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PARTICULATE MATTER IN PARENTERALS: A REVIEW

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ABSTRACT

The presence of foreign visible and sub visible particulate matter in parenteral formulation affects its biological safety. Hence there is need to proper check on the sources of the particulate matters into the formulation. Various regulatory bodies established procedures and standards to ensure the quality of the parenterals. So manufacturers should be to continue to minimize the risk of the particulate and product should meet the specifications. The sources, effects of particulate matters on product quality and safety of the patient and various evaluations parameters are given by USP for particulate matters are discussed.

INTRODUCTION

Particulate matter consist of extraneous substances other than gas bubbles which are present in very minute that why these foreign materials can not detected by chemical analysis. It includes dust, fibres, rubber, glass, other insoluble material, incompatibility precipitate etc.

It also include the insoluble materials from the solute and solvents which is the potential source of the particulate matters into the parenterals. According to USP particulate matter in injection is defined as the mobile undissolved particles other than gas bubbles, unintentionally present into the solution. Sources of these particles leads to the classification as extrinsic and intrinsic particles.

Sources of particulate matters

1. Environmental: Dust, Fibers Biologics—insect parts, microorganisms, pollens Fibers of anthropogenic origin Rust Metal (non-product contact types), Minerals Polymers (unknown source). These sources of particulate is considered as extrinsic because these are not arise from the solution. these particles enter into the solution during manufacturing of the product. Dust, Fibers Biologics—insect parts, microorganisms, pollens, Fibers, Metal (non-product

contact types), Minerals Polymers (unknown source) these are the sources of the extrinsic particles. To avoid the extrinsic particles into the solution the good manufacturing practices should be to continue. The manufacturer should have the understanding of the product and processes and the establishment of methods that can control particulate matter contamination during development, manufacture, and packaging are essential to prevent particulate matter contamination problems.

2. Packaging material : Rubber, glass, polymers, silicon

These also the extrinsic sourses. Packaging materials should be compatible with the formulations to avoid the contaminations. These particulate arises due to the interaction of formulation to the container component.

3. Formulation components: Precipitates, Oligomers, Degradants, Agglomerates, Undissolved material

4. The manufacturing process and variables: The particulate from this sources includes the metal, polymers, silicon etc. GMP practices minimizes the chances of entrance of these particulate matters into the solution.

Particulate Risk for Patients

Administration of the particulate is health hazardous to the patient. Due to the presence of any visible foreign particles the solution intended for the parenteral administration is considered as of inferior quality. Serious health complications includes, phlebitis, pulmonary granuloma, occlusion of blood vessels, thromboembolic events and systemic immune response, blockage and clotting in blood vessels, ischemia, pulmonary emboli, pulmonary dysfunction, pulmonary infarction, and toxicity. In the case of glass particulate, if present in an parenteral drug, may result in local irritation or swelling in response to the foreign material after administration. More serious potential effects includes blockage and clotting in blood vessels. After administration of the solution containing precipitate it may result in formation of a blood clot obstructing the flow of blood which could lead to permanent lung damage.

Quality Control of Particulate

USP sets the limits for the particulate matters into the parenteral preparations. According to this the solution intended for the parenteral administration should be free from the particulate. Particulate matter consist of extraneous substances other than gas bubbles which are present in very minute that why these foreign materials can not detected by chemical analysis. according to usp chapter 788 there are two test methods for the determinations of the

particulate 1. Light obstruction particle count test. 2. Microscopic method. These two methods measures the particulate of the size 10 µm and 25 µm. Mostly light obstruction particle count test is preferred for all the parenterals excepts solution containing emulsions and suspensions where microscopic method is preffered.

The Light obstruction particle count test utilises the laser light obscuration sensor for the determination of particular matters. It works by passing the laser beam of light through the sample liquid and the reduced intensity of the light is measured by the photomultiplier tube detector as a function of the particle size. The USP limits for Light obstruction particle count test is given in following table.

Particle count limit for Light obstruction particle count test		
	10 µm	**25 µm**
Small Volume Parenterals	6000 per container	600 per container
Large Volume Parenterals	25 per millilitre	3 per millilitre

The microscopic method of the particulate analysis is for the solution where the Light obstruction particle count test is not suitable. Such as solution containing emulsions and suspensions. In Microscopic test of analysis the solution is filtered through micro porous membrane filter and particles collected on the are measured by comparing the sizes of the particles to the standard by using binocular microscope. this method also measures the particle sizes of 10 µm and 25 µm. The limits for the microscopic test is given in following table.

Particle count limit for Microscopic method		
	10 µm	**25 µm**
Small Volume Parenterals	3000 per container	300 per container
Large Volume Parenterals	12 per millilitre	2 per millilitre

Particular matters and drug recalls

Drug recall is conducted on a company's own initiative or by FDA request to remove defective drug product from the market to protect the public from the harmful product.

Classification of drug recalls

1. Class I: a dangerous product that could cause serious health problems or death.
2. Class II: the product that might cause a temporary health problems
3. Class III: the products that violates FDA labeling or manufacturing laws.

The following table gives the information about the drug product recalls due to the particulate matters.

Table 3: Drug recalls by FDA due to particular matters in 2018-19.

PRODUCT NAME	MFG BY	REASON FOR RECALL
Labetalol Hydrochloride Injection, USP, 100 mg/20 mL Vial and Labetalol Hydrochloride Injection, USP, Novaplus® (NDC 0409-2267-25)	Hospira, Inc., a Pfizer company	Cracks on the rim surface of vials for these lots, which is covered by the stopper and crimp seal.
Ampicillin and Sulbactam for Injection USP, 3 grams*/ Single-Dose vial	uroMedics Pharma LLC	Red rubber particles
Naloxone Hydrochloride Injection, USP, 0.4 mg/mL, 1 mL in 2.5 mL	Hospira, Inc., a Pfizer company	presence of embedded and loose particulate matter on the syringe plunger.
Ceftriaxone for Injection USP, 250mg, Ceftriaxone for Injection USP, 500mg, Ceftriaxone for Injection USP, 1g, Ceftriaxone for Injection USP, 2g	Lupin Pharmaceuticals, Inc	visual grey particulate matter in reconstituted vials.
Vecuronium Bromide for Injection, 20 mg, Vecuronium Bromide for Injection, 10 mg	Sun Pharmaceutical Industries, Inc.	particulate matter identified as glass.
Furosemide 100 mg in 0.9% Sodium Chloride 100 mL bag	CA Pharmaceuticals LLC	particulate matter believed to be furosemide precipitate.
Piperacillin and Tazobactam for injection, USP 3.375 g	AuroMedics Pharma LLC	particulate matter, identified as glass and silicone material particles

CONCLUSIONS

The presence of foreign visible and sub visible particulate matter in parenteral formulation affects its biological safety. Hence there is need to proper check on the sources of the particulate matters into the formulation. USP established procedures and standards to ensure the quality of the parenterals. So manufacturers should be to continue to minimize the risk of the particulate and product should meet the specifications to minimize the risk to the patients.

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