Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2014; 2(6E):3231-3237 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com **DOI:** 10.36347/sjams.2014.v02i06.075

Review Article

Bioactive Materials: A Comprehensive Review

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Abstract: Bioactive materials have evolved over the past three decades from relatively specialized, highly biocompatible, but low-strength dental materials to new compositions for expanded use in restorative dentistry. The objective of this review is to understand the concept of bioactivity and to compare and contrast the various bioactive materials while shedding light on new applications for this evolving class of materials.
Keywords: Bioactivity, MTA, Biocompatibilty.

INTRODUCTION

The evolution of dentistry is closely associated with the advancements in dental materials. From the dawn of history dental practitioners have been in the quest of ideal restorative dental materials. Though initially ideal restorative materials were thought to be the one which were biologically inert and hence biocompatible the past two decades have seen the emergence of bioactive materials as a promising alternative.

The interaction between restorative dental materials and tooth tissue encompasses multiple aspects of dental anatomy and materials science. Until relatively recently, many adhesive dental restorative materials were thought to have a passive hard tissue interaction based on simple infiltration with the enamel or dentin upon which they were placed. However, there is increasing interest in mapping the interactions between materials and tooth tissues, where the former has a more aggressive interaction with the latter, while promoting "bioactivity".

The objective of this review is to understand the concept of bioactivity and to appraise the various bioactive materials available in the market so as to give the clinician a guide as to which material is favorable for different clinical situations.

BIOACTIVITY

In 1969, Hench gave the concept of bioactivity as "A bioactive material is one that elicits a specific biological response at the interface of the material which results in the formation of a bond between the tissues and the material" [1].

CLASSIFICATION OF BIOACTIVE MATERIALS

Hench introduced some criteria for the evaluation of bioactivity of a material. However, a new classification was proposed in 1994 [2], according to which bioactive materials are divided into 2 groups:

Class A: Osteoproductive Materials

In osteoproductive materials the bioactive surface is colonized by osteogenic stem cells. Class A bioactivity occurs when a material elicits both an *intracellular* and an *extracellular* response at its interface.eg: 45S5 Bioglass. These materials are both osteoproductive and osteoconductive.

Group B: Osteoconductive Materials

The osteoconductive materials simply provide a biocompatible interface along which bone migrates. Osteoconductive bioactivity occurs when a material elicits only an *extracellular* response at its interface.eg: Synthetic hydroxyapatite (HA).

BIOACTIVE MATERIALS IN PRACTICE

Mineral Trioxide Aggregate

Torabinejad first developed mineral trioxide aggregate (MTA) as a surgical root repair material in 1993. Subsequently, significant interest has been shown in MTA, due to its biocompatibility and potential bioactivity.

Mineral trioxide aggregate (MTA) is a mechanical mixture of three powder ingredients: Portland cement (75%), bismuth oxide (20%), and gypsum (5%) [3]. It also contains trace amounts of SiO_2, CaO, MgO, K_2SO_4 and Na_2SO_4. The major component, Portland cement, is

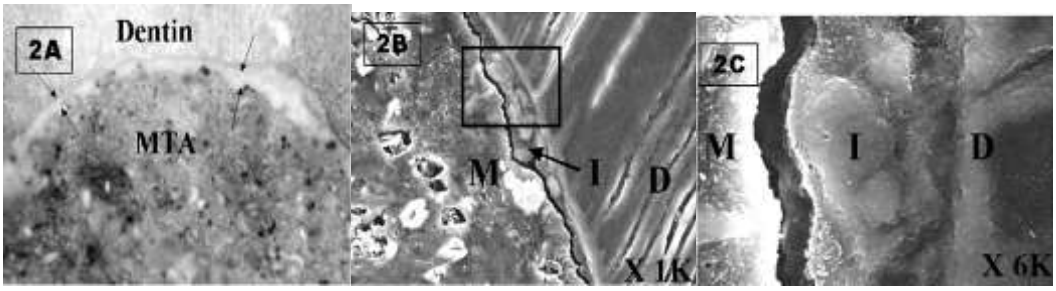
a mixture of dicalcium silicate, tricalcium silicate, tricalcium aluminate, and tetracalcium aluminoferrite.

is prepared as a mixture of powder and water and is used in a slurry form, which gradually hardens in the oral environment. Its excellent biocompatibility has been evidenced in several favorable biologic processes induced by MTA, namely, minimal toxicity and pulpal irritation, mild periapical inflammation, nonmutagenicity, cell adherence and growth, increased levels of alkaline phosphatase and osteocalcin, interleukin production (IL-6, IL-8), periodontal ligament attachment, cementum growth, and dentinal bridge formation [4-16].

Sarkar *et al*. [17] in a landmark study examined the fundamental physicochemical interaction between MTA and the oral environment that instigates those biologic responses. They envisioned that after the placement of MTA in root canals and its gradual dissolution, HA crystals nucleate and grow, filling the microscopic space between MTA and the dentinal wall.

Initially, this seal is mechanical. With time, a diffusion-controlled reaction between the apatite layer and dentin leads to their chemical bonding. The result is the creation of a seal at the MTA-dentine interface. This study showed the growth of crystalline deposits on the surface of MTA and a zone of crystalline structures along the pulp-MTA interface. (Fig.1). The crystalline structure analyzed was found to contain Ca and P, suggesting the formation of HA.

They concluded that MTA is not an inert material in a simulated oral environment; it is bioactive ie. in contact with an STF, it dissolves, releasing all of its major cationic components and triggering the precipitation of HA on its surface and in the surrounding fluid. It appears to bond chemically to dentin when placed against it, possibly via a diffusion controlled reaction between its apatitic surface and dentin. The clinical success of MTA, in terms of its sealability, biocompatibility, and dentinogenic activity, is thus rooted in the aforementioned physicochemical reactions.



(A) (B) (C)

Fig. 1: (A) Typical optical micrograph of a mineral trioxide aggregate— dentin cross-section (X200). (B) Typical scanning electron micrograph of a mineral trioxide aggregate (MTA)—dentin cross-section (X1000). M: MTA; I: interface; D: dentin. (C) Area identified by box in B at a higher magnification: (X6000). Courtesy: Sarkar *et al*. [17]

Host-Response to MTA

A bioactive material should be capable of stimulating specific biological responses via biochemical and biophysical reactions that result in the formation of an apatite layer. The ability to induce the formation of apatite allows the integration of the biomaterial into the environment. However, host responses to biomaterials are dependent on the innate and nonspecific immune responses that occur in the surrounding tissues.

Jessie *et al*. [18] evaluated specific signaling molecules related to the inflammatory process and the biomineralization ability of MTA to assess host-biomaterial interactions in vivo. They showed that MTA induces a proinflammatory and pro–wound healing environment. The biomineralization process occurs simultaneously with the acute inflammatory response. When MTA is implanted, a series of biochemical and biophysical reactions occurs at the MTA-dentin-tissue interface. Subsequently, this activates cellular and tissue events in the inflammatory and biomineralization processes and culminates in the formation of an apatite-like layer that allows the integration of the biomaterial into the environment.

Bioaggregate

Over the past decade, new developments, especially bioceramic nanotechnology, have been brought into endodontic material science [19]. BioAggregate (Innovative Bioceramix, Vancouver, BC, Canada), a novel laboratory-synthesized water-based cement, is reported to present improved performance compared with MTA. As the first nanoparticular mineral cement introduced in the dental market, BioAggregate is produced under controlled conditions, resulting in a pure and fine white hydraulic cementlike powder composed of contamination-free bioceramic nanoparticles [20].

Composition of bioaggregate is similar to MTA. It is described by its manufacturer as an insoluble, radiopaque, and aluminum-free material primarily composed of calcium silicate, calcium hydroxide, and calcium phosphate [21]. BioAggregate has shown excellent sealing ability when used for root-end filling

[22]. Many in vitro studies have shown that BioAggregate exhibits potent antimicrobial action, excellent biocompatibility, and significant induction of bone and periodontal regeneration [23-26]. Moreover, BioAggregate was recently shown to display superior local and systemic biocompatibility in vivo compared with MTA [26, 27]. With respect to pulp capping, a recent study showed that BioAggregate exerts a greater potential to induce odontoblastic differentiation and mineralization than that of MTA [28].

Another study showed that Bioaggregate is able to promote the adhesion, migration, and attachment of HDPCs, indicating its excellent cytocompatibility compared with MTA [29].

Biodentine

In 2011, Biodentine™, a quick-setting calcium-silicate based dental cement, was introduced by Septodont (SaintMaur des Fosses – France). BiodentineTM was developed as a dentin replacement material, a novel clinical application of this family of materials, intending it to function as a coronal restoration.

Biodentine™ is principally composed of a highly purified tri-calcium silicate powder that is pre-pared synthetically in the lab de novo, rather than derived from a clinker product of cement manufacture [30]. Additionally, Biodentine™ contains di-calcium silicate, calcium carbonate and zirconium dioxide as a radiopacifer. The di-calcium and tri-calcium silicate phases form around 70% of the weight of Biodentine's dehydrated powder, which is close to that of white MTA and white Portland cement [31, 32].

Unlike MTA, Biodentine does not contain calcium sulphate, aluminate, or alumino-ferrate. The powder is dispensed in a two part capsule to which is added an aliquot of hydration liquid, com-posed of water, calcium chloride, and a water reducing agent. Despite similar constituents, there is significant variation in calcium-silicate dental cement manufacturing processes. This affects the purity of their constituents and hydration products, as well as their behavior [33].

The relatively short setting time (around 12 min) [30], can enable the use of this cement for restorative procedures; impossible with MTAs that achieve an initial setting 3–4 h [34].

MTAs include impurities and contaminating heavy metals such as chromium, arsenic, and lead [35]. This suggests their manufacture is similar to OPCs but less segregated and refined as the particle sizes also vary more widely [36]. On the other hand, Biodentine™ has been produced under more stringent production conditions from raw materials, in an attempt to avoid any potential contamination of the basic constituents, and to avoid the incorporation of aluminum oxide [33]. This goal has been achieved by Active Biosilicate Technology [30].

A specific feature of Biodentine™ is its capacity to continue improving with time over several days until reaching 300 MPa after one month [30]. This value becomes quite stable and is in the range of the compressive strength of natural dentine i.e., 297 MPa [37].

The interfacial properties of BiodentineTM and a glass-ionomer cement (GIC Fuji IXGP) with dentin have been studied using confocal laser scanning microscopy (CLSM), scanning electron microscopy (SEM), micro-Raman spectroscopy, and two-photon auto-fluorescence and second harmonic-generation (SHG) imaging by Atmeh *et al*. [38]. Their results indicated the formation of tag-like structures alongside an interfacial layer called the "mineral infiltration zone" (Fig. 2), where the alkaline caustic effect of the calcium silicate cement's hydration products degrades the collagenous component of the interfacial dentin. This degradation leads to the formation of a porous structure that facilitates the permeation of high concentrations of Ca2+, OH−, and CO32−ions, leading to increased mineralization in this region. Comparison of the dentin–restorative interfaces shows that there is a dentin-mineral infiltration with the BiodentineTM, whereas polyacrylic and tartaric acids and their salts lead to the diffuse penetration of the GIC; consequently a new type of interfacial interaction, "the mineral infiltration zone", is suggested for these calcium-silicate-based cements.

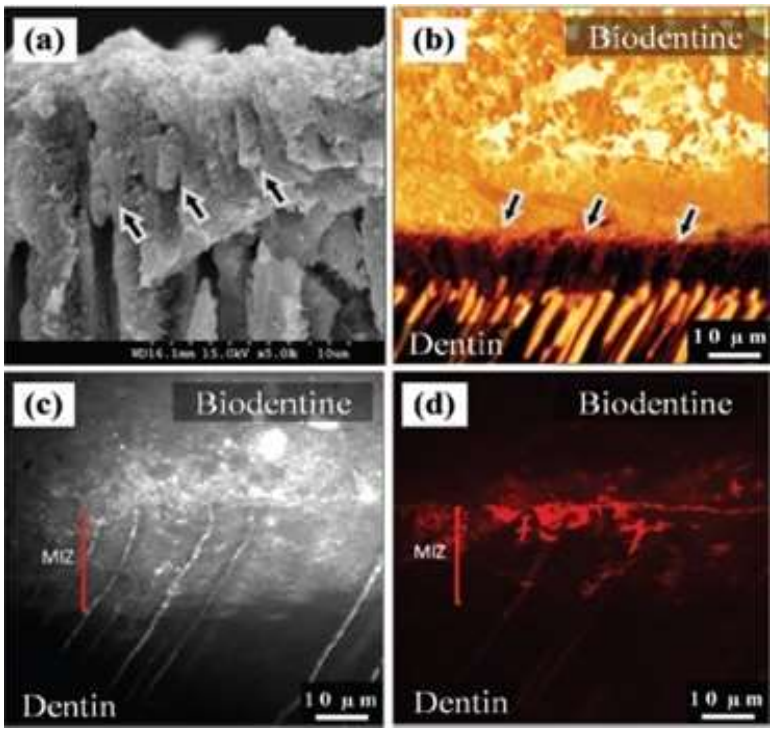


Fig. 2: Interfacial characteristics. (a) SEM micrograph of fractured dentin beneath a Biodentine restoration. Tag-like structures were detected forming within the dentinal tubules (arrows). (b) Fluorescence mode CLSM image showing the cement tags, which appear on the interfacial surface of the fluorescein-labeled Biodentine (above) after it was pulled away from dentin due to desiccation. 63x/1.4NA OI. (c) Reflection-mode TSM image for the dentin/Biodentine interface. The mineral infiltration zone (MIZ) appears as a band of highly reflective dentin beneath the interface, indicating a change in dentin's mineral content within this zone. The fluorescence-mode image of the same area (d) shows the distribution of Rhodamine-B dye, which permeated from the pulp chamber into the interface and cement.
Courtesy: Atmeh *et al.* [38]

Endosequence Root Repair Material

Brasseler USA (Savannah, GA) has recently introduced the EndoSequence Root Repair Material (RRM) and EndoSequence Root Repair Putty (RRP), which use bioceramic technology to address some of the inconsistencies associated with conventional MTA. These new materials are produced as a premixed product to provide the clinician with a homogeneous and consistent material.

Particle size has been shown to affect the early strength of a material. The particle size also affects the ease of handling, which is clinically relevant. ProRoot white MTA and white AMTA particle sizes have been reported anywhere from less than 1 to approximately 30 µm. In comparison, both of the new bioceramic materials from Brasseler report their largest particle size of 0.35 µm, with approximately 50% of the particles being nano (1 X 10^{-3} µm) in size [39]. The drastic reduction in particle size introduced with the Brasseler products directly addresses one of the chief complaints of MTA users i.e. handling characteristics.

hey have excellent physical and biological properties and are easy to work with. They are hydrophilic, insoluble, radiopaque, aluminum-free, and of high pH – 12.8 [39]. Presence of moisture is required for the materials to set and harden.

There is not much literature available regarding ERRM. Alanezi et al[40] were the first to publish a study regarding this material. The authors compared ERRM with MTA (gray and white) using fibroblast cell culture from mice and evaluated cytotoxicity of these materials using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. The results of their study showed that ERRM had similar cytotoxicity with both MTA samples in set and fresh conditions.

Damas *et al*. [41] studied the cytotoxicity of ERRM and 2 different brands of MTA and human dermal fibroblasts using the MTT assay. They showed that all materials had cell viability above 91.8%, and, overall, there was no statistical significant difference between ERRM and MTA-Angelus (Angelus, Londrina, Brazil) and ProRoot MTA.

Bioactive Root Canal Sealers

Bioceramic sealers have been introduced in the market in an attempt to provide an obturation method that can be successfully and predictably performed by a majority of practitioners while taking advantage of its

biocompatibility and physical properties. Eg. BC Sealer (Brasseler USA); iRoot SP (Innovative BioCreamix Inc).

These sealers result in a gap-free interface between gutta-percha (GP), sealer, and dentin. Also, these sealers are highly biocompatible and are antibacterial because of their highly alkaline Ph [42] Although, the use of these sealers should be done cautiously because of concerns regarding endodontic retreatment. A study evaluated the retreatability of BCS. The results indicate obturation with BCS, and a single GP master cone may result in blockage of the apical foramen and a loss of patency in some cases [43].

BIOACTIVE LUTING AGENTS

The most recent modification in bioactive chemically bonded cements with a predominant use in restorative dentistry has been the introduction of a calcium aluminate–glass ionomer luting cement (CM Crown & Bridge, originally named Xera Cem).

The luting cement is actually a hybrid composition combining both calcium aluminate and glass ionomer chemistry. The setting mechanism of Ceramir C&B is a combination of a glass ionomer reaction and an acid-base reaction of the type occurring in hydraulic cements [44, 45].

Glass ionomer component contributes to: Low initial, short-duration pH, improved flow and setting characteristics, early adhesive properties to tooth structure, early strength properties. Calcium aluminate component in the cement contribute to: increased strength and retention over time, biocompatibility, sealing of tooth material interface, bioactivity-apatite formation, stable, sustained long-term properties, lack of solubility/degradation, ultimate development of a stable basic cement pH.

CONCLUSION

From this review of literature it can be concluded that MTA's effectiveness in a variety of clinical indications, including pulp cap, pulpotomy, root ending filling, repair of root resorption, repair of root perforations, and apexification can be attributed to its bioactivity. Additional materials with compositions similar to MTA have been introduced, including Bioaggregate, Biodentine, Endosequence Root Repair Material. iRoot BP, and BP Plus. Clinical indications for use of bioactive cements have expanded further into uses such as lining and bases (Biodentine) and luting cements for crown and bridge applications with the introduction and laboratory/clinical validation of a calcium aluminate/glass ionomer luting cement (CM Crown & Bridge). Strength and physical properties of Bioactive cements have increased gradually and are now approaching the compressive strength range of conventional, water-based GICs.

Thus in the near future it can be envisioned that there will be better alternatives in the field of restorative dentistry in the form of bioactive and biomimetic materials. Various new materials such as capasio, endobinder, fluoride-containing MTA are being extensively researched. New mechanisms for adhesion, integration, and sealing of dentin are in the works using bioactive and biomimetic technologies. These materials will behave more like natural teeth and will change the way we think about restoring teeth.

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