Release Studies of Metronidazole and Doxycycline From Polycaprolactone Films Prepared By Solvent Evaporation

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Abstract: In the present work, metronidazole and doxycycline with different antibacterial spectra are proposed to be formulated as combination therapy to have a broader antibacterial therapy, which is effective against both aerobic and anaerobic periodontal microflora. Simultaneous use of metronidazole and doxycycline is effective against wide range of periodontal pathogens. Metronidazole and doxycycline release from polycaprolactone films was zero-order after an initial period. Significant burst effects were observed with metronidazole and doxycycline (5, 10% w/w).

Key words: Release Studies, Metronidazole And Doxycycline, Polycaprolactone Films, Solvent Evaporation.

Introduction

Dental caries and periodontal disease are generally considered to be the major oral health problems around the world[1]. The risk of systemic side effects and development of bacterial resistance can also be important disadvantage of using systemic antibiotics. The high flow rate of gingival cervical fluid (GCF) will cause a fast evacuation of the already released drug from the pocket to the mouth, thereby depleting the concentration of the drug in the pocket[2]. Bioadhesive polymers appear to be particularly attractive for the development of drug delivery systems to improve intraoral administration and reduce the frequency of application and the amount of drug administered[3]. Consequently, given the importance of bacteria in the etiology / progression of periodontal disease, treatment regimes frequently involve mechanical removal of plaque, usually in conjunction with topical antimicrobial chemotherapy, e.g. and metronidazole (MTZ) and doxycycline (DOX)[4]. Metronidazole is selectively active against gram negative microorganisms. Doxycycline is used clinically as independent non-surgical periodontal therapies for the treatment of periodontal infections. Doxycycline affects specifically the obligately anaerobic part of the oral flora, including P. gingivalis and other black-pigmenting gram-negative organisms but not A. actinomycetemcomitans, a facultative anaerobe[5]. The clinical efficacy of anti-microbial irrigation solutions is low due to the rapid clearance of the solution by the flushing action of the crevicular fluid within the pocket[6]. This efficacy may be improved by the use of drug delivery systems which, following insertion into the periodontal pocket, release antimicrobial agents at a controlled rate into the crevicular fluid [7]. In the present work, metronidazole and doxycycline with different antibacterial spectra are proposed to be formulated as combination therapy to have a broader antibacterial therapy, which is effective against both aerobic and anaerobic periodontal microflora. Simultaneous use of metronidazole and doxycycline is suggested to be effective against wide range of periodontal pathogens.

Materials and methods

Polycaprolactone is a biodegradable, aliphatic polyester which has been used as[8] and in the controlled delivery of drugs[9], and therefore, may be of use as a polymeric carrier for the delivery of antimicrobial agents within the periodontal pocket. This communication reports preliminary observations concerning the in vitro release of and DOX from polycaprolactone films prepared by solvent
evaporation. Films were prepared as follows. Polycaprolactone was dissolved in dichloromethane with stirring. MTZ and DOX was dispersed in dichloromethane and sonicated for 2 min prior to addition to the polymer solution. MTZ and DOX were added directly to the polymer solution. The total concentration of drug and polymer within the casting solution were 5 and 10% w/w. Films were cast onto glass petridishes and the solvent evaporated at room temperature in a vacuum oven. The MTZ and DOX contents of the films were 5 and 10% w/w. Release studies were performed (in duplicate or triplicate) by adhering discs (diameter 1.94 cm) of the films onto microscope slides, immersing in beakers containing 75 ml sodium citrate/sodium hydroxide buffer (pH 6.8, 0.1 M) and placing in a shaking water bath at 37°C and 100 oscillations/min. At selected time intervals, samples were removed and assayed for drug content by HPLC. The HPLC assay was as follows: mobile phase, 27% w/w acetonitrile, 0.15% w/w sodium acetate, 0.5% w/w triethylamine, adjusted to pH 5.0 with glacial acetic acid; column C-18, detector UV, λ max 273.8 nm and 319 nm, flow rate 0.5 ml/min. The calibration curve for MTZ and DOX was linear over the range 0.1-1.0 µg/ml (r = 0.99 with zero intercept).

Result and discussion

Statistical comparisons of release rates and burst effects associated with these films were performed by one-way ANOVA. MTZ and DOX release from polycaprolactone films is graphically illustrated in fig.1. Significant (p <0.05) burst effects were associated with films containing 5 and 10% w/w MTZ and DOX but the magnitude was independent of drug loading (p <0.05). Conversely, there were no burst effects with polycaprolactone films containing MTZ and DOX, regardless of loading, and indeed a significant lag time for release was observed for 10% w/w loaded films (p < 0.05). As the burst effect is due to the immediate release of drug incorporated at the surface of the film, these observations indicate that the distribution of MTZ and DOX within polycaprolactone films. Plots of MTZ and DOX released over time were linear for all films following an initial period. This indicates that MTZ and DOX release follows zero-order. In the preparation of films containing 5% w/w MTZ and DOX, was totally soluble in dichloromethane and, therefore, following evaporation of the casting solvent, may exist in a finely divided uniform state within the film. These films therefore represent a dispersion of MTZ and DOX in poly (ε-caprolactone).

Figure.1 MTZ and DOX release from polycaprolactone films. Drug loadings: (●) 5% MTZ w/w; (□) 10% w/w MTZ; (▲) 5% w/w DOX; (■) 10% w/w DOX. Bars represent standard errors of the mean.
The uniformity of drug dispersion would thus account for the presence of drug at the surface of the film and hence the significant burst effects noted for polycaprolactone films containing MTZ and DOX. One interesting observation is the similarity of the magnitudes of the burst effects associated with polycaprolactone films containing 5 and 10% w/w MTZ and DOX. In the preparation of films containing 10% w/w MTZ and DOX, unlike the 5% w/w films, MTZ and DOX did not exhibit total solubility within the casting solution. Therefore, the insoluble fraction will become suspended within the organic polymeric solution. The similarity of observed burst effects would therefore appear to be due to deposition of drug at the surface of the film, following precipitation from the evaporating organic solvent. At these drug loadings, the suspended drug would therefore contribute little to the burst effect. In conclusion, this study has shown that polycaprolactone may be used as a polymeric carrier for the controlled release of MTZ and DOX.

References

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