Glass and Medicine

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For centuries, glass has been an important part of both the practical and the esthetic aspects of our culture. This paper documents three areas of glass research and development pioneered over the last 40 years that have greatly enhanced the quality of life (bioactive glasses and dental glass–ceramics) and the length of life (radioactive glass microspheres).

Introduction

One of the first major developments leading to saving of lives was the optical microscope. The invention of the microscope using glass spheres to focus light on objects was the seminal step toward discovering microscopic life forms of bacteria, viruses, and fungi, for example pathogens. This discovery led to the treatment and eventually the elimination of many diseases. Use of glass in thermometers, eyeglasses, laboratory ware, pharmaceutical processing, and a myriad other applications were also instrumental in creating the improvements in public health and healthcare that occurred in the 19th and 20th centuries. This enormous social change can be termed a revolution in life preservation. A major consequence of life preservation was an expansion of the human lifespan from an average of 45 years to 78 years. It is projected that by 2050, there will be more than 1 billion people alive on earth aged 60 years or older.

A second revolution in healthcare has occurred during the last 50 years; that is, a revolution in tissue replacement. This revolution has been a consequence of the first revolution. From the age of 30 years onwards, all tissues progressively deteriorate. Thus, an increase in the length of life is accompanied by a decrease in the
quality of life. To repair, replace, and restore the function of the hips, knees, eyes, ears, teeth, hearts, kidneys, etc. is now commonplace. Human “spare parts” is a huge business worth tens of billions of dollars.

The first generation of materials used for tissue replacement was selected by surgeons and materials scientists and engineers to be as biologically inert as possible, and therefore are called bio-inert materials. Corrosion-resistant metals and insoluble, nontoxic polymeric materials became the standard biomaterials. However, all bio-inert materials are a compromise because of the incompatibility of the interface between the material and living tissue. Tissue breakdown and loosening over time is a common mode of failure of devices made from bio-inert materials.

An alternative, second-generation concept for tissue replacement using a special type of glass was discovered in 1969. This concept of “bioactivity” has made it possible to expand greatly the approaches adopted in tissue replacement. Bioactive materials form a bond with living tissues. The first part of this paper discusses the mechanism of bioactive bonding and the clinical applications of bioactive glasses and glass–ceramics. Recent research has discovered that glasses with especially high levels of bioactivity can also be used to activate genes to stimulate the body to repair itself. This discovery has led to the concept of using bioactive resorbable glasses as a third generation of biomaterials designed for tissue regeneration.

The second part of this paper documents the steps involved in going from the concept of delivering high levels of local radiation to kill cancer cells in the liver to achieving a successful glass delivery system for the radiation. The success of this revolutionary approach to cancer therapy is saving the lives of thousands of patients and provides a methodology to target other debilitating diseases that affect the quality of life of aging individuals.

The third part of the paper describes the development of special compositions of glass–ceramics that are designed to restore the appearance and function of teeth. This is a significant improvement in enhancing the quality of oral health and quality of life. It is far more cost effective to maintain healthy natural teeth than to replace them with implants or dentures. Millions of glass–ceramic dental restorations have been used in the last decade, with extremely high levels of success.

These three developments of glass research demonstrate the potential of using the infinite variability of glass composition, combined with controlled levels of crystallization, to create unique methods to enhance both the quality of life and the length of life.

Bioactive Glasses and Glass–Ceramics

Compositions

For millennia, it was understood that any man-made material in the body would result in a foreign body reaction and formation of nonadherent scar tissue at the interface with the material. Thus, the initial emphasis on biomaterials for use in the body was on materials that were as inert as possible when exposed to a physiological environment. This approach to replacement of tissues was irreversibly altered when a special composition of soda–lime–phosphate–silicate glass was prepared by the lead author and implanted in the femurs of rats in 1969.1–3 This glass composition contained 45% SiO$_2$, in wt%, with network modifiers of 24.5% Na$_2$O and 24.5% CaO. In addition, 6% P$_2$O$_5$ was added to the glass composition to simulate the Ca/P constituents of hydroxyapatite, the inorganic mineral phase of bone.

The glass composition was denoted as 45S5 to signify the wt% of silica as the network former and a fivefold molar ratio of Ca/P. The glasses did not form interfacial scar tissue, isolating them from the host femoral bone. Instead, the implants bonded to the living bone and could not be removed from their implant site. This discovery led to the development of a new class of materials, called bioactive materials, for use in implants or prostheses and repair or replacement of bones, joints, and teeth.

Bioactive materials, including bioactive glasses,1–3 and glass–ceramics,4,5 are special compositions prepared typically from the Na$_2$O–CaO–MgO–P$_2$O$_5$–SiO$_2$ system (Table I). All form a mechanically strong bond with bone. The details are reviewed in Hench and colleagues.2,3,6 The rate of bone bonding depends on the composition of the material.3 Glass compositions with the fastest rates of bone bonding also bond to soft tissues.7

Bioactive materials are used as bulk implants to replace bones or teeth, coatings to anchor orthopedic or dental devices, or in the form of powders, as bone grafts, to fill various types of bone defects.2,3,8 When a particulate of bioactive glass is used to fill a bone defect, the rate and quantity of bone regeneration depend on the material’s composition.9 Compositions such as 45S5 Bioglass that have the highest rates of bioactivity lead to rapid regeneration of trabecular bone with an amount,
architecture, and biomechanical quality of bone that matches that originally present in the site. The rapid regeneration of bone is due to a combination of processes called osteostimulation (also called osteoproduction) and osteoconduction.\textsuperscript{8} Large differences in the rates of \textit{in vivo} bone regeneration and extent of bone repair indicate that there are two classes of bioactive materials (Table I).\textsuperscript{8}

Class A bioactivity leads to both osteoconduction and osteostimulation\textsuperscript{8,10} as a consequence of rapid reactions on the bioactive glass surface.\textsuperscript{3,6,8} The surface reactions involve dissolution of critical concentrations of soluble Si and Ca ions that give rise to both intracellular and extracellular responses at the interface of the glass with its physiological environment. The intracellular and extracellular response of osteoprogenitor cells results in the rapid formation of osteoid bridges between particles, followed by mineralization to produce mature bone structures. The rates of osteoproduction of various bioactive particulates have been quantified by Oonishi and colleagues that provide the fundamental \textit{in vivo} comparisons of Class A versus Class B bioactive materials.\textsuperscript{8,9}

**Bioactivity Reaction Stages**

There is a sequence of 11 reaction stages that occur at the surface of a Class A bioactive glass. Figure 1 indicates in the log time axis that the first five stages of

![Fig. 1. Sequence of interfacial reactions between bone and a Class A bioactive glass or glass–ceramic.](image-url)
surface reactions occur very rapidly and go to completion within 24 h for the bioactive glasses with the highest levels of bioactivity, for example 45S5 Bioglass. The effect of the surface reactions is a rapid release of soluble ionic species from the glass into the interfacial solution. A high surface area-hydrated silica and polycrystalline hydroxy carbonate apatite (HCA) bilayer is formed on the glass surface within hours (Stages 1–5). The reaction layers enhance the adsorption and desorption of growth factors (Stage 6) and decrease greatly the length of time macrophages are required to prepare the implant site for tissue repair (Stage 7).

Attachment of stem cells (Stage 8) and synchronized proliferation and differentiation of the cells (Stage 9) rapidly occur on the surface of Class A bioactive materials,11–16 Several weeks are required for similar cellular events to occur on the surface of bio-inert and Class B bioactive materials. Differentiation of progenitor cells into a mature osteoblast phenotype does not occur on bio-inert materials and is rare on Class B bioactive materials because of the lack of ionic stimuli. In contrast, osteoprogenitor cells colonize the surface of Class A bioactive materials within 24–48 h and begin the production of various growth factors that stimulate cell division, mitosis, and the production of extracellular matrix proteins (Stage 10). Mineralization of the matrix follows soon thereafter and mature osteocytes, encased in a collagen–HCA matrix, are the final product by 6–12 days in vitro and in vivo (Stage 11).8–16

**Cell Cycle Control and Gene Activation**

There are very few cells in the bones of older individuals that are capable of dividing and forming new bone. The few (1/100,000) osteoprogenitor cells that are present must receive the correct chemical stimuli from their local environment that instruct them to enter the active segments of the cell cycle, leading to cell division (mitosis) and eventually regeneration of new bone (osteo genesis). Figure 2 summarizes the sequence of cellular events that comprise a cell cycle for a single osteoblast progenitor (adult stem) cell and its division into daughter cells and differentiation into mature bone cells.

Resting cells are in the G0 phase, and unless they are stimulated to enter into active phases of the cell cycle, they will not lead to bone regeneration. A new cell cycle begins after a cell has completed mitosis. A key to regenerative repair of bone is to: (1) control the population of cells that are capable of entering into active phases of the cell cycle, (2) complete the mitosis of cells with accurate replication of genes (cell proliferation),

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**Fig. 2.** Schematic of Osteoblast progenitor cell cycle leading to (1) programmed cell death (apoptosis) (2) mitosis and cell proliferation, or (3) terminal cell differentiation toward an osteocyte.

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and (3) achieve cellular differentiation into a phenotype capable of synthesizing a full complement of extracellular proteins that constitute a mature osteocyte.

The studies reported by Xynos and colleagues showed that such osteoblast cell cycle control is achieved by the controlled release of ionic dissolution products from 45S5 bioactive glass.11–16 Osteoprogenitor cells colonize the surface of the bioactive glass; however, the concentration of soluble Si and Ca ions at the cell-solution interface is critical for controlling the cell cycle and activating a series of seven families of genes responsible for osteogenesis. Controlled rates of dissolution of the glass provide the critical concentration of the biologically active ions to the cells via the interfacial solution. The families of genes that are unregulated and/or activated are shown in Fig. 2 related to the relevant segments of the cell cycle, cell proliferation, and cell differentiation. The details are given in Xynos and colleagues.11,13,14

Clinical Applications

Figure 3 summarizes the time line for the development of clinical products from the date of the first discovery of 45S5 Bioglass in November 1969.

A listing of medical and dental products based on 45S5 Bioglass is given in Table II. The details are discussed in references.3,8 The year 2009 heralds the 40th anniversary of the discovery of 45S5 Bioglass and the landmark sales of the 1 millionth dose of the bone graft product (NovaBone, Jacksonville, FL). This year also marks sales of the 1 millionth tube of tooth paste containing 445S5 particulate (NovaMin) designed to occlude dentinal tubules and remineralize the surface of teeth, thereby eliminating the cause of dentinal hypersensitivity.

Conclusions

The discovery of bonding of bone to specific compositions of glasses led to a new, second generation of bioactive materials for tissue replacement. Understanding gene activation of human progenitor cells by controlled release of ionic dissolution products from bioactive glasses provides the basis for the design of third-generation biomaterials that can be used for tissue regeneration. Thus, glass science and technology continues to be at the forefront of providing innovative approaches to medicine.

Destroying Malignant Tumors with Radioactive Glass Microspheres

Introduction

This section reviews the development and application of radioactive yttrium alumino-silicate glass (hereafter abbreviated as YAS) microspheres that are being used to treat patients17 with a generally inoperable and deadly form of primary liver cancer, called hepatocellular carcinoma (HCC). The incidence of this deadly disease (HCC) is increasing worldwide and is considered the sixth most common cancer in the world (1 million new cases annually) and ranks third as the cause of cancer-related deaths (500,000 deaths per year). In the United States, the National Cancer Institute estimates that there were 19,160 new cases of HCC and 16,780 deaths in 2007. The life expectancy for patients diagnosed with HCC is measured in months.

Malignant tumors are typically treated either surgically, by chemotherapy, or with radiation. Unfortu-
nately, none of these methods have been effective in treating HCC and the 5-year survival rate for patients with HCC is \( \approx 7\% \).\(^{18}\) External beam radiation is used to treat many forms of cancer, but the maximum dose that can be delivered to HCC tumors is limited by the unavoidable damage inflicted to nearby healthy tissue and is too small to be effective (therapeutic). A potential solution to this problem is to place the radiation source inside the diseased tumor, called intra-arterial therapy, so that a larger and therapeutic dose of localized radiation can be delivered to the tumor(s) in situ without damaging nearby healthy tissue.

**Table II. Clinical Medical and Dental Products based on 45S5 Bioglass**

<table>
<thead>
<tr>
<th>Orthopedics</th>
<th>Trauma</th>
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<tbody>
<tr>
<td>Long bone fracture (acute and/or comminuted); alone and with internal fixation</td>
<td>Femoral nonunion repair</td>
</tr>
<tr>
<td>Tibial plateau fracture</td>
<td>Arthroplasty</td>
</tr>
<tr>
<td>Filler around implants (acetabular reconstruction)</td>
<td>Impaction grafting</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Filling of bone after cyst/tumor removal</td>
<td>Spine Fusion</td>
</tr>
<tr>
<td>Interbody fusion (cervical, thoracolumbar, lumbar)</td>
<td>Posterolateral fusion</td>
</tr>
<tr>
<td>Adolescent idiopathic scoliosis</td>
<td>Cranial–Facial</td>
</tr>
<tr>
<td>Cranioplasty</td>
<td>General oral/dental defects</td>
</tr>
<tr>
<td>Extraction sites</td>
<td>Ridge Augmentation</td>
</tr>
<tr>
<td>Sinus elevation</td>
<td>Cystectomies</td>
</tr>
<tr>
<td>Osteotomies</td>
<td>Periodontal Repair</td>
</tr>
<tr>
<td>Dental–Maxillofacial–ENT</td>
<td></td>
</tr>
<tr>
<td>Toothpaste and treatments for dentinal hypersensitivity</td>
<td>Pulp capping</td>
</tr>
<tr>
<td>Sinus obliteration</td>
<td>Repair of orbital floor fracture</td>
</tr>
<tr>
<td>Endosseous ridge maintenance implants</td>
<td>Middle ear ossicular replacements (Douek MED)</td>
</tr>
</tbody>
</table>

For a material, such as glass, to be used for the in situ irradiation of tumors in the liver, or other organs, it must satisfy the following criteria.

a. Biocompatible and nontoxic in the body.

b. Chemically resistant to the body fluids so that none of the radioisotope is released within the body (blood stream). The approach adopted in our work was to incorporate the radioisotope into a chemically durable glass matrix, thereby confining the radioisotope to the target site.

c. If a glass is to be made radioactive by neutron activation, then it must be free of any other elements that form unwanted radioisotopes during neutron activation, other than the desired element being activated. Neutron activation eliminates the need to handle radioactive glass when the microspheres are prepared, but it limits the composition that can be used.

d. The concentration of the neutron-activatable element in the glass must be high enough to provide the level of specific activity required for the desired treatment. This concentration varies with the element being activated, the organ being treated, and the neutron flux and activation time.

e. Capable of being formed into particles of the desired size and shape. The size and shape of the radioactive particles depend on the characteristics of the organ being treated and the method of delivering the particles to the target organ.

Radioactive particles (microspheres) can be delivered to a target organ using either the blood supply to that organ or by direct injection into the tumor. In the case of liver tumors, the plan was to inject radioactive microspheres into the hepatic artery as it is the main blood supply to the malignant tumor(s) in the liver; see Fig. 4. In the early 1960s, polymer microspheres coated with radioactive Y-90 were used\(^{17}\) to irradiate liver tumors in situ, but the radioactive Y-90 could not be confined and so the procedure was discontinued.

**Developing Glass Microspheres**

The key task was to develop a glass composition that fulfilled the preceding requirements. As indicated in Fig. 4, Yttrium-90 was the radioisotope of choice for this application because it could be produced by...
Neutron activation of naturally abundant Y-89, had an acceptable half-life of 64.2 h, and emitted β radiation that had an average range in soft tissue of only 2.5 mm. This short-range radiation minimized the amount of radiation reaching healthy liver tissue. The desire to use neutron activation along with the requirement for an extremely high chemical durability eliminated common glasses that contain elements such as Na, K, Ca, Ba, etc. as they form undesirable radioisotopes during neutron activation. As elemental oxygen, aluminum, and silicon do not form objectionable radioisotopes during neutron activation, an investigation was undertaken of the glass-forming tendency and selected properties of Y₂O₃–Al₂O₃–SiO₂ compositions.

A wide field of glass formation was found for yttria–alumina–silica compositions that melted below 1600°C and that contained sufficient yttrium for this application, up to 55 wt% Y₂O₃. Glasses with an excellent chemical durability were identified and glass microspheres of the desired size (25–35 micrometer) were readily prepared by flame spheroidization.

Laboratory and animal experiments were conducted to determine the safety of using YAS microspheres in humans, followed by clinical studies in Canada, Scotland, and the United States. An initial major concern was the potential leaching of Y-90 from the glass microspheres, as had occurred in earlier studies, where polymer beads coated with Y-90 were used. Experiments quickly showed that no detectable amount of Y-90 was released from a YAS glass with a nominal composition of 40Y₂O₃–20Al₂O₃–40SiO₂ wt%. Microspheres of this YAS glass, which the U.S. Food and Drug Administration considers a medical device (see Fig. 5), have been used in thousands of patients, with no instances of unwanted release of Y-90 from the glass.

**Clinical Results**

Liver cancer, especially HCC, has been and still is a difficult disease to treat, but the availability of Y-90 glass microspheres has opened a new avenue for treating liver cancer, what is called radioembolization. This refers to
the combined effect of the radiation and the embolization of the capillaries in a malignant tumor(s). The Y-90 microspheres not only safely deliver a much larger dose of radiation to the tumor(s), but the roughly 2–8 million glass microspheres in a typical injection become lodged (embolize) in the capillaries, thereby reducing the blood (nourishment) flow to the malignant tumor(s). These two synergetic effects help shrink and destroy the tumor(s).

Typically, the procedure is performed on an outpatient basis, with the patient receiving what amounts to an injection of several million radioactive Y-90 glass microspheres through a catheter inserted into the femoral/hepatic artery; see Fig. 4. The microspheres are released into the blood stream as close as possible to the tumor(s) in order to maximize the number of microspheres deposited in the malignant tumor(s). The microspheres are sized so that they are small enough to enter the capillaries of the tumor(s), but are too large to pass through the capillaries. Only a small fraction, typically 2–10%, of the radioactive microspheres reaches healthy tissue.

After a brief period of observation, the patient is discharged if there are no complications. The inoperable HCC tumor(s) in the patient’s liver continue to be irradiated in situ by the localized Y-90 β radiation as the patients return to their normal routine. In about 4 weeks, the microspheres are no longer radioactive.

Initially, patients received only one injection of Y-90 glass microspheres because the radiation dose was much larger than the doses used previously. As confidence in the safety of in situ irradiation increased and the benefits became better known, patients received multiple injections when necessary. The in situ irradiation of HCC tumors with radioactive YAS glass microspheres is increasingly recognized as having many advantages. With Y-90 radioembolization, it is possible to irradiate multiple, small tumors at much higher doses, 5–50 times, compared with an external beam. The localized β radiation destroys tumors regardless of the tumor origin and the relatively low toxicity of the β radiation toward healthy tissue allows repeated injections. Compared with chemotherapy and other radiation procedures, the side effects are small, and a small fraction of patients report flu-like symptoms such as fatigue, a slight fever, or abdominal pain for a few days.

Of greatest interest are the survival data for patients treated with the Y-90 glass microspheres. For patients with inoperable HCC, the stage of the disease at the time of treatment is especially important to survival. The survival data for a group of 229 patients with HCC who received no specific treatment provide a reference point. The median survival time for this group was 51 days—21 days for patients at an advanced stage and 249 days for patients with an early-stage disease. For a group of 42 patients treated with Y-90 glass microspheres, the median survival was 236 days (advanced stage) and 660 days (early stage). In another group of 150 patients with inoperable HCC, the median survival time for the entire group was 800 days (2.2 years) after treatment with the Y-90 glass microspheres. Finally, the 1-, 2-, and 5-year survival rates for a group

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>1982</td>
<td>Work begins at the University of Missouri-Rolla (now the Missouri University of Science and Technology) and the University of Missouri-Columbia.</td>
</tr>
<tr>
<td>1985</td>
<td>First animal (dogs) experiments at University of Michigan.</td>
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<tr>
<td>1986</td>
<td>Glass microsphere technology licensed by University of Missouri.</td>
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<td>1986</td>
<td>First human trials in Canada.</td>
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<tr>
<td>1987</td>
<td>First human trials in US at University of Michigan</td>
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<tr>
<td>1991</td>
<td>Microspheres approved for use in Canada</td>
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<tr>
<td>1999</td>
<td>US Food and Drug Administration (FDA) grants humanitarian device exemption (HDE) status to YAS microspheres for treating HCC or as bridge to transplantation.</td>
</tr>
<tr>
<td>2002</td>
<td>Microspheres approved for commercial use in US by FDA</td>
</tr>
<tr>
<td>2005</td>
<td>Microspheres granted CE Mark and approved for use in European Union.</td>
</tr>
<tr>
<td>2009</td>
<td>Patients currently being treated with Y-90 glass microspheres in the US at 62 sites in 29 states, in Canada, Europe and elsewhere.</td>
</tr>
</tbody>
</table>

Fig. 5. Time line for the development of YAS-90 glass microspheres.
of 20 patients, ages 42–82, with inoperable HCC and treated with Y-90 glass microspheres were recently reported to be 100%, 75%, and 46%, respectively. These survival rates are encouraging.

**Conclusions**

The radioembolization of HCC tumors with radioactive YAS glass microspheres is recognized as a safe and effective way of treating this deadly form of cancer. Glass technology and science have made an important contribution to the success of this new procedure for treating patients with inoperable liver cancer. There are other organs where microspheres of YAS and other rare-earth YAS glasses can be used as in situ radiation devices to destroy malignant tumors in the body.

**Dental Glass–Ceramics**

**Introduction**

Biomaterials used in restorative dentistry are important products for humans who want to regain the full range of chewing or improve the esthetic appearance of their teeth. Traumatic dental injuries, the processes of aging, and insufficient oral hygiene may require the use of dental inlays, onlays, crowns, veneers bridges, posts, or abutments for implant therapy. These materials must fulfill a combination of requirements. They must be able to match or even surpass the esthetic (optical), chemical, and mechanical properties of natural teeth. Chemical durability is essential to prevent the occurrence of caries. Abrasive wear behavior must be similar to that of natural teeth, whereas the flexural strength and toughness of dental biomaterials must be higher than those of natural teeth to allow construction of functionally adequate dental bridges, posts, or abutments in high-load-bearing regions.

Dental biomaterials also have to possess complex optical properties. They must provide an adequate range of light transmission, that is translucency, which reflects the different levels of translucency occurring in the natural tooth structure. They must exhibit both opalescent properties near the incisal area and fluorescent properties across the entire body of the tooth replacement, similar to natural teeth.

None of the above-mentioned applications requires dental biomaterials to be bioactive, for example to directly form a bond with the natural dental tissues. Dental restorative materials are bonded to the natural tooth structure by means of materials that are specifically formulated for this purpose, such as adhesives.

A historical review of the development of biomaterials for restorative dentistry shows that polycrystalline ceramics were used to produce dental restorations as early as the beginning of the 19th century, that is more than a 100 years ago. However, the optical and mechanical properties of these materials did not meet the clinical requirements. Esthetic veneering of metal frameworks (crowns, bridges) only became possible after leucite-based \((\text{KAlSi}_2\text{O}_6)\) porcelain-fused-to-metal materials were developed.

Significant advances in the development of materials that match, or even outperform, the optical, mechanical, and chemical properties of natural teeth were accomplished with the introduction of glass–ceramics. For the first time, materials capable of meeting the exacting challenges of metal-free tooth replacements became available. Development of these materials followed a complex path. Glass–ceramics for the fabrication of low-load-bearing inlays were introduced first, followed by glass–ceramics for crowns and bridges. This paved the way to gradual replacement of amalgam and metals as framework materials. Furthermore, glass–ceramic dental biomaterials offer an additional advantage over other groups of materials. Because of their advantageous working properties, they allow the application of modern processing techniques, such as viscous flow molding and CAD/CAM machining.

**Mica-Type Glass–Ceramics**

DICOR® (Corning Inc./Dentsply Int.) was the first glass–ceramic developed for restorative tooth replacements (Fig. 6). Mica crystals of the type of tetrasilicic mica, \(\text{KMg}_{2.5}\text{Si}_4\text{O}_{10}\text{F}_2\), were precipitated by means of controlled crystallization in the \(\text{SiO}_2–\text{MgO–K}_2\text{O–F}\) system. First clinical tests with inlays and crowns were performed as early as in 1979. This glass–ceramic featured translucent properties and was capable of reproducing the optical characteristics of natural teeth. Flexural strength was around 150 MPa. This material stood out from others because the base glass was processed by means of molding technology. Additional heat treatment was required to convert the base glass into the glass–ceramic. In addition to applications that involved the use of molding technology, machinable types of
mica glass-ceramics, such as DICOR®, MGC, became available to manufacture dental devices. This was an important development paving the way toward promising new technologies.

**Leucite-Type Glass–Ceramics**

At the end of the 1980s, special molding technology that eliminated the need for additional heat treatment became available, allowing fabrication of inlays and crowns from leucite, KAlSi2O5, and glass–ceramics.29,30 Principles of controlled surface nucleation and surface crystallization in base glasses of the SiO2–Al2O3–K2O–Na2O system were applied in these glass–ceramics.31 The resulting product, IPS Empress® (Ivoclar Vivadent AG, Schaan, Liechtenstein), was introduced worldwide in 1991 (Table III, Fig. 6). From 1991 up to 2008, approximately 36.5 million dental restoration units had been produced using this molding technique (Table IV). With this material, a lost-wax technique and subsequent viscous flow molding processes enable fabrication of highly individualized inlays and crowns, offering a high degree of accuracy of fit. The molding processes are performed in specially designed ceramic press furnaces, for example EP 500, EP 600, EP 3000, and EP 6000 (Ivoclar Vivadent AG), using a temperature range between 1000°C and approximately 1200°C (depending on the specific formulation).

The IPS Empress® glass–ceramic exhibits a coefficient of thermal expansion, CTE, of $15 \times 10^{-6}$ to $18.25 \times 10^{-6}$ K$^{-1}$ m/m (depending on the leucite content). Flexural strengths are approximately 160 MPa, which can be increased by glazing and additional heat treatment. The material’s wear behavior in relation to natural dentition deserves particular mention. Because this glass–ceramic is characterized by similar abrasive properties as natural teeth, the opposing tooth structure of the human dentition is not damaged during mastication.

In 2005, IPS Empress® Esthetics, an even more translucent version of the above leucite glass–ceramic, was developed. Improved optical qualities allow fabrication of dental replacements that are even more similar to natural teeth. Typical applications are dental inlays, veneers, and crowns (Fig. 7).

These glass–ceramics are highly machinable, as the leucite crystals incorporated into them exhibit pronounced polysynthetic twinning.31 Inlays and crowns can be prepared by machining the material with diamond tools in a CEREC unit (Sirona, Bensheim, Germany). As a result, patients only need one appointment to have their restoration completed.

**Lithium Disilicate Glass–Ceramics**

To expand the range of indications of glass–ceramics to include dental bridges, the flexural strength and toughness had to be improved compared with the strength of leucite glass–ceramics. For this purpose, lithium disilicate (Li2Si2O5) glass–ceramics came into use. Wide-ranging developments have taken place in conjunction with this material system.32–38 The main crystal phase is produced in the special base glass of the SiO2–Li2O–K2O–ZnO–P2O5–Al2O3–La2O3 system by means of heterogeneous nucleation and crystallization. In the process, an interlocking microstructure with a crystal content of > 60 vol% is achieved. The resulting product was called IPS Empress® 2 (Ivoclar Vivadent AG) and was launched on the global market in 1999 as a framework material for small three-unit bridges in the anterior region (Fig. 6).

A significant improvement over IPS Empress® 2 was achieved in the SiO2–Li2O–K2O–Al2O3–ZrO2 system and resulted in the development of the product IPS e.max® (Ivoclar Vivadent AG) (Table III, Fig. 6).39–42

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**Table III. Glass-Ceramic Type (Main Crystal Phase)-Base Glass System—Processing Technology**

<table>
<thead>
<tr>
<th>Crystal phase</th>
<th>Glass system</th>
<th>Processing</th>
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<tbody>
<tr>
<td>KAlSi2O5 (leucite)</td>
<td>SiO2–Al2O3–K2O</td>
<td>Molding, machining</td>
</tr>
<tr>
<td>Li2Si2O5 (lithium disilicate)</td>
<td>SiO2–Li2O–P2O5–Al2O3–K2O</td>
<td>Molding, machining</td>
</tr>
<tr>
<td>Ca5(PO4)3F (Fluorapatite)</td>
<td>SiO2–Al2O3–Na2O–CaO–P2O5–F</td>
<td>Sintering, molding</td>
</tr>
<tr>
<td>KAlSi2O5 (leucite) and Ca5(PO4)3F (Fluorapatite)</td>
<td>SiO2–Al2O3–Na2O–K2O–CaO–P2O5–F</td>
<td>Sintering</td>
</tr>
</tbody>
</table>
Intensive study of the fracture propagation in this glass-ceramic showed that the high fracture toughness, measured as a $K_{IC}$ value, of 2.3 MPa m$^{0.5}$ (based on the SEVNB method), was caused by crack deviation in the vicinity of the disilicate crystals. When being deviated, the propagating crack loses a considerable amount of energy. This loss of energy results in a high degree of flexural strength (up to 440 MPa) and toughness.

The product group of IPS e.max® encompasses several types of materials. The biomaterial IPS e.max® Press presents a moldable glass-ceramic and the biomaterial IPS Empress® CAD (and ProCAD):

1979 DICOR® glass-ceramic: first clinical tests as moldable glass-ceramic for dental restoration
1991 IPS Empress®: moldable leucite based glass-ceramic for inlays, crowns, veneers
1997 IPS Empress® Cosmo Post: ZrO$_2$-containing glass-ceramic for fixation of ZrO$_2$ posts
1998 IPS ProCAD®: machinable leucite based glass-ceramic for inlays, crowns, veneers
1999 IPS d.SIGN®: leucite-apatite glass-ceramic to veneer metal frameworks, specially dental crowns and long-span bridges
2000 IPS Empress® 2 / IPS Eris for E2: lithium disilicate glass-ceramic veneered with fluoroapatite glass-ceramic to fabricate dental crowns and small three-unite dental anterior bridges
2004 IPS Empress® Esthetic: leucite based glass-ceramic with high optical properties close to the natural tooth
2005 IPS e.max® Press: lithium disilicate as moldable glass-ceramic for inlays, crowns and small dental bridges
2005 IPS e.max® Zir Press: Fluoroapatite glass-ceramic to veneer high toughness sintered ZrO$_2$ frameworks (specially crowns and posterior bridges)
2005 IPS e.max® CAD: machinable lithium disilicate glass-ceramic, specially for dental inlays and crowns
2009 IPS e.max® Press HT and IPS e.max CAD HT: high translucent (HT) lithium disilicate glass-ceramic as moldable (Press) and machinable (CAD) glass-ceramic for dental application

Table IV. Clinical Applications of Special Types of Glass-Ceramics as Biomaterials for Dental Restoration

<table>
<thead>
<tr>
<th>Product</th>
<th>Number of units (one unit represents one dental crown, inlay, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPS Empress®</td>
<td>36.5 million (1991–2008)</td>
</tr>
<tr>
<td>IPS d.SIGN®</td>
<td>75.5 million (1999–2008)</td>
</tr>
<tr>
<td>IPS Empress® CAD (and ProCAD)</td>
<td>4.5 million (1998–2008)</td>
</tr>
</tbody>
</table>

**Fig. 6. Time line for development of glass–ceramics for dental restorations.**

**Fig. 7. Leucite type glass–ceramics: dental inlay, veneer, crown (from left).**
IPS e.max CAD presents, a machinable glass–ceramic. The IPS e.max Press glass–ceramics are distinguished by the fact that these materials are processed into inlays, crowns, and bridges by the application of molding technology at a temperature of 920°C. The glassy matrix enables the use of viscous flow molding. However, similar to the initial product, the end product exhibits a dense microstructure, while partial crystal orientation caused by the viscous flow process may be present. The glass–ceramic is veneered with fluoroapatite glass–ceramic (Fig. 8).

Compared with leucite-containing glass–ceramics, it may be more difficult, if at all possible, to machine high-toughness and high-strength lithium disilicate glass–ceramics dental restorations with the CEREC* system (Sirona). In order to resolve this problem, an intermediate product, easier to machine, has been developed. This lithium metasilicate glass–ceramic demonstrates a singular blue color. After the blue glass–ceramic has been machined and tried-in in the mouth of the patient, it undergoes a heat treatment at 850°C. During thermal treatment, it is transformed into a lithium disilicate glass–ceramic.

Fluoroapatite Glass–Ceramics

The needle-like fluoroapatite crystals, Ca$_5$(PO$_4$)$_3$F, contained in glass–ceramics (IPS e.max* Ceram, Ivoclar Vivadent AG) may produce such a favorable light-scattering effect that the resulting translucency corresponds to that of natural teeth. The objective was to develop a veneering ceramic that offered tooth-like optical properties. The tooth-like translucency and the CTE of $9.5 \times 10^{-6} \text{K}^{-1} \text{m/m}$ enabled the resulting glass–ceramic to be used on lithium disilicate glass–ceramics as well as on high-toughness $3\text{Y}_2\text{O}_3–\text{ZrO}_2$ sintering ceramics. Sintered glass–ceramic devices are achieved by machining open-pore materials and subsequently sintering them to a high density. The high toughness of approximately 4.5 MPa m$^{0.5}$ (according to SEVNB) allows the fabrication of metal-free long-span bridges.

ZrO$_2$-Containing Glass–Ceramics

With the objective to achieve high levels of toughness and a CTE adjusted to that of ZrO$_2$-sintered ceramics, a ZrO$_2$-containing glass–ceramic (IPS Empress* Cosmo Post, Ivoclar Vivadent AG) was developed. Controlled crystallization was used to produce $\text{Li}_2\text{ZrSi}_6\text{O}_{15}$ as the main crystal phase. This glass–ceramic offers the advantage over other products in that it can be pressed onto ZrO$_2$ posts by means of a molding process. The resulting dental posts are suitable for the buildup of devitalized teeth and offer metal-free, highly esthetic solutions for patients.

Leucite–Apatite Glass–Ceramics

There is still interest from the market to use glass–ceramics for veneering of metal frameworks. In addition to tooth replacements, glass–ceramic-veneered metal restorations may present an optically esthetic solution for some patients. For instance, long-span bridges and high-load-bearing tooth replacements in the posterior region may necessitate a metal-ceramic reconstruction. For this application, a glass–ceramic with a coefficient of thermal expansion matched to that of various dental alloys had to be developed. The resulting material is a leucite–apatite glass–ceramic (IPS d.SIGN*, Ivoclar Vivadent AG) derived from the SiO$_2$–Al$_2$O$_3$–K$_2$O–Na$_2$O–CaO–P$_2$O$_5$–F system (Table IV, Fig. 6). The leucite content enables this glass–ceramic to attain the required CTE of approximately $12 \times 10^{-6} \text{K}^{-1} \text{m/m}$. Fluoroapatite needles provide the product with the required translucent qualities. Nucleation and crystallization in the base glasses of this material are conducted with a twofold reaction. Leucite is formed by surface
crystallization, while apatite is precipitated by the mechanisms of internal (volume) processes.

This glass–ceramic can be applied in two different techniques: the sintering technique is the most widely used; the glass–ceramic powder is applied in the form of a high-viscosity, aqueous slip and sintered at temperatures of approximately 850°C. The restoration is built up to resemble the natural tooth by layering a variety of materials in different shades and degrees of translucency.

The molding technique is the second technique that can be used to process these veneering glass–ceramics. If this technique is used, a glass–ceramic ingot may, for instance, be pressed onto a metal framework according to the principles of the lost-wax technique. This method is particularly convenient for large-scale dental laboratories.

Conclusions

When all the products described above are considered together, glass–ceramic and glass–ceramic composite dental restorative materials cover the entire range of indications for anterior and posterior restorative tooth repair, and therefore, fully fulfill all requirements of patients for functional restoration of teeth. This is a major advance in the healthcare of patients worldwide and represents one of the great contributions of glass and glass–ceramic research to mankind.

References