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Original Research Article

Novel poly herbal muco-adhesive formulation for treatment of oral aphthous ulcer

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ABSTRACT

Background: Oral ulcers are the most frequent lesions that cause discomfort for which the patients seek treatment for alleviating pain and facilitate early healing. Various treatment modalities from modern medicine and Ayurveda are used in the form of ointments and mouthwashes with varying efficacy. Anti-inflammatory medicines, enzymatic preparations, gamma globulins and immune suppressants have been used.

Methods: Extracts of five chosen herbs, *Glycyrrhiza glabra*, *Acacia catechu*, *Punica Granatum*, *Curcuma longa* and *Mentha piperita* were used for preparing mucoadhesive gel for the treatment of oral aphthous ulcers of any etiology. Gel was prepared by cold method of Schmolka at M/s Pharmanza Herbals Pvt. Ltd., India. Five formulations were prepared with using different concentration of active pharmaceutical ingredient (API) extracts.

Results: Formulations were analyzed for different physical and chemical properties. Preliminary trial was done with five formulations. The F5 formulation has the premier viscosity because of its higher polymer content; it is able to remain on mucous surface long enough to release its API effect. Since the uniformity, proper appearance, stability and acceptable viscosity and gel strength the F1 formulation was selected as the superior formulation which could prove ideal for treatment of oral aphthous ulcers.

Conclusions: The results provide strong evidence that polyherbal gel containing extracts of *Glycyrrhiza glabra*, *Acacia catechu*, *Punica granatum*, *Curcuma longa* and *Mentha piperita* on the basis of their analgesic, anti-inflammatory, antioxidant, wound healing, antimicrobial and local anesthetic properties can be used as an effective and safe alternative for the management of aphthous ulcers.

Keywords: Antiulcer, Analgesic, *Glycyrrhiza glabra*, *Acacia catechu*, *Punica Granatum*, *Curcuma longa*

INTRODUCTION

Aphthous ulcer

An oral ulcer which occurs on the mucous membrane of the oral cavity is called aphthous ulcer, or canker sore. Aphthous ulcer, is a common condition affecting oral

mucosa, and has the property of self-healing.¹ It is a known fact that oral aphthous ulcers affect between 5 to 25% of population of any age group. The main types of oral ulcers are minor ulcers. These are around 2-8 mm in diameter and usually clear up in 10 to 15 days. Major ulcers are bigger and deeper, often with a raised or irregular border. These can take several weeks to heal and may leave a scar in the mouth.

Treatment of oral aphthous ulcers

Many therapies have been recommended to treat oral ulcers which aim to decrease the symptoms of pain and duration of ulcers.^{2,3} Antiseptics and anti-inflammatory medicines are considered to be the first line of treatment for aphthous ulcer. Topical antibiotics, topical corticosteroids are used in gel or rinse form.^{4,5}

Mucoadhesive drug delivery system

Mucoadhesive medicine delivery can be defined as absorption of medicine via the mucous membranes of the oral cavity. It is a relatively new drug delivery system which was first introduced in 1980's for delivering the medicine in controlled manner and providing the ease of controlled medicine delivery.

Bioadhesion is commonly defined as the adhesion between two materials, at least one of which is biologic in nature that are held together by means of interfacial forces. Mucoadhesive medicine delivery systems utilize this property and have been developed for oral, nasal, vaginal and rectal routes for systemic and local effects.

Mucoadhesive medicine delivery system remains in close contact with the absorption surface- the mucous membrane, releasing the medicine at the action site leading to better bioavailability and subsequent local and systemic effects. The potential use of mucoadhesive systems as medicine carriers lies in its prolongation of the adherence time at the absorption site, allowing intensified contact with the epithelial barrier.⁶

The efficacy of bioadhesive hydrogel patches, made up of a pharmaceutical grade cellulose derivative aid in the healing and controlling the pain caused by aphthous ulceration.⁷

Many medicinal plants and dietary nutrients have been shown to possess antiulcer activities tulsi, neem, curcumin, liquorice, pomegranate, *Acacia catechu*, *Mentha piperita* and ginger are considered as home remedies in many parts of the country.⁸

The use of herbal products in the treatment of oral aphthous ulcer can provide safety in contrast to the synthetic topical steroids. We intended to develop semisolid muco-adhesive dosage form of polyherbal ingredients for potential treatment of aphthous ulcer. Other reasons for this study are their low cost, safety, better tolerability and improved efficacy.

Aim

Aim of the study was to formulate a poly herbal mucoadhesive gel which can provide effective treatment for oral aphthous ulcers decreasing the healing time following patch therapy, and to assess pharmaceutical parameters of the formulation by in vitro analysis.

METHODS

After a thorough systematic scientific review of literature five herbal extracts were identified and selected on the basis of their documented analgesic, anti-inflammatory, antioxidant, wound healing, antimicrobial and local anesthetic properties on various parameters of oral ulcers. The herbal ingredients used are shown in Table 1.

Equipment and instruments used

The following equipments and instruments were used: digital balance, pH meter, magnetic stirrer, digital water bath, ultra sonicator, Brookfield LVDV-II and pro viscometer, Shimadzu UV 1800 spectrophotometer and high performance liquid chromatography (HPLC).

Preparation of gel formulation

After obtaining clearance from institutional ethics committee vide letter no. IEC-2017/05 the *Glycyrrhiza glabra* extract, pomegranate extract, *Mentha piperita* extract, *Catechu* extract, and *Curcumin longa* extract were procured from M/s Pharmanza Herbs Pvt. Ltd., India. All other reagents and chemicals were locally procured in analytical grade. Method of gel formulation and in vitro evaluation of gel were done with appropriate method.⁹

Table 1: The herbs used and their documented uses.

Name	Scientific name	Parts used	Chemical ingredient	Properties
Liquorice	<i>Glycyrrhiza glabra</i>	Roots, rhizomes	Glycoside glycyrrhizin	Demulcent, anti-inflammatory, antiulcer
Catechu	<i>Acacia catechu</i>	Dried bark heartwood	Tannin flavonoids	Anti-bacterial, astringent and antiulcer
Pomegranate	<i>Punica granatum</i>	Fruit and its skin	Phenolics, flavonoids	Anti-inflammatory, antibacterial, antifungal, antioxidant and antiulcer
Turmeric	<i>Curcuma longa</i>	Roots and rhizomes	Curcumin	Antioxidant, anti-inflammatory, analgesic, anti-fungal
Peppermint	<i>Mentha piperita</i>	Leaves	Essential oils like menthol	Anti-inflammatory, anesthetic, fungicidal



Figure 1: *Glycyrrhiza glabra*, *Acacia catechu*, *Punica Granatum*, *Curcuma longa* and *Mentha piperita*.

Table 2: Ingredients and their concentrations used in the five gel formulations.

Ingredient	F1	F2	F3	F4	F5
Curcuma extract (mg)	10	500	500	10	10
Glycyrrhiza extract (mg)	8	800	800	8	8
Punica extract (mg)	10	500	500	10	10
Acacia extract (mg)	5	500	500	5	5
Menthe oil (mg)	2	200	-	2	2
2 mg HPMC E 50 (%)	3	2	-	3	-
Carbopol 934 P (%)	1	1	1	1	1
Sodium benzoate (%)	0.15	0.15	0.15	0.15	0.15
Propylene glycol (%)	10	10	13	10	10
Water (%)	50	10	100 ml	20	30
Ethanol (%)	40	10	-	30	40

Gel was prepared by cold method of Schmolka at M/s Pharmanza Herbls Pvt. Ltd., India. Carbopol 934 was accurately weighed in a beaker and dispersed in distilled water till the carbopol swelled. After swelling of carbopol, hydroxypropylmethylcellulose (HPMC) E 50 was added and stirred using mechanical/lab stirrer at 1000 rpm for 30-40 m. In another beaker ethanol was taken in required quantity of extracts. Propylene glycol was added in the required quantity. Then preservatives were added along with menthe oil with constant stirring at 1200 rpm. In beaker containing Carbopol the ethanol mixed extracts were transferred and with constant stirring at 1200 rpm.

Finally, water was added for making up the volume. Once the formation of the gel was completed it was packed in airtight container and stored in refrigerator.

RESULTS

Five formulation were prepared by using ingredients at different concentration and *in-vitro* analysis of formulation was done for: pH, viscosity, spreadability, gel strength, muco adhesive strength, and microbial activity.

Preliminary trial was done with five formulations. The F1 formulation has the premier viscosity because of its higher polymer content; it is able to remain on mucous surface long enough to release the effect of its active ingredients. Because of uniformity, proper appearance, stability and acceptable viscosity F1 formulation was selected as the superior formulation for the treatment of oral aphthous ulcers.

Other parameters studied

pH

1 gram of formulation was dispersed in 100 ml purified water and measured through pH meter.^{8,10,11}

Viscosity

Viscosity was measured by Brookfield (DV-III) viscometer. Gel was poured into the container and the proper spindle was attached. Then the viscosity was measured at 25 °C at 50-250 rpm.^{8,10,11}

Spreadability

For the determination of spreadability, excess of sample was applied between two glass slides and was compressed to uniform thickness by placing 10 gm weight for 5 m. The time required to separate the two slides, i.e. the time in which the upper glass slide moves over the lower, was taken as measure of spreadability.^{8,10,11}

Mucoadhesive strength

The tensiometer (Fisher) was calibrated and then the gel brought in contact with sodium alginate (substitute for mucin) for 5 m. Then the required force to detach the gel from solution surface (speed of 0.2 inch/min) was determined in dyne/cm².^{12,13}

Drug release by HPLC method and microbial count by USP <2021>method was done for formulation F1.

Preliminary trial was done with five formulations. The F5 formulation has the premier viscosity because of its higher polymer content; it is able to remain on mucous surface long enough to release its API effect. Since the uniformity,

proper appearance, stability and acceptable viscosity and gel strength the F1 formulation was selected as the superior formulation which could prove ideal for treatment of oral aphthous ulcers.

Table 3: Physical parameters of the formulation.

Parameter	F1	F2	F3	F4	F5
Clarity	Clear	Turbid	Opaque	Opaque	Opaque
Colour	Yellowish brown	Dark yellow	Yellow	Yellow	Yellow
Homogeneity	++++	+++	++	+++	+++
Particulate matter	Not present	Present	Present	Present	Present
Consistency	Smooth	Coarse	Lumps formed	Spreadability was not proper	Gel formed but viscosity was not in range



Figure 3: Polyherbal mucoadhesive gel.

Table 4: Other parameters of gel analysis of F1 formulation.

Parameter	Range
pH	6.8
Viscosity (cps)	5607±154
Spreadability (sec)	10
Mucoadhesive strength (dyne/cm ²)	24.3
Drug release (%)	
Curcuminoids	0.59
Punicalagin	0.1
Glycyrrhetic acid	0.14
Microbial count (total plate count)	<10
Yeast and mold	
<i>Escherichia coli</i>	All absent
<i>Salmonella</i>	
<i>S. Aureus</i>	
<i>Enterobacteriaceae</i>	

DISCUSSION

In the recent past herbal treatments have gained popularity for the oral lesions.⁸ Extracts of herbal plants like aloe, *Terminalia chebula*, *Vetiveria zizanioides*, ginseng, capsicum have been used successfully for the treatment of aphthous ulcers. Alambayan et al concluded that aqueous extract acacia catechu wild displayed antiulcer activity.¹⁴ Some other studies have also mentioned about the role of

herbal plants in treatment of ulcers in cancer patients. Najafi et al showed that aqueous extract of glycyrrhiza can be effective in decreasing the severity of oral mucositis in head and neck cancer patients undergoing radiotherapy.¹⁵ Gupta et al recommended the potential use of licorice as antitubercular agent through systemic experiments and sophisticated anti-TB assay.¹⁶

The *Glycyrrhiza glabra* contains more than 20 triterpenoids and nearly 300 flavonoids. These contents render the glycyrrhiza glabra properties such as antimicrobial, anti-inflammatory, etc.¹⁷ Hasan et al studied effectiveness of mouthwash containing *Glycyrrhiza glabra* in the treatment of stomatitis oral ulcer and found that the application of glycyrrhiza glabra root extract to stomatitis mouth ulcers can reduce ulcer size and speed healing.¹⁸ *Acacia catechu* has anodyne, astringent, bactericide, refrigerant, stimulant, and styptic properties.¹⁹

In the present study the herbal extract was prepared as a mucoadhesive gel formulation. Mucoadhesive gel has the ease of application, good distribution and ability of adhesion and remaining on oral mucosa for a long enough time to release its drug, Aslani et al reported this fact in their study which stated that this formulation can be well accepted for treatment of oral ulcers and diseases such as aphthous.²⁰

CONCLUSION

This study was intended to develop a semisolid mucoadhesive dosage form of polyherbal Ingredients. Herbal medicines utilize the body’s natural healing process for treating conditions. For this reason, five herbal extracts were identified on the basis of their suggested analgesic, anti-inflammatory, antioxidant, wound healing, antimicrobial and local anesthetic properties. These were extracts of *Glycyrrhiza glabra*, *Acacia catechu*, *Punica granatum*, *Curcuma longa* and *Mentha piperita*. In our study the five afore mentioned plant extracts showed good antimicrobial activity.

The results provide strong evidence that polyherbal gel containing *Glycyrrhiza glabra* extract, *Acacia catechu* extract, *Punica granatum* extract, *Curcuma longa* extract

and *Mentha piperita* extract can be used as an effective and safe alternative for the treatment of aphthous ulcers.

Future *in vivo* clinical studies are necessary for examining the role of this topical herbal preparation in the management of oral aphthous ulcers.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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