Bioceramics in ophthalmology

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† Dedicated to the memory of Prof. Giuseppe Heer, Emeritus Head of the Ophthalmology Ward at the "Maria Vittoria" Hospital (Turin, Italy), who passed away in November 2013 after spending his life for ophthalmology.

Abstract

The benefits of ceramics in biomedical applications have been universally appreciated as they exhibit an extraordinarily broad set of physico-chemical, mechanical and biological properties which can be properly tailored by acting on their composition, porosity and surface texture to increase their versatility and suitability for targeted healthcare applications. The use of bioceramics was traditionally addressed to the repair of hard tissues, such as bone and teeth, mainly due to their suitable strength for load-bearing applications, wear resistance (especially alumina, zirconia and composites thereof) and, in some cases, bone-bonding ability (calcium orthophosphates and bioactive glasses). Bioceramics have been also applied in other medical areas, like ophthalmic

surgery; although their use in such a context has been scientifically documented since the late 1700s, the potential and importance of ceramic ocular implants seem to be still underestimated and an exhaustive, critical assessment is currently lacking in the relevant literature. The present review aims to fill this gap giving a comprehensive picture of the ceramic-based materials and implants that are currently used in ophthalmology and pointing out the strengths and weaknesses of the existing devices. A prospect for future research is also provided, highlighting the potential of new, smart bioceramics able to carry specific added values which could have a significant impact for the treatment of ocular diseases.

Keywords: Hydroxyapatite; Bioactive glass; Alumina; Ceramic-based composites; Biocompatibility.

1. Introduction

Bioceramics are a special subset of fully-, partially- or non-crystalline ceramic materials that are specially designed for the repair and reconstruction of diseased or damaged parts of the body. As reported by Dorozhkin in a very comprehensive historical picture [1], the first known bioceramic material was plaster of Paris (calcium sulphate): ancient literature dating back to around 1000 AD notes that calcium sulphate was useful for setting broken bones in *ex vivo* applications and, by the end of the 19th century, orthopaedic surgeons began to use it as a bone filler *in vivo*.

The applications of bioceramics in the medical field have been mainly related to the repair of hard tissues, like bone and teeth, and over the years tens of compositions have been investigated and clinically tested for this purpose. Until the invention of 45S5 Bioglass® by Hench and co-workers in the early 1970s [2], calcium orthophosphates have been considered the ideal materials for bone substitution due to their chemical and crystallographic similarity to the mineral phase of mammalian bones [3]. Bioactive glasses (BGs) and glass-ceramics (BGCs) can bond tightly to bone

creating a stable interface and stimulate new bone formation while dissolving over time [4,5]. Bioinert ceramics, such as alumina, zirconia and composites thereof, are very suitable materials for joint prostheses due to their excellent anti-wear and anti-friction properties [6]. Hydroxyapatite (HA) dense or porous coatings on metal prosthetic components in direct contact with bone (e.g. femur stem) have been also experimented to improve the implant osteointegration [7]; very recently, BGC trabecular coatings on alumina and alumina/zirconia composites have been proposed as the latest evolution of such a strategy [8,9]. Other applications of bioceramics in orthopaedics and dentistry include restoration of bone loss resulting from periodontal disease in infrabony defects, dental porcelain crowns, maxillofacial reconstruction, spinal surgery and bone repair after tumour surgery. All the above-mentioned modes of use were extensively described in valuable reviews compiled by different leading scientists over the two last decades [6,10-13]. Some other authors reported comprehensive pictures focusing on specific classes of bioceramics, like calcium orthophosphates [1,3,14] and BGs [2,4,5], or highlighting their suitability to fabricate bone tissue engineering scaffolds [15,16]. Recent comprehensive overviews addressed particular themes of research, like ceramics for joint prostheses [17], controlled drug delivery [18] and the biological effects of ion dissolution products on cells and tissues [19,20].

After this premise, the use of bioceramics in ophthalmology might seem an unusual, even "exotic" application, since the eye comprises a variety of soft, delicate and often optically transparent tissues that are apparently unmatchable with rigid, stiff and usually opaque bioceramics; in this regard, natural or synthetic polymers, in form of injectable gels or mouldable, flexible products, appear much more appropriate and are actually more commonly adopted in this medical area [21-24]. Reviewing the existing literature, however, we can find clearly-documented evidences of the use of ceramics in ocular surgery dating back to the late 1700s [25] and, since then, they have been experimented and successfully applied in these three fields: (i) oculoplastic surgery for orbital floor repair, (ii) orbital implants and ocular prosthesis for anophthalmic patients and (iii) keratoprotheses (artificial cornea). Some reviews dealing with the various biomaterials used in each of these areas

appeared in recent years [26-30], but major emphasis was given to polymeric substances and devices, thereby confining bioceramics to an apparently marginal role. Little space was dedicated to ocular ceramics even in the major overviews specifically concerning the clinical applications of bioceramics: to the best of the authors' knowledge, only alumina for keratoprostheses and HA/polyethylene (PE) composites for orbital floor repair were cited by Hench in his fundamental publications [10,11,31], and Wilson et al. [32] and Arcos and Vallet-Regi just mentioned the use of curved glass plates for restoring the eye orbit floor [18].

In this work, for the first time the current applications of ceramic-based biomaterials and implants in ophthalmology are systematically and exhaustively reviewed; new research directions are also explored and discussed, highlighting the promises for the future in the light of the recent findings in tissue engineering and bioactive ceramic science.

2. Clinical background and fields of application

This section provides an essential medical overview that can be useful to non-specialist readers for better understanding the key characteristics, advantages and limitations of bioceramic implants used in ocular surgery. Osteoconductive porous bioceramics (e.g. HA) are used by oculoplastic surgeons as implants for orbital floor repair, which is a clinical field bridging ocular surgery and maxillofacial reconstruction. External, traumatic impacts to midface, such as blunt injuries, can lead to orbital blowout fractures in the inferior or medial orbital wall as a result of the abrupt increase in intraorbital pressure [33]. A fracture in the orbital floor commonly causes herniation of the orbital fat and other orbital content into the maxillary sinus located underneath (Fig. 1); the orbital floor is highly vulnerable to fracture because of the remarkable thinness of the roof of the maxillary sinuses (below 0.50 mm). Timing of repair, modality of surgical intervention and type of implanted materials used for bone grafting are all critical issues that strongly affect the overall outcomes of orbital floor fracture treatment [34,35]. Basically, the scope of the implant is to act as a bone graft

ensuring structural support at the bone defect site (fracture); the implanted material is often designed as a porous scaffold to promote bone in-growth and a safe anchorage to surrounding host tissues.

HA and alumina in a porous form are the most commonly used materials for producing orbital implants (Fig. 2), that are placed in the patient's anophthalmic socket at the time of evisceration[1] or enucleation[2] in order to allow adequate volume replacement and transmit good motility to the ocular prosthesis [36,37]. Surgical implantation can be facilitated by wrapping[3] the implant within a foil of a smooth material, which is particularly recommended for the implants, like those made of HA, characterized by an irregular, rough surface. The motility of the aesthetic ocular prosthesis can be improved by placing a peg in the front of the orbital implant in order to guide the prosthesis movement in accordance to that of the orbital implant (Fig. 2). Infections following implant exposure[4] are more amenable to treatment in porous implants with respect to non-porous ones (e.g. silicone or poly(methyl methacrylate) PMMA solid sphere), as vascular in-growth helps to anchor the implant and permits immune surveillance.

Another application of bioceramics in ocular surgery is related to the fabrication of keratoprostheses, which are implanted in the eye to replace the central area of an opacified cornea in patients who are unresponsive to donor corneal transplant. From a general viewpoint, the keratoprosthesis typically comprises a transparent part (made of glass or quartz in the early designs and, more recently, PMMA), which is capable of transmitting light from the exterior of the eye to the retina [26], and a supporting "skirt" around the optical core which keeps the keratoprosthesis

[1] Evisceration involves the removal of the contents of an eyeball, with the sclera and muscle attachments left intact; this procedure is necessary in case of ocular tumour.

[2] Enucleation involves the removal of the globe from the orbital socket, together with the scleral envelope and a portion of the optic nerve, while the conjunctiva, Tenon's capsule and extraocular muscles are usually spared; this procedure is necessary if cancer cells spread to the sclera.

[3] Preoperative strategy involving the wrapping of an orbital implant within a foil of a smooth material with the aim of facilitating its placement within the soft tissues of the eye socket, diminishing tissue drag and helping precise fixation of the rectus muscles to the implant surface. Wrapping is particularly recommended for porous orbital implants in order to provide a physical barrier over their slightly irregular porous surface. Suitable wrapping materials include scleral autografts and allografts, bovine pericardium and synthetic polymer foils.

[4] Break in the conjunctiva overlying the orbital implant, which in serious cases may lead to extrusion of the entire implant. Poor surgical technique, excessively large implant size and implant infection may all contribute to this postoperative complication.

anchored within the cornea. The advantage of using a porous skirt material is that it allows stromal keratocytes to penetrate, proliferate and synthesize connective tissue proteins inside the skirt structure in order to create a natural, strong anchorage between synthetic material and host tissue. With the aim to enhance the bond between keratoprosthesis and surrounding tissues through the promotion of better cell adhesion, Strampelli pioneered the use of the osteo-odonto-keratoprosthesis (OOKP) (Fig. 3), wherein one of the patient's own teeth and part of the jaw bone are used to form a biocompatible skirt around the PMMA core [38,39]. A relatively good, long-term clinical outcome can be achieved with the OOKP; however, disadvantages include the complexity and duration of OOKP surgery and the need for sacrificing the patient's own tissues. Moreover, local inflammation can decrease the pH of the tissue and cause the degradation of tooth and bone, thereby leading to loosening and final loss of the OOKP. In this regard, porous bioceramics and especially BGs, being able to bond also to soft tissues, are very promising options for novel types of OOKPs.

Ocular bioceramics in common use, currently abandoned or recently experimented are collected in Table 1, wherein the specific applications and essential characteristics of the related devices are also summarized for the reader's benefit.

3. Calcium orthophosphates

According to the available literature, calcium orthophosphates (CaPs) were first used in the biomedical field around 1870 by Cravens, who applied a soluble lactic acid/CaP powder composite paste with low viscosity onto the exposed pulp tissue of teeth in the attempt of mimicking natural dentine and keeping the pulp vital. Since then, the main driving force behind the use of CaPs as materials for bone and dental substitution has been their chemical similarity to the mineral component of mammalian bones and teeth [40]: as a result, they are biocompatible, not recognized as foreign materials in the body and, most importantly, can integrate into living bone tissue (osteointegration). Hence, CaPs have been successfully applied as bone grafting materials for the

repair of orbital floor fractures – which would seem the most intuitive, "natural" application; in addition, HA has been also shown suitable for manufacturing porous orbital implants and the porous skirt of experimental keratoprostheses.

3.1. Ivory

Natural ivory, which is commonly associated to the elephant's tusks, is a biocomposite constituted by nano-sized HA-like crystals (about 70 wt.%) and organic matter (a complex network of type I collagen fibres) that is eliminated after the death of the animal [41]. The use of ivory to manufacture spherical orbital implants was cited by Spaeth in the 1940s [42], but since then no other application of such type of biological apatite has been reported in the ophthalmic field.

3.2. Porous HA

3.2.1. Bone-derived HA

In order to overcome the drawbacks associated to glass orbital implants (commonly known as "glass eyes", that are described in the section 4.1), i.e. high brittleness and risk of implosion, at the end of the 19th century Schmidt experimented the mineral matrix of bovine cancellous bone to pioneer the development of porous orbital implants [43]. This early orbital implant was prepared by thermally treating spheres of cancellous bone to destroy all organic matter, leaving only the CaP mineral framework [44] that was predominantly constituted by ultramicroscopic crystals of HA with small amounts of calcium carbonate and calcium citrate [45,46]. The use of Schmidt's bone-derived HA porous spheres was reported until 1930 [47] and the evolution of such an implant, the so-called Guist's sphere constituted by calcined bovine bone [48,49], was recommended by Spaeth as "the most satisfactory of all orbital implants" before the Second World War (WWII) [42].

Since the late 1940s, Guist's porous spheres were progressively replaced by cheaper, biologically-inert solid polymeric spheres (silicone, PMMA) until they were resurrected at the beginning of 1970s by Molteno and co-workers, who reviewed the existing literature on orbital implants and noted that the early HA implants had given good results due to frequent healing of postoperative small exposures [42]. This behavior suggested that the biodegradable nano-crystalline HA matrix of bone would constitute a superior orbital implant since, once organized by host connective tissue, it would not migrate[5] through the tissues while any small exposures would heal spontaneously; furthermore, the host connective tissue incorporating the bone mineral implant would be likely persist unchanged for the patient's whole life. The early trials of this type of implant (Molteno M-Sphere), made of HA from deproteinized (antigen-free) bone of calf fibulae, confirmed that the mineral matrix of cancellous bone was readily incorporated into the tissues and that small exposures were followed by spontaneous crumbling of the exposed bone with healing of the overlying conjunctiva [50,51]. In the early 1990s, other 52 successful cases with up to a 10-year follow-up were reported [52], and ten years later Suter et al. [53] described the long-term good outcomes of the M-Sphere inserted in 120 patients after enucleation between 1977 and 2000. However, bone-derived HA implants are more expensive and less mechanically strong (due to high porosity, see Table 2) than the analogous devices made of HA from other sources, and they may be unable to support a peg to improve the motility of the ocular prosthesis [54,55]; therefore, their diffusion has been and still is quite limited.

3.2.2. Coralline HA

Sea coral HA has been employed to produce bone grafts for orbital floor repair and porous orbital implants for evisceration/enucleation surgery. In 2003 Elmazar et al. [56] compared the efficacy of coralline HA porous implants (mean pore size 400 μm) with that of autologous bone grafts and

[5] The term "migration" describes any unwanted postoperative change in position of the implant.

expanded poly(tetrafluoroethylene) (ePTFE, commercially known as Gore-Tex) for the repair of surgically-induced orbital floor fractures in cats. ePTFE was more easily shapable and contourable than HA, whose major drawback was high brittleness involving difficult implantation and loss of integrity postoperatively. Three years later, Nam et al. [57] reported the currently-available most comprehensive study about the postoperative outcomes associated to the use of coral-derived HA (Biocoral®) orbital floor grafts in human patients (191 cases); a comparison with a group of 214 patients receiving porous PE (Medpor®) implants (214 cases) was also provided. Postoperative enophthalmos[6] was statistically more frequent in HA-treated patients with respect to those receiving porous PE, but no other significant differences in postoperative outcomes between the two groups were found.

In the field of anophthalmic surgery, the use of a coralline porous HA sphere (Bio-Eye®) as an orbital implant was introduced by Perry in the mid 1980s [58] and today it is the most frequently used device after primary enucleation [59]. The interconnected porous structure of coralline HA allows host fibrovascular in-growth (Fig. 4a), which potentially reduces the risk of migration, extrusion[7] and infection discouraging bacterial colonization of the implant surface [60]. The frontal region of Bio-Eye® may be also drilled after some months from surgery to place a peg (Fig. 2), that can be subsequently coupled to the posterior surface of the ocular prosthesis to impart a life-like motility to the artificial eye. The use of porous HA implants in children has been alternatively advocated and castigated as implant exchange should be necessary later since the patient is growing, but its removal is difficult due to fibrovascularization [61,62]; at present, non-porous polymeric implants (e.g. solid silicone and PMMA spheres) remain the preferred choice by surgeons for pediatric population [63]. Coralline HA orbital implants suffer from an unavoidable drawback: due to the brittle nature of HA, direct suturing of the extraocular muscles to the implant

[6] Recession of the ocular globe or orbital implant within the orbit; it may be acquired as a result of trauma (e.g. blow-out fracture of the orbit) or related to postoperative complications of oculo-orbital surgery.

[7] "Extrusion" is the universally accepted surgical term describing the expulsion or spontaneous removal of an ocular implant from the host tissue and will be used throughout this article without any connotation of its meaning in polymer technology.

is precluded [64,65]. Therefore, Bio-Eye® need to be placed within a foil of wrapping material on which the muscles can be attached before introduction into the orbit [66-68]; recently, polymer-coated HA orbital implants have been marketed for this purpose. Moreover, there are convincing evidences that the rough surface of Bio-Eye® contributes to the development of late exposure due to the abrasion of the relatively thin conjunctiva and Tenon's capsule as the implant moves; thus, wrapping is recommended in case of both enucleation and evisceration.

In general, coralline HA is associated to two disadvantages. The first problem is ecological, as the manufacture of such implants involves damage to sea life ecosystems due to the harvesting of natural corals; the second issue is related to the high cost compared to other options (e.g. porous PE plates for orbital floor repair, solid silicone or PMMA sphere or porous PE sphere for enucleation surgery; see Table 2). Mainly in order to reduce the cost of the device, synthetic HA has been proposed as a less expensive material for orbital bone reconstruction and eye socket volume replacement.

3.2.3. Synthetic HA

Powders of *ad-hoc* chemically-synthesized or commercially-available artificial HA were employed to produce 3-D porous implants for orbital floor repair by advanced manufacturing techniques [69-71]. Custom-made HA scaffolds were fabricated through the computer-aided design/computer-aided manufacturing (CAD-CAM) approach using the data obtained through CT as a 3-D virtual template with high anatomic accuracy. Simon et al. [72] reported the direct-write assembly of 3-D periodic scaffolds composed of microporous HA rods arrayed to produce macropores that are size-matched to trabecular bone (Fig. 4b), and highlighted the potential suitability of the produced structures for craniofacial and orbital bone reconstruction. In principle, rapid-prototyped synthetic HA scaffolds represent a good alternative to autologous grafts and polymeric materials in orbital floor surgery but, like in the case of coralline HA [56], problems related to brittleness

(intraoperative difficulty of implantation, postoperative loss of structural and mechanical integrity) are still an issue.

In the field of anophthalmic surgery, synthetic HA orbital implants (FCI3) have been introduced in the clinical practice in the mid 1990s [73]. The chemical composition of such implants is analogous to that of Bio-Eye® and central implant fibrovascularization in a rabbit model appeared to occur in both types without significant differences [74]. However, scanning electron microscopy (SEM) investigations revealed some architectural differences, including lower overall porosity (Table 2), decreased pore uniformity and interconnectivity, presence of blind pouches and closed pores in FCI3 implants with respect to Bio-Eye® [75]. FCI3 implant has gained increasing popularity over the past 10 years especially as it is significantly less expensive than the Bio-Eye® (Table 2) and easier to drill for peg placement due to a lower brittleness. As far as pegging and wrapping procedures are concerned, the same issues discussed about coralline HA porous orbital implants (section 3.2.2) also apply in the case of synthetic HA devices.

Less expensive versions of synthetic HA orbital implants have been also developed and are currently in use in some countries; however, they exhibit some drawbacks that strongly limit the economic advantages over the other available models. Some of these implants have been reported to contain CaO impurities that, after hydration in host tissues, may form $Ca(OH)_2$, which is caustic [76,77]. Other implants have higher weight, lower porosity (below 50 vol.%) and lower pore interconnectivity than Bio-Eye® and FCI3 implants, with consequent enhanced risk of implant migration and limited fibrovascularization [78]. Other types of synthetic HA orbital implants (75 vol.% porosity, pore sizes ranging from 100 to 300 μm) were also recently used by Kundu et al. [79] with apparently good outcomes, but the available studies are still too limited (25 patients, 2.5 years of follow-up) to draw definite conclusions on their long-term safety and efficacy.

Recently, synthetic HA was also suggested as a promising material to fabricate the anchoring porous skirt of experimental keratoprostheses. In 2005, Mehta et al. [80] compared adhesion, proliferation and morphology of telomerase transformed keratocytes after 4 h, 24 h and 1 week

from seeding on HA and other commercially-available reference substrates (PTFE, poly(hydroxyethyl methacrylate) and glass). Live cell counts and β1 integrin expression were significantly greater on HA surfaces compared to the other substrates at each time point, and adhesion structures were well expressed in flat, spread out keratocytes. The authors of this research group continued the investigations by carrying out corrosion tests *in vitro* on sintered HA disks immersed in artificial tear fluid solution and implanting the material in subcutaneous pockets in rabbits to evaluate the *in vivo* corrosion and inflammatory response, but at the end of their study another material (titanium oxide) was selected as more promising [81].

3.2.4. Algae-derived HA

Besides synthetic HA, a less expensive and more eco-friendly alternative to coralline HA is represented by algae-derived HA; at present, however, there is high paucity of relevant studies and only the application in orbital floor surgery has been proposed. Poeschl et al [82] evaluated new bone formation and remodelling after grafting of the maxillary sinus of 14 patients with an algae-derived HA (AlgOss-C Graft/Algipore) implant, with or without the addition of platelet-rich plasma (PRP). Both as-such and PRP-treated implants showed good efficacy for bone fracture repair, but statistical evaluation of the samples proved significantly better overall resorption of algae-derived HA and increased new bone formation when PRP was used.

3.3. Hydroxyapatite coatings

HA was also experimented as a coating material on porous orbital implants and solid polymeric or carbon substrates for keratoprostheses.

In the early 2000s, a group of Korean researchers fabricated and investigated a synthetic HA-coated porous alumina (Al_2O_3) orbital implant by the polymeric sponge replication method in order to

overcome the limitations associated to Bio-Eye®; the porous alumina skeleton acted as a load-bearing structure, whereas the 20-µm thick HA coating layer was advocated to provide enhanced biocompatibility and long-term stability in the eye [83]. Seong et al. [84] evaluated the morphologic changes of 12-mm sized HA-coated alumina orbital implants with different pore sizes (300, 500 and 800 µm) after implantation in 18 eviscerated rabbits. Fibrovascularization was noted at the implant periphery in all groups after 2 postoperative weeks and also at the center of the implant after 4 weeks; it was predominant in the group of implants having 500-µm pores compared to the other two groups. In 2002 Jordan's research group reported a comparative study on the implantation of experimental alumina implants coated with HA or calcium metaphosphate in rabbits [85]. Both types of implant had multiple interconnected pores and, in comparison to the uncoated one, the coatings increased the size of the trabeculae from 150 to 300 µm; therefore, the pores appeared smaller but still ranged within 300-750 µm. There was no clinical difference in the anophthalmic socket response between coated or uncoated implants, and histopathological investigations showed that fibrovascularization occurred uniformly throughout each implant after 4, 8 and 12 postoperative weeks. Few years later Chung et al. [86] investigated the fibrovascular in-growth and fibrovascular tissue maturation of HA-coated porous alumina implants in comparison with porous HA sphere in enucleated rabbits over a 24-month follow-up and did not find significant differences between the two groups. To the best of the authors' knowledge, no other studies about HA-coated implants have been reported in the literature. Although these implants showed similar appearance of fibrovascularization and low cost compared to the coralline HA implants (Bio-eye®), probably the absence of a clear advantage from a clinical viewpoint (HA coatings did not seem to facilitate or inhibit fibrovascular in-growth) and the presence of significant amounts of CaO as a contaminant (related to the coating manufacturing) [85] discouraged researchers from further proceeding towards this direction of research.

In the field of artificial cornea, an interesting study was reported in 2003 by Sandeman et al. [87], who considered the use of HA-coated porous carbon matrices as synthetic dental laminate

substitutes in the OOKP design. HA coating, produced by sonoelectrochemical deposition, significantly increased keratocyte adhesion to the carbon mesh and did not induce excessive cytokine production by the adherent keratocytes. In addition, the porous matrices themselves adsorbed significant levels of the cytokine IL-8, thereby contributing to suppress inflammation. In 2011 Wang et al. [88] investigated whether HA coating on model substrates of PMMA (the major component of the widely-used "Boston keratoprothesis") can improve the prosthesis biointegration. The authors tested three different approaches to form HA films on PMMA disks (Fig. 4c): in the first group, PMMA substrates were immersed in 5 M NaOH solution at room temperature for 10 minutes before they were placed into a modified simulated body fluid (m-SBF) solution based on the Kokubo formulation [89]; in the second group, the polymeric disks were soaked in a dilute aqueous solution of dopamine (2 mg ml^{-1} dopamine in 10 mM Tris buffer, pH 8.5) overnight before they were placed in the m-SBF solution; in the third group, the PMMA disks were immersed in dopamine solution overnight, followed by immersion in 11-mercaptoundecanoic acid (11-MUA) solution (50 μM in sodium phosphate buffer, pH 7.8) for 4 hours before they were placed in the m-SBF solution. All samples were incubated in m-SBF at 37 °C for 14 days and the solution was replenished every 24 h; after 2 weeks, the disks were taken back, washed in 100 ml deionized water and dried. Compositional analysis showed that the Ca/P molar ratios were close to that of stoichiometric HA (1.67) in all cases, but the 11-MUA group had the most uniform coating. Cylinders of HA-coated PMMA were implanted in porcine corneas *ex vivo* for 2 weeks for mechanical testing and the inflammatory reaction to HA-coated coated disks was assessed in the rabbit cornea *in vivo*. The HA coating caused an enhancement of keratocyte proliferation compared with unmodified PMMA surfaces; furthermore, the bioceramic coating significantly increased the force and work required to pull PMMA cylinders out of porcine corneas *ex vivo* and reduced the inflammatory response around the implants *in vivo*. These results are encouraging and demonstrate the potential of HA-coated surfaces for use in keratoprostheses.

In another recent study, Fang et al. [90] evaluated the biocompatibility of HA-coated titanium corneal implants in rats and reported that the devices remained stable in the host corneal tissue over a 28-day follow-up period, induced corneal neovascularization and stimulated inflammatory cells and keratocytes to synthesize or activate matrix metalloproteinases.

3.4. Biphasic calcium phosphate (β-tricalcium phosphate/HA)

The general features and biomedical applications of biphasic, triphasic and multiphasic calcium phosphates have been recently reviewed by Dorozhkin [91]. In the field of oculoplastic surgery, we have found just one report by Reyes et al. [92], who fabricated porous biphasic β-tricalcium phosphate (β-TCP)/HA plates (weight ratio β-TCP/HA = 77 : 23) (Fig. 4d) and implanted them in cats as orbital floor facture grafts. These scaffolds were highly biocompatible and did not elicit any kind of adverse postoperative complications; furthermore, their porous network (mean pores size ~198 μm) allowed fibrovascular tissue in-growth inside the implant, thereby increasing its stability *in situ*.

4. Glass

Glass had and currently still has a great importance in ophthalmology due to a number of attractive features, including transparency to visible light, biocompatibility and relative ease of processing; furthermore, some special glasses and glass-ceramics exhibiting the capability to stimulate cell activity and tissue regeneration *in vivo* have been recently proposed for use in ocular surgery.

4.1. Glasses with optical and aesthetic functions

Optical glasses have been used for centuries to correct visual deficiencies, like myopia or other refractive diseases, without the need for surgical operations. Besides this very common application, perhaps the most known use of glass as an ocular implant is the fabrication of artificial eyes. The first evidences of the so-called "glass eyes" date back to the end of 18th century, when Venetian glassmakers, taking inspiration from dolls' eyes, began to produce prosthetic human eyes that were fragile thin glass shells, with poor fit and little comfort [27]. In 1885 Mules first described in detail the surgical placement of a hollow glass sphere into an eviscerated globe [93]. As reviewed later by Guyton [94], in 1886 the same glass implant was placed in the Tenon's capsule of 6 patients after enucleation but the device was retained only in 1 case, and in 1887 Lang [95] implanted a hollow glass sphere in 16 enucleated patients with better results, as the implant was retained in 14 cases. It is worth underlining that orbital volume replacement by implantation of a hollow glass sphere was an important advance which led to the reduction of socket retraction, intraorbital fat redistribution and superior sulcus deformity. Since the early 1900s, glass ocular prostheses began to be coupled with an orbital implant in order to restore a better aesthetic appearance to the patient's face; the prosthesis was a glass shell placed between the closed conjunctival surface covering the orbital implant (bulbar conjunctiva) and the eyelids (palpebral conjunctiva) (see also Fig. 2). Glass eyes had to be worn with caution as they were brittle and prone to implosion with acute changes in temperature; furthermore, they became etched from exposure to body secretions (Figs. 5a and b). Also the hollow glass orbital implant underwent the risk to break *in situ* and, therefore, in 1894 Snellen modified the design of Mules implant developing the so-called "reform eye", that was a still hollow but thick glass eye with the aim of better compensating the volume loss after enucleation and reducing the sunken appearance of ocular prostheses [27,96]. Initially, the glass orbital implant had high extrusion rates (50-90%), that were progressively reduced with the improvement of surgical procedures, although still high compared to modern standards. Verrey reported an extrusion rate of 21% in 343 eyes receiving the Mules implant up to 1898, and Burch in 1944 estimated failures in less than 10% of 52 using the Snellen implant [94]. Glass ocular prostheses and orbital

implants remained the standard until WWII, when they were progressively replaced by PMMA devices [97] that definitely overcame the problems of brittleness, permitted custom fitting at a relatively low cost and allowed better motility of the prosthesis. In the last decades, use of glass spheres as orbital implants has been almost totally abandoned; occasionally, however, glass has been still used in selected cases. In the late 1980s Helms et al. [98] implanted a glass sphere (1 patient) that underwent posterior intracranial migration, and 10 years later Christmas et al. [99] used a glass implant in a single patient without reporting any complication after a 2-year follow-up.

The use of glass in the development of keratoprosthes deserves a special mention, especially for its historical importance. Pellier de Quengsy is traditionally considered as the first who proposed an artificial cornea in his comprehensive treatise of ocular surgery published in 1789 [25]: he suggested the use of a thin silver-rimmed convex glass disc as a keratoprosthesis and described in great detail the surgical instruments suitable for its insertion [100][8]. This was a fundamental contribution not only to ophthalmology but also to biomedical materials science in general: for the first time, glass was rigorously proposed as a key component of an implantable device. Pellier de Quengsy, however, was ahead of his time: there is no proof that an actual implantation of his device was ever performed and none of the ophthalmologists of the period followed his suggestion. After 60 years, Von Nussbaum manufactured and implanted in rabbits a glass keratoprosthesis, conceptually analogous to the Pellier de Quengsy's lens-like model [101]; the first prototype was too large and was extruded in less than 2 weeks but the next evolution, much smaller and with an oblong shape, was so successful in rabbits (retention for 3 years) that was implanted in human patients (retention for 7 months). It was reported by other authors [102] that in 1862, Abbate designed a keratoprosthesis consisting of a glass disk surrounded by a skirt made of two successive rings, the first of gutta-percha and the next of casein. The device was implanted in dog and cat corneas where it was maintained for 1 week before extrusion. Although both the natural polymers

[8] According to the studies by Chirila and Hicks [100], Pellier de Quengsy also suggested a porous periphery for the keratoprosthesis, thus anticipating an important strategy for the prosthesis anchorage which will be developed only several years later.

used as peripheral prosthetic materials underwent rapid degradation *in vivo*, this keratoprosthesis represents the first attempt of making a skirt around the glass optical core in order to promote a better incorporation of the prosthesis into the host cornea. In 1886, Baker [103] implanted a glass keratoprosthesis into one eye of a patient whose corneas and lids were completely destroyed by an acid splash; postoperatively, the vision was partially restored and the device was maintained in the eye for almost 2 years. Over the 20th century, the use of glass was almost abandoned due to the advent of synthetic polymers for corneal implants and the increasing attention towards donor corneal transplants; however, few researchers occasionally experimented new models of glass keratoprostheses. Sommer [104] implanted a glass keratoprosthesis in 3 human patients, whose vision was significantly improved; the prostheses were apparently well integrated with the host tissue in the immediate follow-up, but all were extruded after 1 month due to complications. In 1951, Anderson [105] described in detail the design and manufacture of a device consisted of a central convex glass disk mounted into a tantalum flange provided with anchorage lugs, but there is no evidence that this implant has ever been evaluated *in vivo*. In the 1980s, Worst and co-workers [106] developed a new model of keratoprosthesis shaped as a mushroom and consisted of a glass core mounted in a metal cylinder (platinum or Cr-Ni-Co alloy) provided with a flange, through which four stainless steel wires were passed for the fixation to the sclera. Only the platinum-glass keratoprosthesis was successful in animals and the design was then modified to assume the shape of a "champagne cork" [107]. This corneal prosthesis, known as Worst-Singh-Andel keratoprosthesis, was initially implanted in a large number of cases in India from the 1980s to the early 1990s with an apparently high rate of success [108]. However, these excellent outcomes are questionable as they refer only to the immediate postoperative follow-up and most of patients never came back for subsequent, long-term examination. This prosthesis is still used in recent years because it provides a significantly wider range of vision in comparison to other models [109], but it suffers from late problems with the tension on the stainless steel sutures that causes them to erode through the tissues leading to instability of the implant and damage to the eye.

4.2. BGs and BGCs

As first demonstrated by Hench and co-workers in the early 1970s [110], BGs exhibit the unique property of bonding to bone and stimulating new bone growth. Over the years, these materials have been extensively investigated in the form of dense implants, powders or porous scaffolds by several researchers worldwide especially for orthopaedic and dental applications [2,4,5,15,16]. Recently, the use of S53P4 glass (oxide weight composition: 53% SiO_2, 23% Na_2O, 20% CaO, 4% P_2O_5) was also reported for the repair of orbital bone fractures in a series of publications by the same research group affiliated to Turku University Hospital (Finland) [111-113]. Kinnunen et al. [111] compared the use of melt-derived S53P4 glass plates with conventional cartilage grafts for the repair of orbital floor defects after trauma in 28 patients operated from 1991 to 1995. None of 14 patients receiving the S53P4 plates showed any evidence of implant-related postoperative complications; in addition, their clinical outcomes (only 1 case of infraorbital nerve paraesthesia and 1 case of entropion[9] were registered) were better than those the cartilage group (3 cases of diplopia, 2 case of infraorbital nerve paraesthesia and 1 case of enophthalmos). Aitasalo et al. [112] reported a retrospective study of 36 patients operated from 1995 to 1999: the S53P4 glass implants did not cause a foreign body reaction in the bone or soft tissue and no infection, haemorrhage and implant displacement/extrusion were seen after 1-year follow-up; tomographic scanning qualitatively demonstrated new bone growth around the implanted BG. Peltola et al. [113] showed the results obtained after implanting S53P4 glass plates in 49 patients operated from 1998 to 2001. These authors developed a set of stainless steel templates to guide the selection of the correct glass plate so that it almost perfectly fitted the surrounding orbit bone defect margins and anatomy (Fig. 5c). After a 2-year postoperative follow-up, no signs of implant-related infection, extrusion or

[9] Folding inwards of the eyelid (usually the lower eyelid), which causes the eyelashes to constantly rub against the cornea.

displacement were assessed; furthermore, the implants did not cause any foreign body reaction and only a minor resorption was found on the margins of the glass plates; new bone formation on glass surfaces was also observed. From the data reported in this series of studies, BG plates appear to be a promising and reliable solution for orbital floor reconstruction as S53P4 glass is biocompatible, bioactive (i.e. able to stimulate new bone growth) and slowly biodegradable (thereby ensuring adequate structural support while bone regenerates); furthermore, if the glass implant size and shape are properly selected, excellent functional and aesthetic results can be achieved.

Besides the application as bone-regenerative material in orbital oculoplasty, silicate BG formulations have been also proposed for the manufacture of experimental porous orbital implants, as disclosed in a patent by Richter et al. [114]. There is a paucity of experimental reports on this topic, but the results obtained by Xu et al. [115] are encouraging. These authors implanted BGC porous orbital implants in enucleated rabbits and observed no rejection during a 6-month postoperative follow-up. Ultrasound examination revealed a venous-flow-like spectra in the implants after 3 months, and histological analysis showed that around 90% of the implant pores were filled by fibrovascular tissue after 6 months from operation. Early studies on BG/PE composite orbital implants placed in rabbit and human eyes have been recently carried out [116,117] (the relevant results are discussed in the section 8.3), but further investigations are needed to obtain more substantial conclusions. BG was also used to fill peg tracts and to permit re-pegging in porous HA orbital implants, if the initial drilled tunnel was not perpendicular and central to the implant surface, in order to have a good connection with the ocular prosthesis [118].

A special mention should be dedicated to the use of BGs and BGCs for artificial cornea. Traditionally, glass was used to fabricate the optical part of the keratoprosthesis (the transparent core); over the last three decades, however, some BG compositions began to be experimented for the fabrication of the prosthetic skirt in order to improve the integration of the device in the host tissue. As underlined by Chirila [119], the skirt materials should preferably be hydrophilic in order to encourage the penetration of biological fluids from the host tissue, as an initial step in the

biocolonization of the porous skirt. This requirement could be successfully fulfilled by BGs and BGCs, that are able to expose hydroxyl groups after contact with aqueous solutions and are characterized by a good water wettability. In the late 1970s, some glass-ceramics belonging to the group called "Ceravital" were proposed to fabricate an anchorage skirt around experimental OOKP [120-122]; however, the tendency of the materials to progressively dissolve *in vivo* caused concerns about their long-term suitability for such an application and the studies were discontinued, perhaps also due to the advent of apparently more suitable polymer-based substances, like Proplast (see the section 8.4). After a hiatus of 15 years, Krause resurrected the idea of using glass-ceramics for the keratoprosthetic skirt and studied the intracorneal biocompatibility of Bioverit® I and II in rabbits eye [123]: the materials were incorporated into the host corneal tissue almost without irritation and no toxic or immune reactions were observed. In 1996, Linnola et al. [124] investigated the suitability of an apatite/wollastonite (A/W) glass-ceramic coating to solve a specific problem related to keratoprostheses, i.e. the in-growth of corneal or conjunctival epithelium into the anterior chamber, which may lead to infections and extrusion of the prosthesis as well as to the development of retroprosthetic membrane and secondary glaucoma. The concept behind this study was that a material able to fasten the prosthesis to the corneal tissue before the epithelium grows inward could prevent many of these complications. The tested prostheses had an optic part made of transparent PMMA with a supporting flange constituted of bare or A/W glass-ceramic coated titanium (Fig. 5d); 11 keratoprostheses for each of the two series were implanted in rabbit corneas. Histological analysis showed no significant in-growth of epithelium in 83% and 73% of the analysed areas of the A/W glass-ceramic coated and bare titanium prostheses, respectively; therefore, the authors of this study suggested the use of glass-ceramic coatings as an effective strategy to hinder the corneal epithelium in-growth. In 2013, Huhtinen et al. [125] investigated two experimental silico-boro-phosphate BGs for use as an OOKP skirt substitute. The glasses were produced by melting-quenching route, crushed and sieved into the 250-315 and 315-500 μm size ranges to assess the influence of different dimensional ranges; the particles were then sintered in a graphite mould into

ring shaped structures with interconnected porosity. *In vitro* tests with keratocytes showed that none of the porous BG structures induced a cytokine driven inflammatory response and the adherent keratocytes exhibited a typical elongated, spindle shaped morphology which suggested a good adhesive potential. This preliminary investigations support the use of porous BG as a synthetic OOKP skirt, even if dissolution of the glass over time may destabilise the OOKP, indicating that a composite system with a stable backbone structure would be necessary to maintain the optical core in the correct position while the BG chemically dissolves. Future studies in an animal model are necessary to explore the systemic effects of the dissolution products from these BGs as well as the impact of ion release and pH change in the eye. An interesting *in vivo* investigation was reported by Liang et al. [126], who implanted experimental BGC disks (diameter 8 mm, thickness 0.5 mm, pore diameter 20-70 μm, porosity 37-62 vol.%) in 11 albino rabbit corneas. The implants with higher porosity (51-62 vol.%) were all extruded due to breakage (5 cases); the other major complications included corneal oedema with severe degrees of corneal neovascularization within 1 month postoperatively, opacity of the corneal lamella after 2 months and lipid deposits (4 cases). Furthermore, the implant was too hard to be cut, thus making difficult the histological examination. The chosen glass-ceramic implants were therefore judged unsuitable as peripheral keratoprosthetic materials because of excessive roughness, hardness, thickness and tendency to breakage; perhaps, an optimization of the structural design parameters (e.g. implant thickness, pore size, interconnectivity) maintaining unaltered the material formulation may lead to more satisfactory results.

5. Bioinert ceramics

5.1. Alumina

Besides the well-known applications in orthopaedics for the fabrication of femur heads/acetabular cups of hip joint prosthesis and condylar elements/tibial plates of artificial knee [17], alumina has been also used in the ophthalmic field for the production of keratoprostheses and porous orbital implants. In 1980, Polack and Heimke [127] developed an artificial cornea constituted of an alumina plate with a 3-mm central perforation to which an optical cylinder (60 dioptres of power) was threaded. Experimental studies in human patients showed that soft tissue adhered to the surface of the material, thereby preventing its extrusion and surface epithelial in-growth; furthermore, the technique of implantation was relatively easy. Around a decade later, Caldwell and Jacob-LaBarre [128] designed a keratoprosthesis that was anchored deeply into the sclera through a six-pronged skirt; after testing alumina and six polymers as possible materials for the porous skirt in rabbit eyes, these authors concluded that the most suitable substance was porous PTFE (pore size 15-90 μm) coupled with a polyurethane elastomer for the optic core. Since then, major attention was dedicated to porous polymers and, in recent years, only Tan et al. in 2011 [129] tested 10-mm thick sintered alumina disks *in vitro* for possible use in corneal surgery, using HA as a reference. The achieved results did not demonstrate a clear superiority of alumina with respect to HA: on one hand the bacterial adhesion (*Staphylococcus aureus*) on alumina surface was lower than that on HA substrates, but on the other hand the average keratocyte adhesion strength on alumina disks was lower than that on HA (for this assessment, atomic force microscope (AFM) was used in a frictional mode to monitor single-cell detachment from the substrate and the friction force between keratocytes and the substrates was quantified).

Since the late 1990s, alumina was also proposed in a porous form to fabricate orbital implants for anophthalmic surgery (Fig. 6 and Table 2); this type of device was approved by US Food and Drug Administration (FDA) in 2000 and has been marketed under the commercial name of “Bioceramic implant”. The first *in vivo* study was reported in 1998 by Morel et al. [130], who evaluated the clinical tolerance of porous alumina orbital implants in 16 eviscerated rabbits; only one infection was observed and there was no conjunctival breakdown. Fibrovascular in-growth occurred as soon

as 15 days postoperatively and was complete after 1 month. These promising results was confirmed two years later by Jordan et al. [131], who compared the performance of alumina and coralline HA orbital implants in rabbits. These authors reported that the new alumina implant was as biocompatible as HA but less expensive, and its manufacturing did not involve any damage to marine life ecosystems as may occur in the harvesting of sea coral. A more exhaustive comparison about the proliferation of orbital fibroblasts *in vitro* after exposure to Bioceramic implant was carried out by Mawn et al. [132], who assessed that cell proliferation was higher on alumina compared to coralline and synthetic HA. Furthermore, the fibroblasts growing on the Bio-Eye® and FCI3 implants had debris associated with them, whereas the alumina implant was free of these debris, which was mainly attributed to its fine crystalline microstructure (Table 2). Promising results were also published in 2002 by Akichica et al. [133], who implanted porous spheres of alumina in the eye sockets of albino rabbits: there were no signs of implant rejection or prolapse of the implanted material over a 8-week follow-up, and at the 4th postoperative week fibroblast proliferation and vascular invasion were observed, followed by tissue in-growth by the 8th week. The first outcomes of Bioceramic implant in humans (107 patients over a 3-year follow-up) were reported by Jordan et al. in 2003 [134]: postoperative problems encountered with its use were similar to those observed with coralline HA but appeared to occur rarely; furthermore, the incidence of exposure was lower and no cases of infection were registered. Alumina implant infections are generally rare [135] and, according to a clinical case series of 419 patients, the exposure rate was estimated to be 9.1% with the majority of the exposures occurring after a 3-month follow-up period [136]. Wang et al. [137] reported that exposures of Bioceramic implants occurred after long-term follow-up and were preferentially associated with evisceration, pegging and prior ocular surgeries, whereas no late side effects were found in enucleated eyes; these authors also pointed out that implant wrapping can further prevent exposure. Ramey et al. [138] compared the complication rates of HA and polyglactin-wrapped alumina implants and, interestingly, found that porous alumina devices were associated with higher exposure rates and higher overall complication rates compared

to HA implants, which seems to contradict the conclusions achieved by the majority of authors [135-137]. Recent studied also showed that postoperative exposure of alumina orbital implants can be repaired successfully (good cosmetic outcomes, good fitting with the ocular prosthesis and good recovered motility) by covering the exposed frontal region with an autologous graft [139-140], without the need for implant removal. In summary, there are convincing evidences, supported by several studies, that alumina orbital implant has more advantageous characteristics (e.g. lower tendency to extrusion due to a smoother surface, lower cost) with respect to the coralline HA porous sphere, which is traditionally considered the "gold standard" reference.

5.2. Experimentally used materials: zirconia and titanium oxide

In 2011, Tan et al. [129] compared two synthetic bioinert materials, i.e. sintered titanium oxide (TiO_2) and yttria-stabilized zirconia (YSZ) with density above 95%, with HA as a reference for possible use in corneal surgery. HA disks were produced by spark plasma sintering of HA powder at a nominal pressure of 50 MPa and sintering at 1000 °C, TiO_2 disks were fabricated by pressing the powders at a pressure of 38 MPa and sintering at 1100 °C and YSZ disks were manufactured by pressing the ZrO_2/3 mol.% Y_2O_3 powders at a pressure of 50 MPa and sintering at 1550-1600 °C. The diameters of all disks were 10 mm, and the thicknesses were 2 mm for HA and TiO_2 specimens and 2.5 mm for YSZ samples. Bacterial adhesion (*Staphyloccocus Aureus*) on the TiO_2 and YSZ surfaces were lower than that on HA substrates, and TiO_2 significantly promoted keratocyte proliferation and viability compared with HA and YSZ; furthermore, immunofluorescent imaging analyses, immunoblotting and AFM measurement revealed that TiO_2 surfaces enhanced cell spreading and adhesion compared with HA. These promising results were confirmed by an *in vivo* study in a rabbit skin implantation model carried out by the same research group [81]. Tan et al. concluded that TiO_2 appeared a very promising alternative to existing biomaterials for keratoprosthestic porous skirt because it enhanced cell functions and reduced bacterial adhesion,

which would, in turn, enhance tissue integration and reduce device failure rates during keratoprosthesis surgery. Furthermore, compared to HA, TiO_2 also exhibited superior corrosion resistance *in vitro* (in artificial tears) and *in vivo* (in a rabbit model) [81].

6. Quartz

The use of quartz in ophthalmic implants is limited to keratoprostheses; in the last decades it has completely fallen into disuse with the advent of other, more effective materials but deserves to be mentioned in this review due to its historical importance, as it was the second material proposed in this field after glass. Around 1860, Heusser implanted a quartz keratoprosthesis into the eye of a blind girl [141]: after 6 months, the prosthesis was still in place and the patient had significantly recovered her vision. Fifteen years later, Von Hippel [142,143] unsuccessfully attempted to use quartz disks set in a gold ring as a keratoprosthesis. At the end of the 19th century, Salzer developed a keratoprosthesis made of a quartz disc surrounded by a platinum ring with prongs and implanted it in 4 human patients [144]: in 3 cases the prosthesis was extruded by 1 year, but in 1 patient it lasted almost 3 years. It is interesting to mention that some years later Salzer suggested that the keratoprosthetic optical core should be made of materials lighter than glass and the prosthetic rim should be made of a material able to incorporate the host tissue [145] (he was probably unaware that the same recommendation was already done by the pioneer Pellier De Quengsy in the late 1700s [25,100]). Some occasional studies concerning quartz keratoprostheses were still reported during the WWII: as mentioned by other authors [26], in the 1940s Hess and Vogt implanted a quartz disk surrounded by a platinum ring in rabbit eyes but, although the device was maintained for 1 year in one case, they discontinued the experiments due to the advent of PMMA as a novel material for the optical core of corneal implants.

7. Carbon

Carbon is mainly known in the form of thromboresistant pyrolitic coatings for cardiovascular devices [146], but it was also the first ceramic material to be proposed for the manufacture of a peripheral porous skirt to firmly anchor the keratoprostheses to host tissue. In the mid 1980s, Kain and co-workers [147,148] first designed an artificial cornea consisted of a transparent silicone core surrounded by a porous skirt of carbon fibres that displayed a fibrous structure with contiguous filiform voids able to accommodate the large stromal fibroblasts. The early designs were not successful over a long period in rabbit corneas despite the penetration and proliferation of the host stromal tissue into the fibrous skirt; this device underwent some improvements and the latest evolution exhibited a porous skirt made of silicone rubber coated with a 200 μm thick layer of carbon fibers [149,150]. With a retention time of 2 years in rabbit eyes reported by Kain in 1993 [150], this keratoprosthesis appeared clinically promising but suffered from two main drawbacks: the surgery required for its implantation was quite complex needing a 2-step operation (the transparent optical core had to be implanted 1 month after the porous skirt and connected through an interface to the pre-implanted component) and the carbon fibers were friable [151]. After a hiatus of about 15 years, the use of porous carbon for OOKP was proposed again by Sandeman et al. [87] in combination with a HA coating, as discussed in the section 3.3. Carbon was also used to manufacture composite materials that are presented in the section 8.4.

8. Bioceramic/polymer composites

8.1. HA-containing composites

HA was used for manufacturing HA/PE composite implants that have been marketed under the commercial name of HAPEX^{TM} since more than 20 years and successfully adopted as a bone replacement material in otolaryngology (middle ear bone prostheses) [152] and orbital floor repair

(Fig. 7) [153-156]. The combination of stiff, osteoconductive but brittle HA with low-modulus, tough and bioinert PE produces a biomedical composite exhibiting attractive properties for bone substitution [155]. A detailed review of the clinical applications of HA/PE composites for bone reconstructive surgery was recently reported by Tanner [156].

In the last decade, other HA-containing innovative composites were experimentally proposed for orbital floor reconstruction, but, to the best of the author's knowledge, none of them has been definitely approved for clinical use. In 2010, Asamura et al. [157] developed a 4-layer construct produced by joining a periosteum graft to a HA/PLLA/poly(caprolactone) (PCL) sheet; in this pilot study, autologous iliac crest bone was also implanted in a control group of patients. The anatomical position and movement of the eyeball were postoperatively normal in both groups; therefore, the authors deemed the periosteum/HA/polymer composite as a promising alternative to autologous bone, thereby overcoming the problems of limited autograft availability and possible morbidity at the donor site. Patel et al. [158] incorporated HA nanoparticles (size within 20-70 nm) within cyclic acetal hydrogels to create nanocomposites that were used to repair surgically-created orbital floor defects in an animal model (rabbits). Preliminary histomorphometric results indicated that the nanocomposite material elicited a positive *in vivo* response in terms of bone growth; however, complete restoration of orbital floor defects were not achieved after 28 days of implantation.

In the field of anophthalmic socket surgery, in the early 1990s Guthoff et al. [159] developed a composite orbital implant constituted by a hemispherical anterior part made of synthetic porous HA to guarantee tissue integration joined to a posterior part that was manufactured using silicone rubber; the horizontal and vertical eye muscles were sutured cross-wise in front of the implant to ensure better stability and motility. Overall implant biocompatibility was excellent and the transmission of the motility to the ocular prosthesis was generally acceptable [160,161]. At present this implant is mainly employed in Europe, but its diffusion is limited due to the high cost and complex surgical procedures needed for its implantation compared to "standard" spherical porous implants made of HA, alumina or PE.

It is also interesting to cite few recent works dealing with the development and testing of a nano-sized HA/poly(vinyl alcohol) (PVA) composite hydrogel as an artificial cornea fringe to improve the firm fixation of the keratoprosthesis to surrounding host tissues. Xu et al. [162] reported that this composite had an interconnected porous structure, could absorb a high water content and was highly biocompatible with corneal fibroblasts *in vitro*. Fenglan et al. [163] synthesized an artificial cornea consisting in a porous nano-sized HA/PVA hydrogel skirt and a transparent PVA hydrogel optical core; the composite skirt was homogeneously porous with a high degree of pore interconnectivity, and an interpenetrating network was observed along the interface between the core and the skirt. Once implanted in rabbit corneas, this novel keratoprosthesis displayed a good biocompatibility and interlocking between porous skirt and host tissues was observed. Jiang et al. [164] fabricated an artificial cornea comprising a transparent PVA hydrogel core surrounded by a ringed PVA-matrix composite skirt, that was composed of graphite, Fe-doped nano-sized (Fe-n-HA) and PVA hydrogel. Different ratios of graphite/Fe-n-HA were used to tune the skirt colour from dark brown to light brown, which well simulated the iris colour of Oriental eyes. Morphological and mechanical examination showed that an integrated core-and-skirt artificial cornea was formed from an interpenetrating polymer network, without phase separation at the interface between the core and the skirt.

8.2. β-TCP/poly(trimethylene carbonate) composite

Van Leeuwen et al. [165] fabricated β-TCP/poly(trimethylene carbonate) (PTMC) composite sheets (thickness around 1.0 mm) through co-precipitation followed by compression moulding and suggested their suitability as materials for orbital floor repair; specifically, the effect of different amounts of the ceramic component (15 and 30 vol.%) on the properties of the composite was investigated. Lamination of the composites with minimal amounts of poly(D,L-lactic acid) (PDLLA) was also experimented, as the reconstruction of large defects might necessitate the use of

more rigid materials (the elastic modulus of PDLLA is above 2500 MPa, whereas that of PTMC is within 5-7 MPa). The flexural modulus of the composites reached 17 MPa when introducing 30 vol.% of β-TCP. A laminate of this composite incorporating a PDLLA foil (total thickness 1.0 mm) had a flexural modulus of 64 MPa. These results suggested that, from a mechanical viewpoint, these laminated composite sheets can be suitable for orbital floor reconstruction. The authors hypothesized that, after implantation *in situ*, the polymer component resorbs enzymatically without the formation of acidic compounds, while the ceramic component could induce bone formation; *in vivo* studies are currently in progress.

8.3. BG/PE orbital implants

In 2006, Choi et al. [116] analyzed the effect of BG particulate on the fibrovascular in-growth occurring in porous PE orbital implants in rabbits. Forty-eight rabbits were divided into 4 equally-sized groups, according to the different surgical techniques and implanted materials used: groups 1 and 2 were implanted with a porous PE sphere after enucleation or evisceration, respectively (reference groups), whereas groups 3 and 4 received a porous BG/PE composite implants after enucleation or evisceration, respectively. Histological examinations revealed that there was no statistically significant difference with regard to fibrovascular in-growth among the 4 groups after 1, 2, 4 and 8 weeks of postoperative follow-up. Therefore, in this preliminary study the authors concluded that inclusion of BG particulate did not significantly promote the rate of fibrovascular in-growth into porous PE orbital implants. In 2011, Ma et al. [117] reviewed the clinical outcomes of 170 human patients after placement of porous BG/PE composite orbital implants for primary enucleation or secondary implantation. The majority of patients (161 cases) experienced no complications, the implant motility was generally good and no cases of implant-related conjunctival thinning or inflammation were observed. Excessive discharge and implant postoperative exposure occurred in 2 and 7 cases, respectively (additional surgery was necessary in 8 cases). These results

suggest that the porous glass/PE composite orbital implant may be a useful implant for anophthalmic socket filling, but comparative studies are still necessary to definitely estimate their performance with respect to the commonly available and routinely used implants. Looking at the future, appropriate design of BG composition could be considered to impart angiogenetic properties to the material for enhancing the fibrovascular in-growth, as discussed in the section 11.2.

8.4. Carbon/polytetrafluoroethylene composite

In the 1970s, an inert composite material constituted of PTFE (Teflon) and vitreous carbon fibers, marketed under the commercial name of Proplast I, gained increasing interest in maxillofacial, oculoplastic and corneal surgery. This composite resembled black felt, was wettable and had pore size distribution between 100 and 500 μm. Lyall [166] used Proplast I to manufacture hemispherical orbital implants that, when placed in the eye socket, could be invaded by fibrous tissue and overcoming the problem of extrusion; no rejection was reported after a 18-month follow-up in 16 patients receiving such implants and the motility transmitted to the ocular prosthesis was generally good. Neuhaus et al. [167] tested Proplast I orbital implants in rabbits and observed a high degree of soft tissue fixation preventing implant migration; subsequent use in humans showed good results in 4 patients followed for 2 years and in 6 patients followed for 1 year, with no cases of extrusion or migration in both groups Since the 1990s, however, the popularity of Proplast I as an orbital implant has progressively declined because of long-term postoperative complications, primarily late infections, associated with its use [168].

In the field of corneal surgery, in the late 1970s Lamberts and Grandon [169] demonstrated that Proplast I disks implanted in rabbit corneas were invaded within 30 days by the host tissue and partly neovascularized without significant foreign body reaction; in this first study, no implant extrusion was observed after 70 days. A more detailed study was performed by Barber et al. [170] who also implanted Proplast I disks in rabbit corneas: in all cases, histopathological examination

provided significant evidence for fibroblastic invasion and growth into the material, as well as for neovascularization and superficial epithelialization, but when the disks were not covered by a conjunctival flap, all of them extruded within 4 weeks. Barber also reported the results about the use of a keratoprosthesis with a Proplast I skirt in cat corneas [171]: after 6 months, only 18% of the implants were extruded. In the late 1980s, White and Gona [172] designed a keratoprosthesis having a PMMA cylinder as the optical core and a Proplast I disks as the porous skirt; the joining between the two materials was achieved either by gluing them with cyanoacrylate adhesives during surgery or by screwing a pre-threaded PMMA cylinder into the trephined Proplast I disk that had been implanted 2 months in advance. This keratoprosthesis was successfully experimented in rabbits: a total invasion of stromal fibroblasts into the skirt took place within the first 4 weeks of implantation and some animals retained the prosthesis after 3 years with a clear cornea, limited vascularization and no infection. In 1993 Girard [173] reported the use of a keratoprosthesis with a Proplast I porous skirt in human patients (139 eyes) and described the early results as encouraging (vision significantly improved in 32% of the operated eyes at the time of the report). Since then, however, further investigations on the suitability of Proplast I for corneal surgery were abandoned – due to the above-mentioned problems concerning late infections of orbital implant – and at present this material appears to be no longer available for ophthalmic applications [174].

8.5. Alumina/polytetrafluoroethylene orbital implants

In 1990 Girard and co-workers [175,176] described a new design of porous enucleation implant made of Proplast II, that was different from Proplast I orbital implant in its composition (alumina/Teflon fibres composite) and in having a siliconized non-porous posterior surface to allow smoother movements, together with a porous anterior portion to facilitate fibrovascular in-growth. Proplast implant II had a nipple on its anterior surface (lined by the patient's conjunctiva) that could integrate with a depression on the posterior surface of the ocular prosthesis. Several Proplast

implants II required subsequent removal because of poor motility and, over histopathological examination, were found to be completely avascular and surrounded by a pseudocapsule [177]. Few years later, the use of Proplast II was reported with good outcomes by Shah et al. [178], who employed it to manufacture subperiosteal implants for the correction of anophthalmic enophthalmos in 34 patients having poor orbital volume replacement despite the prior insertion of an adequately-sized spherical implant within the orbital socket. To the best of the authors' knowledge, since then Proplast II was completely fallen into disuse.

9. Bioceramic-based cements

Since the early 1990s, HA and carbonated apatite are commercially available in the form of mouldable pastes, commonly termed as "bone cements", to be used in the broad field of craniofacial reconstruction [179-182]. HA cement is composed of tetracalcium phosphate and dicalcium phosphate (anhydrous); in the presence of water and at physiologic pH, the salts react isothermically to produce a dense paste that can then be shaped intraoperatively and allowed to set for 15 to 30 minutes. The reactants are then reprecipitated until the entire material is converted to microporous HA, which takes approximately 4 to 6 h *in vivo*. The setting time can be properly modulated according to specific surgical needs; for instance, it was observed that mixing the HA cement in 0.25 M sodium phosphate buffer decreased the setting time significantly [183]. Mathur et al. [184] reviewed the use of HA cements in the context of cranio-maxillofacial surgery, including orbital floor repair, and concluded that such materials are excellent choices for reconstruction in the clean field. However, the existing literature suggested that sino-nasal or oral cavity exposure – which is the case of orbital floor repair, wherein HA is exposed to the environment of the maxillary sinus – may predispose the implant to infection, and therefore the material should be used cautiously in these situations.

Looking at the future, an interesting alternative to HA cements for orbital reconstruction might be represented by the use of glass ionomer cement (GIC), that was developed in the 1970s by Wilson and Kent [185] primarily for dental purposes. The GIC inorganic phase is typically a fluoro-alumino-silicate glass powder in the 15-50 μm size range; addition of lanthanum, strontium or barium oxide additives provide radio-opacity. Favourable properties of GIC include firm binding to bare bone surfaces, setting within few minutes – which leaves enough time for manipulation – and eventual formation of a hard, bone-like substance that is water-resistant after setting [186,187]. These attractive features have generated interest in other fields of medicine like otolaryngology and, more recently, maxillofacial reconstruction. Yorgancilar et al. [188] tested the suitability of GIC in 16 New Zealand white rabbits, which were divided into two equal study (8 rabbits) and control (8 rabbits) groups. Experimental defects and fractures were created in the nasal bone, maxilla and zygoma in both groups and were reconstructed by GIC in the study group, whereas the rabbits in the control group were left to natural healing process. GIC showed a slight inflammatory and fibrous reaction in the rabbits of the study group, but no statistical difference was observed with respect to the control group. The results of this study indicated that GIC is a well-tolerated material in maxillofacial reconstruction and it would deserve further investigation in the field of orbital floor repair; at present, however, the paucity of experimental studies precludes to draw definite conclusions on its suitability and long-term performances for this specific application.

10. Discussion

After presenting, in the previous sections, an overview of the different bioceramics that have been used in ocular surgery or have been experimentally proposed in recent years, it is necessary to summarize few key concepts and to provide some highlights for materials improvement and future research directions. From a materials science viewpoint, there are a number of crucial questions to be answered: what is the effect of topography and surface chemistry of the material? How to

consider the role of porosity? Are mechanical properties an important issue in ocular implants? And, finally, how to select the most suitable ceramic material for the repair of orbital floor fractures, orbital implants, artificial cornea? Due to the plurality of factors involved, it is almost impossible to give definite responses to this complex set of questions; nonetheless, some indications can be presented. It is also worth underlining that the choice of an "optimal" ocular biomaterial/implant is deeply influenced by many "extra-material" factors, including the overall cost and economic availability of the patient, the specific characteristics of the injury/disease, the experience/opinion of the surgeon, the patient's clinical history and age.

Looking at the physical, chemical and micro-structural characteristics of ocular bioceramics, exhaustive studies on such topics are quite rare in the literature since the majority of reports focused on the *in vivo* biological compatibility and postoperative performances, giving less importance to the assessment and understanding of the basic properties of the used materials. From a general viewpoint, it is known that cell-substrate interactions can be regarded as one of the major factors ultimately determining the long-term performance of a biomaterial/implant *in situ*. The processes that mediate an altered cell response to micro- and nano-scale surface structure are still partially unclear, but it has been shown that they may be direct, as a result of the direct effect of surface topography on cells, or indirect, where surface features affect the composition, orientation or conformation of the extracellular matrix (ECM) components [189]. In general, cells establish dynamic contact points with the substrate biomaterial (points of focal adhesion), the regulation of which is highly complex and involves initial integrin binding to ECM components and the reinforcement of the adhesion plaque by further protein recruitment. Furthermore, integrins mediate bidirectional signalling between ECM and cells, thereby activating signalling pathways that regulate the activity of transcription factors, direct cell growth and promote cell differentiation. The majority of studies on the topography of biomedical materials have been carried out in the context of bone tissue engineering and some evidences demonstrated that osteoblasts preferentially adhere and spread on finely micro-rough surfaces [190,191]. In this regard, implants made of sintered HA

(commercially available) appear to be very suitable for the repair of orbital bone fractures as their micro-crystalline surface can favour colonization by bone cells; sintered BGs and BGCs, whose surface roughness could be tailored by acting, for instance, on the size of starting glass particles and/or on the sintering parameters to modulate the crystals size, would also deserve investigation in the next future.

Mawn et al. in the late 1990s [75] and more recently Choi et al. [192] investigated by SEM the microstructural and architectural features of coralline HA, synthetic HA and alumina porous orbital implants, also providing a comparison with other polymeric devices available on the marketplace. As shown in Table 2, there were marked variations of crystal size/shape and surface topography amongst the analysed orbital implants. The authors of these studies suggested that surface roughness could influence the inflammatory response after implantation and crystal size could determine the material-induced phagocytic response: in fact, bioceramics with crystal size above 2-3 μm showed greater tissue reaction in comparison to implants with finer grain (the new-generation alumina orbital implants, see Table 2), which was probably due to increased phagocytic activation by crystals of larger size. In this regard, Nagase et al. [193] also showed that smooth HA crystals have been associated with less inflammation than sharp-edged crystals.

An additional issue to be considered is the effect of micro- and nano-scale topography on bacteria, since cells may have to compete with pathogens in the ocular environment. In a fascinating scenario, the surface topography could be purposely designed to encourage cells to colonize while limiting bacterial adhesion [189], thereby reducing the risk of infection that represents one of the major causes of failure of ocular implants. The relationship between the micro- and nano-structural features and the clinical performance of ceramic ocular implants deserves accurate investigation, which could promote the development of novel design and manufacturing strategies to tailor the bioceramic surface with desired textural characteristics (e.g. customized micro- and nano-texturing of the surface depending on the involved cell type/physiological environment, optimization of the

sintering temperature and time to have the development of crystals with a specific size thus creating a customized surface roughness).

Pore size, interconnectivity and overall macro-scale architecture also influence the success of an ocular implant. These features have been shown to be key determinants of tissue in-growth into 3-D tissue engineering scaffolds [194]: a foam-like structure with a 3-D network of highly-interconnected macropores in the 300-700 μm range is ideal to stimulate bone tissue in-growth, allowing the implant colonization by bone cells and blood vessels access. Therefore, 3-D bioceramic foam-like scaffolds, like the calcium phosphate porous plates developed by Reyes et al. [92], could be more effective than dense implants in accelerating the healing of orbital bone fractures. The presence of an interconnected porous network is of utmost importance in ceramic orbital implants to promote fibrovascularization, as blood vessels access favors immune surveillance and allows treatment of infection via systemic antibiotics. Rubin et al. [195] studied the vascularization in porous HA orbital implants with various pore size and suggested that the optimal pore diameter to encourage fibrovascular tissue in-growth should be around 400 μm. As far as artificial cornea is concerned, open porosity of the peripheral skirt is essential to induce the stable anchorage of keratoprostheses to host corneal tissue [26].

Other issues deserving careful attention concern the material surface chemistry and response to biological fluids. In the context of orbital floor repair, where the implant aims at restoring the injured orbital bone, HA implants are a good choice due to the chemical and crystallographic similarity to bone mineral phase. HA does not resorb after contact with biological fluids, allows colonization by bone cells and subsequent bone tissue in-growth, and remains *in situ* permanently. A resorbable implant may be desirable but the resorption kinetics must be compatible with those of bone regeneration, otherwise problems of graft integrity and inadequate support to host tissues may occur. Addition of a soluble calcium phosphate phase (β-TCP) can be useful to tailor the resorption rate of a HA-based implant [90]. Unlike for HA, BGs react with biological fluids through a ion-exchange mechanism and eventually establish a tight bond to host bone. This process was first

described by Hench et al. about 40 years ago [110]; briefly, it involves the rapid release of soluble ionic species due to glass dissolution, ultimately leading to the formation of a hydrated silica/polycrystalline HA bilayer on the glass surface. With the initial formation of an apatitic layer, the biological mechanism of bonding to bone is believed to involve adsorption of growth factors, followed by attachment, proliferation and differentiation of osteoprogenitor cells. Osteoblasts then create ECM, which mineralizes to form a nano-crystalline mineral/collagen composite layer on the surface of the glass implant, while the degradation and conversion of the glass continues over time [196]. It is interesting to note that the nano-crystalline nature of the HA formed on BGs (globular agglomerates constituted by nano-sized needle-like crystals) closely mimics the features of the biological apatite of bones [197], whereas synthetic HA is characterized by larger grain size (Table 2). At present, only a limited number of BGs have been experimented in ophthalmology [111-118,120-126], but a lot of biocompatible compositions have been investigated in the literature, especially in the field of bone tissue engineering [4,15,16].

Considering the possible and various ophthalmic applications, it is worth pointing out an important aspect: osteogenesis stimulation and bone-bonding ability are desirable effects only for an orbital floor graft [110-112]; on the contrary, in the case of orbital implants and porous skirts for keratoprostheses, BG should induce fibrovascular in-growth [115-117] and promote anchorage to host corneal tissue [124,125], respectively. For the sake of discussion it is instructive to underline a further important point: it has been demonstrated that the intrinsic presence of an interconnected 3-D network of macropores is a sufficient condition to encourage fibrovascularization in orbital implants (like in the case of porous HA and alumina) and early studies have recently demonstrated that also bioinert ceramics (e.g. alumina and titanium oxide) are promising candidates as keratoprosthetic porous skirt materials since they allow keratocytes to grow and to proliferate; in this regard, perhaps the most valuable added value of BGs with respect to HA and bioinert ceramics is the ability to selectively release appropriate ions that can eventually induce a specific, desired response *in vivo*, like enhanced fibrovascularization or corneal cells in-growth (see also the section

11.2). BG composition can be properly designed to obtain materials with different degrees of solubility; in this regard, biocompatible phosphate glasses can offer a large versatility of dissolution kinetics [198]. The use of soluble materials as ocular implants, however, may be often inappropriate. As mentioned above, bioceramics used for orbital floor repair can be either non-resorbable (e.g. HA [56,57,69-71]) or characterized by a moderate solubility (e.g. β-TCP/HA porous composite [92] and S53P4 glass plates [111-113]) which must be compatible with bone healing rate. On the contrary, orbital implants have been always conceived as permanent devices, i.e. they must remain *in situ* indefinitely during the patient's whole life without undergoing degradation to ensure an adequate socket volume replacement. However, an interesting (and unique) exception has been disclosed in a patent deposited in the late 1990s by Durette [199], who proposed an orbital implant preferably made of biodegradable material and having a matrix with random voids throughout to enhance tissue in-growth. Indeed, the use of a partially absorbable orbital implant able to increase its porosity *in vivo*, thereby allowing an improved fibrovascularization postoperatively, represents a fascinating concept; however, this approach poses several problems which should be carefully and critically examined, especially concerning the kinetics of socket volume replacement by tissue while the implant resorbs and the ocular prosthesis motility in the partial or total absence of an orbital implant that can transfer movement to it. As to the application of bioceramics for keratoprostheses, resorption of the porous skirt around the optical core is an unwanted effect that would in turn lead to the loss of the anchorage and the failure of the implant [200]; therefore, the use of bioceramics able to maintain adequate integrity is recommended. This requirement may compete with the capability of BGs to release therapeutic ions via controlled dissolution and thus with their ability to be chemically bioactive (see also the section 11.2). In the authors' opinion, this issue will become crucial in the applied research of the next few years: BGs and BGCs are excellent biomaterials to be replaced or invaded (if porous) by regenerating tissues, but if they are used as connecting or joining elements between various

prosthetic permanent components, they must ensure indefinite and safe stability and cannot dissolve in biological fluids.

Prof. Larry L. Hench, the inventor of 45S5 Bioglass®, titled one of his recent publications "Glass and glass-ceramic technologies to transform the world" [201]; this title could not be more fortunate and we believe that BGs could indeed carry a significant contribution in the development of smart ocular biomaterials and implants, as also discussed in the section 11. BGs can be processed through a variety of methods and used to produce 3-D porous scaffolds with different size, shapes, pore architecture and mechanical properties (Fig. 8). In this regard, Table 3 collects a selection of scaffolds based on widely investigated BG formulations [202-224]; some of them (45S5 Bioglass® and 13-93) have received the definite approval by FDA for clinical use. Initially, these BG scaffolds have been all developed for bone tissue engineering and none of them have been ever proposed or investigated for ocular applications; in Table 3, the authors also suggest whether they may deserve testing for possible use in the ocular field, with the aim of providing useful stimuli for further research. Besides the above-mentioned attractive characteristics, BGs also have other two important advantages with respect to HA and alumina. i.e. they can be processed at lower sintering temperatures and have a lower density. The latter could be an important added value especially in the production of orbital implants, that would thus suffer from a lower risk of migration downward with possible ectropion[10] and incorrect replacement of orbital socket volume.

From a general viewpoint, rapid prototyping (RP) techniques can allow custom-made bioceramic scaffolds to be fabricated, as reported for oculoplastic applications in few studies [69-71]. A clever approach could involve the use of microCT- or MRI-derived files as input data for CAD/CAM manufacturing systems in order to produce scaffolds exactly matching the required anatomical dimensions. In this way, the size of porous plates for orbital floor grafting could reproduce the contour of the bone fracture, the orbital implant volume could be properly adapted to fit the individual eye socket, and the porous skirt of keratoprostheses could be tailored according to the

[10] Turning out of the eyelid (usually the lower eyelid), whose inner surface is exposed.

features of each patient's eye. In this regard, few additional considerations should be dedicated to the anchorage skirt of artificial cornea. As highlighted by Chirila et al. [26], the tissue proliferation in the peripheral prosthetic material should occur within voids of confined width but unlimited length (i.e. contiguous) that are large enough to accommodate the stromal fibroblasts. A tight interpenetration of the tissue and material should result, which was never achieved within large voids such as those offered by holes, fenestrations or meshworks. The attempts to achieve this led relatively recently to the use of porous polymers as materials for the prosthetic skirt; a promising alternative could raise from porous bioceramics fabricated by manufacturing techniques, like RP methods, that allow an accurate control over pore features, arrangement and interconnectivity. A general advantage of the availability of custom-made implants is the shortening of surgery time, as intraoperative implant shaping by the surgeon would no longer be necessary. On the other hand, to date the major disadvantage of this approach is the high cost required for customized implant manufacturing. Alternative less expensive methods to produce customized porous bioceramics could include the sponge replication method (Fig. 8a,b) and the use of polymeric additives (e.g. PE particles [213,225,226], starch [227], rice husk [228]) as thermally-removable pore-former agents. It is worth mentioning the approach proposed by Fu et al. [229], who recently treated sea coral by means of a hydrothermal process for partial conversion of carbonate to phosphate in order to obtain a coralline HA/calcium carbonate porous composite, followed by acid corrosion to increase the pore diameter to 200 μm.

A final key aspect, which has been often ignored in existing reports, is related to the mechanical properties of ocular implants. Bioceramics have a generally good mechanical compatibility with the orbital bone (see some examples in Table 3 [202-232]) but are remarkably stiffer than the ocular and intraorbital tissues [233]. From an operative viewpoint, the use of stiff materials has indeed a number of advantages: for example, the surgeon can easily handle and place the ceramic orbital implant within the orbit with a great control over its position. However, compliance mismatch between orbital implant and overlying conjunctiva/soft tissues, in combination with repetitive

movement of the implant by the extraocular muscles, might contribute to inflammation and soft tissue necrosis which eventually lead to implant exposure. A crucial question to be considered is the following: what are the most significant mechanical properties of bioceramics (and biomaterials in general, too) to be assessed in order to correctly evaluate their suitability for ocular applications? Elastic modulus is indeed a key property, but its assessment is complex to be performed for both natural tissues (see the high dispersion of data referring to cornea and sclera in Table 3) and porous bioceramics, and the obtained results are often difficult to interpret. Assessment of the elastic modulus of ceramics from the linear region of the stress-strain curve is easy to perform but often leads to an underestimation of the correct value [222]; some authors suggested ultrasonic characterization to partially solve this problem [234], but testing specimens need to have precise sizes and shape. Looking at the data in Table 3, the elastic moduli of human cornea and sclera are close to that of porous HA, but are significantly lower than those of BG scaffolds that have been experimented to date in the literature. Future research work should be addressed to understand whether this mismatch can compromise the suitability of such new potential porous implants for ocular applications, and how it is possible to tailor the elastic properties by acting on the material porosity and composition. Another important property is the tensile strength, which is very difficult to assess in the case of porous bioceramics due to the need for an *ad-hoc* developed testing equipment, as underlined in the few existing studies [205,219,220,222]. As reported in Table 3, porous SCNA has a tensile strength very close to that of cornea, which may suggest its suitability as keratoprosthetic skirt material. The paucity of literature about these topics gives further motivation to these investigations and, from a general perspective, it is apparent that future research directions should be addressed to the development and testing of more compliant biomaterials, such as bioceramic/polymer constructs. The polymeric phase might be selected in the class of biocompatible hydrogels (see the recent works by Xu et al. [162] and Fenglan et al. [163]), that have similar physico-mechanical properties to living soft tissues due to the ability of absorbing

water and have been already successfully experimented in ocular surgery as vitreous substitutes [224,235-237].

As closing remarks, few methodological considerations, which can be extended to the broad field of ocular biomaterials in general, need to be presented. The history of the development of ocular bioceramic implants has witnessed that often some key characteristics, such as mid- and long-term solubility in physiological media, mechanical properties and even biocompatibility, have not been systematically investigated or considered prior to *in vivo* testing. *In vitro* cytotoxicity testing with appropriate cells should be commonly recognized as an early eliminatory criterion in the selection of ceramics and biomaterials in general for ocular applications. Such tests are useful because they avoid unnecessary, time-consuming and expensive animal experiments. In this regard, Sandeman et al. [238] proposed a series of *in vitro* screening assays for the preliminary selection of biomaterials (polyurethanes in that specific case) for use in the fabrication of artificial corneas; these tests assessed the initial binding of inflammatory and cell adhesive proteins, activation of inflammatory proteins, adhesion of keratocytes, epithelial cells and macrophages, and the production of inflammatory cytokines by keratocytes contacting biomaterials; green fluorescent protein gene transfer was innovatively experimented to investigate cell invasion in the absence of external staining techniques. From a general viewpoint, it is of utmost importance that researchers have well clear in mind the specific application for each biomaterial, in order to develop the most suitable testing protocol for each case as well as to interpret correctly the obtained results. For instance, according to Sandeman et al. [151], central optic biomaterials should be selected on the basis of low inflammatory and cell adhesion potential, whereas peripheral skirt materials should be selected on the basis of low-inflammatory potential but good cell adhesion to anchor the implant within the host cornea.

Furthermore, a consensus should be achieved on what mechanical characteristics to assess and testing methods to apply or develop *ex novo*; some authors, for instance, suggested the use of *ex vivo* eyes for a preliminary evaluation of the mechanical compatibility between experimental

keratoprosthetic skirt and corneal tissue [88]. Standard media (e.g. artificial tear fluid [81]) for the *in vitro* assessment of material solubility and ion leaching also need to be critically and univocally selected, in order to closely mimic the conditions of the physiological environment where the ocular implant will be placed. Finally, the design of suitable and consistent *in vivo* animal studies is fundamental to obtain reliable, key results and a definite scientific consensus should be achieved for this purpose. The following example is particularly instructive: the majority of researchers have investigated the *in vivo* suitability of new keratoprosthetic materials by direct implantation in animal corneas [88,90,120,123,124], whereas Tan et al. [81] recently evaluated HA and titanium oxide for the same application in a rabbit skin implantation model. Some key issues should be therefore considered, such as the methods to correlate and interpret the results deriving from different *in vivo* studies, the selection of the most appropriate animal models and the sequence to follow in performing the experiments. Hence, taking the suggestions emerging from recent studies as a starting point, in the next future there will be the need for developing well-defined protocols and experimental approaches to select and investigate potential ocular bioceramics, which can be a significant support to the researchers working on these topics.

11. A picture for the future: ocular bioceramics with smart properties

Prof. Larry L. Hench recently stated that "creative studies of novel glasses and glass-ceramics are needed more than ever to cope with the problems of a world that has finite resources but infinite desires" [201]. The authors believe that this sentence could be rightly extended to bioceramics in general and, taking it as a leitmotiv, wish to depict few "hot" topics of prospective research related to bioceramics that could have a significant impact in ophthalmology in the next future. The outlined approaches are novel in the ocular field and an effort was made in this section to critically adapt them from the original context to the new purpose, when appropriate and suitable. The relevant, original literature is also cited to provide an adequate background to interested readers.

11.1. Drug delivery

Improvement of the biological activity and performance of biomaterials through the uptake and subsequent release of therapeutic agents is one of the most challenging research fields of biomedical sciences. In recent years, two interesting approaches based on the use of mesoporous oxide-based bioceramics, exhibiting an ordered texture of nanopores in the 2-50 nm range, have been successfully proposed (Fig. 9). The first approach (Fig. 9a) involves the fabrication of a bioceramic hierarchical porous structure wherein drug molecules are incorporated into mesoporous silica [225,236-241]. However, genotoxicity of sub-micrometric mesoporous silica spheres was observed *in vitro* (stress and damage to DNA) [242]; therefore, the fate of mesoporous ceramic particles after implantation (e.g. impact on cell genes, solubility) will be a key aspect deserving careful investigation in the next future. The second approach (Fig. 9b) involves the fabrication of a monomaterial bioactive scaffold with a multi-scale porosity by using mesoporous BGs (MBGs) [243]. Studies of drug incorporation and release from MBG membranes were also recently performed [244].

Mesoporous bioceramics hosting anti-inflammatory drugs or antibiotics could really impart a significant added value to ocular biomaterials, as intra- or postoperative infections are one of the major causes of failure for implantable ocular devices. Before implantation, porous biomaterials are usually soaked by the ophthalmic surgeons in an antibiotic solution; however, this common practice is quite rough and the antibiotic is released as a burst after contact with biological fluids *in situ*. Drug release from mesoporous ceramics will allow a more effective therapy to be performed, with a higher control on the amount of incorporated drug and the release kinetics, which both can be pre-determined as a function of the mesopores shape and size. Mesoporous ceramics can also host and then release specific drugs for cancer therapy [18], which could be useful for the treatment of orbital bone tumours: in this way, MBGs could not only promote tissue regeneration at the bone

defect site created by tumour resection but also locally release therapeutic agents that kill residual or newly formed cancer cells. Antineoplastic drugs released by mesoporus ceramics could also open novel perspectives for the treatment of intra-orbital and ocular tumours, like retinoblastoma, which is the major cause of enucleation: orbital implants comprising a mesoporous phase would allow a prolonged, targeted therapy to be performed *in situ* also in the region around the severed optic nerve to avoid the spreading of cancer cells through it.

Despite these attractive scenarios, an unavoidable drawback of MBG constructs is the high brittleness due to the presence of an intrinsic mesoporous texture, which poses serious problems for material shaping at the time of surgery and safe implantation without loss of integrity. Wu et al. [245] tried to improve the mechanical strength of foam-like MBG scaffolds by soaking them in a silk solution: silk-induced modification improved the uniformity and continuity of scaffold pore network and led to an increased strength (250 kPa in compression vs. 60 kPa of the uncoated scaffolds), while maintaining a high porosity (94 vol.% with pore size in the 200-400 μm range). RP techniques were also suggested to improve the strength of MBG constructs, with the advantage of finely tailoring the implant porosity and architecture [246,247].

11.2. Therapeutic effects and biological responses mediated by released ions

It has been reported that ionic dissolution products play a key role in affecting the biological response of biomaterials *in vitro* and *in vivo*, stimulating the expression of cells at the genetic level; in this regard, BGs have received great attention by researchers due to their adjustable reactivity in the biological environment [19,20]. Since many trace elements present in the human body are known for their anabolic effects in cells metabolism, a new approach for designing glass-derived products able to elicit a desired biological response (or, in other words, for acting on the material bioactivity) could imply the introduction of therapeutic ions into the BG formulation. The subsequent release of these ions after exposure to a physiological environment is believed to exhibit

possible osteogenetic [19], antibacterial [248] or anti-inflammatory [249] effects, and to selectively affect the response of human cells towards angiogenesis [250-255]. *In vitro* experiments have shown that BGs stimulate the secretion of angiogenic growth factors in fibroblasts, the proliferation of endothelial cells and the formation of endothelial tubules [250,254], and *in vivo* results have confirmed that neovascularization in porous BG scaffolds occur [252,254,255]. This ability could be exploited for the development of a new generation of porous orbital implants that stimulate fibrovascularization at the genetic level; however, as pointed out in the section 10, BG solubility should be carefully considered in this context.

After reviewing the relevant literature, it was noted that metal ions incorporated in biomaterials for subsequent release usually belong to the group comprising essential enzymatic cofactors [20,256,257]. Each metal ion possesses a specific therapeutic significance and can alter cell functions and metabolism by binding to biological macromolecules, such as enzymes or nucleic acids, or activating ion channels and secondary signalling. Incorporation of metal ions exhibiting magnetic properties can be useful for *in situ* cancer treatment through hyperthermia, as discussed in the section 11.4. The possible toxicity related to the ions (e.g. problems of local accumulation, unwanted interactions with cells, biomolecules or other ions, phenomena of systemic toxicity) is a complex, crucial and still partially unknown issue that must be carefully taken into account in the development of such kind of smart bioceramics.

From a technological viewpoint, introduction of metal ions is usually economic and compatible with the typical processes used for bioceramics production (e.g. high-temperature sintering), which instead are often incompatible with the incorporation and stability of organic moieties and drugs that might be used for the same purpose [258].

Perhaps the most promising bioceramics that can be exploited for targeted therapies via metal ion release belong to the group of phosphate glasses [259]. Their solubility in biological fluids is strongly dependent on their composition, and thus their degradation rate can be tailored by proper addition of metal oxides, such as TiO_2, CuO, AgO and Fe_2O_3, that, once released, are also able to

exert an antibacterial effect [198], which would really be a key added value for ocular implants (see the section 11.6).

11.3. Surface modifications

The biological performances of bioceramics could be improved following the approach of surface functionalization. For example, it was demonstrated that silicate BGs and BGCs can easily expose reactive hydroxyls groups on their surface by simple water treatments, and these functionalities can be employed for the grafting of appropriate biomolecules to elicit specific therapeutic actions [260]. Functionalization of pore walls in mesoporous ceramics (Fig. 9d) has also been successfully experimented [12]. The idea of grafting specific growth factors, like the vascular endothelial growth factor (VEGF), to enhance vascularization, or drugs to reduce inflammation and infection, could be of high interest in the field of orbital implants.

Bioceramics could be also surface doped with metal ions eliciting an antiseptic effect. The feasibility of this approach has been successfully demonstrated (Fig. 10a) by applying an ion-exchange technique to dope with silver the surface of dense and porous glass-ceramics [261]. Looking at the future, this strategy could be experimented for the surface doping of already clinically used glass-derived ocular implants, such as BG plates for orbital floor repair and glass/PE composite orbital implants, as well as experimental glass skirt for keratoprostheses.

11.4. Magnetic properties for hyperthermia

Tumours affecting the orbital bone or ocular tissues are one of the main non-traumatic causes that require the surgical resection of orbital bone or the removal of the ocular globe. The surgical procedure typically comprises two stages: (i) removal of the diseased tissue (orbital bone portions and/or the eyeball) and (ii) implantation of an appropriate biomaterial or device (orbital bone grafts

and/or orbital implant replacing the socket volume). Therefore, the clinical challenge is twofold: it is necessary not only to successfully restore the surgically-induced defect, but also to avoid the re-development of the tumour. In this regard, hyperthermia using implantable magnetic bioceramics has emerged as a promising option for the localized treatment of malignant tumours [12]. At present, the research and clinical applications of hyperthermia mediated by magnetic materials are mainly addressed to the treatment of bone tumours; the suitability of this approach to treat orbital bone/intra-orbital malignancies would deserve consideration in the next future. These smart biomaterials are designed to be magnetic and, when exposed to an external magnetic field, they can produce heat within the diseased tissue region. It is known that cancer cells are killed if exposed at temperatures above 43 °C, whereas healthy cells can survive in such conditions. A variety of bioceramics, including calcium phosphates [262], glasses and glass-ceramics [263-265], mesoporous silica [266], ceramic-based composites [267] and cements [268] have been considered and properly processed for possible application in hyperthermia. These materials have been prepared and tested in the form of bulk implants, thermoseeds, particles, fine powder and, very recently, porous scaffolds. Wu et al. [269] proposed an innovative approach combining hyperthermia therapy and local drug delivery in a multifunctional Fe-containing hierarchical porous MBG scaffold prepared through a co-templating method. Large macropores are useful to permit healthy tissue in-growth, mesopores allow sustained drug release and the magnetic properties of the Fe-containing glass can be exploited for *in situ* cancer treatment by hyperthermia. Although this strategy is highly fascinating, one of the major limitations of these Fe-MBG scaffolds is the high brittleness (compressive strength around 50 kPa), which dramatically limits the perspectives of a clinical application. Perhaps, injectable magnetic MBG pastes could be suitable in the repair of cancer-derived orbital bone defects or injected intraorbitally in the region around the severed optic nerve to kill the residual cancer cells that might migrate through it after enucleation.

11.5. Radioactive bioceramics

The surgical procedures that are necessary to remove orbital or ocular malignancies are highly invasive and require additional oculoplastic treatments. Ideally, a less invasive approach, like radiotherapy, would be preferable but, at present, its application to the ocular and periocular tissues is very difficult. Furthermore, a significant problem in the radiation treatment of cancer is the serious systemic side effects. Localization of the radiation at the site of the tumour can decrease the radiation dosage required to kill the cancer cells, thereby minimizing side effect toxicities. An innovative approach to the localized delivery of radioactive isotopes to treat liver and kidney cancer has been developed using glass microspheres [270]. Briefly, a ^{89}Y-containing glass in the Y_2O_3-Al_2O_3-SiO_2 system was produced in the form of 25-μm microspheres (TheraSphere®); before arterial infusion, the glass beads were bombarded by neutrons that create ^{90}Y, a radioisotope that is a short-half-life (64 h), short-range β-rays emitter. In this way, a localized dosage of up to 15000 rad was delivered, whereas a maximum of 3000 rad under external radiation can be tolerated by the patient. The selected ternary glass system provided excellent chemical durability in the body in order to avoid dissolution and migration of the radioisotope via the blood circulation; this method is currently approved for patients as an adjuvant to liver surgery by the FDA and is being used at a number of clinical centres in the USA. Molecular dynamics simulations have been recently carried out on this glass to obtain more information about its long-term fate and durability *in vivo* [271]. Indeed, the applications initially proposed by Day and Day [270] are far from the ophthalmic field, but this strategy deserves to be mentioned in this review as a possible input for the future development of radioactive ceramics for ocular cancer therapy, under the appropriate adaptations.

11.6. Smart coatings

As reviewed by other authors [258,272], bioceramics can be coated by thin films of biodegradable polymers acting as matrices for the incorporation and subsequent release of biomolecules, drugs or

organic moieties for therapeutic applications. This approach could be particularly useful for those ceramic devices, such as orbital implants and keratoprosthetic porous skirts, that should ideally be non-absorbable and maintain adequate structural/mechanical integrity.

Another added value that could be provided by smart coatings is an antibacterial/antifungal effect, which would be of great importance in ophthalmic biomaterials since implant-related ocular infections can cause serious postoperative problems requiring expensive and stressful extra-treatments for the patients [135,273-278]. A promising strategy, that was disclosed in a patent by Baino et al. [279], involves the deposition of an oxide-based composite film via sputtering on the surface of a wide range of biomaterials, including bioceramics, for ocular prostheses and orbital implants. The coating, whose thickness can range from few nanometers to 1 μm, is preferentially constituted by silver nanoclusters embedded in a silica matrix (Fig. 10b), but also other matrix materials (e.g. alumina, TiO_2) and antibacterial metal agents (e.g. copper, zinc) may be experimented to find the best solution depending on the type of substrate material to be coated and on the biological environment wherein the antibacterial device will exert its function. Co-sputtering of silver and silica has the advantage to allow the tuning of film thickness as well as the antibacterial metal concentration through the control of the deposition parameters (e.g. power and pressure in the deposition chamber) [280-282]. Preliminary studies on film-coated ceramic substrates showed that the silver nanoclusters in the as-sputtered coating have a diameter within 5-10 nm (Fig. 10b) and can increase their size upon thermal treatments at 500-600 °C [280]. Leaching tests in different conditions (water or SBF at 37 °C) revealed that the coatings were able to exert an antibacterial activity for around 1 month [280]. Furthermore, there are preliminary evidences suggesting that silver is released in ionic form instead of nanoparticles: this is a significant added value overcoming the toxicity issues related to the release of metal nanoparticles *in vivo* [283-285]. Moreover, the use of metals as antibacterial agents instead of antibiotics, commonly employed in therapy and prevention of implant-related infections, could overcome the problem of bacterial resistance and can be effective also on resistant bacterial strains. However, it should be taken into

account that the ocular environment is highly complex and several parameters should be taken in account, such as the solubility of the silica matrix, the interaction of metal ions with the tears, the fate of the released ions and the possible ion-induced eye tissue necrosis.

12. Conclusions

The role of bioceramics in ophthalmology is still underestimated with respect to other fields of application such as orthopaedics and dentistry. The most common medical uses of implantable bioceramics are associated to hard tissues; however – and it is the major message of this review – they can have a great potential also in ophthalmic surgery due to a set of unique properties that can be properly and successfully exploited for ocular applications. Looking at the modern story of biomaterials science, we need to remember that only 40 years ago the concept of a material that would be able to actively stimulate tissue regeneration seemed impossible. This remote dream became reality with the invention of 45S5 Bioglass®, but none of the high-impact future applications were forecast when the research began. Over the years more and more knowledge has been acquired and the contexts of application of bioceramics expanded accordingly. Unlike metals and polymers, only BGs and, to some extent, calcium orthophosphates can bond to bone promoting new tissue growth, which is a key added value for implants devoted to the repair of orbital floor fractures. Porous bioceramics have been shown to allow and even stimulate keratocytes adhesion and proliferation, which make them promising candidates for the development of a new class of skirt keratoprostheses. Porous bioceramics can also stimulate fibrovascular in-growth, which is a fundamental characteristic to ensure an adequate motility of orbital implants and to reduce the risk of postoperative infection. Novel perspectives could raise from the use of mesoporous oxide-based materials for *in situ* drug release, magnetic and radioactive bioceramics for ocular tumour treatment, and BGs and BGCs whose ion dissolution products can elicit angiogenetic and antibacterial effects. In summary, an increasing collaboration between ceramic scientists, ophthalmologists and

oculoplastic/maxillofacial surgeons is needed more than ever to open new scenarios of research and, as a final result, to further improve the life quality of mankind.

Disclosures

The authors have no conflict of interest with regard to any of the companies whose products are mentioned in the manuscript.

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Figure legends

Fig. 1. Orbital floor fracture: (a) tomographical image (coronal plane) showing the patient's left orbital floor fracture (region F; note the vertical elongation of the left orbit and, accordingly, a reduction in size of the left maxillary sinus lying underneath); (b) fracture stabilization with a proper implant material (autologous bone in A or man-made implant in B) (images adapted from Ducic and Verret [34] © American Academy of Otolaryngology - Head and Neck Surgery Foundation).

Fig. 2. Placement of an orbital implant in the anophthalmic socket following enucleation surgery: 1 = orbital implant (a porous sphere in this case); 2 = wrapping material (e.g. scleral allograft or xenograft, dermis, synthetic polymer foil) that wraps the orbital implant to facilitate its insertion into the anophthalmic socket and to avoid erosion of surrounding tissues by the irregular surface of the porous sphere; 3 = fibrovascular in-growth allowed by the interconnected porous network of the orbital implant; 4 = extraocular muscles that are sutured on the wrapping material; 5 = patient's conjunctiva; 6 = frontal peg (it is optional and extra-surgery is needed for its placement after 6 weeks from primary surgery); 7 = ocular prosthesis (with a seat to host the peg); 8 = orbital bone; 9 = severed optical nerve.

Fig. 3. Schematic of a typical osteo-odonto-keratoprosthesis (OOKP) *in situ* (image adapted from Gomaa et al. [39]).

Fig. 4. Calcium orthophosphates ocular implants: (a) SEM micrograph showing the porous structure of a coralline HA orbital implant (Bio-Eye® sphere) (adapted from Jordan and Klapper [63] © Springer); (b) synthetic HA scaffolds fabricated by direct ink writing for potential use in craniofacial and oculoplastic reconstruction (the insert show the ordered porous pattern of stacked

HA rods) (adapted from Simon et al. [72] © Wiley Periodicals); (c) HA coating on PMMA for experimental keratoprostheses (the HA, obtained by controlled precipitation from a modified SBF, exhibits a characteristic globular morphology) (image adapted from Wang et al. [88] © The Association for Research in Vision and Ophthalmology); (d) SEM micrograph of a porous biphasic β-TCP/HA orbital implant exhibiting an interconnected 3-D network of pores (adapted from Reyes et al. [92]).

Fig. 5. Use of glass in the fabrication of ocular devices: (a) frontal and (b) posterior view of a damaged ocular prosthesis made of coloured glass (glass eyes are fragile and prone to implosion with acute changes in temperature; furthermore, over time they become etched from exposure to body secretions) (images adapted from Sami et al. [27] © Elsevier); (c) bioactive glass plates (objects 3 and 4) with their corresponding "kidney-shaped" and "drop-shaped" (objects 1 and 2) stainless steel templates (adapted from Peltola et al. [113] © American Association of Oral and Maxillofacial Surgeons); (d) histological picture of an eye with a keratoprosthesis supported by bioactive glass-ceramic coated titanium flange (main image: the small arrow point to the intact aspect of the cornea under the optic "O", whereas the large arrow points to the hole in the left half of the supporting flange; insert: there is a tight contact between the glass-ceramic coating and the corneal matrix tissue, and the corneal epithelium "e" shows no in-growth but has attached to the bioactive glass-ceramic (bgc) coating on the part supporting the optic) (images adapted from Linnola et al. [124] © Academic Press Limited).

Fig. 6. Alumina porous orbital implants: (a) photograph of alumina implants of different size; (b) SEM micrograph showing the porous structure of an alumina implant (adapted from Jordan and Klapper [63] © Springer).

Fig. 7. HA/polyethylene composite (HAPEX) implant (region H) in the orbital floor of a patient who has lost the right eye (the implant is shown with the same radiographic density as the bone to which it is bonded, while the spherical black object is a glass ball implanted earlier to restore the volume of the orbital socket) (adapted from Tanner [156] © The Royal Society).

Fig. 8. The potential and versatility of 3-D glass-ceramic scaffolds for orbital floor repair: (a) scaffolds of different sizes and shapes produced by sponge replication method (the scaffold dimensions can be properly tailored by shaping the starting polymeric template in order to fit the geometry of the orbital wall defect) (image adapted from Vitale-Brovarone et al. [215] © Springer); (b) SEM micrograph showing the 3-D highly interconnected porous network of foam-like scaffolds (adapted from Renghini et al. [204] © Elsevier); (c) 45S5 Bioglass® cellular structure fabricated by lithography-based additive manufacturing after sintering and (d) proposal for a customized implant for orbital floor repair (images adapted from Tesavibul et al. [206] © Elsevier).

Fig. 9. Smart strategies for controlled drug delivery by using mesoporous bioceramics: (a) MCM-41 mesoporous silica spheres anchored on the pores walls and struts of a macroporous glass-ceramic scaffold; (b) ordered pore arrangement (pores with a diameter of about 5 nm disposed according to a hexagonal symmetry, see the arrow) of a mesoporous bioactive glass (SiO_2-CaO-P_2O_5 system) wherein therapeutic agents, drugs or suitable organic moieties could be incorporated for subsequent release *in situ*, as schematically illustrated in (c); (d) parameters involved in the adsorption ability of mesoporous bioceramics (image adapted from Vallet-Regi and Ruiz-Hernandez [12] © Wiley-VCH).

Fig. 10. Smart strategies to impart antibacterial properties to bioceramics by using silver as an antiseptic agent: (a) surface silver doping (the cross-sectional SEM micrograph shows the silver diffusion profile from the surface (right side) to the core of a silver-doped SiO_2-CaO-Na_2O glass)

(image adapted from Verné et al. [261] © Elsevier); (b) deposition of a silver nanoclusters/silica composite thin film by radio-frequency co-sputtering (the high-resolution TEM micrograph shows such a coating produced on glass; the dark circles correspond to silver nanoclusters embedded in the silica matrix) (image adapted from Ferraris et al. [280] © Elsevier).

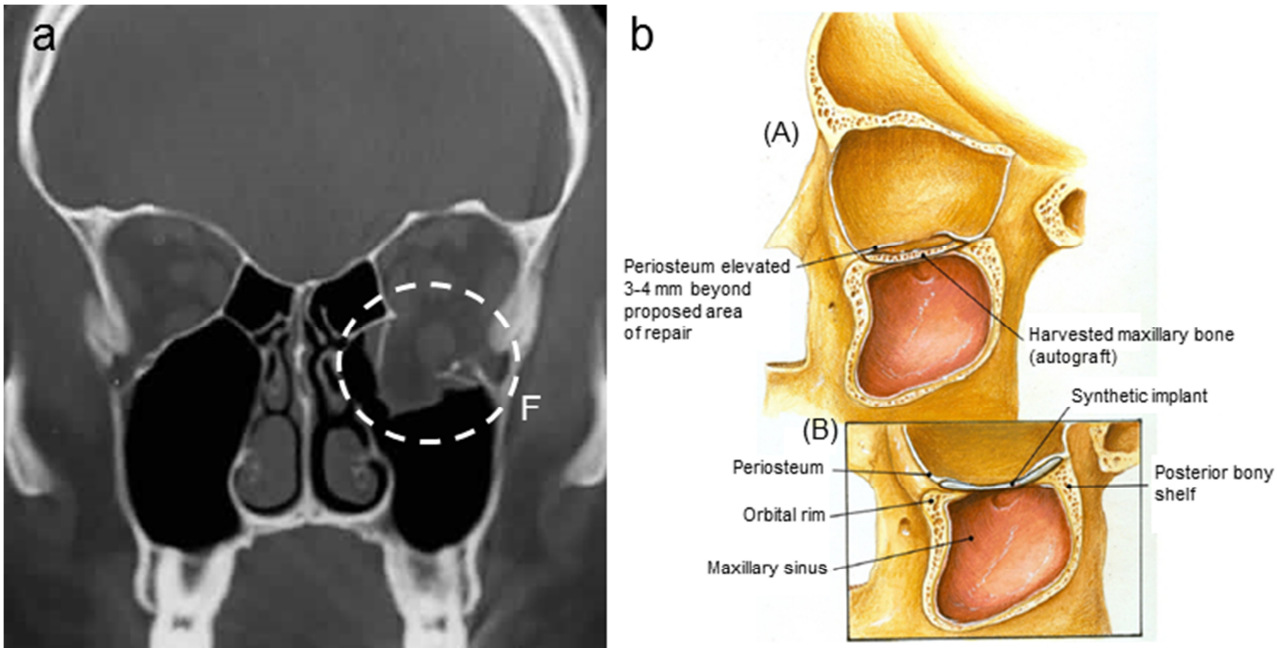
a
F
b
(A)
Periosteum elevated
3-4 mm beyond
proposed area
of repair
Harvested maxillary bone
(autograft)
Synthetic implant
(B)
Periosteum
Orbital rim
Maxillary sinus
Posterior bony
shelf

Fig. 1

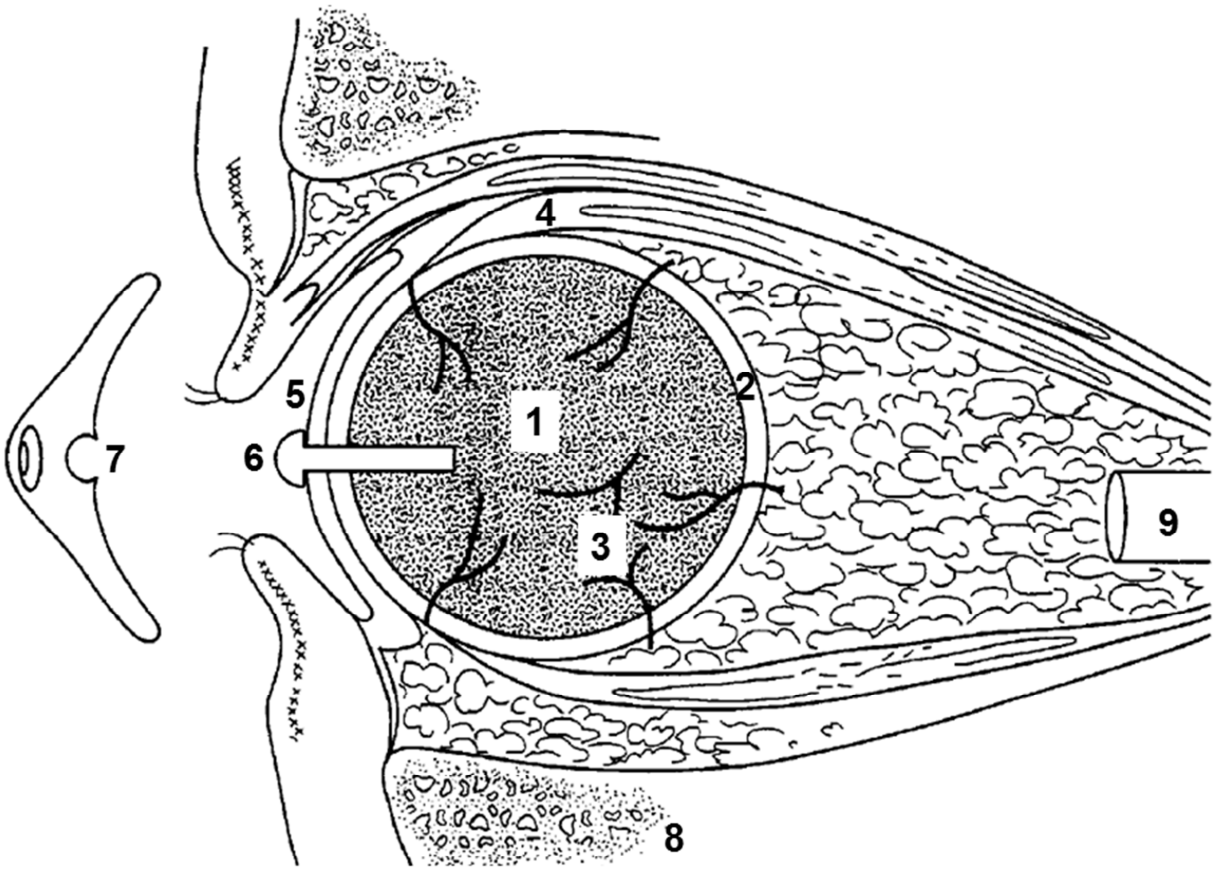
1
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Fig. 2

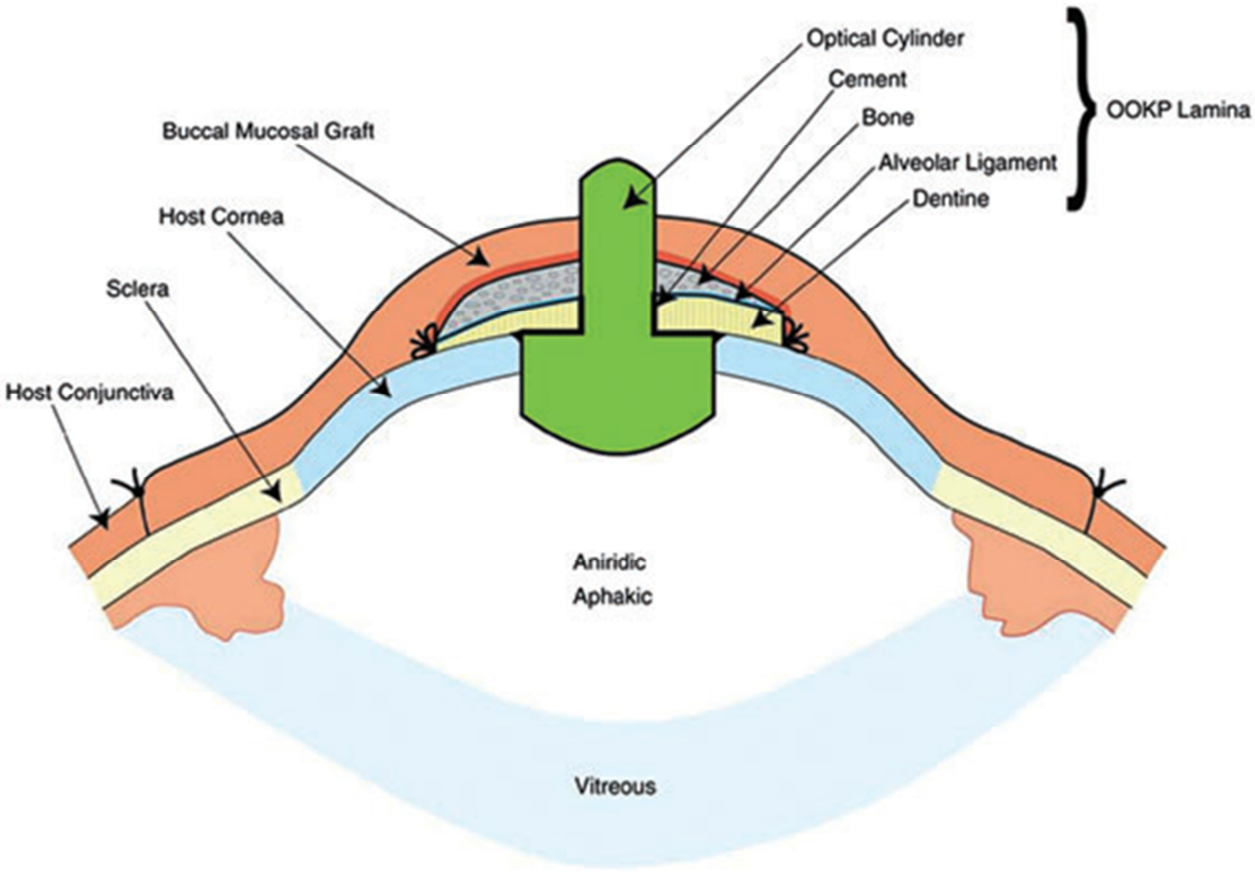
Optical Cylinder
Cement
Bone
Alveolar Ligament
Dentine
OOKP Lamina
Buccal Mucosal Graft
Host Cornea
Sclera
Host Conjunctiva
Aniridic
Aphakic
Vitreous

Fig. 3

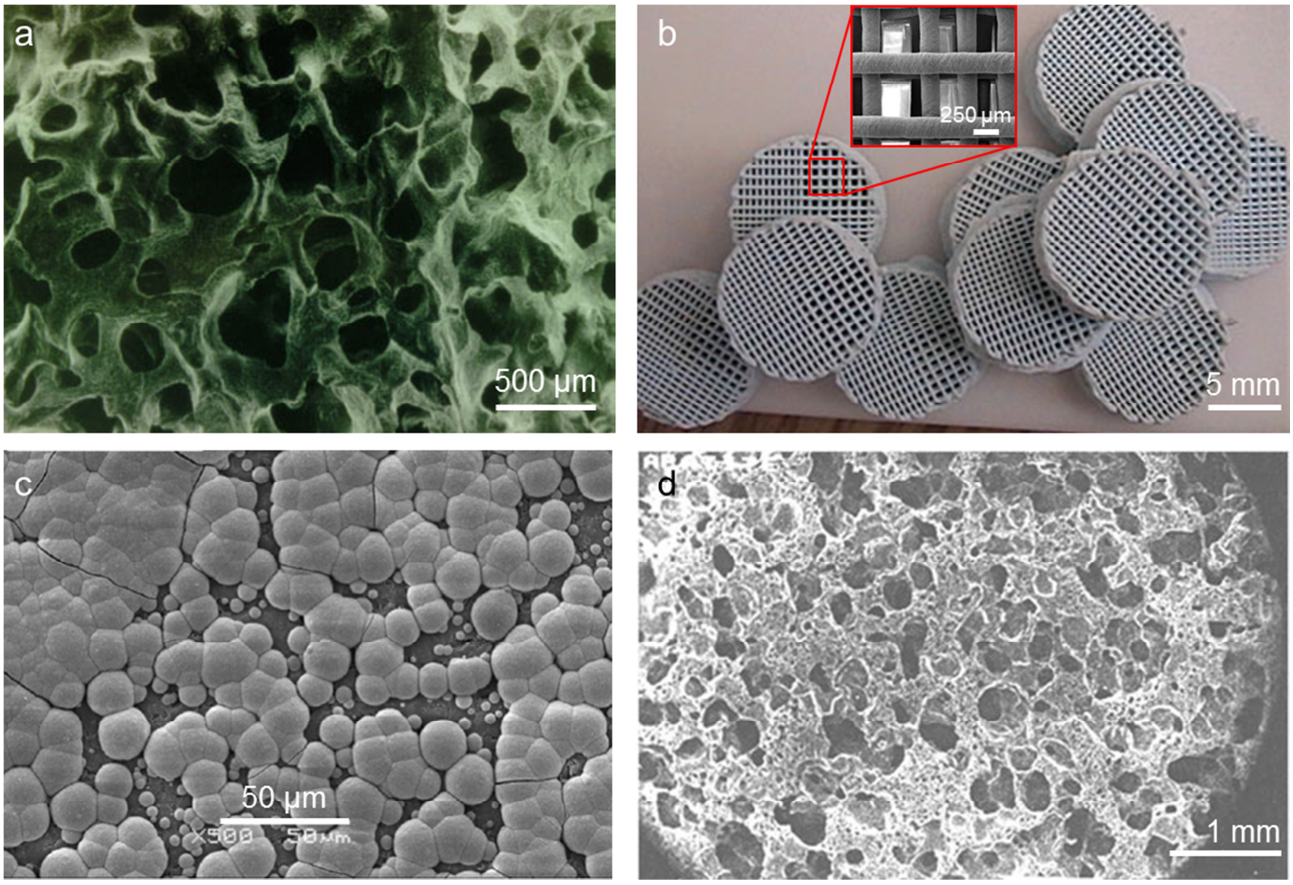

Fig. 4

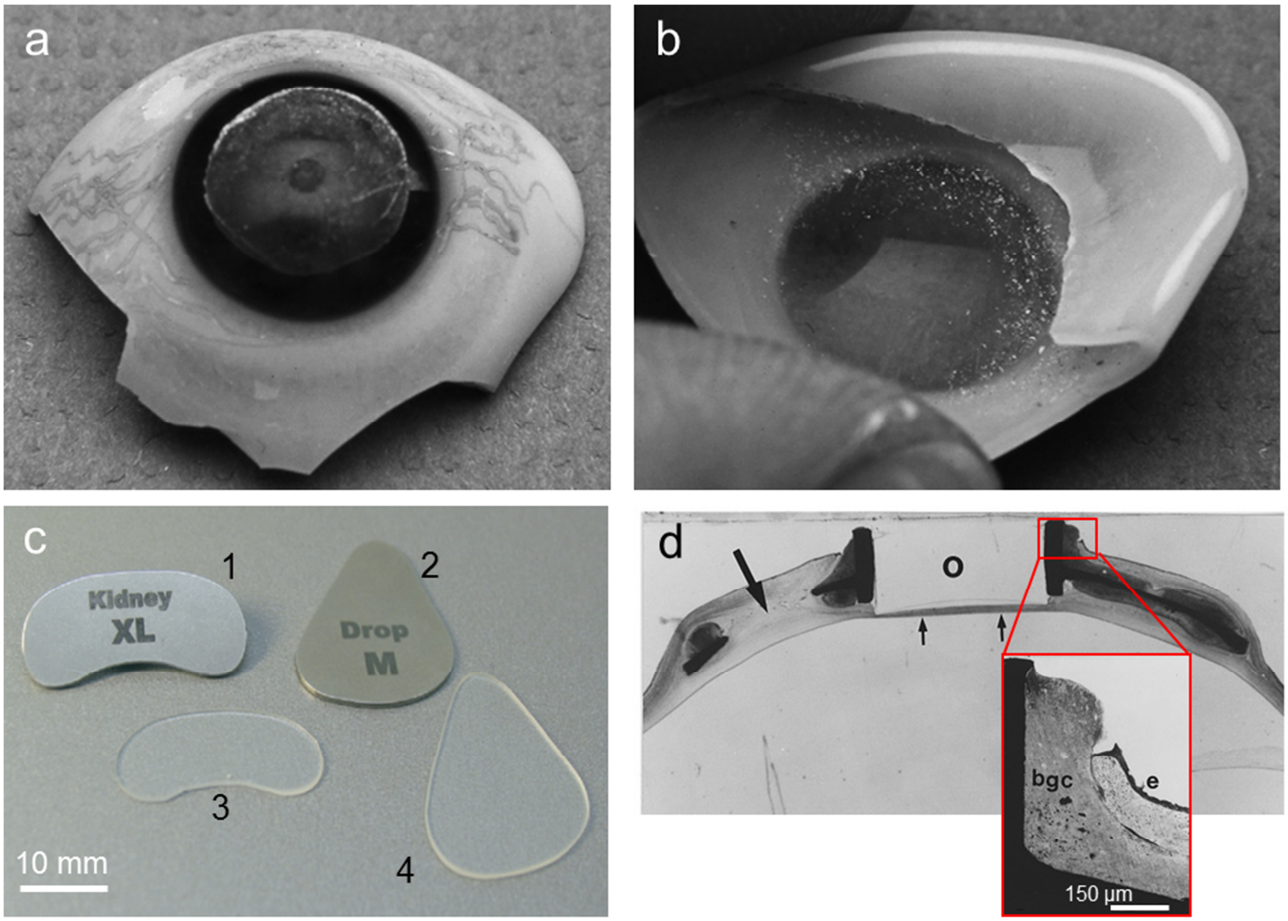

Fig. 5

Fig. 6

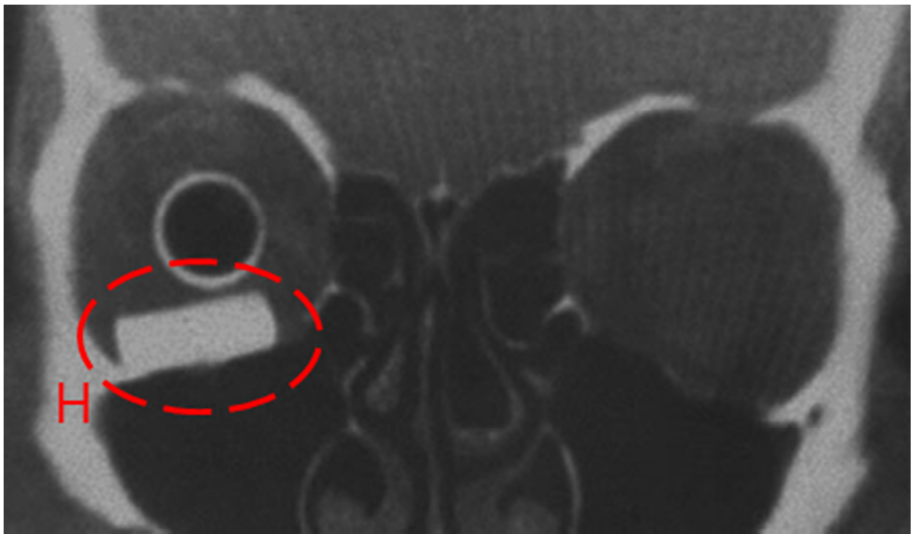

Fig. 7

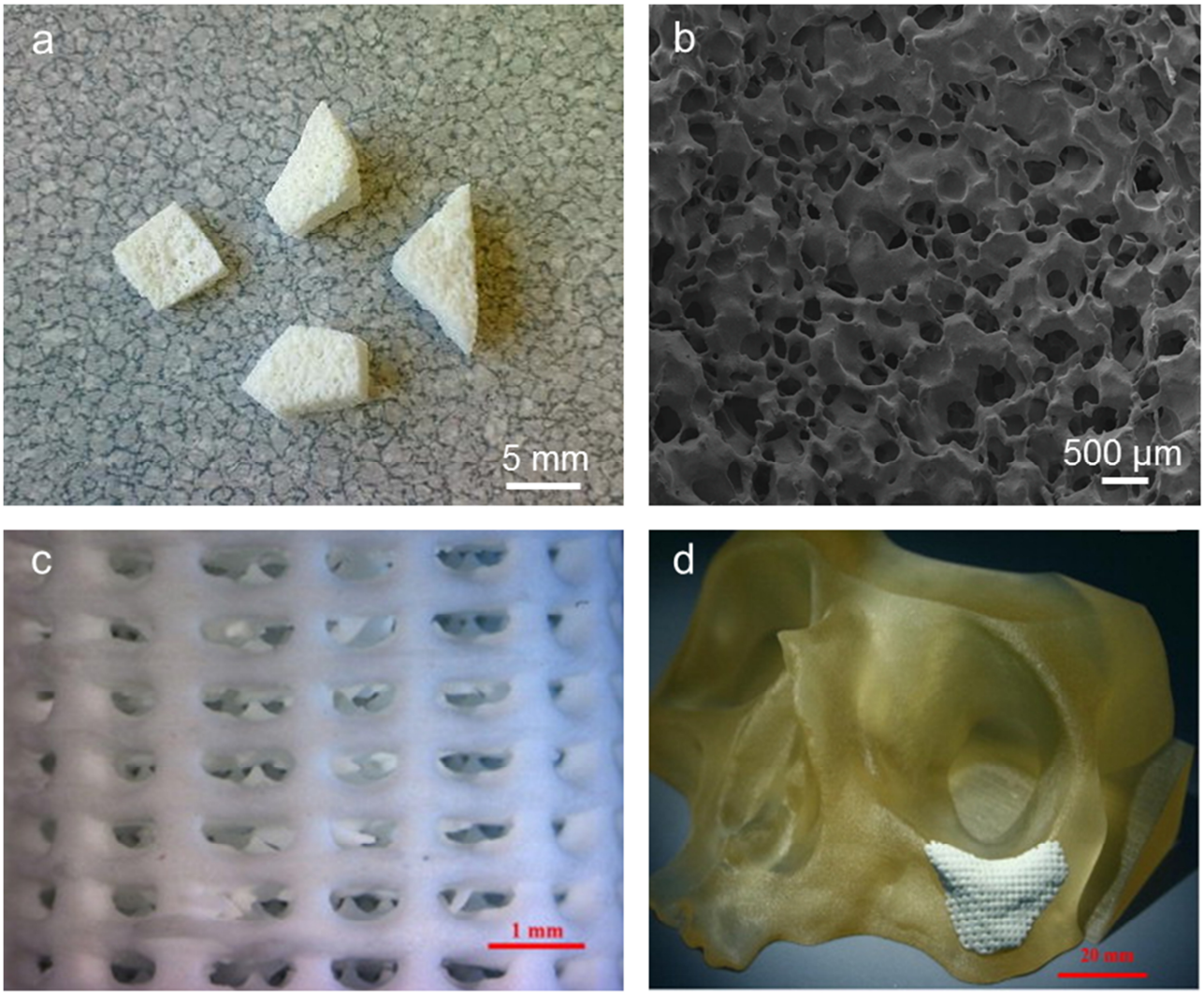

Fig. 8

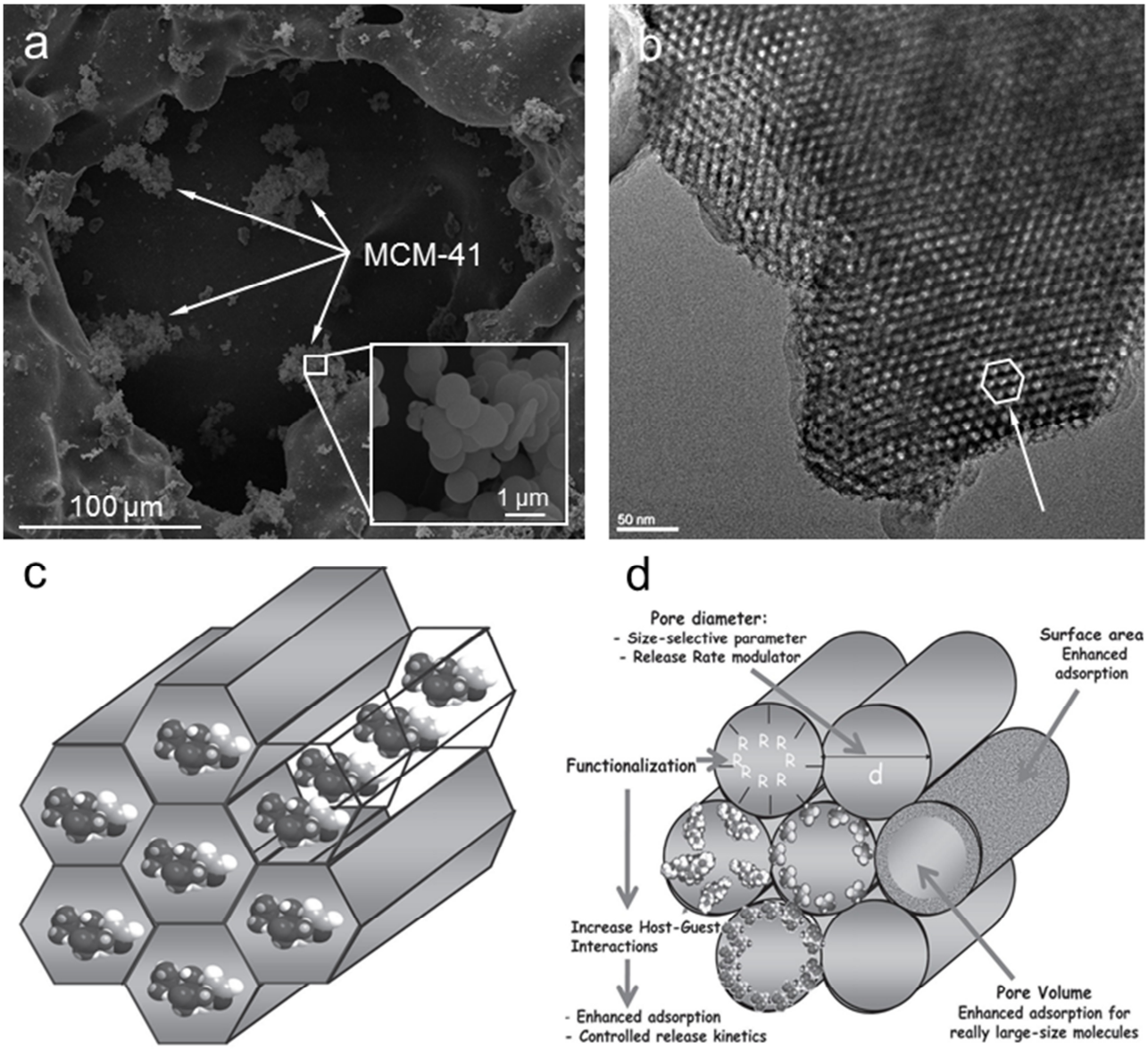
a
MCM-41
100 µm
1 µm
b
50 nm
c
d
Pore diameter:
- Size-selective parameter
- Release Rate modulator
Surface area
Enhanced
adsorption
Functionalization
R
d
Increase Host-Guest
Interactions
- Enhanced adsorption
- Controlled release kinetics
Pore Volume
Enhanced adsorption for
really large-size molecules

Fig. 9

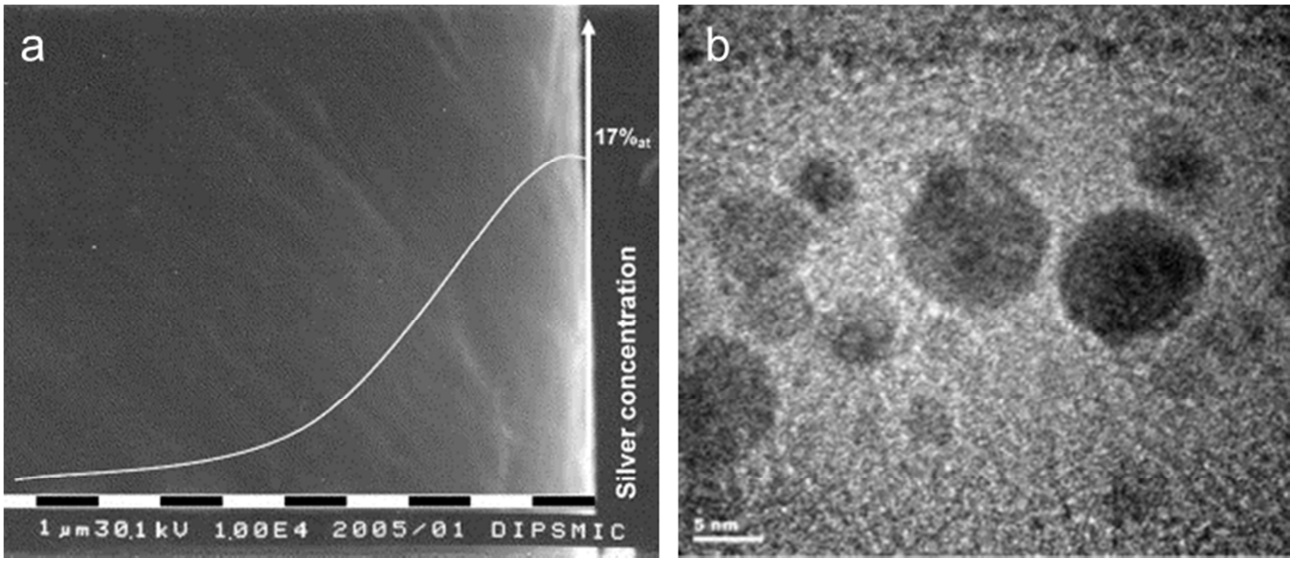
a
17%at
Silver concentration
1 µm30.1 kV 1.00E4 2005/01 DIPSMIC
b
5 nm

Fig. 10