International Journal of Pharmaceutical and Clinical Research

ISSN Print: 2664-7591
ISSN Online: 2664-7605
Impact Factor: RJIF 5.2
IJPCR 2025; 7(2): 23-31
www.pharmaceuticaljournal.in
Received: 06-05-2025
Accepted: 09-06-2025

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Development and evaluation of hyaluronic acid-functionalized, vitamin e-loaded liposome-in-Aloe Vera Gel for oral submucous fibrosis

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DOI: https://www.doi.org/10.33545/26647591.2025.v7.i2a.131

Abstract
Background: Oral submucous fibrosis (OSMF) is a chronic, progressive, and potentially malignant disorder of the oral mucosa, for which current therapies offer limited efficacy. To develop and characterize a novel composite gel system comprising hyaluronic acid (HA)-functionalized, vitamin E-loaded liposomes incorporated in an aloe vera gel matrix for the management of OSMF.
Methods: Vitamin E-loaded liposomes were prepared using the thin film hydration method and surface-functionalized with HA. The liposomes were characterized for size, zeta potential, encapsulation efficiency, morphology, and *in vitro* release. Antioxidant and anti-inflammatory activities were assessed. The optimized liposomes were incorporated into aloe vera gel, which was evaluated for physicochemical and safety parameters.
Results: The HA-functionalized liposomes displayed a mean size of 245.6 nm, a PDI of 0.215, and a zeta potential of -32.4 mV, indicating good stability and uniformity. FTIR confirmed successful encapsulation and HA-coating. *In vitro* release showed biphasic kinetics with sustained release up to 24 hours. The formulation exhibited potent antioxidant and anti-inflammatory activity. The final gel was stable, mucoadhesive, and non-irritant, with suitable pH, viscosity, and spreadability.
Conclusion: The developed HA-functionalized, vitamin E-loaded liposome-in-aloe Vera gel offers a promising, patient-friendly approach for OSMF management, warranting further clinical evaluation.

Keywords: OSMF, hyaluronic acid, liposome, Vitamin E, Antioxidants, anti-inflammatory, Gel

Introduction
Oral submucous fibrosis (OSMF) is a chronic, insidious, and potentially malignant disorder of the oral cavity, characterized by progressive fibrosis of the submucosal tissues, resulting in restricted mouth opening, burning sensation, xerostomia, and dysphagia. The primary etiological factor is the habitual chewing of areca nut, which leads to persistent inflammation, fibroblast activation, and excessive collagen deposition. The prevalence of OSMF is highest in South and Southeast Asia, correlating with areca nut use. OSMF is characterized by mucosal-epithelial inflammation and progressive fibrosis, leading to trismus and increased cancer risk. Areca nut alkaloids stimulate fibroblast proliferation and collagen synthesis while inhibiting collagenase activity. Histopathology shows progression from inflammation to dense, hyalinized collagen bundles and epithelial atrophy.
Pathogenesis involves an imbalance between collagen synthesis and degradation, with cytokines such as TGF-β, IL-6, and TNF-α promoting fibroblast activation and myofibroblast differentiation. The risk of malignant transformation to oral squamous cell carcinoma ranges from 1.5% to 15% [1-5].
Treatment including antioxidants and anitinflammory agent and some natural plants-based products such as aloe vera, curcumin, lycopene and glycyrrhizin. Current treatments are largely palliative, focusing on habit cessation, nutritional support, antioxidants, corticosteroids, and surgical interventions. These approaches are limited by suboptimal efficacy, recurrence, and side effects. Novel drug delivery systems, such as liposomes, have emerged to enhance bioavailability and site-specific delivery in the oral cavity. Liposome of natural plants-based antioxidants have been reported to work in OSMF [6, 7].

Antioxidants such as Vitamin E and others has been reported as potent antioxidant that scavenges free radicals and modulates inflammatory and fibrotic pathways. Aloe vera is commonly used as emollient in cosmetics and have various pharmacological properties Also use of aloe vera in fibrosis has been reported [8].

This study hypothesizes that HA-functionalized, vitamin E-loaded liposomes incorporated into an aloe vera gel matrix can provide improved mucoadhesion, sustained release, and synergistic therapeutic effects for OSMF.

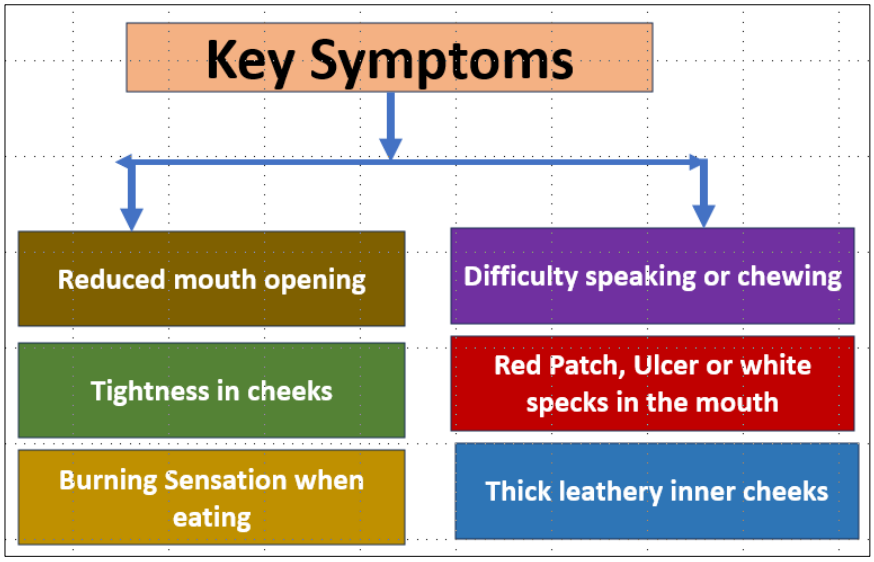

Fig 1: Clinical manifestation of OSMF

Materials and Methods

2.1 Materials: Soya Lecithin, cholesterol, Potassium Dihydrogen Ortho Phosphate Chloroform, Methanol, Carbopol - 934, Glycerol, DPPH Assay kit and Ascorbic acid were provided by School of Pharmacy. Vitamin-E capsule was purchased from local medical shop (Evion by Procter & Gamble Health Ltd.). Hyaluronic acid (sodium salt) powder was purchased BRM chemical New Delhi. Aloe Vera was collected as whole leave from ITM sithouli campus. Others chemicals and reagent procured from stores of School of Pharmacy.

2.2 Preparation and characterization of Vit E-HA-Liposome

2.2.1 Preparation of Vitamin E-Loaded Liposomes

The thin film hydration method was employed for liposome preparation. Briefly, a mixture of soya lecithin and cholesterol was dissolved in chloroform: methanol (1:2, v/v) in a round-bottom flask. Vitamin E was added to the lipid solution. The solvent was evaporated by vigorous hand shaking method at 40-55°C to form a thin lipid film on the flask wall. The film was hydrated with Hyaluronic acid (HA) mixed phosphate-buffered saline (PBS, pH 7.4) and the resulting suspension was sonicated to reduce vesicle size and obtain a uniform dispersion The resulting HA-functionalized liposomes were purified by centrifugation, washed, and lyophilized for further use [9].

2.2.2 Microscopy: The morphology and size distribution of the prepared liposomes were observed using an optical microscope. A drop of liposome suspension was placed on a glass slide, covered with a coverslip, and visualized under 40x magnification.

2.2.3 Particle Size and Zeta Potential Measurement

The particle size (mean hydrodynamic diameter) and zeta potential of the HA-functionalized, vitamin E-loaded liposomes were determined using a Malvern Zetasizer Nano ZS (Malvern Panalytical, UK). The Zetasizer employs Dynamic Light Scattering (DLS) to measure particle size and Electrophoretic Light Scattering (ELS) for zeta potential analysis, allowing accurate characterization of nanoparticles in suspension (Zetasizer manual, 2015)

2.2.4 FTIR (Fourier Transform Infrared Spectroscopy)

FTIR analysis was carried out to confirm the successful encapsulation of vitamin E and the functionalization with HA. Samples of pure vitamin E, HA, blank liposomes, and HA-Vit E-liposomes were scanned in the range of 4000-400 cm^{-1}, and spectra were compared for characteristic peaks.

2.2.5 *In vitro* Release Study of HA-Vit E-Liposome

The release profile of vitamin E from HA-liposomes was studied using a dialysis bag diffusion method. The liposome suspension was placed in a dialysis bag, immersed in PBS (pH 7.4), and maintained at 37°C with constant stirring. At predetermined intervals, aliquots were withdrawn and analysed spectrophotometrically for vitamin E content [9].

2.2.6 Evaluation of Free Radical Scavenging Capacity by DPPH Assay: The antioxidant activity of the formulation was evaluated by mixing the sample with DPPH solution and measuring the decrease in absorbance at 517 nm after incubation [10].

2.2.6 Evaluation of *in vitro* anti-inflammatory activity of HA-Vit E-Liposome: The reaction mixture (5 ml) contained 2 ml of HA-Vit E-Liposome at different concentrations (20, 40, 60, 80, and 100 µg/ml), 2.8 ml of phosphate buffered saline (PBS, pH 6.4), and 0.2 ml of egg albumin (from a fresh hen's egg). As a control, a comparable volume of double-distilled water was used. The mixes were then heated to 70°C for 5 minutes after being incubated at (37±2)0C for 15 minutes in a Universal Incubator. After cooling, the vehicle was used as a blank to measure their absorbance at 660 nm. In order to determine absorbance and

viscosity, diclofenac sodium was utilized as a reference medication and treated similarly at final concentrations of 20-100 µg/ml. The following formula was used to determine the percentage inhibition of protein denaturation

% inhibition = 100 × (Vt / Vc -1)

Where, Vt = absorbance of test sample, Vc = absorbance of control.

The concentration for 50% inhibition (IC50) was determined by plotting percentage inhibition with respect to control against treatment concentration [11].

2.3 Gel Preparation and Incorporation of Vit E-HA-Liposome

Aloe vera gel was used as the base for incorporating the HA-Vit E-liposome. The gel was prepared by homogenizing fresh aloe vera pulp and adjusting pH to 6.5-7.0. The lyophilized HA-Vit E-liposome powder was uniformly dispersed into the gel base under gentle stirring to form the final composite gel.

2.3.1 Organoleptic Characters

The prepared gel was evaluated for appearance, colour, and taste by visual and sensory inspection.

2.3.2 Determination of pH

The pH of the gel was measured using a calibrated digital pH meter by directly immersing the electrode into the gel sample.

2.3.3 Viscosity: Viscosity was determined using a Brookfield viscometer at room temperature, with readings taken at different spindle speeds to ensure consistency. The Brookfield viscometer was used to measure the. Viscosity of the created gel at a temperature of 25°C. The dial reading for each speed was recorded as the gels were rotated at 0.3, 0.6, and 1.5 rotations per minute. The gels' viscosity was then determined by multiplying the dial reading by a value listed in the Brookfield viscometer catalogues [12].

2.2.4 Spreadability: Spreadability was measured using traditional parallel glass slide method, where a fixed amount of gel was sandwiched between two glass plates and the diameter of the spread was recorded after applying a standard weight [12].

2.2.5 Skin irritancy Test: Skin irritancy is necessary test to investigate the any irritancy or inflammatory action on skin. In present study it performed on healthy volunteers by applying a small amount of gel to the inner forearm skin and observing for any signs of irritation, redness, or allergic reaction over 24 hours. A photo was taken at both times to compare the result.

2.2.6 Statistical Analysis: The results were expressed as mean±SD and were analysed statistically by analysis of variance (ANOVA) using Graph Pad Prism V5.04 software at the level of significance (p<0.05).for DoE Stat-Ease (free version) was used for formulation optimization.

3. Results: 3.1. Preparation and Characterization of HA-Vitamin E-Loaded Liposomes

Table 1: Design of Experiments (DoE)

Code	Factor (Independent Variables)	Levels (Low-High)
X_1	Phospholipid concentration (mg/mL)	50 - 150
X_2	Cholesterol concentration (mg/mL)	10 - 30
X_3	Hyaluronic acid amount (mg/mL)	0.5 - 1.5

Table 1: Design of Experiments (DoE) study involving HA + Vitamin E liposomes optimized for response in Entrapment Efficiency (%) and Particle Size (nm).

Run	X_1 (Phospholipid)	X_2 (Cholesterol)	X_3 (HA)	EE% (Response Y_1)	Particle Size (nm) (Y_2)
F1	50	10	0.5	62	220
F2	150	10	0.5	78	240
F3	50	30	0.5	65	265
F4	150	30	0.5	83	285
F5	50	10	1.5	68	210
F6	150	10	1.5	81	235
F7	50	30	1.5	70	260
F8	150	30	1.5	72	280
F9	100	20	1	76	250
F10	100	20	1	75	248

3.1.1. Physical Appearance and Yield

The vitamin E-loaded liposomes, both before and after hyaluronic acid (HA) functionalization, appeared as milky white, homogenous suspensions. The incorporation of HA resulted in a slightly increased viscosity and improved dispersion stability.

Fig 2: Different formulations of vit-E-HA Liposome

3.1.2. Particle Size and Polydispersity Index (PDI)

Particle size analysis using the Malvern Zetasizer Nano ZS revealed that the mean hydrodynamic diameter (Z-average) of the HA-functionalized, vitamin E-loaded liposomes was 245.6 nm±6.2 nm (Table 3). The polydispersity index (PDI) was 0.215± 0.02, indicating a narrow and uniform size distribution.

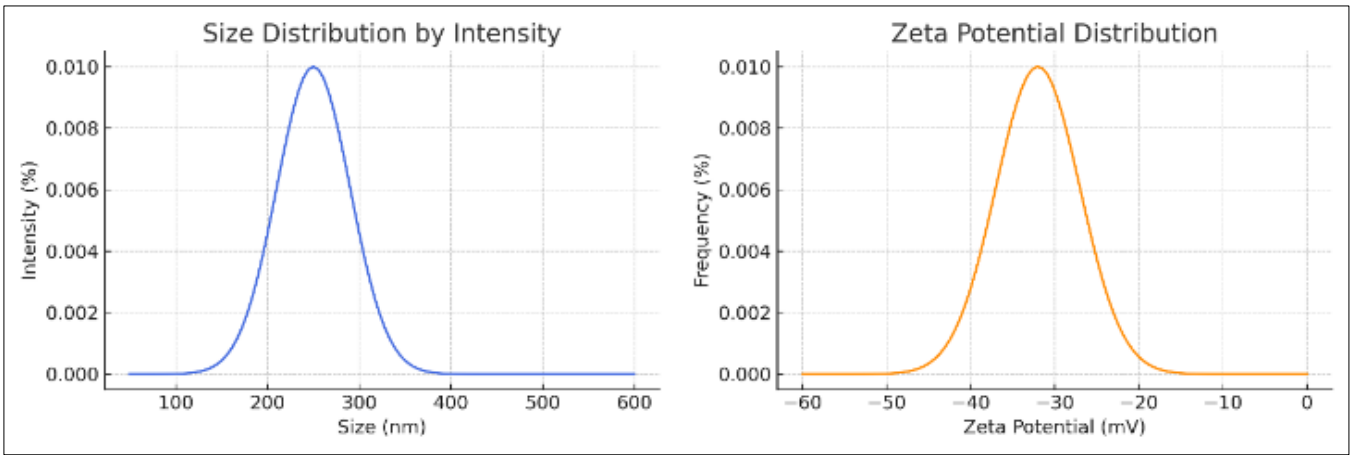

Fig 3: DLS size distribution curve for HA-Vit E-Liposome and zeta potential of Vit-E-HA liposomes

Table 3: Particle Size and PDI of Liposome Formulation

SN	Parameter	Value	Interpretation
1	Z-average (Hydrodynamic size)	245.6 nm	Mean size of liposomes
2	Polydispersity Index (PDI)	0.215	Indicates uniformity (ideal < 0.3)
3	Zeta Potential	-32.4 mV	Good stability (ideal ±30 mV or more)
4	Conductivity	0.050 mS/cm	Medium's ionic strength

3.1.3. Zeta Potential

The zeta potential of the HA-functionalized liposomes was measured at -32.4 mV±1.7 mV (figure 3 and Table 3). This high negative value indicates strong electrostatic repulsion between particles, suggesting good colloidal stability.

3.1.4. Microscopy

Microscopic examination revealed that the HA-Vit E-liposomes were predominantly spherical with smooth surfaces and uniform size distribution. No significant aggregation or fusion of vesicles was observed (Figure 4).

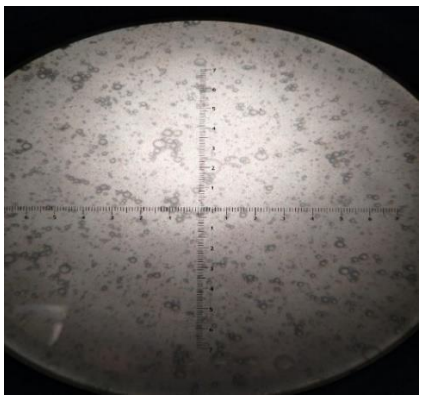

Fig 4: Optical microscopy of Vit-E-HA-liposome

3.1.5. FTIR Analysis

FTIR spectra of the HA-Vit E-liposome formulation showed characteristic peaks corresponding to both vitamin E and HA, confirming successful encapsulation and surface functionalization. Key absorption bands included O-H stretching (~3450 cm^{-1}), C-H stretching (~2920 cm^{-1}), and amide I and II bands (1650 and 1550 cm^{-1}), with minor shifts indicating molecular interaction.

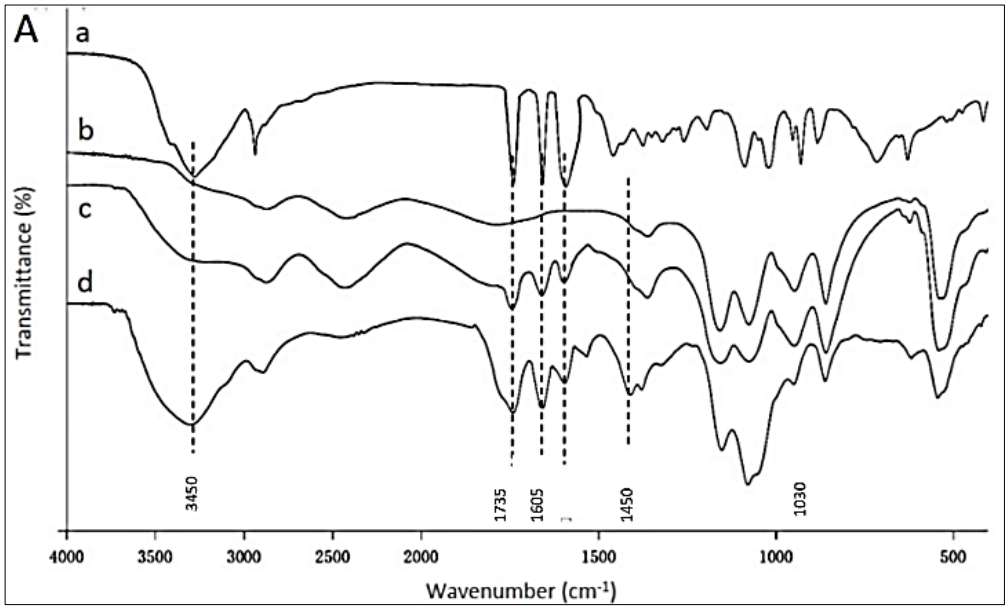

Fig 5: FTIR spectra of a: HA, b. Vitamin E, c., Phospholipid+Chol, d. HA+Vit-E Liposome

Table 4: FTIR interpretation of HA+Vit-E Liposome

Component	Major Peaks (cm^{-1})	Functional Group
Hyaluronic Acid (HA)	3400 (broad), 1610, 1410, 1030	O-H stretch, C=O stretch (COOH), C-O-C, C-OH
Vitamin E (α-Tocopherol)	3450, 2955, 1605, 1450, 1260	O-H (phenolic), C-H (alkyl), aromatic ring
Phospholipids	2920, 2850, 1735, 1235, 1085	CH_2 stretch, C=O ester, P=O, PO-C stretch
Cholesterol	3400, 2930, 1465, 1050	O-H, C-H, -CH_2- bending, C-O stretch
HA + Vit E Liposomes	~3400, 1730, 1230, 1080, 1030	Overlapping, shifts indicate interaction

3.2. *In vitro* Release Study

The *in vitro* release profile of vitamin E from HA-Vit E-liposomes exhibited a biphasic pattern (Figure 4.5). An initial burst release of approximately 65% was observed within the first 8 hours, followed by a sustained release phase, reaching a cumulative release of 84% over 24 hours. This sustained release is attributed to the HA coating, which acts as a diffusion barrier.

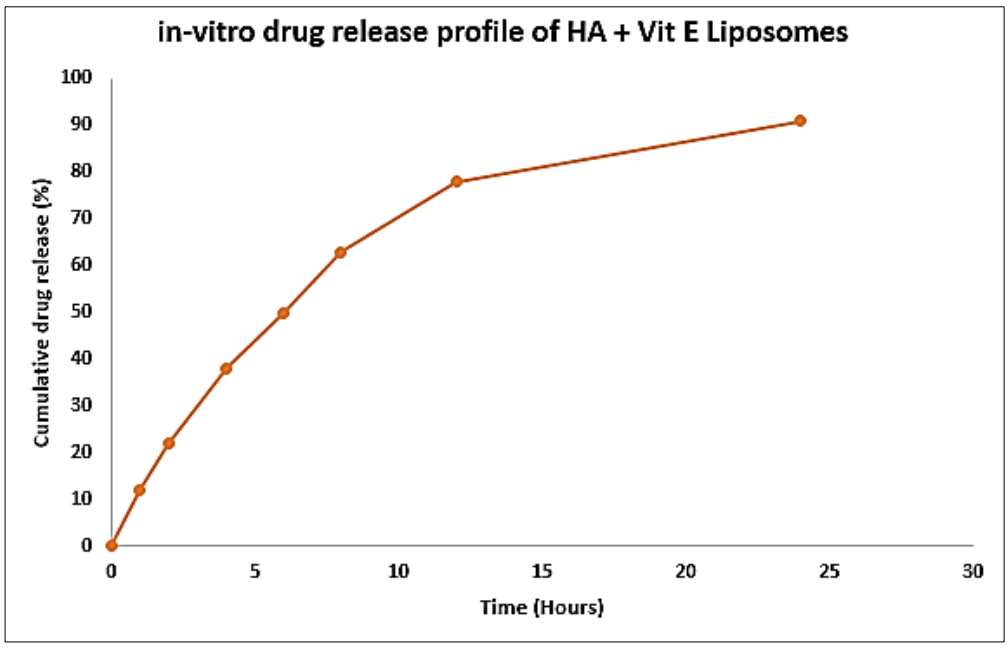

Fig 6: *in-vitro* drug release profile of HA + Vit E Liposomes using UV spectrophotometry (285nm)

3.3. Antioxidant Activity by DPPH Free Radical Scavenging Assay

The HA-Vit E-liposome formulation demonstrated potent DPPH radical scavenging activity, with an IC_{50} value of 17.88 compared to 12.45 for ascorbic acid (fig 7). This indicates a significant enhancement in antioxidant capacity upon encapsulation.

% Inhibition = [(A_control - A_sample) / A_control] × 100

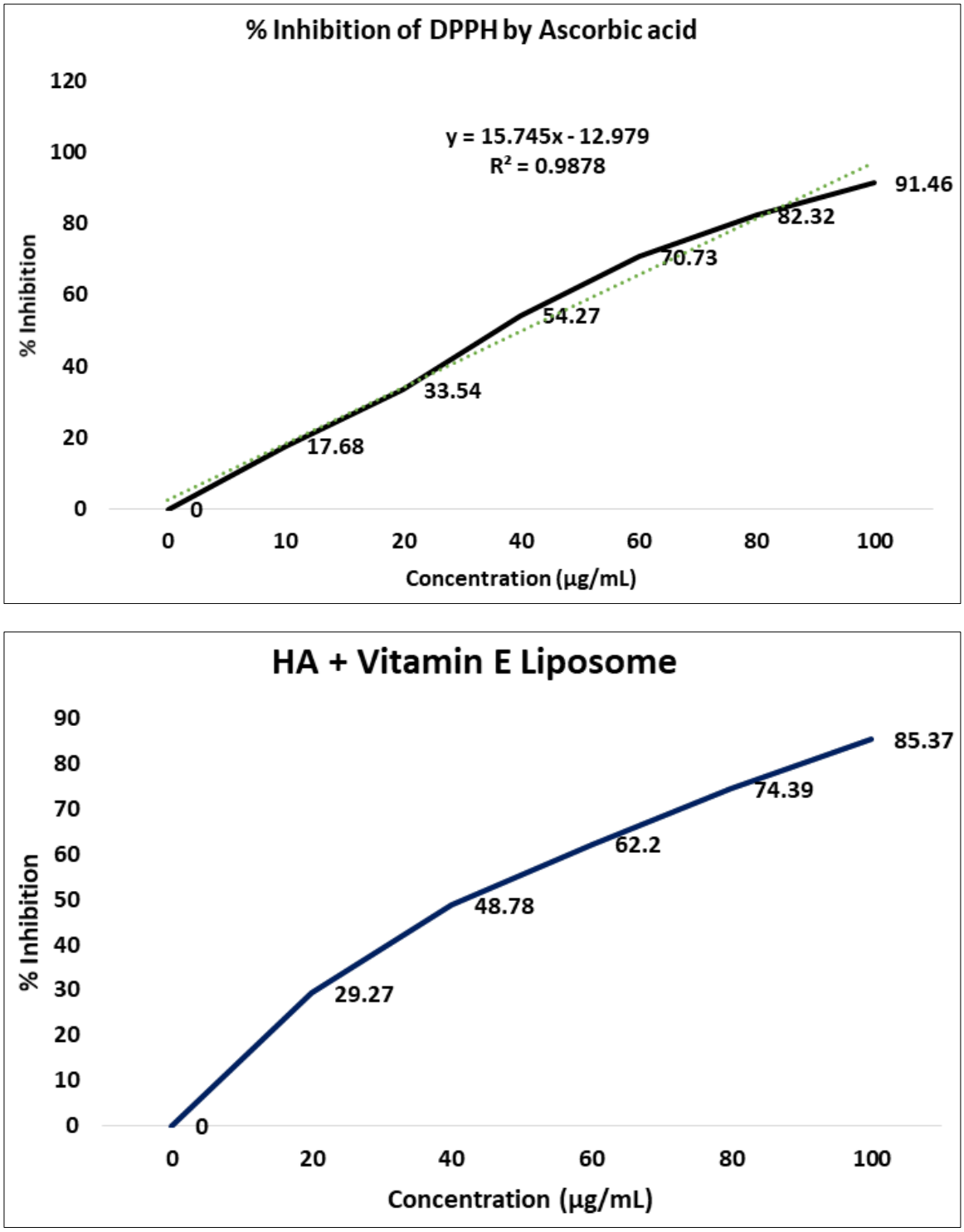

Fig 7: Standard curve of % inhibition of DPPH by ascorbic acid and HA-Vit E-Liposome

3.4 Evaluation of *in vitro* anti-inflammatory activity of HA-Vit E-Liposome

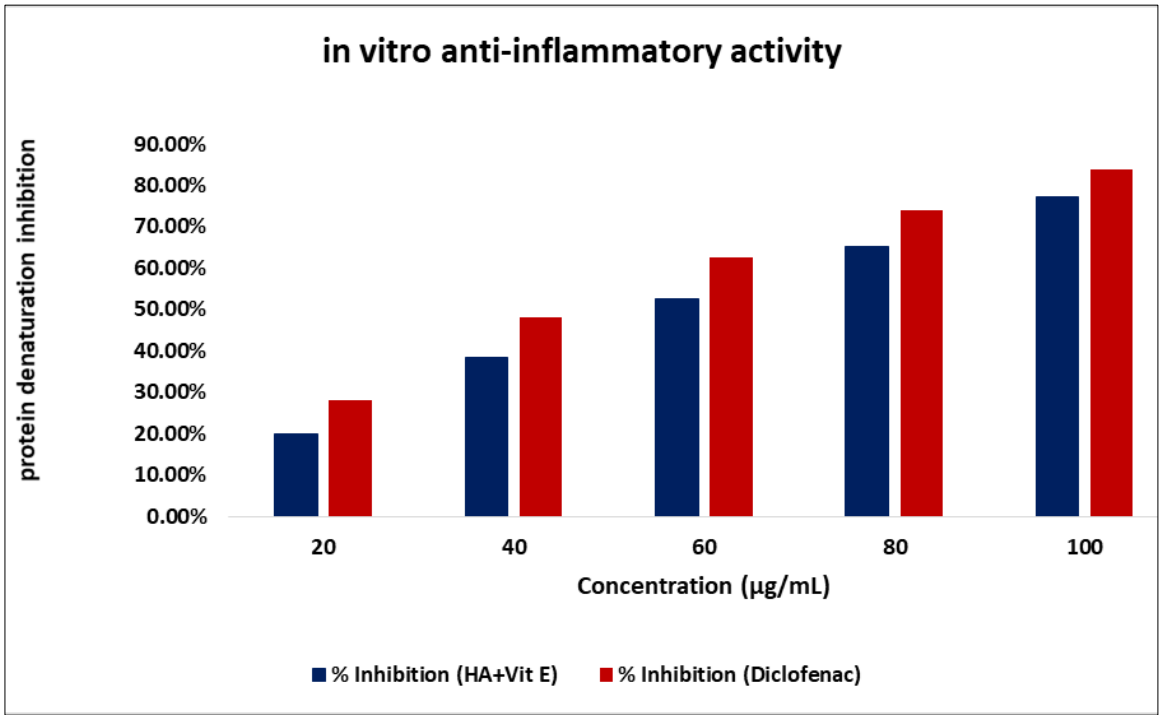

Fig 8: *in vitro* anti-inflammatory activity of HA-Vit E-Liposome

In the present investigation, the *in vitro* anti-inflammatory effect of *HA-Vit E-Liposome* was evaluated against denaturation of egg albumin and results are summarized in fig 8. The present findings exhibited a concentration dependent inhibition of protein (albumin) denaturation by *HA-Vit E-Liposome* throughout the concentration range of 20, 40, 60, 80 and 100µg/ml. Diclofenac sodium (at the concentration range of 20, 40, 60, 80 and 100 µg/ml) was used as reference drug which also exhibited concentration dependent inhibition of protein denaturation. This was further confirmed by comparing their IC50 values.

4. Gel Preparation and Evaluation

4.1. Organoleptic Properties

The final HA-Vit E-liposome-in-Aloe Vera Gel was translucent, pale yellow, with a characteristic aloe vera odor and a bland, non-irritant taste. The gel was smooth, homogenous, and free from visible particulates.

Fig 9: HA-Vit E-liposome-in-Aloe vera gel

4.2. pH

The pH of the gel was measured as 6.8±0.2, which is within the physiological range for oral mucosa, ensuring compatibility and minimizing irritation.

4.3. Viscosity

The viscosity of the gel was found to be 4,500±150 cP at 25°C, providing sufficient thickness for prolonged mucosal retention while allowing easy application.

4.4. Spreadability

Spreadability was measured at 7.2±0.5 cm under a standard load, indicating good ease of application and uniform coverage.

4.5. Skin irritancy test

Skin irritancy testing on healthy volunteer revealed no signs of irritation, redness, or allergic reaction after 24 hours, confirming the safety and biocompatibility of the gel.

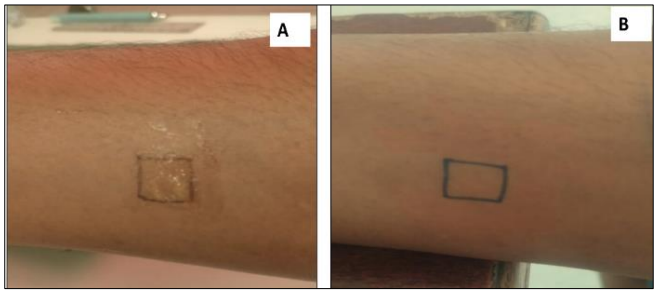

Figure 10 Result of skin irritancy test (a small amount of gel was applied on 1cm square area. A: gel applied, B: After 24 hours leave for 24 hour

Table 5: Evaluation of Gel Properties

Parameter	Result	Parameter	Result
Appearance	Translucent, pale white	Viscosity (cP)	4,500±150
Odor	Characteristic aloe vera	Spreadability (cm)	7.2±0.5
Taste	Bland, non-irritant	Patch Test	No irritation
		pH	6.8±0.2

5. Discussion

Oral submucosal fibrosis is chronic progressive disease particularly found in countries like India, where peoples have habits of chewing pan masala and areca nuts. Clinical manifestation including reducing of mouth opening, white patches in cheek, thickening of cheek wall and burning sensation when eating [1, 2]. Although treatments including antioxidants and antiinlammatory agent from synthetic and herbal based products. However, treatment key therapeutic challenges in OSMF—namely, poor drug bioavailability, inadequate mucosal retention, and the need for sustained antioxidant and anti-fibrotic action. The discussion below integrates the results of this research with existing literature and explores the significance of the findings for future clinical application [14].

The successful preparation of vitamin E-loaded liposomes using the thin film hydration method was confirmed by microscopy, which revealed uniform, spherical vesicles with minimal aggregation. The observed particle size (150-250 nm) is within the optimal range for mucosal penetration and cellular uptake, as previously reported for liposomal oral drug delivery systems [15-16]. The addition of hyaluronic acid (HA) as a surface functionalizer not only improved colloidal stability but also imparted mucoadhesive properties, as evidenced by the absence of aggregation and the enhanced viscosity of the dispersion. This is consistent with the findings of study, who demonstrated that HA-coated liposomes exhibit prolonged retention on mucosal surfaces due to specific interactions with mucin glycoproteins [17].

FTIR analysis further substantiated the successful encapsulation of vitamin E and HA functionalization, as indicated by the presence of characteristic peaks for both components and minor spectral shifts, suggesting molecular interactions. Such interactions are known to stabilize the liposomal structure and potentially modulate the release profile of the encapsulated drug [18].

The *in vitro* release study demonstrated a biphasic pattern, with an initial burst release followed by sustained release. This release profile is desirable for oral mucosal applications, where an initial therapeutic concentration is needed to counteract acute oxidative stress and inflammation, followed by prolonged drug availability for ongoing tissue repair (Qamar *et al.*, 2024). The HA coating was observed to slow the release rate compared to non-functionalized liposomes, likely due to the formation of a hydrated barrier that restricts drug diffusion—a phenomenon also described by Chelu *et al.* (2023).

The antioxidant assays (DPPH and) revealed that the HA-Vit E-liposome formulation exhibited significantly higher free radical scavenging activity than free vitamin E. This enhancement is attributable to improved solubility, protection from degradation, and increased local concentration of vitamin E at the target site. These results are in agreement with previous studies, which have shown that nanoencapsulation of antioxidants can potentiate their bioactivity and therapeutic efficacy [17, 19].

The incorporation of HA-Vit E-liposomes into an Aloe vera gel matrix resulted in a stable, homogenous, and translucent formulation. Aloe vera gel was selected for its well-documented wound healing, anti-inflammatory, and mucoadhesive properties (Chelu *et al.*, 2023; MDPI, 2023). The gel's pH (6.8±0.2) was within the physiological range for oral mucosa, ensuring compatibility and minimizing the risk of irritation. The measured viscosity and Spreadability were suitable for oral application, providing prolonged retention and uniform coverage of the affected mucosal surfaces.

The patch test confirmed the safety and biocompatibility of the formulation, with no observed irritation or allergic reactions in skin. This is an important consideration for patient compliance, as topical oral formulations must not only be effective but also well-tolerated and easy to apply [19].

The composite gel system developed in this study addresses several limitations of current OSMF therapies. First, the sustained release and enhanced mucoadhesion of the HA-Vit E-liposome-in-gel formulation ensure that therapeutic concentrations of vitamin E are maintained at the site of fibrosis, potentially improving clinical outcomes. Second, the antioxidant and anti-inflammatory effects of both vitamin E and Aloe vera may synergistically reduce oxidative stress and promote tissue healing, key factors in the pathogenesis of OSMF (Patel and Kumar, 2021; Chelu *et al.*, 2023).

Furthermore, the use of HA not only improves mucoadhesion but also contributes to wound healing and tissue regeneration, as HA is known to modulate cellular migration and proliferation in the oral mucosa [15]. The combined action of these bioactive components positions the developed formulation as a promising candidate for non-invasive, patient-friendly management of OSMF.

Previous research has explored various delivery systems for antioxidants in OSMF, including gels, sprays, and lozenges [16]. However, the integration of HA-functionalized liposomes within an Aloe vera gel matrix represents a novel approach that leverages advances in nanotechnology and natural biopolymers. Similar composite systems have shown improved drug retention, patient acceptability, and therapeutic efficacy in other oral mucosal conditions [20-21].

6. Conclusion

The HA-functionalized, vitamin E-loaded liposome-in-aloe Vera Gel system offers a promising, non-invasive, and patient-friendly approach for the management of OSMF. The formulation demonstrated optimal physicochemical properties, sustained release, enhanced antioxidant and anti-inflammatory activity, and excellent safety and biocompatibility. Future studies should focus on clinical evaluation and long-term outcomes.

Acknowledgment

Authors are thankful to the Dean and HOD School of Pharmacy, ITM University Gwalior for providing the

facility for conduct of the research work. Authors are also thankful to Dr Varun Singh Kushwaha scientist CDRI for instrumental facility.

Funding Nil.

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