APPROACH TO SELECTION OF STERILIZATION METHOD FOR BIODEGRADABLE POLYMERIC MEDICAL DEVICE

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Introduction

Designing of a new medical device, besides such indispensable factors as shape configuration, dimensions, selection of biomaterials, involved manufacturing processes, should also encompass a potential sterilization method. Scientists, especially in academia, involved in early stage development often underestimate the possible detrimental effect of sterilization on material properties, although sterilization is critically needed when it comes to commercialization of the new device.

Validation of chosen sterilization method in terms of its efficacy, reliability and reproducibility is one of the requirements the manufacturer is requested to demonstrate to the notifying or certifying authorities, and its account is included in a 'technical file' of a new device. In order to fulfil the obligations, the manufacturer intended to distribute medical products within EU should follow regulations specified in directives of 90/385/EEC, 93/42/EEC, 98/79/EC with regards to sterilization, and further, the guidance of ISO standards. Those standards address general requirements (e.g. EN 556) and provide recommendations to the most common sterilization methods.

Those applicable for medical devices encompass moist heat, formaldehyde, ethylene oxide, radiation and plasma. Particularly, implants based on biodegradable synthetic polymers require special concern with regards to their sterilization. In principle, only low-temperature methods are acceptable. Simple implants, designed for load bearing applications, i.e. of polylactides, are typically treated with EO. Other chemical methods should be avoided since sterilizing agents may interact with polymers in terms of chemical reactions, or modify greatly its surface chemistry, e.g. hydrogen peroxide plasma. Moreover, polymeric biomaterials are not inert to (high energy) radiation. Irradiation of a polymer generates radicals, precursors of reaction leading either to crosslinking or degradation. The latter case is usually detrimental to polymer physical properties, thus a number of polymers cannot withstand radiation sterilization. Polyesters degrade when exposed to ionizing radiation, yet those possessing in their chemical structures secondary carbon atoms may simultaneously undergo crosslinking. A good example is poly(ε-caprolactone) (PCL) in which radiation causes broadening of molecular weight but ultimately, at higher doses, a gel is formed.

A short review of regulatory requirements will be presented, and followed by a case study of sterilization approach applied for a biodegradable medical device comprising a polymer with supramolecular chemistry based on ureidopyrimidinone (UPy) (FIG. 1). Implantable electrospun mesh is intended to be used for reinforcement and repair of soft tissue, e.g. operational treatment of pelvic organ prolapse and stress urinary incontinence, frequent disorders in ageing women.

Materials and Methods

Ureidopyrimidinone modified PCL was synthesized based on know-how of SupraPolix [1]. Electrospinning system of Coloplast was applied in order to fabricate nonwoven mesh. Various methods of sterilization were challenged, such as ethylene oxide (EO), hydrogen peroxide plasma, hot steam, electron beam (EB) and gamma radiations. Tensile testing of the implant and molecular weight changes of the UPy-PCL were followed by cytotoxicity testing with LDH and XTT assays.

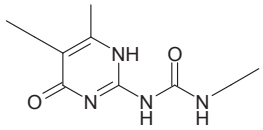

FIG. 1. Ureidopyrimidinone moiety incorporated into PCL chain.

Results and Discussion

Since UPy-PCL is sensitive to elevated temperature, and autoclaving melted the polymer, only low-temperature methods were further considered for sterilization of this biomaterial and consecutive implants. Sterilization with EO resulted in partial deformation of the implant and fusion of the mesh fibers – the temperature of the process, i.e. even up to 60°C is too high. Sterilisation with low temperature plasma did not deformed the implant, yet the method was considered to be not full reliable since one cannot be assured that entire high density mesh with porosity of c.a. 10 μm is effectively penetrated with the ionised gas, therefore it was impossible to demonstrate microbiological cleanness of the implant.

Studies on radiation sterilization of the implant by either electron beam and gamma rays showed suitability of the radiation method. Changes in mechanical properties of the mesh caused by irradiation with 25 kGy were minor, and resulted from small reduction in molecular weight of the polymer (c.a. 10% for EB). Gamma irradiation had somewhat greater negative impact on the material performance. Significance of dose rate was proved. Validation of radiation method based on ISO11137 of VD_{max} approach was conducted [2].

Quantitative cytotoxicity tests of radiation sterilised UPy-PCL mesh implant showed that the material does not induced detrimental effect towards cells, what demonstrated that radiation sterilization does not alter biological safety of the material.

Conclusions

Selection of potential sterilization methods, their comprehensive review at the early stage of implant development should be followed by testing of biomaterials exposed to predetermined most promising sterilization factor, which in turn may be beneficial in further work and cost reduction related to accomplishment of certification requirements. Radiation sterilization of EB was demonstrated to be the most suitable among low temperature sterilization methods towards an implant of e-spun mesh based on supramolecular UPy-PCL.

Acknowledgments

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