

Formulation and Evaluation Of Polyherbal Mouth Ulcer Gel

Monali Bharat More¹, Dr. Mithun G. Maniyar², Dr. Vrunal V. More³

¹PG student, Department of Pharmaceutics, SVERI's College of Pharmacy, Pandharpur,
Email ID- moremonali956@gmail.com

²Principal, SVERI's College of Pharmacy, Pandharpur

³Professor, Department of Pharmaceutics, SVERI's College of Pharmacy, Pandharpur

ABSTRACT

Background: Oral ulcers are common painful lesions of the oral mucosa that may interfere with eating, speaking, and overall quality of life. Herbal-based topical formulations may offer a useful approach for local management because of their potential antimicrobial, antioxidant, anti-inflammatory, and wound-healing properties. The present study aimed to formulate, optimize, and evaluate a polyherbal mouth ulcer gel containing *Aloe vera*, neem (*Azadirachta indica*), and licorice (*Glycyrrhiza glabra*) extracts.

Materials and Methods: The selected herbal materials were subjected to morphological evaluation, solubility assessment, phytochemical screening, and hydroalcoholic extraction. Carbopol 934-based gel formulations were developed and optimized using a response-surface Design of Experiments approach. The formulations were evaluated for organoleptic properties, pH, moisture content, viscosity, spreadability, drug-content uniformity, *in vitro* release, antimicrobial activity against *Escherichia coli* ATCC 8739, and DPPH free-radical scavenging activity.

Results and Discussion: Among the prepared formulations, F5 showed the most satisfactory overall characteristics, with a pH of 6.07, moisture content of 11.7%, viscosity of 23 cP, spreadability of 8.408 g·cm/s. *In vitro* release studies demonstrated gradual release of all three herbal constituents over 240 min, with *Aloe vera*, neem, and licorice showing best-fit kinetics with zero-order, first-order, and Korsmeyer–Peppas models, respectively. The optimized gel produced zones of inhibition of 14 and 19 mm against *E. coli* at 5 and 10 mg/mL, respectively, compared with 32 mm for streptomycin at 1 mg/mL. In the DPPH assay, the gel showed concentration-dependent antioxidant activity, reaching 96.36–97.39% scavenging at 60–100 µg/mL, which was comparable to ascorbic acid at higher concentrations.

Keywords: Polyherbal gel; Mouth ulcer; *Aloe vera*; *Azadirachta indica*; *Glycyrrhiza glabra*.

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INTRODUCTION

Oral ulcers are painful lesions that can affect the oral mucosa and are often associated with inflammation, burning, discomfort, and problems with eating, drinking, and speaking. They are also one of the most prevalent types of oral mucosal lesions.^[1] When non-keratinized areas of the mouth get infected with recurrent aphthous stomatitis, it can lead to oral ulceration in the form of a single lesion or numerous lesions.^[2,3] Oral ulcers have a complex and multifactorial aetiology; however, they are thought to be caused by a combination of factors such as genetic predisposition, hormonal imbalances, oxidative stress, microbial involvement, psychological stress, and nutritional deficiencies. This patient's quality of life can take a hit if the inflammatory reaction at the ulcerated site prolongs the time it takes for tissues to heal and makes pain worse.^[4]

Pain and inflammation reduction, secondary infection prevention, and acceleration of healing are the primary goals of conventional care of mouth ulcers. Topical corticosteroids, local anaesthetics, antiseptic solutions, antibacterial agents, and protective formulations are typical components of therapeutic treatments.^[5] Local irritation, changed oral microbial flora, hypersensitivity, and other side effects may occur with the incorrect or long-term use of certain conventional treatments. In addition, traditional topical medicines have a short residence period, which can decrease drug retention at the ulcerated site, as does the continual movement of the tongue, salivary production, swallowing, and other oral processes. Safe, effective, and patient-friendly topical administration systems that can maintain extended contact with the afflicted oral mucosa have been developed in response to these restrictions.^[6,7]

Because medicinal plants contain a wide variety of phytoconstituents—including flavonoids, tannins, phenolic compounds, alkaloids, terpenoids, glycosides, and other bioactive components—herbal remedies have recently

attracted a lot of interest for the treatment of oral problems.^[8] Several of these substances have properties that could be useful in treating oral ulcers, such as being antioxidants, anti-inflammatory, antibacterial, analgesic, astringent, and wound-healing. Combining medicinal plants with different but complementary pharmacological characteristics is called a polyherbal strategy, and it has the potential to give more comprehensive therapeutic effects than any one herb alone. So, it's possible to promote epithelial regeneration and wound healing with the help of the right herbal mixture, all while controlling inflammation and microbial contamination.^[9,10]

Because of their pleasant appearance, smooth consistency, ease of administration, and good spreadability, gels are ideal topical dose forms for the oral mucosa. They also allow therapeutic substances to come into close contact with the affected tissue.^[11] The herbal ingredients can be more evenly distributed and retained over the ulcerated area with a gel that is well-formulated. An important factor in the pharmaceutical quality and possible therapeutic performance of a formulation is its physicochemical properties, which include things like viscosity, homogeneity, extrudability, stability, pH, and drug or phytoconstituent concentration. To minimise irritation at the injured mucosal surface, it is particularly necessary to maintain a formulation pH appropriate with the oral environment.^[12,15]

Therefore, it is reasonable to combine the medicinal plant's curative properties with the benefits of a targeted topical medication delivery system to create a polyherbal mouth ulcer gel.^[9] Due to the fact that variations in herbal raw materials, extraction conditions, formulation composition, and manufacturing methods might impact the quality and reproducibility of herbal preparations, it is vital to standardise and conduct systematic pharmaceutical evaluation. Scientific proof on formulation quality and the identification of an optimised formulation suitable for further inquiry can be obtained by evaluating pertinent physicochemical,

phytochemical, antimicrobial, release, and stability factors.^[10,11]

MATERIALS AND METHODS

Materials

Kawathekar, Pandharpur, Maharashtra, India was the source of the aloe vera, neem, and liquorice dried root powders. The gelling polymer utilised was carbopol 934, and the humectant and co-solvent were propylene glycol and glycerin, respectively. Incorporating propyl paraben as a preservative, triethanolamine was utilised for neutralisation and to modify the gel's consistency and pH. To begin with, we extracted and performed preliminary phytochemical screening using a variety of analytical-grade reagents, including methanol, distilled water, ferric chloride, acetic anhydride, sulphuric acid, sodium hydroxide, hydrochloric acid, Dragendorff's reagent, chloroform, ammonia solution, and a number of others. The test microbe utilised in the antimicrobial investigation was *Escherichia coli* ATCC 8739, and the medium used was Antibiotic Assay Medium No. 19, which contains peptone, yeast extract, beef extract, sodium chloride, and dextrose. When testing for microbes, dimethyl sulfoxide was utilised as the control group's negative agent. The antioxidant activity was measured using DPPH (2,2-diphenyl-1-picrylhydrazyl), with ascorbic acid serving as the reference antioxidant standard. The in vitro diffusion investigation utilised a phosphate buffer with a pH of 7.4 and a cellulose membrane. The study used only analytical grade chemicals, solvents, and reagents, which were used exactly as received, unless otherwise noted.

Methods

A. Preparation of Plant Materials: The dried powders of *Aloe vera*, *Azadirachta indica* (neem), and *Glycyrrhiza glabra* (licorice) were passed through sieve No. 16 and used for further experimental studies.

B. Morphological Evaluation: Colour, smell, taste, and

Table no. 01 Code level of Design Experiment Software

Independent variables	Coded levels		
X1 (Carbopol)	-1	0	+1
X2 (Glycerine)	-1	0	+1
X3(Triethanolamine)	-1	0	+1

Table no. 02 Experimental runs by 2² factorial design in DoE

Formula tion	X1 Carbo pol (%)	X2 Glycer ine (%)	X3 Triethanolamin e(%)
1	1	5	2
2	3	5	2
3	1	20	2
4	3	20	2

Evaluation

- Organoleptic Properties:** Organoleptic properties such as look, colour, smell, consistency, and homogeneity were assessed in the made-up polyherbal concoctions.
- pH:** A calibrated digital pH meter was used to determine the pH following the formulation's proper dispersion or dilution in distilled water.
- Viscosity:** A Brookfield viscometer was used in a controlled experimental setting with the proper spindle and rotational speed to determine the viscosity.
- Spreadability Study:** The glass-slide method was used to discover the gel's spreadability, which was then computed

overall appearance were some of the morphological attributes used to assess the chosen herbal materials.

C. Preliminary Phytochemical Screening: In order to identify steroids, glycosides, saponins, flavonoids, alkaloids, tannins, phenolic compounds, and anthraquinones, the powdered herbal materials were put through qualitative chemical testing.

D. Hydroalcoholic Extraction: The powdered plant materials were extracted one at a time using a Soxhlet apparatus with about 250 mL of a 1:5 ratio of ethanol to water for about 6-7 hours, after which about 50 g of each material was placed into a cellulose thimble. After passing through a filter, the extracts were concentrated with the help of a rotary evaporator and kept in sterilised glass containers in the fridge.

E. Preparation of Polyherbal Gel: The carbopol 934 was hydrated in distilled water by slowly dispersing it while stirring continuously for 30-60 minutes. The hydrated Carbopol dispersion was made by first mixing the necessary amounts of *Aloe vera*, neem, and liquorice extracts separately, and then adding glycerin, propylene glycol, and propyl paraben. The pH and gel consistency were adjusted by adding triethanolamine dropwise, and the mixture was stirred until it became uniform, smooth, and free of lumps.

F. Design of Experiments and Optimization: The optimisation of the formulation was carried out utilising the quadratic model and randomised Central Composite Design in Design-Expert software version 12.0.3.0. We chose moisture content and viscosity as dependent responses, and carbopol 934, glycerin, triethanolamine, propylene glycol, and propyl paraben were the formulation factors.

G. Selection of Herbal Composition: We created separate experimental batches with varying quantities of *Aloe vera* and neem extracts and tested them for antibacterial activity and pH to determine the optimal herbal composition.

5	1	5	4
6	3	5	4
7	1	20	4
8	3	20	4
9	0.31	12.5	3
10	3.68	12.5	3
11	2	-0.11	3
12	2	25.11	3
13	2	12.5	1.31
14	2	12.5	4.68
15	2	12.5	3
16	2	12.5	3
17	2	12.5	3
18	2	12.5	3
19	2	12.5	3
20	2	12.5	3

using the formula $S = M \times L/T$, where M is the weight applied to the upper slide, L is the distance travelled by the slide, and T is the time required for separation.

- The formulation's moisture content was assessed utilising a loss-on-drying method with a precisely measured amount.

$$\% \text{ Moisture Content} = (W1 - W2) / (W1 - W0) \times 100$$

Where,

W0 weight of empty porcelain dish

W1 wt. porcelain dish+ sample Wt. before drying

W2 wt. porcelain dish+ sample Wt. after drying

- Drug-Content Uniformity:** After collecting samples from

various parts of the gel, they were dissolved in an appropriate methanolic or hydroalcoholic solvent, subjected to sonication for 15 minutes, passed through a 0.45 µm membrane for filtration, and measured by UV-Visible spectrophotometry at around 280 nm for acemannan, 275 nm for nimbidin, and 254 nm for glycyrrhizinic acid.

- g. In-Vitro Diffusion Study:** A cellulose membrane attached to a Franz diffusion cell was covered with around 1 g of gel. The pH 7.4 phosphate buffer was kept in the receptor compartment at $37 \pm 0.5^\circ\text{C}$ with constant stirring, and portions were taken out at set intervals for examination.
- h. Antimicrobial Activity:** Antimicrobial activity was evaluated by the agar-well diffusion method against *Escherichia coli* ATCC 8739 using Antibiotic Assay Medium No. 19. Six-millimetre wells were filled with 100 µL of the test formulation, standard, or DMSO negative control, followed by pre-diffusion at $2-8^\circ\text{C}$ for 15–20 min and incubation at $30-35^\circ\text{C}$ for 24–48 h, after which zones of inhibition were measured in millimetres.

Table no. 03 Formulation of Batches

Ingredients	F1	F2	F3	F4	F5
Carbopol 934 (gm)	0.25	0.75	0.25	0.50	0.50
Glycerin (ml)	3.97	3.97	3.97	2.48	2.48
Triethanolamine	0.45	0.45	0.89	1.03	0.67

RESULTS

Preliminary Phytochemical Screening

Alkaloids, glycosides, flavonoids, and carbohydrates were detected in all three materials, whereas proteins were detected in *Aloe vera* and *Neem* but not in *Licorice*. The occurrence of

Table no. 04 Physicochemical examination study

Parameters	F1	F2	F3	F4	F5
Appearance	Yellowish-brown	Yellowish-brown	Yellowish-brown	Yellowish-brown	Yellowish-brown
Texture	Gel like	Gel like	Gel like	Gel like	Gel like
Phase separation	No	No	No	No	No
Odour	Characteristic	Characteristic	Characteristic	Characteristic	Characteristic

Drug-Content Uniformity

Drug-content uniformity of the optimized F5 formulation was assessed spectrophotometrically using the respective analytical wavelengths for the selected herbal markers. The mean concentrations obtained for *Aloe vera*, neem, and licorice were 0.2005, 0.1945, and 0.2040 µg/mL, respectively. The corresponding drug-content uniformity values were 100.27%, 97.27%, and 102.00%. The percentage relative standard deviation was 2.30% for *Aloe vera*, 1.22% for neem, and 3.01% for licorice, indicating reasonably uniform distribution of the selected herbal constituents within the optimized gel.

- i. DPPH Antioxidant Assay:** Antioxidant activity was determined using the DPPH free-radical scavenging assay. A freshly prepared 0.1 mM DPPH methanolic solution was mixed with different concentrations of gel extract, incubated in the dark at room temperature for 30 min, and absorbance was measured at 517 nm using a UV-Visible spectrophotometer, with ascorbic acid as the reference standard.
- j. Data Analysis and Interpretation:** This optimal polyherbal mouth ulcer gel formulation was determined by comparing and interpreting experimental data from investigations on formulation optimisation, physicochemical evaluation, drug-content analysis, in-vitro diffusion, antibacterial activity, and antioxidants.
- k. Stability study:** For three months, the prepared herbal ointment was placed in aluminum collapsible tubes (5g) and tested for stability at 5°C , $25^\circ\text{C}/60\% \text{ RH}$, $30^\circ\text{C}/65\% \text{ RH}$, and $40^\circ\text{C}/75\% \text{ RH}$. The samples were taken out and assessed for rheological characteristics, pH, and physical appearance.

Propylene glycol(ml)	3.6	3.6	3.6	3.6	3.6
Licorice (gm)	0.25	0.25	0.25	0.25	0.25
Neem (gm)	0.05	0.05	0.05	0.05	0.05
Aloe vera(gm)	0.05	0.05	0.05	0.05	0.05
Water(ml)	16.38	15.88	15.94	17.04	17.4

multiple phytochemical classes supports the phytochemical complexity of the polyherbal system and provided a basis for further evaluation of antioxidant and antimicrobial properties.

Physicochemical evaluation of formulations F1–F5

Lumps	No	No	No	No	No
pH	5.82	5.94	6.01	6.05	6.07
Moisture content (%)	14	13	14.06	9.2	11.7
Viscosity (cP)	18	20	21	23	23
Spreadability (g.cm/s)	-	-	-	-	8.408

In Vitro Release Study

The in vitro release behaviour of *Aloe vera*, neem, and licorice from the optimized polyherbal gel was evaluated over 240 min and fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models. For *Aloe vera*, cumulative drug release increased progressively from 1.28% at 30 min. to 12.76% at 240 min. The zero-order model showed the highest correlation coefficient ($R^2 = 0.9958$), closely followed by the Korsmeyer–Peppas model ($R^2 = 0.9957$), suggesting near-constant release with a strong contribution from matrix-controlled diffusion.

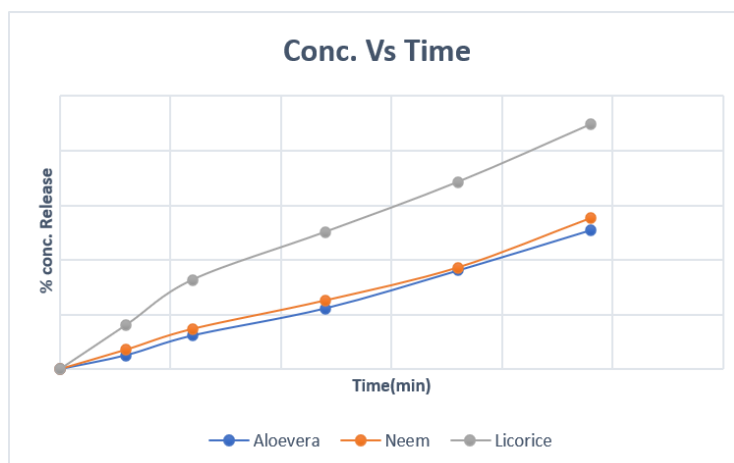


Fig.no.01 Conc. Vs Time plot extract release

Table no. 05 Kinetic data of Formulation F5

Formulation parameter	Aloe vera extract	Neem extract	Licorice extract
Zero order model (R^2)	0.9958	0.9924	0.9871
First order	0.9931	0.9853	0.9948

Antimicrobial Activity

The antibacterial activity of the optimized polyherbal ointment was investigated against *Escherichia coli* using the

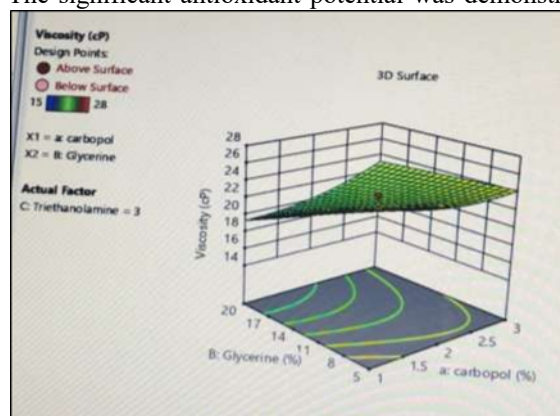
Table no. 06 Antibacterial activity of the optimized polyherbal gel

Sr. No	Sample	Concentration	Zone of Inhibition (mm) <i>E. coli</i>
1.	Control		-

The antimicrobial activity of the optimized polyherbal gel was evaluated against *Escherichia coli* ATCC 8739 by the agar-well diffusion method. Streptomycin at 1 mg/mL produced a zone of inhibition of 32 mm. At concentrations of 5 and 10 mg/mL, respectively, the polyherbal gel exhibited antibacterial action with inhibition zones of 14 and 19 mm, respectively; in contrast, no detectable inhibition zone was observed in the control. The results showed that the new formulation had detectable antibacterial activity, however it was not as effective as the conventional antibiotic in the test.

Antioxidant activity

The antioxidant activity of the mouth ulcer formulation was found to be dose-dependent in the DPPH assay. The formulation's scavenging activity ranged from 22.54 to 33.65% at doses 10-20 $\mu\text{g/mL}$, which was lower than ascorbic acid's. The significant antioxidant potential was demonstrated by an



A expected viscosity of 24.2505 cP was achieved at the optimised point. According to the response surface, the main

model (R^2)			
Higuchi model (R^2)	0.8885	0.8995	0.959
Korsemeyer-Pappas model (R^2)	0.9957	0.9942	0.992

agar-well diffusion method, with streptomycin serving as the reference antibacterial agent.

2.	Standard Streptomycin	1mg/ml	32
3.	Sample- Polyherbal gel	5 mg/mL	14
		10mg/mL	29

inhibition rate of 63.28% at 40 $\mu\text{g/mL}$. The scavenging activity ranged from 96.36% to 97.39%, equal to or slightly higher than that of ascorbic acid, when the concentration was further increased from 60-100 $\mu\text{g/mL}$.

Statistical analysis

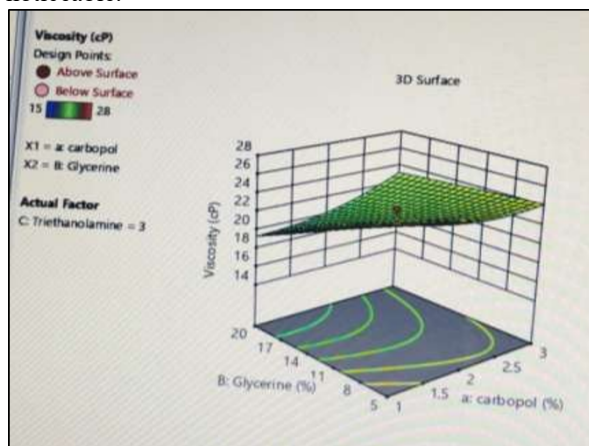
At the optimal point, the anticipated moisture content was 11.333%. Carbopol and glycerin variations affected the formulation's ability to retain moisture. Because of its humectant properties, glycerin tends to raise moisture content when added to solutions, while carbopol changes the gel matrix's water-binding properties when added to solutions.

Y_1 Moisture content (%) = $1.96952 + 0.149021(A) + 0.011655(B) + 0.764070(C) - 0.014021(AB) + 0.001296(B^2) - 0.124762(C^2)$ [A-Carbopol, B-Glycerine, C-Triethanolamine]

Fig.no.02 Response surface 3D graph of Moisture content

factor in the creation of the gel-network was carbopol, since the viscosity rose mainly as the concentration of carbopol

increased. Within the experimental range that was examined, glycerin had a less impact on viscosity, but it was still noticeable.



Response Surface Analysis

The response-surface analysis demonstrated the combined influence of Carbopol and glycerin on the critical quality attributes of the gel. The desirability plot showed a

$$Y_2 \text{ Viscosity (\%)} = 4.23468 - 0.183852 * \text{Carbopol} + 0.041619 * \text{Glycerine} + 0.132402 * \text{Triethanolamine} + 0.019650 * \text{Carbopol} * \text{Glycerine} - 0.002782 * \text{Glycerine}^2$$

Fig.no.03 Response surface 3D graph of Viscosity

desirability value of 1.000 at the selected formulation point, indicating that the imposed optimization criteria were simultaneously satisfied

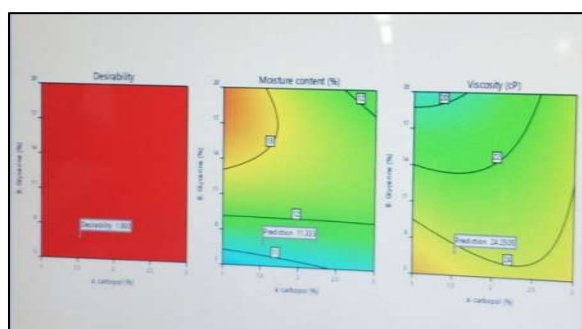


Fig.no.04 Contour plots showing the effect of Carbopol and glycerin on overall desirability, moisture content, Stability Data

The optimized film remained unchanged throughout the study

Table no. 07 Stability data of 3 months

Parameter	Initial	1 month	2 month	3 month
Appearance	Yellowish-brown	Yellowish-brown	Yellowish-brown	Yellowish-brown
Texture	Gel like	Gel like	Gel like	Gel like
Phase separation	No	No	No	No
Lumps	No	No	No	No
pH	6.07	6.08	6.09	6.09
Moisture content (%)	11.07	11.09	11.3	11.3

and viscosity of the polyherbal gel.

time period. No significant change in colour, appearance, texture and other parameters.

DISCUSSION

The present study developed and evaluated a polyherbal mouth ulcer gel containing *Aloe vera*, neem (*Azadirachta indica*), and licorice (*Glycyrrhiza glabra*). Phytochemical analysis revealed carbs, alkaloids, glycosides, and flavonoids in all three plants; protein content in liquorice and *Aloe vera* suggested antibacterial and antioxidant properties.

An experimental strategy known as response-surface Design of Experiments (DoE) was employed to optimise the formulation. The effects of carbopol 934 and glycerin on the gel's characteristics were substantial. Glycerin largely affected moisture retention, whereas carbopol predominantly affected viscosity and consistency; the optimised region displayed a desirability score of 1.000 and was expected to have a moisture content of 11.333% and a viscosity of 24.2505 cP.

An acceptable yellowish-brown appearance, gel-like texture, characteristic fragrance, absence of lumps, and no phase separation were observed in all F1-F5 formulations, which had pH values ranging from 5.82 to 6.15. Since F4 had the best combination of these parameters—pH 6.07, moisture 11.7%, viscosity 23 cP, spreadability 8.408 g.cm/s, and drug content around 98%—it was chosen as the optimised solution. Content uniformity was 100.27% for *Aloe vera*, 97.27% for neem, and 102.00% for licorice.

In-vitro release over 240 min was 12.76% for *Aloe vera* (zero-order, $R^2=0.9958$), 22.38% for neem (first-order, $R^2=0.9948$), and approximately 13.88% for licorice (Korsmeyer–Peppas, $R^2=0.9942$), demonstrating controlled release from the Carbopol matrix.

The optimized gel showed concentration-dependent antibacterial activity against *E. coli* ATCC 8739, with inhibition zones of 14 mm at 5 mg/mL and 19 mm at 10 mg/mL, compared with 32 mm for streptomycin (1 mg/mL). At 10, 20, 40, 60, 80, and 100 µg/mL, the DPPH scavenging activity was 22.54%, 33.65%, 63.28%, 96.36%, 96.55%, and 97.39%, respectively. Additionally, at increasing concentrations, it became equivalent to ascorbic acid.

The physicochemical features, content consistency, antibacterial activity, progressive medication release, and significant antioxidant capacity of F4 were satisfactory, lending credence to its promise for the localised control of mouth ulcers. Efficient and safe use necessitates additional research on stability, mucoadhesion, oral-mucosal safety, broader antibacterial activity, in-vivo and ex-vivo testing, and clinical trials.

CONCLUSION

In this study, a polyherbal mouth ulcer gel was created and optimised utilising a gel method based on Carbopol 934. The gel contained extracts of *Aloe vera*, neem (*Azadirachta indica*), and liquorice (*Glycyrrhiza glabra*). A pH of 6.07, a moisture content of 11.7%, a viscosity of 23 cP, a spreadability of 8.408 g.cm/s, and an overall drug content of almost 98% were some of the good physicochemical properties displayed by the optimised formulation, F4. The in vitro release experiments showed that the three herbal components were uniformly distributed and released over 240 minutes, and the drug-content uniformity indicated that this was an appropriate distribution. At greater concentrations, the gel showed substantial DPPH free-radical scavenging activity, and its antibacterial activity against *Escherichia coli* ATCC 8739 likewise increased with concentration. Its antioxidant activity was comparable to that of ascorbic acid. In order to find a formulation with a balanced moisture content and viscosity, the Design of Experiments method

proved to be quite effective. The results show that the *Aloe vera*-neem-licorice polyherbal gel has good in vitro biological activity and appropriate pharmacological properties for topical use. Before the formulation may be evaluated for therapeutic application in the therapy of mouth ulcers, additional stability, mucoadhesion, oral-mucosal safety, wider antimicrobial, in vivo, and clinical studies are needed.

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