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Research Article

Development and in Vitro Evaluation of *Vitis vinifera* L.-Loaded Oromucosal Mucoadhesive Films for Potential Management of Oral Mucositis

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ABSTRACT

Abstract: Background: Oral mucositis is a painful inflammatory complication of cancer chemotherapy and head-and-neck radiotherapy. Localized mucoadhesive dosage forms may prolong contact of an active material with the oral mucosa. This study aimed to develop Vitis vinifera L.-loaded oromucosal films and compare polymer-based formulations. Methods: Ten solvent-cast formulations (F1–F10) were prepared using hydroxypropyl methylcellulose (HPMC E15) alone or in combination with sodium carboxymethylcellulose, Eudragit RL-100 and Carbopol 934P. Propylene glycol was used as plasticizer. Films were assessed for physical characteristics, surface pH, folding endurance, swelling, residence time, drug content, in-vitro release, ex-vivo permeation and selected in-vitro biological activities. Results: Film surface pH ranged from 6.12 to 6.46. F8 showed the highest folding endurance (178 ± 3 folds), drug content (98.64 ± 0.62%) and a 6-h drug release of 79.6 ± 1.7%. Its residence time was 5.18 ± 0.25 h and cumulative ex-vivo permeation reached 63.7 ± 2.4% at 6 h. F8 also showed FRAP activity of 32.48 µg AAE/g, nitric oxide scavenging of 38.72%, protein-denaturation inhibition of 65.82%, and a 14.2-mm inhibition zone against Streptococcus mutans. Conclusion: Among the tested polymer combinations, F8 demonstrated a balanced

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combination of film integrity, hydration, residence time, drug content and controlled release. The findings support further preclinical investigation; they do not establish clinical efficacy in patients.

INTRODUCTION

Oral mucositis is an inflammatory and ulcerative injury of the oral mucosa that may occur during cytotoxic chemotherapy, radiotherapy involving the head and neck, or haematopoietic stem-cell transplantation. Clinical manifestations include erythema, soreness, ulceration and pain, which can impair eating, swallowing and speaking. Severe mucositis may compromise nutritional intake and interfere with planned cancer treatment [1- 4].

The pathobiology of mucositis is multifactorial. Treatment-related cellular injury initiates oxidative stress and activates inflammatory signalling pathways. Reactive oxygen species, pro-inflammatory cytokines and tissue-damage responses contribute to epithelial breakdown and ulceration. The clinical course therefore involves more than direct epithelial toxicity and may be influenced by treatment regimen, patient-related factors and oral microbial status [3,4].

Current management is based on risk-adapted oral care, prevention, symptom control and interventions supported by clinical evidence. International guidelines emphasize structured oral-care protocols and treatment-specific recommendations. Despite these measures, clinically significant mucositis remains a challenging adverse effect in selected cancer-treatment settings [1,2].

A locally applied dosage form may offer practical advantages by placing the formulation directly at the affected site. Oromucosal films are thin polymeric systems that can hydrate, adhere to mucosal surfaces and release incorporated material over time. Their performance depends on polymer identity and concentration, plasticizer content, film thickness, hydration, mechanical strength and drug-release characteristics [5-7].

Mucoadhesion involves intimate contact between a dosage form and a mucosal surface, followed by interactions between the polymer and mucus or epithelial interface. Hydrophilic polymers can absorb water and form a hydrated interfacial layer, while polymer-chain mobility and interpenetration may contribute to adhesion. The balance between hydration, cohesion and erosion is important: inadequate hydration may limit adhesion, whereas excessive swelling can weaken the film or reduce acceptability.

Vitis vinifera L. is a widely cultivated plant containing diverse phenolic constituents. Grape-derived materials have been investigated for antioxidant and other biological activities. These properties provide a rationale for formulation research, but activity in chemical or in-vitro assays cannot by itself establish therapeutic benefit in oral mucositis.

The present work therefore focused on formulation development and comparative in-vitro evaluation of Vitis vinifera L.-loaded oromucosal adhesive films. Ten polymer-based formulations were prepared and screened to identify a candidate with a useful balance of physical integrity, mucoadhesion-related performance, release and selected biological assay responses.

2. STUDY RATIONALE AND OBJECTIVES

2.1 Rationale

Conventional oral rinses and rapidly cleared topical preparations may provide limited contact time at a localized mucosal site. A thin mucoadhesive film may improve retention and provide a platform for controlled local release. Polymer composition can be adjusted to influence hydration, flexibility, residence time and release rate. Comparing a series of formulations is therefore a suitable preliminary approach to identify a candidate for further development.

2.2 Aim

To formulate and comparatively evaluate Vitis vinifera L.-loaded oromucosal adhesive films for their physicochemical, release and selected in-vitro biological characteristics.

2.3 Objectives

- To assess selected preformulation characteristics of the Vitis vinifera L. extract and its compatibility with the selected excipients.
- To prepare polymer-based oromucosal adhesive films by solvent casting.

- To evaluate physical characteristics, surface pH, folding endurance, swelling, residence time and drug-content uniformity.
- To investigate in-vitro drug release and ex-vivo permeation of the optimized formulation.
- To assess antioxidant, protein-denaturation inhibition and antimicrobial responses under the stated in-vitro test conditions.
- To compare the formulations and select a candidate for further investigation.

3. RELATED SCIENTIFIC BACKGROUND

Clinical reviews and consensus guidance describe oral mucositis as a clinically important complication of cancer therapy and support preventive oral care and evidence-based supportive management [1-4]. Reviews of oral-film technology describe solvent casting as a commonly used manufacturing approach and identify film thickness, mechanical integrity, drug-content uniformity, hydration, mucoadhesion and release as important characterization parameters [5-7].

The present formulation strategy applies these pharmaceutical principles to a plant-derived extract. The work is a formulation and in-vitro screening study; no patient-level efficacy, safety or clinical outcome assessment is reported.

MATERIALS AND METHODS

4.1 Materials

Vitis vinifera L. extract (300 mg per formulation batch) was used as the model active material. HPMC E15 served as the principal film-forming polymer. Sodium carboxymethylcellulose (sodium CMC), Eudragit RL-100 and Carbopol 934P were incorporated in selected combinations to modify film formation, hydration, mucoadhesive behaviour and release. Propylene glycol was used as plasticizer. Ethanol (95%) and purified water were used as processing media as described for the formulation procedure.

4.2 Preformulation assessment

The extract was examined for organoleptic characteristics, solubility in selected solvents, melting point and partition behaviour. Drug–excipient compatibility was screened by comparing FTIR spectra of the extract with physical mixtures containing HPMC E15, Carbopol 934P, sodium CMC, Eudragit RL-100 and propylene glycol. The interpretation considered retention or alteration of characteristic absorption bands. FTIR screening provides preliminary compatibility information and does not replace stability-indicating studies.

4.3 Preparation of films

Ten formulations (F1–F10) were prepared by solvent casting. The calculated quantities of polymers were dispersed in the solvent system. The extract (300 mg) was levigated with propylene glycol and incorporated into the polymeric preparation. The medicated mixtures were allowed to stand overnight to reduce entrapped air and obtain a uniform casting preparation. The mixtures were transferred to aluminium-foil cups of approximately 4.5 cm diameter and dried overnight at room temperature (approximately 25°C). The dried films were removed and cut into circular units of 20 mm diameter. Films were packed in aluminium foil and stored in a desiccator until evaluation.

4.4 Formulation design

F1 contained HPMC E15 as the reference film-forming system. F2–F10 incorporated selected combinations of sodium CMC, Eudragit RL-100 and/or Carbopol 934P with varying HPMC E15 levels. Propylene glycol was maintained at 0.48 mL per formulation in the reported composition design. The formulation series was intended to compare polymer effects rather than different botanical plant parts.

4.5 FORMULATION DESIGN AND EVALUATION

Table 1: Polymer Systems and Intended Formulation Roles

Formulation group	Polymer system	Formulation purpose
F1	HPMC E15	Reference film-forming formulation
F2	HPMC E15 + sodium CMC	Assess sodium CMC contribution to film and mucoadhesion
F3	HPMC E15 + Eudragit RL-100	Assess release-modifying contribution
F4	HPMC E15 + Carbopol 934P	Assess mucoadhesive polymer contribution
F5–F10	HPMC E15 with selected combinations of sodium CMC, Eudragit RL-100 and Carbopol 934P	Compare mixed-polymer systems and polymer-level effects

Each batch contained 0.30 g of Vitis vinifera L. extract. The reported casting volume was 20 mL of solvent medium, and propylene glycol was used as plasticizer. Exact polymer quantities varied across the formulation series.

4.6 Film characterization

Appearance and integrity were assessed visually. Film weight was measured using an analytical balance. Thickness was measured at multiple positions using a calibrated micrometer screw gauge. Surface pH was determined after hydration of the film on agar. Folding endurance was measured by repeatedly folding a film at the same position until cracking or breakage.

Swelling was assessed by recording initial film weight and the hydrated weight at predetermined intervals. Percentage swelling was calculated as $[(W_t - W_0)/W_0] \times 100$, where W_0 is the initial weight and W_t is the weight at the specified time. In-vitro residence time was assessed using a disintegration apparatus with a mucosal membrane fixed to a glass support in phosphate buffer (pH 6.6) at approximately 37 ± 2°C.

Drug content was determined by extracting individual 20-mm film units in phosphate buffer, filtering and analysing suitably diluted samples by UV spectrophotometry at the selected analytical wavelength. Results were expressed as percentage drug content.

4.7 RELEASE, PERMEATION AND BIOLOGICAL EVALUATION

4.7.1 In-vitro drug release

Drug release was studied using a USP dissolution apparatus with 900 mL phosphate buffer (pH 6.6), maintained at 37 ± 0.5°C and 50 rpm for 6 h. Samples were withdrawn at predetermined intervals and replaced with equal volumes of fresh medium maintained at the test temperature. Samples were filtered, diluted and analysed by UV spectrophotometry. Cumulative percentage release was calculated with correction for sample replacement.

4.7.2 Ex-vivo permeation

The optimized film was evaluated using porcine buccal mucosa as the biological membrane. Cumulative permeation was monitored over time. Lag time, flux and permeability coefficient were reported for the optimized formulation.

4.7.3 Antioxidant assays

Ferric reducing antioxidant power (FRAP) was used to assess reducing capacity, expressed as µg ascorbic acid equivalents per gram (µg AAE/g). Nitric oxide radical-scavenging activity was expressed as percentage inhibition. These chemical assays provide comparative in-vitro responses and should not be interpreted as direct evidence of clinical anti-inflammatory efficacy.

4.7.4 Protein-denaturation inhibition assay

In-vitro anti-inflammatory potential was screened by inhibition of heat-induced bovine serum albumin denaturation. The reaction mixture contained 1% w/v BSA and the test preparation. After incubation and heating at 51°C for 20 min, absorbance was measured at 660 nm.

4.7.5 Antimicrobial assay

The optimized F8 film extract was examined by agar-well diffusion against Staphylococcus aureus,

Streptococcus mutans, Escherichia coli and Candida albicans. Zones of inhibition were measured in millimetres and compared with positive and negative controls.

4.8 Data presentation

Numerical results are presented as reported, generally as mean ± standard deviation where available. The underlying individual observations and complete statistical output were not available for independent reanalysis; therefore, no new inferential statistics or claims of statistical significance are made.

RESULTS

5.1 Preformulation findings

The extract was described as a white crystalline, practically odourless solid. Its reported solubility was higher in ethanol (56.06 mg/mL) than in distilled water (5.79 mg/mL), while solubility in phosphate buffer was pH dependent. The reported melting point was 138.35°C. FTIR analysis showed characteristic absorption bands, and the physical-mixture spectra did not show major unexpected changes in the principal bands of the extract with the selected excipients.

5.2 Physical characteristics

Table 2: Physical Characteristics of *Vitis Vinifera* L.-Loaded Films

Formulation	Weight (mg)	Thickness (mm)	Surface pH	Folding endurance
F1	186.4 ± 2.1	0.118 ± 0.004	6.12 ± 0.08	142 ± 4
F2	190.7 ± 2.4	0.124 ± 0.003	6.18 ± 0.06	148 ± 3
F3	193.2 ± 2.0	0.127 ± 0.004	6.21 ± 0.07	151 ± 4
F4	195.6 ± 2.3	0.131 ± 0.005	6.25 ± 0.05	156 ± 3
F5	198.1 ± 2.5	0.135 ± 0.004	6.28 ± 0.06	161 ± 4
F6	201.4 ± 2.2	0.139 ± 0.003	6.31 ± 0.07	166 ± 3
F7	203.6 ± 2.7	0.143 ± 0.005	6.34 ± 0.06	171 ± 4
F8	206.2 ± 2.1	0.146 ± 0.003	6.38 ± 0.05	178 ± 3
F9	209.4 ± 2.6	0.151 ± 0.004	6.42 ± 0.07	174 ± 4
F10	212.8 ± 2.4	0.156 ± 0.005	6.46 ± 0.06	169 ± 3

Film weight and thickness increased progressively across the formulation series. Surface pH ranged from 6.12 to 6.46. F8 showed the highest folding endurance (178 ± 3 folds), indicating the greatest measured flexibility within the tested series.

5.3 SWELLING, RESIDENCE TIME AND DRUG CONTENT

Table 3: Swelling Behaviour and In-Vitro Residence Time

Formulation	1 h (%)	3 h (%)	5 h (%)	Residence (h)
F1	72.4 ± 2.1	118.6 ± 3.2	146.8 ± 3.7	3.12 ± 0.18
F2	78.3 ± 2.4	126.4 ± 3.5	154.7 ± 4.1	3.46 ± 0.21
F3	76.8 ± 2.2	123.7 ± 3.1	151.2 ± 3.8	3.61 ± 0.19
F4	84.6 ± 2.5	138.2 ± 3.6	168.5 ± 4.2	4.18 ± 0.22
F5	81.7 ± 2.3	134.6 ± 3.4	163.8 ± 4.0	4.06 ± 0.20
F6	88.5 ± 2.6	145.3 ± 3.8	176.4 ± 4.3	4.52 ± 0.24
F7	92.7 ± 2.8	151.6 ± 4.0	184.2 ± 4.6	4.76 ± 0.23
F8	90.4 ± 2.5	148.7 ± 3.7	181.6 ± 4.4	5.18 ± 0.25
F9	96.2 ± 2.7	158.4 ± 4.1	192.6 ± 4.8	5.34 ± 0.27
F10	101.8 ± 3.0	165.7 ± 4.3	201.4 ± 5.1	5.48 ± 0.26

All formulations showed progressive hydration. F9 and F10 had higher swelling and residence times than F8, whereas F8 showed a favourable balance of hydration and release characteristics.

Table 4: Drug-content Uniformity

Formulation	Drug content (%)
F1	94.18 ± 1.24
F2	95.36 ± 1.18
F3	96.12 ± 1.09
F4	96.84 ± 1.16
F5	97.26 ± 0.94
F6	97.68 ± 0.88
F7	98.12 ± 0.76
F8	98.64 ± 0.62
F9	98.31 ± 0.71
F10	97.92 ± 0.83

Drug content ranged from 94.18 ± 1.24% to 98.64 ± 0.62%. F8 showed the highest reported content.

5.4 IN-VITRO DRUG RELEASE

All formulations showed progressive release over the 6-h study period. At 6 h, cumulative release ranged from 74.8 ± 1.8% for F10 to 94.8 ± 2.3% for F1. F8 released 79.6 ± 1.7% at 6 h. The slower release observed with the mixed-polymer systems was consistent with increased polymeric control of diffusion.

Table 5: Cumulative In-Vitro Drug Release

Formulation	1 h (%)	2 h (%)	4 h (%)	6 h (%)
F1	28.6	48.7	76.4	94.8
F2	26.8	46.2	73.8	92.6
F3	25.4	43.8	69.7	89.4
F4	24.2	41.6	67.2	87.8
F5	23.6	40.2	65.8	85.6
F6	22.8	38.7	63.4	83.8
F7	21.4	36.8	60.7	81.2
F8	20.8	35.6	58.9	79.6
F9	19.7	34.1	56.8	77.4
F10	18.9	32.8	54.2	74.8

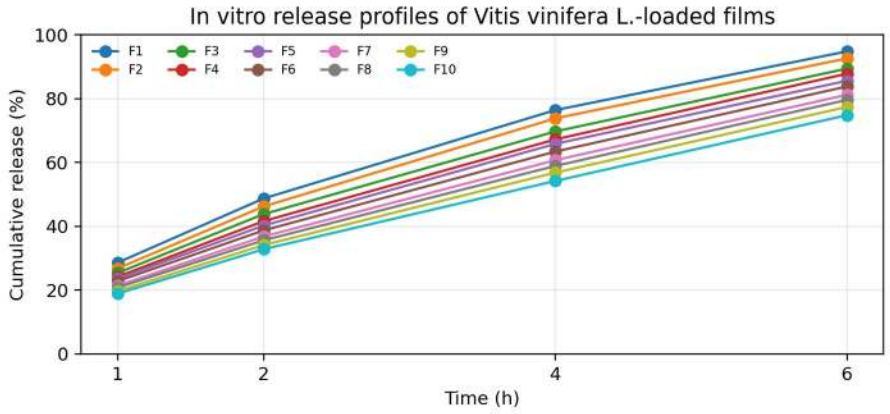


Figure 1: In-vitro Cumulative Release Profiles of Formulations F1–F10.

F1 showed the highest release throughout the study, whereas F9 and F10 showed slower release. F8 was selected as a candidate because it combined substantial release during the 6-h interval with higher measured drug content, folding endurance and residence time than the reference formulation.

5.5 EX-VIVO PERMEATION OF OPTIMIZED FORMULATION

Table 6: Ex-vivo Permeation Characteristics of F8

Parameter	Reported result
Cumulative drug permeated at 1 h	12.8 ± 1.1%

Parameter	Reported result
Cumulative drug permeated at 2 h	24.6 ± 1.5%
Cumulative drug permeated at 4 h	45.8 ± 2.0%
Cumulative drug permeated at 6 h	63.7 ± 2.4%
Lag time	0.72 ± 0.08 h
Flux	18.46 ± 0.82 µg/cm²/h
Permeability coefficient	2.91 ± 0.14 × 10^{-3} cm/h

The cumulative amount permeated through porcine buccal mucosa increased over time and reached 63.7 ± 2.4% at 6 h. The reported flux and permeability coefficient indicate measurable transport under the experimental conditions. These values are specific to the ex-vivo model and should not be extrapolated directly to human absorption or clinical response.

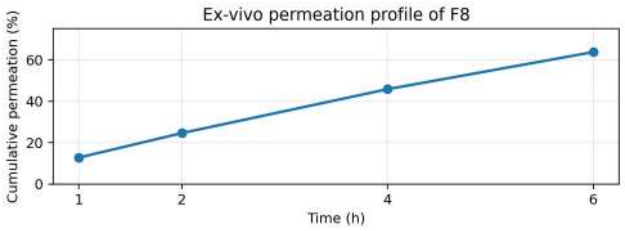


Figure 2: Ex-vivo Permeation Profile of Optimized Formulation F8.

5.6 ANTIOXIDANT AND IN-VITRO ANTI-INFLAMMATORY ASSAYS

Table 7: Antioxidant Assay Responses

Formulation	FRAP (µg AAE/g)	NO scavenging (%)
F1	18.42	18.64
F2	20.16	21.28
F3	21.38	23.46
F4	23.54	26.18
F5	25.72	29.72
F6	27.86	32.84
F7	29.64	35.26
F8	32.48	38.72
F9	30.76	37.16
F10	29.18	35.84

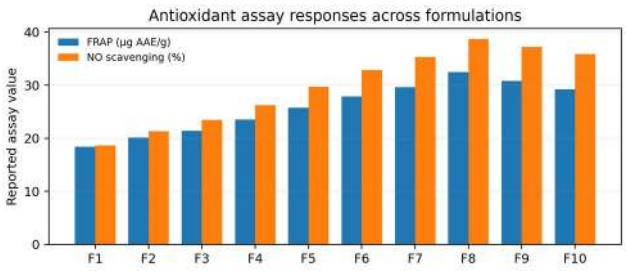


Figure 3: Comparative FRAP and Nitric Oxide-Scavenging Responses.

FRAP activity increased from F1 to F8, reaching 32.48 µg AAE/g, and then declined in F9 and F10. Nitric oxide-scavenging activity followed a similar pattern, with the highest reported value for F8 (38.72%). The pattern identifies F8 as the strongest-performing formulation in these two reported assays.

Table 8: Protein-denaturation Inhibition

Test material	Inhibition (%)
Vitis vinifera L. extract standard	70.46
Optimized film formulation F8	65.82

F8 showed 65.82% inhibition of heat-induced protein denaturation compared with 70.46% for the extract standard. This assay provides an in-vitro screening result only and does not demonstrate clinical anti-inflammatory efficacy.

5.7 ANTIMICROBIAL ACTIVITY OF F8

Table 9: Agar-well Diffusion Results for Optimized Formulation F8

Test microorganism	F8 zone (mm)	Positive control (mm)	Negative control (mm)
Staphylococcus aureus	12.4	22.6	0.0
Streptococcus mutans	14.2	24.8	0.0
Escherichia coli	10.8	21.4	0.0
Candida albicans	11.6	23.2	0.0

The optimized F8 formulation produced measurable inhibition zones against all four test organisms. The largest zone was observed against Streptococcus mutans (14.2 mm), followed by Staphylococcus aureus (12.4 mm), Candida albicans (11.6 mm) and Escherichia coli (10.8 mm). The positive controls produced larger zones, while the negative controls showed no inhibition.

The results indicate antimicrobial activity under the specific agar-diffusion conditions used. Agar diffusion is influenced by sample solubility, diffusion through the medium, inoculum and assay conditions. The data do not establish effectiveness against oral infection or the safety of applying the formulation to damaged mucosa.

5.8 OVERALL FORMULATION SELECTION

F8 was selected as the optimized candidate based on the combined profile: highest folding endurance (178 ± 3 folds), highest drug content (98.64 ± 0.62%), 5.18 ± 0.25 h residence time, 79.6 ± 1.7% release at 6 h, 63.7 ± 2.4% ex-vivo permeation at 6 h, and the highest reported FRAP and nitric oxide-scavenging responses. F9 and F10 showed higher swelling and residence time but slower release.

DISCUSSION

The study demonstrates the feasibility of preparing Vitis vinifera L.-loaded oromucosal films by solvent casting using HPMC E15 and selected secondary polymers. The measured surface pH values (6.12–6.46) were relatively close to neutral, which is a relevant preliminary consideration for mucosal application. Surface pH alone, however, is insufficient to establish mucosal tolerability.

The increase in film weight and thickness across the formulation series reflects changes in polymer composition and loading. Folding endurance increased through F8 and decreased in F9 and F10, suggesting that the polymer balance in F8 provided the best measured resistance to repeated folding. Mechanical testing beyond folding endurance, including tensile strength and elongation, would provide a more complete characterization.

Swelling and residence time increased with changes in polymer composition. F9 and F10 exhibited greater swelling and longer residence times than F8. However, the highest swelling or residence time does not necessarily indicate the most suitable film. Excessive hydration can affect cohesion, handling and release. F8 provided an intermediate swelling response while retaining a residence time exceeding 5 h.

Drug-content values were consistently high across the series, with F8 giving the highest reported result. This suggests reasonably uniform distribution of extract within the tested film units. The release profiles showed that F1 released the greatest proportion of extract, while the polymer-rich systems slowed release. F8 offered a compromise between release extent and prolonged retention-related characteristics.

The ex-vivo permeation study demonstrated time-dependent transport through porcine buccal mucosa. Such an experiment is useful for comparing formulations,

but tissue source, tissue integrity, membrane thickness, exposed area, receptor-medium composition and sink conditions can influence the result. Further validation and detailed reporting of these parameters are needed before translating the findings.

F8 also showed the highest responses in the reported FRAP and nitric oxide-scavenging assays and appreciable inhibition of protein denaturation. These observations are consistent with in-vitro antioxidant and protein-protective responses. The assays are mechanistic screens and should not be interpreted as proof that the formulation prevents or treats mucositis in patients.

The antimicrobial assay showed measurable zones of inhibition, particularly against Streptococcus mutans. The positive controls showed larger zones, and the test should be regarded as preliminary. Additional controls, standardized concentrations, minimum inhibitory concentration testing and evaluation against clinically relevant oral isolates would strengthen the microbiological assessment.

Overall, the comparative data support F8 as a lead formulation for further pharmaceutical development. The study does not include clinical testing, and no conclusion about patient benefit, healing of mucosal lesions or prevention of cancer-treatment interruptions can be drawn.

CONCLUSION

Ten Vitis vinifera L.-loaded oromucosal adhesive film formulations were prepared using solvent casting and evaluated for selected physicochemical, release, permeation and in-vitro biological characteristics. Formulation F8 showed a favourable overall profile, including surface pH of 6.38 ± 0.05, folding endurance of 178 ± 3 folds, swelling of 90.4 ± 2.5%, 148.7 ± 3.7% and 181.6 ± 4.4% at 1, 3 and 5 h, respectively, and residence time of 5.18 ± 0.25 h. Drug content was 98.64 ± 0.62%, and cumulative in-vitro release reached 79.6 ± 1.7% at 6 h. Ex-vivo permeation through porcine buccal mucosa reached 63.7 ± 2.4% at 6 h.

F8 also showed the highest reported FRAP response (32.48 µg AAE/g) and nitric oxide-scavenging activity (38.72%), 65.82% inhibition in the protein-denaturation assay and measurable antimicrobial activity. Based on the combined results, F8 was selected as the most balanced formulation among those evaluated.

8. STUDY LIMITATIONS AND FUTURE WORK

The findings are limited to the reported formulation and in-vitro/ex-vivo tests. The experimental work described evaluates a single Vitis vinifera L. extract rather than separately prepared extracts from different plant parts; therefore, comparative claims between grape skin, seed, pulp, leaf or other plant parts are not supported by these data. The extract identity, plant-part origin, extraction yield and detailed phytochemical standardization should be fully documented in the final submission.

Further work should include validated analytical quantification of marker constituents, complete mechanical characterization, mucoadhesive strength testing, stability studies, microbial quality assessment, mucosal irritation/cytotoxicity studies, and appropriately designed preclinical studies. Clinical evaluation would be required before any therapeutic claim for oral mucositis could be made.

DECLARATIONS

Ethics approval:

Not applicable to the reported in-vitro formulation and assay work; confirm whether institutional approval or tissue-source authorization was required for the porcine buccal membrane study.

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Conflict of interest:

The authors confirms and declare no competing interests.

Author contributions:

K. Gobinath: supervision and conceptual guidance; Vishnu P: experimental work, data compilation and manuscript drafting; P. Perumal: institutional oversight.

Data availability: The data supporting the findings are presented in the tables and figures of this article. Underlying raw observations should be retained by the investigators and made available in accordance with journal policy.

Abbreviations:

BSA, bovine serum albumin; FRAP, ferric reducing antioxidant power; HPMC, hydroxypropyl methylcellulose; NO, nitric oxide; SD, standard deviation.

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