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Original Article

Particulate Contamination in Single-Dose Parenteral Antibiotics in Iran

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Abstract

In order to ensure the safety of parenterals, international pharmacopoeias and national standards have set up stringent guidelines and standards. Particulate contamination is a potential health risk caused by intravenous injection of particles large enough to potentially clog the small arteries. Particles could be produced through manufacturing and packaging or even dispensing of the pharmaceuticals. The nature of the particles are varied and could be of drug itself, packaging debris, rubber, plastic, cotton, fiber and glass particles, which might be produced during the breakage of an ampoule. In this study, some of the small volume parenterals available in Iranian drug market have been investigated for the presence of particles. Although, most of the tested samples passed national standard tests for particulate contamination of small volume parenterals, 40% of the samples were rejected using the same protocols. Therefore, it appears that particulate contamination of parenterals creates an additional source of risk for patients who receive these medications, intravenously.

Keywords: Parenterals; Particulate contamination; Particle size.
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1. Introduction

For safety reasons, all parenteral dosage forms should be essentially free from particles. Therefore, international pharmacopoeias have set stringent guidelines to limit number of particles in these pharmaceuticals. Particles could be produced through manufacturing, packaging, or even dispensing processes of pharmaceuticals. The nature of the particles are varied and could be of drug itself, packaging debris, rubber, plastic, cotton, fiber, or glass particles, which might be produced during the breakage of an ampoule. Opening ampoules, breaking container seals, insertion of syringes or needles during transfer of solvents or additives into the ampoules are among the most common sources of particle

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contaminations [1-5]. Numerous reports in the literature have claimed that particle contamination have caused insult to the brain, lungs, spleen, kidneys, liver and venous system in animals [5]. Particles introduced into a vein could travel to the right heart and then proceed to the right atrium, the right ventricle and then to the pulmonary artery which terminates to a vast capillary bed in the lung. Particulate contamination of intravenous fluids or fluids introduced into the epidural/subarachnoid space has been recognized for years [6-7].

The size of particulates greatly influences the terminal location as well as the chronic complications following their intravenous administration. It has been previously reported that large silica particles with diameters of 10-12 micrometer were commonly found lodged in the pulmonary capillaries and evoked a foreign body response with resultant granuloma formation [3]. Small silica particles were capable of passing through the lung and eventually occupying the liver, spleen, and hepatic lymph nodes. Advanced cirrhosis has been developed as a result of fibrosis, beginning in the portal connective tissue. Large particles may get fixed in the pulmonary capillaries with the potential to interfere with respiratory gas exchange [3]. Particulate contamination plays a role in the development of phlebitis related to infusion, the most common complication of intravenous treatment. In this study, the incidence and nature of particles in some of the injectable pharmaceutical dosage forms in Iranian drug market is investigated.

2. Materials and methods

2.1. Materials

Ceftriaxone, cefotaxime and ceftazidim freeze dried powder for injection and amikacin solution for injection, produced by four different local pharmaceutical companies, were purchased from pharmacies.

2.2. Sample preparations

In order to remove dust from outside of samples, they were wiped using damp cotton cleaner and transferred to a laminar air flow cabinet for further preparation. Distilled water, which was used for preparation of the samples, was filtered through a 0.22 micron filter before use, and was checked for particle contamination using a HIAC-Royco model 3000 particle counter, and was regarded as blank. Possible particle contamination of water was recorded and was subtracted from the value for corresponding samples. Samples' label were removed using either warm water or ethanol. Vials were then rinsed with filtered distilled water under a laminar air flow cabinet. Reconstituted samples with the proper volume (according to the manufacturer instruction) of distilled and filtered water were examined using instrumental and visual inspection, both by unaided eye and microscopic examination. In order to evaluate the effect of sample preparation on particle production, the samples were prepared by breaking ampoules in the patients' room in the hospital, and were pulled into a syringe, as it is in routine practice in clinics and hospitals. The particles in syringes were also examined using a Leitz-Dialux 22 microscope.

2.3. Visual inspection

After removing the labels and preparing the samples, twenty vials/ampoules of each sample were examined according to the monograph of international pharmacopoeia for visual inspection of small volume parenterals [9-11]. Briefly, the vials containing powder for injection were reconstituted by adding the proper volume of distilled and filtered water, and all of the samples were examined in a light box with white and black background by three independent trained examiners. Each examiner scored his/her observation and recorded the results in a separate sheet. However, the national standard

[12], which is a modified version of DAC [13], was used to quantify the samples for the presence of particulates. According to this protocol, samples with SE20 greater than 4.5 were rejected. SE20 is the visual result of the vials tested by examiners and it is calculated by dividing sum of the awarded points by examiners to the vials based on the presence of particles in the vials by 20 (the number of the examined vials).

2.4. Instrumental examination

Samples were counted by a HIAC-Royco model 3000 particle counter according to the international pharmacopoeia and the instrument manufacturer instructions. Powders for injection were reconstituted using filtered distilled water.

2.5. Microscopic examination

Samples were prepared as mentioned above, and were filtered through a 0.44 micron filter using a vacuum pump (20 PSi). Then the filters were examined under a Leitz-Dialux 22 microscope. Particles were counted and their sizes were measured using a micrometer.

3. Results

As shown in Table 1, 60% of the samples of reconstituted powders for injection with filtered distilled water complied with the national standards for the examination of powders for injection. However, three of the freeze dried samples showed substantially higher scores and were unacceptable. Amikacin was practically free from visual size particles. Table 2 shows the average numbers of the large size particles in each sample. Samples with high numbers of the large size particles such as cefotaxime 1 g also showed high SE20 scores (Table 1). The presence of the large size particles in the samples was also confirmed using microscopic examination (Figures 1, 2). The results of the examination of the freeze dried

Table 1. Scores for reconstituted powders for injection and solution samples inspected for the presence of particulates.

Sample name	Mean ± SD	SE20
Cefrtiaxone 250mg-1[a]	27.0 ± 1.6	4.1
Ceftriaxone 500mg-2	24.3 ± 5.9	3.7
Ceftriaxone 1g-2	19.0 ± 2.9	2.9
Ceftriaxone 1g-3	4.7 ± 1.9	0.7
Cefotaxime 500mg-1	109.0 ± 43.9	16.4[b]
Cefotaxime 1g-2	148.7 ± 17.3	22.3[b]
Cefotaxime 1g-3	89.3 ± 45.4	13.4[b]
Ceftazidime 500mg-3	16.7 ± 3.7	2.5
Ceftazidime 500mg-1	38.7 ± 13.1	5.8[b]
Amikacin 100mg-4	4.0 ± 2.2	0.6

Data are mean ± SD of three independent observations. [a]1-4 are samples from different producers. [b]Rejected samples.

Figure 1. Micrograph of a fiber particle in a sample of reconstituted powder for injection (x 100).

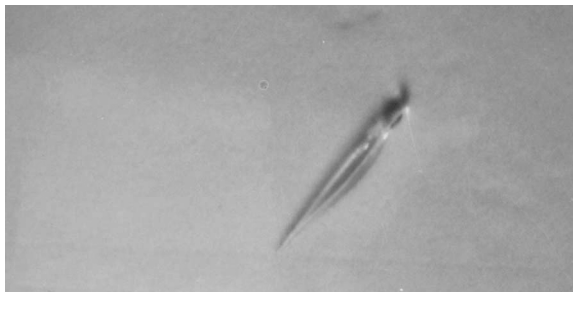

Figure 2. Micrograph of an unidentified particle in a sample of reconstituted powder for injection (x 100).

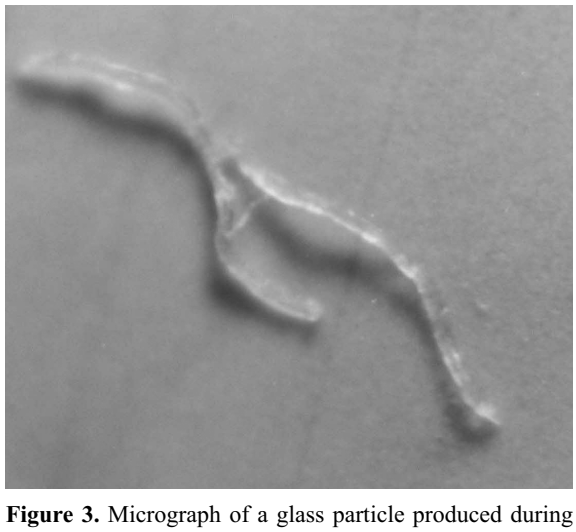

Figure 3. Micrograph of a glass particle produced during opening of an ampoule (x 100).

Table 2. Results of microscopic examination of reconstituted powders for injection and solution samples inspected for the presence of particulates.

Sample name	Average number of particles per sample[a]	
	≥25 μm	≥ 50 μm
Cefrtiaxone 250mg-1[b]	2.3	0.5
Ceftriaxone 500mg-2	1.2	0.8
Ceftriaxone 1g-2	2.4	1.0
Ceftriaxone 1g-3	0.5	0.2
Cefotaxime 500mg-1	2.3	2.0
Cefotaxime 1g-2	35.4	5.4
Cefotaxime 1g-3	6.8	1.9
Ceftazidime 500mg-3	5.0	1.5
Ceftazidime 500mg-1	7.3	1.8

[a]20 vials or ampoules from each drug were examined. [b]1-4 are samples from different producers.

samples with a HIAC/Royco particle counter are summarized in Table 3. Again, cefotaxime 1 g had high numbers of particles. Opening of the amikacin ampoules using the routine practice in clinics created an average of 81 glass particles larger than 10 micrometers per ampoule, of which 18 were larger than 50 micrometers (Figure 3). However, despite the presence of high numbers of small size particles in some of the samples, all of them were in the acceptable range of international pharmacopoeia [9-11].

4. Discussion

Due to the possible health risks of the presence of particles in parenteral preparations, these pharmaceutical dosage forms should essentially be free from visible particles. Since 1972 stringent guidelines for manufactures of large volume parenterals have virtually eliminated this problem. However, despite the existence of similar standards for small volume parenterals and freeze dried powders for injection, there are problems regarding these types of parenterals [14]. Unaided human eye is able to detect particles with a size of 50 micrometers and more [14], and there is general agreement that the presence of particles with these sizes in the parenteral dosage forms should be limited to as low as practically possible. The large size particles are apparently very harmful due to the risk of vascular occlusion in places where compensation by collateral circulation does not occur [1]. Parenteral solutions may be contaminated during manufacture, storage or preparation for use. There have been reports of pulmonary microemboli, thrombi and granulomas as a result of particle contamination with glass, rubber, cellulose fiber, plastics, and drug crystals found in the large volume intravenous infusions. Cases of pulmonary granuloma caused by cellulose fiber and the presence of particles in the lung and brain have been reported previously [3].

Table 3. Particles counted in samples using particle counter instrument.

Sample name	Average number of particles per sample[a]			
	≥ 10 μm	≥ 25 μm	≥ 40 μm	≥ 50 μm
Ceftriaxone 250mg-1[b]	179	6	1	0
Ceftriaxone 500mg-2	193	7	0	0
Ceftriaxone 1g-2	508	4	0	0
Ceftriaxone 1g-3	316	8	0	0
Cefotaxime 500mg-1	126	2	0	0
Cefotaxime 1g-2	1192	28	2	0
Cefotaxime 1g-3	3470	78	14	8
Ceftazidime 500mg-3	74	3	0	0
Ceftazidime 500mg-1	62	3	0	0

[a]20 vials or ampoules from each drug were examined. [b]1-4 are samples from different producers

In this study, some of the freeze dried and solution antibiotics from Iranian market have been examined for the presence of particles. Samples were from four different producers and were purchased from pharmacies. All of the samples were contaminated with visible particles, and 40% of the samples contained unacceptable levels of particles.

Although some of the samples showed substantially high numbers of the small size particles, all of them met the international standards for the presence of the small size particles [9-11]. It has been previously reported that high numbers of the small size

particles could also create substantial health risks [14]. Since the possibilities for counting the large size particles with HIAC/Royco instrument appear to be limited, microscopic and visual counts of samples would be a valuable method [1].

One of the hazards of glass ampoule opening is glass particle contamination. Ampoule neck breakage usually is not uniform and smooth creating breaks which may create particle contamination of the ampoule contents. Several previous reports have examined ampoules following their opening for the presence of glass particles [7, 15]. The results of the present study also shows that opening of ampoules using the routine practice in clinics creates significant numbers of particles, some of them lager than 50 micrometers, which can be hazardous to the patients.

In conclusion, the results of this study showed that the small volume parenteral dosage forms in the Iranian market contain substantial numbers of particles. The use of parenterals is always associated with possible adverse effects such as phlebitis, abscess and infection [16, 17]. Therefore, particle contamination of parenterals may also create an additional risk for the patients. However, the contribution of particulate matters may be reduced by "in line filters" with pore sizes of 0.2-0.5 micrometer. Previously, it was reported that filtering devices placed in-line or contained within the needle used for injection of ampoule contents have successfully reduced the particle load [18, 19]. There are also some contradictory reports indicating that in-line filters may not be effective in reducing the incidence of phlebitis as the most common complication of intravenous therapy [14]. However, they do appear to be effective in reducing the particle loading of the ampoule contents and even syringes and infusion sets in which the presence of particles has been reported, previously [18]. The reduction of particle load will clearly benefit the patients, especially those receiving multiple injections.

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