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Original Article

Mucoadhesive Films of Liquorice and Chlorhexidine Gluconate for Treating Mouth Ulcers

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ABSTRACT

Objectives: Mouth ulcer is a rupture or breaks in the oral mucosal membrane and it leads to atrophy and ulcers in the oral cavity. It increases the risk of infections with the *Candida* species Inherited trauma and aphthous stomatitis, a disorder characterised by the recurrent production of oral ulcers for unknown reasons, are the most common causes of oral ulceration. **Study Design:** This study aimed to develop two separates buccal mucoadhesive films, using model drug deglycyrrhizinated liquorice and chlorhexidine gluconate. The film was assessed for weight, thickness, pH, folding endurance, swelling index, mucoadhesive force, % moisture content, drug uniformity, *in vitro* release of drug, anti-microbial effect including anti-inflammatory activity and scanning electron microscopy. The developed formulations we re-evaluated for surface pH, folding endurance, swelling index, mucoadhesive force, and percentage moisture loss. **Results and Conclusion:** The results showed that the developed oral films were having good anti-inflammatory activity with an anti-microbial effect.

Keywords: Deglycyrrhizinated liquorice, Chlorhexidine gluconate, Mucoadhesive buccal films, Anti-inflammatory activity.

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INTRODUCTION

Oral ulcers lead to disorders of the oral mucosa that affect approximately 20% of the overall population, whereas the young population is more vulnerable. They are typically developed as tender persistent, multiple ulcers, lasting 10-14 days with a little scar-forming potential.[1] These are the lesions or sores, which develop in the mucous membranes of the mouth and the lips. They are caused by lesions in the epithelial lining of the oral cavity.[2] They appear to be round, white or grey, often swollen and red on the edges. Such lesions can appear on the inside of the cheeks, inside of the lips, underneath the tongue, or on the soft palate.[3] The size of the lesions could vary from a millimeter or less in diameter to a few centimeters.

If the mouth ulcers last for less three weeks, they are called "acute," while if they last longer than 3 weeks, they are termed "chronic".[4] Mouth ulcers can be recurring in some circumstances. Oral ulcers could be linked to a systemic condition or a specific medicine.[5]

Liquorice (taproot; *Glycyrrhiza glabra*) belongs to the family *Leguminosae*. Liquorice is one of the most widely used and extensively researched medicinal plants in the world. It is recognized for its anti-inflammatory and anti-allergic effects.[6] This effect is due to the result of glycyrrhizin on the surreal gland, the body's anti-inflammatory steroid hormone, cortisol.[7]

Chlorhexidine is a cationic polybiguanide and functions upon application as an antimicrobial agent. It functions by reducing the number of pathogenic bacteria. The chlorhexidine salt dissolves at physiological pH, as well as the cationic molecule bind to the negative charge of bacterial cell wall, producing a bactericidal action.[8] Mucoadhesion is defined as the attachment of a molecule to a mucosal surface through an adequate transporter owing to the mucous membrane's surface charge. Mucoadhesive buccal films are a novel drug delivery approach that breaks down or dissolves inside the oral cavity.[9] The Mucoadhesion process is the close contact between a bioadhesive material and a biological membrane using ionic interactions upon hydration. Due to retention on the biological absorption site, the penetration of loaded drugs can be enhanced thus bioavailability. The mucoadhesive films can easily hydrate when coming in contact with saliva and stick to the site of application in the oral cavity. This approach could be beneficial in conditions like mouth ulcers with enhanced retention time. As a result, the goal of this research is to create liquorice-based mucoadhesive films in combination of chlorhexidine gluconate to treat the ulcers.

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MATERIALS AND METHODS

Materials

Chlorhexidine gluconate was a generous gift sample received from Unilab Chemicals and Pharmaceuticals Pvt. Ltd., India and Degycyrrhizinated liquorice was purchased from Yucca Enterprises, Mumbai, India. The polymers used were hydroxypropyl methylcellulose 15cps (SD fine-chem limited, India), Polyvinyl alcohol (Research-Lab Fine Chemicals, India) and polyvinyl pyrrolidinone K30 (Spectrochem Pvt. Ltd., India). The propylene glycol (Research-Lab Fine chemicals, India) was used as the plasticizer in the formulations. Ethanol and distilled water were used as casting solvents.

Preparation of deglycyrrhizinated liquorice

Liquorice extract have been shown to hasten the repair of intestinal ulcers (particularly in the esophagus and the stomach), possibly due to its antioxidant properties. About 200 mL of distilled water was boiled in a 1000 mL beaker. To this 50 g of the liquorice powder was added and the temperature was maintained (40-52°C). In the mixture, 4N sulfuric acid was added slowly with continuous stirring for 15 min while maintaining pH at 2.5. After stirring, the solution of syrupy mass was allowed to settle overnight. The solution was decanted and centrifuged at 16000 rpm for 20 min. A brown-colored liquid extract was obtained. The extract was neutralized with pure ammonia. The solution was evaporated at low temperature on a petri dish. The extract was kept for overnight drying in an oven at 40°C.[10]

Preparation of mucoadhesive buccal films of deglycyrrhizinated liquorice

The films were made with polymers polyvinyl alcohol, polyvinyl pyrrolidone K-30, and hydroxypropyl methylcellulose (15cps) in 3%, 1.2%, 1.8% and 2%, 0.8%, 1% w/v respectively, using a solvent casting process. To this polyvinyl alcohol was added slowly in hot water with constant stirring on a magnetic stirrer until a clear solution was obtained. To this polyvinyl pyrrolidone, K30 was added and solubilized followed by cooling at room temperature and addition of ethanol (10 mL) and hydroxypropyl methylcellulose (15cps) under constant stirring. To this Propylene glycol (3 mL) as plasticizer and benzalkonium chloride, 0.01 mL as a preservative were added. The mixture was constantly stirred until a clear solution was obtained. The deglycyrrhizinated liquorice (3.25 g) was progressively introduced to the aforementioned mixture while stirring constantly, and the entrapped air was removed under vacuum. Then the solution was poured into a petri dish and allowed to dry overnight at room temperature followed by drying in the oven at 40°C. The films were then removed carefully, and 1 cm diameter circular films was cut and bundled in aluminium foils before being kept in a desiccator. The compositions of the films are given in Table 1.

Table 1: Compositions of mucoadhesive buccal films of deglycyrrhizinated liquorice.

Pharmacopeial name	Drug loaded batches	
	F1	F2
Deglycyrrhizinated Liquorice	3.25g	3.25g
Polyvinyl Alcohol	900mg	600mg
Polyvinyl pyrrolidone K30	360mg	240mg
Hydroxypropyl methyl cellulose (15 cps)	540mg	300mg
Benzalkonium chloride	0.01ml	0.01ml
Ethanol	10ml	10ml
Propylene glycol	3ml	3ml
Water	Q.S.	Q.S.
Quantity of solution	30ml	30ml

Preparation of mucoadhesive buccal film of chlorhexidine gluconate

Mucoadhesive buccal films of chlorhexidine gluconate were prepared using polyvinyl alcohol, polyvinyl pyrrolidone K30 and hydroxypropyl methylcellulose 15 cps as mucoadhesive polymers. A solvent casting approach was used to create the mucoadhesive films. The required quantity of polyvinyl alcohol (3% and 2% w/v) was gradually added in hot distilled water followed by the addition of polyvinyl pyrrolidone K30 (1.2% and 0.8% w/v) under constant stirring. To the above solution ethanol (10 mL) was added followed by the addition of hydroxypropyl methylcellulose 15 cps at room temperature under stirring to obtain a clear solution. To this solution propylene glycol (3 mL) and benzalkonium chloride, 0.01 mL was added as the plasticizer and preservative respectively. To the above solution, Chlorhexidine gluconate (702 mg) was added drop-wise under stirring. The drug-loaded film contained a final concentration of 10.8 mg of drug per centimetre square of film. The drug solution was poured onto a petri plate and let to completely dry overnight before being dried in a 40°C oven. The films were removed carefully, and circular films with a diameter of 1 cm was cut. The films were preserved in a desiccator after being wrapped in aluminium foil. The compositions of the films are given in Table 2.

Evaluation of the mucoadhesive buccal films

Weight uniformity of the buccal films

The weight homogeneity of 3 distinct films were tested. An analytical balance was used to calculate the average weights of the films.

Thickness of the oral buccal films

A computerized Vernier calliper was used to measure the thickness of the film at three separate places. The film's average thickness was measured and reported.

Table 2: Compositions of mucoadhesive films of chlorhexidine gluconate.

Pharmacopeial name	Drug loaded batches	
	G1	G2
Chlorhexidine gluconate	792.06mg	792.06mg
Polyvinyl alcohol	900mg	600mg
Polyvinyl pyrrolidone (K 30)	360mg	240mg
Hydroxypropyl methyl cellulose (15)	540mg	300mg
Benzalkonium chloride	0.01ml	0.01ml
Ethanol	10ml	10ml
Propylene glycol	3ml	3ml
Water	Q.S.	Q.S.
Quantity of gel	30ml	30ml

Surface pH

The surface pH is indeed an essential parameter since it helps to identify whether or not a product may cause mucosal distress when applied. Warm isotonic phosphate buffer (pH 6.8) was put into a petri dish containing films and left to hydrate at room temp. The surface pH of the swelling mucoadhesive buccal films was determined by putting a pH paper on the surface.

Swelling index

In triplicate, the films were allowed to swell on an agar plate held at 37°C in an incubator. Measurement of the diameter of the swollen mucoadhesive films was done after one-hour intervals and the per cent increase in swelling was calculated as.

$$\text{Percentage swelling} = [(X_t - X_0)/X_0] \times 100$$

Where,

X_t is the diameter of the swollen patch after time

t and X_0 is the original patch diameter at zero time.

Folding endurance

The folding endurance test is used to measure the mucoadhesive films' flexibility during storage. The folding endurance test was performed by physically bending the particular film up to 300 times or until it snapped at the same location. The number of folding durability was defined by the amount of times the film could be folded at the same location without splitting, and the mean was recorded.[11]

Drug content uniformity

A phosphate buffer with a pH of 6.8 was used to dissolve the drug-loaded films. A Whatman filter paper was used to filter the mixture. After sufficient dilutions, the extract was filtered of deglycyrrhizinated liquorice films and chlorhexidine gluconate films were examined using UV spectroscopy at 257 nm and 254 nm, respectively.

Mucoadhesion of the films

A modified assembly was used to determine the films' mucoadhesion. Employing cyanoacrylate glue, the films were adhered to a microscope slide. For initial hydrating and swelling, the film was held in contact with phosphate buffer at pH 6.8 at 37±1 for thirty seconds. To separate the film, this was brought into contact with another slide and weight was applied. The detachment force is used to calculate the buccal film's mucoadhesive strength in gram.[12]

$$\text{Force of adhesion (N)} = \text{Bioadhesive strength (g)} \times 9.8 / 1000$$

$$\text{Bond strength} = \text{Force of adhesion/surface area}$$

Anti-inflammatory activity
Inhibition of protein denaturation

One percent aqueous bovine serum albumin (4.5 mL) was combined with deglycyrrhizinated liquorice (0.5 mL)/ chlorhexidine gluconate in the reaction mixture (0.5 mL). Hydrochloric acid was used to alter the pH of the reaction solution. For 20 min, the reaction samples were incubated at 37°C. After that, the samples were heated to 51°C and kept there for 20 min. The turbidity was measured spectrophotometrically at 660 nm after the materials were cooled. The following formula was used to compute the % inhibition of denaturation of protein:[13]

$$\text{Percentage inhibition} = [(Abs_{control} - Abs_{sample})/ Abs_{control}] \times 100$$

Where,

$Abs_{control}$ = Absorbance of a solution without the drug/extract i.e., with water

Abs_{sample} = Absorbance of a solution with deglycyrrhizinated liquorice /chlorhexidine gluconate

Percentage moisture loss (PML)

Internal moisture was maintained by placing the film in a desiccator containing calcium chloride. The film was removed after 3 days and weighed again to determine the percentage moisture loss using procedure below.[14]

$$\text{Percentage Moisture Loss (PML)} = \text{Initial Weight} - \text{Final weight}/\text{Initial weight} \times 100$$

In vitro drug release study

The *in vitro* drug release investigation was conducted out utilising a Franz diffusion device with phosphate buffer pH 6.8 as the dissolving media and 37 ± 0.5°C as the operating temperature. Cellophane membrane was used as the semi-permeable diffusion membrane. Mucoadhesive films of 1 cm^2 were placed on the diffusion membrane and were continuously hydrated using the

phosphate buffer. At each hour, 1 mL of sample was removed from the receptor compartment to maintain the sink state. UV spectrophotometry was used to examine the specimens.

Determination of the antimicrobial activity

In vitro antimicrobial activity of developed mucoadhesive buccal films was determined using the agar diffusion technique against *Staphylococcus aureus.*[15] The bacterial suspension extended over the nutrient agar surface. The plates were allowed to be set by covering the Petri plate with the lid. The buccal films were placed on the surface of the nutrient agar plate which was inoculated. The plates were kept in an incubator at 37°C for 24 hr, and then the diameters of the inhibition zones formed were measured.

Scanning electron microscopy (SEM)

The surface topography and texture of the film surface, as well as the morphology of the film surface, are determined using scanning electron microscopy.[16] The surfaces of mucoadhesive buccal films with varying medication and polymer proportions; during SEM inspection, the morphology and porosity of the film studies may be determined (The model of the SEM instrument used is FEI QUANTA 200 with 500X, 1000X and 4000X magnification).

RESULTS AND DISCUSSION

The polymers polyvinyl alcohol, polyvinyl pyrrolidone K30, and hydroxypropyl methylcellulose were used to make mucoadhesive films using a solvent casting approach. As a plasticizer and penetration booster, propylene glycol was employed.

Evaluation of mucoadhesive buccal films

Weight fluctuation, thickness, surface pH, percentage of swelling, percentage of moisture loss, folding durability, drug content, mucoadhesive force, and anti-inflammatory efficacy were assessed in mucoadhesive buccal films containing deglycyrrhizinated liquorice and chlorhexidine (Table 3 and Table 4). The *in vitro* drug release and scanning electron microscopy are described below (Figure 1).

Weight of the films

The weight of three films of each formulation taken with the help of digital balance indicate that the film with the least amount of polymer i.e., F2 and G2 have the least weight (Table 3 and Table 4).

Thickness of the films

The thickness of three films of each formulation was taken with the help of a digital Vernier calliper. The results showed that the formulation G1 has a minimum thickness (Table 3 and Table 4).

Surface pH

The surface pH of the films was evaluated because acidic or alkaline pH can alter or induce irritation to the buccal mucosa and influence the rate of hydration of the polymers. The pH range of all mucoadhesive film compositions was within the salivary pH range, ranging from 6.40 to 6.80 (Table 3 and Table 4). Hence, they should not cause any irritation which is important for good patient compliance.

Table 3: Evaluation of mucoadhesive buccal films of deglycyrrhizinated liquorice.

Sl. No.	Evaluation tests	Batch Detail	
		F1	F2
1	Weight (mg)	22.3+1.26	19.97+1.04
2	Thickness (mm)	0.31+2.98	0.33+3.03
3	Surface pH	6.5+3.08	6.4+3.13
4	Swelling index	77.33+3.25	68.67+2.22
5	Folding endurance	305+0.98	300.65+0.63
6	Drug content uniformity	95.36+1.95	93.83+2.05
7	Mucoadhesive force	5.23+0.31	5.1+1.96
8	Anti-inflammatory activity	38.07+0.21	37.37+1.15
9	Percentage Moisture Loss	7.55+0.79	7.90+0.39

Table 4: Evaluation of mucoadhesive buccal films of chlorhexidine gluconate.

Sl. No.	Evaluation tests	Batch Detail	
		G1	G2
1	Weight (mg)	61.23+1.33	58.36+1.29
2	Thickness (mm)	0.76+1.75	0.79+1.27
3	Surface Ph	6.8+2.94	6.57+3.17
4	Swelling index	87+2.30	82.33+1.86
5	Folding endurance	341.33+0.94	318.67+1.10
6	Drug content uniformity	98.67+0.77	94.53+1.00
7	Mucoadhesive force	7.63+0.25	6.53+0.26
8	Anti-inflammatory activity	72.03+0.06	68.75+1.46
9	Percentage Moisture Loss	4.52+0.39	5.35+0.25

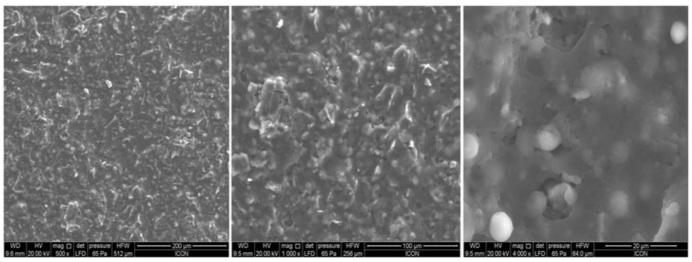

Figure 1: Scanning electron microscopy of mucoadhesive buccal film of Deglycyrrhizinated liquorice and Chlorhexidine gluconate.

Swelling index

The swelling behaviour of the polymer is critical in determining the polymer's bio-adhesive properties. The adhesion happens

quickly after swelling, however the connection is poor. The degree of hydration increases the adhesion until it reaches the point of disentanglement at the polymer tissue surface, when it abruptly drops in adhesive strength due to overhydration. Due to the presence of a larger quantity of HPMC, the formulation DG1/016 demonstrated the highest swelling percentage (87+2.30) (Table 3 and Table 4).

Folding endurance

The folding endurance was measured manually by repeatedly folding the films at a point until they broke. The number of folding without breaking gave the value of the folding endurance. The breakdown time at the eventual end was therefore obtained. The F1 formula reveals optimum endurance for folding. Folding endurance makes the film more acceptable for mouth movement, indicating good resistance and elasticity. Folding endurance testing shows that the films during the regime would maintain dependability with buccal mucosa. The folding endurance was found to have been increased with the addition of PVP with HPMC (Table 3 and Table 4).

Drug content uniformity

The observed results of drug content uniformity indicate the uniform distribution of drugs with minimum variability. The percentage of drug recovery was found to be in the range of 97.8 to 99.2% (Table 3 and Table 4).

Mucoadhesion of the films

Mouth ulcers being painful sores on the inside lining of the mouth have inflammation and redness as the main aetiology. The maximum mucoadhesive force has been observed in the formulation of F1. The combination of hydroxypropyl methylcellulose along with polyvinyl alcohol showed the best mucoadhesion (Table 3 and Table 4).

Anti-inflammatory activity evaluation

Inflammation is the response to injury by living on the tissues. It includes a complex series of activation of enzymes, release of mediators, cell migration, breakdown and repair of tissues.[17] A further method of showing the anti-inflammatory capacity is the reduction in protein denaturation. Protein denaturation is a pathological process in which diminishes their function and lose their configuration. When proteins are subjected to external stress, such as heat, a strong acid, or a strong basic, this happens. External influences induce the organic or inorganic solvents of proteins to lose their tertiary and secondary structure, as well as their functional capabilities. Denaturation of proteins can occur even through autoimmune inflammatory processes in which auto-antigen production is increased as in rheumatoid arthritis. Thus, an effective anti-inflammatory agent can be any product that prevents protein denaturation.

The method described by Mizushima and Kobayashi[18] and Sakat *et al.*[19] was adopted with minor modifications. In contrast to chlorhexidine buccal film; Liquorice's mucoadhesive buccal film showed strong anti-inflammatory efficacy, suggesting apparent therapeutic benefits. The maximum protein denaturation inhibition was detected with formulation F1. Liquorice contains glycyrrhizic acid that inhibits all inflammation-causing factors. It inhibits cyclooxygenase and prostaglandin activity (specifically prostaglandin E2). Thus, ulcer healing is promoted.

Percentage Moisture Loss (PML)

Percentage moisture loss was used to assess the films' physical stability and integrity. The largest percentage of moisture loss was found in the formulation G2, at 7.90+0.39 percent.

In vitro drug release study

Drug release experiments of the mucoadhesive film were carried out *in vitro* with a dissolving media of pH 6.8 phosphate buffer. UV spectrophotometry was used to measure the drug concentration (Figure 2).

The release patterns of deglycyrrhizinated liquorice and Chlorhexidine gluconate film differed significantly (Figure 3).

Antimicrobial activity of the mucoadhesive buccal films

As shown in Figure 4, Chlorhexidine gluconate showed a microbicidal effect against *Staphylococcus aureus,* when evaluated in various concentrations. Whereas no antimicrobial activity was found for deglycyrrhizinated liquorice.[20] Hence it can be concluded that liquorice does not possess antimicrobial activity but is still able to soothe the ulcers by providing an anti-inflammatory effect. Also, the anti-inflammatory activity is enhanced in the presence of glycyrrhizin acid that inhibits all inflammation-causing factors.

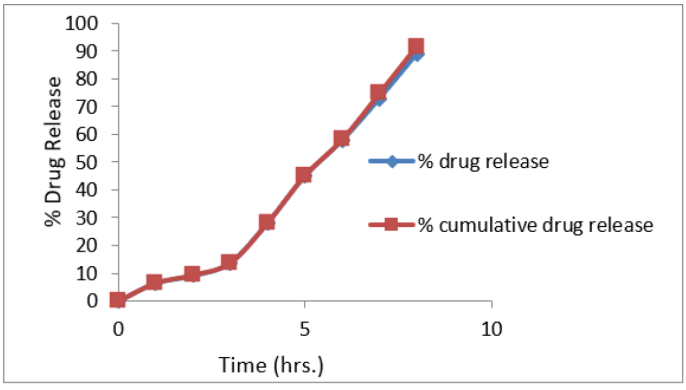

Figure 2: Percentage drug release and percentage cumulative drug release of deglycyrrhizinated liquorice film.

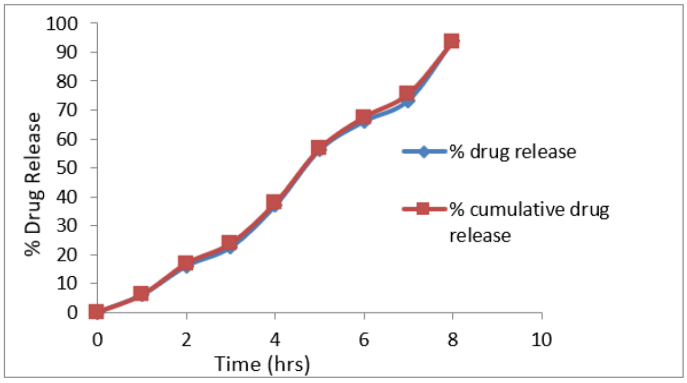

Figure 3: Percentage drug release and percentage cumulative drug release of Chlorhexidine gluconate.

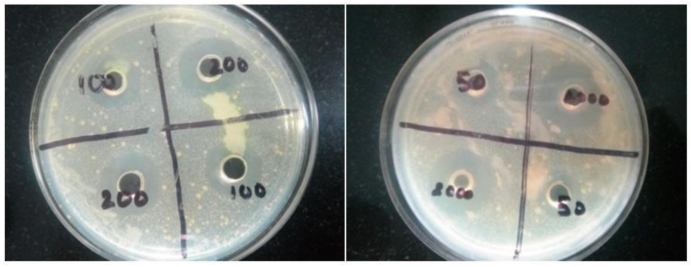

Figure 4: Zone of Inhibition of Chlorhexidine gluconate.

CONCLUSION

Mouth ulcers are painful sores on the inside lining of the mouth that are caused by inflammation and redness. Deglycyrrhizinated liquorice and chlorhexidine gluconate were used to make mucoadhesive buccal films. The mucoadhesive buccal films of deglycyrrhizinated liquorice (F1) were discovered to be the potent formulation for the treatment of mouth ulcers based on the findings of analysing the mucoadhesive buccal films of deglycyrrhizinated liquorice (F1). Thus, it can be concluded that the mucoadhesive film of deglycyrrhizinated liquorice (F1) can be helpful for the effective management of mouth ulcers with the sustained and localized release of deglycyrrhizinated liquorice owing to its anti-inflammatory activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

UV: Ultra violet; **ABS:** Absorbance; **PML:** Percentage moisture loss; **SEM:** Scanning electron microscopy; **HPMC:** Hydroxypropyl methylcellulose.

SUMMARY

- Inflammation and redness are the main causes of mouth ulcers, which are painful sores on the inside lining of the mouth.
- Mucoadhesive buccal films of deglycyrrhizinated liquorice and chlorhexidine gluconate were prepared. Based on the results of evaluating the mucoadhesive buccal films of deglycyrrhizinated liquorice (F1) was found to be the potent formulation for the treatment of mouth ulcers.
- The mucoadhesive film of deglycyrrhizinated liquorice (F1) can be helpful for the effective management of mouth ulcers with the sustained and localized release of deglycyrrhizinated liquorice owing to its anti-inflammatory activity.

REFERENCES

1. Zhang C, Liu Y, Li W, Gao P, Xiang D, Ren X, *et al*. Mucoadhesive buccal film containing ornidazole and dexamethasone for oral ulcers: *In vitro* and *in vivo* studies. Pharm Dev Technol. 2019;24(1):118-26. doi: 10.1080/10837450.2018.1428814, PMID 29334299.
2. Dantas JBdL, Martins GB, Lima HR, Carrera MP, De Almeida Reis SR, Medrado AP. immunopathogenesis of oral mucositis induced by chemotherapy and/or radiotherapy: State of art. Braz J Med Hum Health. 2017;5(2):63-74. doi: 10.17267/2317-3386bjmhh.v5i2.1286.
3. Morbus Adamantiades-Behçet KL. Epidemiologie und Moderne therapeutische Optionen; 2009.
4. Tell A, Egenvall A, Lundström T, Wattle O. The prevalence of oral ulceration in Swedish horses when ridden with bit and bridle and when unridden. Vet J. 2008;178(3):405-10. doi: 10.1016/j.tvjl.2008.09.020, PMID 19027332.
5. Dudding T, Haworth S, Lind PA, Sathirapongsasuti JF, 23 and Me Research Team, Tung JY, *et al*. Genome wide analysis for mouth ulcers identifies associations at immune regulatory loci. Nat Commun. 2019;10(1):1052. doi: 10.1038/s41467-019-08923-6, PMID 30837455.
6. Mamedov NA, Egamberdieva D. Phytochemical constituents and pharmacological effects of licorice: A review. Plant and Human Health, Volume 3. Springer; 2019:1-21.
7. Alagawany M, Elnesr SS, Farag MR. Use of liquorice (*Glycyrrhiza glabra*) in poultry nutrition: Global impacts on performance, carcass and meat quality. Worlds Poult Sci J. 2019;75(2):293-304. doi: 10.1017/S0043933919000059.
8. Linhartová L, Michalíková K, Šrédlová K, Cajthaml T. Biodegradability of dental care antimicrobial agents chlorhexidine and octenidine by ligninolytic fungi. Molecules. 2020;25(2):400. doi: 10.3390/molecules25020400, PMID 31963668.
9. Baus RA, Haug MF, Leichner C, Jelkmann M, Bernkop-Schnürch A. *In vitro-In vivo* Correlation of Mucoadhesion Studies on Buccal Mucosa. Mol Pharm. 2019;16(6):2719-27. doi: 10.1021/acs.molpharmaceut.9b00254, PMID 31038970.
10. Zagt JMA. Process for deglycyrrhizinating licorice: Google Patents 1962.
11. Lei C, Zhang Y, Liu D, Wu K, Fu Q. Metal-levelly robust, folding-endurance and highly temperature-stable MXene-based film with engineered aramid nanofiber for extreme-condition electromagnetic interference shielding applications. ACS Appl Mater Interfaces. 2020;12(23):26485-95. doi: 10.1021/acsami.0c07387, PMID 32432452.
12. Di Prima G, Conigliaro A, De Caro V. Mucoadhesive polymeric films to enhance barbaloin penetration into buccal mucosa: A novel approach to chemoprevention. AAPS Pharm Sci Tech. 2019;20(1):18. doi: 10.1208/s12249-018-1202-1, PMID 30603884.
13. Sangeetha R, Arulpandi I. Anti-inflammatory activity of a serine protease produced from *Bacillus pumilus* SG2. Biocatal Agric Biotechnol. 2019;19:101162. doi: 10.1016/j.bcab.2019.101162.
14. Baskar C, Nesakumar N, Kesavan S, Balaguru Rayappan JBB, Alwarappan S. ATR-FTIR as a versatile analytical tool for the rapid determination of storage life of fresh *Agaricus bisporus* via its moisture content. Postharvest Biol Technol. 2019;154:159-68. doi: 10.1016/j.postharvbio.2019.05.006.
15. Hu W, Li C, Dai J, Cui H, Lin L. Antibacterial activity and mechanism of *Litsea cubeba* essential oil against methicillin-resistant *Staphylococcus aureus* (MRSA). Ind Crops Prod. 2019;130:34-41. doi: 10.1016/j.indcrop.2018.12.078.
16. Verma N, Krishnamurthy G, Tichelaar FD, Böttger AJ. Controlling morphology and texture of sputter-deposited Pd films by tuning the surface topography of the (Ti) adhesive layer. Surf Coatings Technol. 2019;359:24-34. doi: 10.1016/j.surfcoat.2018.12.053.
17. Vane JR, Botting RM. New insights into the mode of action of anti-inflammatory drugs. Inflamm Res. 1995;44(1):1-10. doi: 10.1007/BF01630479, PMID 7664022.
18. Mizushima Y, Kobayashi M. Interaction of anti-inflammatory drugs with serum proteins, especially with some biologically active proteins. J Pharm Pharmacol.

1968;20(3):169-73. doi: 10.1111/j.2042-7158.1968.tb09718.x, PMID 4385045.

19. Sakat S, Tupe P, Juvekar A. Gastroprotective effect of methanol extract of *Oxalis corniculata* Linn. (whole plant) experimental animals. Planta Med. 2010;76(12):090. doi: 10.1055/s-0030-1264388.

20. Abruzzo A, Bigucci F, Cerchiara T, Cruciani F, Vitali B, Luppi B. Mucoadhesive chitosan/gelatin films for buccal delivery of propranolol hydrochloride. Carbohydr Polym. 2012;87(1):581-8. doi: 10.1016/j.carbpol.2011.08.024, PMID 34663007.

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