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

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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.\textsuperscript{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.\textsuperscript{1,5}

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 absorption 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 Pharmazina Herbals Pvt. Ltd., India. All other reagents and chemicals were locally procured in analytical grade. Method of gel formulation and \textit{in vitro} evaluation of gel were done with appropriate method.\textsuperscript{9}

Table 1: The herbs used and their documented uses.

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

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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    | -    |
| Carbolp 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 Herbals 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, spreadibility, 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

Spreadibility

For the determination of spreadibility, 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 spreadibility.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 | Spreadibility was not proper | Gel formed but viscosity was not in range |

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

| Parameter              | Range           |
|------------------------|-----------------|
| pH                     | 6.8             |
| Viscosity (cps)        | 5607±154        |
| Spreadibility (sec)    | 10              |
| Mucoadhesive strength (dyne/cm²) | 24.3          |
| Drug release (%)       |                 |
| Curcuminoids           | 0.59            |
| Punicalagin            | 0.1             |
| Glycyrrhetinic acid    | 0.14            |
| Microbial count (total plate count) | <10          |
| Yeast and mold         |                 |
| Escherichia coli       | All absent      |
| Salmonella             |                 |
| S. Aureus              |                 |
| Enterobacteriaceae     |                 |

DISCUSSION

In the recent past herbal treatments have gained popularity for the oral lesions. 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. 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. Gupta et al recommended the potential use of licorice as antitubercular agent through systemic experiments and sophisticated anti-TB assay. 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. 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. Acacia catechu has anodyne, astringent, bactericide, refrigerant, stimulant, and styptic properties. 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.

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, Punica granatum, Curcuma longa extract, and Mentha piperita have the potential to be developed as a novel dosage form for the treatment of oral aphthous ulcers.
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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