Effect of hypromellose on the antibacterial activity of benzalkonium chloride

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It has been observed that concentrations of 0·5% w/v hypromellose and above markedly inactivate the antibacterial activity of benzalkonium chloride solutions when evaluated using a killing time determination against inocula of *Pseudomonas aeruginosa* NCTC 6750 (Buchart, 1972). Exponential phase cultures of *P. aeruginosa* grown in nutrient broth in the presence of varying concentrations of hypromellose, however, did not show greatly different sensitivities to benzalkonium chloride 60 μg ml^{-1} added under controlled conditions.

This present investigation was to evaluate further the effect of hypromellose on the antibacterial activity of benzalkonium chloride as this interaction is of considerable significance in the formulation of eye-drops and contact lens solutions. Chlorhexidine gluconate was included in the evaluation to determine if it also lost antibacterial activity in the presence of hypromellose 4500.

The ability of each solution to inactivate approximately 5×10^6 ml^{-1} *P. aeruginosa* NCTC 6750 was assessed, using the method of Richards & McBride (1971).

The results (Table 1) indicate that it is the process of autoclaving the benzalkonium chloride in the presence of the hypromellose that causes the inactivation of the antibacterial activity of the benzalkonium. Chlorhexidine is apparently unaffected by autoclaving in the presence of hypromellose.

The effect of viscosity was also investigated. Solutions of sucrose having an equivalent viscosity to hypromellose 0·5% w/v were prepared and the experiments with benzalkonium 0·01% v/v were repeated using sucrose instead of hypromellose. Reduction of antibacterial activity resulted in the solution which was prepared by autoclaving the sucrose and the benzalkonium together (killing time for inoculum of approximately 5×10^6 ml^{-1} *P. aeruginosa* 90–120 min). The solution prepared by autoclaving the benzalkonium and sucrose separately had a killing time of 30–60 min. This appears to confirm that the reaction occurring on autoclaving benzalkonium chloride with a viscous agent is of greater significance in reducing the antibacterial activity, at this viscosity, than the actual viscosity of the solution. However, it is possible that at greater viscosities the viscosity of the solution will have an increasing role in maintaining the viability of the organism.

Table 1. *Killing times for solutions of benzalkonium and chlorhexidine alone and in the presence of hypromellose, but prepared in different ways, against inocula of* 5×10^6 *ml*$^{-1}$ P. aeruginosa (*NCTC* 6750).

	Antibacterial agent (0·01% v/v)		Hypromellose	Autoclaved 115° 30 min			
pH	Benzalkonium	Chlorhexidine	0·5% w/v	Together	Separately	Alone	Killing time (min)
8·4	P	—	P	P	—	—	>180
6·7	P	—	P	—	P	—	30–60
6·8	P	—	—	—	—	P	<30
8·5	—	P	P	P	—	—	<30
7·8	—	P	P	—	P	—	<30
6·7	—	P	—	—	—	P	<30

P indicates presence of chemical or method of preparation used.
— indicates absence of chemical or method of preparation not used.

The following solutions were prepared: Hypromellose 0·5% w/v + benzalkonium chloride 0·01% v/v autoclaved together at 115° for 30 min. Hypromellose 1·0% w/v + benzalkonium chloride 0·02% v/v autoclaved separately at 115° for 30 min and mixed aseptically to give 0·5% w/v hypromellose and 0·01% v/v benzalkonium chloride. Benzalkonium 0·01% autoclaved alone.

Similarly, solutions of chlorhexidine 0·01% v/v were autoclaved alone, in the presence of hypromellose 0·5% w/v, and autoclaved as a double strength solution and then mixed in equal parts with a 1·0% w/v hypromellose solution which had been autoclaved separately.

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