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COMMUNICATIONS

Particulate contamination in solutions of antibiotics packed as dry powders in vials

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Abstract—The particulate contamination in 12 formulations of antibiotic solutions in vials packed as dry powders from five South African sources has been analysed quantitatively using a HIAC PC 320 light blockage particle analyser linked to a CMB 60 sensor. Results showed that the level of particulate contamination fell well within the limits set by the USP XXIst Edition for Small Volume Parenterals although four formulations contained some particles $\geqslant 50$ μm. There was no apparent difference between the quality of the same antibiotics from different sources or between vials of the same antibiotics packed in different strengths.

Setting limits for particulate contamination in small volume parenterals (SVPs) has been a topic of interest (Spence 1981; Haines-Nutt 1983; Taylor & Spence 1983; Alexander & Veltman 1985; Gillies et al 1986; Groves & Wong 1986). The USP XXIst Edition has specifications limiting the number of particles per container, whether single or multidose, to $10\,000 \geqslant 10$ μm and $1000 \geqslant 25$ μm; the limits do not relate to dose. Neither the BP nor EP have set such limits at the present time.

The results of a study of the levels of particulate contamination in 33 batches of South African manufactured ampoules were reported by Alexander & Veltman (1985). This study has now been extended with this quantitative examination of the particles present in a number of antibiotic solutions prepared from dry powders packed in vials.

Methods and materials

Water for reconstitution and rinsing was distilled and filtered through a Pall 0·22 μm cartridge filter into a pressure vessel to which a filter gun with a Pall 0·22 μm disposable filter was attached.

A HIAC PC 320 Particle Size Analyser linked to a CMB 60 sensor with its channels set to count the total number of particles $\geqslant 5$, $\geqslant 10$, $\geqslant 15$, $\geqslant 20$, $\geqslant 25$ and $\geqslant 50$ μm was used to analyse the particulate contamination in the vial solutions, check the quality of the twice filtered water and confirm the cleanliness of the glassware and syringes.

The USP method for opening the vials, reconstituting, shaking, extracting and diluting the liquid was tested with twice filtered water. Less than 1 particle per mL $\geqslant 5$ μm was introduced. However, when the powders were reconstituted, 25 inversions in 10 s were inadequate and so inversions were increased to 50 in 20 s. Foaming also presented a problem which was overcome by introducing the diluting fluid carefully down the side of the flask and also by increasing the time of sonication. With these modifications the USP method was used throughout the project.

Twelve batches of five vials from five sources (A–E) were analysed. The method adopted was used for all the batches with the exception of rolitetracycline i.v. and benzylpenicillin 3 g.

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Method. The water in a container of twice-filtered water was analysed to ensure that it contained no particles $\geqslant 5$ μm. With a 2·5 mL syringe, 2 mL of the twice-filtered water was slowly added to each of 5 vials and the powder dissolved ensuring that it was not displaced from the vials. These were then sonicated for 60 s. From each vial, 1 mL was transferred to a particle-free 25 mL flask and, with a 10 mL syringe, 9 mL of twice-filtered water was added by gently running it down the side of the flask to reduce foaming; the contents were then mixed by swirling.

The flasks were allowed to stand for 30 min and immediately before analysis they were sonicated for 30 s. The particles in four 1 mL samples were counted; the flask was gently swirled between each count and the sensor was rinsed with particle-free water between each flask change. The twice-filtered water was finally checked to ensure that no particulate contamination had been introduced during the test.

The method for rolitetracycline i.v. differed in that the powder was dissolved in 10 mL water. Two mL of the solution was diluted with 8 mL water before analysis. Benzylpenicillin 3 g was also dissolved in 10 mL water; 5 mL of this solution was diluted with an equal volume of water.

Results

The data from the first counts in each sample was discarded and the mean and standard deviations of counts 2 to 4 in the ranges $\geqslant 5$, 10, $\geqslant 25$ and $\geqslant 50$ μm were calculated and from the figures the mean counts and standard deviations of the contaminants per batch were calculated (Table 1).

On the basis of a log-log plot with the x axis denoting log particle size and the y axis log cumulative numbers the intercept

Table 1. Analysis of particulate contamination in batches of reconstituted antibiotic solutions.

	Mean total counts of particles per container (5 containers per product)			
Antibiotic	$\geqslant 5$ μm	$\geqslant 10$ μm	$\geqslant 25$ μm	$\geqslant 50$ μm
Ampicillin 250 mg (A)	1588 (360)	142 (84)	4 (6)	0
Ampicillin 250 mg (C)	1028 (430)	358 (156)	14 (10)	0
Ampicillin 500 mg (A)	6778 (1852)	426 (96)	8 (10)	0
Ampicillin 500 mg (C)	2720 (480)	152 (102)	12 (12)	0
Benzylpenicillin 600 mg (D)	1208 (220)	98 (58)	4 (6)	0
Benzylpenicillin 3 g (D)	1260 (304)	230 (60)	12 (6)	2 (6)
Cephazolin sodium 500 mg (E)	1182 (280)	112 (40)	4 (4)	0
Cloxacillin 500 mg (A)	9694 (1352)	484 (128)	4 (4)	0
Kanamycin 500 mg (D)	1106 (212)	96 (38)	8 (10)	6 (8)
Rolitetracycline i.v. 275 mg (B)	5620 (1076)	418 (110)	14 (12)	0 0
Rolitetracycline i.m. 150 mg (B)	3121 (288)	688 (277)	40 (26)	(4) (6)
Rolitetracycline i.m. 350 mg (B)	5944 (2176)	1082 (690)	38 (30)	4 (6)

Table 2. Statistical information obtained from log-log graphs of particle size v cumulative particle numbers.

Antibiotic	Y intercept	Slope	Stand. error	% Confidence	Number of particles $\geqslant 2$ μm per container
Ampicillin 250 mg (A)	5·82	−3·72	0·036	100	51 000
Ampicillin 250 mg (C)	4·99	−2·60	0·167	97	19 000
Ampicillin 500 mg (A)	6·78	−4·17	0·075	100	190 000
Ampicillin 600 mg (C)	5·74	−3·44	0·102	99	65 000
Benzylpenicillin 600 mg (B)	5·52	−3·51	0·018	100	32 000
Benzylpenicillin 3 g (B)	5·19	−2·99	0·059	100	21 000
Cephazolin sodium 500 mg (E)	5·29	−3·20	0·031	100	24 500
Cloxacillin 500 mg (A)	7·07	−4·40	0·041	100	460 000
Kanamycin 500 mg (D)	5·32	−3·29	0·037	100	24 500
Rolitetracycline i.v. 275 mg (B)	6·27	−3·59	0·075	100	180 000
Rolitetracycline i.m. 150 mg (B)	5·52	−2·77	0·115	99	55 000
Rolitetracycline i.m. 350 mg (B)	6·01	−3·06	0·111	99	265 000

(the number of particles $\geqslant 1$ μm), the slope, the standard error and the % confidence were determined using a programmable calculator (Table 2). With this information graphs were plotted and the number of particles $\geqslant 2$ μm per container were read. As it had been found previously that where particle numbers per size range were less than 10 the level of accuracy diminished (Alexander & Veltman 1985), these figures were not included in the calculations.

Discussion

The raw data revealed that the standard deviation of the counts from three samples taken from each vial was relatively low, but Table 1 indicates that there was a considerable variation in particulate contamination from vial to vial from the same batch. This could be a reflection of the problem of limiting particulate contamination in sterile dry preparations. Nevertheless, particle numbers in the individual vials all fell within the USP limits for particulate contaminations in SVPs with sources D and E apparently maintaining particularly high levels of Good Manufacturing Practice.

The BP states that injection solutions should be "practically free" from particles, which is a very subjective specification. Although four solutions contained particles $\geqslant 50$ μm which were visible to the naked eye, the need to dilute the samples so that the particle count did not exceed the maximum numbers laid down by the HIAC manufacturer distorted the results in the larger size ranges as shown by the relative increase in standard deviations. In fact, most of the vials were free of particles of this size and all the batches would probably have met the BP specifications for SVPs. However, if the solutions had been added to 100 mL minibags, the total number of particles $\geqslant 5$ and $\geqslant 2$ μm would in certain cases, have exceeded the BP limits for particulate contamination in injections of 100 mL or more. The BP specifies that there should not be more than 500 particles $\geqslant 2$ and 80 particles $\geqslant 5$ μm. Table 3 shows that the addition of cloxacillin injection would increase the counts to above the permitted level of both $\geqslant 5$ and $\geqslant 2$ μm particles, and the addition of ampicillin 500 mg injection (source A) and rolitetracycline i.v. injection would cause unacceptable particle numbers in $\geqslant 2$ μm range. When the standard deviations are considered it is possible that ampicillin 500 mg injection (source A) would also raise the numbers of particles $\geqslant 5$ μm to more than 80.

Slopes of the log-log graphs of the particulate contamination in the vials of ampicillin from source A were steeper than those of source C indicating they contained a greater number of small particles while the vials from source C contained a larger number of particles $\geqslant 25$ μm (Tables 1, 2).

The results from benzylpenicillin, the ampicillins and rolitetracycline showed that the higher dosage vials, with the exception of ampicillin (source C), contained higher levels of contamination than the low dosage vials (Table 1). However the steeper slope in the log-log graph for the 500 mg ampicillin (source C) resulted in a greater count of small particles in this dose compared with the 250 mg dose. This effect was reversed for the benzylpenicillin vials where the 600 mg vial had a steeper slope and therefore a higher count of small particles (Table 2).

This comparison of the contamination in vials of the same antibiotic, ampicillin, manufactured by different manufacturers and in vials of the same antibiotic packed in different strengths, did not reveal a clear picture consequently no conclusions could be drawn from it.

Conclusion. This preliminary study has shown that injections packed as dry powders in vials meet the requirements of the USP XXIst Edition which indicates that the level of Good Manufacturing Practice in South Africa is of a commendably high standard. However further work in this field is required. It would be advantageous to include a qualitative analysis using scanning electron microscopy and extend the range of preparations in vials to include those packed as solutions.

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