Review Article

PARTICULATE MATTERS IN PARENTERAL PREPARATIONS AND ITS POSSIBLE IMPLICATIONS IN CRITICAL CONDITIONS WITH PREVENTIVE MEASURES

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ABSTRACT

By increased use of cheap and counterfeit medicines, the contamination of injectable preparations by particulate matter poses an increasing health hazard. The mechanism of action of such contamination has never been demonstrated properly. Here we will have an overview of effect of particulate matters in intravenous preparations on human body as well as on animal. The present review looks at and an approach to setting particulate matter standards for small volume parenterals and issues related to particulate risk management programme.

Keywords: Contamination, Particulate matter, Parenterals, Standards, Risk management programme.

DISASTER ASSOCIATED WITH PARTICULATE MATTERS

Although particulate matter contamination does not have any adverse effect on the physiological status of the healthy population but it surely have some severe detrimental effects on the health of in critically ill patients. The disasters associated with particulate matter contamination are as follows:

1. The particle count of small volume parenterals [SVP] may have possible implications in the development of Multiple Organ Dysfunction syndrome [MODS] and in Adult Respiratory Distress Syndrome [ARDS].[1]

2. Jacques and Mariscal found that the number of cotton fiber granulomas in the lungs was linked to the amount of fluid administered parenterally to the patients in the days before death[2].

3. Sarrut and Nezelof, who described 25 cases of pulmonary arterial lesions in autopsy specimens from premature infants who had received intravenous injections of large volumes of fluids[3].

4. Several reports have described harmful consequences in intravenous drug users due to particle contaminants, ranging from ophthalmologic complications, tissue infarction [4, 5]

5. Ophthalmologic complications[6, 7], tissue infarction, severe pulmonary distress, lethal acute congestive heart failure.[8, 9]

6. Several reports have pointed toward pulmonary complications due to particulate matter contaminants in cardioplegic solutions.[10, 11]

7. Most microthrombi were associated with particles less than 2 µm in diameter [glass, latex, and polymers], which constitute the bulk of particulate matter contaminants in intravenous fluids [12] .

8. Intravenous injection of cotton fibers in rabbits causes the formation of Pulmonary granulomas around fibers lodged within the pulmonary microcirculation[13].

9. Particulate matter contaminations adversely affected the post ischemic, not the normal, microcirculation [14].

Effect of particulate matters and its range for different preparations

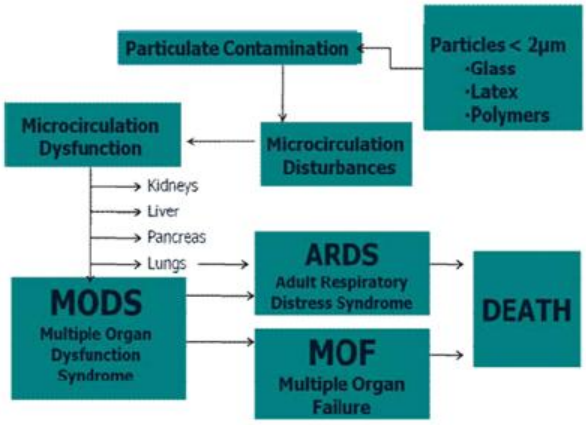

Figure 1: Effect of particulate matters on human having size <2µm[12]

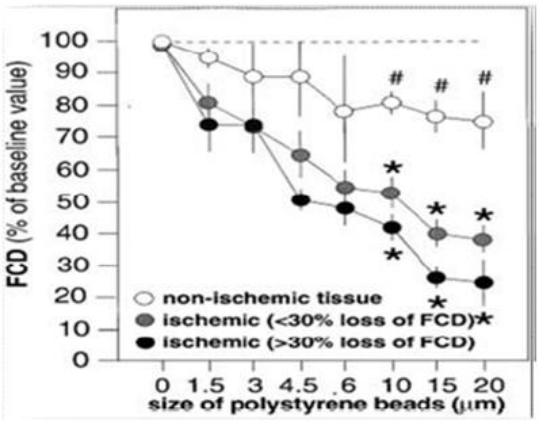

Figure 2: Effect of particulate matters of different size in healthy and critical condition[14]

PARTICULATE MATTER CONTAMINATION IN THREE DIFFERENT ANTIBIOTIC FORMULATIONS*

	Antibiotic		
	A (Claforan)	B (Cefantral)	C (Taxim)
HIAC (no. of particles)			
> 2 µm	539	16,728	17,362
> 10 µm	12	87	152
> 25 µm	1	10	13
Filter (no. of particles)			
> 25 µm	3	32	80
50–100 µm	1	9	16
> 100 µm	0	2	7

* Mean numbers of particles per 1-g vial of three different antibiotic preparations, as assessed by light blockade particle counter (HIAC/ROYCO) or by membrane filter technique (301-mm² i.d. filtration funnel). Values represent means of three different determinations of three (HIAC/ROYCO) or five (filter technique) 1-g vials tested in each determination.

Figure 3: Count of particulate matters according to size: 'A' Branded Cefotaxime 'B' and 'C' Generic Cefotaxime[14]

Table 1: Pharmacopoeial limit of particle counts of various size in intravenous formulations[15-17]

Pharmacopoeia	Small Volume Parenterals	Large Volume Parenterals
US Pharmacopoeia	<6000 @ 10 µm < 600 @ 25 µm	<25/ml @ 10 µm < 3/ml @ 25 µm
European Pharmacopoeia	<6000 @ 10 µm < 600 @ 25 µm	<25/ml @ 10 µm < 3/ml @ 25 µm
Japanese Pharmacopoeia	<6000 @ 10 µm < 600 @ 25 µm	<25/ml @ 10 µm < 3/ml @ 25 µm

PROBABILITY OF SOLUTIONS

Particulate matter is an intrinsic element of the manufacturing process.

Intrinsic Elements

Formulation, Processing Equipment, Primary Package

• Qualified product contact materials [e.g. stainless steel, aluminum, glass, rubber, silicone oil]

Review critical variables in the inspection process

• Define visibility of particulates through reference inspection method

I] Manual, single container inspection

II] 500 lux, 18% gray background

III] No magnification

IV] Inspection duration TBD

- Review impact of probabilistic inspection results on acceptance sampling plans and associated AQL values.

• Review particle identification methods and their use in a risk-based inspection plan.

Figure 4: Particulate Risk Management Program Life Cycle

Developing Historical Profiles

Particle frequency or the number of rejected units specific sources:
• Particle classification
- Common categories of matter
- Source of particles
• Indigenous or intrinsic to the process
• Foreign or extrinsic to the process
• Particle Size.

Particulate Sources

Particles originate from

- Bulk drug substance

- Utilities, Water, HVAC, Gases
- Manufacturing Equipment
- Processing or Filling Equipment
- Environment
- Personnel
- Cleaning Processes
- Container / Closure Systems

Preventive Measures

Filtration
- In-line during filling
- At point of use
• Vial and Stopper Washing Equipment Design and Operation
• Clean room Design and Operation
- Isolator/Barrier Technology
• Inspection Technology

Critical Inspection Parameters

Lighting
Illumination Intensity
Uniformity and Flicker
Type
Background
Black / White
18% Gray

CONCLUSION

Figure "1"

It can be concluded that particulate matters having size <2µm, might be the reason for the detrimental consequences associated with particulate matters .

Figure "2"

Although particulate matter contamination does not have any adverse effect on the physiological status of the healthy population but it surely have some severe detrimental effects on the health of in critically ill patients.

Figure "3"

Observations reveals that there the count of particulate matters having size less than 2µm differs significantly in Cefotaxime Antibiotic preparation, which are supposed to the administered to critically ill patients.

Table "1"

Shows that there are no standard limits for the particulate matters having size less than 2µm.

So, there must be standard limits for the particulate matters having size less than 2µm.

And as a preventive measure super critical fluid process can be adopted to manufacture antibiotics which is very much help full in preventing occurrence of particulate matters[18].

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