Formulation And Evaluation of Polyherbal Gel for Treatment of Mouth Ulcer

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***Abstract*—Mouth ulcer, sometimes referred to as canker sores or aphthous ulcer, are painful lesions that affect the oral mucosa and make eating, speaking, and swallowing uncomfortable. The current study used natural herbal components with antibacterial, anti-inflammatory, antioxidant, calming and wound healing capabilities to formulate and assess a polyherbal oral gel for the successful treatment of mouth ulcers. The active herbal ingredients in the polyherbal gel were aloe vera, betel leaf extract (Piper betle), and guava leaf extract (Psidium guajava). Alkaloids, flavonoids, tannins, glycosides, saponins, and phenolic substances were validated by preliminary phytochemical screening of the extracts, which were prepared by cold maceration using a hydroalcoholic solvent. Chitosan was utilised as a mucoadhesive polymer and carbapol 934 as a gelling agent. Using a Franz diffusion cell, various gel formulation (F1-F5) were made and assessed for physicochemical characteristics as colour, odor, consistency, pH, spreadibility, homogeneity, grittiness, and in-vitro drug diffusion. Every formulation had a pleasing look, a smooth consistency, acceptable homogeneity, and no grittiness. It was determined that the formulation pH was appropriate for oral use. Out of all the formulations, batch F3 showed the best drug diffusion properties with prolonged release behaviour, the maximum spreadability, and the ideal pH. The study found that by lowering inflammation, microbial growth, discomfort, irritation while accelerating healing, the produced polyherbal gel has promising therapeutic potential for the treatment of mouth ulcers. As a result, the formulation might be a safe, efficient, affordable, and patient-friendly herbal substitute for traditional oral ulcer therapy.**

***Index Terms*—Aphthous stomatitis, chitosan, Franz diffusion study, mouth ulcer, mucoadhesive gel, herbal formulation**

I. INTRODUCTION

Recurrent, painful ulcers in the mouth and throat are the hallmark of aphthous stomatitis, also referred to as canker sores or mouth ulcers [1]. Mouth ulcers or canker sores are small painful lesions that appear inside the mouth, such as on the gums, cheeks, tongue, or roof of the mouth. They can be brought on by minor injuries, acidic or spicy foods, stress, hormonal changes, nutritional deficiencies like iron, zinc, or vitamin B, and specific medical problems like autoimmune disease or infections. These ulcers usually heal on their own in 1-2 weeks without leaving scars, despite the fact that they can be unpleasant and irritating. Treatment options include over-the-counter lotions, mouthwashes, saltwater rinses, and natural therapies like honey to reduce irritation and speed recovery. If ulcers are frequent, persistent, or accompanied by symptoms like fever or difficulty swallowing, medical help is necessary [2]. Mouth ulcers are painful sores that develop inside the mouth and can be caused by a variety of factors, including cheek biting, hot meals, stress, hormonal fluctuations, vitamin deficiencies, infections, allergies, drugs, braces, or genetics. They appear as little white or yellowish lesions on the oral mucosa [3].

There are several causes of mouth ulcers, such as:

1) Minor injury: Inadvertent biting of the interior of the mouth or injuries from hard or sharp foods can cause ulcers.
2) Specific foods: Foods that are spicy, acidic, or have a rough texture might irritate mucosal membranes and cause ulcers to form.

3) Stress or hormonal fluctuations: During menstruation, mouth ulcers are more likely to develop due to emotional stress or hormonal variations.
4) Nutritional deficits: Oral ulcers can be caused by shortages in iron, zinc, and vitamins in particular.
5) Underlying medical conditions: Viral infections can cause autoimmune illnesses, gastrointestinal problems, and recurring mouth ulcers. Most mouth ulcers go away on their own in one to two weeks without leaving any scars. However, they could be painful and uncomfortable right now [2].

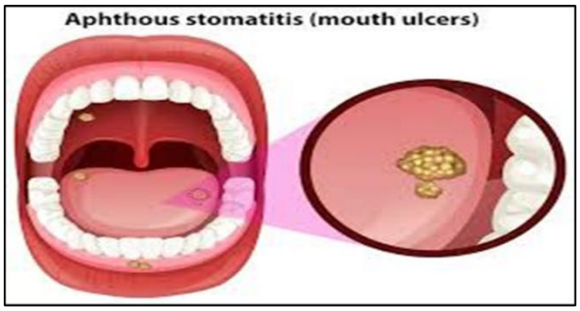

Fig. No.1 Mouth Ulcer

Polyherbal Gel

A polyherbal gel is a semi-solid topical formulation that has therapeutic effects by combining extracts or active ingredients from two or more medicinal plants in a gel base. Because of the synergistic action of several herbal ingredients, it is easy to apply to the skin or mucosal surfaces and provides increased efficacy.

Gels are mostly semi-solid dosage forms made of a liquid phase trapped in a three-dimensional network of polymers created by appropriate gelling agents. Because of their smooth texture, simplicity of administration, non-greasy nature, and capacity to efficiently transport active substances to specified areas, these formulations are frequently utilized in pharmaceutical and cosmetic applications [4].

Topical gel formulations are intended to be applied to the skin or mucosal surfaces, where they may act locally or aid in the percutaneous penetration of medications. Because they stick effectively to the mucosal lining, offer extended contact duration, and guarantee sustained release of active herbal ingredients, gels are very helpful in dental care, increasing therapeutic effectiveness [5]. Herbal gels for dental care are a creative way to combine traditional herbal medicine with contemporary dental hygiene techniques. These products offer a comprehensive strategy for preserving dental health by utilizing bioactive substances obtained from plants. These gels are intended to prevent microbial infections, enhance gum health, and improve general oral hygiene in addition to treating oral disorders. Natural extracts like aloe vera (Aloe barbadensis), betel leaves (Piper betle), and guava leaves (Psidium guajava) are frequently added to herbal oral gels to enhance their antibacterial, anti-inflammatory, antioxidant, and wound healing properties. Because of its potent antibacterial and anti-inflammatory qualities, Psidium guajava leaves are frequently used to oral gel formulations. They contain bioactive substances like flavonoids, tannins, and phenolic components that assist tissue healing in the oral cavity, lessen inflammation, and prevent the growth of oral infections. Because of these characteristics, guava leaf extract is quite useful for treating ailments like gingivitis, mouth ulcers, and minor oral infections. Because of its wide range of medicinal properties, piper betle extract is very frequently utilized in oral pharmaceutical compositions. It has strong antioxidant, anti-inflammatory, and antibacterial qualities. Its capacity to inhibit bacterial growth, lessen oral inflammation, and promote general oral health is facilitated by the presence of active substances such eugenol, chavicol, and phenolic derivatives [6]. It is especially helpful for keeping teeth clean and controlling gingival infections. All things considered, the combination of these plant extracts in a gel basis has a synergistic effect that increases antibacterial action, lowers inflammation, encourages wound healing, and enhances mouth comfort, making it a potential natural choice for managing oral healthcare [7].

II. MATERIALS AND METHODS

Drug Profile

1. Guava Leaves

Synonyms: Peru, Jaam, Amrood.

Biological source: The dried leaves of Psidium guajava L. a member of the Myrtaceae family.

Chemical constituents: Tannins, triterpenes and flavonoids, quercetin, pentacyclic triterpenoid, guajanoic acid, saponin, carotene, lectins, leucocyanidin, ellagic acid, amritoside, uvaol,

oleanolic acid, and ursolic acid are among its significant phytoconstituents.
Uses: Antioxidant, anti-inflammatory, antibacterial, and anti-ulcer [8].

Fig. No.2 Guava Leaves

2. Betel Leaves
Synonyms: .
Biological source: Dried piper betle leaves from the Piperaceae family.
Chemical constituents: Aterpinine, P-cymene, carvacrol, chavicol and its derivatives, allylcatechol, eugenol, estragol, oxalic acid, malic acid, and amino acids are among the chemical constituents found in plants, vitamins, especially nicotinic acid, ascorbic acid, and carotin, are abundant in leaves. Additionally, they have substantial concentrations of every necessary amino acid, with the exception of arginine, histidine, and lycine.
Uses: Anti-inflammatory, anti-ulcer, antiseptic, and antibacterial [9].

Fig. No. 3 Betel Leaves

Collection and Aunthentication
The Guava leaves and betel leaves collected from sukh samrudhi nursery, cherpoli, shahapur. Authentication were doned by Dr. Vilas M. Suroshe, MSc, Ph.D (Ethnobotanist) Vidyamandir High School and Junior College Shivale.
Preparation Of Extract: Method Used For Extraction

PLANT	METHOD FOR EXTRACTION	SOLVENT
Psidium guajava	Cold maceration	Ethanol
Piper betle	Cold maceration	Ethanol

Table No.1 Preparation of Extract

Extraction Process
1) Collection of Leaves: To get rid of undesirable items and broken leaves, fresh leaves were gathered and thoroughly cleaned.
2) Cleaning: To get rid of dust, filth, and other contaminants, the gathered leaves were carefully cleaned with clean water.
3) Drying in the shade: To eliminate moisture and shield the active ingredients from direct sunshine, the cleaned leaves were shade-dried for roughly seven days at room temperature.
4) Grinding: The leaves were ground into a coarse powder using a grinder once they had completely dried.
5) Sorting: To achieve a consistent particle size, the powdered material was run through filter number 44.
6) Weighing: A precise weight of about 25 g of guava leaf powder was measured [10].
7) Solvent Preparation: 175 milliliters of ethanol and 75 milliliters of water were combined to create a 250 milliliter hydroalcoholic solvent. The Process of Maceration: The prepared solvent was added to a clean conical flask along with the weighed powder. To guarantee adequate phytoconstituent extraction, the mixture was held for 48–72 hours for cold maceration with sporadic shaking.
8) Filtration: The liquid extract was separated from the marc by filtering the mixture through muslin cloth or filter paper after maceration.
9) Extract Concentration: To get a thick extract, the filtrate was concentrated by evaporating the solvent.
10) The finished product: For use in future formulation research, a semi-solid mass of guava leaf extract was produced and kept in an airtight container [11].

Phytochemical Investigation:

Sr. No.	Test	Observation
1	Test for Alkaloid: Hager's Test Fill a test tube with two milliliters of plant extract. Add a few drops of Hager's reagent, a saturated picric acid solution. Gently shake and watch.	A precipitate with a yellow hue forms.
2	Test foe Flavonoid: Alkaline Reagent Test Fill a test tube with two milliliters of the extract. A few drops of sodium hydroxide (NaOH) solution should be added. A yellow hue emerges. Add a small amount of hydrochloric acid (HCl).	When diluted HCl is added, the yellow color vanishes.
3	Test for Tannins: Ferric Chloride Test Fill a test tube with two milliliters of the extract. Add a few drops of the solution containing ferric chloride.	The colour turns greenish-black.
4	Test for Phenolic compound: Lead Acetate Test Take two milliliters of the extract. A few drops of lead acetate solution should be added.	A white precipitate forms.
5	Test for Glycosides: Legal's Test Take two milliliters of the extract. Add the sodium nitroprusside solution and pyridine. Use a solution of sodium hydroxide to make it alkaline.	A pink/red colour
6	Test for Saponin: Foam Test Mix 5 ml of distilled water with 2 ml of the extract. Give it a good shake for two to three minutes.	The result is persistent foam.

Table No.2 Phytochemical Investigation [12,13]

Fig. No.4 Phytochemical Test

Method Of Preparation

1) Preparation of Carbopol 934 Gel Base: Carbopol 934 was dispersed in purified water with continuous stirring and allowed to hydrate overnight. The swollen gel was triturated to obtain a smooth consistency, and Triethanolamine (TEA) was added dropwise to adjust the pH to 6.5–7 and form a clear gel base.
2) Preparation of Chitosan Solution: Chitosan was dissolved in 1% v/v acetic acid solution with continuous stirring until a clear viscous solution was obtained.
3) Preparation of Herbal Phase: Guava leaf extract, Betel leaf extract, and Aloe vera gel were mixed thoroughly. PEG 400 was added slowly with continuous stirring to improve solubility, texture.
4) Addition of Preservatives: Sodium benzoate and Potassium sorbate were dissolved in purified water and added to the herbal phase with continuous stirring.

5) Incorporation into Gel Base: The chitosan solution was added slowly into the Carbopol gel base, followed by gradual addition of the herbal phase with continuous stirring until a smooth and homogeneous gel was formed.
6) Addition of Flavoring Agent: Peppermint oil was added and mixed uniformly throughout the formulation.
7) Removal of Air Bubbles and Volume Adjustment: The gel was kept undisturbed to remove entrapped air bubbles, and the final volume was adjusted with purified water if required.
8) Packaging and Storage: The prepared polyherbal gel was transferred into airtight containers, labeled properly, and stored in a cool and dry place for further evaluation [2].

Formulation Table

Sr. No.	Ingredients	F1(gm)	F2(gm)	F3(gm)	F4(gm)	F5(gm)
1	Guava leaf extract	0.10	0.15	0.20	0.25	0.30
2	Betel leaf extract	0.05	0.075	0.10	0.15	0.20
3	Aloe vera	1.0	1.0	1.0	1.0	1.0
4	Carbapol gel base	8.66	8.58	8.51	8.41	8.31
5	Chitosan	0.1	0.1	0.1	0.1	0.1
6	PEG 400	0.05	0.05	0.05	0.05	0.05
7	Peppermint oil	0.01	0.01	0.01	0.01	0.01
8	Sodium benzoate	0.02	0.02	0.02	0.02	0.02
9	Potassium sorbate	0.01	0.01	0.01	0.01	0.01

Table No.3 Formulation Table

Formulated gel

Fig. No.5 Formulated Gel

Evaluation Parameter

1. Physical Evaluation

The prepared polyherbal gel formulation were evaluated for various physical parameters such as colour, odor, and consistency by visual inspection and manual examination.

2. Colour: The colour of the prepared formulations was examined visually under normal daylight conditions to check for uniformity and appearance.
3. Consistency: The consistency of the formulation was evaluated by applying a small quantity of gel on the skin and observing its smoothness, homogeneity, and ease of application.
4. Odor: The odor of the formulations was determined by dispersing a small quantity of gel in water and observing the characteristic smell manually [14].

Fig. No.6 Physical Evaluation

5. Measurement of pH

1) Switch on the digital pH meter and allow it to stabilize.

2) Calibrate the pH meter using standard phosphate buffer solutions
3) Take a small quantity of the gel formulation in a clean beaker
4) Dip the electrode of the pH meter completely into the gel formulation [15].
5) Allow the reading to stabilize for a few seconds.
6) Record the observed pH value.
7) Wash the electrode with distilled water after each measurement and dry gently using tissue paper [16].

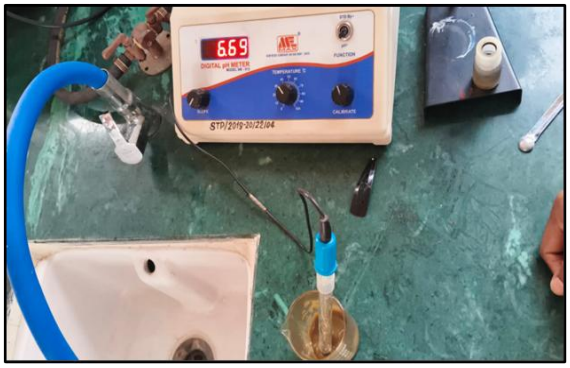

Fig. No.7 Measurement of Ph

6. Spreadability

1) Take two clean glass slides and wash them properly with water. Dry the slides completely.
2) Place approximately 0.5 g of gel between the two glass slides.
3) Place a weight of 100 g on the upper slide to form a thin uniform layer of gel between the slides.
4) Allow the setup to stand for 10 minutes to ensure uniform spreading.
5) After removing the excess gel from the edges, attach a suitable weight to the upper slide.
6) Measure the time taken by the upper slide to move a specified distance and separate from the lower slide.

Calculate the spreadability using the following formula:

$S = M \times L/T$

Where,

S = Spreadability

M = Weight tied to the upper slide

L = Length moved by the glass slide

T = Time taken to separate the slides [17].

Fig. No.8 Spreadability

7. Homogeneity

1) The homogeneity of the prepared polyherbal gel formulations was evaluated by visual inspection after the gel was filled into the containers.
2) Transfer the prepared gel formulation into a clean container and allow it to set properly.
3) Observe the gel visually for its appearance and uniformity.
4) Check the formulation for the presence of: Aggregates, Lumps, Phase separation.
5) Examine the smoothness and consistency of the gel by gentle application on the skin.
6) Record the homogeneity of the formulation based on its uniform appearance and absence of visible particles or aggregates [1].

8. Grittiness Test

1) The grittiness of the prepared polyherbal gel formulations was evaluated manually by sensory examination.
2) Take a small quantity of the prepared gel formulation.
3) Press the gel gently between the thumb and index finger.
4) Rub the formulation softly to observe the presence of any coarse particles or grittiness.
5) Evaluate the immediate skin feel and smoothness of the formulation.
6) Record the formulation as gritty or non-gritty based on the presence or absence of particulate matter [1].

9. Franz Diffusion

1) The Franz diffusion study is an in-vitro diffusion technique used to evaluate the rate and extent of drug release and permeation from topical

formulations such as gels through a membrane [18].

2) In the present study, Franz diffusion cell fitted with a dialysis membrane (12 k Da–14 k Da molecular weight cut-off) was used to assess the drug diffusion characteristics of the prepared polyherbal gel formulations [19].

III. RESULT

Phytochemical Investigation:

Sr. No.	Phytoconstituent	Hydroalcoholic Extract of Guava Leaf	Hydroalcoholic Extract of Betel Leaf
1	Alkaloid	+	+
2	Flavonoid	+	+
3	Saponin	+	+
4	Glycosides	+	+
5	Tannins	+	+
6	Phenolic compound	+	+

Table No.4 Phytochemical Test

Physical Evaluation Of Gel Formulation

Formulation	Colour	Consistency	odour
F1	Light amber yellow	Smooth	Aromatic
F2	Pale brown	Smooth	Aromatic
F3	Honey brown	Smooth	Aromatic
F4	Golden brown	Smooth	Aromatic
F5	Amber	Smooth	Aromatic

Table No.5 Physical Evaluation

pH Of Gel Formulation

Formulation	pH
F1	4.01
F2	6.02
F3	6.69
F4	5.09
F5	4.81

Table No.6 pH

Spreadability Of Gel Formulation

Formulation	Spreadability (Gm.cm/sec)
F1	19
F2	17
F3	24
F4	22
F5	20

Table No.7 Spreadability

Homogeneity Of Gel

Formulation	Homogeneity
F1	Good
F2	Good
F3	Good
F4	Good
F5	Good

Table No. 8 Homogeneity

Grittiness Of Gel

Formulation	Grittiness
F1	No grittiness
F2	No grittiness
F3	No grittiness
F4	No grittiness
F5	No grittiness

Table No.9 Grittiness

Franz Diffusion

Callibration Curve

Concentration	Absorbance
10	0.301
20	0.552
30	0.801
40	1.005
50	1.258
60	1.45

Table No.10 Conc. Vs Abs.

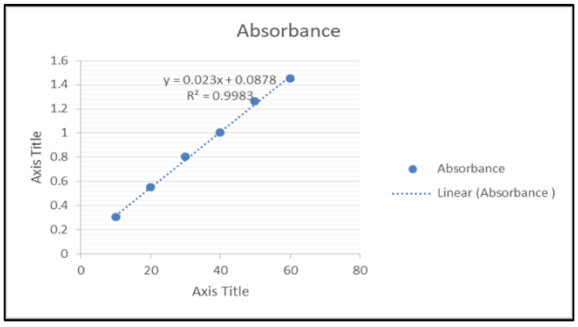

Fig. No.9 Callibration Curve Graph

Drug Release

Time (min)	Absorbance (Y= 0.2399X+0.0878)	Concentration (µg/mL)	Dilution factor (30X)
30	0.206	0.492705294	24.63526469
60	0.255	0.696957065	34.84785327
120	0.36	1.134639433	56.73197165
180	0.68	2.468528554	123.4264277
240	0.84	3.135473114	156.7736557
300	1.46	5.719883285	285.9941642
360	1.89	7.51229679	375.6148395
480	2.206	8.829512297	441.4756148
600	2.604	10.48853689	524.4268445
720	2.845	11.49312213	574.6561067

Total Drug in 20 mL (µg)	Corrected Cumulative Drug (µg)	% Drug Release	Flux (µg/cm²/min)
492.7052939	492.7052939	2.463526469	0.026135439
696.9570654	721.5923301	3.607961651	0.01913835
1134.639433	1169.487286	5.847436432	0.015508796
2468.528554	2525.260525	12.62630263	0.022325311
3135.473114	3258.899541	16.29449771	0.021608447
5719.883285	5876.65694	29.3832847	0.031172591
7512.29679	7798.290955	38.99145477	0.034471546
8829.512297	9205.127136	46.02563568	0.030517741
10488.53689	10930.01251	54.65006253	0.028989
11493.12213	12017.54898	60.08774489	0.026561172

Table No.11 Drug Release % Drug Release Vs Time

Time (min)	Batch F3
30	2.463526469
60	3.607961651
120	5.847436432
180	12.62630263
240	16.29449771
300	29.3832847
360	38.99145477
480	46.02563568
600	54.65006253
720	60.08774489

Table No.12 % Drug Release Vs Time

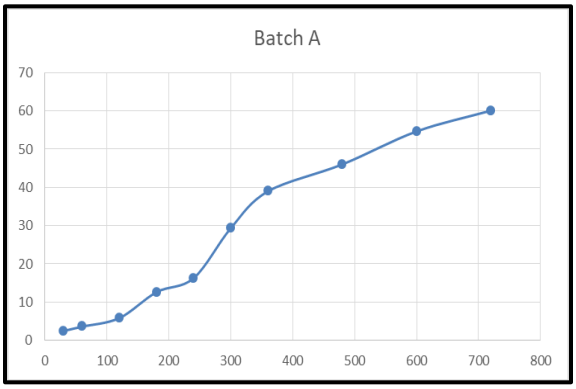

Fig. No.10 Drug Release Graph

Steady State Flux for Batch F3

Time (min)	Batch F3
30	4.042718447
60	5.204854369
120	10.32815534
180	19.90194175
240	25.02815534
300	43.31941748
360	56.74660194
480	43.72561484
600	52.35004168
720	57.78772405

Table No.13 Steady State Flux

Slop (dQ/dt): 0.1467

Area: 3.142

Flux = dQ/dt.A = 0.046690006

IV. DISCUSSION

The goal of the current study was to assess a polyherbal gel that contains aloe vera, betel leaf extract, and guava leaf extract for the treatment of mouth ulcers. Herbal formulations are popular because of their natural origin, safety, low side effects, and therapeutic efficacy. The chosen herbal ingredients have antimicrobial, anti-inflammatory, antioxidant, and wound healing qualities, making them appropriate for treating oral ulcers. Alkaloids, flavonoids, tannins, glycosides, saponins, and phenolic compounds were among the significant phytoconstituents found in guava and betel leaf extracts, according to preliminary phytochemical screening. These components are in charge of lowering inflammation, regulating bacterial growth, easing discomfort, and accelerating ulcer healing. The physical properties of the obtained gel formulations, including their smooth consistency, pleasant fragrant odor, attractive appearance, and lack of phase separation, were adequate. The uniform distribution of chemicals inside the gel basis was demonstrated by the homogeneity and lack of grittiness of all formulations. Chitosan enhanced the formulation's mucoadhesion and retention at the ulcer site, while carbopol 934 supplied an appropriate gel consistency. The formulations' pH ranged from 4.01 to 6.69, which is compatible with oral mucosa and suitable for oral administration. F3 was deemed more appropriate out of all the formulations since it displayed a pH that was closer to the typical oral pH. All formulations could be applied over the affected area with ease, according to spreadability experiments. The highest spreadability was shown by formulation F3, which could enhance patient convenience and appropriate medication distribution. The Franz diffusion investigation showed that the gel formulation's active ingredients were released steadily over an extended length of time. When compared to other batches, Formulation F3 demonstrated superior diffusion characteristics and a satisfactory cumulative drug release. The longer therapeutic action and better mouth ulcer healing may be facilitated by the sustained release behavior. Overall, the the study showed that the prepared polyherbal gel has good physicochemical qualities and a promising therapeutic potential for mouth ulcer treatment. Based on evaluation parameters and diffusion studies, it was determined that F3 was the best formulation out of all of them.

V. CONCLUSION

In order to effectively treat mouth ulcers, the current study developed and assessed a polyherbal oral gel that contained aloe vera, betel leaf extract, and guava leaf extract. Important phytoconstituents that support antibacterial, anti-inflammatory, antioxidant, and wound healing properties were found in the herbal extracts, including flavonoids, tannins, alkaloids, glycosides, phenolic compounds, and saponins. Good appearance, smooth consistency, acceptable pH, good homogeneity, lack of grittiness, and appropriate spreadability were among the favorable physicochemical characteristics of the developed gel compositions. Sustained release of active ingredients from the gel formulation was shown in the Franz diffusion research, which may improve therapeutic efficacy and extend medication action at the ulcer site. Batch F3 demonstrated the best overall performance of all the created formulations, exhibiting the highest spreadability, optimal pH, and a good drug diffusion profile. Carbopol 934 and chitosan together produced a gel viscosity that was appropriate and enhanced the formulation's retention on the oral mucosa. With fewer adverse effects and better patient compliance, the created polyherbal gel can be regarded as a safe, efficient, and promising herbal formulation for the treatment of mouth ulcers. To validate its long-term safety and therapeutic efficacy, more pharmacological and clinical research is necessary.

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