Mechanical Properties and Loading Techniques of Mucoadhesive Films for Treatment of Oral Dysplasia

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Introduction

Oral cancers remain a significant health concern, with nearly 36,000 new cases and 8,000 deaths expected in the U.S. alone in 2009 (Cancer Facts and Figures, 2009). Current treatments primarily center on invasive surgical resection, radiation, and chemotherapy of tumors after the disease has already progressed to oral squamous cell carcinoma (OSCC). However, treatment of precancerous lesions can halt progression to malignant cancer, decrease incidence, metastasis, and significantly improve survival periods. Hence the overall aim of this work is to develop a noninvasive mucoadhesive drug delivery system loaded with immune response modifier (imiquimod) to prevent progression of dysplastic lesions to OSCC. The present study explored various ways of loading imiquimod into the system to achieve clinically relevant doses. Tensile and shear adhesion properties of films with differing ratios of film-forming and mucoadhesive components were compared to identify a composition for better handling and drug release properties.

Methods

Patches were made from a blend of film-forming polymer, polyvinylpyrrolidone (PVP), and mucoadhesive polymer, carboxymethylcellulose (CMC). Five different films were prepared with different compositions of PVP and CMC.

Owing to the hydrophobicity of imiquimod, it was complexed with amphiphilic hydroxypropyl-β-cyclodextrin (HPβCD) in 1:1 ratio by co-evaporation to improve its solubility. Differential scanning calorimetry was performed on lyophilized complexes. Solubility of imiquimod in polymeric solutions was also improved by using 3:7 [methanol:acetate buffer (100mM, pH4.0)]. PVP and CMC solutions were added to drug solution, thoroughly mixed, and left overnight at 4ºC. The films were cast in Teflon dishes and dried at 60ºC.

Mechanical properties of films were determined by uniaxial tensile testing with displacement rate of 3mm/sec. Shear adhesion properties were determined by testing at rate of 0.1mm/sec. Films were pre-wetted with 20µl of simulated saliva and attached to 4%w/v mucin-coated membranes for 5 minutes.

Results and Discussion

Both HPβCD and acetate buffer improved the solubility of imiquimod and its uniformity of distribution in mucoadhesive films. DSC studies confirmed the formation of complexes (Figure 1), resulting in an aqueous solubility of 1:1 (HPβCD:imiquimod) of 100µg/ml. By comparison, solubility of imquimod in acetate buffer was 2.2mg/ml, and even with the acidic solution, the resulting films had surface pH of 7. The acetate formulation thus can achieve clinically relevant dosages ranging from 0.3 to 0.625mg/cm^2 (Aldara®).

The 2:3 PVP:CMC films had the highest elastic modulus and ultimate tensile strength compared to other films (Figure 2), which may be attributed to better alignment of both polymers (PVP and CMC) and lower moisture content of films.

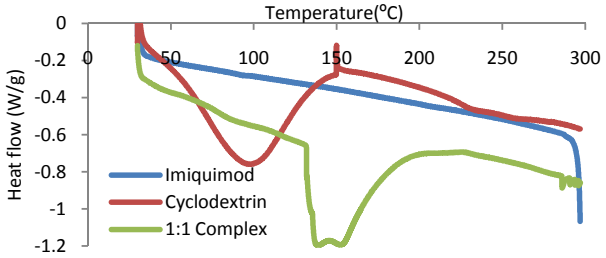

Figure 1. DSC plots of drug and complexes.

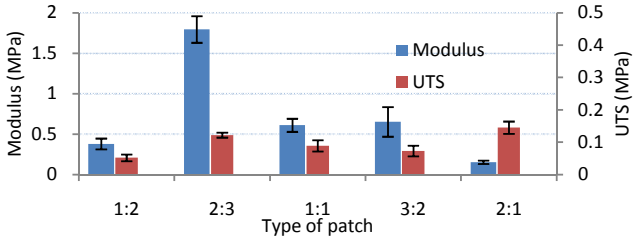

Figure 2. Tensile properties of films.

Shear adhesion of the films increased with increasing PVP content (Figure 3), which likely is a result of the hygroscopic nature of PVP. No significant difference in adhesion force was found between 1:2, 2:3 and 1:1 formulations.

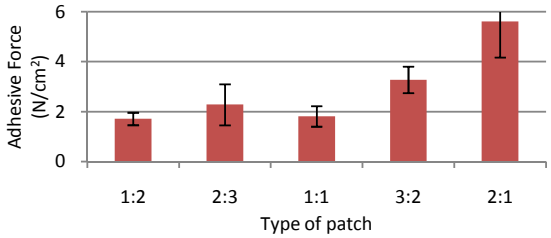

Figure 3. Shear adhesive force of films.

Conclusions

Although cyclodextrin can complex with imiquimod and increase its solubility, it was not sufficient to achieve clinically required doses in films, but this could be achieved by using acetate buffer. The 2:3 PVP:CMC films are a good choice with a compromise between obtaining sustained imiquimod release and robust mechanical and shear adhesive properties.

Acknowledgement

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