BIOCOMPATIBILITY STUDY OF IMPLANTABLE DEVICE FOR THERAPEUTIC DELIVERY STERILIZED BY ETHYLENE OXIDE

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Introduction

The purpose of the work was to select the most suitable sterilization method and evaluate biocompatibility by in vitro methods of the bio-electronic implant intended for therapeutics delivery secreted by confined genetically engineered cells upon stimulation by light (FIG. 1).

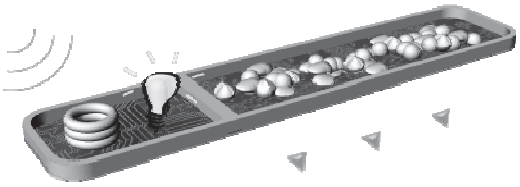

FIG. 1. A concept of wireless-powered cell-based implant for therapeutic delivery[1].

The device should fulfil essential requirements, such as mechanical and chemical stability in physiological environment during treatment of a disease or during their lifespan, and then be explanted or gradually degraded. In order to guarantee proper operation of such systems, especially in the case of their complex configuration or multifunctional tasks of the implant (e.g. active medical devices), besides selection of biomaterials and involved manufacturing processes, the designer should also consider potential sterilization method. Validation of selected sterilization technique in terms of its effectiveness, reliability and reproducibility is the prerequisite the manufacturer demonstrates to the notifying authorities in order to prove microbiological safety of the device.[2] Biocompatibility assessment is a part of validation of materials and components, including electronics towards following in vivo functionality testing.

Materials and Methods

Knowing the properties of polymeric materials comprising the implant, the complexity of its design and the presence of sensitive components and subsystems (FIG. 1), the ethylene oxide method was selected and applied for its sterilization. The device should be provided sterile for cells loading, therefore terminal sterilization of manufactured implant or aseptic assembling of pre-sterilized components may be applied. Validation of ethylene oxide sterilization method for the device under development was accomplished by overkill approach. In order to evaluate the biocompatibility of the components and the entire implant against human fibroblast cells (PCS-201-012™ ATCC) in vitro test recommended by the ISO 10993 – as for 'permanent implant contacting with tissue' – were carried out using XTT test, Live/Dead viability-cytotoxicity method, 2D-DIGE electrophoresis following changes in the proteome of the cells, and alternatively with irritation assay using skin model ex vivo.

Results and Discussion

A number of both physical and chemical processes can be used to properly sterilize a medical device, however steam sterilization, dry heat sterilization, chemical sterilization using gases like ethylene oxide, and radiation are among the most common. The choice of sterilization technique depends on the material composition of the medical device, how it's classified, and its intended use. Ethylene oxide (EO) is a chemical sterilization method usually suitable for complex or multi-material/component medical devices and was selected for current optogenetic implant. Because unlike steam sterilization and dry heat sterilization which require the medical device to be heat stable, a variety of materials – like plastics and electronic components – can be exposed to ethylene oxide without distorting the medical device form or its functioning. In the case of EO sterilization, besides rapid pressure changes, a dissolution of the gas (highly toxic) in the polymeric biomaterial and possible chemical reactions with the polymer should be examined.

Therefore, once the sterilization method that best suits a particular medical device is chosen, it is validated. Process Qualification at validation of EO method was demonstrated by application of sub-lethal, half and full sterilization cycles with the use of biological indicators confined in the cell chamber of the optogenetic implant. Moreover, the implant was examined to ensure that the applied sterilization procedure has not an adverse effect on the quality or integrity of the device or its components.

The biocompatibility of the materials after processing, and manufactured subcomponents comprising the implant, and the whole implant were examined by several in vitro assays. The cytotoxicity and viability showed no toxic effects towards fibroblast. The test to evaluate changes in cells proteome, comet assay and the potential to irritation gave results, as compared to controls, allowing qualification the device as biocompatible within the applied test conditions – no adverse effects were detected.

Conclusions

The applicability of ethylene oxide sterilization method for the developed implantable bio-electronic device for therapeutics delivery was presented. The biocompatibility tests results verified that the materials and components comprising this complex device, combined with the method of EO sterilization, are safe and can be applied in animal trials and in further clinical studies.

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