Preparation and In Vitro Evaluation of Multifunctional Oral Drug Delivery System

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ABSTRACT
The aim of this research is to develop a novel multifunctional drug delivery system for local and sustained delivery of anti-inflammatory and anti-fungal drugs in the oral environment. This multifunctional drug delivery system is composed of a tissue conditioner based on PEMA polymer, an anti-inflammatory drug and anti-fungal drug. The PEMA tissue conditioner plays two important roles: 1) reduce the damage of unfit denture by cushioning the hard denture base against the healing extraction sites, and 2) served as a depot for drugs. This novel polymeric device creates a synergistic effect of physical/chemical therapy for treating the denture related stomatitis.

INTRODUCTION
The oral cavity diseases are among the most common, costly, and preventable of all health problems in mankind. As such, there has been great interest in developing new therapeutic strategies for oral cavity diseases. Among these strategies, the local drug delivery of the therapeutics via oral cavity has gained a lot interests due to its advantages such as (i) convenience for drugs to be delivered to the diseases site, (ii) high drug delivery efficiency by avoiding first pass effect, and (iii) low systemic side effect. Despite its advantages, the drug delivery in the oral cavity faced a lot of obstacles such as drug loss by saliva, enzyme degradation, taste, and choking. Therefore, novel local drug delivery systems that can avoid these limits and prolong the therapeutics in the oral cavity will benefit the treatments of the oral cavity diseases.

The aim of this research is to develop a novel multifunctional drug delivery system for local and sustained delivery of anti-inflammatory and anti-fungal drugs in the oral environment. This multifunctional drug delivery system is composed of a tissue conditioner, an anti-inflammatory drug and anti-fungal drug. This drug incorporated tissue conditioner provides two unique properties for treating denture-related stomatitis: (1) tissue conditioner is used to reduce the damage of unfit denture by cushioning the hard denture base against the healing extraction sites. (2) tissue conditioner is served as a depot for both anti-inflammatory drug (Flubiprofen, FB) and anti-fungal drug (Itraconazole, ITZ). This novel polymeric device generate a synergistic effect of physical/chemical therapy for treating the denture related stomatitis.

EXPERIMENTAL METHODS
Preparation of drug loaded tissue conditioners
Four different tissue conditioners (Blank tissue conditioner, FB-loaded tissue conditioner, ITZ-loaded tissue conditioners, and FB-ITZ-loaded tissue conditioner) were prepared in this study. Blank tissue conditioners (blank TC) were prepared by mixing the PEMA powder with 0.73mL of liquid (90 wt% Pthaly butyl glycolate, 90% ethanol). FB-loaded tissue conditioners (FB-TC) were prepared by mixing the 1g of PEMA powder with 0.73mL of liquid containing 10 and 50 mg of FB. ITZ-loaded tissue conditioners (ITZ-TC) were prepared by mixing 1g of ITZ-PEMA microparticles (containing 10 or 50 mg of ITZ) with 0.73 mL of liquid. And FB-ITZ-loaded tissue conditioner (FB-ITZ-TC) were prepared by mixing 1g of ITZ-PEMA microparticles (containing 5 or 25 mg of ITZ) with 0.73 mL of liquid containing 10 and 50 mg of FB. These four types of tissue conditioner mixtures were placed in a glass mold overnight to form 2 mm thick tissue conditioner. The resulting tissue conditioner were cut by a hole puncher to form tissue conditioner disc (6 mm diameter, 2 mm thick)

Release kinetics of drug loaded tissue conditioners
The release kinetics of the FB-TC, ITZ-MP-TC and FB-ITZ-MP TCs were measured by a reversed-phase chromatography method. Briefly, a known weight of TC disc of was placed a 50 mL centrifuge tube and suspended with 10mL of PBS (pH 7.4) or 10 mL of acetic acid buffer (pH=5.0). The centrifuge tubes were shaken at 120 rpm, 37°C. At different time intervals (1, 2, 7, 10 and 14 days), a 9 mL volume of the supernatant was pipetted out and the same volume of fresh buffer was added to...
the tube. The concentrations of FB and ITZ released into the supernatant were measured by reversed phase HPLC at λ = 248 nm and λ = 264 nm respectively. At the last time point (14 days) the remaining discs were hydrolyzed and the amount of unreleased drugs of the TC discs were measured and used to calculate the percentage of FB and ITZ released at each time point. The morphology of tissue conditioners was characterized by using SEM, and the antifungal effect of drug loaded tissue conditioner were also evaluated by measuring the inhibitory width of C. Albicans.

RESULTS AND DISCUSSION

The drug incorporated tissue conditioner showed a dual-phase release kinetics. The hydrophilic anti-inflammatory drug was rapidly released (96% of FB was released in a 7 day period, Figure 1) and the hydrophobic anti-fungal drug was released at a relatively slow pattern (30% of ITZ was released within 7 days, and 33% released within 14 days, Figure 2). We also observed a similar release kinetics of FB and ITZ from FB-ITZ-TCs. Although, there is no significant difference between the release kinetics of ITZ from ITZ-TC and FB-ITZ-TC, the FB-ITZ-TC exhibited higher inhibitory effects on C. Albicans than ITZ-TC.

CONCLUSION

In this study, a drug incorporated tissue conditioner is developed for the delivery of Flurbiprofen (FB), an anti-inflammatory drug, and itraconazole (ITZ), an anti-fungal drug in the oral environment. This drug incorporated tissue conditioner showed a dual-phase release kinetics. The hydrophilic anti-inflammatory drug was rapidly released (96% of FB was released in a 7 day period) and the hydrophobic anti-fungal drug was released at a relatively slow pattern (30% of ITZ was released within 7 days, and 33% released within 14 days). We expected this drug incorporated tissue conditioner will create a synergistic effect of physical/chemical therapy for treating denture related stomatitis.

REFERENCES


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