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Short Communication

Chlorhexidine loss from simulated contact lens solutions stored in glass and plastic packages

S. PINZAUTI[1]*, E. LA PORTA[1] and G. PAPESCHI[2]

[1] *Dipartimento di Scienze Farmaceutiche*
[2] *Dipartimento di Chimica, Università di Firenze, Via G. Capponi 9, I-50121 Firenze, Italy*

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Introduction

A storage test on chlorhexidine gluconate (0.004%) in aqueous or simulated contact lens solutions, conducted for 6 months in various containers, suggested [1] that loss of activity by a surface adsorption process was occurring. It has been reported [2] that contact lens solutions containing chlorhexidine gluconate (0.005%) stored at room temperature in the dark for 6 months in polypropylene, polyethylene, and amber and clear glass, showed an antiseptic loss of 4–10% in plastic containers and, unexpectedly, of 16% and 25% in amber and clear glass respectively. However, the type of glass employed was not stated. More recently [3], storage experiments on ophthalmic drops containing benzalkonium chloride or chlorhexidine acetate indicated no adsorption by glass or polyethylene containers. The colorimetric method [4] used in this case for assaying the preservatives has been criticized as yielding large errors [5] and as unsuitable for the determination of chlorhexidine salts [6].

Chlorhexidine gluconate (0.001–0.006%), combined with benzalkonium chloride or thiomersal, is widely employed as a preservative in contact lens solutions. These solutions are commonly packaged in polyolefin containers and many regulatory authorities demand that there should be no container–preservative interaction.

Recently the present workers described [6] a rapid and reliable colorimetric method for determining chlorhexidine gluconate in commercial contact lens solutions through the formation of a stable ion-pair with methyl orange. The ion pair can be extracted with chloroform without interference from other ingredients or from 4-chloroaniline, the main breakdown product of chlorhexidine. The present paper reports the application of

* To whom correspondence should be addressed.

this method to the analysis of chlorhexidine in aqueous or simulated contact lens solutions stored in polyolefin, brown or clear soda-lime glass, and neutral glass containers. The effects of the formulatory adjuvants on the sorption process are discussed.

Experimental

Materials

Simulated contact lens solutions (ionic strength 0.2 M) contained 0.005% chlorhexidine gluconate in an aqueous medium containing 0.65% sodium chloride, 0.1% disodium edetate, 0.9% sodium phosphate, 0.13% sodium acid phosphate, 0.002% thiomersal and 0.3% hydroxyethylcellulose (Viscontran HEC 30,000 PR, Henkel). To assess the influence of the formulatory adjuvants on the adsorption process, pure aqueous solutions containing 0.005% chlorhexidine gluconate were also prepared. Solutions were stored in new polypropylene (Kartell, Milan), low density polyethylene (Il Politene, Milan), type III [7] brown or clear soft glass (Vetrerie Bagni, Florence), or type I [7] borosilicate glass (Sovirel, France) containers, of 250 ml nominal volume and fitted with screw caps. The plastic bottles were claimed to be without additives. The type III brown soda-lime glass bottles claimed the same composition as the type III clear glass ones, apart from the presence of 0.9% ferric oxide. Assay of the hydrolytic resistance of glass containers [7] gave the following results, as ml of 0.01 M hydrochloric acid per 100 ml of test solution: type III clear soft samples, 2.7; type III brown soft samples, 1.9; type I borosilicate samples, 0.16.

Storage studies

Storage tests on pure aqueous and simulated contact lens solutions were carried out for 12 months at room temperature (15–26°C) in a laboratory with normal lighting, or for 6 months at 40°C in a thermostated oven. Eight bottles of each type were used. The contents were gently swirled just prior to removal of an aliquot for analysis. The chlorhexidine gluconate concentration in the sample aliquots (diluted with bidistilled water to obtain concentrations of 10–20 μg/ml) was determined colorimetrically [6] using 2 ml of diluted solution. The results were calculated using a calibration curve over a chlorhexidine gluconate concentration range 2–40 μg/ml. A Perkin–Elmer 552S spectrophotometer was used.

Sorption–desorption isotherm with type III glass

A type III glass bed (clear glass spherules 2.5 mm in diameter) was conditioned in bidistilled water for about 24 h and dried at 105°C for 1 h. In preliminary experiments 40 g samples of the glass bed were placed in a series of 100 ml Pyrex glass bottles fitted with screw caps. The glass was incubated with 20 ml of various concentrations of pure aqueous chlorhexidine gluconate solution or simulated contact lens solution for 8–120 h, at 30±0.5°C with shaking at 350 cycles min^{-1} (IKA shaker, Vibrax VXR). Maximum uptake was always established within 18 h, and a standard shaking time of 24 h was adopted for all subsequent experiments. The amount of preservative adsorbed was calculated by subtraction after colorimetric assay of the supernatant. The desorption isotherm was determined by removing 10 ml of the supernatant after equilibrium had been established and adding 10 ml of chlorhexidine-free simulated contact lens solution. After allowing 24 h for re-equilibration, a sample of supernatant was withdrawn and

assayed. Each result of the sorption–desorption isotherm was the mean of four replicates.

Results and Discussion

The results of the analyses (Figs 1 and 2) were plotted as the percentage residual chlorhexidine gluconate concentration remaining after each time interval. The relative standard deviations ranged from 0.9 to 2.3% (n = 4). It is apparent (Fig. 1) that the chlorhexidine content of simple aqueous solutions, at room temperature or at 40°C, was essentially unchanged at the end of the storage tests in plastic, type I and type III brown glass containers. On the other hand, the final pH values differed from the initial value of 6.0 for the type III glass bottles, and especially for the clear glass ones whose poor hydrolytic resistance is more evident at 40°C. In this case there was destabilization of the chlorhexidinium cation and high loss of the preservative through precipitation of the free base.

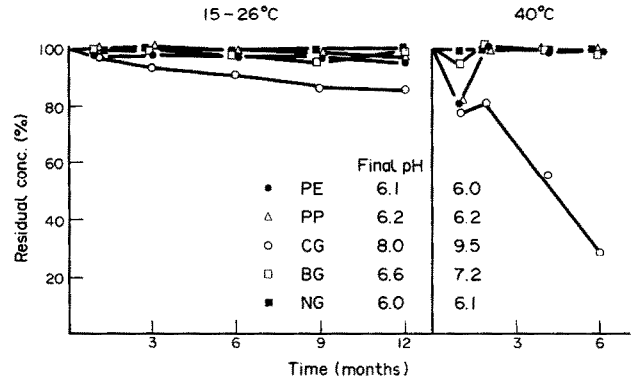

Figure 1
Loss of chlorhexidine gluconate (initial concentration 50 μg ml^{-1}) from aqueous solutions (initial pH = 6.0) stored in polyethylene (PE), polypropylene (PP), clear glass (CG), brown glass (BG) and neutral glass (NG) containers.

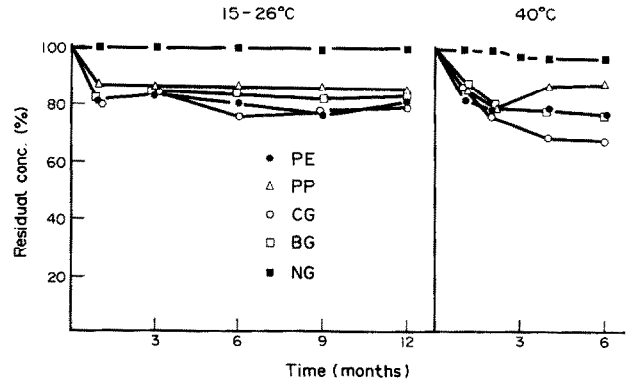

Figure 2
Loss of chlorhexidine gluconate (initial concentration 50 μg ml^{-1}) from simulated contact lens solutions stored in various containers (cf Fig. 1).

The simulated contact lens solutions showed (Fig. 2), except in the type I glass bottles, an initial loss with a subsequent stabilization of the process. This result suggests a surface adsorption depending on the surface area at equilibrium. The final losses were up to 12% and 32% for polypropylene and type III clear glass, respectively. The samples packaged in type I glass showed great stability at room temperature, and only a small loss (3.5%) at 40°C. No pH variations for these buffered solutions were seen in the type III soda-lime glass bottles.

The differences between the simple aqueous solutions and the simulated ones are important, only in the latter is the adsorption process observed. Similar behaviour in the presence of electrolytes and viscosity agents has been described for the adsorption of chlorhexidine on to the polymeric material of hydrogel contact lenses [8]. The presence of a hydrophilic viscolizer would be expected to reduce the container–preservative interaction, raising the affinity of the preservative for the aqueous phase [8]. However, the neutral electrolyte present could exert an opposite influence, both by reducing the solubility of the adsorbable species [9] and above all by decreasing the electrical repulsion between similarly charged adsorbed ions and approaching ions, thus permitting closer packing of the adsorbed species [10]. The latter phenomenon has been observed for the adsorption of ionic surfactants at the solid–liquid interface, at concentrations below the critical micellar concentration (c.m.c.) [10].

The adsorption mechanism for such different substrates (non-polar hydrophobic polyolefins, and soft glass with strongly charged sites) are bound to differ. In the case of the plastic containers, dispersion forces such as London–van der Waals interactions should be involved [10, 11]. For soda-lime glass containers, whose surface at neutral pH is negatively charged [12, 13] due to the presence of anionic silanol sites [14, 15], ion exchange, ion pairing and hydrophobic attraction should occur [10]. In the hydrophobic bonding mechanism, the neutral electrolyte could cause an increase in the chlorhexidine adsorption through closer packing, as indicated above.

In neutral glass a modifying oxide like boric anhydride greatly alters the surface characteristics of the material, lowering the diffusion coefficients of alkali ions [15, 16] and creating Lewis acid sites, which are more readily available for the coordination of nucleophiles [15] than for the adsorption of cations. However, the uncertain nature of the glass structure, which remains despite the use of modern techniques such as synchrotron radiation [17], complicates speculation on the nature of the glass-solute interaction [18].

As indicated by the desorption isotherm for chlorhexidine gluconate from simulated contact lens solutions on to soft glass (Fig. 3), adsorption was partially reversible. A similar result was obtained for the interaction of the preservative with hydrogel lens material [19]. The isotherm is similar in shape to those recorded below the c.m.c. for cationic surfactants on porous glass used for chromatographic separations [13]. Such an isotherm, S-shaped at low concentrations, should reach a maximum or a limiting value close to the c.m.c. [10, 20]. This effect could not be observed in this work because of the relatively high c.m.c. of chlorhexidine salts [21], and the presence of buffering phosphate anions which allow much lower chlorhexidinium ion availability. The Langmuir type isotherm would indicate weak intermolecular attraction [11] with contributions from multilayer formation [10, 13, 20] and/or attractive lateral interactions between hydrophobic groups [10, 13].

Very little work has been described on the suitability of glass for packaging contact lens solutions. These results indicate that, apart from the near-acceptable behaviour of the

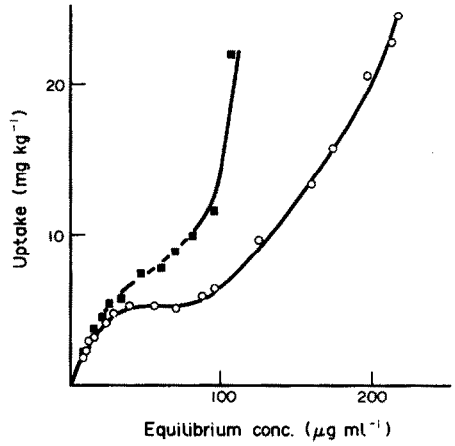

Figure 3
Uptake of chlorhexidine gluconate by soft glass spherules from simulated contact lens solutions at 30°C. ○ Sorption; ■ desorption.

polypropylene containers, the only material tested that really guarantees stability for the packing of chlorhexidine-containing contact lens solutions is type I glass, which is at present not used at all for this purpose. The present data suggest that the earlier report [2] of a large glass–chlorhexidine interaction were obtained using type III glass.

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