Review

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 voids[4)], lateral canals[5)], 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 types[10-16)]. 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 rheology[19)], radiopacity[20)], and tooth discoloration[21-23)] 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) ligands[24)]. 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 solidify[25)]. 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 1936[28)] 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 gel[31)]. Residual zinc oxide powder remains in the gel, forming a rigid matrix[32)]. 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

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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 lodide
		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, Bismus trioxide, Fumed silica, Titanium dioxide,
		Paste B	Fumed silica, Titanium dioxide, Tricalcium silicaate, Dicalcium silicate, Calcium oxide, Tricalcium alminate, 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 collophonium, 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 alminium lanthanum fluorosilicate glass, Calcium volframate, 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, Amantiameamine, 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, Bismus subcarbonate
		Catalyst	Hexamehtylenetetramine, 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

Tricalcium silicate (MTA/ Bioceramic)	Grey & Neo MTA Plus (NuSmile Avalon Biomed, USA)	Powder	Tricaclium 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
	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
Methacrylate resin	EndoREZ (Ultradent, USA)	Base	UDMA, Benzoyl peroxide
		Catalyst	Triethylene glycol dimethacrylate, p-Tolyldiethanolamine
	Epiphany (Resilon Research, USA)	Paste A Paste B	[After mixing] UDMA, PEGDMA, EBPADMA, Bis-GMA, Barium borosilicate glasses treated with silane, Barium sulfate, Silica, Calcium hydroxide, Bismuth oxychloride, Thiosinamine, 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-methacryloxyethy 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 use[33]. 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 areas[34]; this sealer was toxic to periradicular tissues[35] and contraindicated. Sargenti introduced N2 sealer in 1973[36], which contained lead and mercury. The toxic metals were reported to be found in distant organ systems, having migrated from the radicular spaces[37]. N2 was not cleared by the U.S. Food and Drug Administration[38].

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 hydroxyapatite[40], 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 sealer[41]. However, calcium hydroxide does not set and is slightly soluble in water. It must be used within a matrix to be an effective sealer[42]. Sealers containing calcium hydroxide were intended to promote osteogenesis and cementogenesis as well as create an antimicrobial environment[43]. 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 deposition[45]. 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 possible[48].

Similar to the above sealers, MTA Fillapex (Angelus, Londrina, Brazil) is a unique salicylate resin-based sealer that contains 15% MTA powder[49]. MTA Fillapex should not be regarded as a tricalcium silicate (MTA, a bioactive ceramic) sealer since its composition is primarily resin[49]. 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 outcomes[50-53]. 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 rosin[29]. Rosin contains several resin acids, the most abundant being abietic acid, which are derived from coniferous trees[54]. Nogenol (GC America, Alsip, IL, USA) is another fatty acid-zinc oxide sealer made with lauric acid.

Ionomer 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 ionomer[55]. 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 structure[56], 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 catalyst[58]. Epoxy resin-based sealers follow a more traditional organic addition reaction, where epoxide monomers react with amines to create a rigid material[59].

1. Silicone-based sealers

In 1972, Davis *et al.* used injectable silicone impression material into the prepared root canals[60]. Silicone-based sealers are composed of polymethyvinylsiloxane 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 polymer[58]. 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 1950s[63]. Guttuso studied AH 26 using rat in 1963 and found moderate tissue response in 16 days[64]. Feldmann and Nyborg found AH 26, implanted after one day hardening, caused much more tissue irritation than did pure silver in rabbit study in 1964[65]. In 1993, Spångberg *et al.* reported that AH 26 releases formaldehyde[66], 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 1990s[67], 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 ions[47] . 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 capping[72], and pulpotomies[72]. 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 biocompatibility[75-78]. 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 setting[47]. 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 sealing[83]. 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 1982[48], 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 Bioceramix, 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 Bioceramix). The setting mechanism of single-paste tricalcium silicate-based sealers is water absorption from dentin tubules[84] 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 effect[87].

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-1970s[90-92]. Wichterle and Lim, contact lens researchers, developed Hydron in the 1960[93]. 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 1980s[88].

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 adhesive[94]. 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 materials[95]. 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 dentistry[96]. 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 matrix[98]. 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 monoblock[99]. RealSeal SE (Kerr) was a commercial product similar to Epiphany[98,100] but with less etching ability than RealSeal[101]. These systems are no longer sold because they were susceptible to degradation of their ester bonds[102]

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 generation[103]. Hybrid Root SEAL hybridized dentin more resistant to low pH[104], which was most effective after EDTA irrigation[105] and may reduce microleakage[106].

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 to more suitable for mimicking masticatory stress and strain[112]. 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 standards[113] 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 re-treatment, 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 solvents[117].

Ketac-Endo, a glass ionomer sealer, was found to have a setting time of 2.5 h[118]. 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 loss[119]. 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 min[117].

GuttaFlow, a silicone-based sealer, was found to have a setting time of 17.4 min, the shortest setting time of sealer types considered[120]. GuttaFlow had only 0.13% solubility in water, meeting the ADA and ISO specifications for solubility[119].

Setting times for tricalcium silicate-based sealers, including EndoSequence BC Sealer, also known as iRoot SP have even been shown to exceed one month[121]; 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 compositions[122]. The solubility may be attributed to the formation of calcium hydroxide during setting of tricalcium silicates, which is dissolved in the ISO 6876 solubility test[123]. 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 without[124]. However, the same study found EndoSequence BC Sealer had significantly more residual material remaining after re-treatment compared with AH Plus[124]. 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 sealers[125].

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 requirements[122], with 0.16% solubility in water[119]. AH Plus was significantly more soluble in halothane, yielding 68% weight losses after 10 min[117], 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 min[126]. 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 specifications[119].

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 requirements[122]. Solubility in halothane for the salicylate-based sealer such as Apexit was comparable with that of ZOE sealers[117].

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) sealers[127-130], 6 data points for silicone sealers[131-136], 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 μL/min using the fluid filtration method, while GuttaFlow exhibits a microleakage of 0.08 μL/min. GuttaFlow therefore has 0.47 times the microleakage of AH Plus within the 6th h for this individual study[133]. 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	0.38	1.51	0.67	Least**	127-130)	4
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 sealers[166].

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 sealers[146]. 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 walls[167]. ProRoot MTA, which is not indicated as a sealer, had significantly more microleakage when used as a sealer[168] 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 anatomy[169]. RoekoSeal had the better sealing ability than GuttaFlow when measured with a dye diffusion test in extracted human teeth sectioned both horizontally and vertically[169]. RoekoSeal has been found to expand 0.2% upon setting (exceeding the ADA 57 requirement), which may be beneficial[170]. 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 shrinkage[171)]. Epoxy resin-based sealers have been shown by stereomicroscopy to have moderate sealing capacity, but superior to ZOE-based sealers[136)].

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 teeth[136)]. The salicylate-based MTA Fillapex sealer had more microleakage than conventional epoxy resin-based sealers in a dye penetration study[168)].

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 sealers[136)]. 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 interface[118)].

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 obturation[173)]. Bacterial leakage tests with *Streptococcus mutans* and *Enterococcus faecalis* reflect lower microleakage as well[96)]. 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 stereomicroscopy[174)]. 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 seal[107)]. 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 resin[175)]. The dye penetration of Endoresin-2, an experimental MMA-TBB resin sealer, was 0.17 mm after 2 days[175)], 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 material[95)].

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 tissue[176)] 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 proteins[177)]. 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 sealers[178)]. Fluoride ions inhibit also bacterial growth, but glass ionomer sealers have demonstrated minimal antimicrobial activity[179)]. 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 sealers[180)]. 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 contradictory[73)]. In a study by Torabinejad *et al.*, MTA was demonstrated to have an antimicrobial effect on facultative bacteria and no effect on obligate anaerobes[182)]. 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 sealers[188)]. 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 effect[189)]. 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 h[181]. 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 Sealapex[191]. 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 agar[190]. Calcium-hydroxide-based sealers proved to have a greater zone of inhibition than ZOE sealers[190]. Supercal (Ozdent, Sydney, Australia), another calcium-hydroxide-containing glycerol sealer, was more antibacterial than MTA and AH Plus sealers[193].

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 sulfate[198], which are known to be biocompatible[199]. Because eugenol is cytotoxic and evokes an inflammatory response, zinc oxide non-eugenol sealers such as Canals-N[29] 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 months[202]. 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 release[203]. 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 test[180].

Tricalcium silicate-based sealers have exhibited both beneficial and deleterious effects in terms of biocompatibility[16]. 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 inflammation[188]. 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 weeks[208]. 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 biomineralization[209]. Osteoinductive properties and cytocompatibility were superior for BioRoot RCS compared to the ZOE Kerr's Pulp Canal Sealer[210]. Over time, EndoSequence BC sealer retains more pronounced cytotoxicity to osteoblast progenitors than AH Plus, even after six weeks[211].

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 formaldehyde[212]. 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 mixed[66]. AH Plus is modified such that formaldehyde is not released[35]. 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 tissue[214].

Methacrylate polymer has negligible cytotoxicity when set and demonstrated cytotoxicity or inflammation only early in the setting process[215]. Incompletely cured methyl methacrylate (MMA), monomer/polymer is cytotoxic although considered the least toxic monomer used in dentistry[216-218]. 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 death[219]. 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 biomarkers[221]. 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 cultures[222]. 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 seal[223]. *In vivo* degradation of sealer and incomplete fills may be the reason for added inflammation in these cases[223]. 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 mixed[70]. 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 h[224].

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 choice[226]. The technical quality of the coronal restoration is more important than the technical quality of the endodontic treatment for apical periodontal health[227]. 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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