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FORMULATION DEVELOPMENT& EVALUATION OF HERBAL MEDICATED CHEWING GUM

Virashri Dhumal*, Mohit Raskar, Yashasvi kale, Sakshi khadke, Smita haral, Dr.Ashwini Devhadrao, Dr.Pramod Ingale

1. Dnyanvilas college of pharmacy,, Gat No.76, Dudulgaon, Pimpri-Chinchwad Corporation Area, Alandi - Moshi Rd, Pimpri-Chinchwad, Maharashtra 412105

Corresponding author- Virashri Dhumal*. Dnyanvilas college of pharmacy, Dudulgaon, Contact mail- dhumalvirashri790@gmail.com

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ABSTRACT: Maintaining good oral health is essential to overall health, but it can be difficult to prevent conditions including dental caries, periodontal disease, localized soft tissue infections, mouth ulcers, and halitosis. The goal of this work was to create a novel natural oral care product by utilizing eugenol, a bioactive component of clove oil, to create a new herbal chewing gum formulation.
Eugenol, a phenolic molecule, is a great option to be incorporated in dental care products because it has demonstrated antibacterial, antioxidant, and analgesic properties effects. Chewing gum provides a number of benefits as a delivery method, such as easy and non-invasive dosing, the potential for buccal absorption, and the gradual release of bioactive substances into the oral cavity.
OBJECTIVE: To Create a Eugenol Herbal Medicated Chewing Gum. **METHOD:** Natural food-grade components, such as a gum base made from the ***Manilkara zapota*** tree, honey as a binder, sucrose as a sweetener, and saffron as a coloring agent, were used to make the herbal chewing gum formulations. As the active component, eugenol was isolated from clove oil *(Syzygium aromaticum)*. Numerous evaluation tests, such as stickiness, percent drug content, organoleptic features, and in vitro drug release investigations, were performed on the formulations.
RESULT: The in vitro study on medication release showed that the herbal chewing gum formulations had sufficient drug release when tested using a self-fabricated dissolving device. The batch F3, comprising 2 grams of gum base and 15 milligrams of eugenol, demonstrated a 97.15% drug release percentage and was determined to be the optimal formulation based on all assessed criteria. Stability tests and an evaluation of the chewing gum's antibacterial efficacy against mutant Streptococcus, the bacterium that causes tooth decay, provided more evidence that the herbal chewing gum may be a successful oral care product.
CONCLUSION: The study shows how a novel herbal chewing gum containing eugenol was successfully formulated and evaluated, providing a practical and natural way to maintain oral hygiene and prevent dental caries and other oral disorders. The new formulation has potential as a feasible substitute for conventional oral care products, offering advantages for different age groups, such as pediatric and geriatric populations.

KEYWORDS: anti-microbial activity, chewing gum made of herbs, clove oil (Eugenol), and tooth decay.

1. INTRODUCTION-

To produce a systemic or local pharmacological effect, medications are typically manufactured in a range of dosage forms, such as tablets, capsules, injections, inhalers, and ointments, among others. Because oral medication distribution is easier to use than other dose forms, it is the most widely accepted method of drug administration. Chewing gum has a confectionery role, but now days, because it absorbs substances quickly through the mouth cavity, it also demonstrates the greatest and most convenient medicine delivery technology [01].

Since ancient, humans discovered how enjoyable it was to chew a variety of substances. Chewing gum has been used all across the world. A thousand years ago, the Mayan Indians chewed tree resin from the sapodilla tree to clean their teeth and freshen their breath [02].

Compared to tablets, capsules, or liquids, parents are more willing to allow their kids use chewing gum that is medicated with herbs. Chewing gum with medication is used to administer medication either locally or overall. For oral therapy, the drug may be released locally or quickly absorbed by the oral mucosa for systemic diseases, resulting in a quick start of action and high bioavailability. This prevents both gastrointestinal tract metabolism and first-pass metabolism [03].

In comparison to pills and syrups, herbal medicated chewing gum is a more favored medication delivery strategy due to its widespread use and capacity to release bioactive ingredients in the mouth cavity for a prolonged amount of time [04].

Additional patient benefits like discrete and convenient administration and the possibility of buccal absorption, which results in a prompt onset of action, are anticipated from a novel drug delivery method [05]

Chewing gum is typically made up of a gum base a water-insoluble phase as well as other components. These include glucose, which acts as a humectant and coats the sugar particles to stabilize their suspension and keep the gum flexible, various softeners, food coloring, preservatives, flavorings, etc., the quantity and size of the powdered sugar determines how brittle the final gum will be. Once a prescription chewing gum has been chewed for the necessary amount of time to deliver the dose, the residual bulk needs to be thrown away [06].

The prevention of dental caries, periodontal disorders, and halitosis remains a major challenge in modern culture, despite the fact that oral health is an essential component of general well-being. Even while brushing and flossing are good oral hygiene habits, there is a growing need for complementary and alternative methods that have further advantages. In the field of oral healthcare products, the use of natural, bioactive substances produced from plants has attracted a lot of attention [07].

The well-known and historically utilized plant, clove is used extensively for a variety of reasons in medicine, cookery, and scientific study since its benefits and values have been demonstrated in numerous publications, experiments, and studies [08].

It has long been known that eugenol, a phenolic molecule present in clove oil and other plant sources, has a wide range of medicinal uses, including the ability to treat diabetes, cancer, infections, inflammation, hypo-lipidemia, and pain. Eugenol is a desirable option for adding to oral care products, like chewing gums, in order to improve oral health and address common dental problems because of these qualities [09].

Essential Features and Properties of Herbal Medicated Chewing Gum [10-12]:

i. It should be chewable and supple.
ii. It need to possess the appropriate flexibility.
iii. Chewing gum bases ought to be non-toxic.
iv. It needs to be packed such that it is easy to use and carry.
v. It should have a flavor that is pleasing and enduring.

Benefits of Herbal Medicated Chewing Gum [13-14]-

Medicines have higher bioavailability due to the avoidance of hepatic first-pass metabolism. Because large plasma peak concentrations are avoided, the regulated release of the active components reduces negative effects. Children accept it very well and behave quickly. Chewing gum has been used extensively to treat oral diseases such as fungal infections, mouth ulcers, bad breath, dental plaques, and sore throats because it allows the medication to stay in the affected area for a longer period of time because the formulation's active ingredients release over time. Patient compliance is higher because it is easy to give and does not require water to be swallowed.

Drawback of Herbal Medicated Chewing Gum[10-14]-

One drawback of using herbal medicated chewing gum is the possibility of overdosing. The formulation's sorbitol content may result in diarrhea and gas. Flavoring agents, licorice, and cinnamon can all result in hypertension and mouth ulcers.

2. MATERIAL & METHOD-

Material: Distilled water is utilized as the extraction solvent after cloves are gathered from the market.

Method of Preparation-

i. Extracting the Oil from Cloves
ii. Formulation of Gum Base
iii. Formulation of Herbal Medicated Chewing gum

Extraction Clove Oil from Cloves-

Pinch off 60 grams of cloves and grind them into a fine powder. Transfer the fine powder into the RBF and add enough distilled water to it. Insert the RBF into the heating mantle, attach the Clevenger apparatus, and conduct a two-hour hydro distillation. The clove oil obtained using the Clevenger equipment is gathered and placed in a beaker.

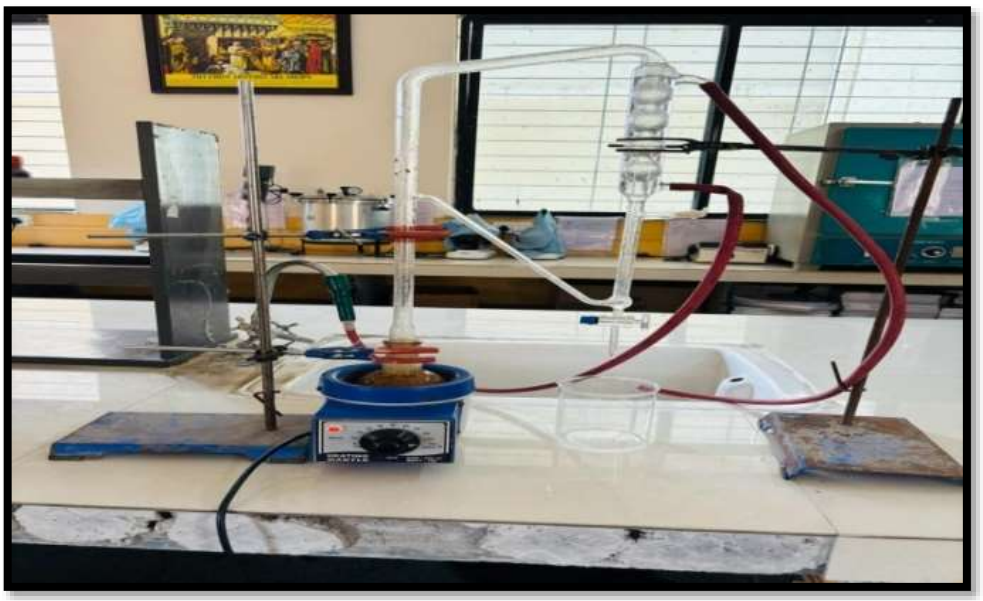

Fig no 01- Hydro-distillation Process

Formulation of Gum Base-

Table no 01 – The Formulation Table

Ingredients	Quantity taken	Use
Rubber latex (Chicle)	40gm	Gum base
Lecithin	8gm	Emulsifier
Glycerol	4.6ml	Softening Agent
Talc	q.s.	Filler

Procedure [16-17]-

Weigh 40 gm of the rubber latex (Chicle) obtained from Sapodilla tree (Chikoo) in a clean and dry metal dish. Heat / Melt the Chicle gum on water bath. Then add 8 gm of Lecithin to the gum by maintaining the temp. 60^0 C for 45 mins. Then add 4.6 ml glycerol to decrease the stickiness of gum in little amount. Then add talc as filler which provides the right texture. The gum base is then stored in amber colored glass bottle.

Formulation of Herbal Medicated Chewing Gum:

Ingredients: Gum base, Honey, Sucrose, Coloring & flavoring agents

Active Ingredient: Eugenol

Table no 02 - Detail Formulation table

Ingredients	Quantity taken				Use
	F_1	F_2	F_3	F_4	
Gum base	1gm	1.5gm	2gm	2.5gm	Provides elasticity
Clove oil (Eugenol)	15mg	15mg	15mg	15mg	Anti-microbial, anti-inflammatory

Honey	1.0gm	1.0gm	1.0gm	1.0gm	Used as anti- septic and as well as a Binder
Sucrose	1.0gm	1.0gm	1.0gm	1.0gm	Sweetening agent
Saffron	q.s	q.s	q.s	q.s	Coloring agent

Procedure: (Conventional / Fusion Method) [18-19]

All ingredients were weighed accurately as shown in formulation table. The required quantity of gum base was transferred in porcelain dish and melted on water bath; the temperature was maintained at about 50-60^{0}C. Honey and sucrose was added into the molten gum base with continuous stirring and after homogenous mixing eugenol was added to it. Flavor and color was added at the end and the mass was allowed to cool at room temperature on a slab. The mass was rolled evenly and cut into small pieces of uniform size and were wrapped.

Fig. no 02- Herbal Medicated Chewing Gum

3. EVALUATION STUDY [15-20]-

Table no 03 -Evaluation Chemical Tests for Eugenol-

Bromine Water Test	Ferric Chloride Test	$KMnO_4$ Test
Add 2-3 drops of clove oil in a test tube containing bromine. If the bromines reddish-brown color	Add 2-3 drops of clove oil in ferric chloride solution. If eugenol present will turn the	Add 2-3 drops of clove oil to $KMnO_4$ solution in a test tube. The change in color from deep purple to

disappears it indicates the presence of eugenol.	ferric chloride solution to bluish or light green color.	brown indicates presence of eugenol.
Result: The above 3 tests conducted showed positive results i.e. (Presence of Eugenol.)		

a. Thin Layer Chromatography (TLC) Analysis-

Prepare TLC plate-

Apply the adsorbent (Silica Gel) on the glass slide and air dry for 10 min, then dry it in hot air oven for 10 min. at 121^0C.

Fig no 03 - Prepare TLC

Sample Application-

Dissolve 1ml of sample in solvent (i.e. Ethanol) and give spot on the TLC plate at 1.5 cm above the bottom end of slide.

Development of Plate-

Place the plate in a developing chamber containing suitable solvent (i.e. ethyl acetate: n hexane) of ratio (9:1) and keep it until the solvent has reached ¾ of the plate.

Detection-

Remove the plate and let it air dry for few minutes. Afterwards observe the plate under UV – Cabinet or in iodine chamber. Calculate the Rf value and compare with standard Rf value.

$$(Rf) = \frac{\text{Distance travelled by solute}}{\text{Distance travelled by solvent}}$$

The obtained Rf value was found to be 0.63 and the standard Rf value of eugenol is 0.65 Fig.3. TLC of Eugenol

4. EVALUATION TESTS FOR CHEWING GUM-

A. Organoleptic Characteristics-

Color-

The color of herbal medicates chewing gum was checked manually by visual inspection.

Odor-

The odor of herbal medicated chewing gum was checked manually.

Texture-

The texture of herbal medicated chewing gum was determined manually by pressing the gum between thumb and the finger. The texture feel was characterized into sticky, good and solid mass.

Thickness (mm)-

The thickness of chewing gum is determined using a Vernier caliper scale. It ranges from 3 – 4.8 mm.

Elasticity-

Chewing gum's elasticity is one of its most important parameter. Elasticity is important for better patient compliance as well as proper release of the active ingredient from the product. The elasticity of herbal chewing was checked manually by stretching between two fingers.

Stickiness-

The formulated herbal chewing was placed on plane surface and a mass of 250 gm was hammered on it for 10 mins. After 10 mins, the sticking of mass to hammered surface was observed.

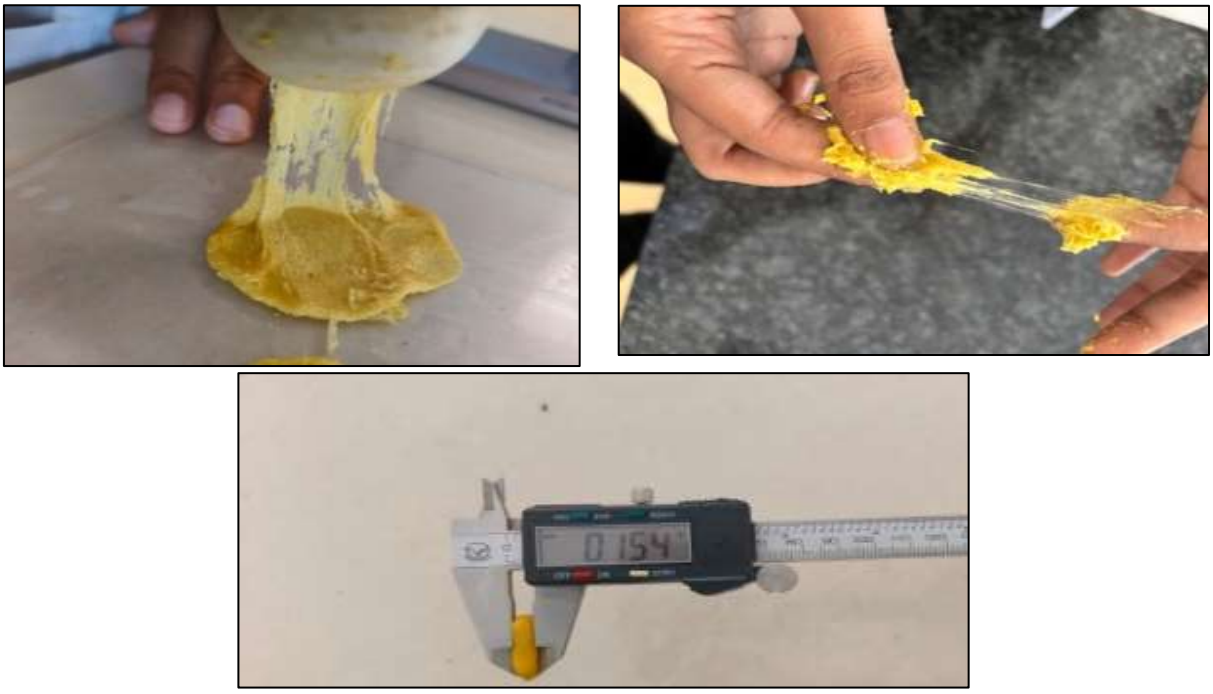

Fig no- 04- Determination of Stickiness, Elasticity & Thickness

B. Softening point-

Softening point of gum base was observed by heating the base in petri dish. The base's softening point is the temperature at which it begins to melt. It was found to be 54-57^{0}C. The standard softening point of herbal chewing gum is 55-60^{0}C.

C. % Drug Content-

To determine the % drug content in a herbal gum sample first obtain a calibration curve of eugenol oil

5. RESULT & DISCUSSION-

Calibration Curve of Eugenol Oil-

To obtain calibration curve of eugenol oil, the stock solution of eugenol was prepared by dissolving 10mg API in ethanol and make up 100 ml. Suitable dilutions were made from the stock solution (0.1, 0.2, 0.3, 0.4, and 0.5 µg/ml) and the absorbance was noted at 280 nm. A graph is obtained, Concentration v/s absorbance with straight line equation (y = mx + c)

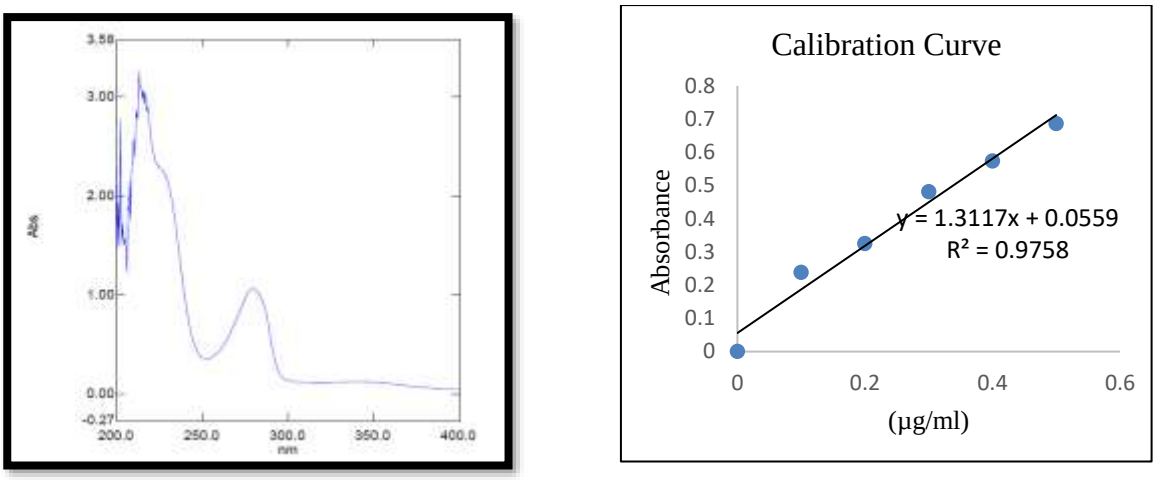

Fig. no 05- UV spectra of API

Table no 04– The Concentration & Absorbance of Calibration curve

Concentration (µg/ml)	Absorbance
0	0
0.1	0.238
0.2	0.325
0.3	0.481
0.4	0.573
0.5	0.686

Process:

Now for % drug content, one gram of formulation taken in mortar, to this about 20ml of 6.8 phosphate buffer was added and triturate. This was transferred to conical flask. About 30ml of 6.8 phosphate buffer was added to this and shaken well for about 3 hours using orbital shaking incubator at 100rpm. Then it was filtered and the filtrate was made up to make with the same

buffer solution. Suitable dilutions were made, and the drug concentration was determined by measuring the absorbance at 280nm. Then substitute absorbance on the place of y in above straight line equation, the value for x will be obtained. Divide the value of x with the total drug in one gram of gum and multiply with 100. (%) drug content is obtained. The percent drug content was found to be 97.58%.

D. In- Vitro Release Test-

In vitro drug relies on testing apparatus for chewing gum, was a self-fabricated where the glass beaker was used as dissolution basket and magnetic stirrer with hot plate was used for stirring of herbal chewing gum and to maintain temperature of phosphate buffer that of human body. The sample was set to stirrer 50 cycles per min. In the glass cylinder of 900ml capacity, the temperature was maintained at 37±5.

Process:

The sample was hanged with a thread in a glass beaker and placed in 900 ml of PH 6.8 phosphate buffer solution in a beaker. At intervals (0, 2, 4, 6, 8, 10,12 and 14min.) 5ml of sample was withdrawn and replaced with 5ml of fresh PH 6.8 phosphate buffer Absorbance was recorded by ultraviolet spectrophotometer at 280nm. The % of drug released for herbal medicated chewing was determined. The maximum in-vitro release of drug from herbal medicated chewing gum should be not more than 15 mins.

Fig no 06- Self- Fabricated Dissolution Apparatus

Table no 05 - % Drug Release of API

Sr.no.	Time (min)	% Drug Release
1	0	0%
2	1	14.02%
3	2	27.54%
4	4	40.37%
5	6	52.48%
6	8	63.18%
7	10	75.79%
8	12	86.87%
9	14	98.23%

Table no -06 % Drug Release of Sample

Sr.no.	Time (min)	% Drug Release
1	0	0%
2	1	13.63%
3	2	25.15%
4	4	32.10%
5	6	45.65%
6	8	60.48%
7	10	83.77%
8	12	90.21%
9	14	97.15%

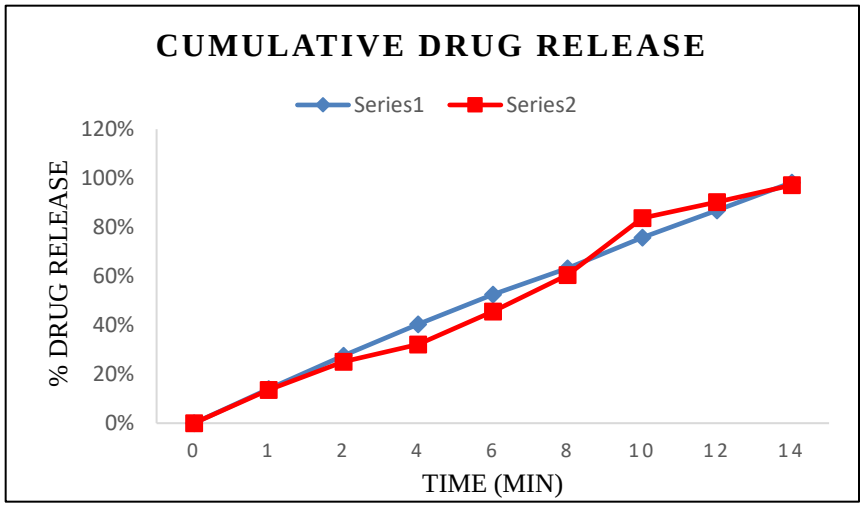

Fig no 07- Graph of Cumulative Drug Release

E. StabilityStudies

The batch F3 has shown maximum drug content and all acceptable parameters as compared to others batches and also maximum percentage cumulative drug release, stability studies were performed for the batch F3. In the stability studies, stability of gum was checked by keeping formulation 40^0C +-/75%, RH+-5% RH for 15 days in stability chamber.

Table no 07 - The Various parameters of Stability study & its observation

Sr.no.	**Properties**	**Observations**
1.	Color (initial)	Yellow
2.	Color (after 15 days)	Yellow
3.	Softening point (initial)	57.2^0C
4.	Softening point (after 15 days)	57.2^0C
5.	Texture	Good

F. Antimicrobial Activity on Streptococcus mutants:

The anti-microbial activity was carried out on Streptococcus mutants. To determine the activity cup plate method was used, in which the bacterial suspension was inoculated in culture media then the cup was formed and in that the drug was introduced. The plate was incubated to 24-48 hrs. The zone of inhibition was determined after incubation period. The zone of inhibition was found to be after 24 hrs.2.8 cm.

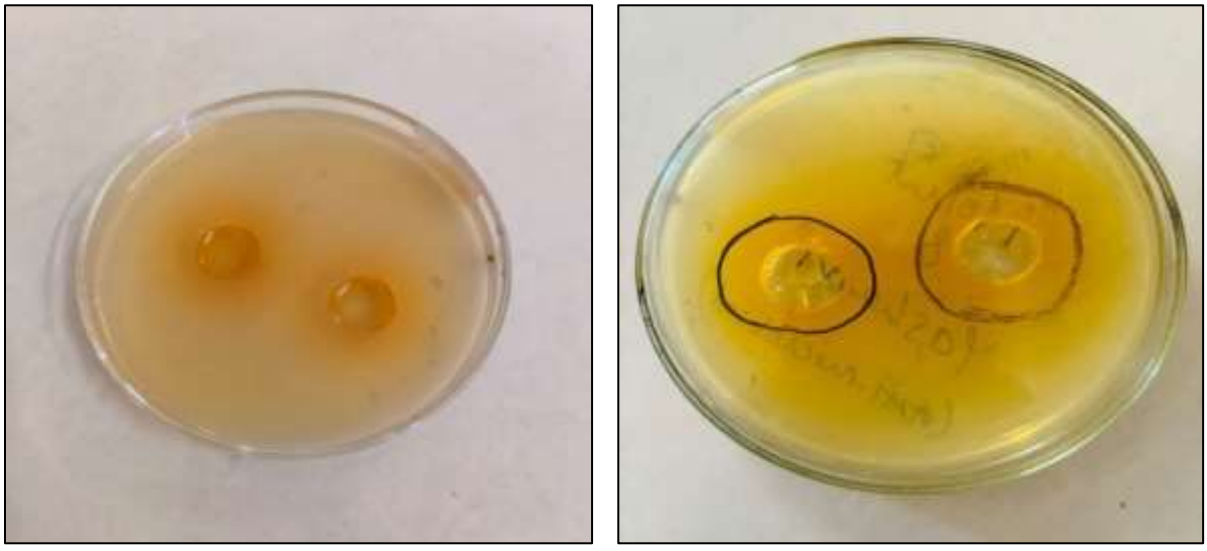

Fig no 08 – Zone of inhibition

Table no 08 - Chemical Evaluation Taste for Eugenol

Sr.no.	**Test**	**Result**
a. Chemical Tests	Bromine Water Test	Test Passed (Presence of Eugenol)
	Ferric Chloride Test	Test Passed (Presence of Eugenol)
	$KMnO_4$ Test	Test Passed (Presence of Eugenol)
b. TLC Analysis	Rf value	0.63
Evaluation tests for Chewing Gum		
A. Organoleptic Characteristics		
i.	Color	Yellow
ii.	Odor	Pleasant
iii.	Texture	Good
iv.	Thickness	3.81
v.	Elasticity	Good
vi.	Stickiness	Sticky
vii.	Weight	3 gm
B. Softening Point		$55\text{-}60^0C$
C. %Drug Content:		97.58%
D. In- Vitro Release Test:		At 14 mins drug release is 97.15%
E. Stability Studies		
i.	Color (initial)	Yellow
ii.	Color (after 15 days)	Yellow
iii.	Softening point (initial)	57.2^0C
iv.	Softening point (after 15 days)	57.2^0C
v.	Texture	Good
F. Antimicrobial Activity on Streptococcus mutants		The zone of inhibition was found to be 2.8 cm after 24 hrs.

6. FUTURE TRENDS-

Herbal medicated chewing gum not only offers clinical benefits but also is an attractive, discrete and efficient drug delivery system. People are becoming more interested in using natural remedies and herbs for health purposes. The properties of clove oil, like anti-microbial, anti- inflammatory and analgesic may attract health-conscious individuals to try clove chewing gums. A few decades ago, the only treatment for tooth decay was surgical procedure but now it can be prevented and treated with clove oil medicated chewing gums. Generally, it takes time for a new formulation to establish itself in the market and gain acceptance by patients, however herbal chewing gum of clove oil is believed to demonstrate its status as a practical and beneficial medication delivery technology. The potential of herbal medicated chewing gums for buccal delivery, fast onset of action and the opportunity for product line extension makes it an attractive delivery form. Hence after the pre-clinical and clinical studies the herbal medicated chewing gum of clove oil will get a wide range of market and will gain acceptance by geriatric, pediatric, and general populations.

7. CONCLUSION-

The present work was aimed to develop the herbal medicated chewing gum as novel drug delivery system for clove oil (Eugenol) having antimicrobial activity. Herbal medicated chewing gum formulations were prepared by using Natural food graded gum base, honey, sugar, coloring and flavoring agent was successfully prepared by using different concentrations of clove oil. Herbal chewing gum formulations were evaluated for different parameters such as organoleptic characteristics; stickiness, percent drug content, in-vitro drug release test, stability test and antimicrobial activity were performed. Herbal medicated chewing gums because of its simplicity, improved patient compliance, and ease of administration without water we can conclude that it will gain more acceptances by patients in the future, including geriatric, pediatric, and general populations.

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