



Stopper fragments in parenteral preparations: a potential problem

Fragmentos de rolha em preparações parenterais: um problema potencial

Fragmentos de corcho en preparaciones parenterales: un problema potencial

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ABSTRACT

Introduction: The presence of extrinsic particles in injectable solutions is a medication error of usual occurrence that may have important clinical significance. This study aimed to evaluate the presence of stopper fragments in solution derived from bottle-vial after the preparation of drugs using different sorts of needles. **Outline:** experimental study, wherein 50 bottles-vials were used, divided into groups. Group 1: stopper perforated with three-bevel tip needle; Group 2: stopper perforated with blunt tip needle; Group 3: without perforation of the stopper. The figure and the size of the particles were determined through optic microscopy. The data were analyzed by means of descriptive statistics and the differences among the groups were analyzed through Fischer's Exact Test. **Results:** it was verified the presence of six stopper fragments in the solution derived from five bottles which had the stoppers perforated by three-bevel tip needle (29.4%) and the two fragments in two bottles which had the stoppers perforated with blunt tip needle (11.8%), with significant difference ($p=0.044$) in the comparison among the groups. The three-bevel tip needle produces larger particles (0.36 mm^2) than the blunt tip needle (0.12 mm^2). **Implications:** risk evaluations must enable the limitation, the detection, and the rejection of atypical unities at the time of the drugs' preparations, preserving patient safety.

DESCRIPTORS

Drug Contamination; Drug Packaging; Rubber; Patient Safety; Medication Errors.

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INTRODUCTION

The pharmacovigilance is the set of activities of detection, evaluation, comprehension and prevention of Adverse Events associated with the use of Drugs (AED), in order to ensure patient's protection and to promote information to the health professionals, favoring the rational use of medicaments, screening and preventing either potential or real Medication Errors (ME).¹⁻²

The ME is any avoidable event that can lead to the inappropriate use of medicaments or bring about harm to a patient, while the drug is under the control of the health professionals, patients or consumer. This event can be related with the professional practice or with the products, procedures and adopted systems.²⁻³

In this light, it is highlighted the phenomenon known in the international literature as *coring*,^{4,5} which characterizes a ME that involves the involuntary presence of extraneous, movable and undissolved particles in the solution contained, for instance, in shots or inoculations to be administered.⁶ Such presence of particulate material in parenteral products is a complex subject matter, but the occurrence is habitual, ranging from 3.1% to 97%. The increased variation in the frequency can stem from the detection method applied, from the quality and kind of the studies supplies, multiplicity of use and the angle of insertion of the needles in the bottles' stoppers.⁷

Depending on the route of administration, on the size, composition and number of injected particles, as well as the characteristics of the patient, the clinical events associated with the injection of the particle or strange body in the organism at the time of parenteral administration of drugs can be either acute or chronic. They include phlebitis, pulmonary embolism, neurological sequelae of paradoxical embolism, granuloma, immune system

dysfunction, myocardial infarction, anaphylaxis in patients with hypersensitivity to latex and death.⁸⁻⁹

However, the clinical significance and the microembolic consequences of accidental injection of undesirable fragments have not yet been enough known and described, may be underestimated and underreported, possibly due to the difficulty of immediate detection of the event.⁴

The presence of particles in injectable drugs can assume two classifications, based on the source of the particulate matter: intrinsic particles (originally associated with the solution) and extrinsic particles (that enter either in the container or in the solution). The general sources of such particles include the environment, the packaging, the components of the formulation, the interaction between product and packaging, and the ones caused by process. For instance, it has already been suggested that the refrigeration of the bottles of medication raises the incidence of microscopic fragments of rubber in the lumen of the needle before the shot due the change of the physical properties of the rubber stopper.¹⁰

In its turn, the Brazilian Health Regulatory Agency (ANVISA), ranks the matter foreign to the drug into three types: parts of the organisms from which the drug derives above of the specified tolerance limit; any organisms, portions or products of organisms beyond the ones specified in the definition and description of the drug; impurities of mineral or organic nature, not inherent to the drug.¹¹

The event can be minimized by the visual inspection of the presence of particles by the professional, but this evaluation is easily impaired by factors as: tiny size of the particles; situation in which the drug was diluted; reduced luminosity in the ambient; quality of the eyesight of the drug administrator; drug's coloration; place where the fragment is housed in the needle or in the vial; lack of knowledge of the drug administrator.¹²

The supplies employed in the preparation of injectable drugs can also contribute for the occurrence of contamination by atypical unities. A study mentioned the presence of stopper fragments sizing 0.4x1.5 millimeters (mm) obstructing the light of a flexible catheter, during the intravenous administration of anesthetic. For the researchers, the embolization was only avoided because the catheter had a reduced lumen. Posterior tests indicated that bodies of rubber fragments in bottles of the same anesthetic were detected when utilized cannulae without cut for the aspiration, but not when utilizing sharp 20 Gauges or 18 Gauges (G) needles, so that the researchers did not recommend the use of cannulae without cut for the aspiration of drugs.¹³

Based on the principle of that the strength required to perforate a rubber stopper with the needle depends on the perforating angle, other studios ones determined the incidence of fragments after puncture of anesthetic vials' stoppers, with short chamfered and sharp needles, by two different angles (approximately 90° and 45°) and identified significant reduction of 47.8% in the event when the angular puncture technique was used.¹⁴

Other authors and the pharmaceutical industry itself recommend the use of aspiration needles without cut and/or with filter for the same purpose, although the literature still lacks studies on this thematic. It was observed that needles with filter can make the aspiration process to happen slowly and to favor the formation of air bubbles, making it difficult their use in practice.^{4,14}

For Lehr et al.¹⁵, the contamination of parenteral fluids and drugs by particles can be further amplified by the use cheaper medicaments or even counterfeit ones. In an experimental study, the authors injected particles of three different prepares of antibiotic into hamsters and viewed the capillary functional density in the striated muscle. They observed that the injection of particles of two preparations of generic drugs, but not the original

preparation or the saline control, significantly reduced the capillary perfusion in the muscular tissue. According to the researchers, particles' contaminants cannot represent a great threat to the intact tissue but are capable of gravely compromising the tissue perfusion in patients with previous microvascular impairment of vital organs and, therefore, predispose to multiple complications.

Other strategies for reduction of the event depend on commercial initiative and include the manufacture of stoppers in colors that favor the seeing of fragments on the vial and the mandatory supply of single-use drugs' bottles. The drugs can also be provided into previously filled syringes, with the additional benefit that no stopper perforation is required, removing the risk of contamination in latex-allergic patients.^{4,16}

For these reasons, this study aims to evaluate the presence and penetrability of stopper fragments in the solution contained on the bottle-vial after the perforation of the stopper for reconstitution and aspiration of the medicament using different sorts of needles.

METHOD

Analytical, interventional and experimental study.

There were used bottles of medicaments like the ones provided by popular drugstore, consumed on a large scale (Injectable Benzathine benzylpenicillin 1.200.000 IU). All the bottles were identical, of flat bottom, colorless glass, transparent and neutral, reconstituted with the same volume of sterile solution. They had a stopper of butylated rubber (copolymer of isobutylene 98% and isoprene 2%), gray in color, 20mm diameter, aluminum seal.

For stopper's perforation, there were used two different kinds of needles, compounding three experimental groups:

- Group 1: the stopper of the bottle-vial was perforated with sterile needle, without filter, stainless steel cannula, siliconized, with long three-bevel tip, 0.8mm outside diameter, 25mm gauge (21G1");

- Group 2: the stopper of the bottle-vial was perforated with sterile aspiration needle, without filter, stainless steel cannula, siliconized, simple bevel and blunt tip, 12mm outside diameter, 40mm gauge (18G1 ½");

- Group 3 (control): bottles without stopper's perforation.

In the group 1, the needle was similar (same gauge and manufacturer) to the one provided in the health unities for the preparation and injection of the drug used in the present study.

Each sort of needle perforated 17 bottles in the groups of intervention (Groups 1 and 2) and 16 bottles in the control group, adding up 50 samples. Furthermore, each bottle received a unique code, recognized only by the main researcher.

Procedure

With the hypodermic needle selected, adjusted to a 10ml sterile syringe, the rated capacity of diluent, or 5ml, was injected inside of each bottle. A new needle was used for each lid, checking if it had not been damaged during the test. The perforation of each lid was performed by a single previously trained researcher, to minimize possible biases related to the exerted strength or used technique at the perforation time. Each stopper was perforated twice, being one perforation for diluent's injection and another for aspiration of the content, after salt's reconstitution.

In the negative control (bottles without perforation), the stopper was removed for reconstitution and aspiration of the content without the use of needles.

The steps of reconstitution and aspiration of bottles' contents were carried out at a simulated practice laboratory, in order to ensure similarity to

what is accomplished in the real scenarios. The procedure was carried out in accordance with the literature recommendations for the preparation of injectables drugs, including: disinfection of bench and of tray, previous hand hygiene, packages' open, functionality test of the supplies and connection of the needle to the syringe; removal of the center metallic seal that protects the stopper; disinfection of both bottleneck of the vial of diluent and of the center of the stopper of the medicine bottle, using cotton soaked in 70% ethyl alcohol; opening of the bottleneck of diluent's vial and aspiration of the volume of diluent, introduction of the volume of diluent; introduction of the diluent on the bottle-vial, perforation the rubber lid with the needle perpendicular to bottles' surface, respecting the area indicated in the packaging (the aim); homogenization of the medicament after removing the needle from the bottle; reintroduction of the needle in the bottle-vial, perforating the stopper in a different place from the one previously used; aspiration of bottles' content; identification of the syringe.

It was also carried out the control of the diluent by means of filtration and evaluation of bottles' content over microscopy, in order to rule out the possibility of obtaining particles from this source.

Evaluation of the presence of fragment by visual inspection

The evaluation of the presence of fragments by visual inspection (with the naked eye) was performed by the researcher through the bottles, after reconstitution of the drugs and in the syringes filled with the solution of the bottles. The preparations were viewed under good conditions of diffuse daylight, five minutes after preparation, observing, vertically, against a background of single and light color.¹¹

After this inspection, the solutions were sent to a specialized laboratory, contained within the bottles or aspirated in syringe, remaining in rest for 16 hours,

where they were analyzed by an armored investigator that had no knowledge to which group each bottle or syringe belonged.

Filtration of the samples

Sixteen hours after the reconstitution and/or aspiration procedure, the total volume of all syringes and bottles was filtered. In addition to the content of the syringes, there were added eight ml of 1N (4%) solution of sodium hydroxide (NaOH), being six ml for solubilization of the salt of benzylpenicillin and two ml bottles' cleaning. Posteriorly, filtering of the solutions was performed with the aid of a vacuum pump coupled to a Kitasato flask with a funnel and filter paper with one ml pores. The bottles of the control group also were cleaned with six ml of NaOH solution for salt's solubilization. The material resulting from the filtration of the contents of the bottles and syringes, contained in the filter paper, it was observed both macro and microscopically.

The macroscopically visible rubber fragments on filter's surface were counted. Posteriorly, the number and the size of hidden and apparent particles were determined through microscopy.

Analysis of the number and size of the fragments

For the test of particles computing through optic microscopy, it was used a suitable binocular stereo microscope (NIKON, JP), set for an until 80 times magnification and equipped with a calibrated ocular micrometer, a micrometer objective lens, a cross movement stage and two suitable illuminators, which enabled both episcopic and oblique light.

The area of the fragments was determined using a stereo zoom microscope in 40x magnifications and measured through the software NIS - Elements Basic Research (3.22.14 version).

Pretest

During the data collect, adjustments in the procedures were required, that set the need for

performing of a pretest. The pretest was carried out in 50 samples. It included the reconstitution and aspiration of bottles' contents, the evaluation of presence of fragment by visual inspection, the filtration of the samples and the computing of the particles using the stereo microscope.

Initially, a fourth group, in which stopper's perforation occurred using needles without filter, was included. Thus, each pretest group was composed by 12 to 13 samples.

In the first stage, composed by reconstitution and aspiration of the drug, the use of blunt needles with filter was discharged, choosing by the exclusion of this experimental group, what configured the first adjustment in the study. It was verified that this kind of needle does not allow the aspiration of the reconstituted drug, with the inference that such supplies were not designed for use in concentrated solutions. Perhaps the fact is due the high selectivity of the needle (five micrometers), the only one found in the national market.

In this stage, it is highlighted the presence of stopper fragments noticeable by visual inspection in two samples belonging to the first group (stopper perforated with 21G1 needle and three-bevel tip), adding up 4% of the general sample and 15.4% of the sample of the group.

During the process, it was also detected the need to adjust the process of filtration of the solutions derived from the bottles, that precedes particles' computing by optic microscopy. Antibiotic's insolubility made it difficult the effective filtration of the samples by the previously selected method. For such reasons, tests were carried out for the adequacy of the solubility of the Benzylpenicillin sodium salt before filtration, a problem contoured before the definitive analysis with the introduction of the use of the NaOH.

After the necessary adjustments in the method, the definitive test was carried out, which

also included the measurement of the sizes of the fragments observed through the microscope.

Statistical Analysis

It was elaborated a data sheet containing a dictionary (codebook) and two inputs, used for the double entry validation with analysis of internal consistence of the database. After the final management, the data were compiled, processed through the software Statistical Package for the Social Science (SPSS), version 16.0, and underwent to the simple descriptive statistical analysis with the calculation of absolute and relative frequencies. The

description of the “proportional differences” among the groups, with comparison of the variables of interest was made by means of application of Fischer’s Exact Test. In all analyses, the significance level of 5% ($p < 0.05$) was adopted.

RESULTS

Table 1 shows the results regarding the presence of rubber particles in the bottles of the intervention groups (Groups 1 and 2) and control group (Group 3) after the experiment.

Table 1 – Presence of stopper particles in the bottles of the intervention groups (perforation of the stopper using either needle with three-bevel tip or blunt tip needle) and control group (no stopper’s perforation). Ribeirão Preto, Brazil, 2019.

Presence of particles	Groups							
	Needle with three-bevel tip (n=17)		Blunt tip needle (n=17)		Control (n=16)		Total	
	n	%	n	%	n	%	n	%
No	12	70.6	15	88.2	16	100	43	86
Yes	05	29.4	02	11.8	0	-	07	14

*Three-bevel tip vs control ($p=0.044$)

In the Group 1 (needle with three-bevel tip), one of the bottles contained two fragments. The Other fragments pertained to different bottles, adding up seven fragments in six bottles in Group 1 and two fragments, contained into two different bottles, in Group 2 (blunt tip needle). All the particles were aspirated for the syringes.

In the comparison between Groups 1 (needle with three-bevel tip) and Group 3 (control), it was found association ($p=0.044$). There was no association ($p=0.055$) in the simultaneous comparison of the three groups. Likewise, no association was observed ($p=0.398$) in the comparison between Groups 1 and 2 (three-bevel tip needle and blunt tip needle, respectively). There was also no association (0.485)

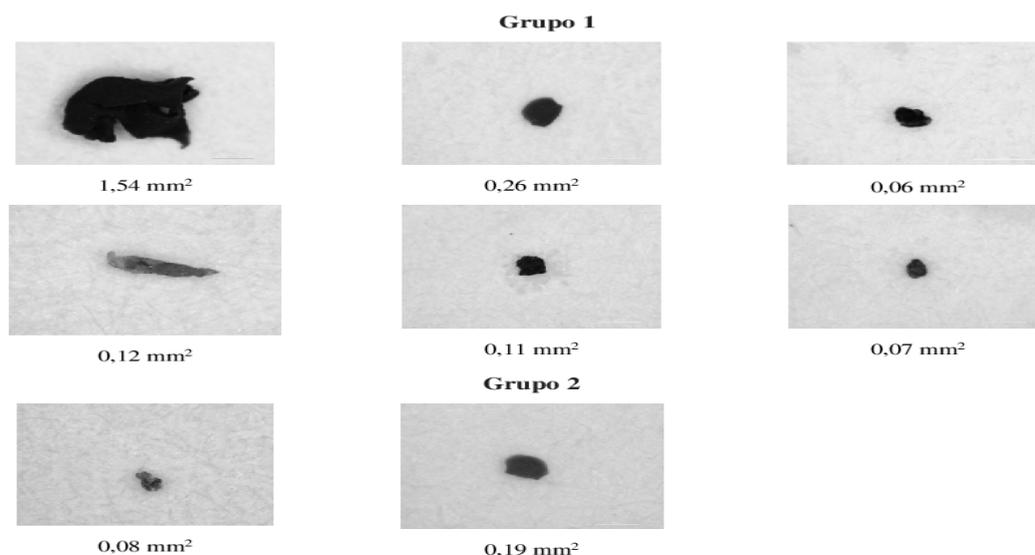
between Groups 2 (blunt tip needle) and Groups 3 (control).

Through microscopic counting three stopper fragments were observed in the Group 1 (three-bevel tip needle).

Figure 1 shows images of different sizes of particles detected in Groups 1 and 2, observed through optical microscopy. After the determination of the area of the fragments, it was verified that the biggest of them belonged to the Group 1 (1.54mm^2). The average fragment areas were 0.36mm^2 in the Group 1 and 0.12mm^2 in the Group 2.

Stranger particles were not detected in the content obtained from the vials of diluent.

Figure 1 – Size of rubber stopper particles into reconstituted and aspirated solution using the needle with three-bevel tip needle (Group 1) and blunt tip needle (Group 2). Ribeirão Preto, Brazil, 2019.



Source: produced by the authors.

DISCUSSION

In the present study, it was verified the presence of stopper fragments in the solution reconstituted and aspirated from the bottles which had the stopper perforated with three-bevel tip needle and bottles which had the stopper perforated with blunt tip needle, since the three-bevel tip one produces more and higher particles in comparison to the blunt tip one, designed for content's aspiration.

All rubber fragments were dragged by needle's bevel into the bottle-vial and, posteriorly, aspirated into the syringe, immersed in the reconstituted solution. Therewith, it is opened the possibility of inadvertent injection of the fragment through different ways, depending on the prescription of the drug.

Wani et al.¹⁷ also found fragments into bottles of drug which were perforated with distinct needles. Although, inversely to our findings, the percentage of fragments was higher ($p < 0.0001$) in the bottles lid perforated by blunt tip needle (40.8%) in comparison to those perforated with sharp needle (4.2%).

Another study verified the presence of fragments after the insertion 18G gauge needles in rubber stoppers of prednisolone bottles. The event

occurred in 21 of 200 samples (10.5%) and was visually detected in the syringe filled with the drug in 11 of 21 cases. Ten additional hidden fragments, ranging in size from 0.6 to 1.1 mm, were only detected after disassembling and rinsing the syringes and needles, one of which (4.7%) was able to be ejected from a 20-gauge needle.¹⁸

An already mentioned possibility to avoid the event would be the commercialization of pre-filled syringes, avoiding the reconstitution and aspiration of the contents from bottles and vials.¹⁶ Other strategies to minimize different occurrences include the identification and rejection of bottles with stoppers made of natural rubber, limiting the risk to sensibilization to the latex, the removal of the stopper from the bottle before aspirating the drug and restriction of the number of stopper's perforation to only one needle introduction. In the present study, the needle positioning was kept in such a way to avoid the perforation of the stopper in a ticker area, ensuring the insertion of the device on target, where the rubber thickness is less and offers less resistance.

For Kordi et al.⁷, a potential and worrisome complication is the inadvertent injection of a nucleated particle into an artery, which,

theoretically, could result in ischemia of the perfused tissue. According to the authors, this possibility can be minimized keeping the bevel upward, in an angle of 45° to 60°, when inserting the needle into the stopper, without rotating the device and using different points at each puncture, in the case of multidose bottles.

Other scientists investigated and quantified the formation of particles caused by coring associated with Other potential causal factors, like the nature and thickness of the rubber stopper, kind of bevel of the metallic needle utilized to perforate the stopper and puncture technique.²⁰ In sixteen different situations, 40 rubber stoppers for drugs' bottles were perforated and the content was filtered and examined under optic microscopy, being the particles countered and measured. The authors reported that the incidence of formation of particles ranged from 0 to 75%, depending on the situation. The average particle length was in the 0.98 ± 0.39 mm range. The largest number of particles (75%; 30/40) was observed when using a short, beveled needle, a 4mm thick stopper of butyl rubber and a puncture angle of 90°. The puncture technique reduced the formation of particles by more than 50% for the highest risk situation, but without extinguishing the formation of particles (22.5% residual formation; 11/40). The use of beveled or blunt needle completely eliminated the occurrence of visible particles. To a lesser extent, the thickness of the rubber and the nature of the elastomer were variables associated with the incidence of coring.

Additionally, authors considered the use of needles with filters in specific situations, as by means of the use of glass bottles.¹⁰ However, it is important to highlight the weaknesses regarding to the usage of aspiration needles with filter observed in the present study. The devices, which should minimize the presence of fragments in the final solution to be injected in the patient, besides of reducing the accidents with penetrating and sharp objects, did not

fulfilled to the described purposes due the unfeasibility of the use, once the ultra-selective filters did not allow the aspiration of the solution, possibly because of the high density of the content. Thus, we recommend the manufacturers to evaluate the functionality of the needles with filter, so that the device become effective in the aspiration of concentrated solutions or even the viscous ones.

The results of this investigation also showed that, macroscopically, there were observed three particles after the perforation of the stoppers with the three-bevel tip. Although the bottles and syringes were translucent, the physical aspect of the reconstituted drug was of a whitish and dense suspension, which may have made it difficult to visually detect the particles.

Mathonet et al.⁶ discuss that the odds of seeing a particle into a recipient of drug ranges accordingly with the size and the nature of the particles and depends on the conditions of the recipient and of the inspection. They accent that the expression "without visible particles" can assume different meanings, as "no particle", "zero strange visible particles" or "zero protein particles". Anyway, both American and European regulatory agencies demand the parenteral drugs to be "practically free" or "essentially free" of visible particles. Both terms recognize the probabilistic nature of the visual inspection of particles.

A limitation of the present study may have been the reduced size of the sample. It is suggested the conduction of other investigations with a greater number of bottles/vials or with other kinds of primary packages and/or application accessories.

It is highlighted that, if there is no technology able to either avoid or eliminate all the particles from pharmaceutical products, wide risk evaluations must be carry out to identify the capability of the manufacture systems on limiting particles and detecting and rejecting atypical unities, including the comprehension of the potential impact of the

injected or infused particles can have for a patient who receives those drugs.²¹

CONCLUSION

The usage of blunt-tipped needles minimized the occurrence of the event but did not prevent that stopper fragments produced by three-bevel tip needles and by the blunt-tipped ones, contained in the reconstituted solution, were aspirated from the bottle-vial into the syringes.

Careful inspection of the products is recommended before administering drugs, discarding them if they have visible particles. Furthermore, it is noteworthy that measures should be instituted by manufacturers of hospital supplies and pharmaceutical industries in order to prevent the presence of particulate matter in parenteral products, limiting the risk of MS.

RESUMO

Introdução: A presença de partículas extrínsecas em soluções injetáveis configura um erro de medicação de ocorrência habitual que pode ter importante significado clínico. Este estudo teve por objetivo avaliar a presença de fragmentos de rolha em solução derivada de frasco-ampola após o preparo de medicamentos utilizando diferentes tipos de agulhas. **Delineamento:** estudo de caráter experimental, em que foram utilizados 50 frascos-ampola, divididos em grupos. Grupo 1: rolha perfurada com agulha de bisel trifacetado; Grupo 2: rolha perfurada com agulha de ponta romba; Grupo 3: sem perfuração da rolha. O número e o tamanho das partículas foram determinados por microscopia óptica. Os dados foram analisados por estatística descritiva e as diferenças entre os grupos pelo Teste Exato de Fisher. **Resultados:** constatou-se a presença de seis fragmentos de rolha na solução derivada de cinco frascos que tiveram a rolha perfurada por agulha trifacetada (29,4%) e de dois fragmentos em dois frascos que tiveram a rolha perfurada com agulha de ponta romba (11,8%), com diferença significativa ($p=0,044$) na comparação entre os grupos. A agulha trifacetada produz partículas de maior tamanho (0,36 mm²) que a agulha ponta romba (0,12 mm). **Implicações:** avaliações de risco devem permitir a limitação, detecção e rejeição de unidades atípicas no momento do preparo de medicamentos, preservando a segurança do paciente.

DESCRITORES

Contaminação de medicamentos; Embalagem de Medicamentos; Borracha; Segurança do Paciente; Erros de Medicação.

RESUMEN

Introducción: La presencia de partículas extrínsecas en soluciones inyectables constituye un error de medicación frecuente que puede tener un significado clínico importante. Este estudio tuvo como objetivo evaluar la presencia de fragmentos de corcho en una solución derivada de un vial después de la preparación de medicamentos utilizando diferentes tipos de agujas. **Delineación:** estudio experimental, en el que se utilizaron 50 viales, divididos en grupos. Grupo 1: tapón perforado con aguja de bisel trifacetado; Grupo 2: corcho perforado con una aguja roma; Grupo 3: sin perforación de corcho. El número y tamaño de las partículas se determinaron mediante microscopía óptica. Los datos fueron analizados por estadística descriptiva y las diferencias entre grupos por la Prueba Exacta de Fisher. **Resultados:** se constató la presencia de seis fragmentos de tapón en la solución derivada de cinco viales que tenían el tapón perforado con aguja trifacetada (29,4%) y dos fragmentos en dos viales que tenían el tapón perforado con aguja roma (29,4%) (11,8%), con diferencia significativa ($p=0,044$) en la comparación entre los grupos. La aguja de tres lados produce partículas más grandes (0,36 mm²) que la aguja de punta roma (0,12 mm). **Implicaciones:** las evaluaciones de riesgo deben permitir la limitación, detección y rechazo de unidades atípicas en el momento de la preparación del fármaco, preservando la seguridad del paciente.

DESCRIPTORES

Contaminación de Medicamentos; Embalaje de Medicamentos; Goma; Seguridad del Paciente; Errores de Medicación.

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COLLABORATIONS

JGP: substantial contributions in the data collect, analysis and interpretation of the results, manuscript's writing. EW: substantial contributions in the data collect, analysis and interpretation of the results, critical review and formatting of the manuscript. SG: substantial contributions in the critical review and manuscript's formatting. RMM e PCAD: substantial contributions in the data collect and manuscript's formation. LMMA: substantial contributions in research's conception and

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CONFLICTS OF INTEREST

There are no conflicts of interest to declare.