Competing Properties of Mucoadhesive Films that Release Immune Response Modifiers

S.K. Ramineni[1], L.L. Cunningham, Jr.[2], and D.A. Puleo[1]
[1] Center for Biomedical Engineering, University of Kentucky, Lexington, KY, USA
[2] College of Dentistry, University of Kentucky, Lexington, KY, USA

Introduction

The mortality rate due to oral cancer has not been improved over the last two decades, despite significant advances in treatment (*J Oral Oncol* 42: 448;2006). Hence the aim of this work was to design mucoadhesive films that can act as useful vehicles for localized delivery of an immune response modifier (imiquimod) to prevent progression of dysplastic lesions to squamous cell carcinoma. This study compared release profiles, degradation rates, and adhesive properties of films with differing ratios of film-forming and mucoadhesive components to identify a composition for further biological testing. The problem of uniformity of drug content in films was also addressed.

Methods

Patches were made from a blend of film-forming polymer, polyvinylpyrrolidone (PVP), and mucoadhesive polymer, carboxymethylcellulose (CMC). All components used were USP/NF grade. PVP (40% w/v) was dissolved in water, and then ethanol was added at 1:1 v/v ratio (PVP solution to ethanol) followed by 50% propylene glycol as plasticizer. Concurrently, an aqueous solution of CMC (2% w/v) was made. Owing to hydrophobicity of imiquimod, it was complexed with amphiphilic hydroxypropyl-β-cyclodextrin (HPβCD) by coevaporation to improve its solubility. After each was dissolved, the PVP and CMC solutions were added to the drug solution, thoroughly mixed, and left overnight at 4°C. The films were cast in Teflon dishes and dried at 60ºC.

Films with 1:2 and 2:1 ratios of PVP:CMC were prepared, and release studies were performed for each to find which ratio provided a more sustained release of imiquimod. Degradation studies were then conducted for each type of patch to study the dependence of drug release on the erosion properties of the mucoadhesives.

The mucoadhesive properties 1:2, 2:3, 1:1, and 2:1 PVP:CMC) films were determined by pull-off testing. Samples were applied to prehydrated porcine buccal mucosa and held at 10N for 2 min. The films were then pulled away from tissue at a rate of 0.1 mm/s, and the adhesion strength was determined by the maximum force divided by the contact area.

To address the problem of aggregation of HPβCD/imiquimod complexes, which results in nonuniformity during preparation of the films, mucoadhesives were cast in customized made 9cm^2 Teflon wells in and compared with films made in conventional 60cm^2 casting dishes.

Results and Discussion

Complexation of imiquimod with HPβCD improved its solubility and uniformity of distribution in mucoadhesive films. Although sustained release for approximately two hours was achieved for 1:2 PVP:CMC films, most of the imiquimod was released from 2:1 PVP:CMC films over the first hour, and release continually decreased over time.

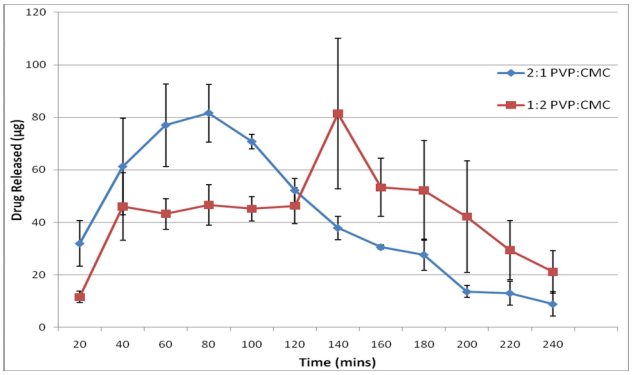

Figure 1. Imiquimod release from 1:2 and 2:1PVP:CMC films.

Degradation studies showed that while release patterns for 1:2 films was governed mostly by erosion, release from 2:1 films was occurred by both erosion and diffusion of imiquimod from the material.

The adhesion force of the films was recorded as shown in Table 1. The force increased with increasing PVP content. Although sustained release of drug was achieved for 1:2 PVP:CMC, films they were less adhesive. Hence the choice of optimum combination has to be investigated.

The uniformity of the polymer and drug distribution was compared between conventional dishes and small wells based on coefficient of variation (CV) (Table 2). The small films were able to increase the uniformity of samples by reducing CV by 50%.

Table 1: Adhesive strength of PVP:CMC films.

PVP:CMC	Adhesion (N/cm^2)	CV
1:2	0.41±0.02	6.9
2:3	0.7±0.05	7.1
1:1	0.716±0.160	22
2:1	1.01±0.1	9.7

Table 2: Comparison of small wells and conventional dishes.

	CV (small well)	CV (large dish)
Sample mass	8	16-18
Drug content	5-7	11-13
Drug release	11-13	30

Conclusions

Competing performance characteristics, e.g., degradation and release vs. adhesion, were observed for mucoadhesive films made from blends of PVP and CMC. Future bioactivity studies will determine which properties are most important for treating oral mucosal dysplasia.

Acknowledgement

This work was supported by NIH/NIDCR (DE019645).