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Particulate contamination in parenteral type medical devices

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Summary

Attention drawn in these last few years on particulate contamination in injectable preparations for i.v. use is now broadening to include also the checking of possible particulate contamination sources such as the infusion devices, for which no standards are yet available guaranteeing quality and safety of use. This investigation was aimed at gathering useful information on the degree of foreign particle contamination in tubular sets for arteriovenous use, and at contributing to the development of a method able to measure the contamination released by such apparatus. To that purpose, we analyzed 5 different types of hemodialysis venous lines (6 sets per type) and 10 types of administration sets (5 sets per type), produced in Italy by different manufacturers. The administration sets were submitted to treatment simulating the actual conditions of use of such equipment. The analyses were carried out with instrumental methods (light blockage and electric zone-sensing method) and with a microscope. All the specimens were previously inspected visually. The results of such analyses were compared with the limits of the F.U. IX edn., for L.V. parenteral products. Usually, the particulate contamination detected did not exceed such standards. The values obtained upon microscope examination corresponded to those found with the light blockage apparatus. In the hemodialysis administration devices, the degree of contamination did not seem to be related to the type of administration set, but rather to the treatment to which it has been submitted. The introduction of Good Manufacturing Practices, Guidelines for Producer, directions for users and qualitative standards appears to be highly desirable.

Introduction

Studies on contamination of large-volume (LV) parenteral solutions by foreign particulate matter has led to the establishment of official limits for such contamination, with a consequent, marked improvement of production quality.

The search for higher qualitative standards is aimed at minimizing the number of foreign particles the patient will receive. Therefore, other possible sources of particulate contamination should be taken into account, such as infusion and extracorporeal circulation devices.

No standards are yet available for the number or size of accepted particles, nor with regard to the methods to be used in order to measure particulate contamination in such apparatus. However, the World Health Organization is considering the introduction, in a new edition of the International Pharmacopoeia, of particulate contamination limits for such devices. In the Information Letter N. 672 on "particulate contamination in medical devices", issued by the Health Protection Branch of the Bureau of Medical Devices, Health and Welfare, Canada, a proposal is made, according to which the contamination due to infusion devices should not exceed that allowed by U.S.P. XXI for LV parenteral products.

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It therefore appeared interesting and useful to carry out a preliminary investigation on the quality of parenteral type medical devices, produced in Italy, with an analytical method able to detect the highest number of particles present. Two routes might be followed in the preparation of the samples to be analyzed: one implied the mere rinsing of the device with the minimum amount of ultraclean water and the counting of the particulate matter in the rinsing water (Gour, 1987), the other one called for a treatment simulating the actual conditions under which such devices are used.

We preferred this latter method, also because no data on the subject are yet available in the literature and a need for them has been expressed (Gour, 1987). The analysis was made on 5 different types of hemodialysis venous lines and on 10 types of administration sets.

Materials and Methods

Equipment

- HIAC/ROYCO mod. 3000, equipped with HR60H sensor, size range 1–60 μm, with LV sampler. The apparatus was supplied by the manufacturer calibrated with standard spherical material.
- Coulter counter, mod. TA II, equipped with a 100 μm orifice tube (Coulter Electronics Ltd), calibrated with a 10.5 μm latex suspension.
- LeitzLaborlux 11 Pol transmitted light microscope, 200 ×.
- Dialysis peristaltic pump, flow rate 200 ml/min.
- Distilled water filtered through Millipore (0.8 μm, 0.45 μm, 0.22 μm).
- Glycerol U.S.P., Carlo Erba.

Analyzed administration sets

Hemodialysis administration sets. Five different types of hemodialysis venous lines were checked, chosen among those commercially available in Italy and supplied by 4 different manufacturers.

For each type of administration set, we analyzed 6 specimens belonging to the same lot, 3 of which were treated with filtered water at room temperature, and 3 with a solution of 40% glycerin in water at 37 °C. All the administration sets were analyzed with a light blockage method, while one set per type, among those treated with water, was checked both with the instrumental method and under the microscope.

Phleboclysis administration sets. Ten different types of administration sets were checked, taken from those commercially available in Italy, and supplied by 7 different manufacturers. Five such devices per type were examined. The analyses were carried out with an HIAC/ROYCO light blockage apparatus. One set was simultaneously analyzed with the HIAC and under the microscope, while another one was simultaneously examined with the HIAC and the Coulter counter.

All the examined sets, both for hemodialysis and for phleboclysis, were previously inspected visually, by examining the effluent on both a light and a dark background.

Sample preparation for hemodialysis administration sets

All the glassware and the materials used were carefully washed according to the procedure described by U.S.P. XXI (The United States Pharmacopeia XXI, 1985). Sample preparation was carried out in a clean environment, under a laminar flow hood equipped with HEPA filters. Each device was put into a dialysis pump and then rinsed by allowing 2000 ml of filtered water to run through it, as suggested by the manufacturer. A flask containing 2200 ml of filtered water or of a 40% glycerin solution in water at 37 °C was prepared, and the first 200 ml (representing the sample at $t = 0$) were allowed to flow. The device was then kept into the dialysis pump for 6 h, with recirculation of 2000 ml of cold filtered water or of the 40% glycerin aqueous solution at 37 °C. For each administration set we examined:

(a) two 200-ml samples respectively collected at the beginning and at the end of rinsing;
(b) the first 200 ml flowing through the device after rinsing ($t = 0$);
(c) 3 200-ml samples after 6 h' recirculation of 2000 ml of fluid through the administration set. Three samples were collected, one at the beginning of flask emptying, one in the middle and one at the end, so as to obtain a mean

value representative of the overall contamination released by the administration set in the 2000 ml of recirculated fluid ($t = 6$ h). Both the water and the glycerin aqueous solution were always previously analyzed and considered as blanks, not included in sample countings.

Sample preparation for phleboclysis administration sets

900 ml of an 0.9% NaCl solution prepared in our laboratory from 3 bottles of 500 ml each were allowed to flow through the above devices. Before capping the bottles, 200 ml of solution were collected from each of them. The samples were analyzed and considered the "blank" comprising the possible contamination coming from the solution, the glass and the rubber closure. The administration set was then inserted into the first bottle and the first 50 ml flowing through the device, and then the remaining 250 ml, were collected and analyzed.

The device was subsequently inserted into the second bottle and samples were collected as above. The same was done with the third bottle. We thus intended to reproduce the situation that can practically occur when one administration set is used for several bottles.

Analysis of hemodialysis and phleboclysis administration sets

Analysis with the HIAC/ROYCO apparatus. The analyses were carried out for the following particulate sizes: $\geqslant 2$ μm, $\geqslant 5$ μm, $\geqslant 10$ μm, $\geqslant 20$ μm, $\geqslant 25$ μm, $\geqslant 50$ μm.

Three 10-ml specimens were collected for each sample. The mean contamination values/ml recorded in the checked administration sets are shown in Tables 1 and 3.

Coulter counter analysis. Coulter counter analyses were made only on the phleboclysis devices in the 2–40 μm size range. From each sample, five 2-ml aliquots were collected. The mean cumulative contamination values calculated for each sample are reported in Table 4.

Microscope analysis. 25 ml of solution coming from the same submitted to instrumental analysis were filtered through membranes. The membranes were analyzed with a transmitted light microscope (200 ×) in the 25–500 μm size range. The contamination values recorded under the microscope are reported in Tables 2 and 5.

Statistical analysis of results

The data collected according to the above described experimental design were statistically analyzed with univariate descriptive statistics and verification of the assumptions concerning the multivariate analysis of variance for repeated measurements. For all the steps, the procedures of the SPSS/PC + were used (Norusis, 1986). In the statistical analysis only the values recorded for particles having diameters of $\geqslant 2$, $\geqslant 5$, $\geqslant 10$ μm were studied, since for greater sizes (diameter $\geqslant 20$ μm) the number of missing data was too high.

Results and Discussion

Hemodialysis venous lines

Table 1 reports the cumulative contamination values per ml obtained with the light blockage method for the 5 types of devices examined with the two treatments (water or glycerin). Such values were compared with the limits reported in F.U. IX edn. for LV parenteral products (Fig. 1).

Of all the venous lines examined, one (no. 6/2) exceeded the F.U. IX edn. limits for the $\geqslant 5$ μm size in the rinsing sample, another one (no. 5/5) exceeded such limits in the time zero sample, and no. 3/3 was above the limits both at time zero and after 6 h treatment.

At $\geqslant 5$ μm, the maximum particle number recorded was 175. At $\geqslant 20$ μm, the degree of contamination always proved lower than the F.U. IX edn. limits, except for venous line n. 1/3 which had 7 particles/ml and for n. 5/4 which had 18 particles instead of the 4 allowed.

Table 2 shows the particulate contamination values found at the microscope for the same devices. In 3 out of the 5 devices examined > 100 μm particles were detected; these also show visible particles. Some > 500 μm long fibers were found in one of the devices.

The statistical analysis showed that:

- the type of solution used for washing the devices significantly affected the values recorded,

TABLE 1

Analysis of particulate contamination in hemodialysis venous lines

Cumulative values/ml for the different threshold sizes, as determined by the HIAC/ROYCO.

Set no.	Type	Batch	Mfg.	Rinsing sample					$t = 0$ sample					$t = 6$h sample				
				≥ 2 μm	≥ 5 μm	≥ 10 μm	≥ 20 μm	≥ 25 μm	≥ 2 μm	≥ 5 μm	≥ 10 μm	≥ 20 μm	≥ 25 μm	≥ 2 μm	≥ 5 μm	≥ 10 μm	≥ 20 μm	≥ 25 μm
1	1	a	a	150	25	3	0	0	167	33	12	1	0	135	18	5	0.3	0
2	1	a	a	50	13	4	0	0	111	19	6	0	0	157	15	4	0	0
3	1	a	a	228	47	6	0	0	101	29	11	1	0	112	16	5	0	0
4	1	a	a	162	21	2	0	0	102	17	3	0	0	140	23	4	0	0
5	1	a	a	80	20	3	0	0	55	9	5	0	0	75	10	3	0	0
6	1	a	a	462	83	11	1	0	57	3	2	0	0	23	0	0	0	0
1	2	b	a	64	11	5	0	0	98	22	9	0.4	0	112	14	6	0.3	0
2	2	b	a	195	36	5	0	0	101	29	11	1	1	111	14	5	0	0
3	2	b	a	62	13	2	0	0	59	14	4	0	0	97	14	5	0	0
4	2	b	a	346	53	7	0	0	483	92	18	1	1	43	9	2	0	0
5	2	b	a	145	23	2	0	0	74	18	3	0	0	85	20	3	0	0
6	2	b	a	1329	175	21	1	0	0	0	0	0	0	0	0	0	0	0
1	3	c	b	224	22	4	0	0	72	30	16	7	0	60	10	3	0	0
2	3	c	b	411	49	4	0	0	99	23	10	1	0	71	12	5	0	0
3	3	c	b	175	38	11	0	0	867	151	20	4	1	1094	159	17	2	1
4	3	c	b	144	23	2	0	0	68	17	3	0	0	208	45	10	1	0
5	3	c	b	523	92	10	0	0	58	10	4	0	0	43	7	4	0	0
6	3	c	b	97	10	3	0	0	267	60	15	1	0	37	31	12	2	2
1	4	d	c	46	9	3	0	0	166	42	5	0	0	70	15	3	0	0
2	4	d	c	48	17	3	0	0	72	14	11	0	0	72	12	5	0	0
3	4	d	c	49	15	5	0	0	141	28	15	1	0	68	14	5	0	0
4	4	d	c	113	21	3	0	0	87	22	3	0	0	152	30	7	0	0
5	4	d	c	213	29	2	0	0	91	33	21	18	17	28	7	0	0	0
6	4	d	c	43	7	0	0	0	0	0	0	0	0	0	0	0	0	0
1	5	e	d	58	15	5	0	0	151	36	12	1	0	95	16	5	0	0
2	5	e	d	45	11	4	0	0	79	13	5	1	0	143	20	7	0	0
3	5	e	d	40	11	5	0	0	104	31	13	1	0	109	22	7	0	0
4	5	e	d	240	46	5	0	0	0	0	0	0	0	0	0	0	0	0
5	5	e	d	256	39	3	0	0	928	130	32	0	0	86	0	0	0	0
6	5	e	d	89	15	1	0	0	63	12	2	0	0	58	10	2	0	0
Mean				203	33	5	0	0	157	32	9	1	0	116	19	4	0	0
S.D.				249	34	4			220	36	7	3		191	28	4		
FU.I. IX edn. limit values					100		4			100		4			100		4	

Administration sets 1–3 were treated with water at room temperature.

Administration sets 4–6 were treated with a 40% aqueous solution of glycerin at 37 °C.

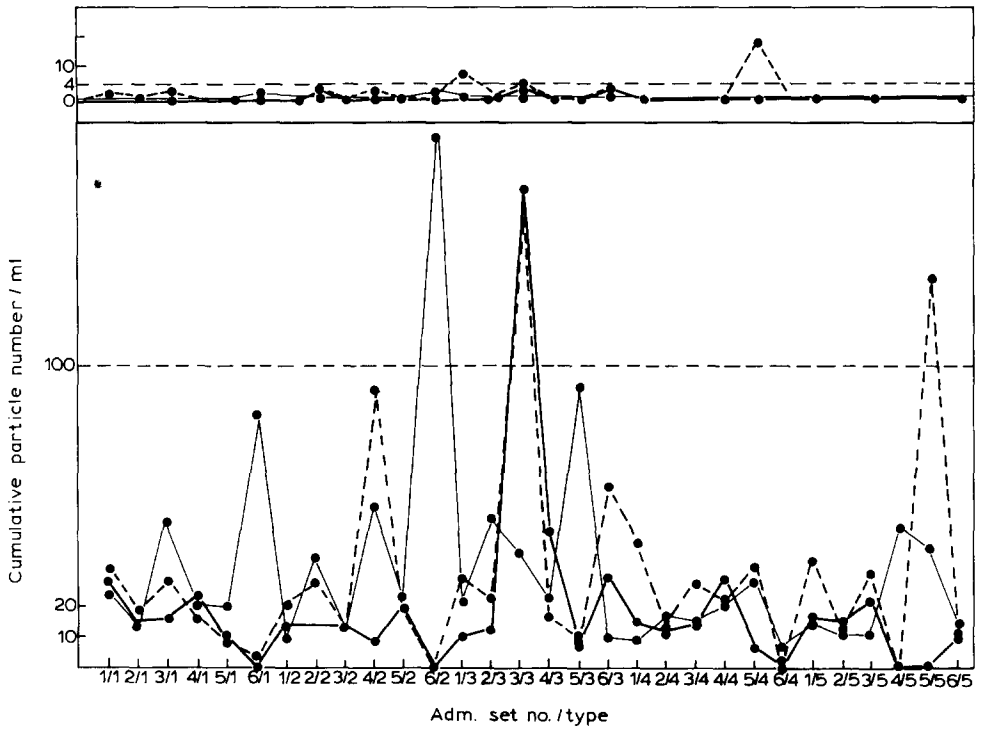

Fig. 1. Analysis of particulate contamination in hemodialysis venous lines. Mean cumulative values/ml for $\geqslant 5$ μm, $\geqslant 10$ μm, $\geqslant 20$ μm threshold sizes, determined with the light blockage apparatus. Rinsing sample, (———); sample at $t = 0$, (- - - - -); sample at $t = 6$ h, (———).

TABLE 2

Analysis of particulate contamination in hemodialysis venous lines

Mean values/ml for the different threshold sizes as determined with the microscopic method.

Type	Batch	Mfg.	Sample	25–50 μm	50–100 μm	100–500 μm	> 500 μm
1	b	a	1	0.3	0.1	0.1	1 Fiber
			$t = 0$	0.2	0.1	0	0
			$t = 6$ h	0.3	0	0	1 Fiber
2	a	a	1	0.3	0.1	0	0
			$t = 0$	0.4	0.2	0.1	0
			$t = 6$ h	0.3	0.1	0	0
3	a	b	1	0.3	0.2	0	0
			$t = 0$	0.2	0.1	0	0
			$t = 6$ h	0.4	0.1	0	0
4	a	c	1	0.2	0	0	0
			$t = 0$	0.2	0	0	0
			$t = 6$ h	0.2	0.1	0	0
5	a	b	1	0.5	0.6	0.1	0
			$t = 0$	0.2	0	0	0
			$t = 6$ h	0.6	0.5	0.1	0

1 = Sample of the first 2000 ml of rinsing fluid; $t = 0$, sample of the first 200 ml after rinsing; $t = 6$ h, sample taken after 6 h in dialysis pump.

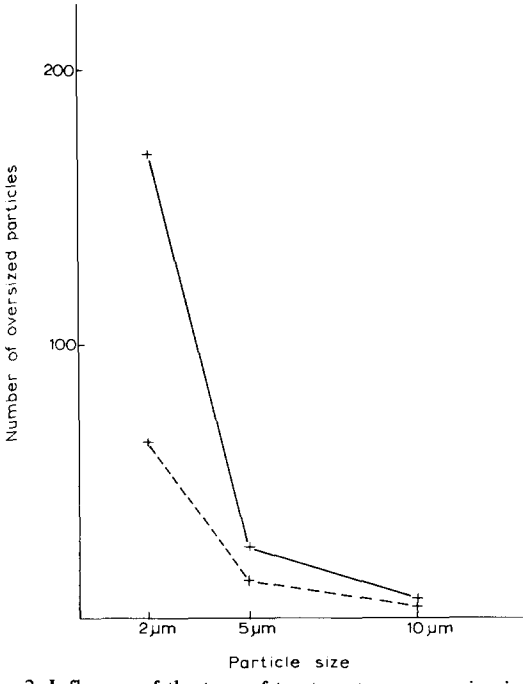

Fig. 2. Influence of the type of treatment on contamination in hemodialysis venous lines. Mean cumulative values/ml, for $\geqslant 2$ μm, $\geqslant 5$ μm, $\geqslant 10$ μm threshold sizes. 40% Glycerin at 37 °C, (- - - - -); water at room temperature, (———).

when the significance ($P < 0.05$) of the multivariate tests was taken into account. As illustrated in Fig. 2, the mean contamination value recorded at the different sizes in glycerin-treated hemodialysis venous lines was lower than that found in the water-treated ones;

- the type of device did not cause any significant difference among the data recorded;
- no effect was observed due to the interaction between the two factors (type of solution, type of device) within the experimental units.

The degree of contamination found in the water-treated venous lines at the 3 recording times (rinsing, $t = 0$, $t = 6$ h) tended to decrease in 46% of the cases; in 27% it oscillated with no regular pattern, while in 27% it was increased at 6 h over the rinsing time. In the glycerin treated devices a decrease of contamination was observed in 67% of the cases and an increase in 33%.

Figs. 3 and 4 show the graphs representing the mean pattern of particulate matter contamination ($\geqslant 2$ μm, $\geqslant 5$ μm, $\geqslant 10$ μm) for the 2 different treatments at the 3 collection times (rinsing, $t = 0$, $t = 6$h). Contamination dramatically decreased after 6 hours of treatment with glycerin (Fig. 3) whereas in the devices treated with water contamination was increased both at time zero and at 6 h with respect to the rinsing time (Fig. 4). The phenomenon was evident especially for the smaller particles ($\geqslant 2$ μm), and less evident for those exceeding 10 μm. As a consequence, rinsing does not always appear enough to "clean" the plastic device: it may be assumed that some particles adhere to the plastic for a certain time and are subsequently removed by the fluid (Williams and Barnett, 1973; Warren et al., 1978).

From the results obtained the following conclusions can be drawn:

(a) The quality of the examined hemodialysis venous lines can be regarded as sufficiently good and is independent of the material mak-

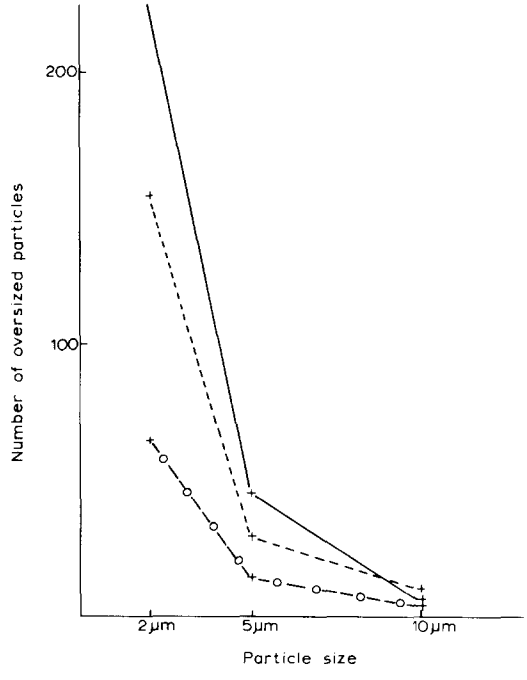

Fig. 3. Time course of contamination in hemodialysis venous lines treated with 40% glycerin at 37 °C. Mean cumulative values/ml recorded for $\geqslant 2$ μm, $\geqslant 5$ μm, $\geqslant 10$ μm threshold sizes. Rinsing, (———); $t = 0$, (- - - - - -); $t = 6$ h, (○ — — ○).

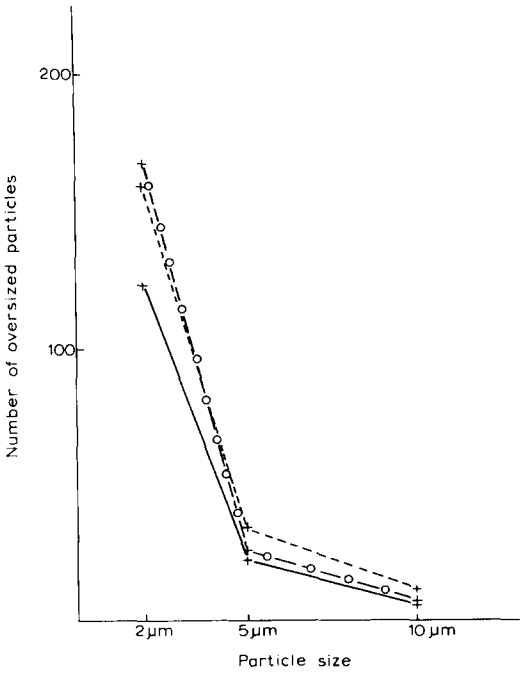

Fig. 4. Time course of contamination in hemodialysis venous lines treated with water at room temperature. Mean cumulative values/ml for ≥ 2 μm, ≥ 5 μm, ≥ 10 μm threshold sizes. Rinsing, (———); $t = 0$, (- - - - -); $t = 6$h, (○ — — ○).

ing up the device, or of the manufacturing procedure.

(b) Treatment with warm glycerin (the closest to the actual conditions of use) was found to be the least drastic. In a control method it is therefore preferable to use simply water at room temperature as the effluent fluid.

(c) In order to evaluate particulate matter release, it is not sufficient to treat the device with a limited amount of fluid (100–150 ml) as reported by other authors (Gour, 1987) since the sample obtained is far from representative of the degree of contamination occurring during the use of the apparatus.

(d) Since in some instances > 500 μm particles or fibers have been found, the check must include also visual inspection of the washing fluid of the devices employed.

Phleboclysis administration sets

Tables 3 and 4 report the mean cumulative contamination values found with instrumental methods in the 10 types of devices examined. Table 5 shows the results of the microscope analysis of 7 out of the 10 types of administration sets examined.

The particulate contamination values recorded with the light blockage apparatus were always lower than the F.U. IX edn. limits for LV parenteral products (Fig. 5): at ≥ 20 μm they were all equal to 0 and at 5 μm they were at the most 1/4 of the upper limit values.

The values obtained with the Coulter counter, though always below the F.U. IX edn. limits for LV parenteral products were higher than those found with the previously mentioned apparatus, for the > 5 μm size. On the other hand, the values obtained at the microscope for the 25–50 μm size range were always higher than those recorded with instrumental methods. In one administration set (4/b) one > 500 μm particle was found. The time trend of contamination, as a function of the effluent volume was similar with both the Coulter counter and the HIAC. In 70% of the cases after the first 50 ml of effluent the particulate contamination decreased, as reported also by other authors (Williams and Barnett, 1973). Upon bottle change a small increase was observed that however never exceeded the values of the first collection.

Fig. 6 shows, as an example, the trend of contamination with respect to the effluent volume in administration set 8/e, recorded with instrumental methods.

These results allow us to state that:

(a) All the analyzed products can be regarded as being of a sufficiently good quality and do not seem to contribute any important contamination to the solution.

(b) The connection of the administration set is a contaminating step and should be performed with the utmost care.

(c) The analytical methods used proved equally suitable for the routine analysis of the examined apparatus.

(d) In an analytical method, it is sufficient to analyze the first 50 ml of effluent since it was observed that usually the particulate population does not increase after the flowing through

TABLE 3

Analysis of particulate contamination in phleboclysis administration sets

Mean cumulative values (S.D.) for the different threshold sizes as determined by the HIAC/ROYCO.

Vol. (ml)	μm	Batch no./Manufacturer										Mean
		1/a	2/a	3/b	4/b	5/c	6/c	7/d	8/e	9/f	10/g	
50	⩾ 2	87	85	168	125	76	55	143	98	64	400	130
		(22)	(22)	(203)	(78)	(44)	(14)	(46)	(43)	(23)	(231)	(101)
	⩾ 5	16	10	20	22	10	7	10	12	10	19	13
		(4)	(3)	(24)	(5)	(3)	(3)	(5)	(4)	(5)	(8)	(5)
	⩾ 10	3	2	2	3	2	2	2	2	2	3	2
		(2)	(1)	(1)	(2)	(0.5)	(1)	(1)	(1)	(0.5)	(1)	(0.4)
300	⩾ 2	48	45	37	52	69	33	63	29	36	93	51
		(27)	(11)	(15)	(36)	(11)	(19)	(21)	(9)	(15)	(21)	(20)
	⩾ 5	7	7	4	20	10	5	8	5	6	7	8
		(3)	(1)	(2)	(6)	(3)	(3)	(4)	(1)	(2)	(2)	(5)
	⩾ 10	1	1	1	1	2	1	2	1	1	1	1
		(0.5)	(0.5)	(0.5)	(0.8)	(0.5)	(1)	(0.5)	(0)	(0.5)	(0.5)	(0.4)
350	⩾ 2	64	161	74	94	46	171	60	92	123	182	107
		(37)	(107)	(38)	(75)	(18)	(173)	(30)	(54)	(101)	(143)	(50)
	⩾ 5	8	10	12	11	6	14	6	11	20	8	11
		(5)	(7)	(6)	(6)	(1)	(12)	(4)	(8)	(16)	(8)	(12)
	⩾ 10	1	2	2	2	1	11	1	3	4	2	3
		(1.5)	(2)	(1)	(1.4)	(0.5)	(15)	(0)	(4)	(3)	(1)	(3)
600	⩾ 2	33	38	45	45	45	31	51	50	81	59	48
		(12)	(19)	(15)	(40)	(7)	(4)	(23)	(24)	(76)	(31)	(14)
	⩾ 5	4	5	7	7	6	6	7	10	13	6	7
		(0.5)	(3)	(2)	(6)	(2)	(0.5)	(3)	(4)	(15)	(4)	(3)
	⩾ 10	1	1	1	1	1	1	2	2	2	1	1
		(0.5)	(0.7)	(0.5)	(0.5)	(0.8)	(0)	(0.9)	(1)	(2)	(1)	(0.4)
650	⩾ 2	39	81	101	71	80	76	58	70	99	368	104
		(28)	(40)	(74)	(58)	(50)	(60)	(8)	(44)	(103)	(279)	(94)
	⩾ 5	6	7	20	11	10	15	6	10	19	11	12
		(4)	(3)	(19)	(8)	(5)	(18)	(2)	(5)	(20)	(13)	(5)
	⩾ 10	1	1	5	2	1	1	1	2	3	2	2
		(1)	(0.8)	(5)	(1)	(0.5)	(0.8)	(0.5)	(0.8)	(2)	(1)	(1)
900	⩾ 2	17	54	36	63	44	28	97	81	31	121	57
		(3)	(35)	(11)	(49)	(17)	(13)	(105)	(52)	(17)	(60)	(33)
	⩾ 5	3	9	6	11	6	4	11	10	5	4	7
		(0.5)	(5)	(2)	(7)	(2)	(1)	(9)	(7)	(1)	(1)	(3)
	⩾ 10	0	2	1	2	1	2	2	2	1	1	1
			(1)	(0.5)	(1)	(0.9)	(0.5)	(0.5)	(1)	(0.8)	(0)	(1)

of a further effluent volume (900 ml), as also reported by other authors (Warren et al., 1978).

(e) Since particles > 500 μm have been found, the effluent fluid should be also inspected visually.

Conclusions

The devices analyzed in this paper did not contribute to any notable extent to the contamination of the solutions used for control purposes. In

TABLE 4

Analysis of particulate contamination in phleboclysis administration sets

Cumulative values/ml for the different threshold sizes, as determined by the Coulter counter.

Eff. vol. (ml)	μm	Batch no./Manufacturer										Mean (S.D.)	
		1/a	2/a	3/b	4/b	5/c	6/c	7/d	8/e	9/f	10/g		
50	⩾ 2	169	154	711	614	631	672	184	390	1765	316	561	(476)
	⩾ 5	8	7	26	34	25	23	9	22	23	13	19	(9)
	⩾ 10	2	1	2	2	2	6	1	1	3	2	2	(1)
	⩾ 20	1	0	0	0	0	1	0	0	1	0	0.3	(0.4)
300	⩾ 2	160	157	289	590	408	448	121	324	563	243	330	(168)
	⩾ 5	3	6	10	29	18	21	6	17	19	10	14	(8)
	⩾ 10	1	1	1	2	2	2	0	0	4	2	1	(1)
	⩾ 20	0	0	0	0	0	0	0	0	0	0	0	
350	⩾ 2	228	309	414	476	353	387	323	345	1185	219	424	(278)
	⩾ 5	6	20	20	25	15	16	11	14	25	6	16	(7)
	⩾ 10	1	6	2	2	2	2	3	2	2	0	2	(1)
	⩾ 20	0	0	1	0	1	0	0	0	0	0	0	
600	⩾ 2	80	75	354	457	313	342	168	215	517	211	273	(149)
	⩾ 5	4	3	13	23	13	16	9	7	17	7	11	(6)
	⩾ 10	0	1	1	1	1	2	2	1	2	1	1	(0.6)
	⩾ 20	0	0	0	0	0	0	0	0	0	0	0	
650	⩾ 2	105	187	385	572	351	315	295	223	1798	270	450	(490)
	⩾ 5	5	8	19	33	6	29	15	11	46	16	19	(13)
	⩾ 10	1	2	5	3	0	1	1	2	3	3	2	(1.4)
	⩾ 20	0	0	1	0	0	0	0	1	1	0	0.3	(0.4)
900	⩾ 2	74	255	221	550	448	1933	558	104	371	236	475	(539)
	⩾ 5	6	11	10	30	11	89	14	5	14	9	20	(25)
	⩾ 10	2	1	1	3	1	4	2	1	3	1	2	(1)
	⩾ 20	0	0	0	0	0	0	0	0	1	0	0	

TABLE 5

Analysis of particulate contamination in phleboclysis administration sets

Mean values/ml for the different threshold sizes, as determined with the microscopic method.

Batch no.	Manufacturer	25–50 μm	50–100 μm	100–500 μm	> 500 μm
1	a	1	0.2	0	0
2	a	0.4	0.2	0.1	0.1
4	b	1	0.4	0.1	0.3
5	c	0.3	0	0	0
6	c	1.2	0.5	0.1	0
7	d	1.4	0	0	0
10	g	1	0.2	0.1	0

our view, for the dialysis equipment, the test should be initially carried out with the described method, in order to find out whether the device releases plastic particles due to the prolonged and repeated flaking of the tubes in the dialysis pump. Once it has been ascertained that the material does not undergo any damage during the 6 h of use, one may just routinely examine the 2000 ml of rinsing fluid and the first 200 ml immediately following rinsing (since they were found to be the most highly contaminated).

The number of specimens to be examined will be at the manufacturer's discretion, with a minimum of 10 (Advisor Committee on Particulate Contamination in Medical Devices, 1986). The

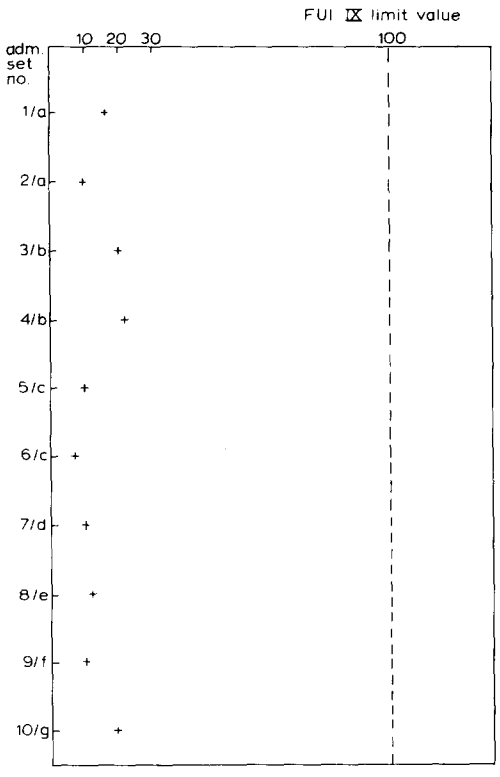

Fig 5. Analysis of particulate matter contamination in phleboclysis administration sets. Mean cumulative values/ml for the 5 μm threshold size, as determined with the light blockage apparatus.

analysis can be easily carried out with an instrumental method. Checking must include also a visual inspection of the effluent fluid.

For phleboclysis administration sets, it is sufficient to analyze the first 50 ml of solution flowing through the device. Our investigation has in fact demonstrated that the contamination usually drops drastically after the first 50 ml of washing fluid. Also with regard to these devices, examination should include the visual inspection of the effluent. In addition, the package must bear the warning to the user that the first 50 ml of effluent must be discarded, as suggested for the first 2000 ml in the case of the hemodialysis devices.

Also for those devices, the contamination limits should be chosen on the basis of the levels reasonably attainable with presently available methods, without making the cost of the apparatus prohibitive. The limits so far adopted in Italy for large volume parenteral solutions, perfusion solutions, dialysis, anticoagulants appear to be adequate, when the washing solution volumes and the method described in this paper are used, since most of the administration sets analyzed by us were well within the established limits.

Qualitative standards are most of all necessary for the extracorporeal circulation sets, if one considers that through such sets flow about 72 litres of blood and that the use of a peristaltic pump may facilitate the detachment of particles from the walls of the set: furthermore, the patient is exposed to the treatment throughout life, 3 times a week.

Many authors (e.g. Olson, 1980; Advisory Committee on Particulate Contamination in Medical Devices, 1986; Backhouse et al., 1987) have proposed final filters as a solution to the problem for many administration sets. The filters would apparently be effective not only against the particulate matter present in the tubular sets before use, but also against the fragments formed during use (rubber stopper fragments, fragments

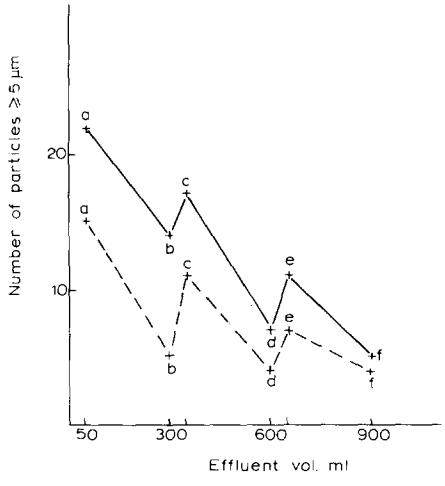

Fig. 6. Contamination recorded with instrumental methods (size ≥ 5 μm) as a function of the effluent volume. Coulter counter (———); HIAC/ROYCO (- - - - -).

due to the continuous line compression in the peristaltic pumps).

However, the efficacy of the filters is limited by practical considerations such as resistance to flow, damage to blood cells (Advisory Committee on Particulate Contamination in Medical Devices, 1986) and cost.

In conclusion, we hope that also in Italy attention will be focused on the problem of the release of foreign particles from the plastic administration sets for arteriovenous use and that adequate measures will be introduced such as Good Manufacturing Practices, Guidelines for Manufacturers, controls, as well as directions for users and qualitative standards.

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