"Formulation and evaluation of lozenges containing tannic acid for its antifungal activity against (candida albicans) and antibacterial activity against (streptococcus mutants)"

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Abstract:

The Tannic acid lozenges was successfully formulated and evaluated in the study. Initially, tannic acid lozenges was prepared using heating and congealing method. The formulation of tannic acid lozenges using different excipients with changing the concentration of Sucrose, Binder, Lubricant, Whipping agent, and Water. Evaluation result indicated that the content of sucrose, pectin, corn syrup, menthol, magnesium stearate, methyl paraben significantly influenced the properties of tannic acid lozenges. The F4 batch was identified as optimized batch. Which indicated good stability. The optimized F4 batch resulting tannic acid lozenges had a pH of 5.7 ± 0.1, Suitable for oral application. The appearance of medicated lozenges exhibited a rich brown coloration. The glossy surface observed were characteristic of hard candies. The texture hard and glassy. The Thickness was found to be in acceptable range i.e. 10.32 ± 0.48mm. The hardness was found to be 2.533 ± 0.15 kg/cm^2. The drug content was found to be 95.93 ± 0.24. The *In vitro* drug release study show that the drug was released about 93.226 ± 1.3% at 30 min. The medicated lozenges of tannic acid show the antifungal activity against (Candida albicans) with 22 mm zone of inhibition and Antibacterial activity against (Streptococcus mutans) with a concentration of 5 mg/ml, the zone of inhibition was 8 mm, which increased to 13 mm at 10 mg/ml.

Key Words: Hard candy lozenges, Tannic acid, Heating and congealing method, Antibacterial and Antifungal activity, Oral cavity infection.

Introduction: The French word "Lozenge," which describes a four-sided geometric diamond shape, is where the word "Lozenge" originates.[1] The invention of lozenges started in the 20th century, and since then, their commercial manufacture has remained due to their continuous market popularity. Lozenges are a firm, pleasant dose form that is administered orally. In order to have a local or systemic effect, they are intended to dissolve in the mouth or throat. As medicinal formulations, lozenge tablets offer a number of benefits. Drug delivery via the buccal, labial, gingival, and sublingual routes can all be delivered with lozenges as a dose form. They can also contain several medications for the treatment of chronic illnesses. Lozenges make it possible to load various kinds of active substances for oral systemic administration of drugs. Soft caramel-based lozenges, hard candy lozenges, and compressed tablet lozenges with medications for oral infections, sore throats, and mouth fresheners are all forms of over-the-counter medications. Tablets are the most widely used dosage form, and oral drug delivery is the most flavorful way to administer a variety of medications. Solid dosage types are popular because they are simple to administer, give precise dosage, enable self-medication, reduce discomfort, and above all ensure patient compliance. Due to physiological changes in those groups, dysphasia, or difficulty swallowing, is a prevalent issue in people of all ages, although it is especially common in youngsters and the elderly. The mentally ill, the uncompromising, and patients with motion sickness, nausea, acute allergic reactions, or coughing were among the other groups that had trouble ingesting traditional oral dosage forms. When water is rare it can occasionally be challenging to swallow conventional products. Beautiful, taste-masking formulations are now essential because of these issues, which resulted in the development of a novel type of solid oral dosage form.[2] Lozenges are medicinal dosage forms with flavors that are intended to be sucked and kept in the mouth or pharynx. They typically include one or more medications in a sweetened base. Lozenges are utilized for systemic drug absorption as well as to treat oropharyngeal symptoms, which are typically brought on by local infections. The purpose of medicated lozenges is to improve dosage form retention in the oral cavity, which boosts bioavailability, lessens stomach discomfort, and avoids first-pass metabolism. Lozenges are used for medications that are intended to be given gradually to provide a stable level of medicine and for patients who are unable to take solid oral dosage forms. Lozenges take around 30 minutes to dissolve, though this also depends on the patient, who regulates the rate of absorption and dissolution by sucking on the lozenges until they disintegrate. Analgesics, anti-tussives, aromatics, astringents, corticosteroids, decongestants, demulcents, and many more supplements are frequently used in lozenges. Lozenges should have a rather smooth texture, dissolve gently in the mouth, and have a round shape. Lozenges come in a variety of shapes, including rod-shaped, biconvex, octagonal, round, and flat.[3] The purpose of lozenges is to cool and purr the throat in a specific area. They are sometimes used to relaxed coughs. A lozenge is a solid dosage form that usually includes both a flavoring agent and a drugs medication.[1]

Tannic acid is a polyphenolic compound. It is one of the tannins that is available commercially. It has weak acidic properties. The nutgalls that insects produce on the twigs of some oak trees (Quercus infectoria and other Quercus species) contain tannic acid. They take it out and utilize it as medicine. It served as an antidote to various toxins in the past. Tannic acid is now utilized topically to treat poison ivy, fever blisters, diaper rash, and cold sores. In addition, tannic acid

can be taken orally and administered directly to treat cancer, painful joints, persistent coughs, bloody urine, chronic diarrhea, and bleeding. Its potential health benefits, such as its antibacterial, antifungal, and anti-inflammatory qualities. [4,5,6,7]

The fungus Candida albicans, commonly referred to as oral candidiasis, causes oral thrush, an infection of the mouth. Between 30% and 40% of people have Candida albicans, a common oral cavity bacteria. Oral candidiasis typically manifests as an adhesive, white, curd-like, encircling plaque in any part of the oral cavity. A common fungus in the mouth is called Candida. However, it can cause a number of symptoms if it grows too much. Pale white patches that are usually observed on the inside of your cheeks or the surface of your tongue are the result of oral thrush. It is typical for oral thrush to spread to the back of your throat, your gums or tonsils, or the roof of your mouth. While anyone can get an infection from oral thrush, babies and the elderly are more likely to have it. immune systems that are underdeveloped or impaired in a variety of people [8]

The main cause of periodontal disease, also called gum disease, is the buildup of bacteria and plaque on teeth. Plaque is a sticky film made up of bacteria that forms on teeth and gums. If it is not removed by regular brushing and flossing, it can harden into tartar, which further irritates and inflames the gums. Dental plaque contains bacteria that can both produce acid (acidogenic) and survive in acidic environments (aciduric). While many different bacterial subspecies have been linked to caries, Streptococcus mutans is the main bacterium involved in the development and progression of this disease, especially when combined with lactobacilli. Streptococcus mutans is a Gram-positive coccus (spherical bacterium) that is facultatively anaerobic, meaning it can survive with or without oxygen. It is also known for being acidogenic, meaning it can produce acid, and aciduric, meaning it can grow in acidic conditions. Because it breaks down carbohydrates to create acids that demineralize tooth enamel, these characteristics make it well adapted to causing dental caries, or tooth decay. [9,10]

MATERIALS AND METHODS:

Materials

The Tannic acid was procured from S D LAB Mumbai-2 (INDIA), Sucrose and corn syrup was purchased from S D LAB CHEM MUMBAI, Pectin was procured from LOBA CHEMIE LABOATORY REAGENTS AND FINE CHEMICALS, Menthol, Magnesium stearate and Methyl paraben was purchased from RESEARCH- LAB FINE CHEM INDUSTIRES Mumbai.

Methodologies:

A. PREFORMULATIONS:

1. Organoleptic characteristics of drug

The organoleptic characteristics of the drug were evaluated through visual inspection for colour and smell assessment for odour.

2. Melting point determination.

Melting point was determined by using the capillary tube method. Firstly, the dru was filled in the capillary tube sealed at one end and placed in melting point apparatus and slowely the temperature was increased and the temperature at which solid starts converting into liquid was recorded.

3. Solubility determination of drug

The solubility of drug was assessed in water, ethanol, acetone and a pH 6.8 buffer solution. Drug was weighed and added to a specific volume of each solvent. The mixture were stirred continuously at room temperature. After stirring, the solution were observed for complete dissolution or the presence of undissolved particle, indicating solubility.

4. UV analysis of Tannic acid

Preparation of Standard stock solution:

A stock solution was prepared by dissolving 50 mg of Tannic acid in 50 ml of phosphate buffer (pH 6.8) to obtain a standard stock solution with a concentration of 1 mg/ml.

Determination of λmax:

To determination of λmax of Tannic acid at a concentration of 10μg/ml, the sample was dissolved in a phosphate buffer solution with a pH of 6.8 and analysed using a UV-Vis

spectrophotometer. The instrument was set to scan from 200 to 400 nm. The obtained spectrum was documented, evaluated and confirmed the identity and purity of Tannic acid.

Determination of Calibration curve:

From the stock solution, 5 ml was transferred into a 50 ml volumetric flask and diluted to the mark with phosphate buffer (pH 6.8) to create a 100μg/ml working solution. . A liquots of 1ml, 2ml, 3ml, 4ml, 5ml of this 100 μg/ml solution were then taken and transferred into separate 25 ml volumetric flask. Each aliquot was diluted to the mark with phosphate buffer (pH 6.8) to produce solutions with final concentration of 4 μg/ml, 8 μg/ml, 12 μg/ml, 16 μg/ml, and 20 μg/ml, respectively. These prepared solutions were subsequently analyzed using a UV-Vis spectrophotometer, with absorbance measured at the λmax for Tannic aicd. The absorbance values obtained were plotted against the corresponding concentrations to construct a calibration curve. This calibration curve was used to confirm the linear relationship between concentration

and absorbance, which was essential for the accurate quantitative analysis conducted in the study.

5.Drug and excipient compatibility study by FTIR:

The FTIR analysis for drug-excipient compatibility was conducted by first preparing samples of Tannic acid as well as the excipient. Physical mixture was also prepared by mixing drug with the excipient in 1:1 ratio. The FTIR spectra were recorded over a wavelength range of 4000 to 400cm^{-1} The spectra of the drug were compared with those of the physical mixture to identify any shifts, changes, or interactions, indicating potential incompatibilities between the drug and the excipient.

Method of Preparation of Medicated Tannic acid lozenges:

Heating and congealing method

- **Steps:**
  - Preparation of sugar syrup
  - Addition of excipients
  - Incorporation of API
  - Cooking to hard crack stage
  - Packaging

A heating and congealing process is used to prepare the lozenges. In a beaker, the necessary amounts of sugar are first dissolved in water to make a syrup basis. After that, this combination is warmed on a hot plate. Until the syrup thickens, the temperature is kept between 105°C and 110°C. All excipients are manually added to the sugar base and properly mixed while heating for another half hour. Drug (Tannic acid) is added to the mixture after 45 minutes of heating, and the mixture is cooked through to the hard crack stage. After cooling and lubricating the mold, the thickened syrup foundation is poured into it and let to set for ten to fifteen minutes. Finally, the lozenges are taken out of the mold and allowed to pack and air dry.

2^3full factorial design for formulation of medicated lozenges[54]

2^3 full factorial design is the design of experiments (DOE) test setup through which each three factors were studied at two different levels for their interaction effects on the response variable The 2FI (Two-Factor Interaction) factorial model suggested by the Design Expert software, was used to analyze how each factors interacted and influenced the response together. This model helped to identify which factor interactions significantly influenced the results, showing

which factors and combinations had the most effect on the response. This was essential for understanding the complex relationships in the factorial design experiments.

Formulation of medicated lozenges using 2^3 full factorial design.

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Tannic acid (mg)	40	40	40	40	40	40	40	40
Sucrose (gm)	12	10	12	12	10	10	10	12
Pectin (mg)	80	60	60	60	80	60	80	80
Corn syrup (ml)	2	2	2	1	2	1	1	1
Menthol (mg)	10	10	10	10	10	10	10	10
Magnesium stearate (mg)	25	25	25	25	25	25	25	25
Methyl paraben (mg)	20	20	20	20	20	20	20	20
Distilled water (ml)	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

Evaluation medicated tannic acid lozenges:

1. Appearance: To make sure the medicated lozenges were symmetrical, smooth, and uniformity and color consistency were first examined with the naked eye. The absence of any cracks, dents, or deviations was confirmed.

2. Texture: The medicated lozenges were examined visually for consistency and smoothness, looking for any indications of graininess or uneven texture.

3. pH:

The medicinal lozenges were first dissolved in a tiny amount of distilled water to determine their pH. A digital pH meter (REMI, India) was used to measure the pH of the resultant solution after the lozenges had completely dissolved. The pH reading revealed whether the lozenges was acidic or alkaline.

4. Weight variation test:[11]

Each of the twenty medicated lozenges was weighed separately using digital analytical weighing balance (Adventure, Ohaus, USA), the total was weighed, and the average weight was calculated. The individual weights were compared to the average weight. This criterion, which is similar to the dosage form for tablets, according to USP standards, the batch passed

the weight variation test if no more than two lozenges were outside the ±5% limit, and if no lozenges differed by more than twice this limit. The percentage variance for each lozenge was calculated using the formula:

$$weight\ variation = \frac{Average\ weight\ - Initial\ weight}{Average\ weight} \times 100$$

5. Thickness :[12]

Variations in the thickness of medicated lozenges can cause issues with counting and packaging. as well as result in weight variations beyond acceptable limits. The thickness of a medicated lozenges was measured using a digital vernier caliper (Zart Electronics). Thickness values were recorded in millimeters.

6. Hardness:[13]

The lozenges required a certain amount of strength or hardness, to withstand mechanical shocks of handling during its manufacture, packaging and transport. Hardness of the lozenges is defined as the force required in breaking a lozenges in a diametric compression test. It was measured using Monsanto tablet hardness tester (Rolex scientific engineers Limited). The values were expressed in kg/cm^2.

7. Drug content: The drug content for the medicated lozenges was determined by using the UV Spectrophotometric technique. The stock solution of formulation was prepared by dissolving it into 100ml phosphate buffer with a pH of 6.8. 1ml stock solution was pipette out and transfer into 100ml capacity of volumetric flask. The solution was diluted to 100ml with phosphate buffer (pH 6.8). The resulting solution was tested using a UV-Vis double beam Spectrophotometer-2202 TS (Systronics India Ltd., Mumbai) using spectrophotometry at a wavelength of 273nm.

8. *In vitro* dissolution studies:[14]

The dissolution Parameters details:

- Apparatus: USP Dissolution apparatus, Type II (Paddle).
- Medium: 900ml of buffer solution of pH 6.8.
- RPM: 50.
- Temperature: 37°C ±0.5°C.
- Sampling interval: 5, 10, 15, 20, 25 and 30.
- Sample withdrawn: 1 ml.
- Wavelength: 221nm.

- Instrument: UV-Vis double beam Spectrophotometer-2202 TS (Systronics India Ltd., Mumbai)

The in-vitro dissolution tests of medicated lozenges were carried out with dissolution apparatus USP Type II (paddle). The volume of dissolving medium (buffer solution of pH (6.8) [58,59] used was 900 ml and the temperature was maintained at 37±0.5°C. The speed of the paddle was fixed at 50 rpm. One medicated lozenge was put in every jar of dissolution equipment. 5 ml of sample from each jar was taken at every 5 minutes intervals up to 30 minutes and same volume of dissolving medium was replaced to each dissolution jar, so that volume of the dissolving medium was maintained to 900 ml. The sample was filtered and diluted with dissolving medium and the quantity of Tannic acid released from medicated lozenges was measured through UV Visible spectrophotometer at 273 nm using buffer solution of pH 6.8 as blank.

9. Stability studies:[15]

Stability testing was performed for the optimized batch of medicated lozenges formulation by using environmental stability chamber (REMI, Vasai, India) at 40±2°C/75%+5% RH for 6 months. The chosen formulation batch of medicated lozenges was kept at 40±2°C/75%+5% RH for 6 months and for confectionery products like lozenges, monitoring hardness, drug release and disintegration time were analyzed at specific intervals of time (0, 1, 2, 3, and 6 months).

D. ANTIFUNGAL ACTIVITY [16]

To assess the antifungal activity against Candida albicans, the Stepwise details of antifungal activity were as follows

- **Materials were used for the study**

Sterilized Petri plates, cotton plugs, and micropipettes. Sterile syringes, sterile test tubes, sterile volumetric flasks, sterile spatula, sterile cork borer, and spreader.

- **Microorganism used for the antifungal study**

Candida albicans culture was obtained from Yashwantrao Chavan Institute of Science College, Satara. The process is as follows:

- **Agar well diffusion method:** The SDA was melted, cooled and poured into sterile petri dishes and allowed it to solidify. The solidified SDA plates were inoculated with the Candida albicans suspension by swabbing the surface. Using a sterile cork borer, three

wells (6 mm in diameter) were made on the agar surface. Three wells were filled with sterile water (negative control), Ketoconazole (positive control) and optimized medicated lozenges solution (test solution) respectively and labelled accordingly. The plate was incubated at 37°C for 24-48 hours. After incubation, the diameter of the inhibition zones around each well was measured with scale. The Inhibition zone (mm) of optimized medicated lozenges formulation was compared with that of standard solution.

E. ANTIBACTERIAL ACTIVITY [17,18,19]

To assess the antibacterial activity against Streptococcus mutans, the Stepwise details of antibacterial activity were as follows

Equipment were used for the study

Analytical Balance, Vernier caliper, Water bath, Incubator- 20 to 25 ° , Laminar Air Flow, Incubator- 30 to 35 "C, Colorimeter, Refrigerator-2 to 8 °C, Zone Reader, Cyclomixer, Sonicator, Micro-pipettes.

Microorganism used for the antibacterial study

Streptococcus mutants culture was obtained from Biocyte Microbiological Testing Center, Sangli. The process is as follows:

- **Analysis:** The volume of solution added to each cylinder or cavity must be uniform and sufficient almost to fill the holes when these are used.
  Add 100 µl 1mg/ml Solution A to agar cup labelled as STD.

Add 100 µl 1 mg/ml = Solution B to agar cup labelled for each compound ID labelled on plate. Add 100 µl DMSO to agar cup labelled as N (Negative).

Leave the dishes or plates standing for 15-20 min. at 2-8°C or as appropriate, as a period of pre- incubation diffusion to minimize the effects of variation in time between the applications of the different solutions. Incubate them for about 24-48 hours at the temperature 30-35°C for bacteria and 20-25°C for yeast and mould. After completion of incubation accurately measure the diameters or areas of the circular inhibition zones and record the results.

Result and discussion:

A. Preformulation study:

1. Organoleptic characteristics of drug

Tannic acid was usually inspected for colour and odour. The result of organoleptic characteristics are shown in Table 8.

Table 1: Organoleptic characteristics of Tannic acid

Sr. No	Parameters	Observation
1	Colour	Light-yellowish
2	Odour	Earthy or Musty
3	Physical state	Solid

2. Melting point determination:

- **Using the Capillary Method**

The reported melting point is 218ºC and the melting point of the drug procured was determined in the range of 215ºC-220ºC, which complies with the reported value.

3. Solubility determination:

The drug are freely soluble in ethanol, acetone, water and buffer solution pH 6.8

4. UV analysis:

Determination of λmax of Tannic acid:

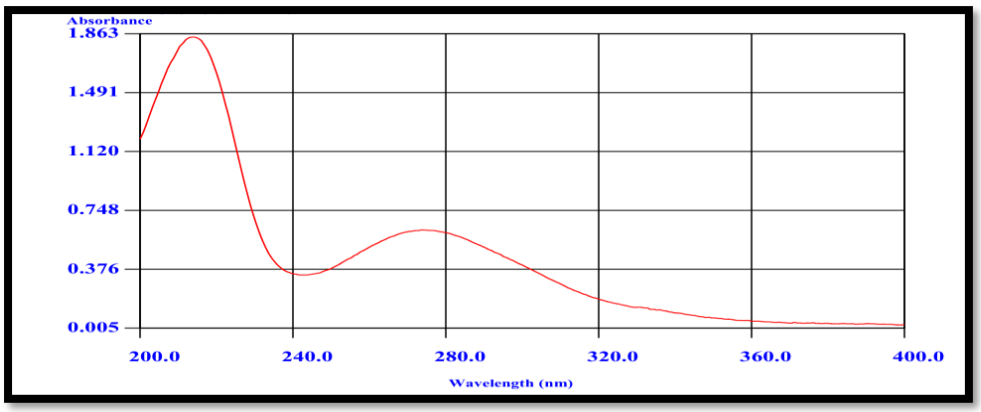

Fig 1: UV spectra of Tannic acid

The UV spectra of Tannic acid was obtained and the maximum absorbance was found at 273 nm. The result of λmax of Tannic acid shown in Figure 1.

B. EVALUATION OF OPTIMIZED BATCH

Table 2: Results of Optimized Batch

Parameters	Thickness (mm)	Hardness (kg/cm2)	Weight Variation (%)	Drug Content (%)	Drug release (%)
Results	10.32 ±0.48	2.533 ±0.15	2.44 ±0.08	95.93 ±0.24	93.226 ±1.3

All Values are expressed as Mean ± SD

1. Appearance: The medicated lozenges examined in this study exhibited a rich, brown coloration. The color was uniformly distributed throughout the medicated lozenges.

2. Texture: The texture of the medicated lozenges was hard and glassy, as expected from hard candies. When held, the medicated lozenges feel solid and firm.

3. pH: The pH of medicated lozenges was found to be 5.7 which is often desirable for a tangy and refreshing taste without being overly sour.

4. Thickness: The uniform thickness of the medicated lozenges observed in this study indicated that the production process is reliable, implying the use of adequate quality control procedures. The average thickness of optimized batch of medicated lozenges was found to be in acceptable range i.e. 10.32 ±0.48 mm.

5. Hardness: Hardness was measured by a Monsanto hardness tester. The average hardness of optimized batch of medicated lozenges was found to be in acceptable range i.e. 2.533 ±0.15 kg/cm2.

6. Weight variation: Optimized lozenges batch succeeded the weight variation test since the results were between the permissible variation limit (±5%) of the lozenges.

7. Drug Content: Average drug content of optimized medicated lozenges formulation batch was found to be 95.93 ±0.24.

8. In vitro drug release study: The percentage of drug released over a 30-minute period. From drug release study it was observed that the drug was released about 93.226 ±1.3% at 30 min.

C. ANTIFUNGAL ACTIVITY AGAINST CANDIDA ALBICANS

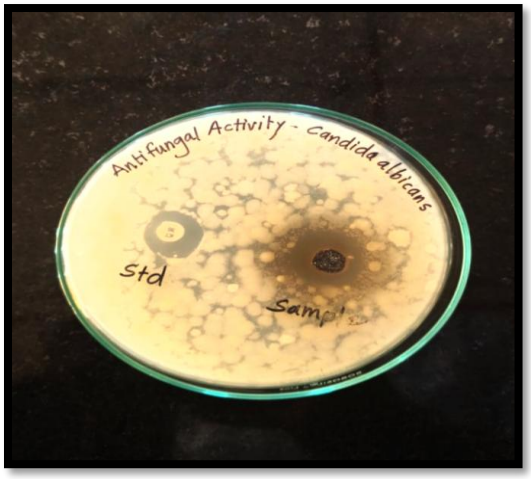

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Figure 2: Antifungal activity of optimized medicated lozenges against candida albicans

- Standard antifungal drug= Ketoconazole
- Test= Optimized medicated lozenges

Figure 2 shows the zones of inhibition for optimized medicated lozenges against candida albicans. Zone of inhibition for optimized medicated lozenges 22 mm respectively. Table 3 illustrates the zones of inhibition for Optimized medicated lozenges and Ketoconazole. Based on the results medicated lozenges formulation confirmed the antifungal activity against candida albicans. In the case of the medicated lozenges, the combination of other excipients may work together to enhance the overall antifungal activity, leading to a larger zone of inhibition.

Table 3: Data of Zone of inhibition

Sr. No.	Sample Name	Concentration (µg/ml)	Zone of Inhibition (mm)
1	Medicated lozenges	100	22
2	Standard (Ketoconazole)	30	20

D. Antibacterial Activity Against Streptococcus Mutants

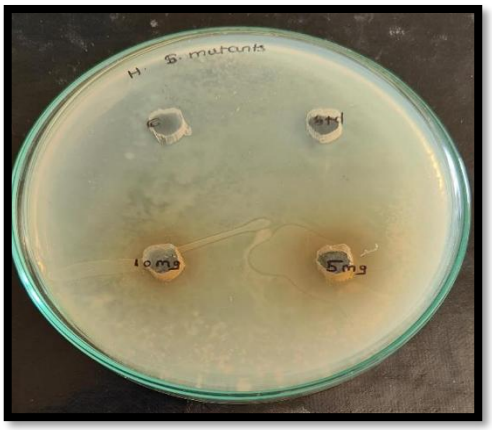

Figure 3: Antibacterial Activity Against Streptococcus Mutants

- Standard antibacterial drug = Streptomycin
- Negative control= Distilled water
- Test = Optimized medicated lozenges

Figure 3 shows the zones of inhibition for optimized medicated lozenges against Streptococcus mutants. The tested sample demonstrated dose-dependent antibacterial activity against Streptococcus mutans. At a concentration of 5 mg/ml, the zone of inhibition was 8 mm, which increased to 13 mm at 10 mg/ml. Although this activity is lower than the standard antibiotic streptomycin (25 mm at 1 mg/ml), it indicates that Sample-413 possesses moderate antibacterial potential

Table 4: Data of Zone of inhibition

Sr.No	Sample Name	Concentration (mg/ml)	Zone of Inhibition (mm)
1	Medicated lozenges	5	08
		10	13
2	Standard (Streptomycin)	1	25

CONCLUSION: The medicated Tannic acid lozenges was successfully formulated and demonstrated strong potential as antifungal agent and antibacterial agent. The possible interaction between the drug and excipient was determined by FTIR spectroscopy which indicated that there was no interaction between the chosen drug and excipients. Lozenges were successfully prepared by heat coagulating method. In vitro drug release indicated that the drug release was most extreme in formulation F4 (93.226 ±1.3) at 30 min. The optimized medicated lozenges showed effective antifungal activity against Candida albicans and antibacterial activity against Streptococcus mutants and greater stability.

CONFLICT OF INTEREST: The authors declare that there are no conflicts of interest associated with this work

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