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Challenges facing sterilization and depyrogenation of nanoparticles: Effects on structural stability and biomedical applications

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Abstract

This review outlines and compares techniques that are currently available for the sterilization of nanoparticles and addresses the topic of endotoxin contamination. Several techniques are available for the removal of microbial contamination from nanoparticles developed for use in nanomedicine applications. These techniques include filtration, autoclaving and irradiation, as well as formaldehyde, ethylene oxide and gas plasma treatments. Of these sterilization methodologies, filtration may potentially remove microbial contamination without altering the physicochemical properties of the carrier nanoparticles, nor affecting their toxicity and functionality. However, no single process may be applied to all nanoparticle preparations and, therefore, it is recommended that each nanoparticle-drug system be validated on a case-by-case basis.
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Key words: Nanoparticles; Sterilization; Endotoxin

Introduction

The unique physical and chemical properties of nanoparticles (NPs) have resulted in substantial research being performed on their potential applications in various fields including biology and medicine. Nanomedicine applications include the development of "lab-on-chip" technology in order to assess biomarkers, drug and gene delivery, tissue engineering, and cancer therapy.[1,2] Any nanoparticle-drug based formulation requires the solvent to be sterile and apyrogenic, in addition to being safe, non-toxic and non-irritating for both *in vitro* and *in vivo* applications. The term sterility refers to the absence of viable microorganisms that could pose a risk when administered. The current accepted sterility assurance level (SAL) is limited to 10^{-6}, that is to say not more than one viable microorganism in one million parts of final product is allowed.[3] Manufacturers of medical devices are required to ensure that their products meet established quality requirements and specifications, including regulations regarding microbial contamination. Potential sources of microbial contamination during production of pharmaceutics include the raw materials,

Abbreviations: ^{60}Co, Cobalt-60; ^{137}Cs, Cesium-137; AuNPs, gold nanoparticles; β-CDC6, Amphiphilic β-cyclodextrin; Cu/LDPE, Copper/low-density polyethylene; DLS, dynamic light scattering; e-beam, electron beam; EO, Ethylene oxide; EDS, Energy-dispersive spectroscopy; ESD, Emulsion Solvent Diffusion; FDA, Food and Drug Administration; FTIR, Fourier transform infrared; Hap, hydroxyapatite; HS, hydrothermal synthesis; IUDs, intrauterine devices; LAL, limulus amoebocyte lysate; LPS, LPS lipopolysaccharide; NP, nanoparticle; PBCA, poly(butyl cyanoacrylate); PBLG, poly(γ-benzyl-L-glutamate); PEC, poly(ε -caprolactone); PEG, poly (ethylene glycol); PEG-AuNPs, poly(ethylene glycol) coated gold nanoparticles; PLGA, poly(DL-lactide-co-glycolide); SAL, sterility assurance level; SLNs, solid lipid nanoparticles; TEM, transmission electron microscopy; TiO_2, titanium dioxide; tiopronin-AuNPs, tiopronin coated gold nanoparticles; UV-Vis, ultraviolet-visible; WCS, wet chemical synthesis.

The authors declare that there are no competing interests.

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t1.1 Table 1
t1.2 Summary of the effects of filtration on nanoparticles.

	Pore size of filter	Type of nanoparticle	Mean approximate size	Effect of sterilization on nanoparticle	Outcome of sterilization method	Authors
t1.4	0.2 μm	Poly(ε-caprolactone) nanospheres	130 nm; 160-180 nm	No aggregation and no effect on the nanoparticle morphology	Not tested	7
t1.5	0.22 μm	PEGylated poly(γ-benzyl-L-glutamate) nanoparticles	50 nm	No change in size or polydispersity index. Slight change in zeta potential.	No detectable growth of bacteria, yeast or fungi	8
t1.6	0.22 μm	Polyester nanoparticles	sub 200 nm	No clogging of the membrane filters. No significant change in particle size and size distribution	No bacterial contamination	9
t1.7	0.2 μm	Poly(DL-lactide-co-glycolide) nanospheres	200-300 nm 103-163 nm	Less than 10% of nanospheres passed through filter. 100-98% of nanospheres passed through filter.	Passed bacterial sterility test	12

equipment and processes used during production, in addition to the facility and personnel.[4]

Potential contaminating microorganisms include bacteria, fungi and mould; however the removal of endotoxins, the lipopolysaccharides in the cell membrane of Gram-negative bacteria, must also be addressed. Magalhães and colleagues[5] provided a review of endotoxins and their removal from biological preparations. They discussed the pathophysiological effects of endotoxins, as caused by activation of the immune system and release of pro-inflammatory mediators, which lead to endotoxin shock, tissue injury and sometimes death. Since the effects of endotoxin are related to the amount of endotoxin present, in the case of drug products, this would imply that the endotoxin limit would be dependent on the amount of drug product administered to the patient. The formula for the endotoxin limit provided by the Food and Drug Administration (FDA) is K/M; where K is 5.0 EU/kilogram, and M is the maximum recommended dose of product per kilogram of body weight administered in 1 h.[6]

Although numerous well-established sterilization techniques exist, concerns have been raised regarding the adverse effects that these techniques may have on the physicochemical characteristics of the nanoparticles. A change in these characteristics could potentially affect both the toxicity and the efficacy of the sterilized nanoparticles. This paper reviews various sterilization methodologies that have been assessed for the removal of microbial and endotoxin contamination from nanoparticle preparations with the aim of providing a possible recommendation on a suitable methodology for nanomedicine production and sterilization.

Methodologies implemented for the sterilization of nanoparticles

A literature survey of publications obtained from reputable journals shows that several conventionally used methodologies such as filtration, autoclaving, irradiation, as well as treatment with formaldehyde, ethylene oxide and gas plasma, have been implemented for the sterilization of nanoparticles.

Filtration

Sterile filtration is a commonly used method for the physical removal of microorganisms from chemically and thermally sensitive liquids, through the use of 0.22 μm membrane filters. This technique has been shown to be widely applicable as it does not appear to have any adverse effects on the nanoparticles (Table 1). Poly(ε-caprolactone) (PEC) nanospheres of mean diameter below 200 nm were successfully sterilized by filtration with 0.2 μm cellulose acetate membrane filters without alteration of their size, morphology or concentration.[7] Filter sterilization through 0.22 μm filters has also successfully been implemented for the sterilization of PEGylated poly(γ-benzyl-L-glutamate) (PBLG) NPs[8] and polyester NPs.[9]

The use of 0.2 μm or 0.22 μm filters may not always be possible if the NPs are larger than, or close to, the pore size of the filters since clogging can occur resulting in a decreased yield.[10,11] For example, filtration of 200-300 nm poly(DL-lactide-co-glycolide) (PLGA) nanospheres prepared using the standard Emulsion Solvent Diffusion (ESD) method resulted in less than 10% of the nanospheres passing through the membrane filter.[12] This problem was circumvented by optimizing the synthesis methodology to produce nanospheres with a particle diameter of 103-163 nm, of which 100-98% could pass through the membrane filter and successfully pass bacterial sterility tests. However adjusting the size of the nanoparticles in order to enable them to pass through a membrane filter may not always be feasible.

Sterile filtration may therefore present itself as a reasonable method for the removal of bacterial contamination, provided that a sufficiently high percentage of nanoparticles can be recovered following filtration.

Autoclaving

Autoclaving kills microbes with high pressurized steam, at a minimum temperature of 121 °C, within 15-20 min depending on the size of the load and the contents to be sterilized. This methodology has been shown to have a number of effects on the nanoparticles sterilized (Table 2). Fesharaki and colleagues synthesized selenium nanoparticles using *Klebsiella pneumonia* bacteria followed by recovery of the nanoparticles from the bacteria by autoclaving at 121 °C, 17 psi for 20 min. Energy-dispersive spectroscopy (EDS) confirmed chemical stability of the selenium nanoparticles before and after sterilization.[13] On the other hand, autoclaving PBLG NPs at 121 °C for 20 min resulted in the aggregation and a drastic increase in size of these

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