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DESIGN AND EVALUATION OF MUCOADHESIVE ANTIMICROBIAL DENTAL GEL OF *LANTANA CAMARA* LINN ROOTS EXTRACT

Dilnawaz Pathan[1], Akula Niharik[a2], Kondampalli Priyanka[3], Kushangi Shrivastava[4], Dr.Mahendra Singh solanki[5], Mr. Prabhakar Singh Tiwari[6], Arindam Chatterjee[7],Dr. Anant Kumar Patel[*8]

[1]Department of Pharmaceutics, KJEI's Trinity College of Pharmacy, Pune. Maharashtra.India.
[2]Associate Professor, SreeDattha Institute of Pharmacy
[3]Assistant professor, SreeDattha Institute of Pharmacy
[4]Intern, Sri Aurobindo college of Dentistry, SAIMS Campus, sanwe road near MR 10, Bhanwarsala, Indore (M.P.)
[5]Assistant Professor, Dept.of Pharmaceutical chemistry, B.N. Institute of pharmaceutical sciences, Bhupal Nobles University. Udaipur
[6]Associate Professor, Rajiv Gandhi Institute of Pharmacy,Faculty of Pharmaceutical Science & Technology, AKS University Satna, MP-India
[7]Professor, Institute of Pharmacy, Assam Don Bosco University, Tepesia, Assam, India
[8]Professor, Swami Vivekanand College of Pharmacy, Indore

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Abstract:
In order to prevent and treat dental plaque, dental caries, and periodontitis, the current study aims to formulate and evaluate a herbal mucoadhesive antimicrobial dental gel using *Lantana camara* Linn'sroots extract. The disintegration of teeth caused by acid, produced by bacteria such as *Streptococcus mutans* is known as tooth decay, dental caries, or cavity. Globally, dental caries has been the most prevalent issue related to oral health. Dental caries is characterized as a pathological process of external origin that is confined, post-eruptive, and involves weakening of the hard tooth tissue before a cavity form. The extract from the roots of *Lantana camara* Linn is obtained by maceration process with solvent ethanol and water (60:40 v/v). TheFolin-Ciocalteu spectrophotometric technique was used to determine the extract's total phenolic content. Using polyethylene glycol (PEG) 400 as a penetration enhancer and carbopol 934 as a bioadhesive polymer, a mucoadhesive gel was formulated. Several characteristics, including appearance, pH, viscosity, spreadability, and *in vitro*mucoadhesion studies, were assessed for the dental gel formulation. Using the disc diffusion method, the dental gel's antibacterial activity against *Streptococcus mutans* was tested on Mueller Hinton agar media. Additionally, a stability study spanning a month is examined. The

Mucoadhesive Dental gel of *L. camara* roots extract has the desired qualities in terms of color, odor, consistency, grittiness, uniformity, stickiness, and homogeneity, according to the results of a physiochemical evaluation research. The developed oral gel's assessment criteria show that it is a mucoadhesive, stable, and effective drug delivery system that contains antimicrobial phytoconstituents to prevent periodontitis, tooth caries, and plaque development.

Keywords: Herbal, *Lantana camara,* Roots, Mucoadhesive, Dental gel, *Streptococcus mutans,* Antimicrobial activity, Folin-Ciocalteu, Total Phenol Content.

Introduction

According to WHO (2023), dental problems are the most common chronic illnesses globally and a significant financial burden on health care systems. The term "periodontia" refers to a group of pathological disorders marked by inflammation and degradation of the dental cementum, alveolar bone, gums, and periodontal ligaments (Vyas et al., 2000). It is a localized inflammatory response brought on by subgingival plaque and bacterial infection of a periodontal pocket (Haffajee and Socransky, 1986). The disintegration of teeth caused by acid produced by bacteria such as *Streptococcus mutans* is known as tooth decay, dental caries, or cavity.

Worldwide, dental caries has been the most prevalent issue related to oral health. Dental caries is characterized as a pathological process of external origin that is confined, post-eruptive, and involves weakening of the hard tooth tissue before a cavity form. Left untreated, dental caries can lead to pain or annoyance, tooth loss, and poor oral functionality, all of which can lower quality of life (Alshahrani et al., 2018). Cavities and demineralization of dental enamel are the results of acid generation by bacteria that ferment carbohydrates, which is the cause of dental caries. The bacteria live on the dental enamel as a component of the oral biofilm, often known as the dental plaque (Nguyen et al., 2015). This viewpoint makes use of a variety of treatment and preventive techniques, such as lasers, ultrasonic scalers, manual scaling and root planning, gingival irrigations, and oral hygiene. The non-surgical treatment of periodontal infections involves the use of mechanical instrumentation, complete mouth cleaning, host modulation, and antimicrobial medication (Tariq et al., 2012). The adverse effects of antibiotics and antibacterial compounds have led dental product manufacturers to turn to herbal remedies as a way to mitigate these effects. According to certain research, natural herbs may be able to prevent periodontitis from developing. (Ananthathavam and Ramamurthy ,2014)

The plant*Lantana camara*Linn commonly referred to as red or wild sage belongs to family Verbanaceae. This woody straggling plant, which has flowers in the hues pink, red, yellow, violet, and white, is the most common species in the genus (Kumarasamyraja et al., 2012). One of the most widely distributed medicinal weeds in the world is *Lantana camara*. In traditional medicine, plant extracts have been used to treat a variety of illnesses, including cancer, tetanus, rheumatism, eczema, asthma, chicken pox, measles, ulcers, swellings, and tumors. Additionally, there is documented use for it as an antiseptic for wounds, a cure for skin rashes, and an external treatment for scabies and leprosy(Barreto et al., 2010). This plant's leaves have been utilized as a tonic, expectorant, antitumoral, antimicrobial, and antihypertensive agent (Taoubi et al., 1997). The roots are used to treat dermatitis, eczema, associated mycotic infections, rheumatism, malaria, and skin rashes. They are also useful in managing respiratory tract infections, such as influenza and tuberculosis (Verma et al., 2013 and Chharba., 1993). The fruits are useful in treating fistula, pustules, tumors, and rheumatism (Chopra, 1956; CSIR, 1992). The hill tribes employ a decoction of fresh roots as a gargle for all kinds of dysenteryand also forodontalgia(Sharma et al.,1988).Pharmacological activities against alloxan-induced diabetic rats, as well as hepatoprotective, thrombin inhibitory, termiticidal, antimotility, antifilarial, in

vitro cytotoxic, and antimicrobial properties, have been reported for various parts of the plant (Verma et al., 2013).

Roots are a rich source of oleanolic acid (OA), which can be found there as aglycones or free acid (Hart et al., 1976). In fact, the rootlets and root bark of *L. camara*provide a plentiful (2%) supply of oleanolic acid (Misra et al. 1997), which is the focus of following research due to its wide applicability similar to use for anti-cancer, anti-AIDS, anti-inflammatory, antimicrobial activity, and hepatoprotective (Sharma et al, 2007).

Mucoadhesive gel formulation delivered locally will have a longer formulation residence period, absorb faster, enhance patient compliance, and be easier to administer (Mathew, 2015). Consequently, an attempt is made in the subsequent study to develop and evaluate an antimicrobial mucoadhesive dental gel containing an extract from the roots of *L. camara* for the purpose of preventing and treating dental plaque, dental caries, and periodontitis.

Materials and Methods

Collection and authentication of plant material

Roots of *L. camara* were procured from the Botanical garden of Career point University. Kota, India.The roots of *L. camara* were validated and an herbarium specimen was stored for future reference.

Chemicals

Carbopol 934, polyethylene glycol (PEG 400), FolinCiocalteu reagent, methylparaben, propylparaben, triethanolamine, sodium carbonate and gallic acid were obtained from LobaChemie Pvt. Ltd, Mumbai.

Preparation of extract

After being cleansed, the roots of *L. camara* were rinsed. After rinsing, the roots were cut into small pieces and shade-dried. After being pounded into a fine powder and sieved using a 20-mesh screen, the powder was kept fresh in an airtight glass container. To produce the *L. camara* root extracts, a small modification was made to the procedure described in the literature (Barreto et al., 2010). The maceration procedure was utilized to prepare the *L. camara* root extract. 500 g powder of roots of *L. camara* were placed in a flask filled with hydroethanolic solvent (Ethanol and water in a 60:40 ratio) and left to stand at room temperature for 72 hours. Under reduced pressure, the hydroethanolic solvent was extracted from the extract using a rotary vacuum pump extractor. After being weighted, the extract was preserved for further process

Total phenolic content

Using the FolinCiocalteau reagent, the total phenolic content of the *L.camara* root extract was calculated (Singleton and Rossi, 1965). By combining 1 ml aliquots of 20, 40, 60, 80, and 100 µg/ml of gallic acid solutions with 5.0 ml of tenfold-diluted FolinCiocalteu reagent and 4.0 ml of sodium carbonate solution (75 g/l).. After 30 minutes, the absorbance was measured at 765 nm and the calibration curve is drawn as shown in Figure no. 2. The same reagents with same procedure, were combined with 1ml (1gm/100ml) of *L. camara* root extracts. Using the below mentioned formula, the absorbance was measured after one hour to ascertain the extract's total phenolic content.

$C = C_1 \times V/m$

where C = total phenolic content in mg/g, in GAE (Gallic acid equivalent),

C_1 = concentration of Gallic acid established from the calibration curve in mg/ml,

V = volume of extract in ml,

and m = the weight of the plant extract in g.

Preparation of gel formulation

In order to prepare the mucoadhesive oral gel, first a solution of methylparaben and propyl paraben was made in water. Carbopol 934 was then steeped in the water for 24 hours, and the pH of the mixture was then adjusted with triethanolamine to 6.8. Solutions of mentioned amount of *Lantana camara* root extracts in 5 mL of ethanol, was added to the gel and thenrequired amount of polyethylene glycol (PEG 400) was added. Table no. 1 displays the mucoadhesive gel's composition. Figure no. 1 shows the prepared herbal dental gel of *Lantana camara* roots extract

Table no.1: Composition of Oral Mucoadhesive herbal dental gel of *Lantana camara* roots extract

S. No.	Ingredients	Quantity Taken
1	*L. camara* extract (mg)	50
2	Carbopol 934 (g)	0.6
3	PEG 400 (ml)	13
4	Methyl paraben (g)	0.18
5	Propyl paraben (g)	0.02
6	Ethanol (ml)	5
7	Triethanolamine (ml)	q.s
8	Distilled water up to (ml)	100

Figure no. 1. Mucoadhesive dental gel of *L.camara* root extract

Evaluation of Mucoadhesive Dental gel

Antimicrobial activity

Preparation of microbiological culture media

The ampoule containing the freeze-dried culture of the *S. mutans* bacterial strain was obtained. Ampoule handling procedures included taking the necessary safety measures and disinfecting the

ampoule's surface. Microbiological culture media were filled with 2 ml of isotonic solution after the ampoule was gently broken open. From the undiluted solution, serial dilutions were made.

Preparation of Mueller hinton agar media

The 38 g of media was suspended in 1000 ml of distilled water and brought to a boil to dissolve it entirely. After autoclaving it for 15 minutes at 15 lbspressure, 121 °C, and cooling it to 45 to 50 °C, it was properly mixed and put into sterile petri dishes(Maragathavalli et al., 2012).

Determination of antimicrobial activity

The dental gel of *L. camara* roots extract was tested for antibacterial activity against the *Streptococcus mutans* bacterial strain using the disc diffusion method. Mueller Hinton agar medium was utilized to screen for *in vitro* antibacterial activity. Following sterilization, the media was aseptically moved to sterile petridishes and left to stand for 20 minutes. After agar plates solidified, 1ml of bacterial culture was dispersed across their surface using a sterilized glass spreader. Whatman filter paper sterile discs were utilized in antibacterial investigation. *L. camara* roots extract dental gel was used to impregnate the discs(Onywer et al., 2016) as sample, solution of chlorhexidinegluconate (0.2 percent w/v) as positive and ethanol as a blank (Fini et al., 2011) The plates were incubated at 37 °C for 24 hours. After the incubation period, the zones of inhibition that developed around the disc were measured using a clear scale (in millimeters).

Statistical Analysis

The Mean zone of inhibition was calculated as means ± SD. The significance was evaluated by analysis of variance (ANOVA) using Microsoft Excel program.

Physical appearance of gel formulations

Gel formulation was visually inspected for colour, odour, consistency, grittiness, uniformity stickiness and homogeneity (Aslani et al., 2013).

Gel formulations were visually inspected for clarity, color, homogeneity, consistency and presence of the formulations, a small quantity of gel was pressed between the thumb and the index □ngers and the consistency of the gel was noticed

pH measurement

A pH meter that was calibrated with standard buffer solutions at pH 4 and pH 7 before to each usage was used to measure pH. A precise gram of the gel mixture was weighed and then dispersed in 10 milliliters of distilled water. Ten minutes before the room temperature reading was taken, the electrode was placed into the sample. The formulation's pH was measured three times, and the average result was computed(Saleem et al., 2010).

Viscosity

The produced gel's viscosity was assessed using spindle number 6 on a Brookfield viscometer set at 100 rpm. At room temperature viscosities were recorded.(Aslani et al., 2013).

Spreadability

For patient compliance, spreadability is a crucial dental formulation feature. A glass plate was placed over the second glass plate, and approximately 0.5 g of gel was spread out inside a pre-marked circle with a diameter of 1 cm. One hundred grams of weight was permitted to settle on the top glass plate.The increase in the diameter due to the spreading of the gels was noted (Helal et al., 2012).

Mucoadhesive strength measurement:

After calibrating the tensiometer (Fisher), the gel was exposed to sodium alginate, a mucin replacement, for five minutes. Then how much force was needed to separate the gel from the solution surface at a speed of 0.2 inch/min was calculated in dyne/cm^2(Sahu et al., 2021).

Stability study

Centrifugal test

After 48 hours of preparation, the formulation's stability was investigated against the centrifugal force. A centrifugal device was used to transfer the formulation into a tube and centrifuge it for 60 minutes at 2000 rpm. The formulation's stability was assessed at a different time interval(15, 30 and 60 min) (Aslani et al., 2013).

Thermal test

Three samples were kept at different temperatures for 48 hours following production in order to test the oral gel's stability in various weather and seasonal circumstances (4°C, 25°C, and 45°C). The gel formulation was assessed after 24 hours, a week, and a month(Aslani et al., 2013).

Freeze and thaw test

48 hours after manufacture, 15 g of oral gel was placed to -8°C for 48 hours, followed by six periods of 25°C for 48 hours to examine the stability of the gel at extremely cold temperatures. Then the gel formulation's stability was assessed (Aslani et al., 2013).

Cooling and heating test

48 hours after preparation, 15 g of gel was placed at 45°C for 48 hours, followed by 48 hours at 4°C for six periods, to test the formulations' resistance to drastic temperature changes. The gel formulation's stability was assessed (Aslani et al., 2013).

Results and Discussion

The process of maceration is used for the extraction of *L. camara* root using hydroethanolic solvent in the ratio (Water: Ethanol in 40:60). The percentage yield of*L. camara* root extract was found to be 4.11 %.

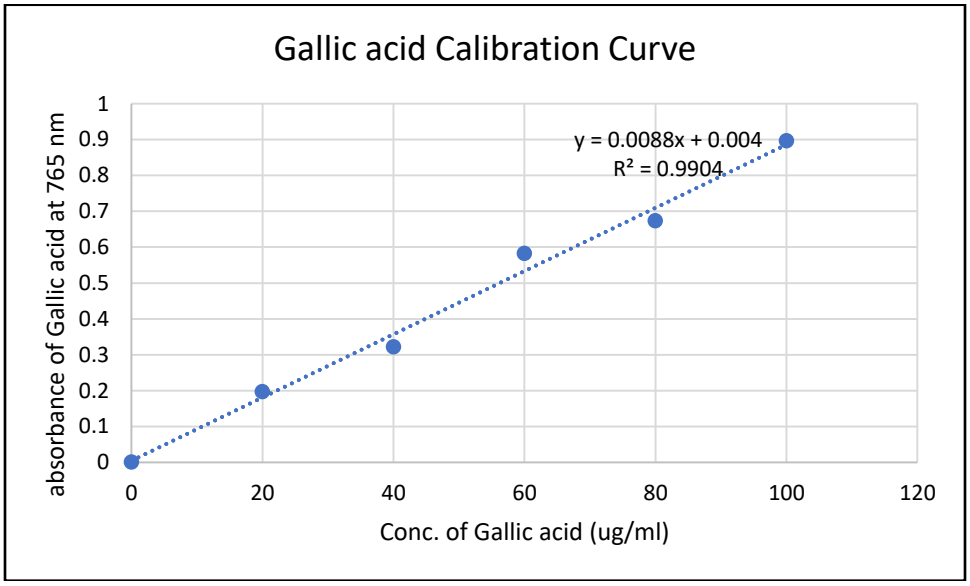

Figure no.2. Gallic acid standard curve for the total phenolic content determination of *L. camara* root extract

Table no. 2. Total phenol content of *L.camara* root extract.

Total Phenol Content (TPC)(mg GAE/g dry extract)	
Root extract	86.82 ± 2.4

GAE: gallic acid equivalents, (mean ± standard deviation of three independent tests).
Using the Folin-Ciocalteu assay, the total phenol content is measured at 765 nm, the results were reported as one milligram of gallic acid equivalent per one gram of extract (mg GAE/g of extract). The results were derived from a calibration curve ($y = 0.0088x + 0.004$, $R^2 = 0.9904$) of gallic acid (0–100 µg/mL) and expressed in gallic acid equivalents (GAE) per gram dry extract weight (Figure no.2).According to Table No. 2, the amount of phenolics as GAE was 86.82 ± 2.4 mg/g of extract. Polyphenols have *in vitro* antibacterial action against periodontal infections. Polyphenols strengthen oral fluids' antioxidant capacity and guard against periodontal disease (Petti and Scully, 2009). Locally, polyphenolic substances may reduce inflammation by forming an impermeable barrier with protein or polysaccharide. According to a study that assessed the anti-inflammatory properties of tannins, these scavenging activities help tannins reduce inflammation. Tannins reduce free radicals and oxidize the tannin to decrease inflammatory indicators(Jeffers; 2006)
The disk diffusion method was used on Mueller Hinton agar medium enriched with bacteria to assess the antibacterial activity of dental gel derived from the extract of *L. camara* roots against the strain of *Streptococcus mutans*. The growth inhibition zones were measured.Dental gel containing *L. camara* root extract showed distinct zones of inhibition following a 24-hour incubation period as shown in Figure no.3. There was no apparent inhibition of the microorganisms by the sterile filter disc used as a negative control as shown in figure no. 3. Table 3 displays the diameter of the inhibition zones for *Streptococcus mutans* in *L. camara* roots mucoadhesive gel and Chlorhexidinegluconate [Positive control] (0.2 % w/v) disc.
The mean inhibition zone for the dental gel containing *L. camara* roots extract was 15.9±0.60 mm, according to the data. The mean inhibitory zone for the positive control, chlorhexidinegluconate disc, was 18 ±0.2 mm. The zone of inhibition produced by 0.2% w/v of chlorhexidine is closer to the zone of inhibition obtained by *L. camara* roots extract dental gel. *L. camara* is used in traditional medicine and is a rich source of many bioactive components (Sastri, 1962). According to certain reports, its roots are highly concentrated in the triterpenoidoleanolic acid (Misra et al., 2007). Oleanolic acid has been shown to have a wide range of important biological effects, such as anti-inflammatory, anti-hyperlipidemic, antiulcer, antioxidant, and hepatoprotective properties(Gupta et al., 2022). Many Gram-positive bacteria, such as *L. monocytogenes*, *E. faecalis*, *E. faecium*, *Streptococcus mutans*, and *Streptococcus sanguis*, are susceptible to the antimicrobial effects of oleanolic acid, according to earlier research (Kozai et al., 1999; Horiuchi et al., 2007; Jiménez et al., 2007; Fontanay et al., 2008).
Itwas
postulated that oleanolic acid and ursolic acid target peptidoglycan metabolism within cells, and that oleanolic acid may kill Grampositive bacterialike *S. mutans* by damaging the bacterial cell membrane (Kurek et al., 2010). Additional research indicates that OA affects a number of genes related to S. mutans' central metabolism, inhibiting the manufacture of fatty acids, amino acids, glycolysis, and peptidoglycans, all of which are important for the bacteria's ability to resist infection (Park et al., 2018).

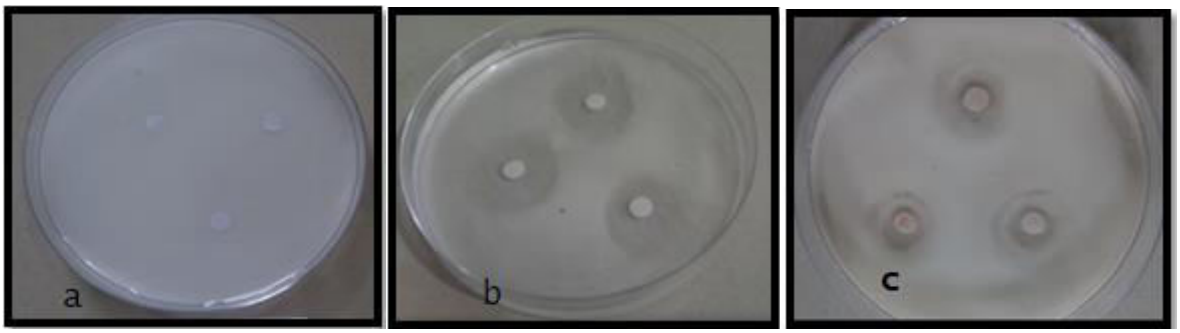

Figure no. 3. Antimicrobial activity of a) Ethanol, (b) 0.2 % chlorhexidinegluconate solution and (c) Dental gel of *L. camara* roots extract

Table no. 3 Antimicrobial activity of dental gel of *L. camara* roots extract and 0.2 % chlorhexidinegluconate solution

Parameters	**Dental gel of *L. camara* roots extract**	**Chlorhexidinegluconate (0.2 % w/v)**
Zone of inhibition (mm)	15.3	18.2
	16.5	18
	15.8	17.8
Mean zone of inhibition±SD (mm)	15.9±0.60	18 ±0.2

The Mucoadhesive Dental gel of *L. camara* roots extract has the desired qualities in terms of color, odor, consistency, grittiness, uniformity, stickiness, and homogeneity, according to the results of a physiochemical evaluation research. Table no. 4 displays the findings of physical characteristics of dental gel of *L. camara* roots extract.

Table no.4: Results of Physical characteristicsparameters of dental gel of *L. camara* roots extract

Parameters	**Results**
Color	Light Brown
Odor	Characteristic
Consistency	Smooth
Grittiness	None
Uniformity	Good
Stickiness	Good

Table no.5: Results of Physicochemical characteristics parameters of dental gel of *L. camara* roots extract

Parameters	**Results**
pH	6.6 ±0.14
Viscosity(cps)	3530
Spreadability (cm)	5.2 ±0.11
Mucoadhesive strength (dyne/cm^2)	25.03±1.46

Data are means of three replicates (n = 3) ± standard error.

Oral gel has a pH of 6.6 ±0.14, which is in between 6.6 and 6.8 as the range of salivary pH. It is therefore anticipated that the gels won't irritate the oral mucosa.

The ability of a gel preparation to be distributed across the skin's surface is known as its spreadability (Danimayostu et al., 2017). The surface area that the gel can reach increases with increasing scatter diameter. When applied to the skin, a gel with good spreadability will ensure that it is distributed evenly; this ranges from 5-7 cm(Saryanti and Zulfa; 2017). The *L. camara* roots herbal oral gel's spread test results show a value of 5.2 ±0.11cm (Table no.5), indicating that the gel has a good spreadability. The spreadability of the gel preparations is significantly influenced by carbopol 940(Rowe et al., 2009), which is employed as a thickener, stabilizer, surfactant, or thickener(Saryanti and Zulfa; 2017). The spreadability of the gel formulations decreases with increasing carbopol 940 concentration. A fluid's viscosity can be used to gauge its thickness (Danimayostu et al., 2017). According to Table no. 5, the oral herbal gel's viscosity test result was 3530cps. Spreadability and viscosity are negatively correlated; the higher the viscosity, the lower the spreadability.Increasing the carbopol 940 concentrations causes viscosity to rise. The synthetic polymer, carbopol 940 is made of acrylic acid and is hygroscopic, somewhat acidic, and highly ionized. The gel's viscosity is mostly controlled by the gelling ingredient Carbopol940 (Rowe et al., 2009).

Mucoadhesive strength, or the oral gel's ability to stick to the mucosa in the tooth pocket, is an important feature. Longer residency and contact times as well as improved clinical efficacy are the outcomes of good gel adherence to the mucosal surface (Bansal et al., 2009). In addition to extending the gel's residency and contact times with the mucosa, medication release from the gel needs to be regulated(Paulsson;2001).Drug release can be regulated by gels (Jelvehgari et al., 2006).As indic ated in Table no.5, the findings of measuring mucoadhesive strength using a modified tensiometer method were 25.03± 1.46dyne/cm^2.This may result in a strong adhesion, which could prolong medication release because the formulation's washout effect would be reduced the stronger the mucoadhesive stren gth.

Table no. 6 Results of stability study

Stability Study	Conditions	Observation		
		Color	pH	Viscosity (Cps)
Centrifuge test	2000 RPM (15 min)	Light brown	6.6 ±0.14	3530
	2000 RPM (30 min)	Light brown	6.6 ±0.14	3530
	2000 RPM (60 min)	Light brown	6.6 ±0.14	3530
Thermal test	4 °C (24 h, 1 w, 1 mo)	Light brown	6.6 ±0.14	3530
	25 °C (24 h, 1 w, 1 mo)	Light brown	6.6 ±0.13	3530
	45 °C (24 h, 1 w, 1 mo)	Light brown	6.6 ±0.13	3529
Freeze and thaw test	-8 °C	Light brown	6.6 ±0.14	3530
	25 °C	Light brown	6.6 ±0.13	3530
Cooling and heating test	4 °C	Light brown	6.6 ±0.14	3530
	45 °C	Light brown	6.6 ±0.14	3529

The *L. camara roots* extract herbal oral gel formulation was shown to be completely stable after a month of storage at various temperatures, where the post formulation parameters showed no significant modifications. Table 6 displays the findings from the stability analysis of the herbal oral gel formulation of *L. camara* roots extract.

Conclusion

As Natural therapies are thought to be safer and have fewer adverse effects than synthetic medications, they are more widely accepted. Herbal remedies are becoming more and more popular on the global market these days. A mucoadhesive oral gel formulation containing *L.camara*'s root extract had been developed in this study. A Mucoadhesive dental gel is easy to use, distributes well, and sticks to the oral mucosa for a sufficient amount of time to release the medication. The study's data showed that the developed herbal gel formulation has a significant, clinically effective, appropriate, low-cost, but unquestionably high-potential drug delivery mechanism. The result of the study showed that developed new herbal gel formulation having good antifungal activity and stable at temperature variation.

Conflicts of interest:

The authors declare that they have no conflicts of interest to disclose.

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