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Particulate matter contamination of small volume parenterals

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Summary

Particulate contamination in 34 types of liquid and 16 types of dry small volume parenterals (SVPs) manufactured in Italy have been studied. Particle counting was performed by a light blockage method. All the examined products met the SVP-USP XXI standard; the powders in general were more contaminated than liquids, overall for the largest particle sizes. The current USP particulate matter limits for SVPs can be regarded as suitable for the sterile powders, but appear to be too broad for the liquids. The LVP-USP contamination standard is adequate to the presently available quality of liquid SVPs and could be adopted for this dosage form.

Introduction

The recent introduction of limits for allowable particulate contamination in small volume parenterals (SVPs) by the United States Pharmacopeia (XXI Ed.) has drawn attention to the problem of establishing standards. Particulate matter limits proposed by USP XXI for SVPs, based upon the current limits for LVPs and the "one-fifth rule" (Pharmacopeial Forum, 1984), have been established on a "per container" basis, irrespective of product type and size. The requirement is that the number of particles per container should not exceed 10,000 particles >10 μm and 1000 particles >25 μm.

This criterion is no doubt questionable and raised several questions (DeLuca et al., 1986; Oppenheim et al., 1986; Bachouse et al., 1987). At present, since there are no adequate clinical data on the hazards of particulate matter, the contamination level of the products should be considered as an index of compliance with GMP during manufacturing. From this point of view its evaluation on a "per ml" basis gives more significant indications about the product quality.

In order to propose this approach to setting standards, more information is required on the contamination level obtainable with present manufacturing technologies in the different types of products.

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Data reported in the literature on particle burden of SVPs manufactured in Italy are scanty (Montanari et al., 1982); for this reason we planned a preliminary investigation on the matter. We considered 50 types of products, 34 of them were liquids and 16 powders. More than one batch from the same manufacturer and also from different ones were examined for some products. A total of 60 batches were examined (42 of liquid products and 18 of dry products). To reliably assess the contamination level of the products and its variability within the batch, 30 units per batch were individually analyzed.

Batch acceptability on the basis of statistically correct criteria is also discussed.

Particle counting was performed by the light blockage method following the USP XXI (1985) procedure.

Materials and Methods

Materials and equipment used for the particulate matter test of small volume injections

HIAC/ROYCO mod. 3000, fitted with a small sampler probe (1 ml volume) and HR60H sensor with standard size range of 1–60 μm, flow rate 10 ml/min. The instrument was supplied by the manufacturer already calibrated with standard spherical material; calibration was periodically checked using the ASTM 658-80 procedure.

Sensor resolution was verified to be less than 10% and sample volume accuracy was between $\pm 5\%$ (USP XXI 4th Suppl., 1986).

1800 containers of small volume injectable products from 60 batches and supplied by 11 manufacturers.

Suspension of monodimensional polystyrene microspheres of the following average sizes: 10, 20, 30 μm, used to calibrate the particle counter.

Sample preparation and analysis

Samples were prepared and analyzed according to the USP XXI (1985) procedure. Analyses were made by means of an electronic liquid particle counter system, with counting at the following size levels: >2, >3.5, >5, >10, >20 and >25 μm.

Results and Discussion

Particulate contamination calculated on a "per container" basis

Table 1 reports the mean particulate contamination values per container at the different particle sizes in liquid products, and Table 2 gives the values in powder or freeze-dried products. The values at >10 μm and >25 μm size levels were always found to be lower than the USP XXI limits.

In the solutions, the highest number of particles recorded was 763 at >10 μm (Table 1, no. 9) and 24 at >25 μm (Table 1, No. 1). Such values correspond, respectively, to 13% and 2.4% of the USP XXI limits.

The powders were usually found to be more contaminated than the liquids, especially with regard to the largest particle sizes. The highest number of particles recorded was 1705 at >10 μm (Table 2, no 3P) and 834 at >25 μm (Table 2, no. 2P). Such values are respectively 17% and 83% of the USP XXI limits.

Appreciable contamination differences are observed in the same or similar types of product supplied by different manufacturers (Table 1, nos. 2 and 3; nos. 9 and 10) and also by the same manufacturer (Table 1, nos. 32–34).

For all the products examined we verified the size distribution of particulate contamination through linear regression analysis of the 6 pairs of log of cumulative particle number – log of particle size values in the >2 μm $\rightarrow$ 25 μm size range. The correlation coefficients found for each product, reported in Tables 1 and 2, were between 0.94 and 0.99. The only exception was product no. 2P (Table 2) whose correlation coefficient was 0.89. Groves and Wong (1986) have suggested that a correlation coefficient of 0.9 or better be chosen as sufficient evidence of linearity or compliance with a log/log plot. Accepting this suggestion, we can confirm that linearity of distribution in the considered size range is a general rule in both the liquid and the powder products examined.

Tables 1 and 2 report also the slopes of the regression lines calculated for each product. They range between -3.4 and -1.6 for the liquid products, and between -5.3 and -0.9 for the powders.

TABLE 1

Particulate matter in small volume parenterals – liquid products

Cumulative particle number per container at the different size levels (mean of 30 containers per batch).

No.	Product	Mfg. [a]	Vol. (ml)	⩾ 2 μm	⩾ 3.5 μm	⩾ 5 μm	⩾ 10 μm	⩾ 20 μm	⩾ 25 μm	r [b]	m [c]
1	Dextrose 5%	a	20	7512	3359	1917	507	61	24	0.98	−2.25
2	Dextrose 5%	a	10	4011	1878	936	155	13	1	0.96	−3.09
3	Dextrose 5%	i	10	622	384	265	72	11	3	0.96	−2.07
4	Dextrose 10%	a	10	4430	2570	1467	294	27	9	0.97	−2.49
5	Dextrose 10%	i	10	1258	740	453	91	7	2	0.97	−2.57
6	Dextrose 20%	i	10	728	409	260	73	12	5	0.98	−1.97
7	Dextrose 33%	i	10	1024	432	281	67	30	2	0.94	−2.19
8	Fructose	i	10	2506	1095	556	96	14	8	0.99	−2.35
9	Ca gluconate	a	10	21856	8692	4476	763	60	23	0.98	−2.73
10	Ca gluconate	i	10	1860	978	595	126	12	3	0.97	−2.51
11	Ca,Mg chloride	i	10	1004	648	445	120	17	5	0.96	−2.07
12	Mg sulphate	a	10	6844	2978	1552	320	34	14	0.98	−2.47
13	Potassium chloride	i	10	1040	531	307	60	1	0	0.94	−2.92
14	Potassium lactate	i	10	860	414	243	52	3	2	0.98	−2.53
15	Potassium phosphate	i	10	593	373	262	84	9	4	0.96	−2.01
16	Sodium bicarbonate	i	10	922	439	313	105	23	17	0.99	−1.62
17	Sodium chloride 0.9%	i	10	1489	953	671	212	24	11	0.97	−1.98
18	Sodium lactate	i	10	713	488	350	125	25	9	0.96	−1.7
19	Water for injections	b	10	922	405	169	30	2	1	0.98	−2.8
20	Water for injections	i	10	305	187	120	30	3	1	0.97	−2.28
21	Water for injections	f	10	1748	1108	739	206	37	22	0.98	−1.8
22	Aminophylline	e	10	1193	727	463	92	14	9	0.98	−2.05
23	Aminophylline	e	10	5423	2173	995	105	5	1	0.98	−3.41
24	Aminophylline	l	10	593	416	281	77	7	2	0.95	−2.25
25	Water for injections	a	5	2906	788	255	34	4	1	0.99	−3.09
26	Water for injections	i	5	148	78	51	12	3	2	0.99	−1.77
27	Ranitidinium	c	5	396	233	140	41	6	2	0.97	−2.07
28	Fazadinium bromide	c	5	3453	1586	789	172	22	10	0.99	−2.34
29	Buflomedilum hydrochloride	f	5	695	457	338	128	13	6	0.96	−1.91
30	Lidocaine hydrochloride	g	3	1058	669	487	289	26	10	0.94	−1.8
31	Hydroxycobalamin	c	2.5	207	90	41	8	1	0	0.98	−2.66
32	Water for injections	a	2	176	54	22	3	0	0	0.99	−2.54
33	Betamethasone 4 mg	c	2	639	340	193	58	9	5	0.98	−1.96
34	Betamethasone 1.5 mg	c	2	2428	1196	613	109	12	6	0.98	−2.46
35	Gentamicin sulphate 20 mg	b	2	799	252	117	33	14	12	0.99	−1.66
36	Clindamycin phosphate 300 mg	h	2	244	121	80	69	1	1	0.96	−2.65
37	Lincomycin 600 mg	h	2	62	33	21	5	1	1	0.99	−1.77
38	Metaraminol bitartrate	a	1	967	325	125	7	0	0	0.98	−3.07
39	Chlorpheniramine maleate	b	1	832	315	150	22	2	0	0.97	−3.11
40	Dexchlorpheniramine maleate	b	1	870	291	127	26	0	0	0.99	−2.19
41	Sodium citrate	a	1	264	60	31	3	0	0	0.99	−2.76
42	Atropine sulphate	a	1	336	102	39	3	0	0	0.98	−2.94
	USP XXI limit values						10000		1000		

[a] Manufacturer.
[b] Correlation coefficient.
[c] Slope.

TABLE 2

Particulate matter in small volume parenterals – dry or lyophilized products

Cumulative particle number per container at the different size levels (mean of 30 containers per batch).

No.	Product	Mfg. [b]	g/ml	⩾ 2 μm	⩾ 3.5 μm	⩾ 5 μm	⩾ 10 μm	⩾ 20 μm	⩾ 25 μm	r [c]	m [d]
1P	Cefuroxime	c	2/20	323 982	69 420	10 845	67	0	0	0.97	−5.33
2P	Ceftazidinum	c	2/20	12 952	2 611	1 625	997	852	834	0.89	−0.93
3P	Ethacrynate sodium [a]	a	0.05/20	35 301	16 023	8 226	1 705	209	71	0.98	−2.45
4P	Cephalotin sodium	c	1/18	1 550	616	299	34	0	0	0.97	−3.8
5P	Cephalotin sodium	c	2/10	4 977	2 153	1 415	613	295	256	0.99	−1.16
6P	Ceftazidinum	c	2/10	5 974	1 803	840	89	14	9	0.98	−2.9
7P	Cephalotine sodium	c	1/10	2 966	916	480	87	17	14	0.99	−2.19
8P	Ceftazidinum	c	1/10	1 870	577	263	70	16	12	0.99	−1.96
9P	Erythromycin lactobionate	f	0.5/10	5 920	938	358	106	40	34	0.98	−1.96
10P	Cephalotin sodium	c	1/4	1 974	569	247	37	2	1	0.99	−3.07
11P	Cefamandole nafate	g	1/3	8 807	1 737	703	185	133	128	0.96	−1.62
12P	Cefamandole nafate	g	1/3	61 151	10 827	2 987	266	57	46	0.99	−2.92
13P	Hyaluronidase [a]	a	300ui/3	4 183	1 682	831	136	11	3	0.98	−2.85
14P	Ceftazidinum	c	1/3	2 093	481	238	47	9	7	0.99	−2.2
15P	Vitamins combination [a]	a	0.07/2	27 684	7 579	3 158	327	25	10	0.99	−3.18
16P	Corticis renalis extractum	a	0.2/2	1 765	639	324	56	2	0	0.97	−2.8
17P	Indomethacin [a]	d	0.077/2	1 522	736	423	73	10	6	0.99	−2.29
18P	Indomethacin [a]	d	0.077/2	15 567	6 088	3 048	463	24	11	0.99	−2.96
	USP XXI limit values						10 000		1 000		

[a] Lyophilized.
[b] Manufacturer.
[c] Correlation coefficient.
[d] Slope.

Such values emphasize the greater variability of the contamination pattern in the powders with respect to the liquids.

Particulate contamination calculated on a "per ml" basis

Counts per ml for the liquid and powder products examined were plotted on a linear scale arranged in order of increasing counts at the > 10 μm and > 25 μm size levels (Figs. 1, 2).

In order to determine trends for the definition of particulate limits per unit of volume, for liquid SVPs we compared the contamination values obtained for the liquid products examined with the LVP-USP XXI limits, which are the following: not more than 50 particles/μl > 10 μm, and not more than 5 particles/ml > 25 μm. At the > 10 μm size level 93% of the samples and at the > 25 μm

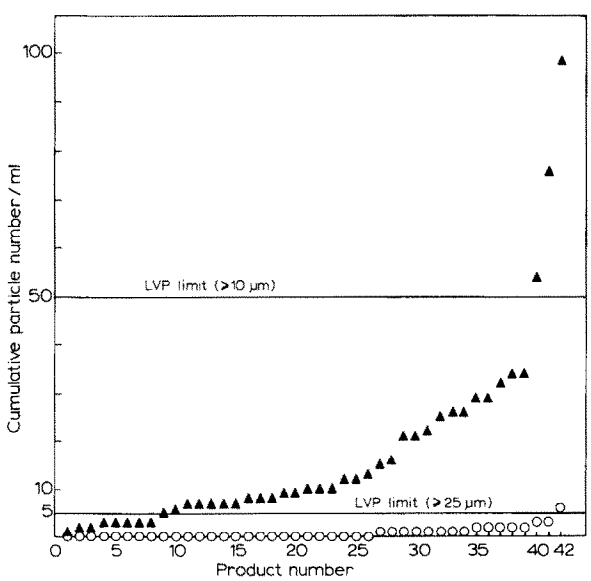

Fig. 1. Liquid products. Cumulative particle numbers per ml arranged in order of increasing population at size levels ⩾ 10 μ (▲) and ⩾ 25 μm (○).

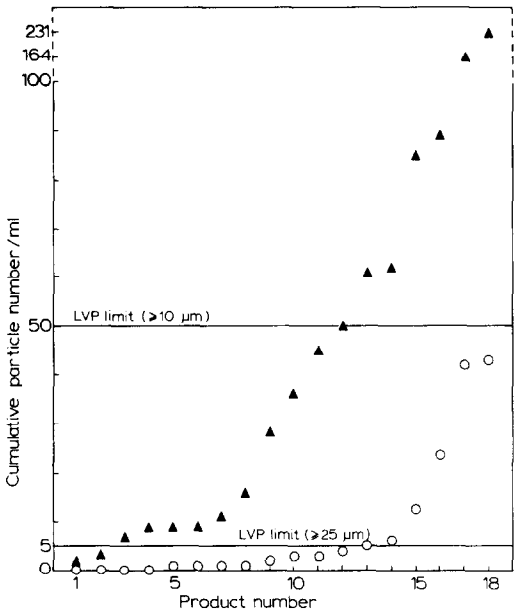

Fig. 2. Powder products. Cumulative particle numbers per ml arranged in order of increasing population at size levels ≥ 10 μm (▲) and ≥ 25 μm (○).

size level 98% of the samples were found to comply with such a standard. These percentages could be further increased. Results reported in Table 1 (nos. 9 and 10; nos. 33–34) show that the rejected products can be produced according to the LVP-USP XXI standard.

In order to tentatively quantify the contamination differences between liquids and powders, at each size level we calculated the mean cumulative particle numbers per ml in the two classes (Table 3). With regard to the powders, the cumulative particle numbers per ml varied, according to the size level considered, from about three to more than ten times that found in the liquids. Because of a high variability of contamination levels, more data are needed to define adequate limits in powders.

Evaluation of batch acceptability

Table 4 reports some significative examples of minimum and maximum contamination values found in containers from the same batch and also the mean contamination of the batch considered. Differences were quite high with regard to solutions and, as expected, even more striking for powders.

In some batches, some units were found to conform to the SVP standard, while others failed to do so. For example, 7 units of product no. 2P and 1 unit of product no. 5P exceeded the limit of 1000 particles > 25 μm per container while the mean contamination of the corresponding batches conformed to USP standard. In such an instance, batch acceptability may be questionable, without defining the sampling plan on the basis of the preset assurance level that the fraction of bad containers is less than a specified threshold. We consider it sufficient assurance that the batches showing more than 10% of the units with number of particles exceeding the Pharmacopoeia limits have a 95% probability of being rejected. If adopting this criterion, for batches with sizes exceeding 1000 units, the sampling plan should require the examination of 30 units per batch with zero defective units being tolerated (Cucconi et al., 1980). It is therefore necessary to examine individually the units which represent the batch. From this point of view the current USP XXI procedure, which calls for the examination of a sample obtained by combining the contents of not less than 10 containers without defining the level of assurance

TABLE 3

Mean of the cumulative particle numbers / ml ± S.D. at the different size levels for liquid and powder products

Products	Mean (± s.d.)				
	≥ 2 μm	≥ 5 μm	≥ 10 μm	≥ 20 μm	≥ 25 μm
Liquids	317	76	17	2	1
	(405)	(83)	(19)	(2)	(1)
Powders	3981	362	51	11	9
	(6300)	(495)	(61)	(14)	(14)

TABLE 4

Contamination values detected within the same batch

Cumulative particle number per container at the different size levels.

No.	Product		⩾ 2 μm	⩾ 3.5 μm	⩾ 5 μm	⩾ 10 μm	⩾ 20 μm	⩾ 25 μm
6	Dextrose 20% [a]	Min	40	30	20	0	0	0
		Max	3260	2040	1340	370	40	30
		M [c]	728	409	260	73	12	5
7	Dextrose 33% [a]	Min	240	170	110	20	0	0
		Max	1400	770	510	150	40	20
		M [c]	1024	432	281	67	30	2
9	Calcium gluconate [a]	Min	3310	1470	700	180	10	0
		Max	30820	18600	10400	2240	140	80
		M [c]	21856	8692	4476	763	60	25
37	Lincomycin 600 mg [a]	Min	168	60	22	0	0	0
		Max	1584	510	172	48	0	0
		M [c]	62	33	21	5	0	0
2P	Ceftazidinum (h)	Min	6820	1000	540	60	0	0
		Max	23400	4080	3420	2850	2820	2800
		M [c]	12952	2611	1625	997	852	834
3P	Ethacrynate sodium [b]	Min	13220	9800	1400	460	20	20
		Max	82060	37140	20680	4640	700	286
		M [c]	35301	16023	8226	1705	209	71
5P	Cephalotin sodium [b]	Min	2150	1020	620	130	30	20
		Max	15500	6880	5340	3760	2590	2230
		M(c)	4977	2153	1415	613	295	258

[a] Liquid products.
[b] Powder products.
[c] Mean contamination value of the batch.

requested, yields no reliable information of batch acceptability.

Conclusions

The particulate matter level of SVPs is a valid indicator of good manufacturing practice in production and should be controlled by regulatory authorities. Compendial particulate matter limits must guarantee the injectable products the highest quality obtainable with the current technology while at the same time avoiding at any rate too great a difficulty to manufacturers.

All the examined SVPs met the USP XXI standard but there is a wide disparity in particulate counts between solutions filled into ampoules or vials and sterile dry powders. It seems therefore more correct to assign different limits for different types of products, as already proposed by other authors (DeLuca et al., 1986; Barber et al., 1987).

Based on our results, it seems that the current USP standard for SVPs is suitable for the powders, but appears to be too broad for the liquids.

The particulate contamination levels detected in liquids, expressed as cumulative number per ml, can be compared with the USP limits for LVPs. In our opinion, the LVP-USP contamination standard is adequate for the presently available quality of liquid SVPs and could be adopted for this dosage form too.

The mean cumulative particle number per ml in the powders was found to be 3–10 times higher

than the one found in the liquids, according to the size range considered. As a consequence, the standard should accommodate the difference, but more data are needed which will allow the assignment of an appropriate contamination limit on a "milliliter" basis for sterile powders.

The high variability of the contamination level found in units belonging to the same batch makes questionable the evaluation of batch acceptability. It is therefore necessary to define the sampling plan on the basis of a preset assurance level, that should be defined by regulatory authorities.

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