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Editorial

Designing Cu-Based Nanotechnologies for Oro-Dental and Craniomaxillofacial Applications

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Received: March 21, 2023; **Published:** April 08, 2023

Keywords: *Antimicrobials; Antibacterial; Biofilm; Biomaterials; Copper; Nanodentistry; Cranio-Maxillofacial; Regenerative Medicine; Drug Delivery; Nanoparticles; Oral Healthcare*

Dentistry is an ever-evolving field that has seen significant advances in recent years. Particularly, research interest in nanomaterials has amplified exponentially mainly due to the unique, diverse, and versatile physico-chemico-mechanical and biological features they offer to our clinical as well as surgical armamentarium. Herein, copper-based/-incorporated nanoparticles and controlled pharmaceutic delivery and release systems are a fine example. Indeed, for the improvement of the properties of dental materials, the inclusion of metal oxide nanoparticles such as copper oxide (CuO) nanoparticles have been demonstrated to improve the physio-mechanical properties whilst safely enhancing the biocidal anti-microbial bio-efficacy. Briefly, copper nanoparticles are tiny particles of copper with dimensions ranging from 1 to 100 nanometers (nm). They are commonly synthesized through various physical and chemical methods such as chemical reduction, electro-chemistry, hydro-thermal, thermal oxidation, sol-gel, microwave-assisted and/or green synthesis (using plant extracts) techniques, amongst other techniques. Henceforth, it can be anticipated that, given an accruing clinical demand and surgical interest, the design, development, innovation, characterization, fine-tuning/optimization, and translation of nano-scaled copper-based/-incorporated formulations will be a major focus of researchers, clinicians, and surgeons in the coming period. Generally, the properties and applications of copper nanoparticles are highly dependent on size, surface charge, and surface chemistry, which can be tailored through various synthesis and functionalization methods. It is worth noting herein that the link between oral, dental, cranio-maxillo-facial health and systemic health has also become increasingly recognized in recent years. Therefore, implications for dental and surgical practice and public health are therefore, very relevant and timely. To prevent and treat oral and dental infections, the following lines tackle and summarize the main or ideal properties and characteristics pertinent for nano-CuO (undergoes discoloration due to oxidation, for instance), deemed critical to carefully consider when integrating into oral and cranio-maxillo-facial solutions.

Size: The most important characteristic is the size of the formulated copper nanoparticles, which may be controlled during synthesis and facilitates modulating the biological properties, amongst others. The formulated copper nanoparticles should be small (< 100 nm) to increase their surface area to volume ratio, and so increases their reactivity, catalytic activity, and conductivity, which enhances their anti-microbial and anti-inflammatory activities. The ideal size value to aim for in the design is between 10 - 50 nm.

Stability: Copper nanoparticles should be stable and not undergo significant oxidation or degradation over time. This can be achieved by using stabilizing agents such as sodium alginate, hyaluronan or chitin/chitosan (natural, biodegradable, non-toxic and readily-available biopolymers). Other common stabilizing agents include citrates, silica, polyethylene glycol or PEG and polyvinylpyrrolidone or PVP. The synthetic PVP coating protects the copper nanoparticles from the environment (light exposure and/or reactions with other chemicals) and can prevent discoloration. Ideally, the formulated copper nanoparticles should remain stable (spherical and uniformly dispersed, in solution) for at least 3 months under typical storage (shelfed or cooled) conditions. Note that the choice of the stabilizing agent will depend on the specific application and the compatibility with the other components present in the dental cement or resin biomaterials.

Surface: The surface charge of copper nanoparticles can vary depending on the method of synthesis and the presence of capping agents or stabilizing agents. In general, copper nanoparticles are negatively charged due to the presence of surface-bound oxygen species such as oxide or hydroxide. The surface charge of copper nanoparticles can also be modified via functionalizing the surface with various organic or inorganic molecules.

Safety: Copper nanoparticles should have a low toxicity and not cause any cytotoxic effects. Also, to ensure that they do not cause any adverse effects in the oral cavity, surrounding tissues or site of application/use. The ideal value for biocompatibility to aim for in the nanosystem design is an IC_{50} (half maximal inhibitory concentration) value greater than 100 μg/mL, indicating that the copper nanoparticles are non-toxic to cells.

Adhesion: Copper nanoparticles should have good adhesion to dental surfaces as well as biomaterials to ensure that they stay in place (*in situ*) and maintain their anti-bacterial activity, locally. The ideal value pursued in the design for proper/suitable adhesion is a contact angle of less than 90 degrees, indicating good wetting and adhesion properties.

Compatibility: The formulated copper nanoparticles should be compatible with the other components present in the composition of the dental biomaterials and not negatively affect their mechanical or physical (or chemical) properties. The ideal value for compatibility achieved by the nanosystem design is that the addition of the synthesized copper nanoparticles does not significantly affect the properties of the dental biomaterials.

Pharmacokinetics: Copper nanoparticles should have controlled release properties (pharmaco-kinetics/-dynamics) to ensure that they release copper ions in a sustained manner over a pre-determined period of time, providing long-lasting anti-microbial activity. For localized efficacy, aim in the nanosystem design to achieve a sustained linear release of the copper ions over a period of at least 7 days (per application, administration or use).

Bactericidal: The synthesized copper nanoparticles should have strong/potent anti-bacterial activity (inducing the generation of reactive oxygen species or ROS within the bacterial cells and promoting DNA and mitochondrial damage) against common oral bacteria such as *Streptococcus mutans*. Toxicity of the nanoparticles can be further enhanced by a positive surface charge (think surface coatings and functionalization; core-shell nanocapsular design employing the layer-by-layer step-wise self-assembly technique at our BioMAT'X R&D&I LAB is an appropriate approach), which would facilitate the interactions between the cells and the nanoparticles. The ideal value for MIC (minimum inhibitory concentration) is < 50 μg/mL, indicating strong anti-microbial activity [1-5].

Closing Remarks

In conclusion, various bulk materials, coating agents and formulation or synthesis methods and techniques are now available. Choice and combinations thereof will affect the resulting physico-chemico-mechanical and biological properties (bio-safety and -efficacy) of the formulated copper-based/-incorporated nanoparticles, controlled pharmaceutic delivery and release systems, as a product, whether designed for surface disinfection, or integration into dental materials, implant surface treatments and/or facial prostheses, or for direct clinical application in gel, wound dressing and/or topical formats.

Conflict of Interest

None.

Funding and Acknowledgments

This work was supported by operating grants provided to the HAiDAR R&D&I LAB/BioMAT'X (Laboratorio de Biomateriales, Farmacéuticos y Bioingeniería de Tejidos Cráneo Máxilo-Facial), member of CiiB (Centro de Investigación e Innovación Biomédica), Faculties of Medicine and Dentistry, Universidad de los Andes, Santiago de Chile, through the ANID-NAM (Agencia Nacional de Investigación y Desarrollo, Chile and National Academy of Medicine, NIH, USA) Grant código # NAM21I0022 (2020-2022), CORFO Crea y Valida I+D+i Grant código # 21CVC2-183649 (2021-2023), CORFO Crea y Valida - Proyecto de I+D+i Colaborativo - Reactívate" Grant código # 22CVC2-218196 (2022-2024), and FONDEF Concurso IDEA de I+D, ANID, Grant código # ID22I10215 (2022-2024). The author wishes to acknowledge the exceptional F-ODO students behind inspiring this piece: Yr3 (Andrea Bustos, Ismael Valenzuela and Zabdiel Faundez), Yr4 (Alondra Beniscelli) and Yr6 (Ignacio Fernández).

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Volume 22 Issue 5 May 2023
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