THE ROLE OF NANOMATERIALS IN THE FABRICATION OF MEDICAL DEVICES

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Introduction

The increasing diffusion of nanomaterials (NMs), i.e., materials with at least one external dimension <100 nm, is impacting also the fabrication of medical devices (MDs). The unique properties of materials at the nanoscale are often unexpected, given the corresponding properties that these materials (e.g., gold) present in bulk form.

The remarkable characteristics of nanomaterials (above all, the tunability of their physicochemical properties as a function of their size) are very attractive for biomedical applications, given that it is possible to enhance the biocompatibility of MDs by using NMs.

Besides the theoretical advantages, though, also the associated risks must be carefully considered.

Methods

The principal literature search was performed on the Web of Science Core Collection database. The intersection The intersection of the results pertaining to the keywords "medical device" and "nanomaterial" provided the basis for the analysis of the relevant evidence. The aim was to select the papers which made explicit consideration of MD application(s), in short or long term, of nanomaterials.

The analysis enabled to list the broad areas of application, such as dentistry, orthopedics, etc., without attempting to evaluate the quality of the specific papers in a given area: the low number of the latter's papers would have prevented us from performing a finer-grained analysis.

Not all of the papers from the basic search were found to be useful to give a picture of current nanostructured MDs, for which a proof of principle has been demonstrated. The raw data from the basic literature search have been filtered, discarding non-relevant papers. Other causes for exclusion were insufficient maturity of the application or insufficient focus on application to MDs.

Results

Nine broad application areas have been identified for current (or demonstrably feasible) diagnostic and/or therapeutic applications of nanostructured medical devices. In some of these applications, the release of nanoparticles is explicitly designed (e.g., to improve the antibactericidal properties of the coating of implantable MDs): this approach is somewhat contrasting with the cautionary approach adopted by the Medical Device Regulation (MDR) [1], though, since medical devices incorporating or composed of nanomaterials are categorized under Class III, the highest risk class, if there is a high or medium potential for internal exposure (Rule 19).

Discussion

The MDR reflects the necessity for increased oversight of medical devices containing nanomaterials. Traditionally, ISO 10993 series standards (e.g., [2]) address the biocompatibility and toxicity of biomaterials, but the scope of these standards does not foresee the use of nanostructured materials.

In this regard, ISO published in 2017 a technical report providing guidance for evaluating nanomaterials in MDs [3]. The report highlights that many traditional tests used for evaluating MD biocompatibility may fail in the presence of nano-objects, due to interactions of the latter with dyes used in assays such as MTT, XTT, lactate dehydrogenase, and dichlorofluorescin. For example, regarding cytotoxicity testing according to ISO 10993-5, up to 14% false increases in viability, induced by the NP-dye reaction in the MTT assay, were observed in ref. [4], with a potential underestimation of toxicity.

As underlined in [3], corroboration of several test results from different methodologies might be required for a scientifically sound interpretation.

A remarkable recommendation for designing a test plan is that "In general, nanomaterials themselves need to be evaluated instead of extracts as usually used when testing biomaterials or medical devices". Nanosized extracts may exhibit physicochemical alterations compared to the original nano-objects within the MD, thus extracting them from a final product can lead to inaccuracies in safety assessment.

The cautious risk classification approach outlined in MDR for nanostructured MDs appears the most appropriate, given the absence of relevant standards and the numerous unresolved research issues.

References

1. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices, Amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and Repealing Council Directives 90/385/EEC and 93/42/EEC (Text with EEA Relevance) (OJ L 117 05.05.2017, p. 1, ELI). http://data.europa.eu/eli/reg/2017/745/oj
2. ISO 10993-1:2018; Biological Evaluation of Medical Devices Evaluation and Testing within a Risk Management Process. ISO:Geneva, Switzerland, 2018.
3. ISO/TR 10993-22:2017; Biological Evaluation of Medical Devices—Part 22: Guidance on Nanomaterials. ISO: Geneva, Switzerland, 2017.
4. Lupu, A.R.; Popescu, T. Toxicol. Vitr. **2013**, 27, 1445–1450