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Chlorhexidine release from poly(ε-caprolactone) films prepared by solvent evaporation

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Abstract

The effect of selected formulation variables on the release of chlorhexidine from poly(ε-caprolactone) films was evaluated in vitro using a complete factorial experimental design. Repeated measures analysis of variance showed chlorhexidine type (diacetate or base), drug load (10, 20 or 30% w/w), chlorhexidine particle size (< 63 or 63–125 μm) and film side (upper or lower) significantly affected the percentage released over 10 and 30 days. Significant interactions were also observed between factors. Release from the upper side of films occurred more slowly than from the lower side of films for most formulations. This difference was particularly apparent for films containing chlorhexidine diacetate. The general release equation ($M_t/M_\infty = kt^n$) was fitted to the release data and constants estimated. The value of n, which indicates the mechanism of release, tended towards 0.5 for release at high drug loadings which may suggest release was predominantly diffusion-controlled from these films. Transecting sections of film, prepared with chlorhexidine diacetate < 63 μm (drug loading 20% w/w), and analysing the chlorhexidine content at varying distances from the film surfaces showed a gradient in chlorhexidine concentration through the film, with lower concentrations near the upper side and higher concentrations near the lower side.

Keywords: Chlorhexidine; Poly(ε-caprolactone) films; Formulation variables; Release; Complete factorial

1. Introduction

Chlorhexidine is a bisdiguanide antiseptic widely used in dentistry as an anti-plaque agent (Fardal and Turnbull, 1986) and has demon-

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Table 1
Formulations of poly(ε-caprolactone) films containing chlorhexidine

	Formulation						
	Control	(I)	(II)	(III)	(IV)	(V)	(VI)
Chlorhexidine base (g)	—	0.120	0.240	0.360	—	—	—
Chlorhexidine diacetate (g)	—	—	—	—	0.149	0.297	0.446
Poly(ε-caprolactone) (g)	1.200	1.080	0.960	0.840	1.052	0.903	0.754
Dichloromethane (ml)	8	8	8	8	8	8	8
Theoretical drug load (% w/w)	0	10	20	30	10	20	30

strated good antibacterial activity against a wide range of oral bacteria (Rindom Schiøtt and Löe, 1972; Hennessey, 1977; Stanley et al., 1989; Wade and Addy, 1989). The reason for the effectiveness of chlorhexidine as an anti-plaque agent is, in part, due to its ability to bind reversibly to tissues in the oral cavity (Bonesvoll et al., 1974; Bonesvoll, 1977). In some individuals mouth rinsing with a 0.2% w/w solution can produce anti-plaque concentrations in the saliva for up to 24 h (Bonesvoll et al., 1974). However, it is usual to recommend that mouth rinsing with chlorhexidine be performed twice daily and its effectiveness relies heavily on patient compliance. Development of a tooth-bonded controlled release system for chlorhexidine delivery in the mouth may improve treatment of plaque-associated oral diseases if saliva concentrations can be maintained at effective levels for prolonged periods.

This paper describes the effect of selected formulation variables on the release of chlorhexidine from poly(ε-caprolactone) films using a complete factorial experimental design. Also, since a preliminary study (Medlicott et al., 1992) suggested a difference in release from the upper and lower surfaces of these films, this phenomenon was investigated in more detail.

2. Materials and methods

2.1. Film preparation

Chlorhexidine Diacetate B.P. (I.C.I., Wellington, New Zealand) was recrystallised twice from hot water (m.p. 154–155°C). Chlorhexidine base was prepared by precipitation from Chlorhexidine Diacetate B.P. and was recrystallised twice from methanol (HPLC grade, B.D.H. Chemicals Limited) (m.p. 134°C). Particle size fractions of < 63 and 63–125 μm were obtained by sieving (Endecott, London, UK). Poly(ε-caprolactone) of molecular weight 35 000–45 000 was purchased from Polysciences (Warrington, USA).

Films were prepared by solvent evaporation using dichloromethane (AnalaR Grade, BDH Chemicals) as the casting solvent. Table 1 shows the composition of individual formulations. Duplicate films were prepared, in a random order, for each formulation with chlorhexidine powders of particle sizes < 63 and 63–125 μm. Films were cast into aluminium rings (7.6 cm diameter) on silanised glass plates and the bulk of the solvent was evaporated at 25°C. Following this a vacuum was applied for 12 h (500 mmHg). Films were lifted off the glass plates and the upper and lower sides were marked. The lower side was in contact with the glass plate. All films were stored at 4°C in a desiccator over silica gel until required for the release study. The drug loading of films was confirmed by extraction of chlorhexidine and differed from the theoretical load by less than $\pm$ 7.4%.

2.2. Release studies

In vitro release studies were performed by cutting two discs (0.72 cm diameter) from each film and attaching the upper side of one disc and the lower side of the second disc to individual teflon discs using a silicone adhesive (Bostick RTV sealant, Bostick New Zealand). Discs (0.72 cm diameter) were also cut from two blank poly(ε-

caprolactone) films and attached to teflon discs. Each disc was immersed in 5 ml of sodium citrate/sodium hydroxide buffer (0.1 M sodium citrate, pH 6.6) and placed at a randomly allocated position in a shaking water-bath (Grant Instruments) at 37°C and 100 oscillations min^{-1}.

At selected times, determined so that the chlorhexidine concentration in the release medium would not exceed 10% of its saturated solubility

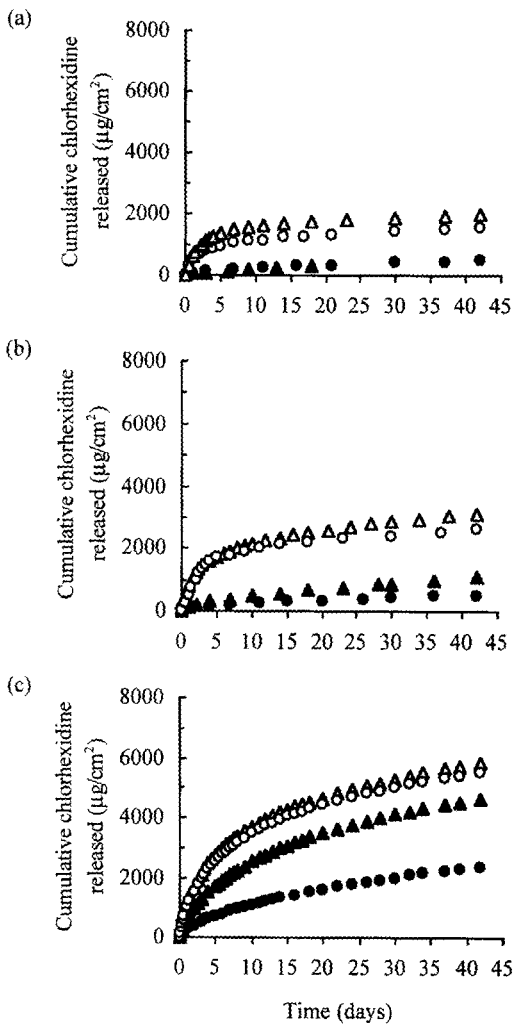

Fig. 1. Mean chlorhexidine released ($n = 2$) from films containing (a) 10, (b) 20 and (c) 30% w/w as the diacetate. (●) Upper side, < 63 μm particles, (○) lower side, < 63 μm particles, (▲) upper side, 63–125 μm particles, (△) lower side, 63–125 μm particles.

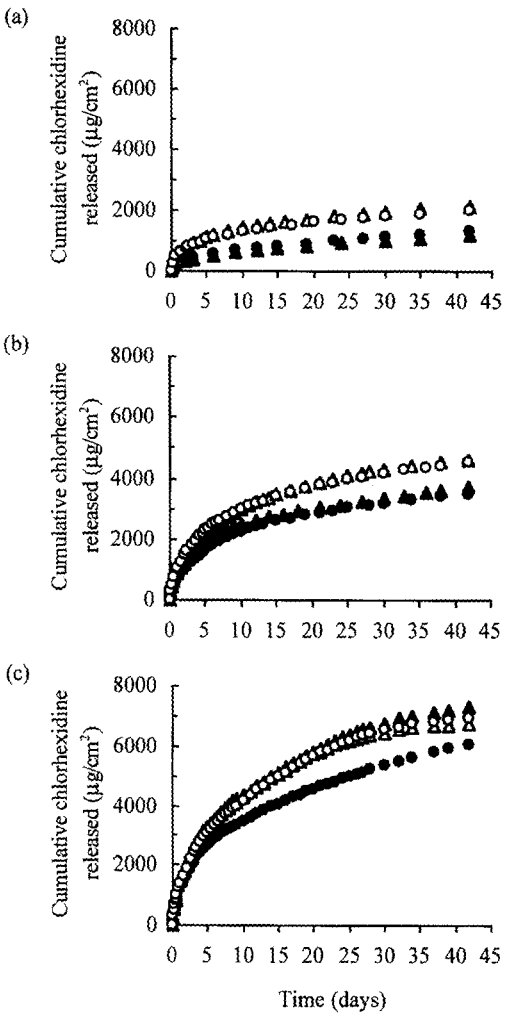

Fig. 2. Mean chlorhexidine released ($n = 2$) from films containing (a) 10, (b) 20 and (c) 30% w/w as the base. (●) Upper side, < 63 μm particles, (○) lower side, < 63 μm particles, (▲) upper side, 63–125 μm particles, (△) lower side, 63–125 μm particles.

at 37°C, samples were removed and assayed for drug content by UV spectroscopy (254 nm). At each sampling time the entire release medium was removed and replaced with fresh pre-warmed buffer.

Following the release study, poly(ε-caprolactone) discs were removed from the teflon discs and the residual chlorhexidine analysed. The initial amount of chlorhexidine in the poly(ε-caprolactone) discs was calculated by summation of the

Table 2
Repeated measures analysis of variance of the percentage chlorhexidine released

Source	Degrees of freedom	Chlorhexidine release period (days)			
		10		30	
		F	p	F	p
Chlorhexidine type (CT)	1	119.86	<0.001	143.47	<0.001
Drug load (DL)	2	16.18	<0.001	33.55	<0.001
Particle size (PS)	1	8.60	0.013	8.74	0.012
Film (CT DL PS)	12	0.99	0.510	1.34	0.309
Film side (FS)	1	246.86	<0.001	245.94	<0.001
CT × DL	2	8.16	0.006	5.38	0.022
CT × PS	1	2.59	0.134	2.81	0.119
CT × FS	1	46.98	<0.001	36.41	<0.001
DL × PS	2	0.33	0.722	1.17	0.344
DL × FS	2	13.81	0.001	11.84	0.001
PS × FS	1	0.90	0.360	2.31	0.154
CT × DL × PS	2	0.86	0.446	0.73	0.504
CT × DL × FS	2	1.12	0.357	1.39	0.286
CT × PS × FS	1	0.54	0.475	0.02	0.880
DL × PS × FS	2	4.84	0.029	4.58	0.033
CT × DL × PS × FS	2	1.95	0.185	1.56	0.249
Error	12				
Total	47				

cumulative amount released over 42 days and the amount remaining in the disc at 42 days. This was compared with the initial amount calculated from the drug loading and disc weight.

The cumulative amount of chlorhexidine released ($\mu g/cm^2$) was plotted against time and the percentages released at 10 and 30 days were used in statistical comparisons performed by repeated measures analysis of variance using Minitab for Windows 9.2. (Minitab, PA, USA).

The general release equation proposed by Gurney et al. (1982), Eq. (1) was fitted to the release profiles by unweighted non-linear least squares regression using Grafit data analysis and graphics program 2.11. (Erthacus Software Limited Portions). For each release profile, residuals were calculated and the Runs test was performed using Minitab for Windows 9.2. to test whether residuals were randomly distributed.

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where M_t/M_∞ is the percentage released at time t (M_∞ = the total mass of chlorhexidine in the poly(ε-caprolactone) disc calculated from the drug loading and the mass of the disc) and k and n are parameters estimated from the data.

2.3. Determination of the chlorhexidine content of film transections

Five discs (diameter 0.7 cm) were cut from each of the two films containing 20% w/w chlorhexidine as the diacetate, < 63 μm. A single piece of approximately 1 × 1 mm was then cut from each disc, set in resin (LR Gold, London Resin) and transected into 2 μm thickness, with an ultramicrotome (Ultra Cut E, Reichert, Austria). Groups of twenty transections (40 μm) were collected on microscope cover slips and viewed (× 500) using a Nikon Optiphot light microscope with a microflex PFX photomicrographic attachment (Nikon Corporation, Japan).

The chlorhexidine content of each group of transections was determined by dissolving the

poly(ϵ-caprolactone) in chloroform (0.5 ml), extracting the chlorhexidine into 1% v/v glacial acetic acid (4 ml) and analysing by HPLC using a Spectra Physics HPLC (Watson Victor, Dunedin, New Zealand). The HPLC system comprised a SP8800/8810 ternary pump, a Spectra System UV 2000 dual wavelength detector, a SP4400 Chromjet integrator and a Rheodyne injector (50 μl sample loop). The stainless steel column (10 mm × 2.1 mm i.d.) was packed with C18 ODS-B Exsil, 5 μm (Hi Chrome, Berkshire, England) and maintained at 30°C. The mobile phase comprised 60% v/v acetonitrile (HPLC grade, BDH Chemicals), 0.2% v/v glacial acetic acid (HPLC grade, Ajax Chemical Company Pty) and 7 mM sodium laurylsulphate (HPLC grade, BDH Chemicals) and was pumped at a rate of 0.5 ml/min. Triplicate standard curves for extraction of chlorhexidine from transections were linear over the range 1–60 μg chlorhexidine ($R^2 > 0.99$).

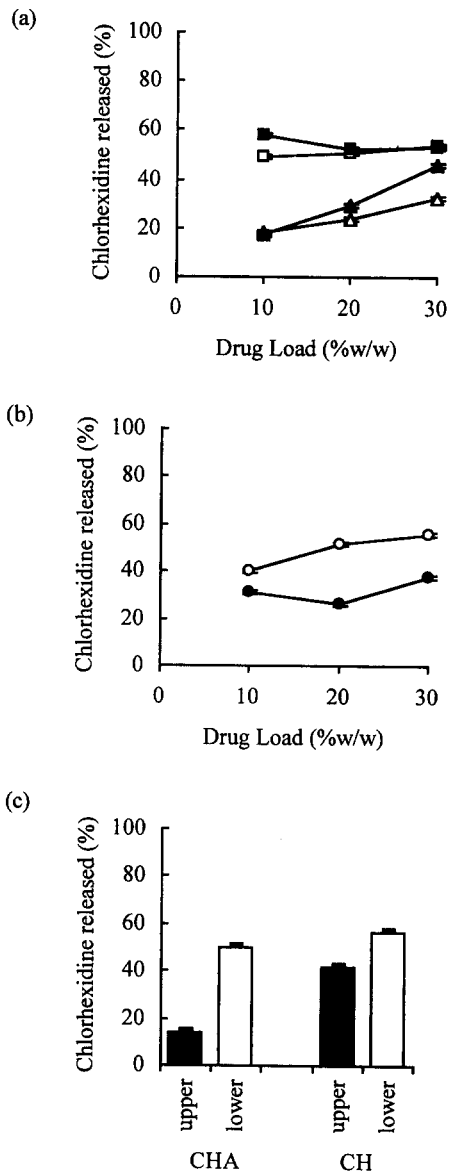

Fig. 3. Significant interactions for the percentage released over 10 days (a) DL × PS × FS, (△) < 63 μm, upper side, (▲) 63–125 μm, upper side, (□) < 63 μm, lower side, (■) 63–125 μm, lower side; (b) CT × DL, (●) chlorhexidine diacetate, (○) chlorhexidine base; (c) CT × FS, CHA, chlorhexidine diacetate, CH, chlorhexidine base. Error bars represent the standard error of the mean calculated from the pooled standard deviation.

3. Results

3.1. Release studies

Chlorhexidine released from poly(ε-caprolactone) films is shown in Figs. 1 and 2. Release from the upper side was markedly slower than release from the lower side for all films containing chlorhexidine as the diacetate, and also from films containing 10 and 20% w/w chlorhexidine as the base. In contrast, films containing 30% w/w chlorhexidine as the base showed a difference in release between the upper and lower sides for films containing chlorhexidine particles of less than 63 μm only (Fig. 2c).

For some films the residual chlorhexidine at 42 days was less than the minimum quantifiable quantity (0.4 mg) of the chlorhexidine extraction assay. For all other films a paired t-test showed no significant difference between drug load calculated from the drug loading and disc weight and summation of chlorhexidine released and chlorhexidine remaining ($P > 0.05$). The maximum difference was 11.8%.

Repeated measures analysis of variance was used to compare the percentage released over 10 and 30 days (Table 2). Significant interactions were observed between chlorhexidine type, drug

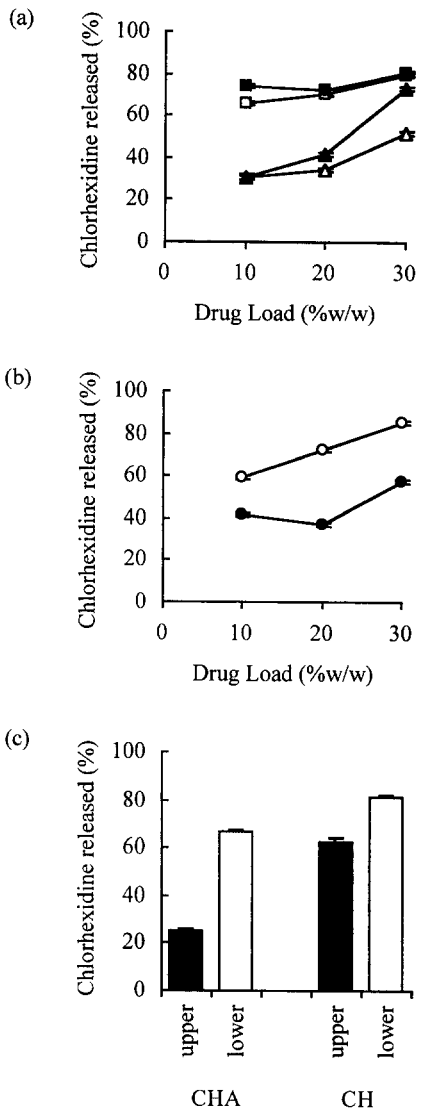

Fig. 4. Significant interactions for the percentage released over 30 days (a) DL × PS × FS, (△) < 63 μm, upper side, (▲) 63–125 μm, upper side, (□) < 63 μm, lower side, (■) 63–125 μm, lower side; (b) CT × DL, (●) chlorhexidine diacetate, (○) chlorhexidine base; (c) CT × FS, CHA, chlorhexidine diacetate, CH, chlorhexidine base. Error bars represent the standard error of the mean calculated from the pooled standard deviation.

load, chlorhexidine particle size and film side ($P < 0.05$) and the effects of these variables are summarised in Figs. 3 and 4.

Parameters, k and n, in the general release equation ($M_t/M\infty = kt^n$) were obtained by fitting the model to the initial 60% of drug release. Run tests performed on the residuals showed the model was adequate to explain release from the upper side of films containing chlorhexidine as the diacetate at drug loadings of 10 and 20% w/w and release from the upper and lower sides of films containing chlorhexidine as the base at a drug loading of 10% w/w ($P > 0.05$). For other formulations significant Run tests were observed ($P < 0.05$) but the magnitude of the residuals were less than ± 6%. Repeated measures analysis of variance of k and n are given in Table 3. Again, significant interactions were observed between variables ($P < 0.05$). Analysis of the effects on the magnitude of k showed similar trends to the percentage released at 10 and 30 days. The effects of chlorhexidine type, drug loading and chlorhexidine particle size and film side on the exponential term, n, are summarised in Fig. 5. A value for n approaching 0.5 would indicate release occurred predominantly by diffusion (Ritger and Peppas, 1987).

3.2. Chlorhexidine content of film transections

Under light microscopy with back illumination, chlorhexidine particles appeared as dark spots. Transections closest to the lower side of the films showed a higher concentration of drug particles than those taken closest to the upper side of the films, although the films were not always complete in these sections and the holes may represent areas where the films adhered to the glass plate during production (Fig. 6). Analysis of variance of the drug loading of transections showed no significant difference between films ($P > 0.05$) but significant differences for groups of transections ($P < 0.05$, Fig. 7).

4. Discussion

Use of a factorial designed experiment to determine the effect of formulation variables on release allows simultaneous determination of the effects of variables or factors and their interactions

Table 3
Results for repeated measures analysis of variance of k and n

Source	Degrees of freedom	k		n	
		F	p	F	p
Chlorhexidine type (CT)	1	293.0	<0.001	20.45	<0.001
Drug load (DL)	2	1.8	0.206	3.75	0.054
Particle size (PS)	1	9.5	0.010	3.63	0.081
Film (CT DL PS)	12	0.3	0.974	0.91	0.567
Film side (FS)	1	271.5	<0.001	30.37	<0.001
CT × DL	2	16.8	<0.001	14.75	0.030
CT × PS	1	0.07	0.795	7.31	0.019
CT × FS	1	62.8	<0.001	35.39	<0.001
DL × PS	2	1.0	0.405	2.85	0.097
DL × FS	2	31.6	<0.001	5.44	0.021
PS × FS	1	2.6	0.136	3.19	0.099
CT × DL × PS	2	1.3	0.314	6.39	0.013
CT × DL × FS	2	1.2	0.348	1.86	0.198
CT × PS × FS	1	0.0	0.954	2.68	0.127
DL × PS × FS	2	2.9	0.093	0.35	0.711
CT × DL × PS × FS	2	0.6	0.574	0.13	0.879
Error	12				
Total	47				

(Bolton, 1990). Chlorhexidine type and drug loading have already been identified as variables which affected release (Medlicott et al., 1992). Also included in the factorially designed experiment was chlorhexidine particle size and release was tested from the upper and lower sides of the films.

The release of drugs from erodable polymeric matrices depends on the mechanism of polymer degradation and the rate of matrix erosion. Various polyesters are available which undergo degradation by bulk hydrolysis of the ester bonds and possess different rates of degradation (Pitt et al., 1981a,b). In most cases drug release from polyester matrices occurs by diffusion before matrix erosion (Baker, 1987). However, changes may occur in the matrix with polymer degradation that affect drug diffusion. Prior to matrix erosion, an increase in poly(ε-caprolactone) crystallinity was reported by Pitt et al. (1979b) which resulted in a corresponding decrease in the rate of release of norgestrol. Also, the degradation rate of poly(ε-caprolactone) has been shown to be increased in the presence of strong bases (Pitt and Gu, 1987) presumably caused by a general base catalysis of ester hydrolysis. In other studies, incorporation of drug salts into poly(ε-caprolactone) matrices has been associated with slow and incomplete release (Wang, 1989 and Goodson et al., 1983) whereas high matrix permeability and rapid release has been reported with a lipid soluble drug, progesterone (Pitt et al., 1979a,b). It may be possible that chlorhexidine base has a higher permeability in poly(ε-caprolactone) than the diacetate. This would contribute to the more rapid chlorhexidine release from films containing the base. Also, inclusion of chlorhexidine base which is a strong base with pKa values of 2.3 and 10.3 (Hugo and Longworth, 1964) may have affected poly(ε-caprolactone) degradation so that matrix erosion accounted for some chlorhexidine release.

Drug loading affects release by changing the porosity of the matrix because channels are formed as solid drug is dissolved and released (Higuchi, 1963; Desai et al., 1965). Bonny and Leuenberger (1991) used percolation theory to explain the release of a water soluble compound from ethylcellulose matrices. At drug loadings of less than 20% w/w, low release rates and incomplete release occurred because no continuous network of drug particles occurs in the matrix. For

drug loadings between 30 and 70% w/w, greater release rates and higher percentages released were attributed to formation of a percolating network of both drug and polymer. For the poly(ε-caprolactone) films in this study, differences in matrix porosity near the upper and lower sides of the films may explain the differences in release from the upper and lower sides of the poly(ε-caprolactone) films. If drug particles sedimented during film preparation, the bottom layer would be expected to contain a greater concentration of drug than upper layers. Therefore, when release occurred from the lower side, the film would effec-

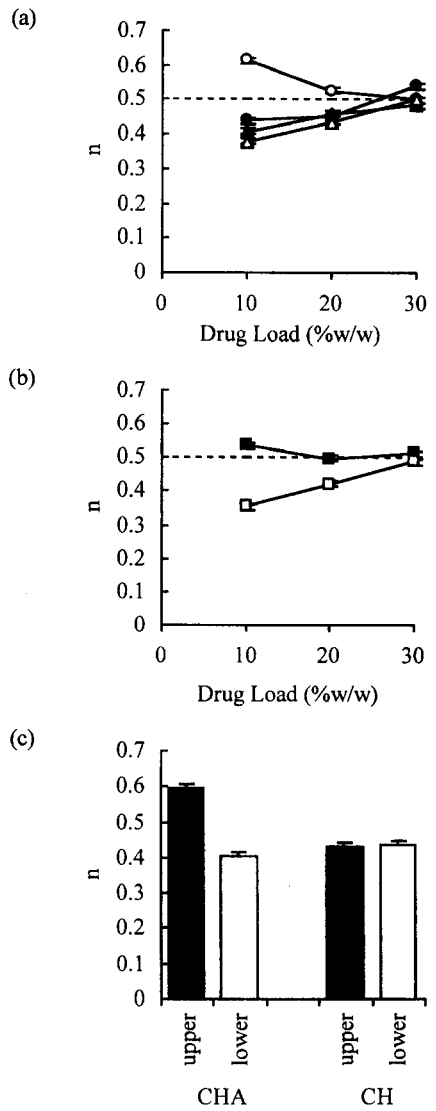

Fig. 5. Significant interactions for *n*. (a) CT × DL × PS; CHA (●) <63 μm, (○) 63–125 μm; CH (▲) <63 μm, (△) 63–125 μm; (b) DL × FS, (■) lower side, (□) upper side; (c) CT × FS, CHA, chlorhexidine diacetate, CH, chlorhexidine base. Error bars represent the standard error of the mean calculated from the pooled standard deviation.

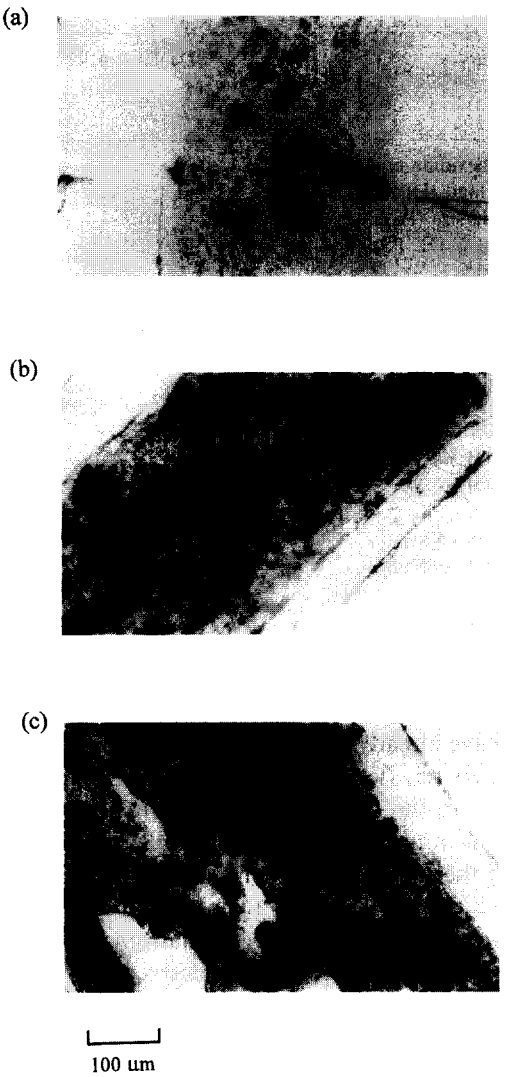

Fig. 6. Transections taken through poly(ε-caprolactone) film containing 20%w/w chlorhexidine diacetate (< 63 μm). Transections from near the (a) upper side (b) middle and (c) lower side of the film.

tively act as though it had a higher drug loading and more rapid release was observed. In comparison, for release from the upper side, the slower rate of release may be attributed to the low drug loading in the upper layers. Further evidence for the non-uniform distribution of chlorhexidine in films prepared with the diacetate was obtained by analysis of transections from films containing 20% w/w chlorhexidine (< 63 μm). From the light microscopy results, it is possible to suggest reasons for the observed chlorhexidine distribution. The smaller percentage of drug load seen in transections near the lower side of the film appeared to be caused by film porosity. Pores may represent areas where drug and/or polymer adhere to the glass plate during film preparation. As a result these transections would contain less mass than those from other groups of transections. In contrast, transections from the upper side of the film appeared to contained a lower concentration of dispersed drug. It was calculated that about 16% of the drug load was contained in the upper 20% thickness. From the release study, less than 10% of the drug load was released from the upper side,

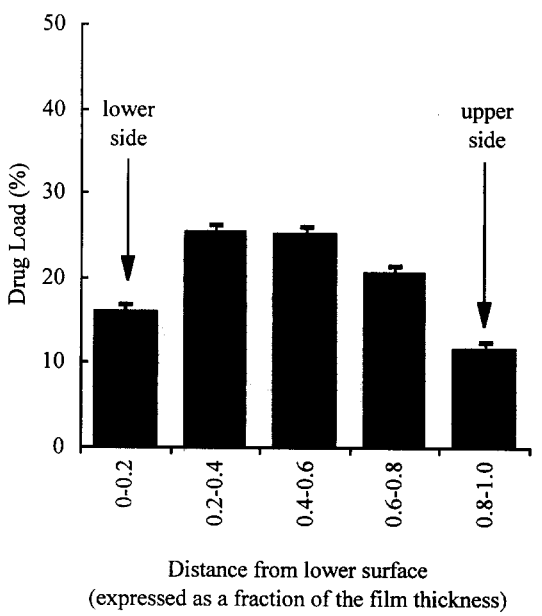

Fig. 7. Effect of distance through the film (transection) on the percentage drug load. Error bars represent the standard error of the mean calculated from the pooled standard deviation.

which may suggest inaccessibility of the release medium to drug embedded in the lower layers. In contrast, about 60% of the drug load was released from the lower side indicating easier access by the dissolution medium when this side of the film is exposed. The greater access of release medium into the poly(ε-caprolactone) matrix from the lower side may be the result of the percolation network caused by the greater drug loading in the lower layers of the film (approximately 25% w/w) and by the presence of pores created in the lower layer during film preparation which would increase the surface area for release. When chlorhexidine base was used to prepare films the magnitude of the difference in release between film sides was generally lower. This may have occurred because chlorhexidine base is more soluble in the casting solvent than chlorhexidine diacetate (Medlicott et al., 1992) and the dissolved portion would probably become uniformly distributed in the film.

Greater release rates were reported by Lazarus et al. (1964) when the particle size of the dispersed drug is increased. They suggested this was due to formation of large cavities in the matrix after drug which is in contact with the dissolution medium was released. In contrast, Ford et al. (1985) suggested particle size should affect matrix tortuosity but reported only marginal increases in the release rate with increasing particle size. For chlorhexidine release from poly(ε-caprolactone), chlorhexidine particle size showed a significant effect on release only from the upper side at a drug loading of 30% w/w. At this loading a significantly greater percentage of the drug load was released if the larger (63–125 μm) chlorhexidine particles were used. Use of this size fraction may have allowed better access to the drug in the lower layers of the film because only two particles would need to stack on each other to span the thickness of the film (approximately 200 μm). In contrast, when chlorhexidine of particle size < 63 μm was used, three to four particles would need to stack on one another to span the film thickness and this may not occur until higher drug loadings ($> 30\%$ w/w) are used.

Fitting of the general release equation (Gurney et al., 1982) was used by Korsmeyer et al. (1983)

to explain the mechanism of release for solutes from hydrophilic polymers. The approach was extended to analysis of drug release from polymer matrices with different geometries (Ritger and Peppas, 1987). For drug release from thin polymer films it was suggested release may be described by coupling a Fickian (diffusion-controlled) and non-Fickian mechanism and the general expression $M_t/M_\infty = kt^n$ was derived. This equation is valid for the first 60% of fractional release (i.e. $M_t/M_\infty < 0.6$) (Ritger and Peppas, 1987). Peppas (1985) proposed the general equation only for systems in which drug diffusion occurs through the polymer structure and for these cases, values for n are expected to fall between 0.5 and 1.0 ($n = 0.5$ represents diffusion-controlled release and $n = 1.0$ represents zero-order release). It was suggested that application of the equation to porous matrices where drug release occurs by diffusion partially through a swollen matrix and partially through water-filled holes would probably lead to $n < 0.5$. In this study, n tended towards 0.5 as the drug loading increased to 30% w/w. One of the assumptions in derivation of the square-root time relationship for diffusion-controlled release is that a uniform distribution of drug occurs in the matrix (Higuchi, 1961, 1963). As discussed above it appears that uniform distribution of chlorhexidine was not achieved in some formulations so the observed deviations from $n = 0.5$ may be the result of a concentration gradient of chlorhexidine through the films. However, formulation of poly(ε-caprolactone) films containing chlorhexidine as the base at high drug loadings is likely to result in a greater uniformity of distribution of chlorhexidine. Therefore, the tendency for n to reach 0.5 may reflect a shift towards a more uniform distribution of drug through the poly(ε-caprolactone). The fit of the model was not as good for these formulation and may indicate a contribution from other mechanisms to the overall release.

In summary, the study reported in this paper shows significant interactions occur between formulation variables which affected the release of chlorhexidine from poly(ε-caprolactone) films. Very slow and incomplete release occurred from the upper side of films if chlorhexidine diacetate was used at drug loadings of 10 and 20% w/w. Differences in release occur between the upper and lower sides but these differences were smallest for films containing high drug loadings of chlorhexidine base of particle size 63–125 μm. Consideration of these interactions during optimisation of the formulation should allow rational development of a system for use in vivo.

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