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# RECENT INNOVATIONS OF NOVEL DRUG DELIVERY SYSTEMS FOR FORMULATION, DEVELOPMENT AND EVALUATION OF METRONIDAZOLE MEDICATED CHEWING GUM TABLETS

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## ABSTRACT
Medicated Chewing Gum 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. In the recent years, patient convenience-oriented exploration in the area of drug delivery has introduced potential innovative medicine delivery systems as Medicated Chewing Gum. Since it can be taken anywhere, a Medicated Chewing Gum formulation is an excellent choice for acute medication. The advantages for children and for patients who find swallowing tablets difficult are obvious. Over the 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. Medicated Chewing Gum is one of the very popular oral confectionary products. The Medicated Chewing Gum has through the recent years gained increasing acceptance as a drug delivery system. Medicated chewing gums have a broad range of potential uses that will be identified in the future. New Medicated Chewing Gum formulations should be considered by scientists and researchers delivers numerous innovative patented applications employed in order to increase Medicated Chewing Gum variants owing to patient preferences and provide a suitable release pattern for Medicated Chewing Gum containing medications. MCG represents the newest system with potential uses in pharmaceuticals, over the counter medicines and nutraceuticals. The potential of Medicated Chewing Gum MCG for buccal delivery, fast onset of action makes it an attractive delivery form. It is considered as vehicle or a drug delivery system to administer active principles that can improve health and pharmaceutical care. Metronidazole benzoate is a derivative of Metronidazole, an antibiotic commonly used for treating bacterial and protozoal infections. The objective of the present study was to formulate Metronidazole benzoate as Medicated Chewing Gum to prove acceptable of patients and enhance its antibiotics as a drug delivery system. It was prepared different Medicated Chewing Gum formulations by different methods such as mixing and direct compression, wet granulation and compression by using tablet compression machine and molding by using cylindrical blister back and evaluation of formulations by using evaluation parameters of Medicated Chewing Gum as a drug delivery system. According to the results it was found to be the difference between formulation at different media and evaluation tests. It was concluded the MCG formulation F20 is the best formulation among the all formulations of Metronidazole benzoate Medicated Chewing Gum as a drug Delivery system and confirmed to evaluated limit specification.

**KEYWORDS:** Metronidazole benzoate, Medicated Chewing Gum, Formulation, Antibiotics, Protozoal infections, Patient compliance.

## INTRODUCTION
### Medicated Chewing Gum MCG[1-100]
Most of the oral pharmaceutical dosage forms like conventional tablets and capsules are formulated to be swallowed or chewed. Elderly people and children sometimes have difficulties in swallowing these dosage forms. Such problem is more serious for bedridden patients. This problem is also applicable to active

working or travelling people who do not have ready access to water. Recent advances in novel drug delivery system aims to provide rational drug therapy by enhanced safety and efficacy of drug molecule by formulating a convenient dosage form for administration and also by ensuring better patient compliance.

Oral drug delivery has been known as the most widely used route of drug administration when compared to all the other routes that have been explored for delivery of different dosage forms to systemic circulation. The reason for such popularity of oral route may be attributed to its ease of administration. Recent advances in novel drug delivery systems (NDDS) aim at formulating a convenient dosage form for administration and to achieve better patient compliance to enhance safety and efficacy of drug molecules.

It is well known that a proper drug delivery system is essential to the success of a pharmaceutical product. The new drug delivery system creates additional patient benefits that will add new benefits to drug competition and thus increase revenue. The oral route is the preferred option between the patient and the nurses because of the various benefits it offers. One of the reasons the oral route has gained such popularity may be partly due to its easy handling. MCG helps increase patient adherence through faster onset and improved drug availability as a certain amount of drug is absorbed through the buccal mucosa. It can also be supplied without water.

**Medicated Chewing Gum- A Novel Targeted Drug Delivery MCG**

Medicated Chewing Gum 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. As shown in Figure 1.

Medicated Chewing Gum is best for health, MCG sugar-free gum has been shown to increase the flow of saliva, thereby reducing plaque acid, strengthening the teeth and reducing tooth decay.

The potential of Medicated Chewing Gum MCG for buccal delivery, fast onset of action makes it an attractive delivery form. It is considered as vehicle or a drug delivery system to administer active principles that can improve health and pharmaceutical care. Chewable tablets and Medicated Chewing Gum MCG permit more rapid therapeutic action compared to per-oral dosage forms. Chewable tablets and MCG have been very well received by the parents for use in children with full dentition. MCG is feasible in local treatment of diseases of oral cavity as well as treatment of systemic conditions.

Medicated Chewing Gum 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.

Pharmacological active agents or drugs are formulated into variety of dosage form such as tablets, capsules, injectables, inhalers, gels, creams etc., considering physiochemical, pharmacokinetic, pharmacodynamic parameters, and biopharmaceutical aspects of drugs. In addition to its confectionary role, Medicated Chewing Gum also has proven value as a delivery vehicle for pharmaceutical and nutraceutical ingredients.

Medicated Chewing Gum antibiotic gels, fibers or chips they can be useful in conjunction with specialist gum health treatments e.g. root planning and scaling or deep cleaning. Some of these topical antibiotic treatments include doxycycline gel and minocycline hydrochloride.

Medicated Chewing Gum good for your brain. Some studies have reported that chewing gum increases blood flow to the brain by 25-40%. Continuous chewing also activates your hippocampus, the part of your brain that's crucial to your memory and learning. Better concentration – besides boosting your memory, chewing gum can also increase your focus and alertness.

Medicated Chewing Gum, it is bad to chem gum every day. Constant chewing of anything, including gum, can lead to sore jaw muscles, headaches, and even TMJ disorder. Chewing gum overworks the temporomandibular joint, causing joint pain, soreness, discomfort, and even chronic headaches. Too much chewing can lead to TMJ disorder.

Medicated Chewing Gum can be an inexpensive and effective way to help relieve anxiety and boost attention. Results across eight research trials that included more than 400 adults found chewing gum more often, compared to never chewing gum.

**Fig. 1: Medicated chewing gum.**

**Advantages of MCG**

1. Useful due to the convenient route of administration.
2. Advantageous for patients with dysphagia because there are no requirements for the swallowing of Medicated Chewing Gum.
3. There is no requirement of water to take this medicament. Therefore, it can be administered anywhere.
4. Higher patient compliance.
5. Helps in counteracting dry mouth (xerostomia) through the stimulation of salivary secretion.
6. Highly accepted by children because of its confectionery like appearance and taste.
7. One of the best options for acute medication.
8. Not allowed to be swallowed. Thus, it increases the bioavailability of the drug by avoiding first-pass metabolism.
9. There is a rapid release of active ingredients in the buccal cavity. Hence, the fast onset of action can be achieved with greater availability.
10. Reduces the risk of intolerance of the gastric mucosa because the stomach does not get in direct contact with a higher concentration of active pharmaceutical ingredients.
11. The saliva which is delivered continuously and regularly to the stomach delivers some amount of drug which is helpful in the enhancement of the duration of action.
12. Provides both local and systemic effects.
13. Fewer side effects.
14. Retains good stability in the oral cavity for a longer duration of time.
15. Some drugs show faster absorption through medicated chewing gum than that of tablets. For example, Aspirin, dimenhydrinate, and caffeine.
16. Helps to neutralize plaque acids that are formed in mouth after eating fermentable carbohydrates.
17. Can increase salivation.
18. The stimulated saliva has a buffering capacity which may help in reducing the acidity of gastric fluid.
19. The amount of gum remained after chewing does not reach the stomach that's why there will be fewer side effects of excipients on GIT.
20. Improves focus and by providing relief from stress.
21. May help in whitening of teeth by reducing and preventing stains.

**Disadvantages of medicated chewing gum**

**Medicated Chewing Gum has several disadvantages as**

1. The drug released in saliva disappears quickly from the oral cavity because of involuntary swallowing.
2. The concentration of medication in the oral cavity is tends to lowering as a result of salivary dilution.
3. The drug release from chewable formulations has strongly influenced by the way patient chews the MCG.
4. The presence of the delivery system in the oral cavity causes disturbance in drinking, eating and speaking therefor administration of such dosage form is restricted to short period of time.
5. Facial muscle pain and ear ache in children.
6. Allergy to Medicated Chewing Gum composition such as flavor and sweetening agents.

**Ideal characteristics of medicated chewing gum**

1. Easy to chew.
2. Palatable (flavorful or worthy of flavor).
3. Appropriate size and shape.
4. Easy to take and useful.
5. All clear dosage forms are the same.
6. Easy to swallow even for people who have difficulty swallowing regular tablets and capsules (about once a time).

7. Reduce the risk of drug-induced esophagitis. This occurs when the tablet becomes trapped in the esophagus and dissolves while still in contact with the delicate lining of the esophagus.
8. Tasty and comes in a variety of flavors.
9. Improve consistency.
10. Dosage forms that do not require water are:
11. Easy to carry on the go.
12. Convenient to carry anywhere anytime.

**The Need for Development of MCG**

New formulations and technologies have been developed through oral drug delivery systems‟ researches. Such researches display significance of oral route amongst patients. We‟ve reviewed all the features associated with Medicated Chewing Gum as a modern drug delivery by introducing the history, advantages and disadvantages, methods of manufacturing, composition differences, evaluation tests and examples of varieties of medicated chewing gums. Acceptance of Medicated Chewing Gum has been augmented through years. The advantages and therapeutic benefits of Medicated Chewing Gum support its development as we can see new formulations with new drugs contained have been produced from past and are going to find a place in market by formulation of new medicated chewing gums. Potential applications of Medicated Chewing Gum 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 Gum as a delivery system too which creates compliance for patients.

**Patient Factors MCG**

Medicated Chewing Gum is utilized for various therapeutic purposes, taking advantage of its unique delivery mechanism and associated benefits.

**Here are several factors for using the patients for medicated chewable gum**

**Convenience and Compliance:** Portability and Discretion: Chewable gum is easy to carry and use discreetly, making it a convenient option for people who may have difficulty swallowing pills or prefer not to take oral liquids.

**Improved patient compliance:** The pleasant taste and the act of chewing itself can enhance patient adherence to the medication regimen, as it may be perceived as less of a chore compared to taking tablets or capsules.

- **Localized effects**
- **Oral health applications:** Medicated gums can be formulated to release active ingredients directly in the oral cavity
- **Controlled release**

**Sustained drug release:** The chewing action can provide a steady release of the medication over an extended period. This can help maintain more consistent blood levels of the drug, enhancing therapeutic effectiveness and reducing side effects.

**Psychological and Behavioral Benefits**

**Behavioral support:** Medicated Chewing Gum can provide a psychological benefit for individuals trying to modify their behavior.

**Addressing special populations**

**Pediatric use:** Medicated Chewing Gum is often favored for children who may find it difficult or unpleasant to ingest traditional dosage forms like pills.

**Geriatric use:** Older adults who have difficulty swallowing tablets may find chewable gum to be a more acceptable and easier-to-use option.

**Effectiveness factors**

**Water solubility:** When the active ingredient is water-soluble, the release of drug gets to the end rather than other active ingredients with slight water-soluble properties, and lipid-soluble drugs face further release problems than others because they are bound to lipophilic substances and gum bases and slowly released into oral cavity.

**Formulation factor:** Mixing of active ingredients with hydrophilic compounds or hydrophobic compounds affects the release of the drug. Sometimes faster release does not mean more complete release of drug; rather formulations with slower release profiles often show more complete release of drug.

**Physicochemical properties:** Ingredients more soluble in saliva will be immediately released within few minutes of chewing, but highly lipid-soluble ingredients are first released into gum base then into saliva. Stability of gum base and its components to salivary enzymes, molecular mass, and ionization play an important role in release and absorption of drug through mucosa.

**Individual characteristics:** Speed, intensity, frequency, and type of chewing characteristics of different individuals affect the release of active ingredients; EP recommends 60 chews/min for appropriate release of active ingredients. But these numbers of chews depend also on the retention time of MCG in the mouth, which in clinical trials, the ordinary and suitable time is about 30 min of chewing. These differences lead to variable results of drug release.

**Taste Masking of MCG**

Medicated Chewing Gum act as an extended-release formulation that delivers a constant release of the contained drug. This elegant, non-invasive drug delivery system could be a boon in treating localized oral disease. There is a monograph in European Pharmacopoeia that defined the term “Medicated Chewing Gum” as a pharmaceutical dosage form in 1991.

It provides a sustained release of the drug after a normal chewing time, i.e. 15-30 min. However, it poses certain problems, as continuous chewing may cause

temporomandibular joint disorder. Medicated Chewing Gum has been exploited for various drugs, such as cetirizine, dextromethorphan hydrobromide, dimenhydrinate hydrochloride, nicotine, antacids, miconazole, aspirin, caffeine, antimicrobial decapeptide, ondansetron hydrochloride, and nystatin Metronidazole, etc.

It provides both local as well as systemic benefits after permeation through the buccal mucosal or from the GIT. The physiochemical characteristics of a drug, such as aqueous solubility, pKa value and partition between gum/saliva, chewing time, chewing frequency, and impacts to the release of drugs from the gum, are some important parameters that should be considered.

Medicated Chewing Gum have a fast onset of action with pleasant taste and high bioavailability. The mechanism of drug release from Medicated Chewing Gum.

It contains two portions, one is a water-insoluble gum base portion (elastomers ,plasticizers or fillers) and the other is a water-soluble bulk portion (active constituents, sweeteners, flavors, anti-tack agents). Elastomers offer flexibility and maintain the gluey texture. Filler's control chewability and impart texture. Various colorants and dyes are used to impart colors and aesthetic appearance to chewing gum. Sweeteners provide the taste masking for bitter drugs present in the gum and can be used as a softener to mix the constituents and preserve moisture. While, flavors are used to improve aroma.

"Taste masking may be described as minimizing the detection of disagreeable taste that would somehow exist. The poor palatability and bitter taste are one of the main reasons for noncompliance with Medicated Chewing Gum formulations. On chewing, the drug partitions into saliva; making taste masking important is done so that the bitter perception of the drug can be reduced. Earlier, Guo and Singh reviewed several emerging strategies, such as the structure of oral mucosa and the basic conditions of mucosal adhesion, and several of the bio-adhesive materials commonly used for oral mucosal administration and oral mucosal adhesion products that have been released into the market. Several peripheral interactions can happen when one compound would interfere with the taste signal mechanism related to another compound, which might lead to taste modification.

MCG Stability Medicated Chewing Gum is a very stable product due to its low moisture content and less reactive nature than that of other oral ingredients. A major challenge in the production of chewing gum is its shelf life, storage conditions and effect of some ingredients that impress stability. Water content can lead to growth of microorganisms and chemical degradation, but water can be bound to other compounds, so that is not noticeably available to active agents, but even if few water existing in the chewing gum is determined annihilator and dangerous for other components, no water can be employed in the manufacturing method. To avoid oxidation of the drug, antioxidants are needed but due to the low content of water, presence of preservatives is not essential.

**Good packaging design**

Proper packaging of medical chewing gum is essential to ensure the product's safety and quality, protecting it from contamination and deterioration. The packaging must consider several factors to ensure its effectiveness and patient safety.

**Here are some important steps and procedures for properly packaging medical chewing gum**

**Choosing the right packaging materials moisture resistance:** The materials used should be moisture-resistant to prevent any negative effects on the Medicated Chewing Gum.

**Preserving flavor and scent:** The materials should be non-reactive with the gum to ensure the flavor and scent are maintained.

**Sustainability:** Prefer using biodegradable or recyclable materials for packaging.

**Package design easy opening:** The package should be easy to open for users of all ages.

**Portability:** The package should be convenient to carry for daily use.

**Appropriate size:** Avoid packaging that is too large or too small; it should be the ideal size for holding the appropriate amount of gum.

**EXCIPIENTS USED IN MCG**

Medicated Chewing Gum composition, water soluble bulk portions.

Gum Base is the nonnutritive part of gum which is not dissolve while chewing gum bases are mixture of natural gums, latex, plastics, solid paraffin, bees‟ wax, but modern gum bases use no natural rubber at all or just a minimal amount, 15-30% of Medicated Chewing Gum is gum base.

Elastomer is a polymer with high elongation properties and elasticity, which make them flexible against its breaking or cracking. Natural and synthetic elastomers are two different materials applied in chewing gum formulations. The ability of formulation process depends on types and amounts of elastomers.

Emulsifier allows two indissoluble phases to disperse in one another and can improve softness and ability to make bubble gums. It contributes to mixing and softness during shelf life and hydration effect while chewing.

Plasticizer is a material to make chewing gum composition softened and consumer-riendly. It promotes gum texture by applying plasticity and reducing brittleness and renders the elastomers soft.

Texturizer supplies overall texture and facilitates blending and other processing stages. Cud size, chewing ability, and stretch are the effects of texturizers‟ level.

Rubber is also associated with the manufacture of bubble gum, it's just the resin used in formulations which also acts as elastomeric plasticizer as well as a binding agent between elastomers and texturizers.

Sweeteners provide the sweetness of formulation and improve the taste. Aqueous sweeteners which include corn syrup, hydrogenated starch, and sorbitol, help to retain moisture and freshness of the final product. They also act as a plasticizer or softening agent and binding agent.

High-intensity artificial sweeteners also provide the sweetness, but a lower calorie is produced by them due to the partial absorbance in the intestine.

Flavoring agents provide an acceptable flavor for the product and can act as taste-masking agents for bitter drugs to cover the taste of active ingredient.

Colorants improve the color of the formulation by producing gentle and soft color.

Anti-oxidants prevent the growth of microorganisms by inhibiting oxidation.

Anti-tack agents eliminate self-adhesiveness known as blocking especially rubbers which have a tendency to stick together. It reduces fragmentation of the gum during mastication and prevents attaching to the teeth.

Anti-caking agents are used to prevent caking and forming lumps. These materials improve flowability and rehydration and help for good packaging. They are added to the formulation to extend shelf life and detract dispersibility.

**Metronidazole**

Chemically metronidazole benzoate (MB) is 2-(2-methyl-5-nitro-1H imidazole-1-yl) ethylbenzoate, belonging to the category of antiprotozoal drug, used to treat various infections including amoebic dysentery, trichomoniasis, periodontitis, giardiasis and many other anaerobic infections. As a prophylactic treatment of infection, MB is used before surgery as well as often used in oral liquid dosage forms due to its known bitter taste.

Metronidazole benzoate is the benzoate ester of Metronidazole. It is a slightly modified version of metronidazole, making it more lipophilic. This modification can help in different pharmacokinetic properties, such as absorption.

The mechanism of action of metronidazole has not been fully elucidated. However, its nitro group reduction by anaerobic organisms appears Metronidazole is an antibiotic and antiprotozoal medication used to treat various infections. Its effects on enzymes involve several mechanisms.

Mechanism of Action in Microorganisms: DNA Disruption: Metronidazole works by penetrating susceptible organisms and causing breaks in their DNA. Inside anaerobic bacteria and protozoa, metronidazole is reduced by enzymes such as nitro reductase. This reduction process transforms metronidazole into active compounds that bind to DNA, leading to strand breaks and cell death.

Therapeutic Use: Selective Toxicity: The selective activation of metronidazole in anaerobic microorganisms compared to human cells underlies its therapeutic use, allowing it to target infections with limited impact on human host cells.

It is always important to use metronidazole under the guidance of a healthcare provider to minimize any potential adverse effects and interactions with other medications.

**Future trends**

Future of Medicated Chewing Gum will reveal all of the scientists‟ efforts for the development of Medicated Chewing Gum as a modern drug delivery system and progress of MCG production technology. In the future, other attempts will be seen to formulate more drugs using Medicated Chewing Gum as a drug delivery system. Treatment of fungal diseases, prevention of caries and other dental health issues, smoking cessation, etc., are common health work of MCGs. But remineralization of teeth, cold relief, energy enhancing, anti-nausea and so many new advantages of this novel drug delivery system are going to play an important role through future studies. MCGs are admissible alternatives of chewable or standard tablets and oral disintegrated dosage forms.

Actually, it takes time for to get acceptance by people as a drug delivery system, but we hope that MCG finds its real place in industry and market and between patients soon, through its numerous advantages. Long lasting flavored, filled gums, timed-release, and other new MCGs formulated for diseases that previous delivery systems have been used for, are trendy products to be seen in the future as a new kind of Medicated Chewing Gum which is made biodegradable and can be dissolve in around 1 month. We predict a brighter future for MCG as a novel drug delivery system than previous oral systems.

Innovating multiple methods of drug formulation requires a preformulation studies stage of drug with excipients, formulations studies stage and the evaluation studies stage after formulation to choose the best formulations, and it coincides with drug stability studies. Creating the idea of drug formulation in a new

pharmaceutical dosage form and advanced drug delivery systems must combine the various stages and conclude a new research path for formulation and development, and all of this is extracted from the integrated efforts of pharmaceutical scientists to innovate novel drug delivery systems that are drug compatible with excipients, drug use, achieve the goal of the drug, and innovate different research paths for pharmaceutical scientific research, from which ideas, conclusions, and results were concluded and conclusions are drawn from multiple experiments and from the research of pharmaceutical scientists with experience in precise specialization in drug formulation, development, evaluation and ADDS in linking the most important pharmaceutical information related to the good manufacturing practice according to pharmaceutical standards for industrial and natural sources with recent pharmaceutical dosage form and ADDS.

**The best antibiotics for gingivitis:** The best antibiotics for specific types of gum infections for gingivitis which is characterized by inflammation and swelling of the gums a common antibiotic prescribed is Metronidazole, as shown in Figure 2.

**Fig. 2: Inflammation and Swelling-Gingivitis.**

In the present study, it was proposed to formulate Medicated Chewing Gum of Metronidazole by using wet granulation and direct compression technique methods, developing a Medicated Chewing Gum as a medical treatment regimen could have several goals related to improving the quality of life of patients, enhancing health well-being, and providing more effective and convenient treatment methods and to make MCG by using Metronidazole benzoate to resolve of bitter taste of antibiotic and fix problems of taking drugs in children.

## MATERIALS AND METHODS

**As shwon in Table 1.**

**Table 1: List of Materials.**

| NO | Name of Materials |
|---|---|
| 1 | Metronidazole Benzoate |
| 2 | Acacia gum HPLC- MUMBAI |
| 3 | Xanthan Gum |
| 4 | PEG 6000 |
| 5 | Povidone 30 |
| 6 | Natural Gum |
| 7 | Masticatory Gum Base |
| 8 | Bees Wax |
| 9 | Aspartame |
| 10 | Sodium Saccharine |
| 11 | Sucralose |
| 12 | Mannitol |
| 13 | Sorbitol |
| 14 | Glycerol |
| 15 | Mint. Powder |
| 16 | Strawberry Liquid |
| 17 | Orange Liquid |
| 18 | Calcium Carbonate |
| 19 | Talc |
| 20 | CMC |

| | |
|---|---|
| 21 | MCC |
| 22 | Magnesium Stearate |
| 23 | Aerosil 200 |
| 24 | Sodium Stearyl Fumarate |
| 25 | Ascorbic Acid |
| 26 | Stearic Acid |
| 27 | Beta Cyclodextrin |
| 28 | Potassium Dihydrogen Phosphate |
| 29 | Palm Oil |
| 30 | Ethanol 99.9% |
| 31 | Glacial Acetic Acid |
| 32 | Acetonitrile |
| 33 | Phosphate Buffer |
| Most of the materials a gift sample by Global Pharmaceutical Industry Company- Sana'a, Yemen. Phosphate buffers a gift sample by Shiba Pharmaceutical Industry Company- Sana'a, Yemen. Acacia gum HPLC- MUMBAI, Natural gum, Masticatory gum base and Ethanol were purchase from the local market. | |

**The equipments used as shown in Table 2.**

**Table 2: The Equipment's Used.**

| No | Equipment's |
|---|---|
| 1 | Fourier Transform Infrared Spectrophotometer |
| 2 | UV/VIS Spectrophotometer |
| 3 | Melting Point Tester |
| 4 | Moisture Tester |
| 5 | Density Tester |
| 6 | pH Meter |
| 7 | Ultra-sonic |
| 8 | Tablet machine |
| 9 | Accelerate Stability Study Chamber |
| 10 | Electronic Balance |

**Formulation and Evaluation of metronidazole benzoate medicated chewing gum[21-141]**

The MCG formulations were prepared by different methods such as mixing and direct compression (F1, F2, F3, F6, F8, F19, F20, F21, F,22, F23, F24), wet granulation and compression (F4, F5, F7, F9, F10, F11), by using tablet compression machine using compressor number 6,11,13 mm round and cylindric shaped and molding (F12, F13, F14, F15, F16, F17, F18) by using cylindrical blister back. The formulations were prepared by using gum base 15-45% (natural gum, Masticatory gum base, acacia gum, polyethylene glycol, povidone) fillers up to 50%(calcium carbonate, talc, carboxymethyl cellulose, Microcrystalline cellulose, mannitol, sorbitol) softeners and plasticizers 0.5-15% (bees wax, glycerin, sorbitol, stearic acid) sweeteners(natural 30-60% mannitol, sorbitol)(artificial 0.02-8% aspartame, sucralose, sodium saccharine) flavors 0.01-1% (mint powder, strawberry liquid, orange liquid), ant-adherent 0.5-2%(aerosil 200), lubricant 0.5-2%(magnesium stearate, sodium stearyl fumarate) anti -oxidant (ascorbic acid) buffering agent (potassium dihydrogen phosphate) coating agents(beta cyclodextrin).

All the ingredients of the 24 MCG formulations are shown in Tables 3 and 4.

**Table 3: Composition of Formulations of Metronidazole Benzoate Medicated Chewing Gum.**

| Ingredients | Quantity Per MCG Tablet (mg) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 |
| Metronidazole Benzoate | 200 | 200 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| Arabic Gum | --- | --- | 350 | 400 | 350 | 400 | 450 | 400 | 400 | --- | 450 |
| PEG 6000 | --- | 300 | --- | --- | --- | --- | --- | --- | --- | 400 | --- |
| CaCO3 | --- | --- | 10 | 10 | 10 | 10 | 10 | 10 | --- | 10 | 10 |
| Talc | --- | --- | --- | --- | 10 | --- | 10 | --- | --- | --- | --- |
| CMC | --- | --- | --- | --- | --- | 10 | --- | 10 | 10 | --- | 60 |
| MCC | --- | --- | --- | --- | 2mg | --- | --- | --- | --- | --- | --- |
| Bees Wax | 105 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| Glycerin | --- | --- | --- | 300 | 300 | --- | 200 | --- | 300 | 250 | 290 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sorbitol | --- | --- | 200 | --- | --- | 300 | --- | 250 | ---- | --- | --- |
| Sodium Saccharine | --- | --- | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Mint Powder | 2.5 | 3 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | --- | --- |
| Orange Liquid | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | 10 |
| Strawberry liquid | --- | --- | --- | --- | --- | --- | --- | --- | --- | 10 | --- |
| Ascorbic Acid | --- | --- | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Magnesium Stearate | 7 | 7 | --- | --- | --- | --- | --- | --- | --- | --- | 10 |
| Beta Cyclodextrin | --- | --- | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Potassium Dihydrogen Phosphate | --- | --- | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Aerosil 200 | 5 | 5 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Mannitol | | | --- | --- | --- | --- | --- | --- | --- | 60 | --- |
| Acacia Gum | 210 | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Xanthan Gum | --- | 330 | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Povidone 30 | --- | 300 | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Aspartame | 3.5 | 5 | --- | --- | --- | --- | --- | --- | --- | --- | --- |

**Table 4: Composition of final formulations of metronidazole benzoate medicated chewing gum.**

| Ingredients | Quantity Per MCG Tablet (mg) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F12 | F13 | F14 | F15 | F16 | F17 | F18 | F19 | F20 | F21 | F22 | F23 | F24 |
| Metronidazole Benzoate | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 |
| CaCO3 | --- | --- | 50 | 50 | 50 | -- | 50 | --- | --- | --- | --- | --- | --- |
| PEG | 45 | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Stearic Acid | --- | 15 | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Glycerin | 20 | 20 | 20 | 20 | 20 | 20 | 20 | --- | --- | --- | --- | --- | --- |
| Palm Oil | 50 | 50 | 50 | 50 | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Sorbitol | 55 | 55 | 55 | 55 | 50 | 50 | 50 | --- | --- | --- | --- | --- | --- |
| Arabic Gum | 20 | 20 | 20 | 20 | 20 | 20 | 20 | --- | --- | --- | --- | --- | --- |
| Masticatory Gum Base | --- | --- | --- | --- | --- | --- | --- | 120 | 30 | 60 | 90 | 120 | 150 |
| Natural Gum | --- | --- | --- | --- | 150 | 250 | 140 | 700 | 600 | 600 | 600 | 600 | 600 |
| Bees wax | 482 | 482 | 482 | 482 | 350 | 260 | 20 | 16 | 4 | 12 | 18 | 24 | 60 |
| Sucralose | --- | --- | --- | --- | --- | --- | --- | 10 | 4 | 4 | 4 | 4 | 4 |
| Aspartame | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 30 | 6 | 12 | 18 | 24 | 30 |
| Mint Powder | 63 | 63 | 63 | 70 | 50 | 10 | 10 | 10 | 2 | 4 | 6 | 8 | 10 |
| Aerosil 200 | --- | --- | --- | --- | --- | --- | --- | 30 | 10 | 10 | 10 | 10 | 10 |
| Mg Stearate | --- | --- | --- | --- | --- | --- | --- | 10 | 10 | 20 | 30 | 40 | 50 |
| Sodium Stearyl Fumarate | --- | --- | --- | --- | --- | --- | --- | --- | 10 | 20 | 30 | 40 | 50 |
| Mannitol | 150 | 150 | 150 | 150 | 100 | 100 | 100 | --- | 297 | 233 | 169 | 105 | 11 |

**Amount of MCG Drug and Drug Release Studies**

**Preparation of Phosphate Buffer Solution Method (I)**

0.896 g of NaOH and 6.804 g of KH2PO4 dissolve in sufficient quantity of water, the volume was completed to 1000 ml with distilled water and mix well by sonication**.**

**Preparation of Diluent Solution Method (II)**

Solution A: 1ml of glacial acetic acid was completed to 1000 ml of distilled water: Acetonitrile and Solution A (40:60).

**Preparation of Diluent Solution Method (III)**

1ml of glacial acetic acid was completed to 1000 ml of distilled water, and 300 ml of acetonitrile was completed to 500 ml of distilled water. Acetonitrile and glacial acetic acid (40:60) were taken**.**

**Procedure of MCG Drug Release Studies**

The drug release of Metronidazole benzoate from MCG during mastication was studied by recruiting a panel of three numbers of volunteers and scheduled chew-out studies for determination of percentage drug release from MCG.

Each person was allowed to chew one sample of the Metronidazole benzoate MCG for a particular time period, i.e. 1, 5, and 15min. After chewing, chewed out gum samples were collected from volunteers, stretched out up to maximum and cut into small pieces and dispersed in a 100 ml volumetric flask then 50 ml volumetric flask containing diluent, which was then sonicated for 20 min with heating. The sonicated sample was filtered and analyzed by a UV spectrophotometer at 318nm to determine the residual drug content present in MCG. The „„amount of drug released during

mastication"" was calculated by subtracting the ,,,,amount of the residual active ingredient 'presents in the gum after chewing from ,,,,the total content""

Amount of drug released during mastication = Total content - Amount of the drug in residual active ingredient.

## RESULTS AND DISCUSSION

### Evaluation of metronidazole benzoate medicated chewing gum

### General appearance

### Post Compression MCG Parameters

The prepared Medicated Chewing Gum were evaluated for various post compression parameters. The results are presented in Table 5.

**Table 5: Post Compression MCG Parameters.**

| Parameters / Formulation | Taste | Consistency | Softness | Flavor Lasting Time | Chewability |
|---|---|---|---|---|---|
| F1 | Bitter | --- | --- | --- | --- |
| F2 | Bitter | --- | --- | --- | --- |
| F3 | Bitter | --- | --- | --- | --- |
| F4 | Bitter | --- | --- | --- | --- |
| F5 | Bitter | --- | --- | --- | --- |
| F6 | Bitter | --- | --- | --- | --- |
| F7 | Bitter | --- | --- | --- | --- |
| F8 | Bitter | --- | --- | --- | --- |
| F9 | Bitter | --- | --- | --- | --- |
| F10 | Bitter | --- | --- | --- | --- |
| F11 | Bitter | --- | --- | --- | --- |
| F12 | --- | Low | Soft | 30 min | Chewable |
| F13 | --- | Low | Soft | 30 min | Chewable |
| F14 | --- | Moderate | Soft | 30 min | Chewable |
| F15 | Sweet | Moderate | Hard | 40 min | Chewable |
| F16 | --- | Moderate | Hard | 30 min | Chewable |
| F17 | --- | Moderate | Soft | 10 min | Chewable |
| F18 | --- | High | Hard | 10 min | Chewable |
| F19 | Sweet | High | Soft | 10 min | Chewable |
| F20 | Sweet | High | Soft | 10 min | Chewable |
| F21 | Sweet | High | Soft | 20 min | Chewable |
| F22 | Sweet | High | Soft | 30 min | Chewable |
| F23 | Bitter | High | Soft | 40 min | Chewable |
| F24 | Bitter | High | Soft | 50 min | Chewable |

MCG formulations F1and F2 when initially bitten, it adheres to the teeth and then disintegrates, resulting in no chewability. The taste is bitter due to the presence of only one artificial sweetener in a small quantity. Given the lack of chewability and the disintegration of the formulation, further evaluation of other parameters is not possible. The cause of the formulation's disintegration is the acacia gum, which itself does not allow for chewability. The method used was dry mixing and direct compression for both formulations. The experiment's objective was solely to test compressibility in MCG formulations F3 to F11, materials such as buffer solution, beta cyclodextrin, and fillers were added in an attempt to achieve chewable consistency. MCG formulations F3, F9, and F11 contain acacia gum, while formulation F10 contains PEG 6000. For formulations F3, F6, and F8, the dry mixing and direct compression method was used. In contrast, MCG formulations F4, F5, F7, F9, F10, and F11 employed the wet granulation and compression method.

All MCG formulations failed; bitterness persisted, and chewability was not achieved. Additionally, samples adhered to the teeth. MCG formulation F11 could not be compressed at all, while MCG formulations F5, F7, and F9 hardened before compression. Methods were changed from direct compression to molding for MCG formulations F12 - F15. For MCG formulations F12 and F13, the consistency was lower due to the absence of calcium carbonate, and sticking to the teeth was observed. In MCG formulation F14, the consistency was better compared to MCG formulations F12 and F13, and it did not stick to the teeth. Formulation F15 did not stick to the teeth and had a hard consistency. Additionally, the duration of flavor lasting time was higher due to the increased amount of flavoring agent. The same molding method was continued for formulations F16, F17 and F18, but the base was changed to natural gum. MCG formulation F17 soft consistency, does not contain calcium carbonate. MCG formulation F16 moderate consistency, with a calcium carbonate to beeswax ratio of 50: 350mg. MCG formulation F18 high consistency,

with a calcium carbonate to beeswax ratio of 20:50mg. MCG formulation F19, the method used dry mixing and direct compression, consistency high, due to the presence of Masticatory gum base and soft.

The MCG formulations F20-F24 were developed from the MCG formulation F19 as the amount of Masticatory gum base was changed each time, and its impact on the consistency was observed. Additionally, the amount of mannitol was varied as a volume supplement along with changing the quantities of some sweeteners and flavoring agent. MCG formulations F23 and F24 were found to have a bitter taste due to the low quantity of mannitol as a volume supplement, unlike MCG formulations F20, F21, and F22. Consequently, the comparison was made between the formulations that achieved the compliance goal with a secondary consideration, which is the release ratio of drug.

**Amount of MCG Drug and Drug Release Studies**

The Percentage amount and drug release of Metronidazole benzoate MCG studies by different methods the results of studies were shown in the Tables (6-11) respectively.

**Table 6: Percentage Amount of Metronidazole Benzoate Medicated Chewing Gum Formulations (Method I).**

| Time (min) | | Percentage Drug Release (%) | | |
|---|---|---|---|---|
| | | Formulation Code | | |
| | | F20 | F21 | F22 |
| MCG -Without Chewing | | 11.03% | 7.5% | 7% |
| MCG -With Chewing | 1(min) | 8.5% | 3.17% | 2.72% |
| | 5(min) | 4.39% | 2.47% | 2.71% |
| | 15(min) | 2.6% | 2.10% | 2.54% |

**Percentage Amount of Drug (%)**

Amount of Metronidazole benzoate MCG was studied in method (I) for up to 15minutes. The drug amount release of MCG formulations F20, F21and F22 was found to be 11.03%, 7.5% and 7% without chewing. 8.5%,7.5% and 7% at 1 minutes, 4.39%, 2.47% and 2.71% at 5 minutes, 2.6%, 2.10% and 2.54% at 15 minutes respectively. The highest drug amount was observed in MCG formulation F20 due to Masticatory gum base and patient factor such as speed and chewability available of saliva.

**Table 7: The Drug Release Study of Metronidazole Benzoate Medicated Chewing Gum Formulations (Method I).**

| Time(min) | Percentage Drug Release (%) | | |
|---|---|---|---|
| | Formulation Code | | |
| | F20 | F21 | F22 |
| 1(min) | 2.53% | 4.33% | 4.28% |
| 5(min) | 6.64% | 5.03% | 4.29% |
| 15(min) | 8.43% | 5.4% | 4.46% |

**Percentage Drug Release (%)**

Metronidazole benzoate MCG release was studied in method (I) for up to 15 minutes. The drug amount release of MCG formulations F20, F21and F22 was found to be 2.53%, 4.33% and 4.28% at 1 minutes, 6.64%, 5.03% and 4.29% at 5 minutes, 8.43%, 5,4% and 4.46% at 15 minutes respectively. The highest drug release was observed in MCG formulation F20 due to less amount of Masticatory gum base and patient factor such as speed and chewability available of saliva.

**Table 8: Percentage Amount of Metronidazole Benzoate Medicated Chewing Gum Formulation (Method II).**

| Time(min) | | Percentage Drug Release (%) |
|---|---|---|
| | | Formulation Code |
| | | F20 |
| MCG - Without Chewing | | 90% |
| MCG -With Chewing | 1(min) | 89.9% |
| | 5(min) | 78% |
| | 15(min) | 74% |

**Percentage amount of drug (%)**

Amount of Metronidazole benzoate MCG was studied in method (II) for up to 15 minutes.

The drug amount of MCG formulation F20 was found to be 90% without chewing. 89.9% at 1 minutes, 78% at 5 minutes, 74% at 15 minutes respectively. The highest drug amount was observed at 1 minutes.

**Table 9: The Drug Release Study of Metronidazole Benzoate Medicated Chewing Gum Formulation (Method II).**

| Time(min) | Percentage Drug Release (%) |
|---|---|
| | Formulation Code |
| | F20 |
| 1(min) | 0.1% |
| 5(min) | 12% |
| 15(min) | 16% |

**Percentage drug release (%)**

Metronidazole benzoate MCG release was studied in method (II) for up to 15 minutes.

The drug amount release of MCG formulation F20 was found to be 0.1% at 1 minutes, 12% at 5 minutes, 16% at 15 minutes respectively. The highest drug release was observed at 15 minutes.

**Table 10: Percentage Amount of Metronidazole Benzoate Medicated Chewing Gum Formulations (Method III).**

| Time(min) | | Percentage Drug Release (%) | | |
|---|---|---|---|---|
| | | Formulation Code | | |
| | | F20 | F21 | F22 |
| MCG -Without Chewing | | 82% | 72% | 81% |
| MCG -With Chewing | 1(min) | 37% | 33.9% | 35.7% |
| | 5(min) | 34% | 31.6% | 33.5 |
| | 15(min) | 26.5% | 23.5% | 27.3 |

**Percentage amount of drug (%)**

The calculation amount of drug for all formula done by the following equation:

Amount of Metronidazole benzoate MCG was studied in method (III) for up to 15 minutes. The drug amount release of MCG formulations F20, F21 and F22 was found to be 37%, 33.9% and 35.7% at 1 minutes, 34%, 31.6% and 33.5% at 5 minutes, 26.5%, 23.5% and 27.3% at 15 minutes respectively. The highest drug amount was observed in MCG formulation F20 due to Masticatory gum base and patient factor such as speed and chewability available of saliva.

**Table 11: The Drug Release Study of Metronidazole Benzoate Medicated Chewing Gum Formulations (Method III).**

| Time(min) | Percentage Drug Release (%) | | |
|---|---|---|---|
| | Formulation Code | | |
| | F20 | F21 | F22 |
| 1(min) | 45% | 38.1% | 45.3% |
| 5(min) | 48% | 40.4% | 47.5% |
| 15(min) | 55.5% | 48.5% | 53.7% |

**Percentage drug release (%)**

Amount of drug released during mastication = Total content - Amount of the drug in residual active ingredient.

Metronidazole benzoate MCG release was studied in method (III) for up to 15 minutes. The drug amount release of MCG formulations F20, F21 and F22 was found to be 45%, 38.1% and 45.3% at 1 minutes, 48%, 40.4% and 47.5% at 5 minutes, 55.5%, 48.5% and 53.7% at 15 minutes respectively. The highest drug release was observed in MCG formulation F20 due to Masticatory gum base and patient factor such as speed and chewability available of saliva.

## CONCLUSION

The Medicated Chewing Gum MCG for buccal delivery, fast onset of action makes it an attractive delivery form. Medicated Chewing Gum will be much more familiar to patients and the market in the coming years, based on the benefits of Medicated Chewing Gum as a novel drug delivery, such as concurrently supporting both local and systemic delivery, protection against acids and enzymes, low first pass metabolism, elevating alertness and cognitive function, good stability, and much more. Poorly water-soluble drugs require specialized formulation techniques to promote release, and these techniques are reasonably well developed. The reason is simple that the Medicated Chewing Gum delivery system is convenient, easy to administer anywhere, anytime and its pleasant taste improves patient compliance.

Medicated Chewing Gum not only offers clinical benefits but also is an attractive, distinct and efficient drug delivery system. New Medicated Chewing Gum formulations should be considered by scientists and researchers delivers numerous innovative patented

applications employed in order to increase Medicated Chewing Gum variants owing to patient preferences and provide a suitable release pattern for Medicated Chewing Gum containing medications.

It was prepared Medicated Chewing Gum using Metronidazole benzoate to demonstrate its antibacterial effectiveness as a drug delivery system. The preparations were made using various methods such as mixing, direct compression, wet granulation, compression using a tablet press machine, and molding using a cylindrical back bubble. After preparing and testing 24 MCG formulations of Metronidazole benzoate Medicated Chewing Gum, it was concluded that the best formulation F20 (2.7% Masticatory gum base, 0.5% bees wax, 0.5% aspartame, 0.18% Mint powder, 27 %Mannitol), for the composition of Metronidazole benzoate Medicated Chewing Gum as a drug delivery system**.** Finally, in the future, we may see drugs formulated into Medicated Chewing Gum in preference to other delivery systems to deliver drugs for local treatment of mouth diseases or systemic absorption through oral mucosa.

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