichte report. Fifty years later, the chemical was rediscovered as a compound that accelerates the vulcanization of rubber . Although American physician E.E.Williams noted in 1937 that workers at a rubber mill experienced negative physiological effects after taking alcohol, it would take another ten years before this unique action of disulfiram was first investigated for therapeutic usage.

Following encouraging research by Swedish and British scientists demonstrating disulfiram's capacity to treat scabies in domestic animals, Danish researchers Dr. Erik Jacobsen and Dr. Jens Hald developed an interest in the drug in the 1940s . Disulfiram depletes the scabies parasite of its major oxygen transporter by chelating copper, as Jacobsen and Hald found . They proposed that disulfiram would be a useful treatment for intestinal worms in both humans and animals because of this mechanism . Jacobsen and Hald initially tested disulfiram on themselves to determine its safety for clinical use. "The disulfiram tablets really changed the effect of alcohol in a most unpleasant direction ." is what

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Jacobsen wrote after the event. An study examining the physiological effects of disulfiram after alcohol consumption was published in 1948 by Jacobsen and Hald. Participants in the initial research received 30–60 mL of gin after receiving 1–1.5 g of disulfiram (2–3× the current FDA-approved maximum dose of 500 mg). kept an eye out for negative reactions. Increased lung ventilation, tachycardia, and facial vasodilation were observed by Jacobsen and Hald . Hald and Jacobsen postulated that elevated acetaldehyde levels might be the cause of disulfiram's detrimental physiological effects when mixed with alcohol after a collaborator saw the strong acetaldehyde odor in the lab. In order to test this theory, they continuously infused acetaldehyde into volunteers' veins until their blood levels matched those of disulfiram users following alcohol use. The individuals had the same adverse effects as disulfiram at these elevated dosages. Based on these tests, scientists deduced that disulfiram most likely functioned by preventing alcohol from being eliminated normally.

Nearly 150 articles from both Europe and the US examined disulfiram, its effects, and its potential as a treatment for alcohol consumption disorder between 1948 and 1953 . Disulfiram was the first FDA-licensed treatment for alcohol use disorder in the US, having been approved in 1951. Common therapeutic dosages of disulfiram at the time of approval were 1000–3000 mg per day .At these elevated dosages, the medication gained notoriety for producing significant adverse effects and fatalities due to severe disulfiram–ethanol interactions. Subcutaneous disulfiram implants gained popularity in the late 1960s as a way to guarantee treatment compliance for alcohol consumption disorder .However, disulfiram implants have never been approved for use in the US due to a lack of data about the effectiveness and safety of this drug delivery route.

Disulfiram has lost appeal as a treatment for alcohol use disorder after the advent of newer FDA-approved pharmaceutical therapies such acamprosate and naltrexone [6]. As novel mechanisms and potential applications are continuously being found, it continues to be a medication of interest in many areas of clinical medicine. The numerous promising prospective uses for disulfiram in clinical settings are discussed in this narrative review, along with the numerous difficulties associated with its safety, pharmacokinetic variability, and possible side effects.

• DRUG PROFILE:

Disulfiram is an alcohol antagonist drug.

• Chemical Name: bis(diethyl thiocarbamoyl) disulfide.

• Structural Formula:[45]

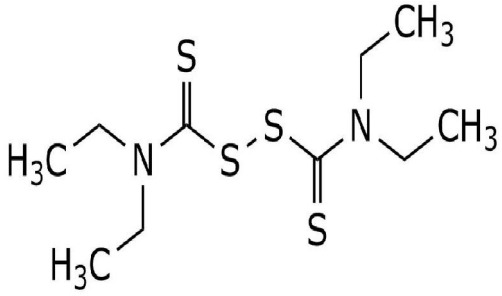

Figure 1: Structure of Disulfiram

• Molecular Formula :-

C10H20N2S4

• 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:

By creating an acute sensitivity to ethanol (drinking alcohol), the drug disulfiram aids in the treatment of persistent alcoholism. Many of the consequences of a hangover occur right after drinking because disulfiram inhibits the enzyme aldehyde dehydrogenase. Even small doses of alcohol combined with disulfiram can cause flushing, a throbbing

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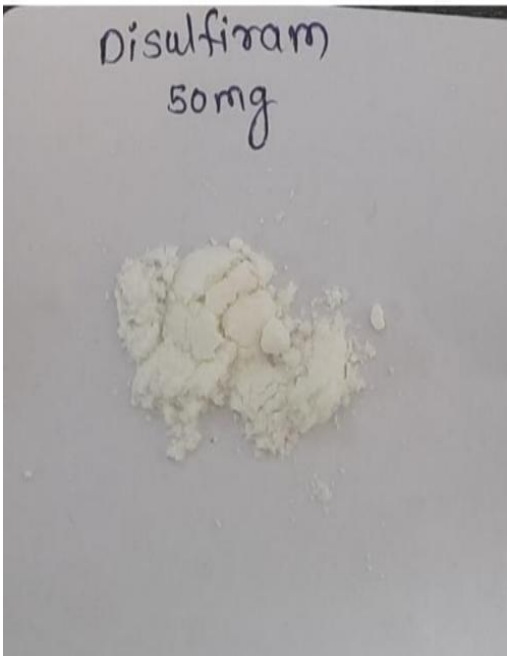
headache, nausea, vomiting, sweating, thirst, chest pain, palpitations, dyspnea, hyperventilation, low blood pressure, fainting, noticeable uneasiness, weakness, vertigo, blurred vision, and confusion. Acute congestive heart failure, heart attacks, irregular cardiac rhythms, respiratory depression, cardiovascular collapse, unconsciousness, convulsions, and death are all possible outcomes of severe reactions.



Acetaldehyde is produced in the body from alcohol and subsequently broken down by acetaldehyde dehydrogenase. Unpleasant side effects result from the accumulation of acetaldehyde caused by inhibition of the dehydrogenase enzyme. Counseling and assistance should be utilized in conjunction with disulfiram.

• Mechanism Of Action

Tetraethylthiuram disulfide, often known as disulfiram, is an electrophilic quaternary ammonium molecule that has been demonstrated to effectively block a wide range of metabolic enzymes. Numerous significant mechanisms of inhibition have been identified, but novel possibilities are still being described by continuing research.

The capacity of disulfiram to chelate metal ions was initially reported by Jacobsen and Hald in the 1940s . Subsequent research revealed that the specific disulfiram metabolite that gives the medication its chelating properties is diethyldithiocarbamate (DDTC). A potent chelator of transition divalent metal ions, such as copper and zinc, DDTC is the reduced version of disulfiram (Figure 1). DDTC might hinder the activity of metal-containing enzymes such as dopamine β-hydroxylase (DBH), carboxylesterase, cholinesterase, superoxide dismutase, and aldehyde dehydrogenase (ADH) by chelating vital cofactors . According to Section 2.6, the active metabolite of disulfiram that gives it its anticancer effects is thought to be the compound of copper and diethyldithiocarbamate Cu (DTC)2.

Disulfiram's (left) and sodium DDTC's (right) chemical structures. Wikimedia provided access to NEUROtiker's "Structure of disulfi-ram," which is in the public domain.

Through the thiol–disulfide exchange process, the free sulfhydryl groups of proteins can easily decrease the disulfide bond seen in disulfiram. Cysteine residues on target enzymes undergo covalent modification in this irreversible process, which inhibits enzymatic activity and releases a DDTC molecule. Aldehyde dehydrogenase, methyltransferase, urease, and kinase are among the enzymes that have been shown to be vulnerable to disulfiram inhibition by this mechanism since the 1940s. By directly or indirectly adjusting the concentration of reactive oxygen species, disulfiram can also change the intracellular environment. Cells naturally produce reactive oxygen species (ROS) when they undergo oxidative phosphorylation or react to external pathogens. Oxidative stress occurs when the concentration of

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ROS surpasses the cell's antioxidant response. Cell death may be the ultimate consequence of oxidative stress, which damages lipid membranes, proteins, and DNA. It is believed that the generation of ROS within a cell is triggered by the chelation reaction between DDTC and metal ions, potentially leading to cellular damage or death . According to certain research, disulfiram has antioxidant qualities that guard against the production or spread of ROS and may eventually help lower inflammation in specific illness conditions. Particularly, it has been documented that thiol compounds, like disulfiram, can scavenge oxygen radicals and eliminate them from the intracellular milieu.

II. DRUG CHARACTERISTICS AND PHARMACOKINETICS

Standard dosages for the oral medication disulfiram range from 250 to 500 mg per day, with a maximum suggested dosage of 500 mg per day. Eighty to ninety percent of the oral disulfiram dosage is absorbed in the gastrointestinal system Disulfiram and its metabolites are broadly distributed into adipose tissue throughout the body and easily pass through the blood–brain barrier because of their high lipid solubility.In a study where rats were given radiolabeled disulfiram, the medication was found in the kidneys and pancreas. Brain, liver, GI tract, fat, blood, and so on, in decreasing order.

Disulfiram's pharmacokinetics (PK) are poorly understood. The half-life elimination of disulfiram and its metabolites in both human volunteers and animals has been the subject of numerous investigations. Comprehensive PK data from these investigations are few, partly because of detection technology limitations and field discrepancies over disulfiram identification in samples.

Disulfiram's clinical use are due to its broad in vivo metabolism and quick biotransformation into metabolic metabolites. All subsequent metabolism of disulfiram occurs through DDTC, which has three potential metabolic outcomes.

1. Spontaneous degradation:

DDTC's half-life is a linear function of pH and it is acid-labile .When DDTC is exposed to acidic conditions, like the stomach, it breaks down into diethylamine and carbon disulfide (CS2). Following the injection of disulfiram, the CS2 can be found in human breath and blood. The half-life of CS2 is approximately 12 hours following oral administration of 250 mg of disulfiram Seventy-two hours after injection, CS2 was detected in the breath.

2. Formation of Glucuron ide:-

The enzyme glucuronosyl transferase, which is extensively expressed in the liver, is responsible for the production of glucuronide. 2-11% of the disulfiram dose that is delivered and eliminated in the urine is due to the glucuronide of DDTC.

3.Formation of Methyl Esters:

The methylation of DDTC is catalyzed by the enzymes thiol methyltransferase (microsomal) and perhaps thiopurine methyltransferase (cytosolic), which are present in the liver and a number of other organs, such as the lungs, kidneys, and gastrointestinal system. The significant lipophilic metabolite DDTC-Me (methyl diethyldithiocarbamate) is produced as a result of this methylation process. Further oxidation of DDTC-Me results in DETC-Me (methyl diethylthiocarbamate), which is then biotransformed into other metabolites that contribute to the ALDH enzyme's irreversible inactivation.

Table 1 lists studies assessing the human elimination rates of disulfiram and a few of its metabolites. The first dose of disulfiram or DDTC given is rapidly reduced in the plasma. In certain instances, a longer terminal elimination phase occurs after this quick fall . When disulfiram is administered to plasma, its in vitro half-life is 2 to 4 minutes. Disulfiram's half-life has been found to range between 10 and 87 minutes in rat and mouse investigations; nevertheless, in the majority of these studies, it is below the detection threshold . According to human research, DDTC and disulfiram have half-lives of 15 and 7 hours, respectively. This large range suggests that levels of disulfiram and its metabolites after oral treatment vary significantly between subjects. Significant and inexplicable variations in plasma disul-firam levels between patients have been seen in other investigations. Following the injection of 250 mg of

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disulfiram to humans, a study conducted in the 1970s using gas chromatography revealed that the plasma concentration ranged from 30 to 1830 ng/m * L, with an average of 590 plus/minus 434 * ng / m * L. After 200 mg of disulfiram was administered to humans, a follow-up study in 1991 using high-performance liquid chromatography revealed that the median plasma DDTC-Me concentration was 15.02 ng/mL with a range of 1.63 - 77.08 ng / m * L. Although these two studies examined different metabolites, they both found significant inter-subject variability in disulfiram metabolism.

Table 1 Disulfiram administration and the metabolites' PK characteristics

	Drug Administered	Route	Dose	Metabolite Measured in Plasma	Cmax(µg/Ml)	T1/2 of The Metabolite Measured
1	Disulfiram	PO	250 mg	Disulfiram DDTC DDTC-Me Diethylamine CS2 CS2 (breath)	0.3,0.4 0.7,1.4 0.3,1.2 1.7,3.8 22,24 37,44	7 h 15 h 22 h 14 h 9 h 13 h
2	Disulfiram	PO	400 mg	DDTC-Me	NA	6 h
3	Disulfiram	PO	400 mg	DDTC-Me DETC-Me	0.05 0.04	6 h 11 h

PO stands for oral; NA for not available; and Cmax for the highest concentration found in the plasma. A single dose is represented by the first Cmax values in #1, whereas the measured quantity following many doses is represented by the later ones.

In a recent study, disulfiram was administered to HIV+ antiretroviral treatment (ART)-suppressed individuals, and ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS) was used to evaluate the plasma concentrations of disulfiram and four metabolites. Disulfiram was completely eradicated after 72 hours. With a clearance of 0.53 L/h, a volume of distribution of 1.3 L, and an absorption constant of 0.08/h, the non-linear elimination of disulfiram was suggested; the half-life was not assessed because it was hypothesized that disulfiram would not follow first-order elimination kinetics. Furthermore, as in earlier research, there was a considerable degree of inter-subject heterogeneity . Although the cause of this variation is unknown, it might be due to variations in the patient's metabolism, lipid composition, enterohepatic circulation, or plasma's ability to bind proteins. Furthermore, it has been discovered that linear increments in disulfiram dosages cause a supra-proportional rise in plasma disulfiram levels; potential causes include cytochrome P450 enzyme saturation and enhanced bioavailability at higher dosages .

The practical use of disulfiram in human treatment is complicated by the significant degree of unpredictability in plasma disulfiram levels, since this variability would affect the drug's safety profile as well as its effectiveness. This variation probably explains why one research of 63 people found that over half of those exposed to alcohol did not experience a disulfiram–ethanol interaction when given a daily dose of 200–300 mg of disulfiram; in others, even a 500 mg dose was not enough to cause this reaction . The uncommon but significant dangers that arise even at the lesser dosage of 250 mg daily may potentially be explained by the variation in blood levels amongst patients. Because there are so few human pharmacokinetic studies, uncertainty about inter-subject variability makes it difficult to assess the safety and effectiveness of disulfiram.

• Methods to increase drug delivery via buccal route :

1. Absorption enhancers:

It has been demonstrated that absorption enhancers are effective in delivering high molecular weight substances, including peptides, which typically have low buccal absorption rates. These can work in a number of ways, including by making the cell membrane more fluid, removing lipids from between and within cells, changing cellular proteins, or

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changing surface mucin. Bile salts, sodium dodecyl sulphate, and fatty acids are the most often used absorption enhancers. Glyceryl monooleates were reported to improve peptide absorption through a cotransport mechanism, while chitosan solutions and gels were also found to facilitate the transport of mannitol and fluorescently labeled dextrans across a tissue culture model of the buccal epithelium.

2. Prodrugsvir

After delivering opioid agonists and antagonists in acrimony prodrug forms, Hussain et al. discovered that the drug had a limited bioavailability. When given to dogs through the buccal mucosa, the bitter medications naloxone and nalbuphine resulted in excessive salivation and swallowing. Consequently, the drug's bioavailability was minimal. When nalbuphine and naloxone were administered in prodrug form, there were no negative side effects, and their bioavailability ranged from 35 to 50%, which is significantly better than their oral bioavailability, which is typically 5% or less.

3.pH:

Numerous in vitro investigations into the kind and quantity of supporting materials and the drug release profile have demonstrated their interdependence. Additionally, single-layered and multi-layered patches had varied drug release patterns.

4. Patch design

Numerous in vitro investigations into the kind and quantity of supporting materials and the drug release profile have demonstrated their interdependence. Additionally, single-layered and multi-layered patches had varied drug release patterns.

• Advantages of medicated chewing gums:

1. More efficacy compared to alternative oral administration methods.
2. Drug distribution is stopped when gum is removed at any time.
3. Decreased chance of overdose when consumed whole.
4. Not needing water to consume
5. Protection of the vulnerable medications against gastrointestinal tract chemical or enzymatic damage.
6. Both local and systemic medication administration.
7. High level of acceptance among kids and teens.
8. Compared to other oral administration systems, chewing gum has a lower dose because of its low first-pass effect.
9. Decreased chance of stomach mucosal intolerance.
10. Strong resistance to moisture, oxygen, and light.
11. Less discomfort and swallowing issues after tonsillectomy.
12. Enhancing cognitive function and professional performance.
13. Quick recovery from bowel surgery following GI surgery.
14. People on antidiabetic medications experience less hypoglycemia shocks.
15. Increasing blood flow to the brain to promote alertness.

• Disadvantages of medicated chewing gums:

1.Compared to chewable tablets or lozenges, which can be taken in large quantities and in a shorter amount of time, there is a risk of overdosing on MCG.

2. Diarrhea and flatulence may result from the sorbitol in the MCG formulation.

3. Gum additives such as flavoring agents, cinnamon, and liquorice might result in oral cavity ulcers and hypertension, respectively.

4. Because of its disagreeable taste and ability to discolor teeth and tongue, chlorhexidine or mucosal application is only recommended for short-term usage.

5. It has been demonstrated that chewing gum adheres to enamel dentures and fillings to varying degrees.

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6. Prolonged gum chewing might cause facial muscular soreness.

• Use of Directl Compressible Chewing Gum Excipients:

The availability of a chewing gum excipient that is directly compressible can speed up the manufacturing process. These can be used to get beyond the constraints of melting and freezing. One such compactable gum solution created by SPI Pharma is PHARMAGUM®. Pharma gum is a chewing gum foundation made of sugars and one or more polyols. It is offered as a free-flowing, immediately compressible powder that can be compressed into a gum tablet using a standard tablet press, allowing for the quick and inexpensive creation of a gum delivery system. They can be regarded as "Generally regarded as safe" since they are produced in accordance with CGMP guidelines and meet FDA and Food Chemicals Codex requirements. Pharmagum® comes in three different forms: S, M, and C. The gum basis of Pharmagum® M is 50% higher than that of Pharmagum® S. The main ingredients of Pharmagum® S are sorbitol and gumbase. Gumbase, mannitol, and isomalt are ingredients in Pharmagum®M. The use of Pharmagum in formulation demonstrated a faster release rate of nicotine compared to Nicorette® made using standard procedures and directly compressible nicotine gum formulations. Pharmaguum® M & S formulations resemble tablets in appearance. By using Pharmagum S, M, and C, formulators can use a gum delivery system more rapidly and affordably than they could with conventional techniques.

• Types of chewing gum :-

1. Cut and Wrap

For this kind of line to endure the stretching that occurs in the cooling tunnel, the gum bases must have a particular amount of flexibility. The larger size of the piece, which is accomplished by adding more liquids to the formula (glucose and sweeteners), should make the chewing gum formulation softer than ordinary chewing gum.

2. Stick and tabes chewing gum

The gum bases used in laminated products should be sufficiently malleable to be molded by the rollers and rigid enough to wrap well after curing. Compared to cut and wrap gum, laminated chewing gum often has a greater gum base percentage. In addition, the amount of glucose must be changed to provide the hardness required for the packaging process while preserving enough elasticity to prevent the pieces from shattering when bent.

3. Pellets/pillows:

Chewing gum is formed like a pellet, just like sticks. The gum bases for laminated products should be sufficiently malleable to be molded by the rolls and rigid enough to endure cooling after the cure period.

4. Hollow balls:

In order to keep their shape and stop leaks (if filled), gum bases for innovative items need to be somewhat elastic (less than cut and wrap products) and plastic. The center needs to be sufficiently firm after curing to endure the coating procedure.

5. Liquid filled gums:

Special qualities should be present in the gum bases of stamped chewing gum:

Enough suppleness to endure the equalizing stages in which the stretching occurs.proper plasticity to swiftly take on the shape created by the shaping machine's dies. The gum base % range of the chewing gum should be such that it promotes proper formation and a good seal. The product will distort if the gum base content is either too high or too low.

6. Compressed chewing gum:-

They are composed of a powder that can be compacted for use in the pharmaceutical and functional industries.

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III. FUTURE SCOPE

• Producing natural gum bases rather than synthetic ones with novel flavors, pharmacological compounds, and healthy gum presents a promising potential for the confectionery industry.
• This evaluation serves as an eye-opener for makers of chewing gum to create a zero-waste technology. Therefore, a novel or contemporary gum basis should be created from a natural source that can last in the mouth while being chewed and be broken down by colonic microbes in the intestine after being chewed and swallowed.
• Medical chewing gum can be made to produce various release profiles of active ingredients, allowing for specific patient group targeting, and it satisfies the rigorous quality criteria of the pharmaceutical business.
• A few decades ago, surgery was the only way to treat certain conditions (like stomach ulcers); today, medication is used to treat an increasing number of illnesses.
• As more diseases can be treated with medication thanks to advanced research techniques, this trend is probably going to continue. Concurrently, there is a need for effective and practical medication delivery methods.
• Generally speaking, it takes time for a new drug delivery system to become well-known and accepted by patients and professionals.
• Gum that offers health benefits to patients draws them in, adds value for them, and sets them apart from the competition.
• An acceptable substitute for conventional chewable or orally disintegrating tablet forms is medicated chewing gum.
• Additionally, chewing gum may be used in studies to treat memory impairments, Alzheimer's disease, and forgetfulness.
• Although there isn't any conclusive proof that chewing gum improves mental performance, some studies and ongoing clinical trials indicate that gum chewing can enhance mood, working memory, episodic memory, and stress reduction.

IV. CONCLUSION

Chewing gum with medication may be an excellent method of supplying the body with a medicament for either a local or systemic effect. The dosage form is straightforward to use, the preparation process is simple, and patient compliance is excellent. Some benefits are also added by the mouth-freshening effect. However, quality testing practices are still lacking in sophistication. The USP lacks an official in vitro drug release study methodology. Therefore, one of the main difficulties is evaluating the prepared chewing gums.

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