Mucoadhesive Patches Delivering Imiquimod for Treatment of Oral Dysplasia

A.V. Boland[1], 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

Imiquimod is an immune response modifier that strengthens the immune response against infected cells, basal and squamous cell carcinomas. Although it may be useful for treating oral mucosal dysplasia, it has not commonly been applied in the oral cavity for lack of an appropriate delivery method. Mucoadhesive films would be a useful vehicle for imiquimod delivery.

Since imiquimod is hydrophobic, homogeneous distribution in the polymer with subsequent uniform release is challenging. This study compared drug release from three possible formulations of imiquimod-loaded mucoadhesive films and films with differing ratios of polymer-forming and mucoadhesive polymers.

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). A plasticizer was then added, 50% propylene glycol. Concurrently, an aqueous solution of CMC (2% w/v) containing imiquimod was made. After each was dissolved, the PVP and CMC solutions were thoroughly mixed, and films were cast in Teflon dishes and dried at 60ºC.

In the first method, sonication was used to disperse imiquimod in the polymer solution. In the second film, linoleic acid was used to enhance the solubility of imiquimod in the solution. In the third, imiquimod was complexed with hydroxypropyl-β-cyclodextrin (HPβCD) with a kneading process using methanol and water, respectively, to dissolve each component.

Patches 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.

Drug release was measured during incubation of films in simulated saliva at 37ºC. Aliquots of the release supernatant were taken at set time intervals. Then the drug concentrations were determined by measuring fluorescence (λ_{ex}=250 nm, λ_{em}=340 nm).

The trend of the mass of imiquimod released versus time for each of these methods was used to evaluate the pattern of release and the amount of imiquimod released. The time required for the film to completely dissolve was also recorded.

Results and Discussion

The sonication method proved inefficient because the small drug particles aggregated during preparation of the mucoadhesive, creating a nonuniform distribution throughout the film. Variances between samples of a patch at equal time suggest nonuniformity of the film as a whole. Consequently, the release profiles were erratic.

Linoleic acid initially increased solubility of imiquimod, but the films became translucent yellow instead of their normal clear color upon drying. Even though linoleic acid increased fluorescence readings, reflecting imiquimod concentration, film integrity was compromised during the release studies. Both the sonication and linoleic acid methods resulted in continually decreasing release of imiquimod over time.

In contrast, HPβCD was successfully used to establish uniform distribution of the drug throughout the mucoadhesive film. In the 1:2 PVP:CMC films using HPβCD, sustained release was achieved for at least two hours, although variability increased toward the end as the materials degraded. However, in the 2:1 PVP:CMC films, most of the imiquimod was released over the first hour, and the release continually decreased over time, even though the patches were longer-lasting.

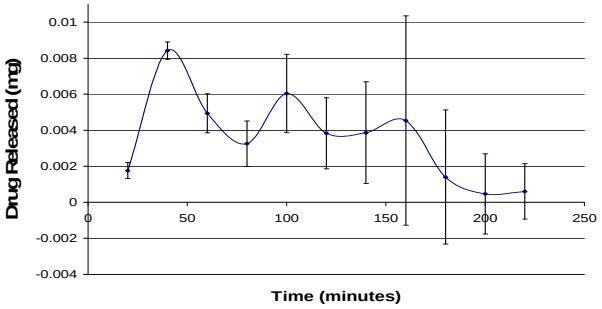

Figure 1. Imiquimod release from 1:2 PVP:CMC films.

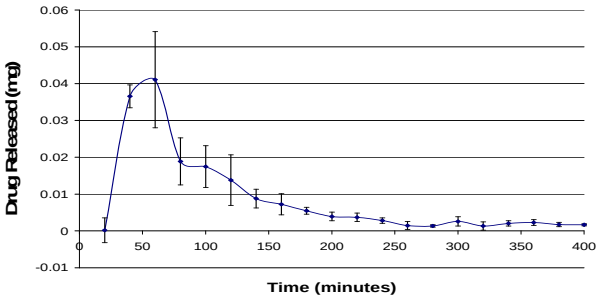

Figure 2. Imiquimod release from 2:1 PVP:CMC films.

Conclusions

Although imiquimod was released from all formulations for up to three hours, complexation with HPβCD resulted in the most uniform distribution of imiquimod in the films. Sustained release obtained from 1:2 PVP:CMC films may be more desirable for use in drug delivery to ensure that dysplastic cells are exposed to an appropriate amount of drug over the treatment period.