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# FORMULATION AND EVALUATION OF FENUGREEK CHEWING GUM FOR TREATMENT OF THROAT INFECTION

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***Abstract:***

Oral drug delivery system is an area of interest for scientist and formulators in past few years to explore at extreme level in various drug delivery systems. The researchers and scientist are focusing on this drug delivery due to feasible and comfortable administration offered by this route to the patient. Therefore drug delivery can be achieved by incorporating medicament in Chewing gum because of higher vascularity in oral mucosa resulting it in a rapid absorption drug into the systemic circulation. Chewing gum is a combination of a water-immiscible phase, known as gum base emulsifiers, antioxidants, softeners, sweeteners, food colourings, flavoring agents, and in case of medicated chewing gum there is an incorporation of active substances in the formulation for getting the desired therapeutic effect. CG can be used in prevention of throat infection, it also prevent the dryness of mouth and help in maintaining oral hygiene. Therefore it can be concluded that oral drug delivery can take superior treatment by this formulation. The main benefit of CG is, it can be taken without water and it reduces the cost of manufacturing when compared with oral liquid preparations. CG with herbal base such as fenugreek can make it as effective as other conventional formulation without any adverse effects.

**Keywords:** Medicated Chewing Gum, Emulsifiers, Antioxidants, Fenugreek.

## INTRODUCTION

### Introduction to Oral Cavity

The oral cavity, also known as our mouth, is the first organ in the gastrointestinal tract. As we consume food, the first step in the digestion process begins here as you chew and breakdown what you eat. Two types of digestion are taking place within the oral cavity: chemical digestion and mechanical digestion. Mechanical digestion happens as you chew the food and break it into small pieces, and chemical digestion takes place as your salivary glands add enzymes to the food for further breakdown. Let's explore the major parts of the oral cavity and what their function is regarding digestion.

### General Structure of the Oral Cavity[1]

On the anterior side, we find the teeth and lips, and opposite of that, we find the oropharynx marking the posterior portion of the mouth. On the superior side of the mouth, we find the hard & soft palates that make up what we would consider the roof of the mouth. And the inferior surface, or the bottom of the oral cavity, is formed by the mylohyoid muscle, which is what the tongue attaches to.

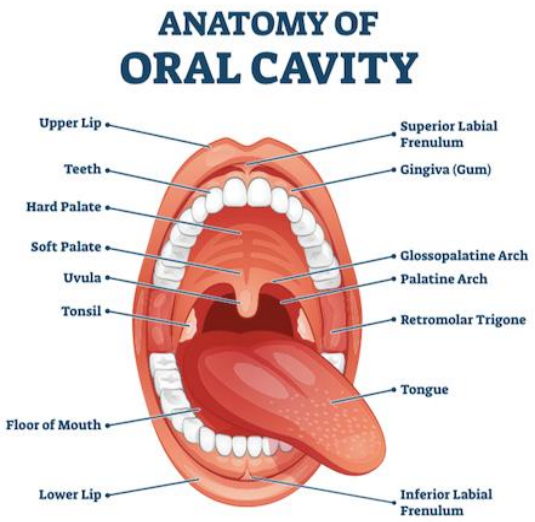


**Figure 1: Basic parts of the oral cavity.**

### 1) Palate, Lips, & Cheeks[2,3]

The superior boundary of the oral cavity is formed by the palate. The hard part on the more anterior portion of the mouth is called the hard palate. Its role is to separate the mouth from the nasal cavity. On the more superior side, we find the soft palate. During the swallowing mechanism of food or drink, soft palate will elevate to close off the opening to the nasopharynx so you don't get food or drink into the nasal cavity. Together, the soft and hard palate play large roles in speech, swallowing, and breathing. The anterior wall of the oral cavity is comprised of the lips or labia. The superior (upper) and inferior (lower) lips connect with the lateral walls of the oral cavity, which are the cheeks. Their role is to close the mouth and keep food inside while chewing. The lips attach to the gingivae (gums) by a thin fold called the labial frenulum. The cheeks form the lateral walls of the oral cavity. There are muscles within the cheeks that help to push food around and compress them against your teeth while chewing.

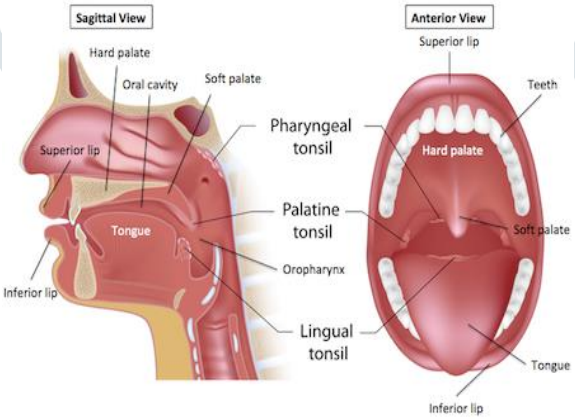


**Figure 2: Sagittal & anterior view of the oral cavity**

**2) The Tongue**

The tongue is considered its own organ that is really just a very strong skeletal muscle. The tongue's role is to help create sounds, mix food during chewing, and compress food into the roof of the mouth (the hard palate) in preparation for swallowing.

The entire surface of the tongue is covered in 'taste buds', sitting on a structure called papillae. These taste buds are connected to nerves that detect common tastes like salty, sweet, sour, savory, and bitter and transmit them through nerves that run to the brain covering the structure of the tongue, papillae come in different types and all taste buds.

The papillae can be broken down into four types:

Vallate ,Fungiform , Foliate, Filiform

While certain tastes may be more commonly picked up in specific areas of the tongue, it is no longer believed that certain parts of the tongue are responsible for certain tastes.

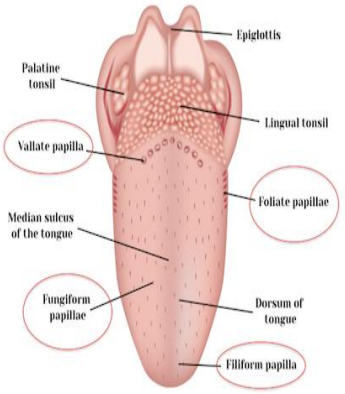


**Figure 3: Location of the four types of papillae found on the human tongue.**

**3) Salivary Glands**

The salivary glands found in the oral cavity collectively produce saliva, a necessary component to be added to food for the digestion process to go forward. Typically, most saliva is produced during mealtimes, but additional amounts are produced to make sure the oral cavity stays moist. Along with making sure ingested and chewed food becomes slippery to slide down the esophagus, saliva also works to clean and moisten the mouth.

The human mouth has three salivary glands: the parotid salivary gland, the sublingual salivary gland, and the Submandibular salivary gland.

Parotid salivary gland - largest, located around the ear, produces 25-30% of your saliva.

Submandibular salivary gland - inferior to the body of the mandible, produces 60-70% of your saliva.

Sublingual salivary glands - inferior to the tongue, only produces 3-5% of your saliva.[1, 2, 3]

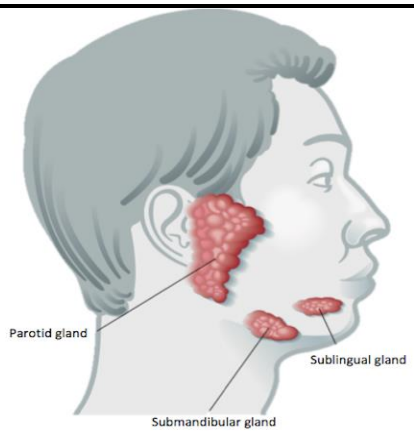


**Figure 4: Three salivary glands in the oral cavity.**

**FENUGREEK**[4,5,6]

Fenugreek (Trigonella foenum graecum) is an annual plant belongs to the family Leguminosae. It is the famous spices in human food. The seeds and green leaves of fenugreek are used in food as well as in medicinal application that is the old practice of human history. It has been used to increase the flavoring and color, and also modifies the texture of food materials. Seeds of fenugreek spice have medicinal properties such as hypocholesterolemic, lactation aid, antibacterial, gastric stimulant, for anorexia, antidiabetic agent, galactogogue, hepatoprotective effect and anticancer. These beneficial physiological effects including the antidiabetic and hypocholesterolemic effects of fenugreek are mainly attributable to the intrinsic dietary fiber constituents which have promising nutraceuticals value.

It is well known for its fiber, gum, other chemical constituents and volatile contents. Dietary fiber of fenugreek seed is about 25% which changes the texture of food. These days it is used as food stabilizer, adhesive and emulsifying agent due to its high fiber, protein and gum content. The protein of fenugreek is found to be more soluble at alkaline pH. Fenugreek is having beneficial influence on digestion and also has the ability to modify the food.[2]

**Figure 5: Fenugreek Plant**

- This is an annual herb, about two feet high.
- THREE PARTS: Leaves, Pea like flowers and seeds.
- DESCRIPTION- The hard, brown, red and yellow seeds are the part used medicinally and in cooking.
- SHAPE & COLOR - Brownish, about 1/8 inch long, oblong, rhomboidal, with a deep furrow dividing them into two unequal lobes.
- QUANTITY- They are contained, ten to twenty together, in long, narrow, sickle-like pods.
- TASTE - Bitter

## HISTORY

Fenugreek is one of the oldest cultivated spice crops in the world; it has been grown for its medicinal value and forage in India, western Africa, and the Nile Valley since remote antiquity and is used for human and animal consumption. The species name, foenum-graecum, means Greek hay (Sinskaja 1961), indicating its historical use as forage crop in the ancient world. In Egypt, it has been cultivated since 1000 BC, and it has been part of the Indian diet for over 3,000 years. It is found growing wild in parts of north India and cultivated all over the subcontinent for its green leaves and seeds. Fenugreek is a native of southeastern Europe and western Asia. India has also been reported to be the native home of fenugreek (Shanmugavelu, Kumar, and Peter 2002), which exists in wild form in Kashmir, Punjab, and the upper Gangetics Plains. The carbonized fenugreek seed from a Rohira village in the Sangrur district of Punjab, India, suggests its use in trade by people of the Harappan civilization as far back as 2000–1700 BC (Saraswat 1984).

**Figure 6: Fenugreek History**

Fenugreek seeds were found in the tomb of Tutankhamun (Manniche 1989). Portius Cato, a Roman authority on animal husbandry in the second century BC, ordered foenum-graecum, which was today's fenugreek, to be sown as fodder for oxen (Fazli and Hardman 1968). In North Africa, it has been cultivated around the Saharan oasis since very early times (Duke 1986). References to the utilization of fenugreek were found as far back as 1578 in the famous Kolozsvar Herbarium compiled by Melius in 1578 and cited by Hidvegi et al. (1984). Fenugreek was introduced into Chinese medicine in the Sung dynasty, AD 1057 (Jones 1989). According to a citation by Miller (1969), in his examination of the definition and function of spices in his materia medica, Dioscorides, a Greek physician of Anazarbus in Cilicia and considered "father of pharmacology" (AD 65), writes that fenugreek is an active compound of ointments and mentions fenugreek as a spice crop in his texts. Dioscorides also mentions that the Egyptians called fenugreek itasin (Manniche 1989). Leaves of fenugreek were one of the components of the celebrated Egyptian incense kuphi, a holy smoke used in fumigation and embalming rites (Rosengarten 1969). According to Fazli and Hardman (1968), Charlemagne encouraged cultivation of fenugreek. Fenugreek is probably one of the forages cultivated before the era of recorded history. As a fodder plant, it is said to be the Hedysarum of Theophrastus and Dioscorides (Leyel 1987). In the middle Ages, it is recorded that fenugreek was added to inferior hay because of its peculiarly pleasant smell (Howard 1987). Fenugreek was known and used for different purposes in ancient times, especially in Greece and Egypt (Rouk and Mangesha 1963). Rosengarten (1969) reported that the Romans obtained the plant from the Greeks and that it became a commercial commodity of the Roman Empire (Miller 1969); Stuart (1986) and Howard (1987) support the contention that Benedictine monks introduced the plant into medieval Europe. Fenugreek was introduced into central Europe at the beginning of the ninth century (Schauenberg and Paris 1990). However, it is not mentioned in any herbal literature until the sixteenth century, when it was recorded as grown in England.[3]

## FENUGREEK SEEDS DESCRIPTION

**Figure 7: Fenugreek Seeds.**

- Fenugreek Seeds are aromatic, bitter, may be eaten raw or cooked.
- Bitterness is mainly due to the oil, steroidal saponins and alkaloids.
- It has a strong and quite peculiar odor, hence, used in a very small quantity as a spice.
- It has beautiful golden yellow color due to its coloring agent called Coumadin.
- That is why fenugreek seeds were used for a yellow dye by ancient Indians and Egyptians.

**SEEDS STRUCTURE OF FENUGREEK (T.S)**

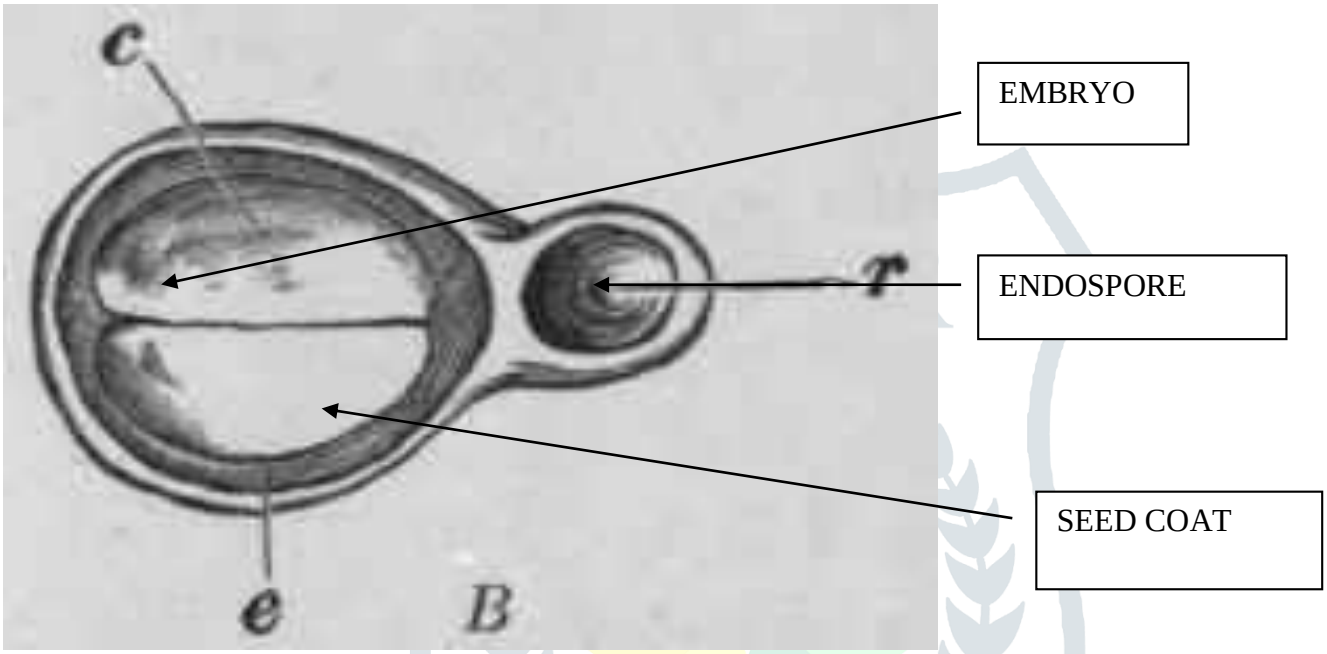


**Figure 8: Fenugreek Seed Structure**

- This endosperm contains galactomannan gum.
- The endosperm is surrounded by a tenacious, dark brown husk. The color of the gum fraction depends upon the amount of outer husk (brown color) and cotyledon (yellow color) present.

**CLASSIFICATION**[7,8]

**Table 1: Classification of Fenugreek**

| **Kingdom** | **Plantae** |
|---|---|
| Division | Magnoliophyta |
| Class | Magnoliopsida |
| Order | Fabales |
| Family | Fabaceae |
| Genus | Trigonella |
| Species | foenum-graecum |
| Binomial name | Trigonella foenum-graecum |

• Other Common Names - Greek hay, Bird's Foot, Boyotu, Chinagreye, Fenegriek, Fenugreek, Foenum Graecum, Greek Hay-seed, Halva, Helba, Hu Lu Pa, K'U Tou, Kelabat, Koroha, Methi, Shimli, Sickle-fruit Fenugreek and Sickle fruit Fenugreek**.**

**CHEMICAL CONSTITUENTS**

**Table 2: Chemical constituents of Fenugreek**

| | |
|---|---|
| **Steroids** | **C27 – Sapogenin( also contibutes to anti-bacterial)** |
| **N- compounds** | **Trigonelline, choline and betaine( anti-diabetic)** |
| **Anthocyanins** | **Anthocyanidin-3-rhamnoside-5-glucosides** |
| **Flavonoids** | **Quercitin, Luteolin ( contibutes to anti-bacterial and anti-microbial activity)** |
| **Volatile** | **Hexenol, aniline, phenol,hexadecane,heptanoic acid.**<br>**Odour – 3-hydroxy-4,5- dimethyl-2-furanone ( HDMF)** |
| **Amino acids** | **Rich in lysine** |
| **Lipids** | **Mono and di galactosyl glycerides ( lenolenic acid) and phospholipids.** |

**FENUGREEK SEED USES**

**Table 3: Uses of Fenugreek seeds**

| FENUGREEK GALACTOMANNAN | VARIOUS INDUSTRIAL APPLICATIONS. |
|---|---|
| **SAPONINS**<br><br>**(DIOSGENIN)** | ❖ Flavoring, sweetening, antioxidant, foaming, complexing, sequestration, anticarcinogenic, Antibacterial and antimicrobial properties<br><br>❖ That's why they are used as nutraceuticals in food, drug, health food and cosmetic industry |
| **FENUGREEK OLEORESINS** | ❖ Used as an ingredient for imitation maple flavors and is effective in butter, butterscotch, black walnut, nut and spice flavors |

**CHEWING GUM:** [9,10]

Chewing gum is a drug delivery system which is going to advance more and more in nowadays researches and it seems to get more standardized in future industry because it can deliver either pharmaceuticals or nutrients which are known as medicated chewing gum (MCG) and non MCG. MCG is supposed to act as an extended release dosage form that provides a continuous release of medicine contained. Ancient Greeks used to get a chewable resin from a tree called mastic but due to archaeological diggings chewing gum-like substances or masticatory resins back to 5000 years ago. Resin pieces have even been found with teeth traces in Finland and Sweden. First marketing of chewing gums was at 1848 when chicle from Sapodilla tree was sapped. John Curtis and his son boiled spruce tree sap and added sugar, flavor, and fillers, then rolled it and first made masticatory sticks which they wrapped in papers and sold them. Over time their company prospered, it was then that the son found they need to improve the company and machines, so he developed a machine which mass produced gums. In 1869, Doctor William F. Semple from Ohio issued the first patent for chewing gum both as a confection and a pharmaceutical to protect teeth. The first MCG was launched in 1924 in United States of America which was called Aspergum® but an admission of chewing gum as a drug delivery system did not gain until nicotine chewing gum was released at the market. Thomas Adams first manufactured MCGs with natural latex-base and issued the first patent of chewing machine render chicle kneaded, and smooth but modern chewing gums often consist of synthetic resins. There is a monograph in European pharmacopoeia (EP) that defines MCG but the term "chewing gum" was first listed in guidelines as pharmaceutical dosage forms in 1991 and approved by the commission of European communities. Due to acceptance of oral drug delivery systems among people, chewing gums soon became friendly to people all around the world because of convenient administration. Besides its enjoyable taste and good feeling, it provides proven health, nutrition, and cognitive benefits. Medicated chewing gums which are marketed for therapeutic purposes are so various; a brief list is given Table.

**Table 4: Therapeutics Purposes of Medicated Chewing Gum**

| Therapeutic use/indication | Drug |
|---|---|
| **Treatment of motion sickness** | Dimenhydrinatehydrochloride,, Diphenhydramine hydrochloride, Ginger |
| **Smoke cessation** | Nicotine |
| **Pain reliever** | Aspirin, lobeline, silver acetate |
| **Anti-plaque and gingivitis, preventing of dental caries and tooth decay** | Xylitol, chlorhexidine, Salvadora persica L. |
| **Oral antifungal** | Miconazole |
| **Treatment of otitis media** | Xylitol |
| **Alertness and CNS stimulant** | Caffeine |
| **Antioxidant** | Green tea |
| **Anti-nausea and anti-emetic (prevention of motion sickness), effective in GI problems** | Ginger |
| **Antioxidant, anti-inflammatory and anti-septic and healing** | Aloe Vera |

**Advantages of medicated chewing gums**

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.

16. Fast bowel recovery after GI surgery.

**Disadvantages of medicated chewing gums:**

Disadvantages of medicated chewing gums

1. Disappearing of drug in oral cavity following salivary dilution.

2. Different release profiles because of chewing style differences.

3. Short time of administration due to eating, speaking, and drinking.

4. Allergic reaction to artificial sweeteners.

5. Continuous stress on jaws that may cause temporomandibular joint disorder.

6. Teeth decay through being coated by sugar.

7. Masseter problems.

8. Stomach irritations, aches, gastric ulcer through continuous swallowing of saliva and even flatulence because of presence of sorbitol in some formulations.

9. Getting choked by swallowing gum in under-aged children.

**CHEWING GUMS TYPES**

Chewing gums come in a variety of flavors, shapes and sizes. There is no standard type of gum, but mostly is a small stick or wad of gum. Chewing gum is basically made by combining a water-insoluble phase with a water-soluble phase of sweeteners, flavoring and food coloring.

**Types:**

1) **Sugar-free gum** - Instead of sugar, sugar-free gum has artificial sweeteners to provide the taste.
2) **Ball Gum** – This gum has shape like ball. It is one of the most popular chewing gums.
3) **Center-filled Gum** – center-filled gum in his center has a soft mass, usually filled with some tasty liquid.
4) **Stick gum** - chewing gum Stick gum is a thin, flat, slab of gum usually in rectangular shape.
5) **Ribbon Gum** - ribbon gum is like the stick gum, only it is longer, coiled up in a cylindrical container, and the consumer tears off a piece of the size he wants.
6) **Tab gum** – tab gum is shorter than stick gum and also thicker.
7) **Tube gum** - tube gum or spaghetti gum comes in a tube and gum inside tube is a very soft bubble gum.
8) **Dragée gum** – dragée gum has the most popular format for chewing gum, dragée gum is a pillow-shaped coated pellet, often packed in blister packs.
9) **Wrap gum** – wrap gum and cut gum is usually in the form of a chunk, cube or cylindrical shape, depending of the machine that wraps it.
10)**Functional Gum** - functional gum is chewing gum that has a practical function attached to it, like chewing gum with vitamins and minerals or something else to the body.
11)**Medicated gum** – medicated gum is a chewing gum with purpose to introduce medicated substances into blood stream faster than pills.
12)**Nicotine gum** – nicotine chewing gum is designed for people who are trying to quit smoking. This gum contains a small amount of nicotine. Idea is to give the smoker something to do, besides hold a cigarette in their mouth.

Several types of chewing gum are designed for dental hygiene. There are gums to whiten teeth, clean teeth and fresh breath.

There are also many different types of chewing gums like: antioxidant gum, dental gum, diet gum, energy gum, thirst quenching gum, herbal gum and vitamin gum.

The most popular flavors are: mint, spearmint, peppermint, wintergreen, cinnamon, licorice, sour apple, cherry, grape, orange, watermelon, strawberry, lemon, and blueberry.

## REVIEW OF LITERATURE

Medicated chewing gums are the most attractive dosage forms which can take by oral route and people of all type like to chew this type of dosage form. Several investigations carried out in the past on the development of medicated chewing gums with different methods and with different plasticizers. The literature survey carried out on such type of investigations which support the present research work for preparation of medicated chewing gums.

**Abin L Alex et.al**[11] Developed chewing gum of antiemetic drug Domperidone. Aim of present of chewing gum of was formulated to accelerate the onset of action and to improve the bioavailability so as to get quick relief from nausea and vomiting with greater patient compliance. In this study, ten formulations of domperidone were formulated as a chewing gum & best formulation was film coated. In each formulation, drug concentration remains the same the excipients concentration was varied.

**Koppula Rajitha et.al**[12] Formulated and evaluated medicated chewing gum of chlorpheniramine maleate. The aim of the work was to achieve better patient compliance and improved the drug release. The medicated chewing gums are prepared by melting method. In this method different concentrations of gum base and plasticizers like glycerol and castor oil. The prepared chewing gums are evaluated for different parameters like appearance, stickiness, weight variation, drug content, hardness, thickness, in vitro drug release. Invitro release profiles of medicated chewing gum during 30 minutes studies were found to have very good release efficacy. It was observed that as the concentration of synthetic gum base increases drug releases was decreases.

**Rahul B.Shete et.al**[13] Formulated medicated chewing gum to prevent motion sickness using natural gum base for faster onset of action, easy administration, anywhere & any time, without access to water. Natural gum base prolamin extracted from wheat, showed good chewing capacity, elasticity, high water retention capacity, and three-level factorial design. Results revealed that medicated chewing gum containing

80 mg of calcium carbonate & 500 mg of gum base showed elasticity and more than 90% drug release with 16 minutes. Thus this study suggested that both good elasticity and chew ability and availability grain can act as a potential gum base for medicated chewing gum.

**Jyoti Ranmale et.al**[14] Developed the formulation development and evaluation of Amoxicillin based medicated chewing gum for its antibacterial activity. The aim of present study was to design and characterize medicated chewing gum for the treatment of bacterial infection using Amoxicillin trihydrate as model drug. The chewing gums were prepared using Health in gum grade 01(HiG -01) as a directly compressible gum base developed by cafosa (S.A.U.) Spain. The effect of concentration of (Base) gum base, (release modifier) Aerosil, and (antiadherant) talc was studies. After oral administration it's rapidly absorbed.

**Padmini Iriventi et. al**[15] Developed the formulation and evaluation of domperidone chewing gum for anti emetic activity. The aim of the work is oral drug delivery systems time as best kind of approach for delivering various drugs but certain drugs given by oral route undergo first pass metabolism which leads to low bioavailability, making them less effective. To overcome these novel oral drug delivery Systems, ie, chewing gums were developed as an alternate for conventional oral systems. These were used for both systemic and local delivery of drugs. Domperidone, anti emetic drugs is poorly water soluble to enhance its solubility, solubilizer were used in various rations for the obtained formulations, and evaluation studies were carried out.

**Poornendra Parouha et.al**[16] Developed medicated chewing gums of Disulfiram were smooth, light yellow in color with a mint flavor. The presence of glycerin at an optimized concentration provided the softness for the medicated chewing gum developed. The average content of the drug in the developed medicated chewing gum was 94.14%, confirming the success of the formulation and the methodology used for its development. The drug release profile for medicated chewing gums can be significantly influenced by the frequency of chewing, therefore the drug release rate from the developed MCG was measured the maximum drug release of 94.37% was reported after 30 minutes of study on the dissolution of Batch F4.

**Abolfazl Aslani et. al**[17] Designed formulation and evaluation of caffeine chewing gum. Aim of this study was to design a new formulation of caffeine chewing gum with desirable taste and assess its physicochemical properties. It was prepared by softening of gum bases and the mixing with other formulation ingredients.

**Ganesh S. Bhoi et. al**[18] Formulated and evaluated medicated chewing gum of chlorpheniramine maleate. This medicated chewing gum was prepared by direct compression method using gum base, sorbitol, mannitol, magnesium stearate, lecithin, menthol. This method consists of gum base & lecithin like 30-35-40% and 5-10-15% accordingly. In this formulation soya lecithin was used as a plasticizer & it was found that it acted on the drug release to some extent. When concentration of soya lecithin was increased, drug release was also found to be increased.

**Ritesh Kumar et. al**[19] Reviewed on chewing gums, chewing gums are mobile drug delivery systems. Unlike chewable tablets medicated gums are not supposed to be swallowed & may be removed from the site of application without resort to invasive means & medicated chewing gum MCG is solid, single dose preparation. As far as patient convenience is concerned that it's discrete and easy administration without water promotes higher compliance.

**Ravindra Semwal et. al**[20] Reviewed on medicated chewing gum. Chewing gums are mobile drug delivery systems. It's a potentially useful means of administering drugs either locally (or) systemically via, the oral cavity the medicated chewing gum has through the year gained increasing acceptance as a drug delivery system.

**Aslani A et. al**[21] Reviewed on medicated chewing gum via oral route for throat infection. Many researches display significance of oral route amongst patients. They have reviewed all the features associated with medicated chewing gum as a modern drug delivery by introducing the history, advantages and disadvantages, methods of manufacturing, evaluation tests and examples of varieties of medicated chewing gums.

## MATERIALS AND EQIUPMENTS

**LIST OF DRUG AND EXCIPIENTS**:

**Table 5: List of Drugs and Chemicals**

| Sr.no | Drug/Polymer/Excipients | Manufacturer |
|---|---|---|
| 1 | Fenugreek Seeds | Local shop |
| 2 | Sucrose | Research-Lab Fine Chem Industries, Mumbai- 400 002 |
| 3 | Glycerin | Research-Lab Fine Chem Industries, Mumbai- 400 002 |
| 4 | Eucalyptus Oil | Research-Lab Fine Chem Industries, Mumbai- 400 002 |
| 5 | Peppermint Oil | Research-Lab Fine Chem Industries, Mumbai- 400 002 |
| 6 | Distilled Water | From Lab |

**LIST OF MACHINES AND EQUIPMENTS**

**Table 6: List of Instruments/Machines**

| Sr.no | Name of Instruments /Machines | Make/Company |
|---|---|---|
| 1 | Weighing Balance | Phoenix |
| 2 | Mixer/Grinder | Bajaj electricals |
| 3 | Hot Air Oven | Labline |
| 4 | pH meter | Labline |
| 5 | U.V Spectrophotometer | Shimadzu |
| 6 | Dissolution test apparatus | Scientific Technology Solution |
| 7 | Bulk Density Apparatus | Labline |
| 8 | Rolling pin board | Local Shop |
| 9 | Vegetable Chopper | Local Shop |

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## DRUG AND EXCIPIENT PROFILE

**Drug profile:**

**1) FENUGREEK SEED[22]**

**Synonym:** Trigonella foenumgraecum, Greek clover.

**Empirical Formula:**
$C_{58}H_{94}O_{27}$

**Chemical Name:**
SAPONIN 8047-15-2 **Cyclamine NSC** 104795 BRN 0078682

**Chemical Data:**

**Boiling Point :** Boiling point of fenugreek is 101.9 °C

**Melting Point:** Melting Point of fenugreek 158°C

**Color:** Yellow crystalline

**Odor:** it is odorless

**Solubility:** It is soluble in cold water.

**Density:** Density of fenugreek is 6.59 g/ml

**Excipient Profile:**

**1) SUCROSE[23]**

**Synonyms:**
Beet sugar, Cane sugar, Refined Sugar

**Empirical formula:**
$C_{12}H_{22}O_{11}$
**Chemical Name:**

B-D- Fructofuranosyl – a- D- glucopyranoside

**Typical Properties:**

**Density (bulk)**

Bulk Density of crystalline sucrose is 0.93 g/cm3 (Crystalline sucrose)
Bulk Density of crystalline sucrose is 0.60 g/cm3 (Powdered sucrose)

**Density (tapped)**

Tapped Density of crystalline sucrose is 1.03 g/cm3
Tapped Density of Powdered sucrose is 0.82 g/cm3

**Density (true)**

True Density of sucrose is 1.6 g/cm3

**Density (Constant)**

PKavalueis12.62

**Flow ability:**

Crystalline sucrose is free flowing, whereas powdered sucrose is a cohesive solid.

**Melting Point:**
160 – 186° C (with decomposition)

**Moisture content:**
Finely divided sucrose is hygroscopic and absorbs up to 1% water

**Functional Category:**

Base for medicated confectionery.

Coating agent
Granulating agent
Sugar Coating adjacent
Suspending agent
Tablet binder

**Description:**
Sucrose is a sugar obtained from sugar cane (Saccharum officinarum Linne) (Family: Graminae) sugar beet (Beta Vulgar is Linne) (Fam. Chenopodiaceae), & other sources. It contains no added substances. Sucrose occurs as colorless crystals, as crystalline masses (or) as a white crystalline powder, it's an odorless & has a sweet taste.

**Pharmacopeial specifications:**

**Solubility:**

**Solvent:** Solubility at 20° C unless otherwise stated
**Chloroform:** Practically Insoluble

**Ethanol:** 1 in 400

**Ethanol (95%):** 1 in 170
**Water:** 1 in 0.5, 1 in 0.2 at 100° C

**2) GLYCERIN[23,24]**

**Synonyms:**
Glycerol, Glycerine, 1,2,3-Propanetriol

**Empirical formula:**

$C_3H_8O_3$

**Chemical Name:**
Propane-1,2,3-triol

**Typical Properties:**

**Density:** Density is 1.26 g/cm³

**Molar mass:** 92.09382 g/mol

**Melting point:** Melting point is 17.8 °C (64.0 °F; 290.9 K)

**Boiling point:** 290 °C (554 °F; 563 K)

**Solubility in water:** Miscible in water

**3) EUCALYPTUS OIL[23.24]**

**Synonyms:**
Fossil oil, Lubricating oil, Calamus oil, Chinese wood oil, Hedeoma oil.

**Empirical formula:** $C_{10}H_{18}O$

**Chemical Name:**

Eucalyptol, Cineole, 1, 8-Cineole

**Typical properties:**

**Molar mass:**
965.51g/mol

**Density:**
Density is 0.9225 g/cm$^3$

**Melting point:**
Melting point is 2.9 °C (37.2 °F; 276.0 K)

**Boiling point:**
Boiling point is 176–177 °C (349–351 °F; 449–450 K)

**Solubility:**
It is insoluble in water, but miscible with organic solvents. Eucalyptol makes up 90% of eucalyptus oil.

## EXPERIMENTAL WORK

**Phase-I:**

**a) Preformulation Study**

**1) Physical Appearance:** Colour, Odour, Texture study of powder was carried out.

**Melting Point:**
M.P was determined by melting fenugreek by melting point apparatus.
The temperature at which drug started melting was noted, average three results was noted.

**2) Standard curves for fenugreek:**

Determination of λ max of fenugreek in Phosphate buffer pH 6.8 was seen at 258nm.

Calibration curve for the fenugreek at max in Phosphate buffer pH 6.8.

**Determination of Bulk density, Tapped density, Hausener's ratio, Carr's index, Angle of repose.**

**3) Bulk Density and tapped density:**

The bulk density and tapped densities of the fenugreek powder was determined by using bulk density apparatus. Required amount of powder is transferred into graduated measuring cylinder; it is fixed to bulk density apparatus and tapped for 100 times, then initial bulk volume and final volumes are noted. Then by using the following formula bulk density and tapped densities are determined.

Weight of powder Bulk density = Bulk volume of powder Weight of powder Tapped density = Tapped volume of powder.

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**4) Hausener's ratio:**

The ratio of tapped density $W/V_{50}$ to fluffy density ($W/V_0$ g/ml) is known as the Hausner ratio. A good flow is indicated by a Hausner ratio greater than 1.25, and a poor flow may have a value of 1.5.

**HAUSNER RATIO VALUES:**

**Table 7: Hausner Ratio**

| Sr.no | Flow Character | Hausner Ratio |
|---|---|---|
| 1 | Excellent | 1.00 - 1.11 |
| 2 | Good | 1.12 - 1.18 |
| 3 | Fair | 1.19 - 1.25 |
| 4 | Passable | 1.26 -1.34 |
| 5 | Poor | 1.35 – 1.45 |
| 6 | Very Poor | 1.46 – 1.59 |
| 7 | Very Very Poor | > 1.60 |

**5) Carr's Index (I):**

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

Carr′s index = tapped density − bulk density tapped density ˣ100

**CARR'S INDEX VALUES:**

**Table 8: Carr's Index**

| Sr.no | Carr's index (%) | Type of flow |
|---|---|---|
| 1 | 5-15 | Excellent |
| 2 | 12-18 | Good |
| 3 | 18-23 | Fair to pass |
| 4 | 23-35 | Poor |
| 5 | 35-38 | Very poor |
| 6 | >40 | Extremely poor |

**6) Angle of Repose (θ):**

Angle of repose is used to determine the flow properties of powders, pellets or granules. The angle of repose of formulations is determined by fixed funnel method.

$\tan \theta = h/r$

Where, h = height of the heap r =Radius of the heap

**ANGLE OF REPOSE VALUES:**

**Table 9: Angle of Repose**

| Sr.no | Angle of Repose | Type of flow |
|---|---|---|
| 1 | <25 | Excellent |
| 2 | 25-30 | Good |
| 3 | 30-40 | Passable |
| 4 | >40 | Very Poor |

**Phase-II**

**b) Methodology**

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**Extraction of fenugreek gum**

The seeds of fenugreek were washed in distilled water and powdered coarsely with grinder. In addition coarse powder was soaked in distilled water for 48 hrs, and the gum was filtered out from the bulk material by using muslin cloth. The filtrate was precipitated with ethanol several times to complete the extraction process. The gum was dried at 40°c, powdered, and packaged into aluminum foil for further use.

**Method preparation of chewing gum**

Preparation of Fenugreek chewing gum was formulated using a mixture of gum base, sucrose, and flavors such as eucalyptus, peppermint oils.

In formulation of Fenugreek chewing gum, Fenugreek seeds were soaked in water for 2 days for preparation of gum base. From which Fenugreek seeds dried extract was collected and the powder was prepared by using mixer. The gum base is softened at the temperature of 60°C in china dish. Fenugreek powder, sucrose, was added to the base. Finally, at the temperature of 40°C, flavors were added and the mixture of chewing gum was cut into pieces of appropriate sizes by the chopper.

**Phase-III**

**c) Evaluation parameters of medicated chewing gum**

Medicated chewing gum was evaluated by performing following tests

**1) Physical Appearance:**

Few batches were visually evaluated for physical appearance, color, odor, and taste. The texture study was performed manually by pressing the gum between the thumb and the finger. The texture feel was characterized into sticky, good, or solid mass.

**2) Determination of Content Uniformity:**

Three chewing gums were selected randomly. Each gum was dissolved in 100 mL phosphate buffer pH 6.8. The amount of Fenugreek was analyzed by measuring the drug absorbance at 258 nm and 540 nm using double beam UV spectrophotometer (UV-1800, Shimadzu, Japan).

**3) Elasticity Study**

Elasticity of chewing gum is one of the important parameters. Appropriate elasticity of chewing gum contributes to increase the patient compliance as well as the proper release of the drug.

**4) Chewing Study of Gum Formulation**

The chewing gum provided good mouth feel and comfort during chewing without sticking to the teeth. However, the amount of saliva secreted contributes mainly in chewing the formulation. It was studied on five volunteers from the college (LCOP Hasegaon) and was found to be feasible for chewing.

**5) Stability Study**

Stability study of chewing gum was studied to obtain a stable product which assures safety and efficacy, till shelf life, at defined storage and package conditions. Stability study was done according to ICH guidelines to assess the combined effect of drug, gum base, and excipients on the stability of the formulation. Optimized formulation was placed in vials and stored in aseptic chamber and normal room 28°C ± 2°C. The samples were evaluated for the color, taste, drug content, *in vitro* drug release study and growth of microorganisms after 7, 15, and 30 days.

## RESULT AND DISCUSSION

**PHASE-I:**

**Bulk Density, Tapped Densit, Porosity, Carr's Index, Angle of Repose and Moisture Content Results of Fenugreek:**

**1) Bulk density:** The bulk density of fenugreek seeds powder ranged from **6.21 to 6.98 g/ml**. The average bulk density was **6.59 g/ml.**

**2) Tapped density:** Tapped density of fenugreek seeds powder ranged from **1.121 to 1.230 g/ml**. The average density of fenugreek seed was **1.175 g/ml**. similar results have been reported.

**3) Porosity:** Porosity of fenugreek seeds powder found to be **42.51%**

**4) Carr's index (%):** Carr's index fenugreek seeds powder found to be **15%.**

**5) Hausner ratio:** Hausner ratio was found to be **1.30.**

**6) Angle of Repose:** Angle of Repose was found to be **25.0°.**

**Table 10: Fenugreek powder properties**

| Property | Results |
|---|---|
| Bulk Density | 6.59 gm/ml |
| Tapped Density | 1.175 gm/ml |
| Porosity | 42.51% |
| Carr's index (%) | 15% |
| Hausner ratio | 1.30 |
| Angle of Repose | 25.0° |
| Moisture Content | 11.21% |

**Table 11: Relationship of different powder properties**

| Angle of Repose | Carr's Index | Hausner's Ratio | Flow Properties |
|---|---|---|---|
| 25-30 | <10 | 1.00-1.11 | Excellent |
| 31-35 | 11-15 | 1.12-1.18 | Good |
| 36-40 | 16-20 | 1.19-1.25 | Fair |
| 41-45 | 21-25 | 1.26-1.34 | Passable |
| 46-55 | 26-31 | 1.35-1.45 | Poor |
| 56-65 | 32-37 | 1.46-1.59 | Very Poor |
| >66 | >38 | >1.60 | Very Very Poor |

**STABILITY STUDIES OF BEST FORMULATION [F3]:**

**Table 12: Stability study data of drug formulation**

| Temperature | Days | Drug Content (%) | Hardness | Drug Release |
|---|---|---|---|---|
| 25˚C | 15 | 98.00 ± 0.13 | 1.63 | 98.2% |
| | 30 | 97.8 ± 0.19 | 1.62 | 98.5% |
| 40˚C/75% RH | 15 | 97.7 ± 0.29 | 2.2 | 97.50% |
| | 30 | 97.5 ± 0.29 | 2.2 | 97.20% |

**STANDARD CURVES FOR FENUGREEK**

**Preparation of Calibration medium:**

The calibration medium pH (6.8) were prepared by using phosphate buffer as per the IP procedure (I.P. 2014)

**Estimation of absorption maximum (λ max):**

The λ max of Fenugreek was estimated by scanning the 10µg/ml concentration of the drug solution in buffer solution of phosphate pH 6.8. It showed the λ max in phosphate buffer solution of pH 6.8 and the results were tabulated.

**Preparation of standard curves:**

The standard curves of Fenugreek prepared by using phosphate buffer pH (6.8). The linear correlation coefficient was found to be 0.999 for pH (6.8) Fenugreek obeys the Beer's law within the concentration range of 2 to 10µg/ml.

**Drug absorbance at 258 nm and 540 nm**

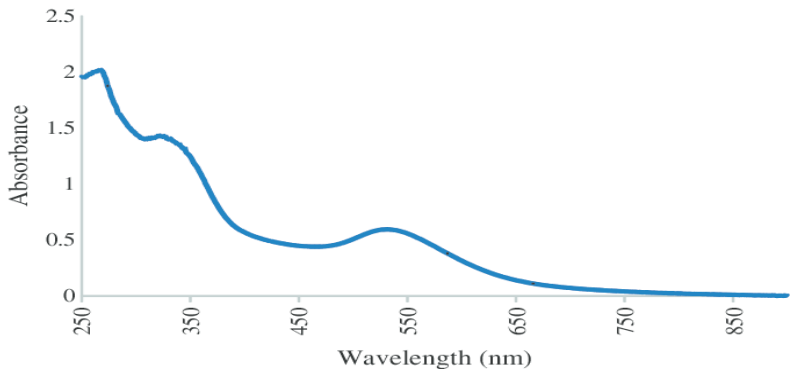


**Figure 9: Absorbance for Fenugreek seed was found to be at 258 nm and 540 nm.**

**hase-II**

**FORMULATION OF FEENUGREEK CHEWING GUM**

The fenugreek chewing gum was prepared by Melting method (Koppula Rajitha et al., 2016). The principles of this method was based on the melting of gum base in a china dish, to this add other ingredients and mixed well and rolled in Sucrose powder, where chewing gum is cut into required size and shape. Basic advantage of the melting technique was it is simple and had a low cost.

Various formulations of fenugreek chewing gums (F1, F2, F3, F4, and F5) were prepared at different concentrations.

**FORMULATION TABLE**

Above formulation is for 1000 mg of medicated Chewing Gum: Each formulation 20 chewing gums were prepared.

**Table 13: Formulation Table of medicated chewing gum**

| Drug/Excipients | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| **Fenugreek Seeds (Powder)** | 500 | 500 | 500 | 500 | 500 |
| **Gum Base** | 400 | 350 | 300 | 250 | 200 |
| **Sucrose** | 95 | 145 | 195 | 245 | 295 |
| **Glycerin** | 3 | 3 | 3 | 3 | 3 |
| **Eucalyptus Oil** | 1 | 1 | 1 | 1 | 1 |
| **Peppermint Oil** | 1 | 1 | 1 | 1 | 1 |
| **Water** | q.s | q.s | q.s | q.s | q.s |

*All the above excipients are in mg.

**Phase-III**

**CHARACTERIZATION OF FENUGREEK CHEWING GUM**

All the formulations were evaluated for its drug content, solubility studies, *in vitro* drug release studies.

**Determination of drug content:**

The drug content of all chewing gum formulations (F1 to F5) was in the range of 90.82% to 98.03%. The results were shown in figure no.10. The results suggest that the process employed to prepare the chewing gum shown distribution of drug.

**Solubility studies:**

The solubility of formulations {F3} and pure drug in phosphate buffer pH (6.8) were 0.5g/10ml and 0.97g/10ml respectively. Thus the solubility of Fenugreek chewing gums was increased approximately by ten folds when compared to pure drug. Hence, the noticeable

increased saturation solubility of Fenugreek in the formulation of chewing gums was mainly attributed to the decreased particle size & increased surface area.

**Drug Release Study**

***In-Vitro* Dissolution Study in Phosphate Buffer**

The dissolution study of the chewing gum is relatively different than the conventional dosage forms. The mechanical force is required to release the drug from the chewing gum. The chewing activity of the patient and oral health of mouth cavity also influences the drug release. Because of these reasons, apparatus consisted of following parameter was considered for the release of gum formulations which simulated human chewing behavior. *In vitro* drug release of Fenugreek chewing gum was performed by using dissolution test apparatus of medicated chewing gum based on European Pharmacopoeia at 40 mL dissolution medium of pH 6.8 phosphate buffer maintained at temperature 37 ± 0.5ºC. Five milliliters of aliquots was withdrawn at periodic time interval and replaced with preheated fresh dissolution media.

***INVITRO* DRUG RELEASE PROFILEOF BEST FORMULATION (F3):**

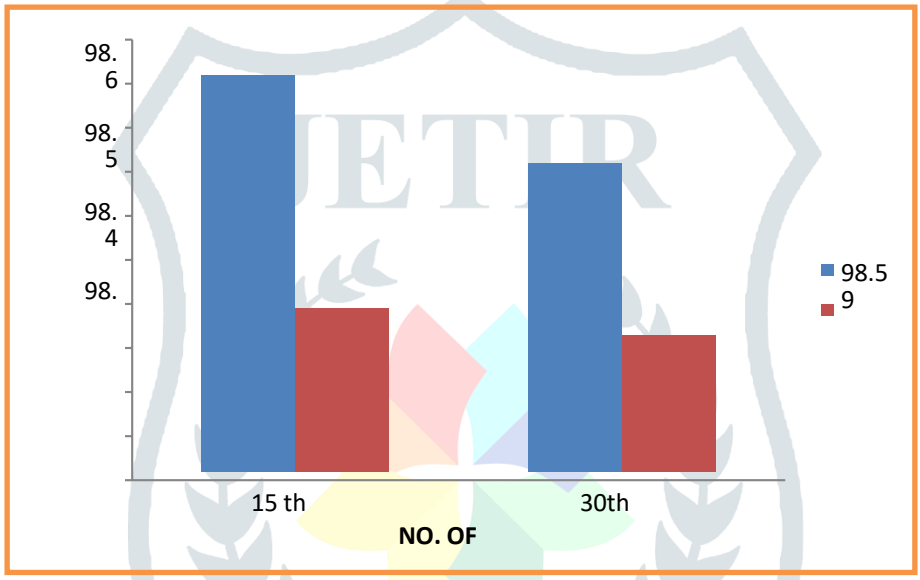


**Figure 10: Cumulative % drug release vs No of Days**

**DRUG CONTENT OF BEST FORMULATION (F3):**

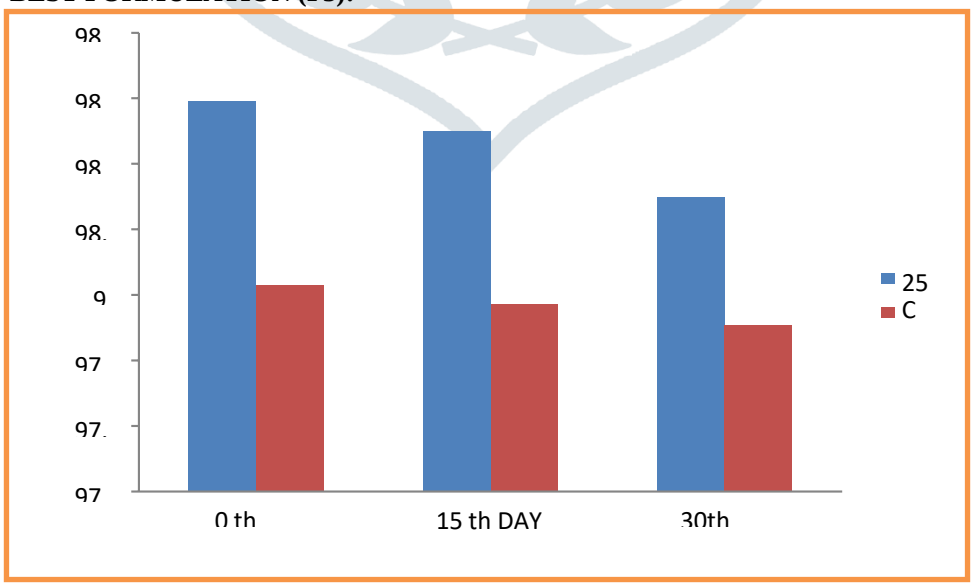


**Figure 11: Drug Content vs No of Days**

## SUMMARY

- In the present study, an attempt has been made to formulate medicated chewing gum of fenugreek in throat infection to achieve better patient compliance and improved drug release.
- Medicated chewing gum of Fenugreek was successfully prepared by melting method using different concentrations of Sucrose, Gum Base, and oils.
- The presence of Sucrose made the chewing gum more stable with increasing drug release. Gum base concentrations are critical parameters which affect the consistency and drug release profile.
- The Drug content of the selected formulations (F3) was 98.03%, which indicates the maximum amount of drug present in the formulation chewing gum.
- *In-Vitro* release study of all the formulations were showed in increase drug release with increase in concentration of Sucrose, Gum Base.
- The dissolution study was carried out in PH 6.8 phosphate buffer for 30 minutes. The formulations shows rapid release of drug in 20 minutes & all formulations showed more than 90% of drug release.
- Medicated chewing gum consisted mainly of sucrose and gum base showed good elasticity, chewability and satisfactory drug release. The selected best formulation was tested for its antibacterial activity.
- In all the formulations, F3 shows highest drug release of in 30 minutes.
- The *in-vitro* release studies revealed that the prepared chewing gums showed a faster drug release.
- The formulations were kept for accelerated stability studies; they showed no change in the drug release profile. Thus stability results prove that the formulation was stable at accelerated conditions.

## CONCLUSION

Hence, it was concluded that medicated chewing gum of Fenugreek was successfully prepared by melting method using different concentrations of Sucrose and Gum base, Formula is optimized by changing the Sucrose and Gum base concentration which are critical parameters which affect the consistency and drug release profile. Based on the drug release of all the formulations, formulation F3 is the optimized formulation kept for stability studies. Thus, it's the better option to prepare Fenugreek into a medicated chewing gum to achieve better patient compliance and improved drug release for throat infection.

From this study it was concluded that chewing gum that contains highest amount of sucrose and gum base showed good release in *invitro* studies. It indicates that sucrose acts as a good solubilizer which enhances the solubility of the drug Fenugreek. Higher ratio of gum base enhances drug solubility, which leads to increase in the amount of drug absorption. By delivering Fenugreek in the form of chewing gum, it directly enters into systemic circulation thus by passes first pass metabolism and hence bioavailability of drug increase.

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