International Journal of Pharmaceutics, 84 (1992) 85–89

IJP 02838

Note

Preliminary release studies of chlorhexidine (base and diacetate) from poly(ε-caprolactone) films prepared by solvent evaporation

Natalie J. Medlicott [a], David S. Jones [a], Ian G. Tucker [a] and Doug Holborow [b]

[a] *School of Pharmacy and* [b] *Department of Periodontology, School of Dentistry, University of Otago, P.O. Box 913, Dunedin (New Zealand)*

(Received 12 December 1991)
(Accepted 27 February 1992)

Key words: Chlorhexidine; Zero-order release; Burst effect; Poly(ε-caprolactone)

Summary

Chlorhexidine release from poly(ε-caprolactone) films was zero-order after an initial period. Significant burst effects were observed with chlorhexidine base (5, 10% w/w) but not diacetate loaded films (10, 15, 20, 30% w/w). These differences may be due to the physicochemical state of chlorhexidine within the films.

Periodontal diseases, e.g., gingivitis and periodontitis, are a group of conditions which affect the supportive structures of the teeth. The development of periodontitis involves a breakdown of the periodontal tissues, probably due to both a direct effect of bacteria on the tissue and also to the associated inflammatory response, and the formation of a space (the periodontal pocket) between the surface of the tooth and the soft tissues (Listgarten, 1987). The periodontal pocket provides a protected environment in which bacteria, e.g., *Bacteroides* spp., *Capnocytophaga* spp. and *Actinobacillus actinomycetemcomitans* flourish (Slots and Genco, 1984). If untreated, increased tooth mobility and possibly tooth loss result.

Correspondence: D.S. Jones, School of Pharmacy, University of Otago, P.O. Box 913, Dunedin, New Zealand.

Treatment usually involves mechanical removal of the plaque, sometimes in conjunction with the use of antimicrobial agents, e.g., chlorhexidine, tetracycline or metronidazole. Mouthwashes may be used to control supragingival plaque but are ineffective against subgingival bacteria due to an inability to penetrate to subgingival areas (Pitchner et al., 1980). Irrigation devices are frequently employed to deliver antimicrobial agents directly to the subgingival regions, however, due to the short duration of action, frequent applications are required (Joyston-Bechal, 1987). Subsequently, there has arisen an interest in polymeric devices which, when inserted into the periodontal pocket, release antimicrobial agents over a sustained period. Examples of polymeric materials examined include ethylcellulose (Friedman and Golomb, 1982), ethylene vinyl acetate, polyethylene, polyurethane, polypropylene, cellulose acetate propionate (Goodson et al., 1983),

cellulose-based dialysis tubing (Coventry and Newman, 1982), acrylic strips (Addy et al., 1985) and polyhydroxybutyrate (Deasy et al., 1989).

Poly(ε-caprolactone) is a biodegradable, aliphatic polyester which has been used as a biomaterial (Woodward et al., 1985) and in the controlled delivery of drugs (Wang, 1989), 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 chlorhexidine, as the diacetate and free base, from poly(ε-caprolactone) films prepared by solvent evaporation.

Chlorhexidine diacetate was purchased from ICI (NZ) Ltd, Wellington. Poly(ε-caprolactone), Mol. Wt 35 000–45 000, was purchased from Polysciences Ltd, Warrington, PA, U.S.A. Chlorhexidine base was prepared from chlorhexidine diacetate by precipitation following the addition of sodium hydroxide (5 M) and recrystallisation from methanol. The purity was confirmed by melting point (134–135°C) and infrared spectroscopy. All other chemicals were AnalaR or equivalent quality.

Films were prepared as follows. Poly(ε-caprolactone) was dissolved in dichloromethane with stirring. Chlorhexidine diacetate (particle size < 63 μM) was dispersed in dichloromethane and sonicated (continuously, 100 W, 55 000 Hz) for 2 min prior to addition to the polymer solution. Chlorhexidine base was added directly to the polymer solution. The total concentration of drug and polymer within the casting solution was 10% w/w. Films were cast onto glass petri dishes and the solvent evaporated at room temperature in a vacuum oven. The chlorhexidine contents of the films were, 10, 15, 20 and 30% w/w as the diacetate, and 5 and 10% w/w as the base.

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 6.6, 0.1 M) and placing in a shaking water bath at 37°C and 100 oscillations/min (Fig. 1). At selected time intervals, samples were removed and assayed for drug content by HPLC. The HPLC assay was as follows: mobile

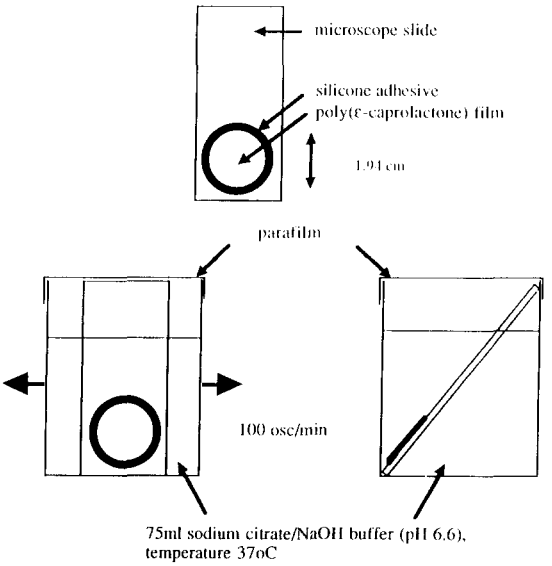

Fig. 1. Diagrammatic representations of the apparatus used to examine the in vitro release of chlorhexidine (base and diacetate) from poly(ε-caprolactone) films.

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 10 cm × 2.1 mm i.d. C-18 ODS Hypersil 5 μm; detector, UV λ_{max} 254 nm; flow rate 0.5 ml/min, internal standard, chlorpheniramine maleate. The calibration curve for chlorhexidine was linear over the range 0.1–1.0 μg/ml ($r = 0.99$ with zero intercept).

Statistical comparisons of release rates and burst effects associated with these films was performed by one-way ANOVA.

Chlorhexidine release from poly(ε-caprolactone) films is graphically illustrated in Figs 2 (base) and 3 (diacetate). Significant ($p < 0.05$) burst effects were associated with films containing 5 and 10% w/w chlorhexidine base but the magnitude was independent of drug loading ($p < 0.05$). Conversely, there were no burst effects with poly(ε-caprolactone) films containing chlorhexidine diacetate, 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,

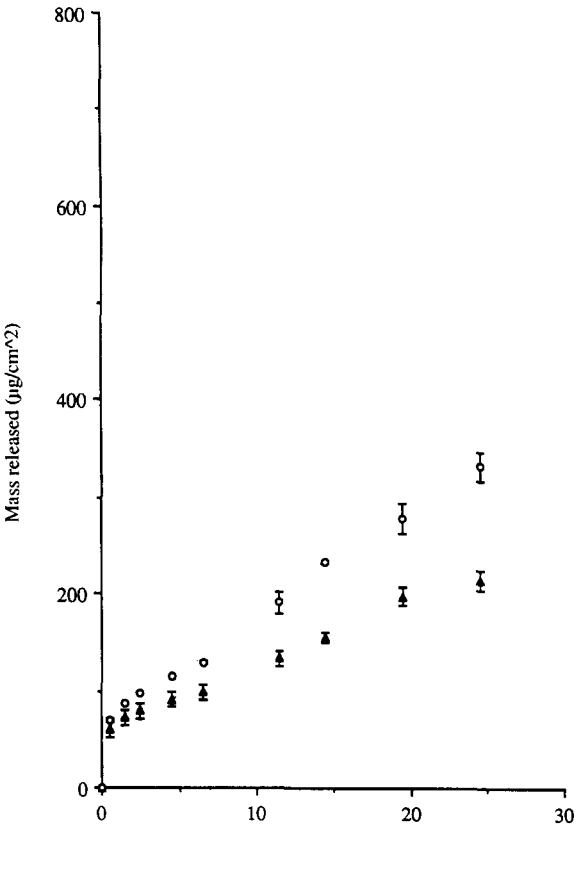

Fig. 2. Chlorhexidine release from poly(ε-caprolactone) films. Drug loadings: (▲) 5% w/w, (○) 10% w/w, chlorhexidine as the free base. Bars represent standard errors of the mean.

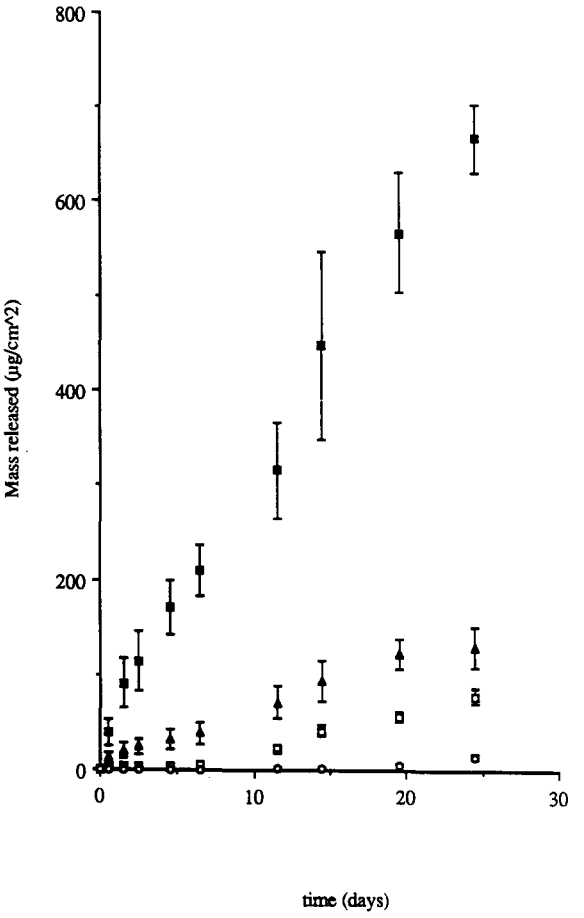

Fig. 3. Chlorhexidine release from poly(ε-caprolactone) films. Drug loadings: (○) 10% w/w; (□) 15% w/w; (▲) 20% w/w; (■) 30% w/w, chlorhexidine as the diacetate salt. Bars represent standard errors of the mean.

TABLE 1

Chlorhexidine release from poly(ε-caprolactone) films containing chlorhexidine base (CH) or chlorhexidine diacetate (CHA)

Drug	Concentration of chlorhexidine in film (% w/w)	Release rate constant (k) [a] ($\mu g\ cm^{-2}\ day^{-1}$)	Standard error	Correlation coefficient	Mean percentage released over duration of study	Standard error
CH	5	6.43	0.090	0.97	25.70	0.40
CH	10	10.85	0.700	0.99	19.80	0.30
CHA	10	1.12	0.004	0.98	0.78	0.30
CHA	15	3.84	0.240	0.96	2.82	0.26
CHA	20	5.26	0.600	0.86	3.73	0.63
CHA	30	26.00	1.000	0.93	12.90	0.50

[a] Release rate constants (k) were determined from the linear portion of the cumulative amount released vs time graphs (Figs 2 and 3), i.e., from 1.5–24.5 days for 5 and 10% w/w chlorhexidine base and 20 and 30% w/w chlorhexidine diacetate; 4.5–24.5 days for 15% w/w chlorhexidine diacetate and 6.5–24.5 days for 10% w/w chlorhexidine diacetate loaded films.

these observations indicate that the distribution of chlorhexidine within poly(ε-caprolactone) films is dependent on the salt used.

Plots of chlorhexidine released over time were linear for all films following an initial period. This indicates that chlorhexidine release follows zero-order kinetics and consequently, a release rate constant may be calculated from the slopes of these plots (Table 1). The greatest release rate was observed for films containing 30% w/w chlorhexidine diacetate (26 ± 1.00 $\mu g/cm^2$ per day), this rate being significantly greater than observed for films containing 10, 15 and 20% w/w of this salt ($p < 0.05$). Similarly, films containing 10% w/w chlorhexidine base exhibited a significantly ($p < 0.05$) greater release rate than films containing 5% w/w base, the respective release rate constants being 10.85 ± 0.7 and 6.43 ± 0.09 $\mu g/cm^2$ per day. Interestingly, when compared on a weight basis (10% w/w), the release rate was significantly ($p < 0.05$) greater for poly(ε-caprolactone) films containing chlorhexidine base than for those containing the diacetate salt. Similar release rate constants were observed for poly(ε-caprolactone) films containing 5% w/w chlorhexidine base and 20% w/w chlorhexidine diacetate ($p > 0.05$).

The relationship between type of chlorhexidine incorporated into poly(ε-caprolactone) films and subsequent release rate is an interesting observation which, to these authors' knowledge, has not been previously reported. A possible explanation for these observations may involve the relative solubilities of chlorhexidine base and chlorhexidine diacetate in the casting solvent. In the preparation of films containing 5% w/w chlorhexidine base, chlorhexidine 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 chlorhexidine base in poly(ε-caprolactone) (Chiou and Riegelman, 1971). 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 poly(ε-caprolactone) films containing chlorhexidine base. Conversely, chlorhexidine diacetate is practically insoluble in dichloromethane and, therefore, when combined with poly(ε-caprolactone), a suspension of chlorhexidine diacetate in an organic polymer solution is produced. Given that the removal of the solvent required 24 h and that the viscosity of the poly(ε-caprolactone) solution was low, it is likely that the suspended particles of chlorhexidine diacetate sedimented to produce a layer of drug particles on the surface of the glass petri dishes onto which the films were cast. As all release studies were carried out using the top surface, the observed lag time for chlorhexidine release and the comparatively (on a weight basis) lower release rates associated with films containing chlorhexidine diacetate may be due to an apparent increase in molecular diffusional path length. One interesting observation is the similarity of the magnitudes of the burst effects associated with poly(ε-caprolactone) films containing 5 and 10% w/w chlorhexidine base. In the preparation of films containing 10% w/w chlorhexidine base, unlike the 5% w/w films, chlorhexidine did not exhibit total solubility within the casting solution. Therefore, the insoluble fraction will become suspended within the organic polymeric solution in a similar fashion to chlorhexidine diacetate. 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 poly(ε-caprolactone) may be used as a polymeric carrier for the controlled release of chlorhexidine (either as the base or diacetate). Differences in the release rates, the presence or absence of burst effects, and the presence of absence of lag effects, between chlorhexidine base and chlorhexidine diacetate loaded poly(ε-caprolactone) films are suggested to be due to the physical state of these agents within such films. Further studies are at present underway to determine the rate of water uptake of poly(ε-caprolactone) films, either containing or devoid of chlorhexidine base and diacetate, and the release rate of chlorhexidine from the underside of the film. In addition, the effect of production and formulation variables on

the release rate of chlorhexidine from such films will be investigated.

References

Addy, M., Langeroudi, M. and Hassan, H., The development and clinical use of acrylic strips containing anti-microbial agents in the management of chronic periodontitis. *Int. Dent. J.*, 35 (1985) 124–132.

Chiou, W.C. and Riegelman, S., Pharmaceutical applications of solid dispersion systems, *J. Pharm. Sci.*, 60 (1971) 1281–1302.

Coventry, J. and Newman, H.N., Experimental use of a slow release device employing chlorhexidine gluconate in areas of acute periodontal inflammation. *J. Clin. Periodontol.*, 9 (1982) 129–133.

Deasy, P.B., Collins, A.E.M., MacCarthy, D.J. and Russell, R.J., Use of strips containing tetracycline hydrochloride or metronidazole for the treatment of advanced periodontal disease. *J. Pharm. Pharmacol.*, 41 (1989) 694–699.

Friedman, M. and Golomb, G., New sustained release dosage form of chlorhexidine for dental use. 1. Development and kinetics of release. *J. Periodontol. Res.*, 17 (1982) 323–328.

Goodson, J.M., Holborow, D., Dunn, R.L., Hogan, P. and Dunham, S., Monolithic tetracycline-containing fibres for controlled delivery to periodontal pockets. *J. Periodontol.*, 54 (1983) 575–579.

Joyston-Bechal, S., Fédération Dentaire Internationale Technical Report No. 26. Topical and systemic antimicrobial agents in the treatment of chronic gingivitis and periodontitis. *Int. Dent. J.*, 37 (1987) 52–62.

Listgarten, M.A., Nature of periodontal diseases: pathogenic mechanisms. *J. Periodontol. Res.*, 22 (1987) 172–178.

Pitchner, G.R., Newman, H.N. and Strahan, J.D., Access to subgingival plaque by disclosing agents using mouthrinsing and direct irrigation. *J. Clin. Periodontol.*, 7 (1980) 300–308.

Slots, J. and Genco, R.J., Black-pigmented *Bacteroides* species, *Capnocytophaga* species and *Actinobacillus actinomycetemcomitans* in human periodontal disease: virulence factors in colonisation, survival and tissue destruction. *J. Dent. Res.*, 63 (1984) 412–421.

Wang, P., Compressed poly(vinyl alcohol)-polycaprolactone admixture as a model to evaluate erodible implants for sustained drug delivery. *J. Biomed. Mater. Res.*, 23 (1989) 91–104.

Woodward, S.C., Brewer, P.S., Moatamed, F., Schindler, A. and Pitt, C.G., The intracellular degradation of poly(ε-caprolactone). *J. Biomed. Mater. Res.*, 19 (1985) 437–444.