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PARENTERAL SOLUTIONS: NATURE OF PARTICULATE MATTER

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ABSTRACT

An investigation on the level and nature of particulate contamination in 36 large volume injectable solutions produced in Italy was performed, using Scanning Electron Microscopic (SEM) and X-ray microanalitic (EDS) techniques.

Wide variability of the contaminant level, even within each individual batch, was observed.

About 20% of the samples revealed a considerable amount of contaminants greater than 20 μm.

Fibers of presumably textiles, cellulose or plastic materials were detected. Other particulate matter, from manifacturing and packaging processes, were observed.

INTRODUCTION

The Italian Official Pharmacopoeia[1] sets standards on the particle contamination of injectable solutions. In detail it states that solutions to be injected, when examined under suitable conditions of visibility, should be clear and practically free from particles. Moreover, when the volume is 100 ml or more, the product must comply with the limit test for particulate matter as follows: not more than 100 particles at 5 micron (or greater) and not more than 4 particles at 20 micron (or greater), per ml of solution.

In order to investigate the contamination in some of the most common injectable solutions produced in Italy [2-4], a preliminary analysis was carried out, using scanning electron microscopic (SEM) and X-ray microanalitic (EDS) techniques [5,6].

The purpose of this investigation was to verify the degree of contamination of such solutions and to identify the particulate matter indicative of good manufacturing practice application [7].

The potential hazards of this contamination such as vascular occlusions, and inflammatory, neoplastic, or allergic responses are due to various factors including, for instance, the number, size, shape, surface and nature of the contaminants [8-10]. The greater the degree of contamination, the greater the possibility of adverse reactions [11]. Although the chances of embolic phenomena occurring increase with particles greater than 5 μm, the possible occurrence of damage in the presence of smaller contaminants cannot be ruled out. Such damage could be induced by the formation of agglomerates, or by the phagocytosis of such particles by the reticuloendothelial system cells and their subsequent retention in the liver and spleen [12,13]. The particle surface is yet another aspect that may influence the degree of potential damage, for a

wrinkled surface is more liable to produce adhesion phenomena [8]. Moreover, some authors [5,14,15] reported on the different degree of danger of contaminants, with regard to the formation of granulomas in the case of particles or fibers and on the possibility that the latter may damage membranes, subsequently inducing the release of autolytic enzymes by the lysosomes. Finally, it is known that the chemical composition of the contaminant plays a fundamental role in the magnitude and nature of the damage possibly occurring.

Therefore, it is very important that as much data as possible be available on the nature and morphology of the particulate, in order to support the official limits.

Furthermore, such data could be useful to identify the sources of contamination, and then they could be used by health authorities for an oriented intervention aiming at reducing contamination to minimal levels.

EXPERIMENTAL

Thirthy-six samples of the most commonly injectable solutions (Sodium bicarbonate 1.4% and 8.4%, Glucose, Ringer lactate), produced by eight manufacturers, were tested by SEM.

The outer surface of the ampoules was washed according to the procedure indicated in the USP XXI [16]. The solutions were filtered through cellulose ester filters (Metricel GN-6-Gelman), with a 25 mm diameter and 0.45 μm pore size. The filter was coated with a layer of carbon [15] and examined under the SEM (Philips 515; 600 - 2000 x). The microscope was coupled to a microanalytical system based on the determination of the characteristic X-ray energy released following high-energy electron interaction (EDAX 9100/60).

Counting was then performed using a computerized automatic system (IBAS II by Kontron).

RESULTS AND DISCUSSION

Tables 1, 2 and 3 show the particle contamination values obtained at different size levels for the individual samples examined.

The accuracy of such contamination values was assessed on the assumption that the distribution of particles on the filter is random, and subsequently that the number of particles per filter surface unit is Poisson-distributed. Consequently the accuracy of the values may simply be evaluated with the percentage standard deviation $1/\sqrt{N}$, with N being equal to the estimated contamination value. The confidence intervals were found in the range from a minimum of 5% to a maximum of 30% of the estimated value, with the large majority around 15%.

Since the adopted method does not ensure that possible aggregates may be distinguished from individual particles, the values found for the different size levels cannot be used to verify whether or not they comply with the limits set by the standards in force. They are instead considered as a purely indicative value of the overall contamination degree.

Six samples (GL 4, SB 2, SB 5, SB 9, SB 11, SB 12), revealed the presence of a rather large number of contaminants, with a size exceeding 20 μm.

A considerable variability of total particle counts was seen not just among different drugs but even within each individual batch.

Table 4 shows the elements found in particulate contaminants. The reported elements do not include those with an atomic number outside the 11-92 range undetectable with the adopted EDS system. This makes it impossible to verify the presence of organic and biological materials. The analysis of

TABLE 1

Particle counts - Sodium bicarbonate (SB)

A) 1.4%

Sample	Manufacturer	Batch	Volume (ml)	pp/ml <5 µm	pp/ml 5-20 µm	pp/ml >20 µm
SB 1			250	24	20	-
SB 2	A	a	250	4	31	10
SB 3			250	1	10	2
SB 4	C	a	500	-	6	3
SB 5			500	85	32	8
SB 6	D	a	500	228	51	3

B) 8,4%

Sample	Manufacturer	Batch	Volume (ml)	pp/ml <5 µm	pp/ml 5-20 µm	pp/ml >20 µm
SB 7	D	a	500	112	10	3
SB 8			500	152	17	3
SB 9	F	a	100	682	39	29
SB 10	G	a	250	114	66	4
SB 11		b	100	23	52	12
SB 12	H	a	100	315	57	8

TABLE 2

Particle counts - Glucose (GL) 10%

Sample	Manufacturer	Batch	Volume (ml)	pp/ml <5 µm	pp/ml 5-20 µm	pp/ml >20 µm
GL 1			500	7	3	1
GL 2	A	a	500	3	8	2
GL 3			500	1	3	1
GL 4			500	196	49	5
GL 5	C	a	500	44	15	2
GL 6			500	8	15	2
GL 7	D	a	500	59	2	1
GL 8			500	3	2	1
GL 9	E	a	500	91	23	-
GL 10			500	76	27	3

TABLE 3

Particle counts - Ringer lactate (RL)*

Sample	Manufacturer	Batch	Volume (ml)	pp/ml <5 µm	pp/ml 5-20 µm	pp/ml >20 µm
RL 1	A	a	500	47	6	3
RL 2		b	500	9	43	-
RL 3	B	a	500	0,5	10	1
RL 4			500	9	23	2
RL 5	C	a	500	61	20	2
RL 6			500	12	14	2
RL 7			500	16	15	1
RL 8		b	500	78	12	2
RL 9			500	20	8	-
RL 10		c	500	14	7	1
RL 11			500	8	12	-
RL 12	D	a	500	123	53	2
RL 13			500	18	22	2
RL 14		b	500	11	22	3

* Composition: sodium lactate 0,32%; sodium chloride 0,60%; potassium chloride 0,04%; calcium chloride dihydrate 0,027%.

TABLE 4

Elements found in particulate contaminants (% samples)

Si (97)	Na (71)	Ni (24)
Al (94)	S (68)	Ti (24)
Ca (85)	Cl (41)	Cr (21)
Fe (85)	Mg (32)	Zn (18)
K (73)	Cu (24)	P (9)

TABLE 5

Nature of particulate matter >20 μm (% samples)

	: fibers	(20)
Unidentified	:	
	: particles	(86)
Si	(40)	
Al	(40)	
Rubber	(10)	
Steel	(3)	

particles showed that silicon, aluminium, calcium and iron were the most commonly found elements.

Finally, Table 5 shows the nature of particulate matter with a size greater than 20 μm. The different nature of these contaminants, constituted by particles and fibers (Figures 1,2,3) suggests their origin may be in manufacture and packaging.

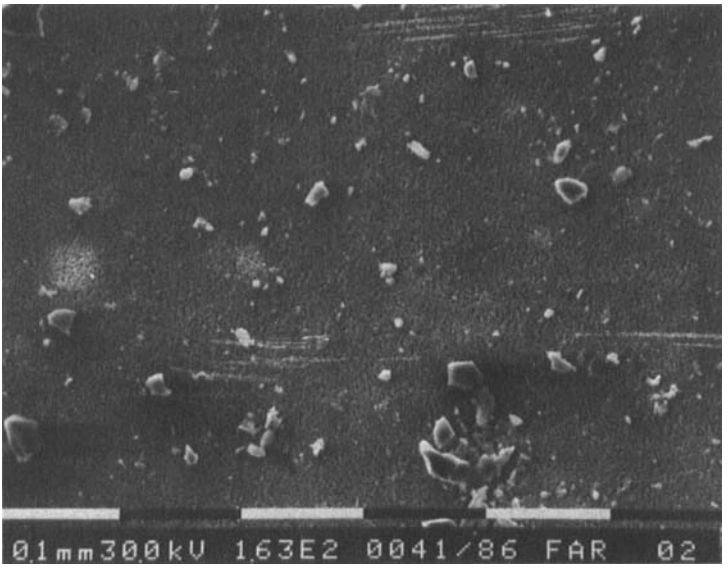

FIGURE 1

SEM picture of rubber particles from a sodium bicarbonate sample. Bars represent 100 um.

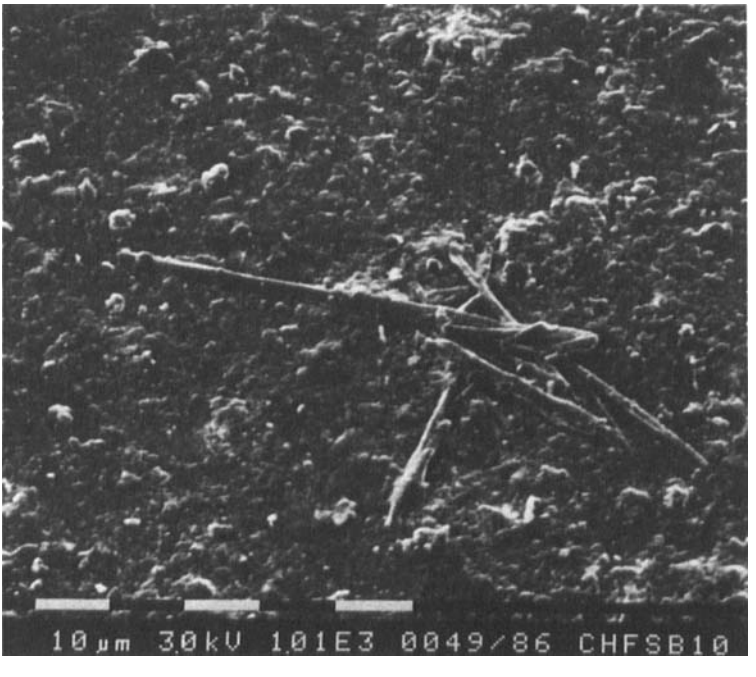

FIGURE 2

SEM picture of fibers from a sodium bicarbonate sample. Bars represent 10 µm.

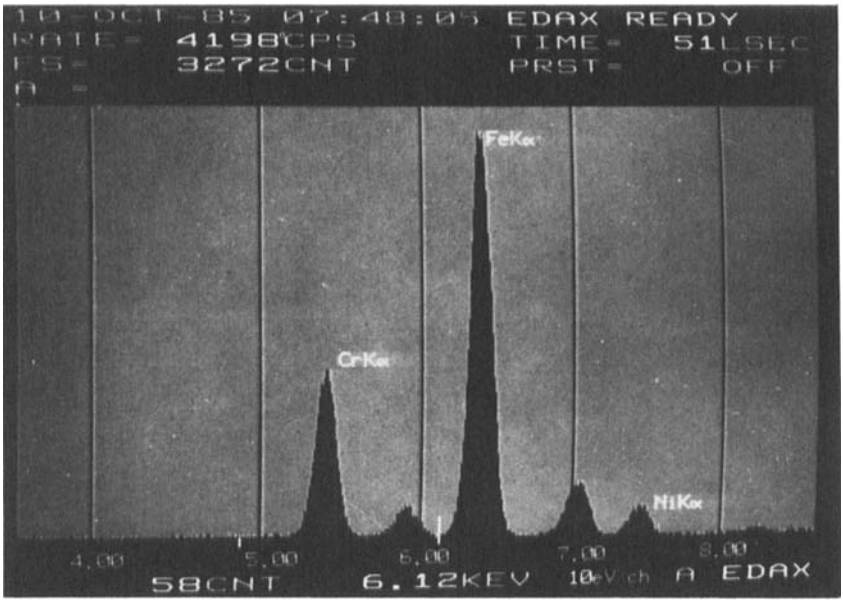

FIGURE 3

EDS spectrum of a steel particle from a Ringer lactate sample.

CONCLUSIONS

The drugs examined exhibited a remarkable variability of the contaminants level, even within each individual batch.

Approximately, 20% of the samples revealed a considerable amount (>4 pp/ml) of contaminants with a size exceeding 20 μm. Some were in the form of fibers, predominantly composed of organic material, which are presumed to originate from textiles, cellulose or plastic. As reported [5,14,15] particular attention was focused on the danger related to fibrous unbiodegradable contaminants.

The other contaminants were not of a considerable level and their source was predominantly traced back to rubber material and metals (Fe, Al, steel). In two samples, the presence of dielectric material containing silicon was also detected, probably fluid and presumably composed of silicon oil.

Such evidence thus suggests that the greatest contamination sources could be attributed to accidental pollution during manufacturing processes (filters, pipes, clothing, etc.) and to the nature of material used for the closure of packages [17-20].

Finally, a greater contamination was detected in sodium bicarbonate solutions, due to the particular stability problems presented by such solutions.

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