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Interactions of parenteral solutions with sulphur-treated glass bottles

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Concern about limited surface durability has been the main reason for recommendations by advisory committees and government health authorities, not to re-use sulphur-treated soda-lime glass (type II) bottles for intravenous solutions. In order to contribute specific data, the interactions of slightly acid and neutral parenteral solutions with ammonium sulphate-treated type II glass bottles have been investigated. It was established that the amounts of silica, sodium and calcium released into the solution are not greater than the potential background contamination from the raw materials. The number of particles in the solution was well below the limits set by the British Pharmacopoeia and not much higher than the lowest background count practically achievable. On an average, bottle surfaces released less material after the first time of use. Bottle-to-bottle variations revealed by scanning electron microscopy point at problems in achieving smooth, evenly surface-treated bottle surfaces during bottle manufacture.

Despite the early work of Bacon & Barber (1948) and, more recently, Persson (1962), the interactions of sulphur-treated soda-lime (type II) glass bottles with parenteral solutions are still an important subject of discussion. Existing data allow different interpretations, especially when extrapolated to specific medicinal and pharmaceutical applications. An important aspect of this problem is the multiple use of type II glass bottles as containers of parenteral solutions. It is feared that the thin protective surface layer of silica formed by the sulphur treatment is destroyed rapidly and excessive amounts of alkali, silica, and particles are released into the solution.

The New Zealand Department of Health (1974) and the New Zealand Transfusion Advisory Committee (1974), in line with the European Pharmacopoeia Commission (1971) and the International Organisation for Standardisation (1977), recommend that type II glass bottles be used only once for intravenous solutions. However, type II glass bottles are still recycled because of economic reasons and manufacturers of intravenous solutions claim that the recycling of these bottles does not cause any greater quality problems than the use of new ones.

The aim of this study was to investigate the effects of repeated autoclaving on the internal surfaces of type II glass bottles filled with parenteral solutions. It was to be established, at what point the surface layer modified by the surface treatment breaks down or begins to loose its protective properties.

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Only bottles treated with ammonium sulphate were used, because this agent has been accepted by most manufacturers of intravenous infusion bottles as superior to sulphur dioxide.

Although it is realized that recycling of infusion bottles creates problems of microbiological contamination, this investigation concentrated strictly on physical and chemical aspects. However, a dry heat sterilization process was included after the bottle cleaning and before the filling. Such a process ought to be Good Manufacturing Practice when bottles are recycled and may have some effect on the glass durability.

MATERIALS AND METHODS

Since most commonly-used parenteral solutions have slightly acid or neutral pH, two solutions were chosen to cover this pH range: 0·9% potassium chloride solution[1] and 1·9% potassium lactate solution[2]. The solutions were prepared using analytical reagents ("Analar" grade) and freshly distilled water.

More than 100 bottles supplied from a British and a New Zealand manufacturer were involved in the testing program. Table 1 lists the bottle compositions as determined in this laboratory. The bottles were filled with the test solutions and subjected up to 16 times to the standard autoclaving procedure of the British Pharmacopoeia 1973 (30 min at 116 °C). In a

[1] Sodium Chloride Injection, U.S. Pharmacopeia 19, pH limits 4·5–7·0.

[2] Sodium Lactate Injection, British Pharmacopoeia 1973, pH limits 5·0–7·0; U.S. Pharmacopeia 19, pH limits 6·0–7·3.

Table 1. Composition of the bottle brands tested.

	Manufacturer A	Manufacturer B	Average Comp. (A,B)
SiO_2	72·5	74·0	73·3
Na_2O	14·9	12·6	13·8
CaO	10·4	11·7	11·1
Al_2O_3	1·5	1·0	1·3
K_2O	0·3	0·3	0·3
MgO	0·3	0·1	0·2
Surface treatment agent	A & B Ammonium sulphate		
Compliance with Hydrolytic Resistance Test, European Pharmacopoeia	A & B complied (< 0·05 ml 0·01 N HCl)		

preliminary trial, the autoclaving times were three hours each. The temperature distribution in the autoclave was continually recorded by means of sets of thermocouples. Before each autoclaving, the bottles were brushed with a detergent solution, rinsed with tap water until no lather was apparent, finally rinsed with filtered distilled water, and sterilized with dry heat, 30 min at 180 °C. After cooling, the bottles were rinsed with freshly prepared test solution, which was filtered through a 0·45 μm membrane filter, and immediately filled with fresh filtered solution of the same kind. In order to minimize the contamination originating from the closures, the bottles were covered with neutral glass covers. These covers were rinsed several times with the appropriate filtered solution before use and were attached to the bottles with adhesive tape. The solutions serving as blanks and the bottles in which they were stored were prepared as described above, but not autoclaved.

After autoclaving and cooling, the solutions were analysed for silica, sodium and calcium, using atomic absorption and flame emisson spectroscopy, and for particulate matter, using a Celloscope, a particle counter based on the Coulter principle. The internal surfaces of a portion of the bottles, selected at random, were investigated for physical changes using scanning electron microscopy.

Approximately 1800 data were subjected to analysis of variance.

RESULTS

Influence of bottle brand. Bottles from source A released significantly* less particles, sodium, calcium and silica into the solutions than bottles from source B (Compare Table 2). However, the general trends in the release pattern over a series of 16 autoclavings were similar for both brands, despite the fact that the data were obtained at different times, with different bottles, even by different operators. Thus it was possible to combine the results of both bottle brands for evaluation.

The internal surfaces of the bottles from source B, investigated under the scanning electron microscope, were as a rule smoother and showed fewer defects than the bottles from source A. The general trends in the changes of the surface appearance over a series of 16 autoclavings were similar for both bottle brands.

Influence of bottle-to-bottle variations. The variations of bottle surface quality were considerable for both bottle types and became strikingly visible under the scanning electron microscope. Some unused sulphur-treated bottles showed entirely smooth, featureless surfaces while others were slightly rippled and, in extreme cases, showed "horseshoe" shaped defects. After repeated or prolonged autoclaving with test solution, some surfaces appeared smooth and featureless, while others were slightly granular with more or less prominent "pock marks".

Influence of the solution. Potassium lactate solution attacked the glass surface significantly more than potassium chloride solution.

Influence of repeated autoclaving. The number of autoclavings have a significant influence on the release of particles, sodium, calcium and silica.

Influence of prolonged storage. Both solutions were prepared under aseptic conditions and stored in bottles of both brands for 6 months at room temperature (≈20 °C), without having been autoclaved. No significant release of sodium, calcium, silica or particles was detected.

Table 2. Amounts of sodium, calcium, silica and particulate matter, released in an average autoclaving process (30 min/116 °C).

	In potassium lactate solution			In potassium chloride solution		
Released material	Bottle A	Bottle B	Grand mean	Bottle A	Bottle B	Grand mean
Sodium (mg litre^{-1})	1·49	1·83	1·67	0·05	0·06	0·05
Calcium (mg litre^{-1})	0·14	0·64	0·39	0·04	0·05	0·04
Silica (mg litre^{-1})	1·30	4·37	2·84	0·11	0·18	0·14
Particles ⩾2 μm	128	155	139	38	60	48
⩾5 μm	15	18	16	5	5	5

* The term "significant" is associated, here and subsequently with the 95% confidence level.

Release pattern of particulate matter ($\geqslant 2\mu m$). With potassium lactate solution, the greatest numbers of particles were released during the first autoclaving, while the autoclavings 5–11 showed a significantly decreased number of particles. The counts increased significantly again after the 11th autoclaving, without significantly exceeding the number released during the first autoclaving. In the case of potassium chloride solution, the particle count after the 9th and after the 13th autoclaving significantly exceeded the counts after the first autoclaving (see Fig. 1).

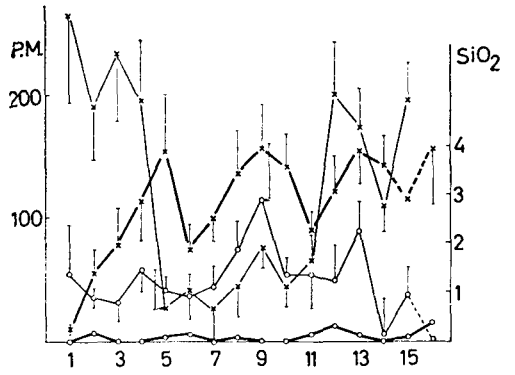

FIG. 1. Release of silica (—) and particles, $\geqslant 2\,\mu m$, (—) into potassium chloride (○) and potassium lactate (×) solutions. Each point a mean of 10 determinations. Bars indicate s.e. For silica in potassium chloride solution s.e.s are too small (0–0·06) to be shown. – – – lead to points comprising many estimated values. Abscissa: number of autoclavings (30 min at 116 °C). Left ordinate: particles in 1 ml. Right ordinate: SiO_2 (mg litre^{-1}).

Release pattern of cations. Most cations were released during the first, during the 4th or 5th, and from the 7th to 9th autoclaving onward. However, the amount released in any of the last autoclavings was not higher than the amount released during any of the first autoclavings (see Fig. 2).

Release pattern of silica. The amounts of silica released into potassium chloride solution were close to, or beneath the detection limit. With potassium lactate, the release of silica followed a similar pattern to that of the cations, from the 3rd autoclaving on. Less silica was released in the initial stages of the autoclaving series (see Figs 1, 3, 4).

Bottle surface changes as observed with scanning electron microscopy. Under the scanning electron microscope, the bottle surface showed with increasing numbers of autoclavings a continuing trend to more irregular features. Defects became more pronounced. However, some new bottles by no means showed smoother surfaces than others exposed to a high number of autoclavings.

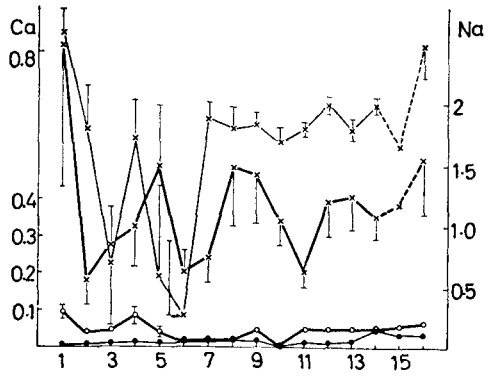

FIG. 2. Release of sodium (—) and calcium (—) into potassium chloride (○, ●) and potassium lactate (×) solutions. Each point is a mean of 10 determinations. Bars indicate s.e. For sodium in potassium chloride solution s.e.s are too small (0–0·04) to be shown. With calcium in potassium chloride solution only s.e. > 0·01 are shown. – – – lead to points comprising many estimated values. Abscissa: number of autoclavings (30 min at 116 °C). Left ordinate: calcium (mg litre^{-1}). Right ordinate: sodium (mg litre^{-1}).

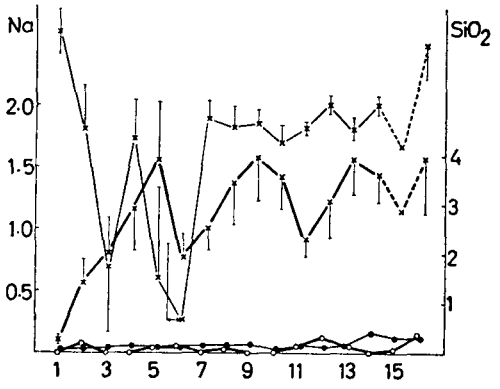

FIG. 3. Release of silica (—) and sodium (—) into potassium chloride (○, ●) and potassium lactate (×) solution. Each point is a mean of 10 determinations. Bars indicate s.e. The s.e. for silica (0–0·06) and for sodium (0–0·04) in potassium chloride solution too small to be shown. – – – lead to points comprising many estimated values. Abscissa: number of autoclavings (30 min at 116 °C). Left ordinate: sodium (mg litre^{-1}). Right ordinate: SiO_2 (mg litre^{-1}).

Changes in the reaction of the solution. The mean pH of potassium chloride solution was 5·8 before autoclaving and 6·7 after autoclaving. The mean pH of potassium lactate solution was 7·2 before autoclaving

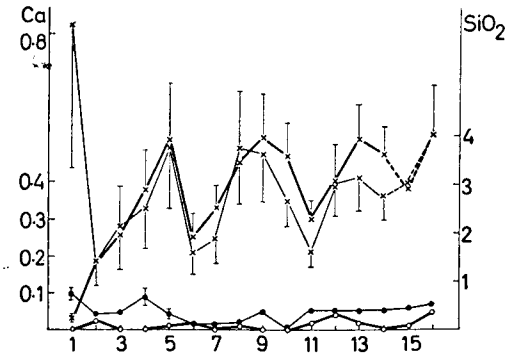

FIG. 4. Release of silica (—) and calcium (—) into potassium chloride (○, ●) and potassium lactate (×) solution. Each point is a mean of 10 determinations. Bars indicate s.e. The s.e. for silica in potassium chloride solution are too small (0–0·06) to be shown. With calcium in potassium chloride solution only s.e.s > 0·01 are shown. – – – lead to points comprising many estimated values. Abscissa: number of autoclavings (30 min at 116°C). Left ordinate: calcium (mg litre^{-1}). Right ordinate: silica (mg litre^{-1}).

and 6·3 after autoclaving. Over the series of 16 autoclavings, the re-use of the bottles did not lead to an increase in the mean pH of the solutions.

Trends in a series with autoclaving periods of 3 h. The release pattern was similar to that in the series with autoclaving times of 30 min (see Fig. 5). Silica values peaked during autoclavings 4 and 10, alkali (in this case potassium) values during autoclavings 1, 5, 8 and 10, calcium during autoclavings 4, 8 and 10 and particulate matter release (here 5 μm and greater) was lowest during autoclavings 4–6.

Average background contamination in freshly prepared unautoclaved test solutions. See Table 3.

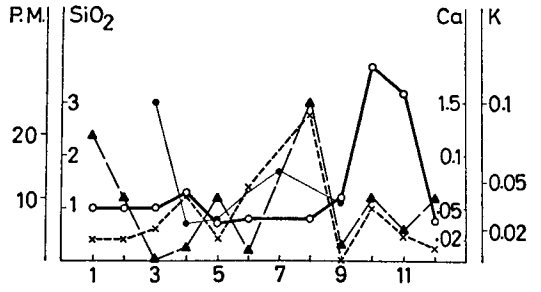

FIG. 5. Release of particles, ≥ 5 μm, (●—●), silica (○—○), calcium (×—×), and potassium (▲—▲) into sodium chloride solution, 0·9 %. Each point is a mean of 10 determinations. Abscissa: number of autoclavings (3 h at 116 °C). Left ordinates: particles (in 1 ml) and SiO_2 (mg litre^{-1}). Right ordinates: calcium and potassium (mg litre^{-1}).

Table 3. Average background contamination in freshly prepared unautoclaved test solutions.

	In potassium lactate solution	In potassium chloride solution
Sodium (mg litre^{-1})	50·9	0·22
Calcium (mg litre^{-1})	0·04	0·17
Silica (mg litre^{-1})	1·52	0·87
Particles ≥ 2 μm	138	49
≥ 5 μm	12	5

DISCUSSION

The maximum amounts of silica, alkali and calcium released over a succession of 16 autoclavings were as a rule not greater than the amounts released during the first autoclaving and were much smaller than the potential background contamination from the raw materials, e.g. according to its label, BDH Analar potassium chloride may contain "up to 500 ppm sodium" and "up to 40 ppm calcium". The European Pharmacopoeia (1969) limits calcium in sodium chloride to 100 ppm and stipulates that sodium chloride used for parenteral administration "contains not more than 0·1 percent of potassium" (1000 ppm!).

Since the values for particulate matter in the solutions were comparatively high during the first autoclavings, it may be assumed that most of these particles originated from material attached to the bottle surface and that the ordinary washing and rinsing procedures are not efficient enough to remove them. Similar conditions were found when neutral-glass flat-bottom flasks were used for storing blank solutions. These flasks released many more particles than used soda-lime glass bottles and had to be autoclaved several times with water to reduce the background count of particulate matter. The low silica values accompanying the high particulate matter counts during the first autoclavings as shown in Fig. 1, seem to indicate that most of the particles may not even contain silicates. Only after the seventh autoclaving do the particulate matter and the silica release follow a similar pattern. From here on, the particles may be due to some surface degradation. Even at this stage, the particulate matter counts are well below the limits set by the British Pharmacopoeia (1973: 1000 particles ≥ 2 μm ml^{-1}) and not much higher than the practically-achievable background contamination.

The depth of the silica layer D_{SiO_2} dissolved over a number of autoclavings can be estimated using the following relationship:

$$D_{SiO_2} = \frac{c \times 10^7}{\%SiO_2 \times A \times d} \times 10^{-1} \text{ nm}$$

where c = mg SiO_2 in the volume of attacking solution; % SiO_2 = percent silica in the glass surface; A = area exposed to the attacking solution (cm^2); d = density of the glass surface.

In this study, the volume of the attacking solution was 500 ml and the area exposed was 300 cm^2. Assuming that the surface treatment has changed the bottle surface into 100% silica, the glass surface density may be taken as 2·2. Using the grand means from Table 2, it may then be calculated that in an average autoclaving process potassium chloride solution, 0·9%, may dissolve a layer of 11×10^{-1} nm while potassium lactate solution, 1·9% may dissolve a layer of 175×10^{-1} nm. Since in practice the surface film contains less than 100% silica (having a density between 2·2 and 2·5), the average layers dissolved would be slightly thicker (13 and 215×10^{-1} nm for a film approaching the bulk glass composition).

The leaching patterns of sodium and calcium are compared in Fig. 2. Apart from the facts, that both calcium and sodium ions are released in considerable amounts during the first autoclaving and that always more sodium is leached out than calcium, the sodium peaks tend to be ahead of the calcium peaks. Figs 3 and 4 indicate, that at least in the case of potassium lactate solution, the leaching pattern of calcium is more closely related to the dissolution pattern of silica. The values obtained with potassium chloride solution may be too small for meaningful interpretation. Furthermore, if the ratio of CaO/SiO_2 released in an average autoclaving process, involving potassium lactate solution, is calculated as 0·19 (0·55/2·84), this is comparable with the ratio in the bulk glass which is 0·15 (11·1/73·3). For Na_2O/SiO_2 the corresponding values are 0·79 (2·25/2·84) in potassium lactate solution, as opposed to 0·19 (13·8/73·3) in the bulk glass. These findings are in line with the results of Clark et al (1976) who found that not only is sodium leached out preferentially, but calcium may even stabilize the silica-rich film. The calcium is then released as the silica network dissolves.

The similarities between the release patterns of the half-hourly and the three-hourly series indicate that the attack of an electrolyte solution on the glass surface may be more related to the number of autoclavings than to the length of the individual autoclaving process.

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