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Comprehensive Review Of Current Endodontic Sealers

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Comprehensive review of current endodontic sealers

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Endodontic sealers for non-surgical root canal treatment (NSRCT) span many compositions and attributes. This comprehensive review discusses current types of endodontic sealers by their setting reaction type, composition, and properties: zinc oxide-eugenol, salicylate, fatty acid, glass ionomer, silicone, epoxy resin, tricalcium silicate, and methacrylate resin sealers. Setting time, solubility, sealing ability, antimicrobial, biocompatibility, and cytotoxicity are all aspects key to the performance of endodontic sealers. Because sealing ability is so important to successful outcomes, the relative degree of microleakage among all the relevant sealers was calculated by way of a meta-analysis of relevant literature. Compared to AH Plus, tricalcium silicate sealers show the lowest relative microleakage among the sealers assessed, followed by silicone sealers and other non-AH Plus epoxy resin sealers. Tricalcium silicate sealers also exhibit the most favorable antimicrobial effect and excellent biocompatibility. Future sealers developed should ideally combine a hermetic seal with therapeutic effects.

Keywords: Endodontic sealers, Biocompatibility, Bioactivity, Dentin-sealer interface, Sealing ability

INTRODUCTION

Choosing an endodontic sealer for clinical use is a decision that contributes to the long-term success of non-surgical root canal treatment (NSRCT)¹. Sealers are used as a thin tacky paste which functions as a lubricant and luting agent during obturation, allowing the core obturation material, such as gutta-percha points or other rigid materials, to slide in and become fixed in the canal^{2,3}. Sealers can fill voids⁴, lateral canals⁵, and accessory canals where core obturation materials cannot infiltrate^{6,7}. If the sealer does not perform its function, microleakage may cause NSRCT failure *via* clinically undetectable passage of bacteria, fluids, molecules or ions between the tooth and restorative material^{8,9}. Knowing the qualities and characteristics of an endodontic sealer is critical to determining the best selection and application for each clinical case.

Endodontic sealers are categorized by composition based on setting reaction and composition: zinc oxide-eugenol, salicylate, fatty acid, glass ionomer, silicone, epoxy resin, tricalcium silicate, and methacrylate resin sealer systems (Table 1). Some novel sealers contain fillers or ceramic powders including calcium hydroxide, mineral trioxide aggregate (MTA), and calcium phosphate; however, they are fundamentally composed of the above sealer matrices. Until recently, many review articles were published within sealer types¹⁰⁻¹⁶. However, few reviews have been published that cover all sealer types^{17,18}. Therefore, in this comprehensive review, a historical perspective of each sealer type will be discussed first, followed by a description of the properties of all sealer types, such as setting time and solubility, sealing ability, antimicrobial activity, and biocompatibility and cytotoxicity. Sealer attributes

such as the rheology¹⁹, radiopacity²⁰, and tooth discoloration²¹⁻²³ have been shown to be satisfactory and will not be discussed in detail.

CURRENT ROOT CANAL SEALERS AND HISTORY

Chelate formation

Many dental luting agents set by way of a chelation reaction, the formation of metal complexes with polydentate (usually organic) ligands²⁴. Two of the most common chelates used in dentistry are eugenolates and salicylates. For eugenolates, the setting reaction starts with water that hydrolyzes the zinc oxide to form zinc hydroxide. The zinc hydroxide and eugenol chelate and solidify²⁵. For salicylates, the ion is calcium, usually formulated using calcium oxide. Although uncommon, fatty acids have also been used as ligands for chelate sealers, in conjunction with zinc oxide.

1. Zinc oxide-eugenol-based sealers

The zinc oxide-eugenol (ZOE) sealer formula developed by Rickert and Dixon^{26,27} in 1931 became Kerr sealer, and the formula developed by Grossman in 1936²⁸ became Proco-Sol sealer (StarDental, Lancaster, PA, USA). The ZOE sealers have been a standard in endodontics since their development, based on their long-term success. ZOE sealers contain zinc oxide powder and eugenol liquid, an essential oil derived from cloves^{29,30}. When mixed and placed in moist root dentin, the zinc oxide and eugenol complex to form an amorphous gel³¹. Residual zinc oxide powder remains in the gel, forming a rigid matrix³². Some of these powder-liquid sealers contain silver in the powder component (Kerr formula) which has caused darkening of the teeth. Silver-free formulas that avoid staining were developed to address this issue; including

Table 1 Endodontic sealer types

Type	Product name (manufacturer, country)		Composition
Zinc oxide-eugenol	Pulp Canal Sealer (Kerr, USA)	Powder	Zinc oxide, Precipitated silver, Oleo resin, Thymol iodide
		Liquid	Oil of cloves, Canada balsam
	Proco-Sol (StarDental, USA)	Powder	Zinc oxide, Staybelite resin, Bismuth subcarbonate, Barium sulfate
		Liquid	Eugenol, Sweet oil of almond
	Tubli-Seal (Kerr, USA)	Base	Zinc oxide, Bismuth trioxide, Oil+wax, Thymol iodide, Barium sulfate
		Catalyst	Eugenol, Polypale resin, Annidalin
	Endofill (Dentsply Petrópolis Ind, Brazil)	Powder	Zinc oxide, Hydrogenated resin, Bismuth subcarbonate, Barium sulfate, Sodium borate, Dexamethasone Acetate, Hydrocortisone Acetate, Polyoxymethylene, Thymol iodide
		Liquid	Eugenol, Oil of sweet almonds
	Rocanal 2 (La Maison, Switzerland)	Powder	Zinc oxide, Titanium oxide, Orthophenylphenol, Calcium tungstate
		Liquid	Eugenol
	Canals (Showa Yakuhin Kano, Japan)	Powder	Zinc oxide, Barium sulfate, Bismuth subcarbonate, Rosin
		Liquid	Clove oil, Olive oil
	Nishika Canal Sealer Eugenol (Nippon Shika Yakuhin, Japan)	Paste A	Eugenol, Rosin, Ester gum
		Paste B	Olive oil, Zinc oxide, Bismuth subcarbonate
	Master-Dent Root Canal Sealer (Dentonics, USA)	Powder	Zinc oxide, Staybelite resin, Bismuth subcarbonate, Barium sulfate, Sodium borate
Liquid		Eugenol	
Pulpdent Root Canal Sealer (Pulpdent, USA)	Powder	Zinc oxide, Calcium phosphate, Zinc stearate, Barium sulfate	
	Liquid	Eugenol, Canada balsam	
CRCS (Ivoclar Vivadent, Lichtenstein)	Powder	Zinc oxide, Calcium hydroxide, Bismuth dioxide, Barium sulfate	
	Liquid	Eugenol, Eucalyptol	
Bioseal (OGNA Pharmaceuticals, Italy)	Powder	Zinc oxide, Natural resin, Calcium hydroxide, Barium sulfate, Hydroxyapatite, Thymol iodide, Zinc acetate	
	Liquid	Purified oleoresin, Bi-distilled eugenol	
Salicylate	Sealapex (Kerr, USA)	Base	N-ethyltoluenesulfonamide, Calcium oxide, Zinc oxide, Silicon dioxide
		Catalyst	Methyl salicylate, 2,2-dimethylpropane-1,3-diol, Isobutyl salicylate, Bismuth trioxide, Titanium dioxide pigment, Zinc stearate
	MTA Fillapex (Angelus, Brazil)	Paste A	Methyl salicylate, Butylene glycol, Colophony, Bismuth trioxide, Fumed silica, Titanium dioxide,
		Paste B	Fumed silica, Titanium dioxide, Tricalcium silicate, Dicalcium silicate, Calcium oxide, Tricalcium aluminate, Pentaerythritol rosinate, p-Toluenesulfonamide

Table 1 continued

Salicylate	Apexit (Ivoclar Vivadent, Lichtenstein)	Base	Calcium hydroxide, Zinc oxide, Calcium oxide, Silicon dioxide, Zinc stearate, Hydrogenised colophony, Tricalcium phosphate, Polydimethylsiloxane
		Activator	Trimethylhexanediol disalicylate, Bismuth carbonate basic, Bismuth oxide, Silicon dioxide, 1,3 Butanediol disalicylate, Hydrogenised colophony, Tricalcium phosphate, Zinc stearate
	Apexit plus (Ivoclar Vivadent, Lichtenstein)	Base	Hydrated colophonium, Calcium hydroxide, Calcium oxide, Silicon dioxide, Phosphoric acid alkyl ester
		Activator	Disalicylate, Bismuth hydroxide, Bismuth carbonate, Silicon dioxide, Phosphoric acid alkyl ester
Zinc oxide-fatty acid	Canals-N (Showa Yakuhin Kano, Japan)	Powder	Zinc oxide, Bismuth subcarbonate
		Liquid	Fatty acids, Propylene glycol
	Nogenol (GC America, USA)	Base	Zinc oxide, Barium sulfate, Bismuth oxychloride, Vegetable oil
		Catalyst	Lauric acid, Chlorothymol, Hydrogenated rosin, Methyl abietate, Salicylic acid
Glass ionomer	Ketac-Endo (3M ESPE, USA)	Powder	Calcium aluminium lanthanum fluorosilicate glass, Calcium wolframate, Silicic acid, Pigments
		Liquid	Water, Tartaric acid, Polyethylene polycarbonic acid/ Maleic acid, copolymer
Silicone	GuttaFlow 2 (Coltene/Whaledent, USA)	Base	Zirconium oxide, Polymethylvinylsiloxane, Polymethylhydrogensiloxane, Gutta-percha
		Catalyst	Zirconium oxide, Polymethylvinylsiloxane, Platinum catalyst
	RoekoSeal (Coltene/Whaledent, USA)	Base	Zirconium oxide, Polymethylvinylsiloxane, Polymethylhydrogensiloxane
		Catalyst	Zirconium oxide, Polymethylvinylsiloxane, Platinum catalyst
Epoxy resin	AH 26 (Dentsply Sirona, Germany)	Powder	Bismuth oxide, Hexamethyleneteramine, Silver powder, Titanium oxide
		Paste	Bisphenol A diglycidyl ether
	AH Plus (Dentsply Sirona, Germany)	Paste A	Bisphenol A epoxy resin, Zirconium oxide, Bisphenol F epoxy resin, Calcium tungstate, Iron oxide, Silica
		Paste B	N,N-dibenzyl-5-oxanonadiamin-1,9, Amantiamine, Tricyclodecane-diamine, Calcium tungstate, Zirconium oxide
	Adseal (Meta Biomed, Korea)	Base	Bisphenol A diglycidyl ether –bisphenol A copolymer, 2-Hydroxyethyl salicylate, Calcium phosphate, Bismuth subcarbonate, Zirconium oxide
		Catalyst	Poly(1,4-butanediol)bis(4-aminobenzoate), Triethanolamine, Calcium phosphate, Bismuth subcarbonate, Zirconium oxide, Calcium oxideopolymer
	Acroseal (Septodont, France)	Base	Bisphenol A diglycidyl ether, Calcium hydroxide, Bismuth subcarbonate
		Catalyst	Hexamethylenetetramine, Venice turpentine, Enoxolone
	MM seal (Micro-Mega, France)	Base	Epoxy oligomer resin, Ethylene glycol salicylate, Calcium phosphate, Bismuth subcarbonate, Zirconium oxide
		Catalyst	Poly aminobenzoate, Triethanolamine, Calcium phosphate, Bismuth subcarbonate, Zirconium oxide, Calcium oxide

Table 1 continued

	Grey & Neo MTA Plus (NuSmile Avalon Biomed, USA)	Powder	Tricalcium silicate, Tantalite, Dicalcium silicate, Calcium sulfate, Silica
		Liquid	Water-based gel
	BioRoot RCS (Septodont, France)	Powder	Tricalcium silicate, Zirconium oxide
		Liquid	Aqueous solution of calcium chloride
Tricalcium silicate (MTA/ Bioceramic)	Endo CPM Sealer (EGEO, Argentina)	Powder	Silicon dioxide, Calcium carbonate, Bismuth trioxide, Barium sulfate, Propylene glycol alginate, Sodium citrate, Calcium chloride
		Liquid	Water-based gel
	iRoot SP/ EndoSequence BC/ Total Fill BC/ Edge Endo Sealer (Innovative Bioceramix, Canada)	One paste	Zirconium oxide, Calcium silicates, Calcium phosphate, Calcium hydroxide, Filler, Thickening agents
	Ceraseal (MetaBiomed, Korea)	One paste	Calcium silicates, Zirconium oxide, Thickening agent
	Endoseal MTA (Maruchi, Korea)	One paste	Calcium silicates, Calcium aluminates, Calcium sulfate, Radiopacifier, Thickening agent
	Bio-C Sealer (Angelus, Brazil)	One paste	Calcium silicates, Calcium aluminates, Calcium oxide, Zirconium oxide, Ferric oxide, Silicon dioxide, Thickening agent
	EndoREZ (Ultradent, USA)	Base	UDMA, Benzoyl peroxide
		Catalyst	Triethylene glycol dimethacrylate, p-Tolyldiethanolamine
Methacrylate resin	Epiphany (Resilon Research, USA)	Paste A	[After mixing] UDMA, PEGDMA, EBPADMA, Bis-GMA, Barium borosilicate glasses treated with silane, Barium sulfate, Silica, Calcium hydroxide, Bismuth oxychloride, Thiosinamine,
		Paste B	Cumene hydroperoxide, Photo initiator, Stabilizers, Pigments
	MetaSEAL (Hybrid Root SEAL) (Parkell, USA)	Powder	Bismuth carbonate, Organic filler, Sodium sulfinate
		Liquid	4-META/HEMA, Dimethacrylates, Photoinitiator, Water
	Super-Bond RC Sealer (Accel) (Sun Medical, Japan)	Powder	Zirconiumdioxide, Poly methyl methacrylate (PMMA)
		Liquid	Methyl methacrylate (MMA), 4-META
		Catalyst	Tributyl borane oxide (TBB), Hexane/Ethanol

UDMA: urethane dimethacrylate, PEGDMA: polyethyleneglycol dimethacrylate, EBPADMA: ethoxylated bisphenol A dimethacrylate, Bis-GMA: bisphenol A-glycidyl methacrylate, 4-META: 4-methacryloxyethyl trimellitate anhydride, HEMA: 2-hydroxyethyl methacrylate

Wach's Paste, the Grossman formulas, Proco-Sol sealer, followed by Tubli-Seal sealer (Kerr, Orange, CA, USA). ZOE sealers remain popular because of slow set, low cost, antibacterial properties, and ease of use³³. Although Roth sealer (Roth International, Chicago, IL, USA) was discontinued in 2018, many are currently commercially available: Pulp Canal Sealer (Kerr), Proco-Sol sealer, Tubli-Seal sealer, Endofill (Dentsply Petrópolis Ind, Rio de Janeiro, Brazil), Rocanal 2 (La Maison, Balzers, Switzerland), Canals (Showa Yakuhin Kano, Tokyo, Japan), Nishika Canal Sealer Eugenol (Nippon Shika Yakuhin, Shimonoseki, Japan), Master-Dent Root Canal

Sealer (Dentonics, Charlotte, NC, USA), and Pulpdent Root Canal Sealer (Pulpdent, Watertown, MA, USA).

Variations in ZOE sealers have been introduced over several decades. A ZOE-containing paraformaldehyde sealer was developed but was unsuccessful because formaldehyde causes coagulative necrosis, and residual formaldehyde disrupts local repair of affected areas³⁴; this sealer was toxic to periradicular tissues³⁵ and contraindicated. Sargenti introduced N2 sealer in 1973³⁶, which contained lead and mercury. The toxic metals were reported to be found in distant organ systems, having migrated from the radicular spaces³⁷. N2 was not

cleared by the U.S. Food and Drug Administration³⁸).

ZOE sealers are also a common matrix for sealers with therapeutic additives. For example, Calciobiotic Root Canal Sealer, CRCS, (Coltene/Whaledent, Cuyahoga Falls, OH, USA), is a ZOE sealer marketed as a “calcium hydroxide sealer”³⁹. Bioseal (OGNA Pharmaceuticals, Muggiò, Italy) is a ZOE-based sealer with added hydroxyapatite⁴⁰, but no special therapeutic effects have been reported.

2. Salicylate-based sealers

Salicylate-based sealers are typically referred to by their marketed therapeutic additives instead of by their composition. For example, Sealapex (Kerr) and Apexit/Apexit Plus (Ivoclar Vivadent, Schaan, Lichtenstein) are examples of a calcium-hydroxide-containing salicylate sealers. Calcium hydroxide [Ca(OH)₂] is both alkaline and antimicrobial, desirable qualities for a therapeutic sealer⁴¹. However, calcium hydroxide does not set and is slightly soluble in water. It must be used within a matrix to be an effective sealer⁴². Sealers containing calcium hydroxide were intended to promote osteogenesis and cementogenesis as well as create an antimicrobial environment⁴³. So-called “calcium hydroxide sealers” are often placed in their own sealer type categories when differentiating sealers. Despite this, all traditional “calcium hydroxide sealers” are composed of another luting matrix.

Unfortunately, Sealapex and Apexit/Apexit Plus have not demonstrated the clinical effects desired^{11,44}, while Sealapex and calcium hydroxide encourage apical closure by cementum deposition⁴⁵. The solvation of calcium hydroxide is required if therapeutic effects are to be achieved^{11,41,46,47}. Effective sealers, however, should not be soluble and should remain intact for as long as possible⁴⁸.

Similar to the above sealers, MTA Fillapex (Angelus, Londrina, Brazil) is a unique salicylate resin-based sealer that contains 15% MTA powder⁴⁹. MTA Fillapex should not be regarded as a tricalcium silicate (MTA, a bioactive ceramic) sealer since its composition is primarily resin⁴⁹. However, many researchers have wrongly referred to this sealer as “MTA-based”.

3. Fatty acid-based sealers

Eugenol is known to be a cytotoxic agent that affects a cell's membrane and respiratory functions, and clinician preparation of ZOE sealers can also affect cytotoxic outcomes⁵⁰⁻⁵³. As a result, non-eugenol zinc oxide sealers were developed to avoid issues with post-operative healing. Fatty acids are used instead of eugenol as chelating agents, although the structure of their metal complexes are typically less defined and consistent than with eugenolates and salicylates by nature of their mixed compositions. Canals-N (Showa Yakuhin Kako) is a fatty acid-zinc oxide sealer that uses linoleic acid, isostearic acid, and rosin²⁹. Rosin contains several resin acids, the most abundant being abietic acid, which are derived from coniferous trees⁵⁴. Nogenol (GC America, Alsip, IL, USA) is another fatty acid-zinc oxide sealer

made with lauric acid.

Inomer formation

1. Glass ionomer-based sealers

Glass ionomer sealer products are made by mixing a fine silicate glass powder with polyacrylic and related acids. When mixed, they form repeating subunits of organic monomer and inorganic ions, creating an inomer⁵⁵. These materials are used for cements and restoratives in dentistry. Glass ionomer cement sealer, KT-308 (GC, Tokyo, Japan), releases fluoride to prevent decay and bond to tooth structure⁵⁶, but this product is no longer commercially available. Ketac-Endo (3M ESPE, St. Paul, MN, USA), a glass ionomer sealer, is available in some parts of the world.

Polymer formation by addition reaction

Silicone and epoxy resin-based sealers both polymerize by way of addition reactions. Addition reactions are differentiated from other polymerization reactions because they co-generate other products (usually water)⁵⁷. Silicone-based sealers form a three-dimensional polymer network by addition polymerization as a series of cross-linkage between divinylpolysiloxane and polymethylhydrosiloxane with a platinum salt as the catalyst⁵⁸. Epoxy resin-based sealers follow a more traditional organic addition reaction, where epoxide monomers react with amines to create a rigid material⁵⁹.

1. Silicone-based sealers

In 1972, Davis *et al.* used injectable silicone impression material into the prepared root canals⁶⁰. Silicone-based sealers are composed of polymethylvinylsiloxane containing a platinum salt and polymethylhydrogensiloxane and set by addition reaction between vinyl groups attached to polydimethylsiloxane chain and hydrosilyl groups attached to polydimethylsiloxane chain, forming polymer⁵⁸. GuttaFlow, GuttaFlow 2, and RoekoSeal (Coltene/Whaledent) are examples of silicone-based sealers^{61,62}. GuttaFlow is triturator-mixed and requires the use of a single master cone whereas GuttaFlow 2 and RoekoSeal are auto-mix.

2. Epoxy resin-based sealers

Epoxy resin was invented in 1938 by P. Castan, a Swiss chemist of de Trey (Zurich, Switzerland), and AH 26 was developed by the same company during 1940s. A prototype AH 26 was clinically tested in the early 1950s⁶³. Guttuso studied AH 26 using rat in 1963 and found moderate tissue response in 16 days⁶⁴. Feldmann and Nyborg found AH 26, implanted after one day hardening, caused much more tissue irritation than did pure silver in rabbit study in 1964⁶⁵. In 1993, Spångberg *et al.* reported that AH 26 releases formaldehyde⁶⁶, which recommended transition from AH 26 to AH Plus, which does not release formaldehyde. Epoxy resin-based sealers, such as AH 26 and AH Plus (Dentsply Sirona, Konstanz, Germany), are composed of low molecular

weight epoxy resins and amines and set by addition reaction between epoxide groups attached to epoxy resins and amines to form polymer.

AH 26 exists in a powder-paste mixture while AH Plus exists in a paste-paste mixture. When sold in an automatic mixing syringe, AH Plus is known as AH Plus Jet. In the United States, AH Plus and AH Plus Jet are sold under several other names, including ThermaSeal Plus and Ribbon sealer, respectively. AH Plus is also known as TopSeal in Europe, Central America, and South America. Adseal (Meta Biomed, Cheongju, Republic of Korea), Acroseal (Septodont, Saint-Maur-des-Fossés, France), and MM seal (Micro-Mega, Besançon, France) are also commercially available.

Hydration

1. Tricalcium silicate-based (MTA/bioceramic) sealers Introduced by Torabinejad and White in the 1990s⁶⁷, MTA is a ceramic cement based on the hydraulic powders of tricalcium silicate and dicalcium silicate. These ceramic powders are the same ceramic phases present in Portland cement^{68,69}, but the dental products are more pure, finer powders, and include radiopaque excipients. Calcium silicate cements and calcium hydroxide are bioactive; that is both ceramics release calcium and hydroxide ions⁴⁷. The ions induce the formation of hydroxyapatite on their surface when body fluids (or synthetic body fluids) are present. ProRoot MTA Gray (Dentsply Sirona, Johnson City, TN, USA) was the original MTA product, marketed in since 1997, but it was only used as a root-end filling material or perforation fill, not as a sealer.

Since their introduction the tricalcium silicate-based materials have been primarily used for perforation repair, retrograde root canal filling after an apicoectomy^{70,71}, pulp capping⁷², and pulpotomies⁷². Bismuth oxide, zirconia, tantalum oxide, barium zirconate have been used for radiopacity^{73,74}. Advantages of the tricalcium silicate products include sealing by HA formation and biocompatibility⁷⁵⁻⁷⁸. When mixed with water, tri- and dicalcium silicate powders react and form a hydrated matrix with embedded calcium hydroxide. The calcium and hydroxide ions continue to be released for about one month after setting⁴⁷. The high pH causes the phosphate ions in body fluids to precipitate hydroxyapatite^{79,80} at the surface. Tricalcium silicate-based sealers have been reported to cause the deposition of apatite-like crystals in the apical and middle thirds of canal walls^{81,82}. While ProRoot MTA is not suitable as an endodontic sealer, Grey & NeoMTA Plus (NuSmile Avalon Biomed, Houston, TX, USA) are indicated for sealing⁸³. Since the MTA Plus product introduction, other powder-liquid commercial tricalcium silicate sealers have been introduced: BioRoot RCS (Septodont) and Endo CPM Sealer (EGEO, Buenos Aires, Argentina).

When Grossman published his eleven criteria of an ideal root canal sealer in 1982⁴⁸, endodontic sealers always consisted of a powder and liquid, but two-paste and single component materials are currently commercially available. Single-paste tricalcium silicate-

based sealers are gaining popularity in clinical practice because they are easy to use, despite their high cost. iRoot SP (Innovative Bioceramics, Vancouver, Canada), EndoSequence BC (Brasseler, Savannah, GA, USA), Total Fill BC (FKG Dentaire, La Chaux-de-Fonds, Switzerland), and Edge Endo Sealer (Edge Endo, Albuquerque, NM, USA) are the same sealer, marketed under different brand names. All four materials are from the same manufacturer (Innovative Bioceramics). The setting mechanism of single-paste tricalcium silicate-based sealers is water absorption from dentin tubules⁸⁴ with the concomitant formation of HA at the surface within the canals. EndoSequence BC Sealer is used with a single-cone technique, a viable option for obturation in NSRCT^{61,85}. Other single-paste sealers containing tricalcium silicate and organic liquids are appearing: CeraSeal (Meta Biomed), Endoseal MTA (Maruchi, Gangwon-do, Republic of Korea), and Bio-C Sealer (Angelus). Three tricalcium silicate powder-liquid systems are known: NeoMTA Plus, BioRoot RCS, and Endo CPM.

Some companies have marketed the tricalcium silicate materials as “bioceramics” or “biosilicates”, but these terms are too general since many dental materials are bioceramics^{15,86}. The tricalcium silicate materials are distinguished by their bioactivity; that is, their ability to form hydroxyapatite on their surface and an osteogenic effect⁸⁷.

Polymer formation by radical polymerization

1. Methacrylate resin-based sealers

The first generation of methacrylate resin-based sealers began with Hydron (Hydron Technologies, St. Petersburg, FL, USA)^{88,89}, which appeared on the market during the mid-1970s⁹⁰⁻⁹². Wichterle and Lim, contact lens researchers, developed Hydron in the 1960⁹³. It was composed of 2-hydroxyethyl methacrylate polymer gel for injection in the canal without the need for a core, such as gutta-percha. However, because of its short working time, very low radiopacity, problems associated with removal from canals, and tendency to irritate the periapical tissues, its use was discontinued in the 1980s⁸⁸.

At the beginning of the 21st century, the desire for bonding between dentin and sealing materials gave way to the second generation of methacrylate sealers. EndoREZ (Ultradent, South Jordan, UT, USA) is a dual-cure sealer that does not require a dentin adhesive⁹⁴. Methacrylate resin has been used without gutta-percha to create a “monoseal”; that is, a sealer which binds to radicular dentin as well as the core obturation materials⁹⁵. A monoseal is achieved when the material creates a gapless interface between the dentinal wall and rigid core (also called a monoblock)¹³.

Third-generation methacrylate-based sealers make use of formulations containing self-etching primers, beginning with Resilon/Epiphany (Resilon Research, Madison, CT, USA); functionally, this addition is analogous to the “all-in-one” adhesives used in restorative dentistry⁹⁶. The Resilon/Epiphany system

was an alternative to conventional gutta-percha/sealer system^{96,97}. The Epiphany primer etched and conditioned the dentinal surface of the canal by demineralizing it and exposing the collagen matrix⁹⁸. The contents of the primer allowed the Epiphany sealer to bond covalently to the dentinal surface during polymerization. The sealer also covalently bonded to the Resilon cone, thereby achieving the monoseal desired with methacrylate-based systems. The Resilon cones contained bioactive glass, which could be resorbed. Because the dentinal wall, sealer and cone are covalently bonded, they form a single unit, known as a monoblock⁹⁹. RealSeal SE (Kerr) was a commercial product similar to Epiphany^{98,100} but with less etching ability than RealSeal¹⁰¹. These systems are no longer sold because they were susceptible to degradation of their ester bonds¹⁰².

Fourth-generation methacrylate-based sealers include a combination of self-activating etchant, primer, and sealer. Hybrid Root SEAL (Sun Medical, Shiga, Japan), also commercialized as MetaSEAL (Parkell, Edgewood, NY, USA) in the United States, is the first commercially available sealers of this generation¹⁰³. Hybrid Root SEAL hybridized dentin more resistant to low pH¹⁰⁴, which was most effective after EDTA irrigation¹⁰⁵ and may reduce microleakage¹⁰⁶.

Super-Bond RC Sealer (Accel) (Sun Medical) is a commercially available methyl methacrylate-tributyl borane (MMA-TBB) resin sealer which uses TBB as an initiator and to induce interfacial polymerization of MMA at the dentin interface^{107,108}. TBB has been shown to cause graft polymerization of MMA onto dentin collagen, creating a collagen-MMA graft polymer^{108,109}. Syudo and Hayashi in 2010 introduced a “floating with accessory point technique” using Super-Bond RC Sealer (Accel). This technique has become synonymous with the single cone technique where the master cone gutta-percha point need not touch the canal walls because its “floating” in the sealer. The benefit of “floating” assures interfacial adhesion between dentin and the sealer for hermetic sealing. After placement of a floating master cone gutta-percha point and accessory points may be inserted to reduce voids/bubbles and increase interfacial contact for adhesion^{110,111}. They also noticed the mixed layer of the resin and gutta-percha at the interface of the canal walls, sealer, and gutta-percha bonded, creating monoblock.

Simultaneous treatment for root canal filling and core construction (STRC), a technique developed by Masaka *et al.*, uses MMA-TBB resin to adhere a fiber post system. The fiber post has an elastic modulus similar to dentin, unlike metal posts, making it more suitable for mimicking masticatory stress and strain¹¹². STRC uses the fiber post system replacing gutta-percha points with a minimum condensing force during the root canal obturation process. STRC is beneficial because it minimizes the number of patient clinical visits and may prevent vertical root fractures as a result of monoblock formation. An outcome study of STRC reports a five year success rate of 90.9%¹¹². While EndoSequence BC Sealer’s single-cone obturation technique in NSRCT^{61,85}

exists, STRC may prove to be a more successful concept for obturation.

PROPERTIES OF SEALERS

An ideal endodontic sealer provides a complete microscopic seal such that microbes cannot pass through the root canal system; it possesses antimicrobial activity against a range of common periodontal microbes, and it accomplishes these goals without causing an inflammatory response in host tissues or demonstrating cytotoxicity. Contemporary sealers excel for some criteria but fall short when evaluated for all of them. The ADA 57 and International Organization for Standardization (ISO) 6876 standards¹¹³ provide some useful tests for measuring sealer attributes, but these tests are not sufficient to determine the performance of one sealer over another. According to the methods in the documents, antimicrobial testing is not part of these standards, and ISO 7045 is used for biocompatibility testing. Following is a proposed modified list of criteria for an endodontic sealer: 1. make a hermetic seal, 2. be tacky and preferably adhesive to dentin and obturation material between it and the canal wall when set, 3. contain fine powders, preferably for anatomical accommodation, 4. radiopacity, 5. dimensionally stable with limited changes before and after setting, 6. color stable, 7. bacteriostatic or antibacterial, 8. set slowly enough for the obturation procedure, 9. insoluble in tissue fluids, 10. biocompatible, including non-mutagenic, non-sensitizing, and non-cytotoxic after setting, 11. capable of removal for retreatment by chemical or mechanical means, 12. preferably bioactive, stimulating the formation of hydroxyapatite in contact with body fluids.

Setting time and solubility

Setting time and solubility are critical components in the sealing ability of sealers. Setting time in particular is clinically important for endodontic treatment. Slow setting times allow for sealer to more readily penetrate intricate canal morphology even after treatment^{114,115}. Faster setting times may be indicated in time sensitive situations, such as when obturation must be completed quickly or a post must be placed sooner.

Setting times for ZOE sealers have shown considerable variation. Among research studies, the setting time of Proco-Sol varies by an order of magnitude (40.5 min to 42 h). Tubli-Seal has been shown to have a setting time of approximately one hour^{19,116}. The need for water to initiate ZOE setting may lead to variations.

ISO 6876 requires less than 3% solubility of sealers in distilled water, and ZOE sealers like Pulp Canal Sealer have met this requirement. However, for retreatment, solubility in a solvent other than water is useful. ZOE sealers showed weight losses of 5.19% in halothane, over 10 min, indicating moderate solubility in common re-treatment solvents¹¹⁷.

Ketac-Endo, a glass ionomer sealer, was found to have a setting time of 2.5 h¹¹⁸. Glass ionomer sealers were also found to have 1.6% solubility in water, which meets

the ISO 6876 and ADA 57 limits of 3% weight loss¹¹⁹. With regard to solvent solubility for re-treatment, glass ionomer sealers were the least soluble in halothane, with weight loss of less than 1% after being exposed for 10 min¹¹⁷.

GuttaFlow, a silicone-based sealer, was found to have a setting time of 17.4 min, the shortest setting time of sealer types considered¹²⁰. GuttaFlow had only 0.13% solubility in water, meeting the ADA and ISO specifications for solubility¹¹⁹.

Setting times for tricalcium silicate-based sealers, including EndoSequence BC Sealer, also known as iRoot SP have even been shown to exceed one month¹²¹; however the setting times for BioRoot RCS, Bio-C, and CeraSeal sealers are 4, 3, and 3.5 h. Tricalcium silicate sealers such as BioRoot RCS and TotalFill BC sealer were found to have significantly higher solubility in distilled water than comparable market sealers of different compositions¹²². The solubility may be attributed to the formation of calcium hydroxide during setting of tricalcium silicates, which is dissolved in the ISO 6876 solubility test¹²³. Although there are no current studies on the solubility of tricalcium silicate-based sealers in organic solvents like halothane, one study evaluating re-treatment found that the re-treatment of maxillary incisors containing EndoSequence BC Sealer with chloroform, an organic solvent that was formerly commonly used, was more facile than without¹²⁴. However, the same study found EndoSequence BC Sealer had significantly more residual material remaining after re-treatment compared with AH Plus¹²⁴. Acids will dissolve tricalcium silicate-based sealers, but the solubility may be too slow for re-treatment. From a clinical perspective, using ultrasonic instruments is more practical than use of solvents for the tricalcium silicate sealers¹²⁵.

AH 26 and AH Plus have been shown to have setting times of 34 and 8 h, respectively^{118,120}. AH Plus meets ISO solubility requirements¹²², with 0.16% solubility in water¹¹⁹. AH Plus was significantly more soluble in halothane, yielding 68% weight losses after 10 min¹¹⁷, making re-treatment viable with a solvent.

Super-Bond RC Sealer (Accel), a methacrylate resin-based sealer, was shown to have a setting time of 42 min¹²⁶. Two methacrylate resin-based sealers, EndoREZ and Epiphany, were shown to have 3.5–4% solubility in water, which did not meet ADA 57 or ISO 6876 specifications¹¹⁹.

Sealapex, a salicylate-based sealer, was found to have an average setting time of 58 min, which is shorter than that of ZOE sealers. Poggio *et al.* reported that Sealapex met the ISO 6876 solubility requirements¹²². Solubility in halothane for the salicylate-based sealer such as Apexit was comparable with that of ZOE sealers¹¹⁷.

In summary, setting times for most sealer types were acceptable and well above one hour, with the exception of silicone-based sealers, which had markedly shorter setting times. Solubility depends on sealer matrix chemistry. For re-treatment, mechanical removal of a sealer will be useful for tricalcium silicate-based sealers

and resin-based sealers.

Sealing ability

Sealing ability is of the utmost importance in sealer. Although many microleakage studies have been published, direct comparison of each sealer is difficult because experimental condition was different in each experiment/research. In many papers each sealer was tested together with AH Plus. Thus it will be convenient to compare sealing ability of each sealer by using AH Plus as a standard. The relative degree of microleakage was calculated by length of microleakage of each sealer divided by that of AH Plus. Table 2 summarizes comparisons of the degree of microleakage of different sealer types. To generate sufficient data on microleakage, an electronic search was conducted using the PubMed database (www.ncbi.nlm.nih.gov) to find studies that evaluated microleakage of the various sealers. “AH Plus”, “Leakage”, and “Sealing” were used as key words. Articles were limited to full-text articles written in English. The electronic search gave 152 publications. After screening by title and abstract, studies were retrieved and then read for relevance. Articles were included if they included microleakage measurements with the sealer types in question. Following discussion, 64 articles out of the 152 searched satisfied criteria and were included. Data points within the articles that compared the microleakage of different sealers were included in calculations for Table 2. Seventy two data points were used: 5 data points for tricalcium silicate (EndoSequence BC) sealers¹²⁷⁻¹³⁰, 6 data points for silicone sealers¹³¹⁻¹³⁶, 7 data points for epoxy resin sealers (other than AH Plus)^{131,137-141}, 9 data points for salicylate sealers^{136,139,142-147}, 6 data points for zinc oxide-eugenol^{133,138,144,146,148,149}, and 6 data points for glass ionomer (Ketac-Endo)^{132,139,142,148,150,151}. Methacrylate resin sealers were itemized by product due to their variation: 22 data points for the Resilon/Epiphany system^{130,133,135,141,142,149,150,152-163}, 6 data points for EndoREZ^{129,146,151,163-165}, and 5 data points for Hybrid Root SEAL^{128,129,157}. Some references contained data on more than one sealer; therefore, the total number of data points is more than the number of references.

Several methods have been used to assess microleakage: dye penetration, fluid filtration, glucose penetration, microbial leakage, and electrochemical leakage tests. To compare the leakage results, independent of each physicochemical method, individual measurements were converted into a ratio using AH Plus (with gutta-percha) as a standard. Sealing ability was also evaluated independent of time and as a whole. That is, time dependent measurements (*e.g.* microleakage at one day, one week, *etc.*) were averaged. For example, Bouillaguet *et al.* stated that within the 6th h of obturation, AH Plus exhibited a microleakage of 0.17 $\mu\text{L}/\text{min}$ using the fluid filtration method, while GuttaFlow exhibits a microleakage of 0.08 $\mu\text{L}/\text{min}$. GuttaFlow therefore has 0.47 times the microleakage of AH Plus within the 6th h for this individual study¹³³. Ratios were calculated and averaged by sealer type. Minima, maxima, and medians were determined for the

Table 2 Comparisons of the degree of microleakage of different sealer types

Sealers	Type	No. of Data [^]	Degree of leakage relative to GP/AH Plus				Leakage	References	No. of Ref ^{^^}
			Mean	Minimum	Maximum	Median			
			Endosequence BC, iRoot SP	Tricalcium silicate	5	0.78			
GuttaFlow, Roeko Seal	Silicone	6	0.83	0.19	1.84	0.65		131-136)	6
AH26, MM seal	Epoxy resin (other than AH Plus)	7	0.84	0.46	1.32	0.90		131, 137-141)	6
MTA Fillapex, Apexit, Sealapex	Salicylate	9	0.98	0.39	1.75	0.94		136, 139, 142-147)	8
Resilon/Epiphany	Methacrylate	22	0.98	0.35	2.34	0.82	Similar to AH Plus*	130, 133, 135, 141, 142, 149, 150, 152-163)	19
Roth, Pulp Canal Sealer, ZOE	Zinc oxide-eugenol	6	1.15	0.82	1.44	1.15		133, 138, 144, 146, 148, 149)	6
Ketac-Endo	Glass ionomer	6	1.15	0.85	1.61	1.08		132, 139, 142, 148, 150, 151)	6
EndoRez	Methacrylate	6	1.17	0.70	1.58	1.18		129, 146, 151, 163-165)	6
Hybrid Root SEAL/MetaSEAL	Methacrylate	5	1.33	0.98	2.14	1.21	Most***	128, 129, 157)	3

The degree of relative microleakage of the above sealers is expressed in a ratio against AH Plus.

* AH Plus therefore has a relative degree of microleakage equal to 1.0.

** Sealers with a relative degree of microleakage less than 1.0 are considered to have less microleakage than AH Plus.

*** Sealers with a relative degree of microleakage more than 1.0 are considered to have more microleakage than AH Plus.

[^] Total number of data points: 72

^{^^} Total number of references: 64

Since some references contain more than one sealers reported, total number of references and total number of data points are not the same.

data sets to describe the ranges of relative sealing ability in the literature. We noted that dye penetration for AH Plus/gutta-percha was: minima 0.37 mm and mean 2.49 mm in 18 tests^{131,134,136-138,140,141,146,148,151,154,158-163,165}. Dye was noted in every sealer regardless of type, suggesting that a complete microscopic seal is not achievable with contemporary sealers¹⁶⁶.

EndoSequence BC, a tricalcium silicate sealer, exhibited the lowest mean relative microleakage across the studies. In stereoscopic dye leakage tests, EndoSequence BC Sealer showed less leakage than AH Plus, Resilon/Epiphany, and ZOE-based sealers¹⁴⁶. However, dye leakage studies are inherently flawed for tricalcium silicate cements, as they absorb water until full setting. Tricalcium silicate sealers other than EndoSequence BC had mixed results. SEM studies indicated inadequate micro-sealing for Endo CPM Sealer, which had poor adaptation to canal walls¹⁶⁷. ProRoot MTA, which is not indicated as a sealer, had

significantly more microleakage when used as a sealer¹⁶⁸ compared with epoxy resin-based sealers AH 26 and Adseal in the dye diffusion test in extracted human teeth stereo-microscopically.

Silicone sealers, which include RoekoSeal and GuttaFlow, had the second lowest relative microleakage. These materials have a low surface tension, which allows for a high flow and low film thickness, enabling the sealer to fill intricate anatomy¹⁶⁹. RoekoSeal had the better sealing ability than GuttaFlow when measured with a dye diffusion test in extracted human teeth sectioned both horizontally and vertically¹⁶⁹. RoekoSeal has been found to expand 0.2% upon setting (exceeding the ADA 57 requirement), which may be beneficial¹⁷⁰. However, silicone sealers only seal the root mechanically (much like a polyvinylsiloxane impression material), and do not create a monoseal bond at the dentin-sealer interface.

Epoxy resin sealers other than AH Plus, namely AH 26 and MM Seal, provided nearly the same low relative

leakage as the silicone sealers; these two sealers also showed better sealing performance than AH Plus. The sealing performance of epoxy resin-based sealers can be compromised due to leaks introduced by polymerization shrinkage¹⁷¹. Epoxy resin-based sealers have been shown by stereomicroscopy to have moderate sealing capacity, but superior to ZOE-based sealers¹³⁶.

Salicylate resin sealers, which include MTA Fillapex, Sealapex, and Apexit, performed the closest to AH Plus. Apexit seals moderately well compared to ZOE, AH Plus, and RoekoSeal Automix, based on the cross-sectional stereomicroscopic analysis of extracted teeth¹³⁶. The salicylate-based MTA Fillapex sealer had more microleakage than conventional epoxy resin-based sealers in a dye penetration study¹⁶⁸.

ZOE sealers demonstrate more microleakage than AH Plus and any of the above-mentioned sealers. Glass ionomer sealers had an identical mean microleakage ratio to ZOE sealers¹³⁶. From the maxima and minima determined for the data set, glass ionomer sealers exhibit marginally more microleakage than ZOE sealers. Glass ionomer sealers have proven to be less than satisfactory with considerable failure risk and inadequate bonding with gutta-percha^{118,136,172}. De Gee *et al.* explained that glass ionomer sealers have low sealing capacity due to leakage pathways at the dentin-sealer interface¹¹⁸.

The variations among methacrylate resin sealers is seen in Table 2. Evaluations of Resilon/Epiphany's sealing ability affirm the monoseal behind methacrylate systems. When compared with gutta-percha and other sealers in dye leakage studies, Resilon/Epiphany resulted in less microleakage up to three months after obturation¹⁷³. Bacterial leakage tests with *Streptococcus mutans* and *Enterococcus faecalis* reflect lower microleakage as well⁹⁶. The Resilon/Epiphany system performed identically to salicylate resins.

Super-Bond RC Sealer, another methacrylate resin sealer, proved to have a better microseal than both Tubli-Seal and Ketac-Endo sealers, in a dye penetration study with stereomicroscopy¹⁷⁴. Resin shrinkage occurs as polymerization begins within the resin. Shrinkage of MMA-TBB resins has been shown to begin at the dentin interface, which creates superb bonding between the resin and dentin and a tight seal¹⁰⁷. Interfacial initiation of the polymerization mechanism begins on the dentin side, where the resin is attracted during polymerization, and leads to the elimination of gap formation between the dentin and resin¹⁷⁵. The dye penetration of Endoresin-2, an experimental MMA-TBB resin sealer, was 0.17 mm after 2 days¹⁷⁵, far less than the minimum value of 0.37 mm reported for AH Plus. Methacrylate resins have also been used with obturation material other than gutta-percha to create a monoseal, with the sealer bonding to both radicular dentin and the core material⁹⁵.

Antimicrobial activity

Antimicrobial activity can be directly caused by a sealer, or indirectly cause by entombing bacteria. Any endodontic sealer that does make a hermetic sealer functions to entomb bacterial within the canal and

tubules, preventing communication of residual bacteria to the apical tissue¹⁷⁶. However, bacteria present at the apex may not be entombed, and would be killed by an antimicrobial endodontic sealer.

Zinc oxide is a well-documented antimicrobial material because it forms a reactive oxygen species and interferes with bacterial membrane proteins¹⁷⁷. ZOE sealers have better antimicrobial effects in a zone of inhibition test for *Streptococcus mutans*, *Staphylococcus aureus*, and *Enterococcus faecalis*, compared with multiple epoxy resin-based sealers¹⁷⁸. Fluoride ions inhibit also bacterial growth, but glass ionomer sealers have demonstrated minimal antimicrobial activity¹⁷⁹. In general, silicone-based sealers are not antimicrobial. For instance, a zone of inhibition study with *Enterococcus faecalis* using of GuttaFlow 2 gave the same results as control groups without sealers¹⁸⁰. Kapralos *et al.* found that GuttaFlow 2 and RoekoSeal have no antibacterial activity against the planktonic growth or 24-h biofilms of *Streptococcus mutans*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Enterococcus faecalis*¹⁸¹.

Evaluations of the antibacterial properties of MTA-type material (including non-sealer tricalcium silicates) have been confusing and sometime contradictory⁷³. In a study by Torabinejad *et al.*, MTA was demonstrated to have an antimicrobial effect on facultative bacteria and no effect on obligate anaerobes¹⁸². Several disk diffusion studies show that MTA and Portland cement have little to no inhibitory effect on species like *Staphylococcus aureus*, *Enterococcus faecalis*, and *Candida albicans*¹⁸³⁻¹⁸⁷. In disk diffusion studies, MTA and Portland cements had antimicrobial effects at least on par with other sealers like ZOE, salicylate-based (Sealapex), and epoxy resin (AH Plus)¹⁸³⁻¹⁸⁷. For similar studies testing only *Enterococcus faecalis*, tricalcium silicate-based sealers like EndoSequence BC Sealer exhibited greater antibacterial properties than did ZOE and epoxy resin sealers¹⁸⁸. It has been demonstrated that tricalcium silicate-based sealers increase the local pH through the release of calcium and hydroxide ions for adding an antimicrobial effect¹⁸⁹. In the same planktonic growth and 24-h biofilm study, Kapralos *et al.* also found that TotalFill BC Sealer had notable antibacterial effect on planktonic bacteria after 7 days, along with an antibacterial effect on biofilms for *Staphylococcus aureus* and *Enterococcus faecalis*¹⁸¹. The same antibacterial effects of calcium hydroxide must accrue to the tricalcium silicates (MTA-type materials) because of the formation of calcium hydroxide as a reaction product from the tri- and di-calcium silicates.

AH Plus sealer had better antimicrobial activity only when compared with GuttaFlow but was less antimicrobial than MTA Fillapex (salicylate-based sealer) and CRCS (ZOE sealer)¹⁹⁰. Compared with other sealer types, epoxy resin sealer (AH Plus) showed no significant difference in antimicrobial activity for *Enterococcus faecalis*. Zone of inhibition tests for a AH Plus were comparable with those for ZOE sealers with *Enterococcus faecalis*. However, Kapralos *et al.* found

that AH Plus had the highest antibacterial activity on both planktonic and biofilm bacteria, but only lasting 24 h¹⁸¹). As stated previously, tricalcium silicate-based sealers/cements (EndoSequence BC Sealer and ProRoot MTA) had higher antimicrobial activity for *Enterococcus faecalis* than both epoxy resin (AH Plus) and ZOE sealers^{180,188}). The methacrylate resin-based sealer EndoREZ had the strongest antibacterial activity among comparable sealers AH Plus and Sealapex¹⁹¹). In an agar diffusion test with plated strains, *Micrococcus luteus* (ATCC9341), *Staphylococcus aureus* (ATCC6538), *Pseudomonas aeruginosa* (ATCC27853), *Candida albicans* (ATCC 10231), and *Enterococcus faecalis* (ATCC 10541), MTA Fillapex, as well as MTA powder, were found to have antimicrobial activity against all tested strains^{185,192}).

Despite limitations, calcium hydroxide-containing sealers have several benefits. CRCS, for example, exhibited better antimicrobial activity than epoxy resin (AH Plus) and MTA sealers when tested against *Enterococcus faecalis* on agar¹⁹⁰). Calcium-hydroxide-based sealers proved to have a greater zone of inhibition than ZOE sealers¹⁹⁰). Supercal (Ozdent, Sydney, Australia), another calcium-hydroxide-containing glycerol sealer, was more antibacterial than MTA and AH Plus sealers¹⁹³).

Biocompatibility and cytotoxicity

ZOE sealers have been shown to be both an irritant and cytotoxic agent^{194,195}) and activate a complement-mediated immune response as well as significant fibroblast cytotoxicity^{196,197}). When implanted subcutaneously in rats, eugenol inhibited the adhesion of immunocompetent cells such as macrophages and also showed more cytotoxic impact on human periodontal ligament than did ceramic powders such as zinc oxide, titanium oxide, or barium sulfate¹⁹⁸), which are known to be biocompatible¹⁹⁹). Because eugenol is cytotoxic and evokes an inflammatory response, zinc oxide non-eugenol sealers such as Canals-N²⁹) and Nogenol^{200,201}) are available in Japan and the United States.

Glass ionomer sealers have also been shown to cause inflammation when implanted subcutaneously into rats, although the inflammation was not histologically detectable after three months²⁰²). Glass ionomer cement (Fuji II, GC) had lower cytotoxicity when freshly mixed compared with resin (Chem-fil II, De Trey, Wiesbaden, West Germany)²⁰³). However, the same studies found that fully set, glass ionomer cement was more cytotoxic than Chem-fil II after setting, because of its fluoride ion release²⁰³). Glass ionomer products have demonstrated a low level of cytotoxicity over long periods of time, indicating they consist of very biocompatible material^{204,205}).

Silicone sealers are recognized as biocompatible, beneficial characteristic of these sealers. Significantly lower cytotoxicity was found when compared with epoxy resin sealers (AH 26 and AH Plus) during the first 11 days of fibroblast suspension cultures, and similar cytotoxicity was measured after 24 h^{206,207}). GuttaFlow

was determined to be biocompatible in a fibroblast incubation test¹⁸⁰).

Tricalcium silicate-based sealers have exhibited both beneficial and deleterious effects in terms of biocompatibility¹⁶). BioRoot RCS and EndoSequence BC Sealer exhibited no cytotoxic effects on human bone marrow mesenchymal cells when compared to AH Plus; EndoSequence BC Sealer has also been shown to have strong cell viability *in vitro*, even decreasing LPS-mediated inflammation¹⁸⁸). However *in vivo* in rats, MTA was found to be cytotoxic when histological sections of pulp tissue were examined by light microscopy at two and seven weeks²⁰⁸). Another study of MTA cytotoxicity on rat subcutaneous tissue found that MTA materials had only moderate inflammation at 7 days and mild inflammation at 30 days, also suggesting that MTA induces biomineralization²⁰⁹). Osteoinductive properties and cytocompatibility were superior for BioRoot RCS compared to the ZOE Kerr's Pulp Canal Sealer²¹⁰). Over time, EndoSequence BC sealer retains more pronounced cytotoxicity to osteoblast progenitors than AH Plus, even after six weeks²¹¹).

Resin sealers as a whole have limited biocompatibility when unset. Unset epoxy sealers are genotoxic in mammalian cell mutation assays, attributed to residual monomer and formaldehyde²¹²). Set sealers show equivocal genotoxic results, and no genotoxic activity was seen after 24 h. However, it has been noted that epoxy sealers like AH 26 release formaldehyde even two days after being mixed⁶⁶). AH Plus is modified such that formaldehyde is not released³⁵). High levels of inflammation have also been detected in periapical and subcutaneous tissues after the use of epoxy resin-based sealers^{198,213}). In a rat model study, AH Plus induced milder inflammatory response than a ZOE sealer in the periapical tissue²¹⁴).

Methacrylate polymer has negligible cytotoxicity when set and demonstrated cytotoxicity or inflammation only early in the setting process²¹⁵). Incompletely cured methyl methacrylate (MMA), monomer/polymer is cytotoxic although considered the least toxic monomer used in dentistry²¹⁶⁻²¹⁸). When paired with TBB, residual MMA is reduced over time^{108,215}). Leachable materials from methacrylate-based materials, including triethyleneglycol dimethacrylate (TEGDMA), urethane dimethacrylate (UDMA), 2-hydroxyethyl methacrylate (HEMA) and polyethylene glycol dimethacrylate (PEGDMA), have shown time-dependent increases in cell death²¹⁹). EndoREZ, a UDMA type of methacrylate-based material, was the most cytotoxic compared to an epoxy resin-based sealer (AH Plus) and a silicone-based sealer (RoekoSeal)²²⁰). Methacrylate resin-based sealers (Real Seal and EndoREZ) have been shown to be more cytotoxic when compared with a salicylate-based (Apexit Plus) or epoxy resin-based sealer (AH Plus), based on a study testing inflammatory biomarkers²²¹). However, in comparison with their epoxy resin-based counterparts (AH Plus), methacrylate-based sealers (Hybrid Root SEAL/ MetaSEAL and Super-Bond RC Sealer (Accel)) are less cytotoxic in plated cultures²²²). This indicates

that methyl methacrylate (MMA)-based products are more suitable in clinics than other methacrylate-based sealers.

Although their components are biocompatible, Sealapex, CRCS, and Apexit are still elicited inflammatory reactions due to poor seal²²³. *In vivo* degradation of sealer and incomplete fills may be the reason for added inflammation in these cases²²³. MTA Fillapex was also found to cause both a high level of cytotoxicity to human fibroblast cells and an increase in inflammatory mediators when freshly mixed as well as five weeks after being mixed⁷⁰. Eight root canal sealers were compared for cytotoxicity for up to 72 h with human gingival fibroblasts. The tricalcium silicates and AH Plus has the highest cell viability at 24 h. However viability diminished with all after 72 h²²⁴.

In summary, poor biocompatibility was noted in ZOE sealers while superior biocompatibility is an attribute for silicone-based sealers and tricalcium silicate-based sealers. AH Plus has better biocompatibility than AH 26 in epoxy resin sealers. Moderate biocompatibility is noted in methacrylate-based systems, glass ionomer sealers, and salicylate-based sealers. In epoxy resin and methacrylate resin sealers, unset sealer is less compatible than set sealer. Better biocompatibility is noted in MMA-TBB resin compared to other resin sealers.

CLINICAL IMPLICATION AND FUTURE DIRECTIONS

Pulp diagnosis as vital or necrotic is important for selection of an endodontic sealer for clinical use. In vital pulp (pulpitis) cases, the therapeutic effects of sealers are not necessary under the asepsis technique NSRCT, based on study by Kakehashi *et al.*²²⁵. Therefore, sealers which have shown effective sealing, summarized in Table 2, are a good choice. While tricalcium silicate sealers show the least leakage, they have slow setting times. Therefore, tricalcium silicate sealers are not a good choice if post/core/build-up must occur on the same day together with endodontic obturation. In necrotic pulp cases, especially cases with large apical radiolucency, the therapeutic effects of tricalcium silicate-based sealers are useful. A medicated sealer to kill bacteria should increase the chances of long-term success. Cases of large apical radiolucency diagnosed with questionable or unfavorable prognoses are expected to benefit from sealer-driven therapeutic effects. Salicylate-based (calcium-hydroxide-containing) are good choices if post/core/build-up is performed immediately after completion of endodontic obturation. A clinician has the responsibility to decide the top priority for the patient: good sealing or a therapeutic effect.

Coronal seal by final permanent restoration is mandatory for long-term clinical success, regardless of sealer choice²²⁶. The technical quality of the coronal restoration is more important than the technical quality of the endodontic treatment for apical periodontal health²²⁷. Currently, manufacturers provide separate systems of endodontic obturation by gutta-percha

and sealer, post/core/build-up, and final permanent restoration. Currently, it is difficult to differentiate sealer from gutta-percha on digital radiograph system and there is a limitation of detail observation of the sealer. In the future, when the current detection level of the clinical three-dimensional cone beam computed tomography (CBCT) system (about 100 μm) approaches that of the research-grade micro computed tomography (micro-CT) machine (several μm)²²⁸, gutta-percha and sealer would be able to differentiate and precise observation of unfilled space or void could be possible. Sealers and obturation techniques will advance significantly together with the advancement of technology. The importance of sealers will become more of a focus in clinical treatment. Clinicians will better understand the sealer's role in preventing bacterial leakage, resulting in a successful outcome in endodontic practice.

This comprehensive review describes current types of endodontic sealers by their setting reaction type, composition, and properties. Because sealing ability is very important in achieving the best clinical outcome, the relative degree of microleakage among all the relevant sealers was calculated by way of a meta-analysis of relevant literature. Compared to AH Plus, tricalcium silicate sealers showed the lowest relative microleakage among the sealers assessed, followed by silicone sealers and other non-AH Plus epoxy resin sealers. Tricalcium silicate sealers also exhibit the most favorable antimicrobial effect and excellent biocompatibility. Future sealers developed should ideally combine a hermetic seal with therapeutic effects.

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REFERENCES

- 1) Lee M, Winkler J, Hartwell G, Stewart J, Caine R. Current trends in endodontic practice: emergency treatments and technological armamentarium. *J Endod* 2009; 35: 35-39.
- 2) Caicedo R, von Fraunhofer JA. The properties of endodontic sealer cements. *J Endod* 1988; 14: 527-534.
- 3) Viapiana R, Guerreiro-Tanomaru J, Tanomaru-Filho M, Camilleri J. Interface of dentine to root canal sealers. *J Dent* 2014; 42: 336-350.
- 4) Bodanezi A, Munhoz EA, Capelozza AL, Bernardineli N, Moraes IG, Garcia RB, *et al.* Influence of root canal sealer on the radiographic appearance of filling voids in maxillary single-rooted teeth. *J Appl Oral Sci* 2012; 20: 404-409.
- 5) Almeida JF, Gomes BP, Ferraz CC, Souza-Filho FJ, Zaia AA. Filling of artificial lateral canals and microleakage and flow of five endodontic sealers. *Int Endod J* 2007; 40: 692-699.
- 6) Salz U, Poppe D, Sbicego S, Roulet JF. Sealing properties of a

- new root canal sealer. *Int Endod J* 2009; 42: 1084-1089.
- 7) Jardine AP, Rosa RA, Santini MF, Wagner M, So MV, Kuga MC, *et al.* The effect of final irrigation on the penetrability of an epoxy resin-based sealer into dentinal tubules: a confocal microscopy study. *Clin Oral Investig* 2016; 20: 117-123.
 - 8) Coronal leakage – Clinical and biological implications in endodontic success. *Endodontics Colleagues for Excellence* 2002; 2-7.
 - 9) Kim SY, Kim KJ, Yi YA, Seo DG. Quantitative microleakage analysis of root canal filling materials in single-rooted canals. *Scanning* 2015; 37: 237-245.
 - 10) Hauman CH, Love RM. Biocompatibility of dental materials used in contemporary endodontic therapy: a review. Part 2. Root-canal-filling materials. *Int Endod J* 2003; 36: 147-160.
 - 11) Desai S, Chandler N. Calcium hydroxide-based root canal sealers: a review. *J Endod* 2009; 35: 475-480.
 - 12) Shrestha D, Wei X, Wu W, Ling J. Resilon: a methacrylate resin-based obturation system. *J Dent Sci* 2010; 5: 47-52.
 - 13) Kim YK, Grandini S, Ames JM, Gu LS, Kim SK, Pashley DH, *et al.* Critical review on methacrylate resin-based root canal sealers. *J Endod* 2010; 36: 383-399.
 - 14) Lotfi M, Ghasemi N, Rahimi S, Vosoughhosseini S, Saghiri MA, Shahidi A. Resilon: a comprehensive literature review. *J Dent Res Dent Clin Dent Prospects* 2013; 7: 119-130.
 - 15) Al-Haddad A, Che Ab Aziz ZA. Bioceramic-based root canal sealers: a review. *Int J Biomater* 2016; 2016: 9753210.
 - 16) Primus CM, Tay FR, Niu LN. Bioactive tri/dicalcium silicate cements for treatment of pulpal and periapical tissues. *Acta Biomater* 2019; 96: 35-54.
 - 17) Tyagi S, Mishra P, Tyagi P. Evolution of root canal sealers: An insight story. *Eur J Gen Dent* 2013; 2: 199-218.
 - 18) Singh H, Markan S, Kaur M, Gupta G. “Endodontic Sealers”: Current concepts and comparative analysis. *Dent Open J* 2015; 2: 32-37
 - 19) Branstetter J, von Fraunhofer JA. The physical properties and sealing action of endodontic sealer cements: a review of the literature. *J Endod* 1982; 8: 312-316.
 - 20) Bodrumlu E, Sumer AP, Gungor K. Radiopacity of a new root canal sealer, Epiphany. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104: e59-61.
 - 21) van der Burgt TP, Mullaney TP, Plasschaert AJ. Tooth discoloration induced by endodontic sealers. *Oral Surg Oral Med Oral Pathol* 1986; 61: 84-89.
 - 22) Ioannidis K, Beltes P, Lambrianidis T, Kapagiannidis D, Karagiannis V. Crown discoloration induced by endodontic sealers: spectrophotometric measurement of Commission International de l’Eclairage’s L*, a*, b* chromatic parameters. *Oper Dent* 2013; 38: E1-12.
 - 23) Tour Savadkouhi S, Fazlyab M. Discoloration potential of endodontic sealers: a brief review. *Iran Endod J* 2016; 11: 250-254.
 - 24) IUPAC. Chelation. 2nd ed. McNaught A, Wilkinson A, editors. Oxford: Blackwell Scientific Publishers; 1997.
 - 25) Primus CM, Shen C. Impression Materials. In: Anusavice K, Phillips R, Shen C, Rawls H, editors. *Phillips’ science of dental materials*. 12th ed. St. Louis, Mo: Elsevier/Saunders; 2013. p. 307-339.
 - 26) Rickert U, Dixon C. The controlling of root surgery. *Congres Dentaire International* 1931: 15-22.
 - 27) Rickert U, Dixon C. The control of root surgery. *Transactions of the 8th International Dental Congress* 1933; 9: 1458.
 - 28) Grossman LI. Filling root canals with silver points. *Dental Cosmos* 1936; 78: 679-687.
 - 29) Araki K, Suda H, Spangberg LS. Indirect longitudinal cytotoxicity of root canal sealers on L929 cells and human periodontal ligament fibroblasts. *J Endod* 1994; 20: 67-70.
 - 30) Fujisawa S, Murakami Y. Eugenol and its role in chronic diseases. In: Gupta S PSAB, editor. *Drug Discovery from Mother Nature Advances in Experimental Medicine and Biology*. 929. Switzerland: Springer International Publishing; 2016. p. 45-66.
 - 31) Wilson AD, Mesley RJ. Zinc oxide-eugenol cements. 3. Infrared spectroscopic studies. *J Dent Res* 1972; 51: 1581-1588.
 - 32) Wilson AD, Mesley RJ. Chemical nature of cementing matrixes of cements formed from zinc oxide and 2-ethoxybenzoic acid-eugenol liquids. *J Dent Res* 1974; 53: 146.
 - 33) Civjan S, Brauer GM. Physical properties of cements, based on zinc oxide, hydrogenated rosin, o-ethoxybenzoic acid, and eugenol. *J Dent Res* 1964; 43: 281-299.
 - 34) Spangberg L, Langeland K. Biologic effects of dental materials. 1. Toxicity of root canal filling materials on HeLa cells in vitro. *Oral Surg Oral Med Oral Pathol* 1973; 35: 402-414.
 - 35) Leonardo MR, Bezerra da Silva LA, Filho MT, Santana da Silva R. Release of formaldehyde by 4 endodontic sealers. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; 88: 221-225.
 - 36) Sargenti A. Debate on N2: Is N2 an acceptable method of treatment? *Trans Int Conf Endod* 1973; 5: 176-195.
 - 37) Oswald RJ, Cohn SA. Systemic distribution of lead from root canal fillings. *J Endod* 1975; 1: 59-63.
 - 38) FDA explains status of N2 material. *J Am Dent Assoc* 1992; 123: 236-237.
 - 39) Cohen T, Gutmann JL, Wagner M. An assessment in vitro of the sealing properties of calciobiotic root canal sealer. *Int Endod J* 1985; 18: 172-178.
 - 40) Gambarini G, Tagger M. Sealing ability of a new hydroxyapatite-containing endodontic sealer using lateral condensation and thermatic compaction of gutta-percha, in vitro. *J Endod* 1996; 22: 165-167.
 - 41) Staehle HJ, Spiess V, Heinecke A, Muller HP. Effect of root canal filling materials containing calcium hydroxide on the alkalinity of root dentin. *Endod Dent Traumatol* 1995; 11: 163-168.
 - 42) Cox CF, Suzuki S. Re-evaluating pulp protection: calcium hydroxide liners vs. cohesive hybridization. *J Am Dent Assoc* 1994; 125: 823-831.
 - 43) Paula-Silva FW, Ghosh A, Arzate H, Kapila S, da Silva LA, Kapila YL. Calcium hydroxide promotes cementogenesis and induces cementoblastic differentiation of mesenchymal periodontal ligament cells in a CEMP1- and ERK-dependent manner. *Calcif Tissue Int* 2010; 87: 144-157.
 - 44) Mohammadi Z, Dummer PM. Properties and applications of calcium hydroxide in endodontics and dental traumatology. *Int Endod J* 2011; 44: 697-730.
 - 45) Holland R, Souza Vd. Ability of a new calcium hydroxide root canal filling material to induce hard tissue formation. *J Endod* 1985; 11: 535-543.
 - 46) Ersahan S, Aydin C. Solubility and apical sealing characteristics of a new calcium silicate-based root canal sealer in comparison to calcium hydroxide-, methacrylate resin- and epoxy resin-based sealers. *Acta Odontol Scand* 2013; 71: 857-862.
 - 47) Gandolfi MG, Siboni F, Botero T, Bossu M, Riccitiello F, Prati C. Calcium silicate and calcium hydroxide materials for pulp capping: biointeractivity, porosity, solubility and bioactivity of current formulations. *J Appl Biomater Funct Mater* 2015; 13: 43-60.
 - 48) Grossman L. *Obturation of root canal*. Endodontic Practice 10th ed. Philadelphia, PA: Lea and Febiger; 1982. p. 297.
 - 49) Jafari F, Jafari S. Composition and physicochemical properties of calcium silicate based sealers: A review article. *J Clin Exp Dent* 2017; 9: e1249-e1255.
 - 50) Lindqvist L, Otteskog P. Eugenol: liberation from dental materials and effect on human diploid fibroblast cells. *Scand J Dent Res* 1980; 88: 552-556.
 - 51) Spangberg LS. In vitro assessment of the toxicity of endodontic

- materials. *Int Endod J* 1981; 14: 27-33.
- 52) Hume WR. Effect of eugenol on respiration and division in human pulp, mouse fibroblasts, and liver cells in vitro. *J Dent Res* 1984; 63: 1262-1265.
- 53) Spangberg L, Pascon EA. The importance of material preparation for the expression of cytotoxicity during in vitro evaluation of biomaterials. *J Endod* 1988; 14: 247-250.
- 54) Fiebach K, Grimm D. Resins, Natural. Ullmann's Encyclopedia of Industrial Chemistry (Ed)2000.
- 55) Berg JH, Croll TP. Glass ionomer restorative cement systems: an update. *Pediatr Dent* 2015; 37: 116-124.
- 56) Ogasawara T, Yoshimine Y, Yamamoto M, Akamine A. Biocompatibility of an experimental glass-ionomer cement sealer in rat mandibular bone. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 96: 458-465.
- 57) Penczek S, Moad G. Glossary of terms related to kinetics, thermodynamics, and mechanisms of polymerization (IUPAC Recommendations 2008). *Pure Appl Chem* 2008; 80: 2163-2193.
- 58) Shen C. Impression Materials. In: Anusavice K, Phillips R, Shen C, Rawls H, editors. Phillips' science of dental materials. 12th ed. St. Louis, Mo: Elsevier/Saunders; 2013. p.151-181.
- 59) Saeb MR, Bakhshandeh E, Khonakdar HA, Mäder E, Scheffler C, Heinrich G. Cure kinetics of epoxy nanocomposites affected by MWCNTs functionalization: A review. *The Scientific World Journal* 2013; 2013: 14.
- 60) Davis SR, Brayton SM, Goldman M. The morphology of the prepared root canal: a study utilizing injectable silicone. *Oral Surg Oral Med Oral Pathol* 1972; 34: 642-648.
- 61) Zhou HM, Shen Y, Zheng W, Li L, Zheng YF, Haapasalo M. Physical properties of 5 root canal sealers. *J Endod* 2013; 39: 1281-1286.
- 62) Gandolfi MG, Siboni F, Prati C. Properties of a novel polysiloxane-guttapercha calcium silicate-bioglass-containing root canal sealer. *Dent Mater* 2016; 32: e113-126.
- 63) Schroeder A. Mitteilungen über die Abschlussdichtigkeit von Wurzelfüllmaterialien und erster Hinweis auf ein neuartiges Wurzelfüllmittel. *Schweizerische Monatszeitschrift für Zahnheilkunde* 1954; 64: 921-931.
- 64) Guttuso J. Histopathologic study of rat connective tissue responses to endodontic materials. *Oral Surg Oral Med Oral Pathol* 1963; 16: 713-727.
- 65) Feldmann G, Nyborg H. Tissue reactions to root filling materials. II. A comparison of implants of silver and root filling material AH 26 in rabbits' jaws. *Odontol Revy* 1964; 15: 33-40.
- 66) Spångberg LS, Barbosa SV, Lavigne GD. AH 26 releases formaldehyde. *J Endod* 1993; 19: 596-598.
- 67) Torabinejad M, White DJ, inventors. Tooth filling material and use. United States Patent & Trademark Office. Patent Number 5,769,638, May 16, 1995.
- 68) Torabinejad M, Watson TF, Pitt Ford TR. Sealing ability of a mineral trioxide aggregate when used as a root end filling material. *J Endod* 1993; 19: 591-595.
- 69) Torabinejad M, White DJ, inventors. Tooth filling material and method of use. United States patent 5,415,547. 1995.
- 70) von Arx T, Hanni S, Jensen SS. 5-year results comparing mineral trioxide aggregate and adhesive resin composite for root-end sealing in apical surgery. *J Endod* 2014; 40: 1077-1081.
- 71) Soundappan S, Sundaramurthy JL, Raghu S, Natanasabapathy V. Biodentine versus mineral trioxide aggregate versus intermediate restorative material for retrograde root end filling: an in vitro study. *J Dent (Tehran)* 2014; 11: 143-149.
- 72) Swarup SJ, Rao A, Boaz K, Srikant N, Shenoy R. Pulpal response to nano hydroxyapatite, mineral trioxide aggregate and calcium hydroxide when used as a direct pulp capping agent: an in vivo study. *J Clin Pediatr Dent* 2014; 38: 201-206.
- 73) Parirokh M, Torabinejad M. Mineral trioxide aggregate: a comprehensive literature review: Part I: chemical, physical, and antibacterial properties. *J Endod* 2010; 36: 16-27.
- 74) Tawil PZ, Duggan DJ, Galicia JC. Mineral trioxide aggregate (MTA): its history, composition, and clinical applications. *Compend Contin Educ Dent* 2015; 36: 247-252; quiz 254, 264.
- 75) Roberts HW, Toth JM, Berzins DW, Charlton DG. Mineral trioxide aggregate material use in endodontic treatment: a review of the literature. *Dent Mater* 2008; 24: 149-164.
- 76) Parirokh M, Torabinejad M. Mineral trioxide aggregate: a comprehensive literature review: Part III: Clinical applications, drawbacks, and mechanism of action. *J Endod* 2010; 36: 400-413.
- 77) Torabinejad M, Parirokh M. Mineral trioxide aggregate: a comprehensive literature review--part II: leakage and biocompatibility investigations. *J Endod* 2010; 36: 190-202.
- 78) Darvell BW, Wu RC. "MTA"-an hydraulic silicate cement: review update and setting reaction. *Dent Mater* 2011; 27: 407-422.
- 79) Aguilar P, Linsuwanont P. Vital pulp therapy in vital permanent teeth with curiously exposed pulp: a systematic review. *J Endod* 2011; 37: 581-587.
- 80) Komabayashi T, Zhu Q, Eberhart R, Imai Y. Current status of direct pulp-capping materials for permanent teeth. *Dent Mater J* 2016; 35: 1-12.
- 81) Camilleri J, Montesin FE, Brady K, Sweeney R, Curtis RV, Ford TR. The constitution of mineral trioxide aggregate. *Dent Mater* 2005; 21: 297-303.
- 82) Gomes-Filho JE, Watanabe S, Bernabe PF, de Moraes Costa MT. A mineral trioxide aggregate sealer stimulated mineralization. *J Endod* 2009; 35: 256-260.
- 83) Siboni F, Taddei P, Prati C, Gandolfi MG. Properties of NeoMTA Plus and MTA Plus cements for endodontics. *Int Endod J* 2017; 50: e83-e94.
- 84) Koch KA, Brave DG, Nasseh AA. Bioceramic technology: closing the endo-restorative circle, Part I. *Dent Today* 2010; 29: 100-105.
- 85) Chybowski EA, Glickman GN, Patel Y, Fleury A, Solomon E, He J. Clinical outcome of non-surgical root canal treatment using a single-cone technique with endosequence bioceramic sealer: a retrospective analysis. *J Endod* 2018; 44: 941-945.
- 86) Jitaru S, Hodisan I, Timis L, Lucian A, Bud M. The use of bioceramics in endodontics — literature review. *Clujul Med* 2016; 89: 470-473.
- 87) Faraco IM, Jr., Holland R. Response of the pulp of dogs to capping with mineral trioxide aggregate or a calcium hydroxide cement. *Dent Traumatol* 2001; 17: 163-166.
- 88) Murrin JR, Reader A, Foreman DW, Beck FM, Meyers WJ. Hydron versus gutta-percha and sealer: A study of endodontic leakage using the scanning electron microscope and energy-dispersive analysis. *J Endod* 1985; 11: 101-109.
- 89) Babb BR, Loushine RJ, Bryan TE, Ames JM, Causey MS, Kim J, *et al.* Bonding of self-adhesive (self-etching) root canal sealers to radicular dentin. *J Endod* 2009; 35: 578-582.
- 90) Rising DW, Goldman M, Brayton SM. Histologic appraisal of 3 experimental root canal filling materials. *J Endod* 1975; 1: 172-177.
- 91) Benkel BH, Rising DW, Goldman LB, Rosen H, Goldman M, Kronman JH. Use of a hydrophilic plastic as a root canal filling material. *J Endod* 1976; 2: 196-202.
- 92) Kronman JH, Goldman M, Goldman LB, Coleman E, Kliment CK. Microbiologic evaluation of poly-HEMA root canal filling material. *Oral Surg Oral Med Oral Pathol* 1979; 48: 175-177.
- 93) Wichterle O, Lim D. Hydrophilic gels for biological use. *Nature* 1960; 185: 117-118.
- 94) De Munck J, Vargas M, Van Landuyt K, Hikita K, Lambrechts P, Van Meerbeek B. Bonding of an auto-adhesive luting

- material to enamel and dentin. *Dent Mater* 2004; 20: 963-971.
- 95) Shrestha D, Wei X, Wu WC, Ling JQ. Resilon: a methacrylate resin-based obturation system. *J Dent Sci* 2010; 5: 47-52.
 - 96) Shipper G, Orstavik D, Teixeira FB, Trope M. An evaluation of microbial leakage in roots filled with a thermoplastic synthetic polymer-based root canal filling material (Resilon). *J Endod* 2004; 30: 342-347.
 - 97) Shipper G, Teixeira FB, Arnold RR, Trope M. Periapical inflammation after coronal microbial inoculation of dog roots filled with gutta-percha or resilon. *J Endod* 2005; 31: 91-96.
 - 98) Teixeira FB, Teixeira EC, Thompson J, Leinfelder KF, Trope M. Dentinal bonding reaches the root canal system. *J Esthet Restor Dent* 2004; 16: 348-354.
 - 99) Teixeira FB, Teixeira EC, Thompson JY, Trope M. Fracture resistance of roots endodontically treated with a new resin filling material. *J Am Dent Assoc* 2004; 135: 646-652.
 - 100) Stelzer R, Schaller HG, Gernhardt CR. Push-out bond strength of RealSeal SE and AH Plus after using different irrigation solutions. *J Endod* 2014; 40: 1654-1657.
 - 101) Kim YK, Mai S, Haycock JR, Kim SK, Loushine RJ, Pashley DH, *et al.* The self-etching potential of RealSeal versus RealSeal SE. *J Endod* 2009; 35: 1264-1269.
 - 102) Payne LA, Tawil PZ, Phillips C, Fouad AF. Resilon: assessment of degraded filling material in nonhealed cases. *J Endod* 2019; 45: 691-695.
 - 103) Lawson MS, Loushine B, Mai S, Weller RN, Pashley DH, Tay FR, *et al.* Resistance of a 4-META-containing, methacrylate-based sealer to dislocation in root canals. *J Endod* 2008; 34: 833-837.
 - 104) Marin-Bauza GA, Rached-Junior FJ, Souza-Gabriel AE, Sousa-Neto MD, Miranda CE, Silva-Sousa YT. Physicochemical properties of methacrylate resin-based root canal sealers. *J Endod* 2010; 36: 1531-1536.
 - 105) Pinna L, Loushine RJ, Bishop FD, Jr., Cotti E, Weller RN, Pashley DH, *et al.* Hybrid Root SEAL (MetaSEAL) creates hybrid layers in radicular dentin only when EDTA is used as the final rinse. *Am J Dent* 2009; 22: 299-303.
 - 106) Ari H, Belli S, Gunes B. Sealing ability of Hybrid Root SEAL (MetaSEAL) in conjunction with different obturation techniques. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; 109: e113-116.
 - 107) Imai Y, Kadoma Y, Kojima K, Akimoto T, Ikakura K, Ohta T. Importance of polymerization initiator systems and interfacial initiation of polymerization in adhesive bonding of resin to dentin. *J Dent Res* 1991; 70: 1088-1091.
 - 108) Taira Y, Imai Y. Review of methyl methacrylate (MMA)/tributylborane (TBB)-initiated resin adhesive to dentin. *Dent Mater J* 2014; 33: 291-304.
 - 109) Masuhara E. [On the chemistry of a new adhesive plastic filling material]. *Dtsch Zahnarztl Z* 1969; 24: 620-628.
 - 110) Syudo M, Hayashi Y. Proposal of the new obturation method for good sealing ability using methyl methacrylate resin-based adhesive sealer. *J Jpn Dent Orient Med* 2010; 29: 28-34.
 - 111) Syudo M, Hayashi Y. Floating technique in root canal obturation. *Nihon Shika Hyoron* 2011; 71: 119-127.
 - 112) Masaka N, Sekiya W, Yineda S, Masaka K, Fukushima Y, Okada T. Clinical result of the method to perform root canal filling and core construction simultaneously. *Adhes Dent* 2015; 33: 37-43.
 - 113) ISO, 6876. Dentistry-Root canal sealing materials. Geneva: International Organization for Standardization; 2012 (E).
 - 114) Allan NA, Walton RE, Schaffer M. Setting times for endodontic sealers under clinical usage and in vitro conditions. *J Endod* 2001; 27: 421-423.
 - 115) Nunes VH, Silva RG, Alfredo E, Sousa-Neto MD, Silva-Sousa YTC. Adhesion of Epiphany and AH Plus sealers to human root dentin treated with different solutions. *Braz Dent J* 2008; 19: 46-50.
 - 116) Grossman LI. Physical properties of root canal cements. *J Endod* 1976; 2: 166-175.
 - 117) Whitworth JM, Boursin EM. Dissolution of root canal sealer cements in volatile solvents. *Int Endod J* 2000; 33: 19-24.
 - 118) De Gee AJ, Wu MK, Wesselink PR. Sealing properties of Ketac-Endo glass ionomer cement and AH26 root canal sealers. *Int Endod J* 1994; 27: 239-244.
 - 119) Donnelly A, Sword J, Nishitani Y, Yoshiyama M, Agee K, Tay FR, *et al.* Water sorption and solubility of methacrylate resin-based root canal sealers. *J Endod* 2007; 33: 990-994.
 - 120) Camargo RV, Silva-Sousa YTC, Rosa R, Mazzi-Chaves JF, Lopes FC, Steier L, *et al.* Evaluation of the physicochemical properties of silicone- and epoxy resin-based root canal sealers. *Braz Oral Res* 2017; 31: e72.
 - 121) Lee JK, Kwak SW, Ha JH, Lee W, Kim HC. Physicochemical properties of epoxy resin-based and bioceramic-based root canal sealers. *Bioinorg Chem Appl* 2017; 2017: 2582849.
 - 122) Poggio C, Arciola CR, Dagna A, Colombo M, Bianchi S, Visai L. Solubility of root canal sealers: a comparative study. *Int J Artif Organs* 2010; 33: 676-681.
 - 123) Huffman BP, Mai S, Pinna L, Weller RN, Primus CM, Gutmann JL, *et al.* Dislocation resistance of ProRoot Endo Sealer, a calcium silicate-based root canal sealer, from radicular dentine. *Int Endod J* 2009; 42: 34-46.
 - 124) Ultra E, Cox TC, LaCourse MR, Johnson JD, Paranjpe A. Retreatability of two endodontic sealers, EndoSequence BC Sealer and AH Plus: a micro-computed tomographic comparison. *Restor Dent Endod* 2017; 42: 19-26.
 - 125) Neelakantan P, Grotra D, Sharma S. Retreatability of 2 mineral trioxide aggregate-based root canal sealers: a cone-beam computed tomography analysis. *J Endod* 2013; 39: 893-896.
 - 126) Garza EG, Wadajkar A, Ahn C, Zhu Q, Opperman LA, Bellinger LL, *et al.* Erratum to "Cytotoxicity evaluation of methacrylate-based resins for clinical endodontics in vitro. *J Oral Sci* 2012; 54: 363.
 - 127) Zhang W, Li Z, Peng B. Assessment of a new root canal sealer's apical sealing ability. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009; 107: e79-82.
 - 128) Onay EO, Orucoglu H, Kiremitci A, Korkmaz Y, Berk G. Effect of Er,Cr:YSGG laser irradiation on the apical sealing ability of AH Plus/gutta-percha and Hybrid Root Seal/Resilon combinations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; 110: 657-664.
 - 129) Ulusoy OI, Nayir Y, Celik K, Yaman SD. Apical microleakage of different root canal sealers after use of maleic acid and EDTA as final irrigants. *Braz Oral Res* 2014; 28: 1-6.
 - 130) Hegde V, Arora S. Sealing ability of three hydrophilic single-cone obturation systems: An in vitro glucose leakage study. *Contemp Clin Dent* 2015; 6: S86-89.
 - 131) Schafer E, Olthoff G. Effect of three different sealers on the sealing ability of both thermafil obturators and cold laterally compacted gutta-percha. *J Endod* 2002; 28: 638-642.
 - 132) Cobankara FK, Adanir N, Belli S, Pashley DH. A quantitative evaluation of apical leakage of four root-canal sealers. *Int Endod J* 2002; 35: 979-984.
 - 133) Bouillaguet S, Shaw L, Barthelemy J, Krejci I, Wataha JC. Long-term sealing ability of Pulp Canal Sealer, AH-Plus, GuttaFlow and Epiphany. *Int Endod J* 2008; 41: 219-226.
 - 134) Savariz A, Gonzalez-Rodriguez MP, Ferrer-Luque CM. Long-term sealing ability of GuttaFlow versus Ah Plus using different obturation techniques. *Med Oral Patol Oral Cir Bucal* 2010; 15: e936-941.
 - 135) Nawal RR, Parande M, Sehgal R, Rao NR, Naik A. A comparative evaluation of 3 root canal filling systems. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2011; 111: 387-393.
 - 136) Patni PM, Chandak M, Jain P, Patni MJ, Jain S, Mishra P,

- et al.* Stereomicroscopic evaluation of sealing ability of four different root canal sealers —an invitro Study. *J Clin Diagn Res* 2016; 10: ZC37-39.
- 137) Zmener O, Spielberg C, Lamberghini F, Rucci M. Sealing properties of a new epoxy resin-based root-canal sealer. *Int Endod J* 1997; 30: 332-334.
- 138) Siqueira JF Jr, Rocas IN, Valois CR. Apical sealing ability of five endodontic sealers. *Aust Endod J* 2001; 27: 33-35.
- 139) Miletic I, Ribaric SP, Karlovic Z, Jukic S, Bosnjak A, Anic I. Apical leakage of five root canal sealers after one year of storage. *J Endod* 2002; 28: 431-432.
- 140) Bodrumlu E, Avsar A, Meydan AD, Tuloglu N. Can radiotherapy affect the apical sealing ability of resin-based root canal sealers? *J Am Dent Assoc* 2009; 140: 326-330.
- 141) Bodrumlu E, Parlak E, Bodrumlu EH. The effect of irrigation solutions on the apical sealing ability in different root canal sealers. *Braz Oral Res* 2010; 24: 165-169.
- 142) Miletic I, Anic I, Pezelj-Ribaric S, Jukic S. Leakage of five root canal sealers. *Int Endod J* 1999; 32: 415-418.
- 143) Pappen AF, Bravo M, Gonzalez-Lopez S, Gonzalez-Rodriguez MP. An in vitro study of coronal leakage after intraradicular preparation of cast-dowel space. *J Prosthet Dent* 2005; 94: 214-218.
- 144) Cobankara FK, Orucoglu H, Sengun A, Belli S. The quantitative evaluation of apical sealing of four endodontic sealers. *J Endod* 2006; 32: 66-68.
- 145) Asawaworarit W, Yachor P, Kijssamamith K, Vongsavan N. Comparison of the apical sealing ability of calcium silicate-based sealer and resin-based sealer using the fluid-filtration technique. *Med Princ Pract* 2016; 25: 561-565.
- 146) Ballullaya SV, Vinay V, Thumu J, Devalla S, Bollu IP, Balla S. Stereomicroscopic dye leakage measurement of six different root canal sealers. *J Clin Diagn Res* 2017; 11: ZC65-ZC68.
- 147) Altan H, Goztas Z, Inci G, Tosun G. Comparative evaluation of apical sealing ability of different root canal sealers. *Eur Oral Res* 2018; 52: 117-121.
- 148) De Almeida WA, Leonardo MR, Tanomaru Filho M, Silva LA. Evaluation of apical sealing of three endodontic sealers. *Int Endod J* 2000; 33: 25-27.
- 149) Biggs SG, Knowles KI, Ibarrola JL, Pashley DH. An in vitro assessment of the sealing ability of Resilon/Epiphany using fluid filtration. *J Endod* 2006; 32: 759-761.
- 150) Kaya BU, Kecici AD, Belli S. Evaluation of the sealing ability of gutta-percha and thermoplastic synthetic polymer-based systems along the root canals through the glucose penetration model. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104: e66-73.
- 151) Nagas E, Altundasar E, Serper A. The effect of master point taper on bond strength and apical sealing ability of different root canal sealers. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009; 107: e61-64.
- 152) Onay EO, Ungor M, Orucoglu H. An in vitro evaluation of the apical sealing ability of a new resin-based root canal obturation system. *J Endod* 2006; 32: 976-978.
- 153) Tunga U, Bodrumlu E. Assessment of the sealing ability of a new root canal obturation material. *J Endod* 2006; 32: 876-878.
- 154) Bodrumlu E, Tunga U. Apical leakage of Resilon obturation material. *J Contemp Dent Pract* 2006; 7: 45-52.
- 155) Bodrumlu E, Tunga U. The apical sealing ability of a new root canal filling material. *Am J Dent* 2007; 20: 295-298.
- 156) Hirai VH, da Silva Neto UX, Westphalen VP, Perin CP, Carneiro E, Fariniuk LF. Comparative analysis of leakage in root canal fillings performed with gutta-percha and Resilon cones with AH Plus and Epiphany sealers. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; 109: e131-135.
- 157) Belli S, Ozcan E, Derinbay O, Eldeniz AU. A comparative evaluation of sealing ability of a new, self-etching, dual-curable sealer: hybrid root SEAL (MetaSEAL). *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008; 106: e45-52.
- 158) Melih I, Jakovljevic A, Popovic M, Pesic D. [Comparative evaluation of sealing ability of different obturation materials]. *Srp Arh Celok Lek* 2010; 138: 287-291.
- 159) Fathia E, Hassan Abu-Bakr N, Yahia I. A comparative study of the microleakage of Resilon/Epiphany and gutta-percha/AH-Plus obturating systems. *Iran Endod J* 2012; 7: 139-143.
- 160) Lambor RT, de Ataide Ide N, Chalakkal P, Akkara F, Shariff SA, Fernandes KS. An in vitro comparison between the apical sealing abilities of resilon with Epiphany sealer and gutta-percha with AH plus sealer. *Indian J Dent Res* 2012; 23: 694.
- 161) Dhaded N, Dhaded S, Patil C, Patil R, Roshan JM. The effect of time of post space preparation on the seal and adaptation of resilon-Epiphany Se & gutta-percha-AH Plus sealer —an sem study. *J Clin Diagn Res* 2014; 8: 217-220.
- 162) Sultana M, Musani MA, Ahmed IM. An in-vitro comparative study for assessment of apical sealing ability of Epiphany/AH Plus sealer with Resilon/gutta-percha root canal filling materials. *J Int Soc Prev Community Dent* 2016; 6: 321-326.
- 163) Kumar SA, Shivanna V, Naian MT, Shivamurthy G. Comparative evaluation of the apical sealing ability and adaptation to dentine of three resin-based sealers: An in vitro study. *J Conserv Dent* 2011; 14: 16-20.
- 164) Kardon BP, Kuttler S, Hardigan P, Dorn SO. An in vitro evaluation of the sealing ability of a new root-canal-obturation system. *J Endod* 2003; 29: 658-661.
- 165) Sevimay S, Kalayci A. Evaluation of apical sealing ability and adaptation to dentine of two resin-based sealers. *J Oral Rehabil* 2005; 32: 105-110.
- 166) Pawar SS, Pujar MA, Makandar SD. Evaluation of the apical sealing ability of bioceramic sealer, AH plus & Epiphany: An in vitro study. *J Conserv Dent* 2014; 17: 579-582.
- 167) Canadas PS, Berastegui E, Gatón-Hernandez P, Silva LA, Leite GA, Silva RS. Physicochemical properties and interfacial adaptation of root canal sealers. *Braz Dent J* 2014; 25: 435-441.
- 168) Ahuja L, Jasuja P, Verma KG, Juneja S, Mathur A, Walia R, *et al.* A comparative evaluation of sealing ability of new MTA based sealers with conventional resin based sealer: an in-vitro study. *J Clin Diagn Res* 2016; 10: ZC76-79.
- 169) Jain P, Pruthi V, Sikri VK. An ex vivo evaluation of the sealing ability of polydimethylsiloxane-based root canal sealers. *Indian J Dent Res* 2014; 25: 336-339.
- 170) Orstavik D, Nordahl I, Tibballs JE. Dimensional change following setting of root canal sealer materials. *Dent Mater* 2001; 17: 512-519.
- 171) Royer K, Liu XJ, Zhu Q, Malmstrom H, Ren YF. Apical and root canal space sealing abilities of resin and glass ionomer-based root canal obturation systems. *Chin J Dent Res* 2013; 16: 47-53.
- 172) Mejare I, Mjor IA. Glass ionomer and resin-based fissure sealants: a clinical study. *Scand J Dent Res* 1990; 98: 345-350.
- 173) Aptekar A, Ginnan K. Comparative analysis of microleakage and seal for 2 obturation materials: Resilon/Epiphany and gutta-percha. *J Can Dent Assoc* 2006; 72: 245.
- 174) Kumar RV, Shruthi C. Evaluation of the sealing ability of resin cement used as a root canal sealer: An in vitro study. *J Conserv Dent* 2012; 15: 274-277.
- 175) Imai Y, Komabayashi T. Properties of a new injectable type of root canal filling resin with adhesiveness to dentin. *J Endod* 2003; 29: 20-23.
- 176) Siqueira JF Jr, Rocas IN. Clinical implications and microbiology of bacterial persistence after treatment procedures. *J Endod* 2008; 34: 1291-1301 e1293.
- 177) Banoee M, Seif S, Nazari ZE, Jafari-Fesharaki P, Shahverdi HR, Moballegheh A, *et al.* ZnO nanoparticles enhanced antibacterial activity of ciprofloxacin against *Staphylococcus*

- aureus and *Escherichia coli*. *J Biomed Mater Res B Appl Biomater* 2010; 93: 557-561.
- 178) Poggio C, Lombardini M, Colombo M, Dagna A, Saino E, Arciola CR, *et al.* Antibacterial effects of six endodontic sealers. *Int J Artif Organs* 2011; 34: 908-913.
- 179) Heling I, Chandler NP. The antimicrobial effect within dentinal tubules of four root canal sealers. *J Endod* 1996; 22: 257-259.
- 180) Wainstein M, Morgental RD, Waltrick SB, Oliveira SD, Vier-Pelisser FV, Figueiredo JA, *et al.* In vitro antibacterial activity of a silicone-based endodontic sealer and two conventional sealers. *Braz Oral Res* 2016; 30: 1-5.
- 181) Kapralos V, Koutroulis A, Ørstavik D, Sunde PT, Rukke HV. Antibacterial activity of endodontic sealers against planktonic bacteria and bacteria in biofilms. *J Endod* 2018; 44: 149-154.
- 182) Torabinejad M, Hong CU, Pitt Ford TR, Kettering JD. Antibacterial effects of some root end filling materials. *J Endod* 1995; 21: 403-406.
- 183) Estrela C, Bammann LL, Estrela CR, Silva RS, Pecora JD. Antimicrobial and chemical study of MTA, Portland cement, calcium hydroxide paste, Sealapex and Dycal. *Braz Dent J* 2000; 11: 3-9.
- 184) Miyagak DC, de Carvalho EM, Robazza CR, Chavasco JK, Levorato GL. In vitro evaluation of the antimicrobial activity of endodontic sealers. *Braz Oral Res* 2006; 20: 303-306.
- 185) Tanomaru-Filho M, Tanomaru JM, Barros DB, Watanabe E, Ito IY. In vitro antimicrobial activity of endodontic sealers, MTA-based cements and Portland cement. *J Oral Sci* 2007; 49: 41-45.
- 186) Asgary S, Kamrani FA. Antibacterial effects of five different root canal sealing materials. *J Oral Sci* 2008; 50: 469-474.
- 187) Okiji T, Yoshida K. Reparative dentinogenesis induced by mineral trioxide aggregate: a review from the biological and physicochemical points of view. *Int J Dent* 2009; 2009: 464280.
- 188) Singh G, Gupta I, Elshamy FM, Boreak N, Homeida HE. In vitro comparison of antibacterial properties of bioceramic-based sealer, resin-based sealer and zinc oxide eugenol based sealer and two mineral trioxide aggregates. *Eur J Dent* 2016; 10: 366-369.
- 189) Duarte MA, Demarchi AC, Yamashita JC, Kuga MC, Fraga Sde C. pH and calcium ion release of 2 root-end filling materials. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 95: 345-347.
- 190) Shakya VK, Gupta P, Tikku AP, Pathak AK, Chandra A, Yadav RK, Bharti R, Singh RK. An in vitro evaluation of antimicrobial efficacy and flow characteristics for AH Plus, MTA Fillapex, CRCS and Gutta Flow 2 root canal sealer. *J Clin Diagn Res* 2016; 10: ZC104-108.
- 191) Zhang H, Shen Y, Ruse ND, Haapasalo M. Antibacterial activity of endodontic sealers by modified direct contact test against *Enterococcus faecalis*. *J Endod* 2009; 35: 1051-1055.
- 192) Tanomaru JM, Tanomaru-Filho M, Hotta J, Watanabe E, Ito IY. Antimicrobial activity of endodontic sealers based on calcium hydroxide and MTA. *Acta Odontol Latinoam* 2008; 21: 147-151.
- 193) Teoh YY, Athanassiadis B, Walsh LJ. Sealing ability of alkaline endodontic cements versus resin cements. *Materials (Basel)* 2017; 10: 1-7.
- 194) Gulati N, Chandra S, Aggarwal PK, Jaiswal JN, Singh M. Cytotoxicity of eugenol in sealer containing zinc-oxide. *Endod Dent Traumatol* 1991; 7: 181-185.
- 195) Kolokouris I, Economides N, Beltes P, Vlemmas I. In vivo comparison of the biocompatibility of two root canal sealers implanted into the subcutaneous connective tissue of rats. *J Endod* 1998; 24: 82-85.
- 196) Serene TP, Vesely J, Boackle RJ. Complement activation as a possible in vitro indication of the inflammatory potential of endodontic materials. *Oral Surg Oral Med Oral Pathol* 1988; 65: 354-357.
- 197) Guigand M, Pellen-Mussi P, Le Goff A, Vulcain JM, Bonnaure-Mallet M. Evaluation of the cytocompatibility of three endodontic materials. *J Endod* 1999; 25: 419-423.
- 198) Cintra LTA, Benetti F, de Azevedo Queiroz IO, Ferreira LL, Massunari L, Bueno CRE, *et al.* Evaluation of the cytotoxicity and biocompatibility of new resin epoxy-based endodontic sealer containing calcium hydroxide. *J Endod* 2017; 43: 2088-2092.
- 199) Pertot WJ, Camps J, Remusat M, Proust JP. In vivo comparison of the biocompatibility of two root canal sealers implanted into the mandibular bone of rabbits. *Oral Surg Oral Med Oral Pathol* 1992; 73: 613-620.
- 200) Nakamura H, Sakakibara F, Matsumoto Y, Hirano S, Hayakawa H, Sakai K, *et al.* Study on the cytotoxicity of root canal filling materials. *J Endod* 1986; 12: 156-160.
- 201) al-Khatib ZZ, Baum RH, Morse DR, Yesilsoy C, Bhamhani S, Furst ML. The antimicrobial effect of various endodontic sealers. *Oral Surg Oral Med Oral Pathol* 1990; 70: 784-790.
- 202) Dahl JE. Toxicity of endodontic filling materials. *Endod Topics* 2005; 12: 39-43.
- 203) Hume WR, Mount GJ. In vitro studies on the potential for pulpal cytotoxicity of glass-ionomer cements. *J Dent Res* 1988; 67: 915-918.
- 204) Zetterqvist L, Anneroth G, Nordenram A. Glass-ionomer cement as retrograde filling material. An experimental investigation in monkeys. *Int J Oral Maxillofac Surg* 1987; 16: 459-464.
- 205) Zetterqvist L, Anneroth G, Danin J, Roding K. Microleakage of retrograde fillings: a comparative investigation between amalgam and glass ionomer cement in vitro. *Int Endod J* 1988; 21: 1-8.
- 206) Briseno BM, Willershausen B. Root canal sealer cytotoxicity on human gingival fibroblasts: 2. Silicone- and resin-based sealers. *J Endod* 1991; 17: 537-540.
- 207) Silva EJ, Neves AA, De-Deus G, Accorsi-Mendonca T, Moraes AP, Valentim RM, *et al.* Cytotoxicity and gelatinolytic activity of a new silicon-based endodontic sealer. *J Appl Biomater Funct Mater* 2015; 13: e376-380.
- 208) Ko H, Yang W, Park K, Kim M. Cytotoxicity of mineral trioxide aggregate (MTA) and bone morphogenetic protein 2 (BMP-2) and response of rat pulp to MTA and BMP-2. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; 109: e103-108.
- 209) Benetti F, Queiroz ÍOda, Cosme-Silva L, Conti LC, Oliveira SHPd, Cintra LTA. Cytotoxicity, biocompatibility and biomimetalization of a new ready-for-use bioceramic repair material. *Braz Dent J* 2019; 30: 325-332.
- 210) Camps J, Jeanneau C, El Ayachi I, Laurent P, About I. Bioactivity of a calcium silicate-based endodontic cement (BioRoot RCS): interactions with human periodontal ligament cells in vitro. *J Endod* 2015; 41: 1469-1473.
- 211) Loushine BA, Bryan TE, Looney SW, Gillen BM, Loushine RJ, Weller RN, *et al.* Setting properties and cytotoxicity evaluation of a premixed bioceramic root canal sealer. *J Endod* 2011; 37: 673-677.
- 212) Huang FM, Tai KW, Chou MY, Chang YC. Cytotoxicity of resin-, zinc oxide-eugenol-, and calcium hydroxide-based root canal sealers on human periodontal ligament cells and permanent V79 cells. *Int Endod J* 2002; 35: 153-158.
- 213) Pascon EA, Leonardo MR, Safavi K, Langeland K. Tissue reaction to endodontic materials: methods, criteria, assessment, and observations. *Oral Surg Oral Med Oral Pathol* 1991; 72: 222-237.
- 214) Mutoh N, Satoh T, Watabe H, Tani-Ishii N. Evaluation of the biocompatibility of resin-based root canal sealers in rat periapical tissue. *Dent Mater J* 2013; 32: 413-419.
- 215) Hirabayashi C, Imai Y. Studies on MMA-TBB resin. I. Comparison of TBB and other initiators in the polymerization

- of PMMA/MMA resin. Dent Mater J 2002; 21: 314-321.
- 216) Imai Y, Watanabe M, Lee HE, Kojima K, Kadoma Y. Cytotoxicity of monomers used in dental resins. Reports Inst Med Dent Eng 1988; 22: 87-90.
- 217) Takeda S, Hashimoto Y, Miura Y, Kimura Y, Nakamura M. Cytotoxicity test of dental monomers using serum-free cell culture (in vitro). Shika Zairyo Kikai 1993; 12: 613-619.
- 218) Yoshii E. Cytotoxic effects of acrylates and methacrylates: relationships of monomer structures and cytotoxicity. J Biomed Mater Res 1997; 37: 517-524.
- 219) Lodiene G, Kopperud HM, Orstavik D, Bruzell EM. Detection of leachables and cytotoxicity after exposure to methacrylate- and epoxy-based root canal sealers in vitro. Eur J Oral Sci 2013; 121: 488-496.
- 220) Camargo CH, Oliveira TR, Silva GO, Rabelo SB, Valera MC, Cavalcanti BN. Setting time affects in vitro biological properties of root canal sealers. J Endod 2014; 40: 530-533.
- 221) Martinho FC, Camargo SEA, Fernandes AMM, Campos MS, Prado RF, Camargo CHR, *et al.* Comparison of cytotoxicity, genotoxicity and immunological inflammatory biomarker activity of several endodontic sealers against immortalized human pulp cells. Int Endod J 2018; 51: 41-57.
- 222) Garza EG, Wadajkar A, Ahn C, Zhu Q, Opperman LA, Bellinger LL, *et al.* Cytotoxicity evaluation of methacrylate-based resins for clinical endodontics in vitro. J Oral Sci 2012; 54: 213-217.
- 223) Leonardo MR, Silva LA, Utrilla LS, Assed S, Ether SS. Calcium hydroxide root canal sealers--histopathologic evaluation of apical and periapical repair after endodontic treatment. J Endod 1997; 23: 428-432.
- 224) Poggio C, Riva P, Chiesa M, Colombo M, Pietrocola G. Comparative cytotoxicity evaluation of eight root canal sealers. J Clin Exp Dent 2017; 9: e574-e578.
- 225) Kakehashi S, Stanley HR, Fitzgerald RJ. The effects of surgical exposures of dental pulps in germ-free and conventional laboratory rats. Oral Surg Oral Med Oral Pathol 1965; 20: 340-349.
- 226) Madison S, Swanson K, Chiles SA. An evaluation of coronal microleakage in endodontically treated teeth. Part II. Sealer types. J Endod 1987; 13: 109-112.
- 227) Ray HA, Trope M. Periapical status of endodontically treated teeth in relation to the technical quality of the root filling and the coronal restoration. Int Endod J 1995; 28: 12-18.
- 228) Gandolfi MG, Parrilli AP, Fini M, Prati C, Dummer PM. 3D micro-CT analysis of the interface voids associated with Thermafil root fillings used with AH Plus or a flowable MTA sealer. Int Endod J 2013; 46: 253-263.