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Note

Casting solvent controlled release of chlorhexidine from ethylcellulose films prepared by solvent evaporation

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Abstract

Chlorhexidine release from ethylcellulose films cast from solvents of different dichloromethane/ethanol compositions was studied. Release rate was proportional to the square root of time. Increased ethanol content within the casting solvent significantly enhanced release rate. Release rate and cumulative mass released at different time periods (5, 10, 15 and 25 days) were proportional to the solubility parameter of the casting solvent.

Keywords: Chlorhexidine; Solubility parameter; Ethylcellulose; Diffusional release

Peridontal diseases are a group of clinical conditions which affect the supportive structures of the teeth and are characterised by infection and inflammation. The development of periodontitis involves periodontal tissue breakdown and results from an interaction between the infecting organisms, e.g., *Bacteroides* spp., *Capnocytophaga* spp. and *Actinbacillus actinomycetemcomitans*, and the host defense mechanism,. If untreated increased tooth mobility and possibly tooth loss may result (Slots and Genco, 1984; Lisgarten, 1987).

Topical antiseptic mouthwashes of antimicrobial agents may be effective in early gingivitis (inflammation of the oral mucosa around the teeth) where the pocket depth is small and for the control supragingival plaque, however, they are ineffective against subgingival bacteria due to the poor ability to effectively penetrate the periodontal pocket (Pitchner et al., 1980). Irrigations of antimicrobial agents have also been employed, however, they require to be inserted at least 3 mm into the pocket to be effective and, in addition, the duration of effect is short thus requiring frequent application (Joyston-Bechal, 1987). As a consequence of the shortcomings of antimicrobial therapy using conventional dosage forms, there has arisen an interest in the controlled sustained delivery of such agents within the periodontal pocket. Consequently, the release of antimicrobial agents from several polymeric systems has been reported (Medlicott et al., 1994).

In the manufacture of polymeric films by the solvent evaporation process, the polymeric mate-

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rial, with or without plasticiser, is dissolved in a solvent or solvent mixture and into this the active constituent is dissolved or dispersed. This solution is then cast onto a suitable substrate and the solvent allowed to evaporate leaving a solid polymeric film containing drug substance (Kanig and Goodman, 1962; Medlicott et al., 1992). Whilst modified release of antimicrobial agents into the peridontal pocket has been achieved by the use of different polymeric mixtures or different polymers (Medlicott et al., 1994), there have been few attempts to modify the release of antimicrobial agents by alteration of the composition of the casting solvent. This communication reports preliminary observations concerning the release of chlorhexidene diacetate from ethylcellulose films cast from different solvent compositions prepared by solvent evaporation.

Chlorhexidine diacetate was purchased from ICI (NZ) Ltd, Wellington. Ethylcellulose N100 was obtained from BDH Chemicals, Poole, Dorset, U.K. All other chemicals were AnalaR or equivalent quality.

Films were prepared as follows. Ethylcellulose N100 (2.25 g) was dissolved in the appropriate solvent, either 70% v/v ethanol/30% v/v dichloromethane; 50% v/v ethanol/50% v/v dichloromethane; 30% v/v ethanol/70% v/v dichloromethane or 100% v/v dichloromethane, with stirring. Chlorhexidine diacetate (particle size < 63 μm; 0.25 g) was added and stirring maintained. Air was removed from the polymeric/drug dispersion by ultrasonication for 5 min. The total concentration of drug and polymer within the casting solution was 10% w/v. Films were cast onto either aluminium (for ethanol/dichloromethane mixtures) or glass (dichloromethane), covered with inverted funnels to ensure controlled evaporation of solvent and placed in a fume cupboard. After evaporation of the solvent, the films were removed and stored in a desiccator prior to use.

Release studies were performed in duplicate as described by Friedman and Golomb (1982). The films were cut to a circular form to fit the diffusion cell (i.e., 13.85 cm^2). Two films, separated by parafilm, were clamped between each compartment of the horizontal dissolution cells. Consequently each compartment of the dissolution cell constituted one experiment. Each compartment of the dissolution cell was filled with distilled water at room temperature (approx. 20°C), stirred using magnetic followers and, at required intervals, the contents of each cell were removed and replaced with fresh release media (distilled water at approx. 20°C) to ensure sink conditions were maintained throughout the course of the experiment. The concentration of chlorhexidine released at each time interval was analysed by ultraviolet spectroscopy ($\lambda = 254$ nm) using a Hewlett-Packard 8452 diode array spectrophotometer linked to an NEC powermate 1 plus 286 computer. The calibration curve for chlorhexidine was linear over the range 0.15–2.5 mg/ml ($r = 0.99$). Ethylcellulose did not interfere with the spectrophotometric analysis.

Statistical comparisons of release rates associated with these films was performed by one-way analysis of variance, $p < 0.05$ indicating significance. Solubility parameters of solvent mixtures used in this study were calculated as described by Rabek (1980).

Chlorhexidine release from ethylcellulose films cast from different solvents is graphically illustrated in Fig. 1. Drug release from ethylcellulose films in all cases was proportional to the square root of time and therefore release is described by the diffusional model proposed by Higuchi (1963). Statistical comparisons of the release rates revealed that casting solvent sigificantly affected chlorhexidine release from ethylcellulose films. Using Fischer PLSD test it was observed that the release of chlorhexidine was significantly different for films cast from each of the solvents. The greatest release was observed whenever 70% v/v ethanol/30% v/v dichloromethane was used as the solvent (0.226 ± 0.002 mg cm^{-2} $days^{-0.5}$) whereas the lowest release was associated with dichloromethane cast films (0.011 ± 0.0003 mg cm^{-2} $days^{-0.5}$). Subsequently, increasing ethanol content of the casting solution resulted in increased chlorhexidine release. Fig. 2 shows the correlation between release rate and the solubility parameter of the casting solvent. Table 1 presents the correlation between the cumulative mass of chlorhexidine released from ethylcellu-

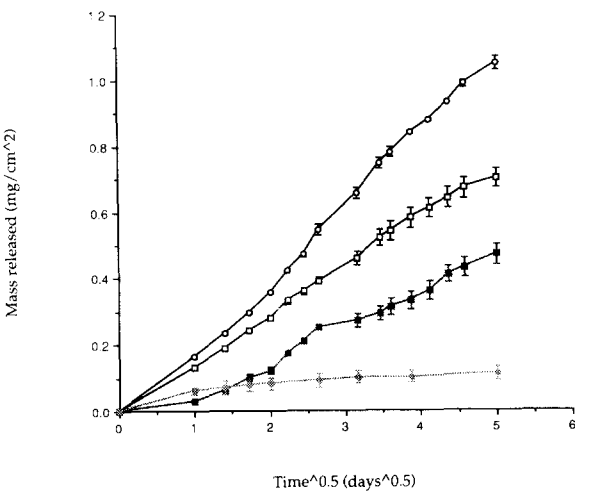

Fig. 1. Cumulative mass of chlorhexidine released from ethylcellulose films cast from different solvents as a function of the square root of time. Casting solvents: (●) dichloromethane, (■) 70% v/v dichloromethane: 30% v/v ethanol, (□) 50% v/v dichloromethane/50% v/v ethanol, (○) 30% v/v dichloromethane/70% v/v ethanol. Bars represent standard errors of the mean.

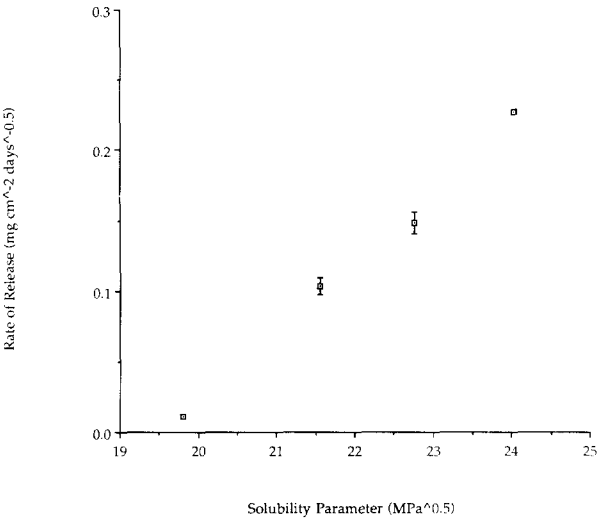

Fig. 2. Correlation ($r^2 = 0.994$) between release rate (mg cm^{-2} $days^{-0.5}$) of chlorhexidine from ethylcellulose films and the solubility parameter of the solvents from which the films were cast. Release rates were obtained from the linear portion of the slopes presented in Fig. 1. Bars represent standard errors of the mean.

lose films at different periods and the solubility parameter of the casting solvents from which the films were cast.

These observed differences in release rate of chlorhexidine from ethylcellulose films cast from different solvents may be explained in part by the state of chlorhexidine in the solid film and also by the conformation of the polymer in solution prior to casting the film. One method by which the solubility of polymers in solvents has been quantified is the solubility parameter approach (Hildebrand and Scott, 1950). In this a good solvent for a polymer will be one which the solubility parameter values of both solvent and polymer are similar. In thermodynamically good solvents, polymer molecules have a dilate coil conformation. Upon evaporation of the solvent there will be an increase in the concentration of dissolved polymer

Table 1
Effect of solubility parameter of casting solvent on the cumulative mass of chlorhexidine released from ethylcellulose films at different time periods

Days	Cumulative mass of chlorhexidine released ± S.E. (mg cm^{-2})				
	(Solubility parameter of casting solvent [a] ($MPa^{0.5}$))				
	19.8 DCM	21.55 (70% v/v DCM/30% v/v EtOH)	22.76 (50% v/v DCM/50% v/v EtOH)	24.02 (30% v/v DCM/70% v/v EtOH)	Correlation coefficient [b]
5	N.D.	0.17 ± 0.003	0.33 ± 0.010	0.42 ± 0.000	0.971
10	0.10 ± 0.020	0.27 ± 0.020	0.46 ± 0.020	0.66 ± 0.018	0.986
15	0.10 ± 0.020	0.33 ± 0.025	0.58 ± 0.030	0.84 ± 0.004	0.987
25	0.11 ± 0.020	0.47 ± 0.030	0.70 ± 0.030	1.05 ± 0.020	0.993

[a] Calculated according to Rabek (1980).[b] Correlation between the cumulative mass of chlorhexidine released ± S.E. (mg cm^{-2}) at each independent time period, i.e., 5, 10 15 and 25 days, and the solubility parameter of the casting solvent from which ethylcellulose films containing chlorhexidine diacetate were cast.
N.D., not determined; DCM, dichloromethane; EtOH, ethanol.

molecules. Thus, the intermolecular forces between chain segments of a polymer molecule and also between chain segments of neighbouring polymer molecules become increasingly effective and, as a result, the resulting film is a homogeneous dense structure with strong interpenetrating chains. In dilute solutions of poor solvents, the polymer coils are compact and only superficially interact whenever the solvent evaporates. The resulting film is distinctly heterogeneous in structure due to the presence of microvoids. Other structural alterations of the polymer structure may be obtained if films are cast from a mixture of good and bad solvents. Due to differing evaporation rates of the individual components of the solvent mixture, a critical composition will occur during film formation in which separation of the polymer from solution occurs (gel formation). The structure of the final polymer film is dependent on the stage at which separation leading to film formation occurs. If separation occurs early in film formation, i.e., before gel formation, then a film consisting of an open porous structure is obtained. If separation occurs at a late stage of film formation, i.e., whenever the polymer molecules already strongly interact (after gel formation), then films of a closed-porous structure are produced. If no separation occurs then a closed dense structure, similar to films prepared from thermodynamically good solvents, will be produced (Banker, 1966; Isihara and Guth, 1968).

In this current study, a range of casting solutions based on dichloromethane and ethanol were employed. The solubility parameter of dichloromethane is 19.8 $MPa^{0.5}$, indicating that it is a good solvent for ethylcellulose (solubility parameter is 21.1 $MPa^{0.5}$) (Brandrup and Immergut, 1975; Kent and Rowe, 1978) and therefore films cast from dichloromethane as a lone solvent will be homogeneous and dense. The solubility parameter for ethanol is 26.0 $MPa^{0.5}$, indicating that it is a poor lone solvent for ethylcellulose. In the process of ethylcellulose film formation from mixtures of dichloromethane and ethanol, dichloromethane will evaporate first (boiling point 40°C) leaving ethylcellulose dissolved in the poor solvent. As the proportion of dichloromethane increases, this will ensure that at the stage at which the solvent system becomes rich in the poor solvent fraction, gel formation has occurred, no phase separation occurs and the formation of a closed dense ethylcellulose film results. The difference in chlorhexidine release from such films may therefore be attributed to the density/porosity of the ethylcellulose film resulting from casting conditions. There will be poor penetration of solvent (distilled water) into dichloromethane cast polymeric films due to the dense polymer network, a slow rate of dissolution and hence slow release of chlorhexidine into the dissolution medium. As the proportion of ethanol increases in the casting solvent, so does the heterogeneity of the film. Thus, water penetration into the film increases allowing dissolution of chlorhexidine and hence comparatively fast drug release.

The correlations between both the release rates and cumulative mass of chlorhexidine released and the solubility parameter of casting solvent (Fig. 2 and Table 1) are interesting and support the above proposal. This correlation may be of use in the design of ethylcellulose films for controlled release of chlorhexidine to the periodontal pocket where a 5–25 day period of controlled drug release is required. It has been reported that there was a corrleation between the release of methylene blue, acid red and clindamycin in vitro and in vivo (into the periodontal pocket) from non-biodegradable films (Higashi et al., 1991). These authors suggested that this would allow estimation of the in vivo release rate from in vitro release studies for films that release by diffusion. Thus, if the required cumulative mass release or release rate is known, then, from the correlation between release of drug and solubility parameter and additionally having examined the correlation between in vitro and in vivo release, the appropriate ratio of dichloromethane/ethanol can be forecast prior to film formation. Hence, in such fashion, it is the casting solvent that is used to control release and thus clinical efficacy.

Finally, one other factor which will influence the rate of release of chlorhexidine from these films is the state of the drug within the film. Whenever dichloromethane/ethanol binary solvent mixtures are employed, chlorhexidine diacetate is dissolved prior to film casting whereas

whenever dichloromethane alone is used, due to its insolubility, chlorhexidine diacetate exists as a suspension within the casting solution. Therefore, the particle size of chlorhexidine diacetate within ethanol/dichloromethane cast films will differ, due to recrystallisation as the casting solution evaporates, from that within dichloromethane cast films. This may therefore alter the rate of chlorhexidine dissolution and hence the release of drug. The state of chlorhexidine within polymeric delivery systems has previously been reported to influence the subsequent release rate of this agent (Medlicott et al., 1992).

Therefore, this study has shown that by careful choice of casting solvent, the release of chlorhexidine from ethylcellulose films may be modified. This approach may be useful in the design of such systems for the delivery of chlorhexidine to the periodontal pocket.

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