Research Article

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Synthesis of nano zirconium oxide and its application in dentistry

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Abstract: Zirconium oxide (ZrO2) is the general material in dental area, with natural color, high toughness and strength. Recent years, small blocks of ZrO2 such as micro/nano powders have been studied and developed widely. Nano scale ZrO2, which shows improved mechanical characteristics and superior biocompatibility, are usually incorporated into different applications used in dentistry and tissue engineering. This review provides an overview of nano-ZrO2 materials and its applications in dentistry. The synthesis of nano-ZrO2 powders were mainly prepared by coprecipitation, hydrothermal method and sol-gel method. Then different applications of nano-ZrO2 biomaterials in dental ceramics, implants, radio pacifying agents, basement and tissue engineering fields were briefly introduced.

1 Introduction

Teeth are essential to oral and overall health, esthetics, speaking, and quality of life. A large majority of the population is suffering from oral diseases, including caries, pulpitis, and periodontal diseases, some of them may lead to defect of teeth and functions [1, 2]. There is thereby an urgent need but it is still a significant challenge to reconstruct or regenerate the heterogeneous and dynamic dental anatomical structure [3–5]. To solve this, the variety of dental materials are studied and develop to be used in rebuilding the curve, color, shape and function of teeth.

In the past few decades, dental materials have developed rapidly, providing more personalized functions for dental treatment. The common materials application in dental restorations and prosthesis are ceramic crown [6, 7] and implants [8]. Ceramic fused metal and all-ceramic crown are often served to repair tooth defects. Compared with ceramic fused metal restorations, all-ceramic materials are preferred due to their natural color, wear resistance, biocompatibility and aesthetics [9]. Titanium implant is the most frequently used in clinic nowadays [10], while recent developments of ZrO2 implants have attracted much attention [11, 12]. Both in vivo and in vitro studied have demonstrated that ZrO2 implants retain the similar or even superior osseointegration than Ti implants [13–16].

High purity ZrO2 is the general material in dental area, ZrO2 is a kind of biomaterial with good natural white color, high toughness, excellent strength, steady chemical properties, good corrosion resistance, which is a source of high-performance ceramic material and especially bio-compatible implant materials [17–20]. In fact, the high strength of ZrO2 indicates that this material is hard to be processed and formed. Although CAD/CAM technique can be used for solving such problems, however, it is hard to reach high accuracy demanded and the fabrication cost is high [21–23]. Hence, it is acceptable to introduced the small blocks of ZrO2 such as micro/nano powders to resolve the problems. Nano-ZrO2 provides more application scenarios, such as nano powders filling [24], nano coating [25, 26], sintering raw material [27] and so on. ZrO2 nanopowders are employed in promoting the bionics and mechanical properties of dental ceramics and tissue engineering scaffolds. Recent studies indicated that the cooperation of ZrO2 nanopowders can significantly strengthen the flexural strength, fracture toughness and shear bond strength of the materials [28, 29]. In another scenario, nano-ZrO2 can served as a powerful porous coating of solid surfaces to provide a nanostructured surface through the modification method that could improve the biocompatibility. For example, nano-ZrO2 coating on the surface of Ti implants or the nano porous ZrO2 implants are able to...
enhance the process of osseointegration [30]. It is considered that surface treatment and bioactivation accelerate the new bone formation.

This review provides an overview of Nano-ZrO₂ biomaterials and its applications in dentistry. Two aspects were discussed in detail. Firstly, the synthesis of nano-ZrO₂ was introduced, and then the applications of nano-ZrO₂ biomaterials on dental ceramics, implants, membranes, basement and tissue engineering are extensively reviewed.

2 Synthesis of nano-ZrO₂

Among the metal oxide ceramics, ZrO₂ has one of the best high-temperature thermal stability and thermal insulation performance. There are three different crystal structure of ZrO₂: cubic (c-ZrO₂), tetragonal (t-ZrO₂) and monoclinic (m-ZrO₂), with each crystal structure keeps stable in different range of temperature. Under certain condition, like pressure and temperature, each of the structure can be transformed mutually, at the same time, their physical properties, volume change in a way that t-ZrO₂ holds the best performance while m-ZrO₂ is the usually form at room temperature. Therefore, it is important to synthesis t-ZrO₂ at moderate temperature to prevent expansion [31]. The advanced application of nano-ZrO₂ powders are containing refractories, abrasives, ceramic pigments, oxygen sensors, catalytic materials [32]. Nano-ZrO₂ powders are mainly prepared by wet-chemical synthesis approaches, such as coprecipitation [27, 33], hydrothermal synthesis [34], sol-gel preparation [35]. The physical method cannot meet the requirement of nano size, while gas-chemical method costs too high to repeat it in practical production.

Coprecipitation is the primary means of wet-chemical precipitation for synthesis ZrO₂ nanopowders. Coprecipitation technique is processing by adding precipitating agent into the mixture solution of water-soluble zirconium salts and stabilizers like Y₂O₃. After the precipitation reaction, the insoluble precipitation as hydroxides is formed which are then dried or calcined to obtain nano-ZrO₂ powders. The group of Wang and Zhai prepared the MgO-Doped ZrO₂ nanopowders with nanosize of 10 mol% [36]. A mixture of water and ethanol(ratio of 1:1) served as the precipitating and washing solvents. On the base of the capability ethanol holds to alleviate the hydrogen bond existing inside of the formed zirconium hydroxide gels, the homogeneous nano-MgO-ZrO₂ were formed, presenting satisfying sintering property. Another study investigated how pH value and residual NH₄Cl interfere crystallization of nano-ZrO₂ powders [37]. Coprecipitation technique is simple and the production is demonstrated to be nice, however, there are a few elements in the initial solution would residue, which could have effects on the sintering properties of the nanopowders.

Sol-gel method is extensively used to prepare solid materials from small molecules at the relatively lower temperature. During the sol-gel process, the main step is the conversion of the precursors into the colloidal or polymeric solution through hydrolysis and condensation reactions [38, 39]. The initial precursors are often metal alkoxides or metal chlorides, which could have an effect on the properties of sol-gel, like drying or firing behavior. Huang and colleague [31] explored how the organic addition influenced the characterization of ZrO₂ nanocrystals. Zirconium oxychloride octahydrate (ZrOCl₂) was used as precursor, while glacial acetic acid (HAc) was applied as the chelating agent during vigorous stirring. N,N-dimethylformamide (DMF) as drying control chemical additives (DCCA) was also added to reduce the cracks when stirring. After calculation, the size of ZrO₂ nanocrystals decreased to 13.94nm by adding HAc and DMF. Shukale and Seal have successfully synthesized nanocrystalline ZrO₂ particles using the sol-gel method [40]. It is worthwhile to highlight that the metastable t-ZrO₂ is stabilized at normal temperature within pure ZrO₂ displaying nonspherical morphology. The unique nature maybe result from the contribution of the interfacial, and strain energies, which balance the size and the shape, stabilizing the t-ZrO₂ nanoparticles.

Hydrothermal method is an advanced technology for preparing inorganic materials particularly particles with nano-sized to submicron crystals by chemical reaction in aqueous solution under high temperature and pressure. Vapors or fluids acts as the tranformation agent for pressure, heat, and mechanical energy [41]. These characteristics facilitate the formation of prepared powders that have uniform microstructure, shape and components. Researchers think that hydrothermal method is considered to be one of the most promising methods to prepare fine particles with controlled forms [41]. Szepesi and colleagues [42] have developed the high yield hydrothermal precipitation procedure and synthesized zirconia or yttrium-doped tetragonal zirconia polycrystals (YTZP) with average size of 8-10 nm. Bicine was served as the complexing solution to reducing the tendency of agglomeration in high-yield batches. Another work built novel ZrO₂ nanorods and nanoparticles from ZrO₂ powders through hydrothermal processing [43]. This long-drawn-out synthesis process was performed in autoclave with NaOH solution as the mineralizer at a temperature of 200°C for totally 7 days. The NaOH mineralizer had different concentrations of 15 M, 20 M and 25 M. Under electron microscopy, the formed...
Table 1: Different methods for synthesis of nano-ZrO$_2$

| Synthesis approaches   | Advantages                                                                 | Disadvantages                                                                 | Size               | Morphology   |
|------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------------|--------------|
| coprecipitation        | simple in preparation; low equipment requirements; commercialized          | low yield and purity of finished products; agglomeration; influenced by many factors like washing solvent, pH value, drying method. | few nm to hundreds nm | particles    |
| sol-gel preparation    | handy operation; high purity; homogeneous distribution; commercialized      | Time-consuming; poor sintering properties                                      | few nm to hundreds nm | particles; nanotubes |
| hydrothermal synthesis | high purity; time-saving; perfect dispersion; various crystal shape; controllable size; minimization of agglomeration. | equipments for stringent; high temperature                                    | few nm to several µm | particles; nanotubes; nanorods; nanobars |

Figure 1: Bright field image of ZrO$_2$ nanobars (20 M NaOH); HRTEM image of zirconia nanobar (25 M NaOH) [43]

nanorods had diameters spanning from 25 to 200 nm and lengths ranging several hundred nm to 2µm (Figure 1).

3 Application of nano-ZrO$_2$ in dentistry

3.1 Application of nano-ZrO$_2$ as dental ceramics

Over the past few decades, the increasing demand of functional and aesthetics effect has hastened the development of ceramic restoration crowns, which are of satisfying natural-tooth like color, bionics and mechanical properties [44, 45]. Among the various dental ceramic materials, ZrO$_2$ is of very superior strength and toughness. ZrO$_2$ is widely used as inlays, partial crowns, veneers and full ceramic crowns. Nevertheless, the high mechanical ZrO$_2$ dooms for the difficulty to machine [46]. To solve this, the block or powder form ZrO$_2$ can be considered to gain more formability.

Researchers have employed nano-ZrO$_2$ for resistance enhancement in diatomite-based ceramics. The method of layer-by-layer (LBL) assembly modification was organized in order to enhance the adsorption of electropositive nano-ZrO$_2$ [29]. The surface of diatomite-based ceramic powder was modified using allylamine hydrochloride (PAH) and sodium 4-styrenesulfonate (PSS), then nano-ZrO$_2$ particles with positive electricity were absorbed to the ceramic powders. After PAH/PSS polyelectrolyte dispersants modification, the size of diatomite particles decreased (from 0.12 to 35 µm); radius narrowed to 0.42 µm. The sintered and shaped ceramics were prepared for further tests, and the results suggested that addition of nano-ZrO$_2$ has led to the higher flexural strength, fracture toughness and shear bond strength value with reduced porosity. The reasons may lay in composite particles with a smaller wideness distribution and less aggregation; the addition of nano-sized, uniform ZrO$_2$, which formed a dense unity with diatomite-based ceramic powders [47, 48]. Another experiment [49] verified that the silica ceramics filled with nano-ZrO$_2$ showed excellent heat shielding and high-temperature ablation properties.

As a biologically inert ceramic, ZrO$_2$ need to combine with other bioactive phase. Nano-ZrO$_2$ can acts as the second phase to enhance the fatigue resistance to nano-HA ceramics [50–54]. When compared with pure nano-HA ceramics, the hybrid ceramics of nano-HA/nano-ZrO$_2$ showed similar cytocompatibility. Besides, wettability of the interfaces of ZrO$_2$-based dental ceramics seems to affect the adhesion properties. Marefati et al. have studied the effect of different size yttria-stabilized tetragonal zir-
conia polycrystals (Y-TZP) cores on wetting behaviour of a molten feldspathic glass-ceramic [55]. There was an enhancement of wettability in nano-sized Y-TZP group. This may be related with the diffusion-assisted atoms through increased surface defects such as grain boundaries and triple junctions.

In the midst of common processing, fracture among the block material can be brought about. This is the main limitation when applying nano-ZrO$_2$. Therefore, the impacts during consolidation process should be deeply studied. Park et al. [56] have explored the method that combined application of magnetic pulsed compaction (MPC) and subsequent sintering for densification of ZrO$_2$ nanopowders. The high density (98%) ZrO$_2$ bulks were obtained. At experiment condition, the authors have found that with increasing MPC pressure, the grain size of zirconia block decreased, while the additional ratio of PVA did not have an obvious effect on the grain size. According to the paper, the optimum way was implemented as following: MPC process (1 GPa compaction pressure and using 1.0 wt. % PVA) and then two-step sintering (first at 1000°C and then at 1450°C). A novel ultrasonic assistant grinding device was designed by the group of Gao [57] to process nanoceramics. The data and AFM picture (Figure 2) revealed the critical ductile depth of cut is deeper compared to whether common grinding or traditional ZrO$_2$ engineering ceramics.

3.2 Application of nano-ZrO$_2$ as dental implants

It is known that dental implants manufactured by titanium (Ti) and its alloys has gradually become the routine treatment for tooth defect or missing. With their excellent mechanical strength and biocompatibility, Ti implants are considered as the suitable substitutes for natural teeth. The dense oxide film on the surface of Ti can form a chemical combination with bone tissue [58–60], however, this level of osseointegration is not able to meet the requirements of the stresses [61, 62]. The close contact between the implants material and alveolar bone tissue means that implant surface modification like roughness and surface treatment play a role in the process of bone regeneration [63, 64]. Therefore, nano-ZrO$_2$ can be served as the promising implants or coating material for better integration.

Considerable research efforts have been devoted to that ZrO$_2$ implants present the similar or even superior osseointegration than Ti implants. ZrO$_2$ is particularly attractive as dental implants or coatings due to the highly chemical stability, biocompatibility, suitable fracture resistance and flexural strength compared with alveolar bone [65, 66]. Fabrication of ZrO$_2$ basement including acid etching [67, 68], plasma spraying [69, 70] and deposition of bioactive layer [71–73] can further increase surface hydrophilic properties. An example of the application of nano-technology treatment of ZrO$_2$ implants is reported by the group of Lee [74]. The authors used micro-structured ZrO$_2$ implants (ZiUnitet™) as substrate and chemical deposited method was applied. ZiUnitet™ were immersed firstly into the phosphorous-rich solution then calcium-rich solution to form the nano coating with a Ca/P ratio of 1.67. Nevertheless, 3-6 weeks in vivo healing study proved there was no significantly difference between the groups, given that it is hard to gain improvement on the base of commercial implants with high level of osseointegration. Another group have used the creative selective infiltration-
etching (SIE) technique to build a highly retentive nanoporous surface beyond ZrO$_2$ basement material. 4-6 weeks in vivo research showed that SIE group had significantly higher bone-implant contact and bone density compared to Ti and control ZrO$_2$ implant group [68].

Electrochemical deposition is also a common used method for the preparation of metal oxide nano-structured arrays [75]. Researchers have prepared a composite layer consisting of nano-ZrO$_2$/hydroxyapatite coating on the surface of Ti allay through the electrochemical method [76, 77]. The tensile test showed the combined strength between uniformly nano-ZrO$_2$/hydroxyapatite coating and titanium basement was 16.3 MPa, owing to the homogeneously distributed nano-ZrO$_2$ were served as buffer layer connecting the mismatching thermal expansion coefficient of HA and Ti alloys.

3.3 Application of nano-ZrO$_2$ as bone tissue engineering scaffolds

Tissue engineering usually combines seed cells, engineering methods, biomaterial scaffolds and physical and chemical factors to restore, maintain, or improve function of organ. And bone tissue engineering method is recognized as the ideal approach to rebuild the bone defects [78, 79]. Biomaterial scaffolds need good mechanical strength to meet the requirement stressed zone. Besides, these scaffolds are required to have certain osteoinductivity and cytocompatibility properties, as well as the interconnection structure to support the growth of osteoblasts, vessels and new bone [80–84].

Researchers have fabricated porous nano-ZrO$_2$ scaffolds through replication technique [85]. A coating polyurethane foam was employed as the template. Then a process of coating-drying-sintering was taken. The prepare scaffolds presented a nano-porous structure with good interconnectivity (Figure 3). ZrO$_2$ ceramic nanoparticles can be an excellent filling material in composite scaffold for the satisfying cytocompatibility and high strength. Gaihre and collaborators functionalized chitosan scaffolds by adding nano-ZrO$_2$ nanopowders [86]. They have found that the additional nano-ZrO$_2$ can significantly enhance the compressive strength and modulus of original porous chitosan, simultaneously the pre-osteoblasts (OB-6) showed higher proliferation on the chitosan scaffolds filled with nano-ZrO$_2$.

Bioactive factors are also the common way to increasing bone regeneration ability of biomaterial scaffolds. MicroRNAs (miRNA) are small non-coding RNAs, which play a role in RNA silencing and post-transcriptional up or down regulation of gene expression. The group of Bala-gangadharan have synthesized and characterized nano-ZrO$_2$/chitosan scaffolds along with miR-590-5p [24], a miRNA that can enhance Runx2 expression, which is a vital signal pathway in osteogenic differentiation of cells. In vitro osteogenic differentiation experiment showed that ALP activity and calcium deposition had significantly increased in miR-590-5p group. Thus, the presence of nano-ZrO$_2$ enhanced the strength of the scaffolds so that they can be used in load-bearing bone defect area.

3.4 Application of nano-ZrO$_2$ as radiopacifying agent

Root canal therapy is considered as the preferred method for treating pulpal and periapical diseases. It should be pointed out that root canal obturation determine whether the success of therapy. Within the process, X-ray film is the primary path to evaluate the root canal obturation. And thus the desired root filling material needs good radiopac-
The effect of different addition levels of ZrO₂ing material, like Bismuth oxide, Niobium oxide and ZrO₂, as good candidates as the radiopacifiers in cement-base filling material, like MTA and PC material, simultaneously, their radiopacity reached the minimum standards by ISO/ADA of 3.0 mmAl. These two researches have supported nano-ZrO₂ as proper alternative radiopacifier.

3.5 Application of nano-ZrO₂ denture base material

The desired denture repair requires accurate tissue fitting, easy to make, matching the natural color, satisfying fracture strength and aging resistance. Denture base is the important branch of removable partial dentures and complete denture. It covers on the alveolar ridge and hard palate, providing the attachment for artificial teeth. According to the curing methods, denture base resins can be classified into the following three categories: heat-curing resin, self-curing resin, light-curing resin. Among these denture base resins, polymethyl methacrylate (PMMA) is the major constituent. Although PMMA can meet the most demand of the denture repair, the lack of flexural strength and impact strength limit its service life when it occurs to masticating accidents or suddenly drops [91–93].

The incorporation of ZrO₂ nanopowders into PMMA has been put forward in order to improve the performance. The effect of different addition levels of ZrO₂ nanopowders on the repair strength of PMMA has been investigated by group of Mohammed and colleagues [28]. Prior to prepare ZrO₂/PMMA nanocomposite, a silanization process of nano-ZrO₂ particles was taken to active reaction area on the surface so that there will be more firm adhesion between nano-ZrO₂ and the resin [94]. Different quantity of silanized nano-ZrO₂ was added into autopolymerized acrylic polymer powder to obtain the final concentration of 2.5 wt%, 5 wt%, and 7.5 wt%. The results displayed that the addition of nano-ZrO₂ increased flexural strength of resin material with great significance. The highest value of flexural strength was shown in 7.5 wt% nano-ZrO₂ group. This may be related with that well-distributed nano-ZrO₂ filled the minute space inside the repair resin matrix, arresting the tiny crack propagation [95]. On the contrary, impact strength test implied that 2.5 wt% nano-ZrO₂ group provided the maximum impact strength, whereas the 5 wt%, and 7.5 wt% nano-ZrO₂ group lowered the resin impact strength. The results was similar to Asopa’ s group [96]. This may be due to self-aggregation of high level ZrO₂ nanoparticles, causing cluster structure formation.

Another group has explored the transverse strength of autopolymerized acrylic resin reinforced with nano-ZrO₂ [97]. Their experiment has demonstrated that nano-ZrO₂ reinforcing denture repair resin can significantly enhance the transverse strength. They thought it was owing to favourable distribution of nano-ZrO₂ that allowed the nanoparticles fill into the space within polymeric chains. In this case, the interfacial shear strength was increased. Nevertheless, further studies need to be investigated to know how nano-ZrO₂ affect the denture resin mechanical properties and what section the best concentration locates.

4 Conclusion and prospective

With the excellent performance, ZrO₂ has gradually become one of the widest used ceramic material in the fields of oral prosthodontics. The nano scale of ZrO₂, including reinforcing fillings, nano-porous coating, noncrystalline powders, provide more opportunity in different application solutions. In this review, we focus on various synthesis method of nano-ZrO₂ and recent progress dental field using nano-ZrO₂ and related nano-composite. The outstanding properties of nano-ZrO₂ such as natural color, high toughness and strength, steady chemical properties, good corrosion resistance determine the wide application prospect.

As clearly highlighted in the paper, nano-ZrO₂ can be employed in dental ceramics, implants, radiopacifying agents, denture basement and tissue engineering. Nearly all the showed works have displayed the characteristics improvement following adding nano-ZrO₂. Besides, nano-ZrO₂ exhibits the superior biocompatibility. Nevertheless, greater depth investigation about the interaction between nano-ZrO₂ and stem cells need to be explored, and more in vivo animal experiments are deserved to be carried out. Overall, the role of nano-ZrO₂ in dental field is essential. With more reliable trials, more of it will be seen.
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