JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A Concise Review on Mucoadhesive Drug Delivery Systems Meant for Oral Ulcers

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Abstract

An oral ulcer generally occurs as a painful, solitary or multiple recurrent, round ulcer lasting 10–14 days with very little chance of scarring. It is characterized by a significant, profoundly indented ulcer healing with a scar accompanied by severe pain. Anaemia, hematinic or mineral deficiency, Gluten-sensitive enteropathy or other immunologically mediated diseases may be associated with the disorder. Topical and systemic treatments are most commonly used to treat oral ulcers. A mucoadhesive film is beneficial in treating oral ulcers because it is easy to administer, has multiple release directions, is flexible, and is well tolerated by patients.Additionally, the films are effective at protecting wound surfaces and reducing pain. Due to these benefits, mucoadhesive films make ideal oral ulcer dosage forms. Finally, this review focuses on the ideal treatment options for mouth ulcers.

Keywords: Oral ulcers, mucoadhesive films, Pain, Oral Mucosa, Local Drug Delivery.

1. Introduction

It is estimated that oral ulcers affect approximately 20% of the general population, with the young and female populations being more vulnerable than males. An oral ulcer generally occurs as a painful, solitary or multiple recurrent, round ulcer lasting 10–14 days with very little chance of scarring. It is characterized by an extensive, profoundly indented ulcer healing with a scar accompanied by severe pain. Anaemia, hematinic or mineral deficiency, Gluten-sensitive enteropathy or other immunologically mediated diseases may be associated with the disorder. Topical and systemic treatments are most commonly used to treat oral ulcers. Anaesthetics, antibiotics, anti-inflammatory drugs, and topical tetracycline treatments are more prevalent than corticosteroids. In addition to relieving pain, topical corticosteroids can shorten ulcer healing times. In addition to the continuous secretion of saliva, the oral cavity mucosa is moist and prone to bacterial infections. In order to treat oral ulcers, a variety of delivery systems must be applied to the mucosal surface of the mouth, such as creams, gels, and pastes, which can quickly become eroded by saliva. It results in high local drug concentrations, short residence times, difficulty administering drugs accurately, and poor treatment outcomes. A mucoadhesive film is beneficial in treating oral ulcers because it is easy to administer, has multiple release directions, is flexible, and is well tolerated by patients.[1]

Additionally, the films are effective at protecting wound surfaces and reducing pain. Due to these benefits, mucoadhesive films make ideal oral ulcer dosage forms. Finally, this review focuses on the ideal treatment options for mouth ulcers (Figure 1) (Table 1).[2]

2. Treatment options available for mouth ulcers.

To treat oral recurrent aphthous ulcers (RAU), oromucoadhesive films were prepared for delivering Propolis extract (PPE) entrapped in niosomes to the buccal cavity. The antimicrobial properties of PPE were studied. Particle size, polydispersity index (PDI), zeta potential, entrapment efficiency and in vitro release were evaluated in niosomes containing span60 and cholesterol.

Niosomal PPE was incorporated into oromucosal films and evaluated for swelling, mucoadhesion, and elasticity. The outcome of 24 patients with RAU, randomly assigned to medication and placebo groups, was examined to determine whether ulcer size reductions, full healing, and pain relief occurred. In the antimicrobial flavonoids analysis by high-resolution liquid chromatography, pinocembrin, pinobanksin, chrysin and galangin were identified with total contents of 158.7 ± 0.15 g quercetin equivalents and phenolic contents of 180.8 ± 0.11 g gallic acid equivalents/mg. The niosomes exhibited a PDI of 0.676 and zeta potential of -4.9. When niosomal dispersion and films were tested for release after 8 hours, 64.05±0.12% were released, respectively. Results showed that the film remained adherent for 2 to 4 hours in both groups. A reduction in ulcer size occurred within two to three days in the medicated group, healing was complete within ten days, and relief of pain lasted for more than four hours compared to the placebo group. This oromucoadhesive film offers controlled drug delivery and can be used as an alternative therapeutic strategy to treat recurrent oral aphthous ulcers.[3]

In order to form mucosal ulcers, epithelial damage must occur, and such damage may result from various causes, including trauma, acute stomatitis, lichen planus, radiation, chemotherapy, and drug-induced hypersensitivity. Films for target drug delivery were investigated using mucositis as an example of oral mucosa diseases. Single clinical trial results were used as a pre-experimental design, and the outcome was tracked for a month. Benzydamine HCl and N-acetyl-cysteine were layered on the fibrous layer to produce the mucoadhesive film. The basal layer of lidocaine HCl was more rapidly released than the apical layer of benzydamine HCl. FTIR, DSC, and SEM were used to assess physical-chemical and morphological characteristics. A cell line MCF7 was tested for cell viability and cytotoxicity. Models of mathematical activity were used to explain the transport mechanisms of drugs and solvents in the basal and apical layers (drug release). A fold endurance test was conducted to assess the effect of movement inside the mouth. Mucoadhesive bilayer film stimulates cellular proliferation while remaining biologically safe. In one study in vivo, a mucoadhesive bilayer film was therapeutic for buccal mucositis.[4]

The formulation was prepared using solvent casting and contained ornidazole (OD) and dexamethasone sodium phosphate (DEX) to treat oral ulcers. In vitro evaluations have been conducted to determine the optimum formulation. OD and DEX have been released in vivo in the human oral cavity and their therapeutic effects in the rabbit oral ulcer model. A mucoadhesive layer containing both OD and DEX was formed with a backing layer of ethyl cellulose. It had a film thickness of 0.427± 0.015 mm, a weight of 55.89 ±0.79 mg, and a pH of 6.34 ± 0.01. The drug content of the best formulation is consistent with its theoretical value (2.959 * 0.106 mg/cm2 for OD, and 0.877 ± 0.031 mg/cm2 for DEX). The composition had a favourable swelling pattern, and both drugs were released at >95% after 4 hours. The compound film developed here can be used as a local drug delivery device for treating oral ulcers due to its promising therapeutic effects.[5]

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Recurrent Aphthous Ulcer (RAU) is a recurrent and painful swelling of the oral mucosa caused by aphthous ulcers. Pain relief and healing are the primary goals in treating the disease to shorten its duration or reduce its recurrence rate. Solvent cast films were prepared and evaluated to ensure optimum film characteristics and in vivo efficiency. Thin, flexible and with good water absorption, mucoadhesive and mechanical properties, the bilayer films were thin and flexible. A non-Fickian kinetics anomaly was observed in the in vitro release of the drug. SEM confirmed a bilayer. Chemical interactions between the layers were not detected by Fourier Transform Infrared Spectroscopy or Differential Scanning Calorimetry. Once-daily application of the studied film led to complete ulcer healing within 4-5 days in rabbits with induced mouth ulcers. In contrast to inflamed tissue on control

sites. As a result of these findings, we found that the bilayer mucoadhesive films developed for the buccal application of 1mg of prednisolone were mucoadhesive, convenient, and promoted RAU healing within a short period.[7]

Adding chemotherapy to irradiation may exacerbate mucositis, a severe complication of irradiation in head and neck tumours. Historically, liquorice has been used to treat peptic ulcers as it is a strong demulcent. A primary objective of this study was to compare the therapeutic safety and efficacy of liquorice (L) and triamcinolone acetonide (T) mucoadhesive films when used to treat oral ulcers and pain associated with oral mucositis. By using independent sample t-tests, the pain scores of the two groups were not significantly different in any consecutive week. The study results confirmed the effectiveness of triamcinolone and liquorice mucoadhesive films for treating oral mucositis during radiation therapy. Additionally, liquorice group members reported more minor oral discomfort than the other group members. Comparing pain scores between two groups, however, revealed no meaningful differences.[8]

The FDA's approval of 3D printed tablets has led to greater 3D printing technology in pharmaceutical applications. Hydrogels and paste-based materials are 3D printed with semi-solid extrusion-type 3D printers. In this study, muco-adhesive oral film formulations were examined to determine whether or not mouth ulcer pharmaceuticals could be 3D bioprinted. Hydrogel formulations based on hydroxypropyl methylcellulose (HPMC)-based catechin (model drug)-loaded HPMC and HPMC-based HPMC were investigated. The viscosity of a hydrogel formulation is dependent on the concentration of HPMC, which is vital to facile 3D printing. Two different drying methods were employed to prepare HPMC-based films (air drying and freeze-drying). As HPMC content in the films increased, drug dissolution was delayed. Different dissolution profiles were observed in the films. A pharmaceutical formulation model is created based on individualized, on-demand films from HPMC-based catechins. Finally, it was demonstrated that semi-solid extrusion-type 3D printers could be successfully used to prepare film formulations by 3D bioprinters.[9]

Nanofibrous meshes can be easily fabricated using electrospinning. Despite this, nanofiber productivity is sometimes limited to the laboratory scale, which cannot meet the demands of practical applications. Further, needleless electrospinning spinnerets using double-ring slits have been developed to fabricate drug-loaded nanofibrous meshes. A needless spinneret produces multiple jets simultaneously during electrospinning, so it is significantly more productive than conventional single-needle electrospinning spinnerets. Our needleless spinneret-based electrospinning device was used to produce curcumin-loaded poly (l-lactic acid) (PLLA) nanofiber meshes on a large scale with various concentrations. Curcumin-loaded PLLA nanofibrous meshes were systematically examined for drug release characteristics, antioxidant properties, anti-inflammatory properties, and cytotoxicity. An electrospinning method with curcumin-loaded PLLA and diclofenac sodium-loaded poly (ethylene oxide) solution resulted in a bilayer nanofibrous composite mesh with potent antibacterial properties. Using the bilayer composite nanofibrous meshes and (Hydroxypropyl) methyl cellulose-based mucoadhesive film, we subsequently assembled novel mucoadhesive patches. Porcine buccal mucosa adheres well to the multi-layered mucoadhesive patch. This invention provides a novel method to fabricate large-scale drug-loaded nanofibrous meshes as mucoadhesive patches using a double-ring slit spinneret. For many treatments of oral diseases, multiple-layered mucoadhesive patches can be incorporated with drugs with various mechanisms of action, such as analgesics, anti-inflammatory components, or antimicrobial compounds.[10]

This study examined the development and characterization of a film containing Calculus Bovis Sativus (CBS) and ornidazole. A uniform mucoadhesive film was successfully obtained by using a film-forming solution containing the insoluble drug. In order for this film to be a valid adjunct for the treatment of oral mucosal ulcers, it had to comprise two main drugs (CBS and ornidazole) and three polymers (hydroxypropylmethylcellulose, chitosan, and poly(vinyl alcohol) (PVA)). The film-forming film was prepared by evaporating the casting solvent from the suspension. Film properties were determined by analyzing drug content, release behaviour, swelling index, and mucoadhesive properties. Next, the prepared film was evaluated in a rabbit model of oral mucosal ulceration induced by glacial acetic acid. In addition, healthy volunteers were also observed to release bilirubin and ornidazole in saliva. It was concluded that the films showed favourable swelling properties and drug release behaviour in vitro. Ornidazole concentrations in saliva were maintained more than the minimal inhibitory concentration against CBS for about two hours with well-tolerated films. CBS and ornidazole constituted a better film than one containing only CBS and ornidazole. For treating oral ulcers, it is, therefore, an effective drug delivery system.[11]

3. Conclusion

Mouth ulcers are the most common type of complication for many people. Several supportive and palliative treatments are already available in the clinic. However, a standard remedy for the ulcers has not been confirmed yet, and its management is mainly through some solid dosage forms. The efficacy of the treatments could be improved by introducing mucoadhesive films that can enhance and optimize local drug delivery and create more significant therapeutic effects with fewer side effects. Further, this review focused on the significance of the mucoadhesive film-based approach for treating mouth ulcers.

4. Acknowledgements

All the authors would like to thank the Daggubati Chenchuramaiah Memorial Pharmacy College for the facilities extended.

5. References

1. Mortazavi H, Safi Y, Baharvand M, Rahmani S. Diagnostic Features of Common Oral Ulcerative Lesions: An Updated Decision Tree. *International Journal of Dentistry* 2016; 2016:7278925.
2. Shaikh R, Raj Singh TR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. Journal of Pharmacy & Bioallied Sciences. 2011;3(1):89-100.
3. Arafa MG, Ghalwash D, El-Kersh DM, Elmazar MM. Propolis-based niosomes as oromuco-adhesive films: A randomized clinical trial of a therapeutic drug delivery platform for the treatment of oral recurrent aphthous ulcers. Scientific Reports 2018 Dec 21;8(1):18056.
4. Alves TFR, Rios AC, da Silva Pontes K, Portella DL, Aranha N, Severino P, Souto EB, Gonsalves JKM, de Souza Nunes R, Chaud MV. Bilayer Mucoadhesive Buccal Film for Mucosal Ulcers Treatment: Development, Characterization, and Single Study Case. Pharmaceutics. 2020 Jul 11;12(7):657.
5. Zhang C, Liu Y, Li W, Gao P, Xiang D, Ren X, Liu D. Mucoadhesive buccal film containing ornidazole and dexamethasone for oral ulcers: in vitro and in vivo studies. Pharmaceutical Development and Technology. 2019 Jan;24(1):118-126.
6. Khan S, Boateng J. Effects of Cyclodextrins (β and γ) and l-Arginine on Stability and Functional Properties of Mucoadhesive Buccal Films Loaded with Omeprazole for Pediatric Patients. Polymers (Basel). 2018 Feb 7;10(2):157.
7. Farid RM, Wen MM. Promote Recurrent Aphthous Ulcer Healing with Low Dose Prednisolone Bilayer Mucoadhesive Buccal Film. Current Drug Delivery. 2017;14(1):123-135.
8. Ghalayani P, Emami H, Pakravan F, Nasr Isfahani M. Comparison of triamcinolone acetonide mucoadhesive film with licorice mucoadhesive film on radiotherapy-induced oral mucositis: A randomized double-blinded clinical trial. Asia-Pacific Journal of Clinical Oncology. 2017 Apr;13(2):e48-e56.
9. Tagami T, Yoshimura N, Goto E, Noda T, Ozeki T. Fabrication of Muco-Adhesive Oral Films by the 3D Printing of Hydroxypropyl Methylcellulose-Based Catechin-Loaded Formulations. Biological and Pharmaceutical Bulletin. 2019;42(11):1898-1905.
10. Wei L, Wu S, Shi W, Aldrich AL, Kielian T, Carlson MA, Sun R, Qin X, Duan B. Large-Scale and Rapid Preparation of Nanofibrous Meshes and Their Application for Drug-Loaded Multilayer Mucoadhesive Patch Fabrication for Mouth Ulcer Treatment. ACS Applied Materials & Interfaces. 2019 Aug 14;11(32):28740-28751.
11. Li W, He W, Gao P, Zhang C, Cai H, Chen Y, Liu D. Preparation, in Vitro and in Vivo Evaluations of Compound Calculus Bovis Sativus and Ornidazole Film. Biological and Pharmaceutical Bulletin. 2016;39(10):1588-1595.

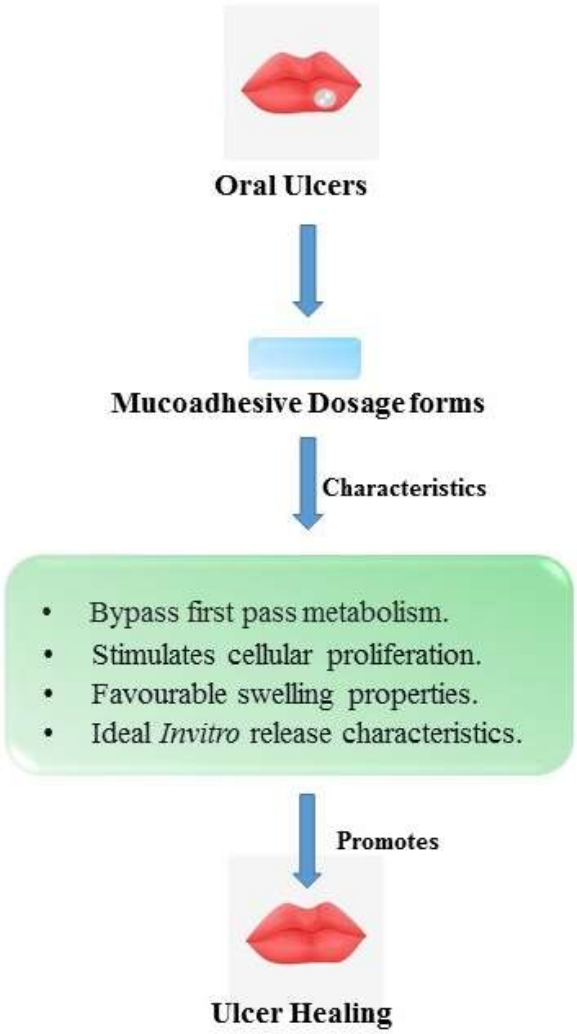

Figure 1. Represents the importance of the Mucoadhesive formulations in the treatment and management of the oral ulcers.

Table 1. Represents the significance of the mucoadhesive formulation in the treatment of the mouth ulcers

S. No	Name of the Author	Significance of the Work
1.	Arafa et al	A reduction in ulcer size occurred within two to three days in the medicated group, healing was complete within ten days, and relief of pain lasted for more than four hours compared to the placebo group.
2.	Alves et al	Mucoadhesive bilayer film stimulates cellular proliferation while remaining biologically safe.
3.	Zhang et al	The composition had a favourable swelling pattern, and both drugs were released at >95% after 4 hours.
4.	Khan et al	The compound film reduced ulcer inflammation and repaired mucosal damage without stimulating the human oral mucosa.
5.	Farid et al	The bilayer mucoadhesive films developed for the buccal application of 1mg of prednisolone were mucoadhesive, convenient, and promoted RAU healing within a short period.
6.	Ghalayani et al	Effectiveness of triamcinolone and liquorice mucoadhesive films for

		treating oral mucositis during radiation therapy.
7.	Tagami et al	The study results confirmed the effectiveness of triamcinolone and liquorice mucoadhesive films for treating oral mucositis during radiation therapy.
8.	Wei et al	This invention provides a novel method to fabricate large-scale drug-loaded nanofibrous meshes as mucoadhesive patches using a double-ring slit spinneret.
9.	Li et al	The films showed favourable swelling properties and drug release behaviour in vitro.