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Chemistry of novel and contemporary resin-based dental adhesives

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Chemistry of novel and contemporary resin-based dental adhesives

Abstract

The chemistry of resin-based dental adhesives is critical for its interaction with dental tissues and long-term bonding stability. Changes in dental adhesives composition influences materials' key physical-chemical properties, such as rate and degree of conversion, water sorption, solubility, flexural strength and modulus, and cohesive strength and improve the biocompatibility to the dental tissues. Maintaining a suitable reactivity between photoinitiators and monomers is important for optimal properties of adhesive systems, in order to enable adequate polymerization and improved chemical, physical and biological properties.

The aim of this article is to review the current state-of-the-art of dental adhesives, approaching its chemical composition and characteristics that influences polymerisation reaction and subsequently materials properties and performance.

Contents

1. Introduction

The development of dental adhesive systems over the last 50 years has provided reliable materials for clinical application in many restorative procedures. Nowadays, there are three types of systems widely used: etch-and-rinse adhesives (ERAs), which use a conditioning stage prior to the bonding application (Pashley et al., 2011; Perdigao et al., 2003); self-etching adhesives (SEAs), which exclude the acid-etching step, as the bonding agent is responsible for simultaneous etching and infiltration of the monomers into tooth substrates; and multi-mode or ”universal” adhesives, which allow the clinician to use the same adhesive resin as self-etching or etch-and-rinse, according to the convenience (Carvalho et al., 2005; Nagarkar et al., 2019; Van Landuyt et al., 2007; Van Meerbeek et al., 2011) .

ERAs are the most traditional adhesive type and require the application of phosphoric acid (35-37%) to the tooth surface, followed by primer application and then the bonding agent (Pashley et al., 2011). The main mechanism of ERAs is supported by the findings of Buonocore (Buonocore, 1955) and Nakabayashi (Nakabayashi et al., 1982). Buonocore was the first to demonstrate that acid-etching can improve bonding to enamel by creating a rough pattern surface, increasing the bond strength between the etched substrate and the resin-based materials (Buonocore, 1955). The mechanical interlocking within dentin differs considerably compared to enamel because in dentin it relies on diffusion of the adhesive within the exposed collagen fibrils on the pre-etched surface, creating a new structure formed by resin matrix and collagen fibrils, known as the “hybrid-layer”, first cited by Nakabayashi [9].

As an alternative approach, SEAs were developed based on the use of primers containing acidic monomers, which are designed to etch and diffuse monomers simultaneously, eliminating the requirement for a separate etching step (De Munck et al., 2005; Van Landuyt et al., 2007; Van Meerbeek et al., 2011).

Multi-mode or the so called universal adhesives, as previously described, can be used as etch-and-rinse systems, as well as a self-etching agent, excluding the step of dentin acid etching, but still requiring enamel selective etching for improved bonding on this highly mineralized tissue (Cuevas-Suarez et al., 2019; Nagarkar et al., 2019). The chemical formulation of the current commercial dental adhesives according to its classification is listed in Table A.1.

The key parameters for success of dental resin-based adhesives include an effective marginal sealing and a reliable and long-lasting bond to both enamel and dentin. Adhesive chemistries are constantly researched and in development to optimise materials properties such as decreased water sorption and solubility, improved polymerisation, and physical properties to provide adequate resistance to counteract polymerisation stresses generated during resin-based materials reaction, and masticatory forces. Further, the development of modern adhesive formulations strives towards self-etching capabilities and bioactive properties that may assist in maintenance of hybrid layer and even remineralisation of damaged tissues. Therefore, a sound knowledge of adhesive resin chemical components and its role is critical for understanding key material properties and how it can be improved. The present review aims to provide a critical appraisal of current and emerging dental adhesive compositions, and how differences in materials chemistry and curing mechanisms affect material properties and function.

2. Resin adhesive chemistry: components and characteristics

The key properties of adhesive systems for ideal bonding characteristics include: 1) intimate adaptation, marginal sealing and reliable bond strength; 2) a high degree of conversion, suitable strength and stiffness to withstand forces of shrinkage stress and mastication; 3) low water sorption and solubility for long-term bonding stability and; 4) compatibility with dental tissue, and ideally bioactive properties to prevent biofilm adhesion and promote remineralisation. Although adhesives can be divided into three groups (ERAs, SEAs and universal), all systems have similar components, such as monomers, initiators and solvents, regardless of the number of steps. Regardless of dental adhesive classification, there are similarities in chemical composition; hydrophilic monomers, with affinity for the organic components of the dental substrate, and hydrophobic monomers, which favour bonding with restorative resin composites placed on top of the adhesive layer. In addition, solvents, photo- and/or chemical initiators, co-initiators, inhibitors and, in some compositions, small amounts of filler particles are present.

2.1 Monomers

Dimethacrylate-based chemistries are used in adhesive dentistry due to their superior reactivity, excellent optical and mechanical properties, and potential for high crosslinking density (Asmussen and Peutzfeldt, 2001). The molecular structure of adhesive resins contain a polymerizable groups, spacer and functional groups (Van Landuyt et al., 2007), where adjustments to the latter usually occurs in some types of monomers commonly present in SEAs.

2.1.1 Mono- and Multi-functional methacrylates

The crosslink density of dental adhesive monomers significantly affects mechanical properties and integrity of the bonding interface (Asmussen and Peutzfeldt, 2001). With fewer crosslinks, the polymer exhibits reduced mechanical properties, higher flexibility and increased susceptibility to solvent degradation. Consequently, mono- and multifunctional monomers are used as crosslink agents, and base monomers provide a more rigid and stable polymer to promote reliable bonding. Examples of base monomers widely used in current dental adhesives include 2-hydroxyethyl methacrylate (HEMA); bisphenol-A-diglycidylmethacrylate (Bis-GMA), triethyleneglycol-dimethacrylate (TEGDMA) and urethane dimethacrylate (UDMA) (Figure 1).

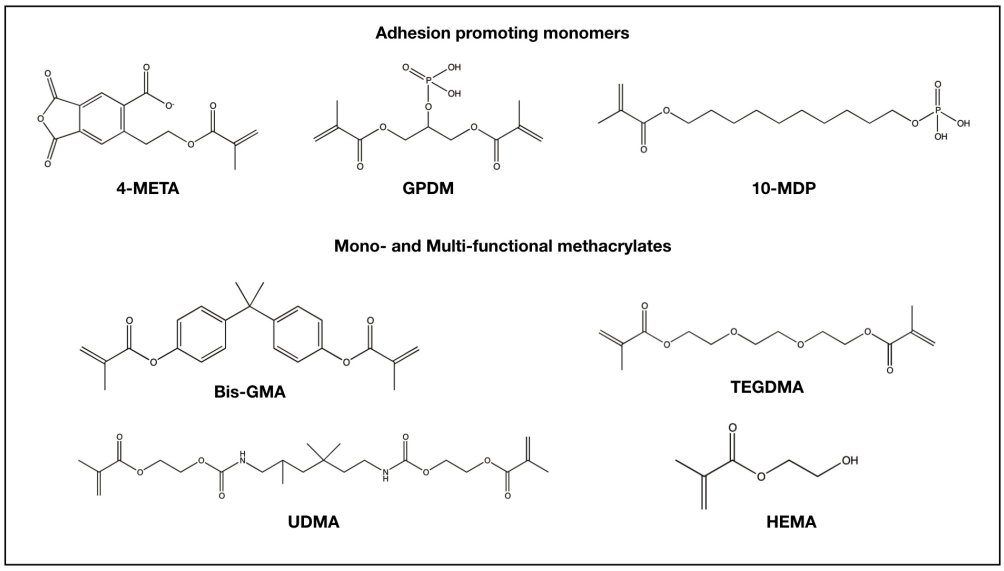

Fig. 1 – Chemical structure of adhesion promoting monomers and mono- and multi-functional monomers most used in dental adhesives

2.1.1.1 Bisphenol-A-diglycidylmethacrylate (Bis-GMA)

Bis-GMA is a reaction product of bisphenol A and glycidyl ester methacrylate (GMA) and forms the backbone of most dental adhesives currently marketed

(Sideridou et al., 2002). The steric hindrance of the monomer chain around the large phenyl ring structures and presence of hydroxyl groups (Figure 1) results in a highly viscous and hydrophobic chemistry. The reduced chain mobility results in a decreased rate of polymerisation and degree of conversion (Goncalves et al., 2009). The presence of aromatic rigid cores on the Bis-GMA chain, and strong polar bonding, increases the glass transition temperature (Tg), also reducing the flexibility of the monomer. The rigid network of the polymer exhibits a high degree of intermolecular bonding (Davy et al., 1998) and high flexural strength [43].

To obviate the negative effects of low polymer conversion, other aliphatic monomers with lower molecular weight, such as HEMA and TEGDMA, can be admixed with Bis-GMA (Gajewski et al., 2012).

2.1.1.2 Urethane dimethacrylate (UDMA)

UDMA is a large dimethacrylate monomer (Figure 1) with reduced molecular weight and viscosity compared with Bis-GMA. UDMA is typically used in combination with Bis-GMA and/or TEGDMA, modulating the properties of the mixture, increasing degree of conversion and co-polymer hardness (Barszczewska-Rybarek, 2009). The lower molecular weight and reduced steric hindrance of UDMA allow for higher flexibility, lower intermolecular bonding and viscosity of the monomer compared with that of Bis-GMA (Floyd and Dickens, 2006). Such properties provide improved monomeric diffusion into dental substrates and enables incorporation of filler providing opportunity for higher bond strengths (Asmussen and Peutzfeldt, 1998; Papakonstantinou et al., 2013). Further, UDMA can acts as a hydrogen donor, similar (but less effective) to the function of the tertiary amine co-initiator, improving radical formation and degree of conversion. The combined abstraction of hydrogen from the

amine, and UDMA counteract the potential negative effects of higher mobility systems, mutual radical annihilation and reduced conversion. (Asmusen et al., 2009)

2.1.1.3 Triethyleneglycol-dimethacrylate (TEGDMA)

TEGDMA is a low viscosity, diluent monomer, that exhibits a more flexible chain and reduced intermolecular bonding (due to the absence of –OH groups, Figure 1), and provides improved wettability and reduced hydrophobicity compared with Bis-GMA alone (Gajewski et al., 2012). A Bis-GMA/TEGDMA co-monomer mixture is commonly used due to its high reactivity, improving degree of conversion of the monomer mixture (Lovell et al., 1999). However, increased hydrophilicity of the cured system due to the ether links present in both monomers, may ultimately result in higher water sorption and degradation of the polymer (Ito et al., 2005).

2.1.1.4 2-hydroxyethyl methacrylate (HEMA)

HEMA is a mono-functional monomer with low molecular weight (Figure 1). It has a high allergenic potential in its uncured state (Goossens, 2004), although following effective polymerisation, low cytotoxicity of HEMA has been reported (Geurtsen, 2000). However, compared with other monomers used in dentistry, the low molecular weight and increased mobility of HEMA facilitates greater diffusion of uncured monomers to the dental pulp, causing significant damage to the specific cell types (Chang et al., 2005; Mantellini et al., 2006; Massaro et al., 2019). Nonetheless, the polar characteristics and its water-soluble properties increase wettability, flow and diffusion through the collagen fibril network in dentine (Nakabayashi and Takarada, 1992; Van Landuyt et al., 2008a). The alcohol group and the hydrophilic

characteristics have a positive influence on bond strength of adhesives, improving the miscibility of hydrophobic and hydrophilic monomers, reducing phase separation of simplified adhesives that contain multiple monomers in the same bottle, i.e. SEAs (Van Landuyt et al., 2005; Van Landuyt et al., 2008b). Phase separation is still a challenge regarding simplified adhesives, as solvent evaporation can promote or accelerate this process (Van Landuyt et al., 2005; Ye et al., 2009). However, in presence of HEMA, when solvent is vaporised, this monomer acts as a substitute, maintaining the components in a homogenised solution, reducing the undesirable effect of phase separation (Van Landuyt et al., 2005; Van Landuyt et al., 2008a).

In order to improve bond strength, the ideal concentration of HEMA in the primer solution of two-bottle SEAs is around 30–40 wt%, and 5–25 wt% in single-bottle adhesives (Van Landuyt et al., 2008a). Due to its high hydrophilicity, HEMA can increase water sorption and solubility of dental adhesives (Munchow et al., 2014). In addition, higher HEMA concentrations can influence negatively on solvent evaporation when water is used, since the monomer can reduce the vapour pressure of the solvent (Pashley et al., 1998). The potential for reduced degree of conversion is also increased with adhesive formulations that contain higher concentrations of HEMA, as well as reduced mechanical properties (Collares et al., 2011; Munchow et al., 2014). Previous research has also suggested the negative influence of HEMA on interactions between phosphate groups of 10-MDP with HAp, which may compromise bond strength of SEAs containing high amounts of HEMA (Yoshida et al., 2012). For this reason, it is suggested to remove HEMA from SEAs, as these systems present other monomers that exhibit similar ability to infiltrate, wet, and diffuse through the dental substrate (Van Meerbeek et al., 2011).

2.1.2 Adhesion promoting monomers

The functional group of adhesion promoting monomers are designed to allow demineralisation and chemical bonding to different substrates, such as dental tissue, and in the case of resin cements , also to ceramic and metal alloy surfaces [18].

Functional groups such as carboxyl, phosphate and phosphonate have hydrophilic properties and are easily ionised, improving the bonding capability of monomers to inorganic components of dental tissue. A potential adhesion mechanism of mild SEAs has been previously suggested, so-called the “adhesion-decalcification concept” (AD-concept) (Yoshida et al., 2004; Yoshioka et al., 2002). Here, the functional monomer interacts ionically with calcium ions bound to hydroxyapatite (HAp) and through demineralisation, releases calcium and phosphate from the tooth structure. When the ionic link remains stable, calcium salts are formed, copolymerising with the adhesive monomers, establishing a chemical bond with calcium ions (Yoshioka et al., 2002). Regarding SEAs, ‘strong’ adhesives (pH<1) are likely to result in less stable ionic bonds than ‘mild’ adhesives (pH>1). Therefore, the effectiveness of any chemical bond formation in SEAs will depend on the functionality of chemical moieties within the adhesive (Yoshida et al., 2004). In this category, the functional monomers mostly used are 4-methacryloyloxyethyl trimellitate anhydride (4-META), glycero-phosphate dimethacrylate (GPDM) and 10-methacryloyloxy-decyl-dihydrogen-phosphate (10-MDP), tethered to methyl methacrylate chains.

2.1.2.1 4-methacryloyloxyethyl trimellitate anhydride (4-META)

4-META has a hydrophobic aromatic group, and functional hydrophilic carboxyl groups, with demineralising properties (Figure 1), which provides amphiphilic behaviour and improves wettability (Hosoya and Tay, 2014; Van Landuyt et al., 2007).

The adhesion mechanism of this monomer relies on carboxyl groups interacting with the substrate, replacing phosphate ions, establishing ionic bonds between the calcium (Ca) ions in HAp (Nagakane et al., 2006). The chemical reaction with the substrate forms 4-META-Ca, which has low chemical stability. This process is followed by the superficial dissolution of HAp through the attack of hydronium ions (H_3O) originated from the water protonation reaction with 4-META. Following extraction of calcium, phosphate (PO_4^{3-}) and hydroxyl ions (OH^-) from the apatite surface, the solution becomes acidic, allowing for the deposition of dicalcium phosphate dihydrate (DCPD) precipitate. Yoshida et al. (2004) reported faster solubilisation of 4-META-Ca compared with 10-MDP-Ca, resulting in lower stability of the molecule. This fact corroborates the AD-concept, which states that the lower the solubility of calcium salt by the acidic molecule, the greater the intensity and stability of adhesion with the HAp substrate (14). The bonding potential and diffusion of 4-META on enamel and dentin have been well described in the literature, and the efficiency of 4-META has been reported as lower compared with that of 10-MDP (Yoshida et al., 2004).

2.1.2.2 2 glycero-phosphate dimethacrylate (GPDM)

GPDM is a functional monomer used in both etch-and-rinse and self-etching adhesive formulations. This monomer has two methacrylate groups and one phosphate acidic functional group, linked by a short carbon spacer (Figure 1). The hydrophilic characteristic of GPDM can improve the interaction between dentin and the adhesive agents, working similarly to HEMA monomer helping to promote the diffusion of adhesive into the demineralised dentin (Yoshihara et al., 2018b).

However, GPDM can promote better polymer formation than HEMA, or even the other functional monomers, such as 4-META and 10-MDP, due to the presence of two polimerisable methacrylate groups (Yoshihara et al., 2018b).

The interaction between GPDM and Hap is similar to 4-META, with the formation of DCPD after 24h of contact with Hap, with an instable GPDM-Ca salt (Yoshihara et al., 2018a; Yoshihara et al., 2018b). GPDM acts by a decalcification route, promoting the formation of a thick hybrid layer with exposed collagen, different than 10-MDP, which does not expose collagen, forming nano-layers of MDP-Ca salts (Yoshihara et al., 2018b). However, the differences in chemical bonding do not exclude the effective bonding of adhesives containing GPDM. Considering the interesting clinical data obtained until this moment, the interaction between GPDM and the co-monomers should be evaluated to better understand the positive results regarding bonding longevity of adhesives containing this monomer.

2.1.2.3 10-methacryloyloxy-decyl-dihydrogen-phosphate (10-MDP)

10-MDP is the most commonly acidic monomer used in SEAs, and first synthesised by Kuraray (Osaka, Japan) and subsequently applied by several companies after the patent expiration in 2000. Remarkable results of bond strength to dentin and restoration longevity using 10-MDP-based adhesives have been demonstrated in clinical and laboratory studies (Kubo et al., 2006; Peumans et al., 2010; Van Landuyt et al., 2008b).

In addition to a longer spacer chain, the MDP molecule has a polar functional group of dihydrogen-phosphate–dihydrogen acids with ability to dissociate and form protons (Figure 1) (Hayakawa et al., 1998). The functional group has the ability to form

strong ionic bonds with calcium due to the slow dissolution of the calcium salts present in the tooth structure, resulting in a better association of the functional group and the dental substrate (Nurrohman et al., 2012). The carbon spacer chain is responsible for the flexibility, solubility, wettability and amphiphilic equilibrium of the monomer (Yoshihara et al., 2013). The long carbonyl chain gives a hydrophobic character to the material and, for this reason, the best solvents for 10-MDP are alcohol and acetone (Van Landuyt et al., 2007).

The degradation of MDP, even with the hydrophobic chains, may occur when the adhesive is inappropriately stored (i.e. non-refrigerated; >4^{o}C), for long periods. The degradation occurs by the hydrolysis of the functional group, generating products such as methacrylic acid and 10-hydroxydecyl dihydrogen phosphate, which may ultimately result in a weak hybrid layer, due to poor monomer diffusion, infiltration and curing (Teshima, 2010).

The adhesion process associated with MDP to the tooth substrate is known to be the most chemically resistant among the adhesion promoting monomer types currently used in dentistry, being able to create an acid-base resistant zone beneath the hybrid layer having a preventive effect on restoration margins (Giannini et al., 2015). The formation of calcium salts from the acidic molecule (10-MDP-Ca) provides greater chemical stablility compared with 4-META-Ca (Yoshida et al., 2004). In the MDP reaction, superficial HAp is dissolved by the hydronium ions and extracts a higher quantity of calcium ions compared with 4-META. Nucleation and growth of 10-MDP-Ca crystals that occur on the HAp surface, form a 4nm layered structure consisting of two molecules of MDP, with methacrylate groups aligned towards each other and functional groups directed away from each molecule. Such nano-sized molecular

alignment is not observed in 4-META bonding to dentin (Yoshihara et al., 2011; Yoshihara et al., 2010). Subsequently, the excess calcium, phosphate and hydroxyl ions are extracted from the apatite surface and saturated in the acidic solution, forming DCPD salts (Yoshioka et al., 2002). This bonding is more stable and stronger than that formed by 4-META and GPDM (Inoue et al., 2005; Yoshihara et al., 2018a; Yoshihara et al., 2018b), confirmed by bond strength tests and transmission electron microscopy (TEM) after long-term thermocycling. (Inoue et al., 2005) However, the chemical interaction of the functional groups with the HAp crystals in enamel is not effective as in dentin, probably due to the HAp crystal structure and/or size (Yoshihara et al., 2011), highlighting the need for enamel acid etching prior to the adhesive procedures using self-etching or universal adhesives; the so-called “selective enamel etching” approach.

2.2 Solvents

The solvent content of the adhesive is crucial for displacement of moisture and diffusion of the resin within the dental substrate. The solvent dilutes the co-monomer mixture, increase the wettability, and facilitate expansion of collagen fibrils after the acid-etching process in ERAs (Pashley et al., 2011; Tay and Pashley, 2003; Van Landuyt et al., 2007). Besides, the aqueous solvent solutions also guarantee ionisation of the acidic monomers in SEAs (Tay et al., 2002; van Meerbeek et al., 2005). The main solvents used are water, ethanol, and acetone, and are present in the primers of two-bottle adhesives or mixed with other components in single-bottle adhesives (Pashley et al., 2011; Van Meerbeek et al., 2011).

Some characteristics are important for solvents used in dental adhesives, such as the vapour pressure. Substances with high vapour pressure and low boiling points can be easily removed by vaporisation (Zheng et al., 2001), facilitating its removal along with water from the substrate. Another important aspect is the ability to bond to hydrogen, allowing re-expansion of the collagen fibrils after dehydration, improving the resin diffusion and penetration, and consequently the bonding itself. These characteristics according to the different solvents used in dental adhesives are listed in Table 1.

Table 1 – Properties of solvents most used in dental adhesives

	Dipole moment	**Dieletric constant**	**Boiling point**	**Vapor pressure (mmHG 25o C)**	**Ability to form hydrogen bonds**
Water	1.85	80	100	23.8	High
Ethanol	1.69	24.3	78.5	54.1	Medium
Acetone	2.88	20.7	56.2	200	Low
Tert-Butanol	1.7	12.5	82.4	46	Medium

2.2.1 Water

Water is a polar solvent with high potential to break hydrogen bonds among collagen fibrils, allowing their re-expansion and further resin infiltration, which is critical for the formation of a hybrid layer in ERAs (Pashley et al., 2011). Another important characteristic of this solvent, previously discussed, is the ability to ionise acidic monomers present in SEAs, responsible for chemical adhesion of these systems (Tay and Pashley, 2001).

Nevertheless, the low vapour pressure of water makes its removal from the adhesive layer difficult (Tay et al., 1998). Because of that, the combination with other solvents is recommended in order to provide better vaporization, and with that a

higher degree of conversion of the adhesive and a better quality hybrid layer, improving the bonding.

2.2.2 Ethanol

Ethanol is a polar substance that forms hydrogen bonds with compatible substances, such as water (Simoes et al., 2014). Despite the higher vapour pressure compared to water, is not possible the complete removal of this solvent from the dental adhesive on clinical viable time. Previous study demonstrated that even after 60s of volatilization ethanol can be found in the adhesive (Cadenaro et al., 2009). The excess of ethanol can compromise the rate of curing, sorption and solubility of dental adhesives (Cadenaro et al., 2009). The ideal concentration of ethanol in adhesive systems is reported to be 20% or lower, which is enough to reduce resin viscosity, improving molecular mobility and polymer conversion (Ye et al., 2007). In higher concentrations it can compromise the mechanical properties of the adhesive and promote phase separation of hydrophobic/hydrophilic components (Malacarne-Zanon et al., 2009)

Ethanol can expand and increase the stiffness of collagen matrix, facilitating infiltration of monomers through the collagen network of the demineralized dentin. (Manso et al., 2014; Simoes et al., 2014). However, the ethanol used in SEAs, combined with monomers that present carboxyl groups (such as 10-MDP), may affect the ability of the acidified chains to etch the tooth surface due to esterification of the carboxylic groups by the hydroxyl group of ethanol (Van Landuyt et al., 2007). In addition, excess ethanol that remains after air-drying may increase water sorption and solubility of the adhesive, increasing hydrolytic degradation (Malacarne-Zanon et al.,

2009), as well as increase the cytotoxicity to human dental pulp cells (Massaro et al., 2019).

Ethanol has the potential to prevent phase separation of hydrophobic and hydrophilic monomers contained in the single-bottle adhesives. In addition, the aqueous ethanol solution forms an azeotrope, improving vaporisation of the residual water present within demineralised dentin (Simoes et al., 2014). Nevertheless, the complete removal of bound and unbound water from demineralized dentin is not possible (Gregoire et al., 2013), with ethanol presenting reduced vaporisation compared to acetone (Agee et al., 2015).

2.2.3 Acetone

With acetone, both dipole moment and the dielectric constant allow the mixture of polar/nonpolar compounds, being useful for single-bottle adhesives that combine both hydrophobic and hydrophilic monomers. However, its high vapour pressure increases volatility compared with ethanol, and therefore increased solvent concentration is required, which reduces monomer concentration and usually require application of at least two bonding layers in order promote optimal bond strength (Elkassas et al., 2009). Indeed, lower bond strength using adhesives that contain acetone compared with ethanol-based systems have been reported (Cardoso et al., 2005; Manso et al., 2008; Reis and Loguercio, 2009). Furthermore, the higher volatilisation of acetone compared with other solvents is likely to reduce shelf-life and may preclude its use by some manufacturers (Perdigao et al., 1999).

2.2.4 Tert-Butanol

Tert-butanol or 2-methyl-2-propanol has a molecular chain with fewer hydrogens and higher molecular weight compared with other alcohols. The molecular structure consists of 4 carbons, with one alcohol group surrounded by three methyl groups, providing higher stability and compatibility with both water and polymerizable resins compared with ethanol-based systems (de Barros et al., 2013; Gregoire et al., 2011). Further, the lower boiling point of tert-butanol compared with ethanol and acetone, results in slower evaporation, increased working time and less shrinkage of the dentin collagen matrix, improving the resistance of hybrid layer in dry or wet dentin. (de Barros et al., 2013; Manhart and Trumm, 2010). Despite the indication of butanol-based adhesives for both a 'wet-bonding' and 'dry' approach, previous reports suggest that bond strength is greater in wet dentin that in dry dentin (Orellana et al., 2009).

2.3 Photoinitiators and co-initiators of polymerisation

Polymerisation of dental adhesives is initiated photochemically through specific wavelengths, usually from 380 to 480 nm, with a irradiance from 500 to 2000 mW/cm^2. Photinitiators (Figure 2) are components that absorb light to initiate the polymerisation process through the generation of free radicals. Whilst the mechanism of radical formation varies between photoinitiator types, the radicals act breaking methacrylate carbon double bonds, to initiate the polymerisation process. Based on the mechanism of radical formation, photoinitiators can be divided into two categories: Norrish Type I and Norrish Type II (Allen, 1996).

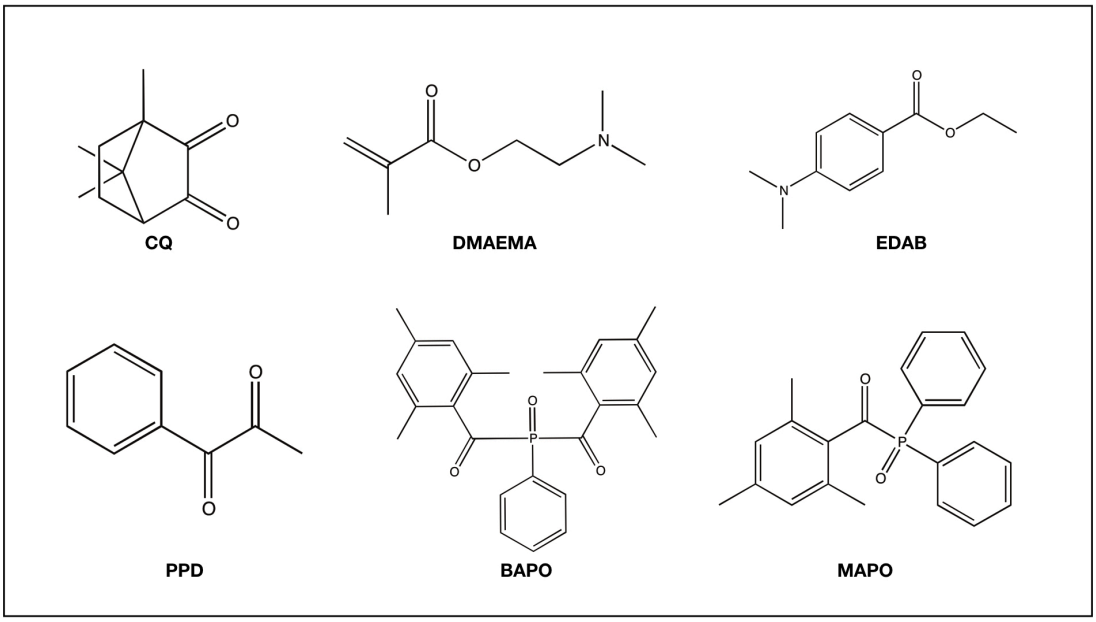

Fig. 2 – Chemical structure of initiators and co-initiators

Norrish type I reactions involve the photochemical cleavage (homolysis) of aldheydes and ketones into two free radical intermediates. The carbonyl group accepts a photon of the correct wavelength and energy and is excited to a photochemical singlet state. A triplet state can then be obtained through intersystem crossing and the cleavage of the α-carbon bond from either side would result in the formation of two radical fragments (Figure 3). The size, nature and stability of the generated radicals depend on several factors that include structure of the substrate, and reaction conditions. Several secondary reaction modes are open to the radical fragments including re-combination to form the original carbonyl compound, the loss of carbon monoxide from the acyl radical, the abstraction of a α-proton from the carbonyl fragment to form a ketene and alkane and the abstraction of a β-proton from the alkyl fragment which may form aldheydes and an alkene.

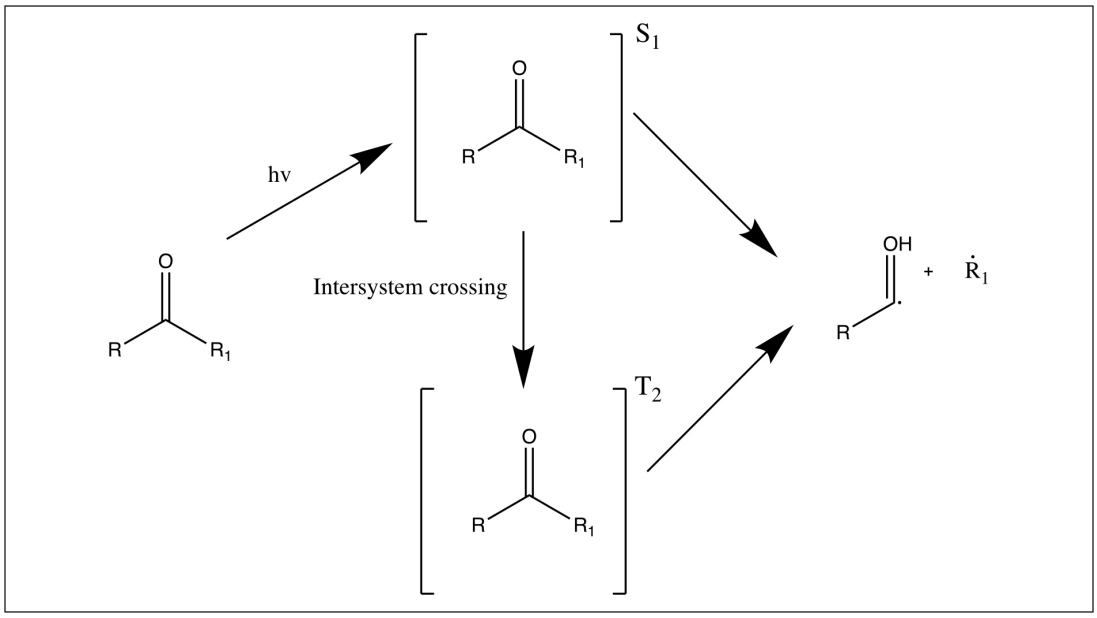

Fig. 3 - The schematic representation of free-radical formation through Norrish Type 1 mechanisms

Norrish type II reactions involve the photochemical intramolecular abstraction of a γ-hydrogen (a hydrogen atom three carbon positions removed from the carbonyl group) by the excited carbonyl compound to produce a 1,4-biradical as a primary photoproduct. This biradical can back hydrogen transfer to give starting material or fragment or cyclize. The latter two reactions are indicative for Norrish type II reactions. The Norrish Type II reaction for aliphatic ketones is only partially quenched by known triplet state quenchers such as tertiary amines. Thus, hydrogen abstraction in aliphatic ketones occurs from both singlet and triplet states. Aryly ketones however, only react from the triplet state. Thus, Norrish type II compounds are typically used with tertiary amine co-initiators from which a hydrogen can be abstracted, making the intermediary steps more efficient (Figure 4).

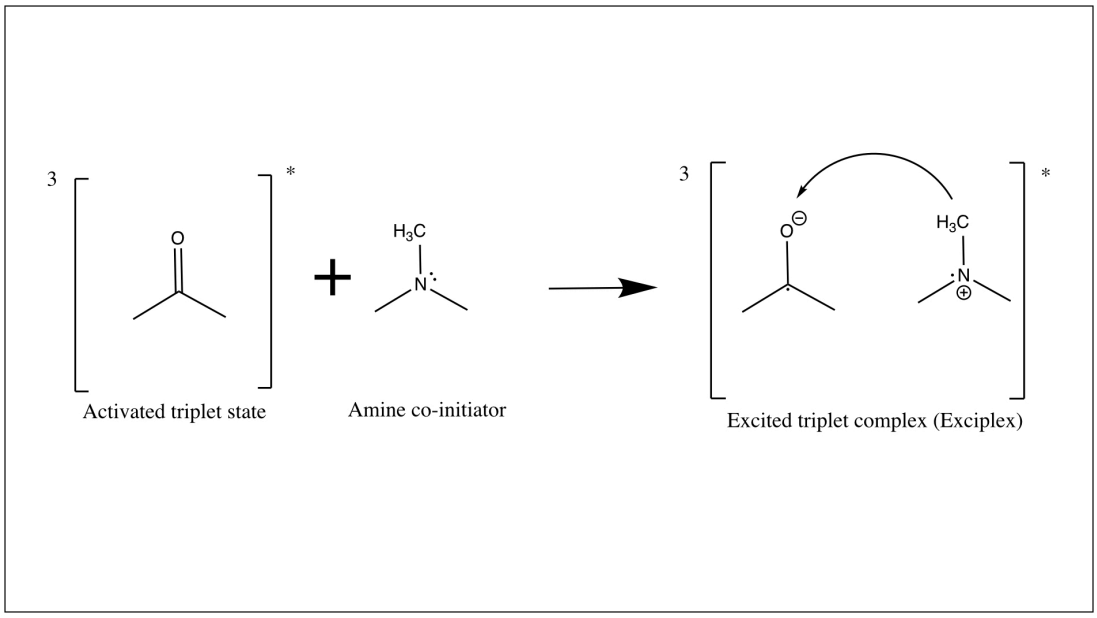

Fig. 4 - Hydrogen abstraction from the amine co-initiators by the excited triplet state photoinitiator

The efficiency of the reaction will depend on the ionising potential of the amine, and the electronic affinity with the ketone. The reaction usually occurs starting with the triplet stage (excited state) of the ketone, depending on the configuration of the triplet state and its energy. The photoreduction ability of the medium is an important factor and is related to the bonded carbon-hydrogen forces of the hydrogen donor.

2.3.1 Camphorquinone

Camphorquinone (1,7,7-trimethylbicylo[2.2.1]heptane-2,3-dione, CQ) belongs to the aliphatic α diketone (Figure 2) and is the most used photoinitiator for light cured dental materials including dental adhesives. CQ has an absorption range between 400 and 500 nm, with its absorption peak at ~470 nm (extinction coefficient: 28 L/mol cm at 470 nm (Neumann et al., 2005); quantum yield 0.066 (Chen et al., 2007)). At room

temperature, it presents as a yellow powder. The efficiency of this photoinitiator alone is insufficient due to the secondary reactions mentioned above. Thus, CQ has a relative short half-life to react with the monomers, requiring an efficient hydrogen donor to improve its efficiency (Meereis et al., 2014b; Ogliari et al., 2007b). The addition of tertiary amines as electron/proton donors or reducing agents, gives a more efficient photoinitiating system due to the ability to quench the molecule in its triplet state. This produces an 'exciplex' which is able to abstract a hydrogen from the tertiary amine resulting in the formation of CQ-cetyl and N-N aminyl free radicals (Figure 5). The amines have a much lower oxidation potential compared with other hydrogen donors, therefore it is assumed that the reaction is facilitated by electron-proton transfer [refs].The CQ-cetyl radical is active in recombination with free radicals and the N-N aminyl radical is responsible for initiating the reticulation process (Cook, 1992; Ikemura and Endo, 2010b).

Currently, there is no consensus about the optimal concentration of CQ on resin formulations. However several studies have utilised concentrations of 0.2-2.0 wt. % (Guimaraes et al., 2014; Musanje et al., 2009; Ogunyinka et al., 2007; Randolph et al., 2014; Randolpha et al., 2014) or 0.5-1.0 mol% (Andrade et al., 2016; Dressano et al., 2016). Since CQ has a yellow pigment and an unbleachable chromophore group, the use of higher concentrations will adversely affect aesthetics and optical properties (Bertolo et al., 2017) (not relevant for dental adhesives), degree of conversion and other mechanical properties (Guimaraes et al., 2014). The use of a high concentrations of CQ (≥ 2.0wt.%) can influence negatively on light transmission through the restorative resin composites, reducing the consumption of the photosensitizer (Guimaraes et al., 2014).

However, the use of CQ-amine photoinitiator system in SEAs presents some disadvantages in terms of stability due to the formation of quaternary ammonium salts from acid/base reactions between the amine co-initiators and the functional acidic group of monomers. Because of that, shelf life and bonding performance can be jeopardized in this case (Ikemura and Endo, 2010a; Meereis et al., 2016).

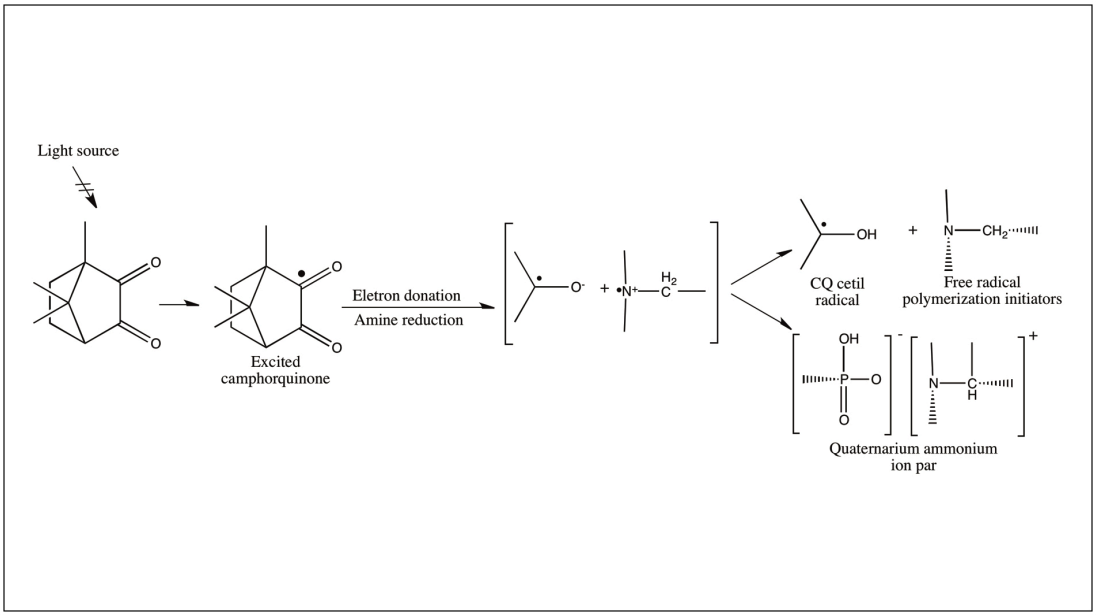

Fig. 5 - Schematic presentation of the camphoroquinone-amine reaction after light exposure

2.3.2 Tertiary amines

As previously discussed, Norrish type II reactions require a co-initiator for satisfactory curing. Free radicals generation is related to the proportion of type II initiators and amine, in which the concentration of amine can vary from 1 to 4 times to that of CQ (Alvim et al., 2007; Guimaraes et al., 2014; Yoshida and Greener, 1994).

Ethyl-4-dimethylaminobenzoate (EDAB) and dimethylaminoethyl methacrylate (DMAEMA) are tertiary amines used in systems for Type II photoinitiators (Figure. 2), such as CQ (Lovell et al., 2003; Teshima et al., 2003). Previous studies have demonstrated greater polymerisation efficiency (e.g. degree of

conversion and polymerization rate) with aromatic teriary amines such as EDAB compared to aliphatic amines such as DMAEMA (Andrade et al., 2016; de Oliveira et al., 2015).

As described, the amine reacts with the triplet state of CQ, forming an exciplex state. This exciplex receives a H^+ from the amine generating a radical that is able to initiate the polymerization process. The nucleophilicity, which is the ability of chemical transferring electrons to an electrophile molecule (e.g. CQ in the triplet state), is an important characteristic of the co-initiator used. The nucleophilicity depends on the structure of the co-initiator, reducing the reactivity with the sensitizer in accordance with the reduced number of C=C bonds present in the molecule (de Oliveira et al., 2015). EDAB presents an aromatic ring on the backbone and higher nucleophilicity when compared with DMAEMA, providing more protons to CQ, increasing reactivity of the systems and consequently improving monomeric conversion (Andrade et al., 2016; de Oliveira et al., 2015) DMAEMA also has a polymerizable group on its backbone, reducing the mobility of the molecule with the development of the conversion (de Oliveira et al., 2015)

In addition to the nucleophilicity, the ration CQ/amine is an important factor in the polymerization reaction. For EDAB, CQ/amine ratio of 1:1 can promote similar degree of conversion using 1mol% of CQ, however, the ratio of 1:2 can promote higher flexural strength (Andrade et al., 2016). A previous study analysing the effect of different CQ/amine ratio observed that for concentration equal or higher 1.5wt. % of initiator system, the ratio did not influence the degree of conversion (Guimaraes et al., 2014). For DMAEMA, concentrations as 0.25 and 0.5 mol% of CQ has better reactivity using CQ ratios of 1:4 and 1:3, respectively. With concentrations of 1 and 2

mol%, the ratio CQ/amine as 1:0.75 and 1:0.125, respectively, are able to promote higher polymerization (Yoshida and Greener, 1994).

2.3.3 1-phenyl-1,2-propanedione (PPD)

In order to improve the curing efficiency of CQ/amine systems, researchers have proposed alternative initiators, such as 1-phenyl-1,2-propanedione (PPD). PPD is a diketone Type I photoinitiator, with an aromatic di-carbonyl at one extremity of the chain, and a methyl group at the other (Figure 2). The absorption spectrum of the wavelength ranges from 350 to 500 nm, with an absorption peak at 398 nm (extinction coefficients: 150 L/mol cm at 398nm)(Chae and Sun, 1998; Neumann et al., 2005). Compared with the CQ, the PPD promotes lower degree of conversion and reduced mechanical properties of the final polymer (Brandt et al., 2013a; Dressano et al., 2016). However, when combined with CQ, the degree of conversion is increased, influencing positively the physical and chemical properties of the polymer [81, 86, 90]

Although this initiator is classified as a Norrish type I, characterised by the generation of radicals without the need for an electron donor agent, PPD has been widely used in combination with tertiary amines, such as DMAEMA and EDMAB, similarly to CQ [81]. Previous research has identified significantly improved properties of the cured material such as hardness and flexural strength when PPD is used in combination with co-initiators (Brandt et al., 2013a; Brandt et al., 2011; Dressano et al., 2016). PPD can also improve the quality of the polymer network formed, yielding higher crosslink density (Brandt et al., 2013b; Schneider et al., 2009).

A disadvantage for commercial dental use of resins containing only PPD is the lower spectral absorption range compared with CQ and the potential mismatch with

spectral emission of blue LED curing units. Some LED units emit light in a narrow wavelength, between 454 and 484 nm, not reaching the absorption peak of PPD (393 nm) (Brandt et al., 2011), which may ultimately jeopardise the polymerization. Therefore, when using PPD, the use of a polywave light-curing unit, which emits both violet and blue wavelengths, is required [81].

Due to the differences in the wavelength spectra and reduced rates of resin polymerisation containing PPD, the combination with CQ has been proposed to improve the chemical and physical properties of the polymer (Park et al., 1999). A synergistic effect between CQ and PPD was previously demonstrated, with increased degree of conversion and mechanical properties (Brandt et al., 2010; Brandt et al., 2013b; Brandt et al., 2011) and attributed to free radical generation by distinct mechanisms: proton abstraction with CQ/amine and PPD amine, as well as the direct photocleavage of PPD (Stansbury, 2000).

2.3.4 Acylphosphine oxides

The main initiators that comprise this category are monoacylphosphine oxide (MAPO or Lucirin TPO) and bisacylphosphine oxide (BAPO) (Figure 2). Both are Type I photoinitiators (Ikemura and Endo, 2010b; Van Landuyt et al., 2007), although MAPO produces two molecules after photocleavage whilst BAPO presents higher reactivity, producing four radicals (Decker, 1996).

The absorption range is around 350–420 nm, with a peak at 381 nm for MAPO (extinction coefficient=520 L/mol cm at 381nm) (Schneider et al., 2012), and 365 to 416 nm, with its peak at 370 nm for BAPO (extinction coefficient=300 L/mol cm at 370nm) (Meereis et al., 2014b). These photoinitiators present a white colour, not

influencing in the final colour of the material. However, for MAPO, the depth of cure is negatively influenced because the molar absorptivity of the sensitizer (around 600). Due to this, the light is absorbed in upper layers of the material, reducing the depth of cure of the resin (Leprince et al., 2011). Additionally, MAPO absorbs shorter wavelength light, which will scatter more, reducing the light transmission through the resin. However, the characteristics cited above should not be a concern to dental adhesives, since these materials are used in thin layers and the light scattering will not jeopardize the polymerisation.

The initiation process occurs with a cleavage α (fragmentation begins at the C-C, adjacent to the carbon with a functional group), from a triplet state. The high reactivity of BAPO favours an additional α-cleavage in one of the radicals formed, producing four radicals from a single precursor (Jockusch and Turro, 1998). The schematic representation of the mechanisms of these initiators can be observed in Figures 6 and 7, illustrating the cleavage of the carbon bond with formation of benzoyl-phosphinoyl radical pair (a and b) (Jockusch and Turro, 1998). The radical (b) can be 2 to 6 times more reactive than (a) (Jockusch et al., 1997).

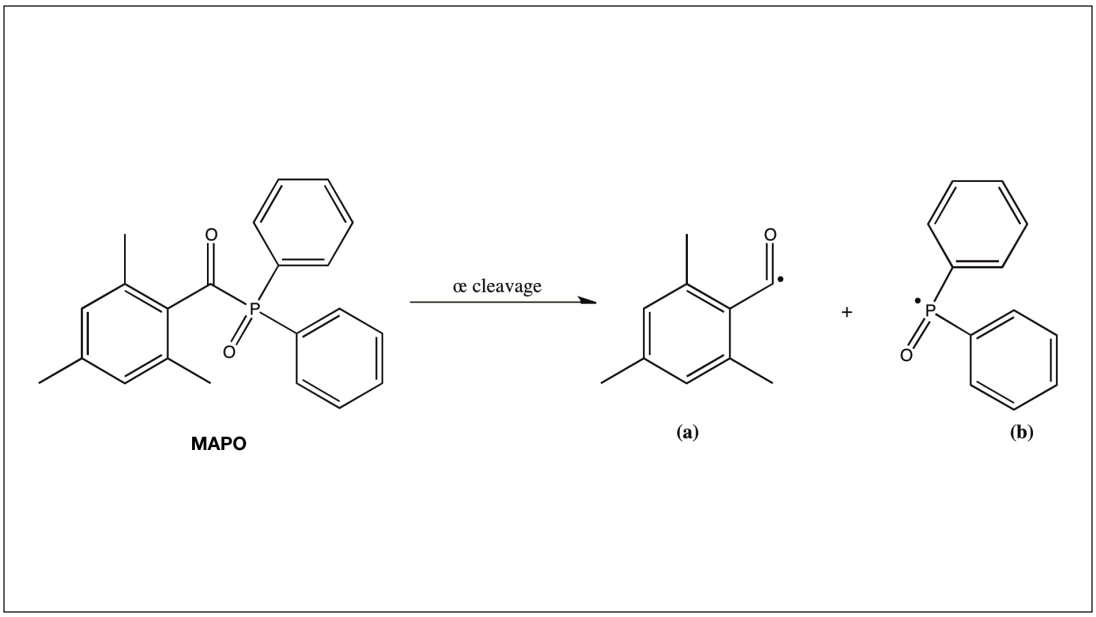

Fig. 6 - Cleavage α of MAPO, with the formation of two radicals (a) and (b).

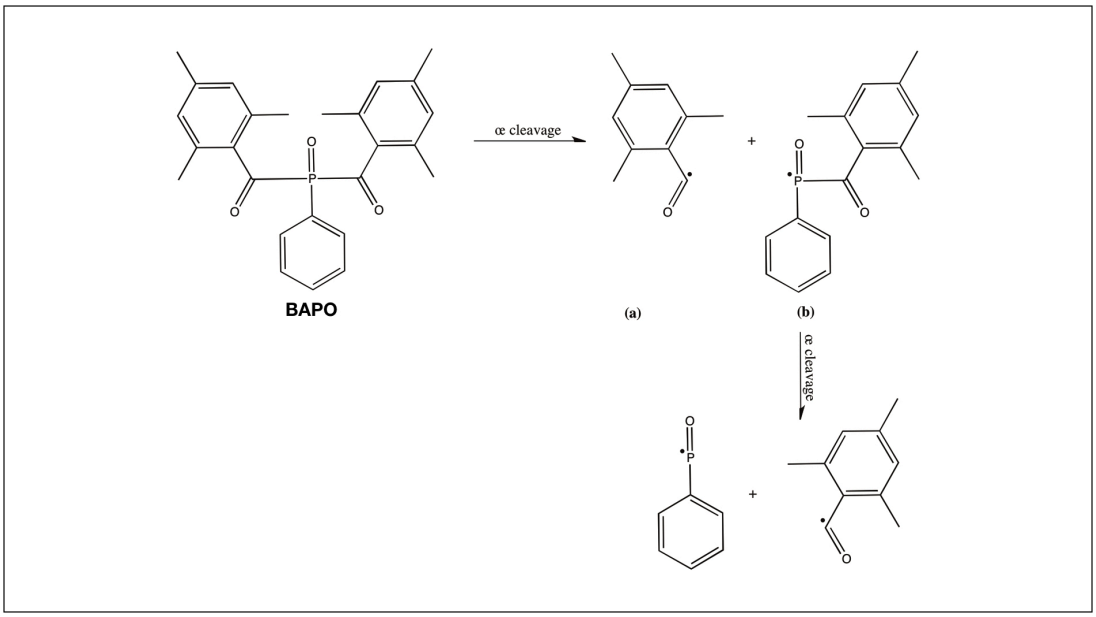

Fig. 7 - Photoinitiation of BAPO, with an additional α cleavage, forming four radicals

The degree of conversion in systems presenting the acylphosphine oxides compared with CQ can be similar or higher, depending on the amount of initiator;

however, the rate of polymerisation is higher for MAPO/BAPO than for CQ/amine systems, due to direct photocleavage.

The same disadvantage for the PPD systems can be observed for the acylphosphine oxides, needing the use of light-curing units presenting a broad wavelength spectrum, such as the quartz-tungsten halogen lamp or the polywave LED units. According to previous studies, low concentrations of these initiators (0.4-1 mol%) are able to provide high degrees of conversion, compared with the materials using CQ as an initiator (Meereis et al., 2014a; Neumann et al., 2005; Randolpha et al., 2014).

2.3.5 Onium salts

The diphenyliodonium salts (DPI) are additives synthesised by Crivello & Lam (1977) (Crivello and Lam, 1977), presented as stable agents in the absence of light. DPI has a short wavelength absorption range in the region of 190 to 200 nm and 230 to 250 nm (Crivello and Lam, 1977), and can be highly reactive when exposed to the appropriate wavelengths to initiate cationic polymerisation. However, DPI can also be used to regenerate radicals and promote radicular polymerisation without primarily absorbing light. Consequently, this agent is classified as a bivalent initiator which is able to initiate the curing process cationically, generating Bronsted acids, as well as promoting radical polymerisation, producing an aryl radical.

Since DPI does not directly interact with the spectral absorbance/irradiance in dental resins, the primary function in this application is to act as a photosensitizer and re-generate free radicals. This mechanism involves the photolysis of CQ by DPI. The DPI radicals formed are broken into phenyl radicals (Figure 8).

The interaction between ketones and onium salts occurs by electron transfer in the singlet and a triplet state. In the triplet state, reaction with CQ occurs, over the long term and at low energy (ca. 50 kcal mol^{-1} compared with CQ). As a result, DPI combined with CQ can increase the kinetics of cure in dental resins, explained by the electron transfer from the salt, related to the light absorption of the CQ and the formation of excited species [CQ]* (Goncalves et al., 2013; Ogliari et al., 2007b).

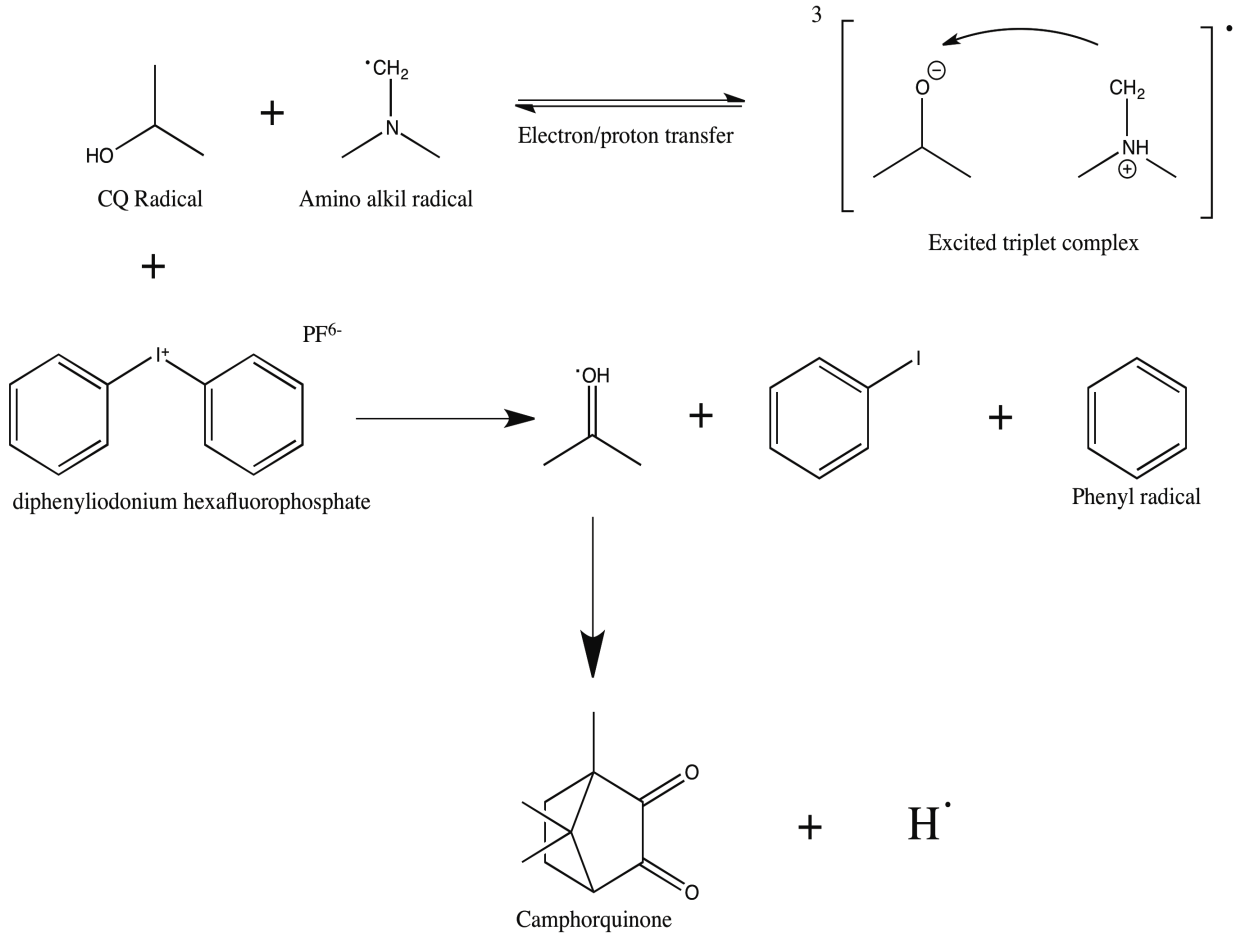

Fig. 8 - The reaction mechanism of three-component photoinitiator systems containing a photoinitiator, a coinitiator and a photosensitizer

Two functions of DPI favour the interaction between the initiators: the regeneration of CQ molecules through substitution of inactive and termination

radicals to active phenyl radicals, and the generation of additional active phenyl radicals (Guo et al., 2008). In this sense, the ternary systems are flexible, faster, more efficient and sensitive than the binary systems (Goncalves et al., 2013; Ogliari et al., 2007b), promoting similar degree of conversion and rate of polymerisation than MAPO and BAPO (Lima et al., 2019).

Diphenyliodonium hexafluorphosphate combined with CQ and PPD, or even with BAPO, can increase the polymerization rate, improving the degree of conversion and the mechanical properties of the adhesives (Dressano et al., 2016; Lopes et al., 2013; Ogliari et al., 2007a), highlighting DPI as an interesting agent to improve the curing of dental resins.

2.4 Bioactive components

Bioactive compounds have been studied and applied to biomaterials in general. In restorative dentistry, bioactive materials encompass antimicrobial properties, in which it contains or release molecules that interact with bacteria, inhibiting its growth or viability, or impairing bacteria adhesion and biofilm formation (Cocco et al., 2015; Makvandi et al., 2020). Also, remineralizing particles that includes molecules that signal, recruit or stimulate resident cells toward mineral formation or release ions that aid in chemical precipitation of new mineral have been developed (Braga, 2019; Braga and Fronza, 2020; Jang et al., 2018). Both strategies are interesting to maintain the hybrid layer and bonding, prevent secondary caries development, and improve restorations' survival (Dai et al., 2019).

2.4.1 Antimicrobial monomers

The addition of silver particles with the resinous compounds was the first alternative to combat the biofilm inherent to the restorative material, once Ag ions promote strong antibacterial, antifungal and antiviral activity (Cocco et al., 2015), as well as low toxicity and biocompatibility with human cells (Xu et al., 2012). Ag ions work inactivating the vital bacterial enzymes, which cause loss of bacterial DNA's ability to replicate, leading to cell death (Cocco et al., 2015). Ag can be incorporated as nanoparticles or microparticles at a concentration of 0.1 to 1% in adhesives or primers (Cocco et al., 2015; Zhang et al., 2013).

At first, it was noticed that polymers with Ag, in general, released a high amount of ions initially, losing their antibacterial activity in a short period (Farrugia and Camilleri, 2015). Thus, the synthesis and incorporation of nanometric Ag particles into the resin promoted polymers with a large reservoir of Ag ions, having ions releasing at a constant rate, allowing long-term antibacterial effects (Andre et al., 2015). These materials can inhibit not only the bacteria present on the surface but also those far away from the surface (Li et al., 2013).

As the antimicrobial activity of Ag occurs by the release of agents from the polymer, it is understandable that it promotes a decrease in long-term antibacterial action (Li et al., 2013). For this reason, a new class of antimicrobial agents that do not release agents was developed in order to guarantee improvements in the material. Such better characteristics reached was: better antimicrobial activity; low toxicity to host tissues, without modifying their immune responses; absence of adverse effects on the physical properties of the polymers; and the impossibility of antibiotic resistance.

With this, monomers based on quaternary ammonium (QA) compounds are materials able to promoting good antimicrobial characteristics, maintaining the physicochemical properties of the resin agent. QAs are agents chemically stable and non-volatile (Huang et al., 2011). Are active against a broad spectrum of microorganisms, such as Gram-positive and Gram-negative bacteria, fungi, and some types of virus (Cocco et al., 2015; Makvandi et al., 2018). Its includes polymers with polymerisable groups of QA which are immobilised in the polymer backbone and confer long-term antibacterial activity to the material (He et al., 2013).

However, the bactericidal activity of QA can be based on three possible processes: 1) Contact of negatively charged bacteria with positively charged QA, disturbing the electrical balance, leading to bacterial lysis (Namba et al., 2009); 2) Diffusion through the cell wall and connection to the cytoplasmic membrane; and 3) rupture of the cytoplasmic membrane, with release of cytoplasmic constituents and cell death (Cocco et al., 2015).

Imazato was the first to successfully synthesize a new QA monomer mixing alkylpyridinium (a type of QA) with a methacrylate grouping, resulting in the 12-methacryloyloxyydodecylperidinium bromide antimicrobial monomer (MDPB). This monomer is currently the most popular used and studied in the literature (Imazato and McCabe, 1994; Imazato et al., 1995; Imazato et al., 1994). While the QA group is responsible for the antibacterial activity of MDPB, the methacrylate allows copolymerization with other conventional monomers. As the antibacterial monomers are trapped in the resin matrix and not leached after curing, the incorporation of these monomers does not impose a negative effect to the mechanical properties of the

polymer and establish regular contact and long-term antibacterial effects (Imazato et al., 1994).

MDPB has been well established in the literature. This agent has an antibacterial activity against several oral bacteria, including facultative as well as obligate anaerobes in coronal lesions (Hirose et al., 2016; Imazato, 2009; Pinto et al., 2015). This effect is seen after polymerisation, either in adhesives or composites, without influencing the bond strength and the properties of the material (Imazato et al., 2003). MDPB has been pointed out as a potential metalloproteases inhibitor (Tezvergil-Mutluay et al., 2015; Tezvergil-Mutluay et al., 2011), improving the bonding durability (Hashimoto et al., 2018).

With the success of MDPB-containing resinous materials, several different polymerizable antibacterial monomers have been developed for use in dental restorative materials, with different approaches and action mechanisms. Due to the variety of components and complexity of this topic, its impossible to review all agents in few paragraphs. For reviews on antibacterial agents, see refs.(Chen et al., 2018; Cocco et al., 2015; Ferrando-Magraner et al., 2020; Makvandi et al., 2020; Makvandi et al., 2018).

2.4.2 Remineralizing particles

The remineralization potential of adhesives and restorative materials has been study in order to assist the remineralization process of caries affected dentin, e.g. selective caries removal in minimally invasive intervention operative procedures (Bertassoni et al., 2010; He et al., 2019), as well as to replace water from water-rich resin-sparse regions and intrafibrillar gaps of the hybrid layer with apatite crystallites,

in order to restore mechanical properties and protect the exposed collagen from external challenges, preserving the longevity of resin-dentin bonds (Garcia et al., 2017; Wu et al., 2017). The restorative bonding procedures promotes demineralization of dental tissues via acids, chelating agents, or acidic monomers that remove part of the mineral content in order to create a more favorable substrate for adhesion and micromechanical retention of resins (Giannini et al., 2015; Pashley et al., 2011). The contemporary adhesive systems are not able of water displacement from the extrafibrillar and intrafibrillar compartments and infiltrate the collagen network completely with resin monomers, which results in water-rich spaces along collagen fibrils responsible for micropermeability and nanoleakage of hybrid layers (Carvalho et al., 2012).

Bioactive fillers have been tested as additives of commercial and experimental adhesives. The main purpose of adding such fillers in adhesives is to promote the replacement of the lost mineral within the collagen network and protect the collagen fibrils from degradation (Profeta et al., 2013). Among the particles studied are the bioactive glasses (BAGs), calcium silicates (CaS), and calcium orthophosphates (CaP), that function as ion-releasing materials such as F^-, Ca^{2+}, and PO_4^{2-}, which aid chemical precipitation of mineral (Braga, 2019; O'Neill et al., 2018). The apatite seed crystallites left in the intrafibrillar regions of partially demineralized dentin serve as nucleation sites for calcium and phosphate ions precipitation followed by epitaxial crystal growth, as explained by the ion-based crystallization concept (Veis and Dorvee, 2013).

In fact, interfaces of adhesives containing 30 to 40% of BAGs or CaS fillers demonstrated reduced micro-permeability after six months related to mineral precipitation within the hybrid layer (Jang et al., 2018; Profeta et al., 2013; Sauro et

al., 2012a). Some studies also demonstrated that incorporation of metallic ions such as Zn, Cu, and Nb to BAG or CaP increase mineral deposition (Balbinot et al., 2020; Sauro et al., 2013; Sauro et al., 2012a).

Regarding bond strength, the incorporation of ion-releasing particles in experimental adhesives presented controversial outcomes. Some studies reported no differences between adhesives containing bioactive fillers and the unfilled controls (Sauro et al., 2013; Sauro et al., 2012b) (ref), while other reported the maintenance of bond strength after three or six months of storage when these particles are present (Bauer et al., 2019; Profeta et al., 2013; Profeta et al., 2012). Although, the hydrophilicity of the particles also seems to have an effect in the bond strength, once long-term results are influenced by adhesive hydrophilicity and susceptibility to hydrolysis (Braga and Fronza, 2020; Profeta et al., 2013). Nevertheless, the elastic modulus of adhesive layers evaluated by nanoindentation presented an increase after three months when adhesives containing 33% CaS or CaP, or 40 wt% BAG particles where used, while the control adhesive without fillers demonstrated the opposite performance (Sauro et al., 2013; Sauro et al., 2012a).

Besides, these fillers can also reduce the collagen degradation via ions binding to specific sites of collagen fibrils, which modifies its spatial configuration and protects sensitive cleavage sites, also by reducing enzymatic activity of metalloproteinases through the ions released (Braga, 2019; Ye et al., 2017). It was demonstrated that one adhesive containing 40 wt% of BAG reduced significantly the enzymatic activity of demineralized dentin samples, and an adhesive containing CaS/CaP particles was able to reduce the collagen degradation, with major effects when these fillers were

modified by zinc oxide, which contributes to pH control and apatite precipitation (Osorio et al., 2012, 2014).

Despite promising *in vitro* results using bioactive particles in dental adhesion, more studies are necessary to establish parameters to introduce it into commercial adhesive systems. Besides, the combination of these components with biomimetic analogues during bonding procedures, to induce ion sequestration and directed crystal nucleation for remineralisation seems prudential (Braga and Fronza, 2020).

3. Future Prospects

As demonstrated in this paper, the development and improvements of dental adhesives are continuous and fast. Studies improving polymerisation of adhesive systems are relevant once these materials are usually applied to water-containing tissues and cured applied on places with under significantly reduced irradiance difficult clinical access, such as in deep cavities. These facts highlight that initiator systems with better performance may promote a better degree of conversion and properties.

Respecting the monomeric phase, the development of new monomers such as methacrylate-methacrilamyde (Barcelos et al., 2020; Fugolin et al., 2019a; Fugolin et al., 2019b; Rodrigues et al., 2018) seems to be an interesting and promising alternative to improve the hydrolytic stability of the hybrid-layer. Future studies should focus on developing new monomers with an optimal diffusion through the dentin and collagen, filling all spaces created by the acid etching and/or acidic primer application, reducing the collagen degradation. Also, monomers with a great interaction with the components of the adhesives, providing better mechanical

reinforcement to the polymer matrices, and consequently improving the hybrid layer formed.

Another relevant topic related to monomers is the creation of new and more efficient adhesion promoting monomers. Despite the excellent clinical performance of MDP containing adhesive agents, especially related to the two-bottle systems, monomers with better chemical interaction with the tooth substrate, including enamel and its high mineralised characteristics, as well as to the organic collagen part, should be developed. The best interaction and bonding to the enamel (better etching pattern combined with chemical bonding) without needs of an acid etching can make the application easier, with reduced steps and technique sensitivity. Also, it may improve the longevity of bonding procedures with SEAs. Nowadays, the selective enamel etching is crucial for the self-etching and universal adhesives in order to guarantee a reliable bonding. Despite a simple procedure, a more easy-to-use agent is always preferable to avoid clinical mistakes.

Regarding the etch-and-rinse approach, the developing of monomers with chemical adhesion to the dentin collagen as recently published (Xu et al., 2019; Yu et al., 2020), seems to be an exciting and promising alternative to improve the long term bond stability of restorative procedures, without adding additional clinical steps to the protocol.

Noticeably, two topics are in evidence due to the importance of the biological/bioactive properties within adhesive systems: the antibacterial and remineralising ability of these agents (Braga, 2019; Braga and Fronza, 2020; Cocco et al., 2015; Makvandi et al., 2020; Makvandi et al., 2018; Profeta et al., 2013; Sauro et al., 2013). Nowadays, the bioactive compounds (antibacterial and remineralising

agents) are one of the most studied fields on dental adhesive research, since it may promote better marginal sealing and reduced biofilm formation, searching a more stable and long-term bonding. Future studies should aim to develop new components with antibacterial characteristics that present a more stable release and long term protection, increasing the efficacy of the antibacterial monomers on the reduction of secondary caries formation. Also, it is essential the continue developing of bioactive agents helping to remineralise non-infiltrated regions within the hybrid layer. The demineralised collagen, exposed by the acid etching or even by strong functional monomers present in some self-etching/universal adhesives is a great problem on adhesive longevity. The effective remineralising agents can improve the bond stability reducing the collagen degradation over time.

Based on the exposes, it cannot be denied that these new pathways will increase the complexity of the development of the adhesives (Spencer et al., 2019). The development of adhesives systems with improved curing, reduced degradation and better interaction with dental tissues, as well as long-term bioactive properties will be able to improve bonding and consequently and long-lasting restorations.

4. Conclusion

Dental adhesive systems are complex mixtures whose properties can be influenced by the presence and/or quantity of any component. The improvement of its physical-chemical properties, as well their bonding efficiency to tooth substrates is directly influenced by the type and ratio of monomers, solvents and initiators used. In this sense, the knowledge of the components and their interaction is important not

only for designing new materials, but also to properly indicate clinical application in each scenario.

Conflict of Interest

The authors confirm that there are no conflicts of interest associated with this publication.

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Figure Captions

Fig. 1 – Chemical structure of adhesion promoting monomers and mono- and multi-functional monomers most used in dental adhesives

Fig. 2 – Chemical structure of initiators and co-initiators

Fig. 3 - The schematic representation of free-radical formation through Norrish Type 1 mechanisms

Fig. 4 - Hydrogen abstraction from the amine co-initiators by the excited triplet state photoinitiator

Fig. 5 - Schematic presentation of the camphoroquinone-amine reaction after light exposure

Fig. 6 - Cleavage α of MAPO, with the formation of two radicals (a) and (b).

Fig. 7 - Photoinitiation of BAPO, with an additional α cleavage, forming four radicals

Fig. 8 - The reaction mechanism of three-component photoinitiator systems containing a photoinitiator, a coinitiator and a photosensitizer

Table 1 – Properties of solvents most used in dental adhesives

	Dipole moment	Dieletric constant	Boiling point	Vapor pressure (mmHG 25o C)	Ability to form hydrogen bonds
Water	1.85	80	100	23.8	High
Ethanol	1.69	24.3	78.5	54.1	Medium
Acetone	2.88	20.7	56.2	200	Low
Tert-Butanol	1.7	12.5	82.4	46	Medium

Table A.1. Chemical composition of current comercial dental adhesive systems

ADHESIVE SYSTEM	ADHESIVE SYSTEM TRADE NAME	MANUFACTURER	COMPOSITION	PH
Three-step etch & rinse adhesives	Adper Scotchbond Multi-Purpose Plus	3M ESPE, St Paul, MN, USA	*Primer*: water; HEMA; copolymer of acrylic and itaconic acids. *Adhesive*: Bis-GMA; HEMA.	*Primer*: 2.9 - 4 *Adhesive:* Not Determined
	Optibond FL	Kerr, Orange, CA, USA	*Primer*: HEMA; MMEP; GPDM. *Adhesive*: HEMA; MEMO; 2-hydroxy-1,3-propanediyl bismethacrylate; alkali fluorosilicates(Na).	*Primer:* 2 *Adhesive:* 5
	Syntac	Ivoclar Vivadent, Schaan, Liechtenstein	*Primer*: acetone; TEGDMA; polyethylene glycol dimethacrylate; maleic acid. *Adhesive*: polyethylene glycol dimethacrylate; glutaral.	*Primer:* Not Determined *Bond:* Not Determined
	Gluma Solid Bond	Heraeus Kulzer, Hanau, Germany	*Primer:* HEMA; ethanol; Poly(methacrylic-oligo-acrylic acid); TEGDMA; 2MEM; maleic acid *Sealer*: TEGDMA; 2MEM; Lucirin BDK.	*Primer:* Not Determined *Sealer:* Not Determined
Two-step etch&rinse adhesives	PQ1	Ultradent Products Inc; S. Jordan, UT, USA	ethyl acohol; HEMA; methacrylic acid; Parbenate	Not Determined
	3M ESPE ADPER SINGLE BOND 2	3M ESPE, St Paul, MN, USA	ethyl Alcohol; Bis-GMA; silane treated silica; HEMA; copolymer of acrylic and itaconic Acids; glycerol 1,3 dimethacrylate; UDMA; water; DPI.	Not Determined
	XP Bond	Dentsply Sirona Pty Ltd, Australia	methacrylate; tertiary butanol; acrylates	2.5
	OptiBond Solo Plus	Kerr, Orange, CA, USA	ethanol; HEMA; glycerol 1,3-dimethacrylate; alkali fluorosilicates(Na).	Not Determined
Two-step self-etch adhesives	Clearfil Protect Bond	Kuraray Noritake Dental Inc, Tokyo, Japan	*Primer*: HEMA; 10-MDP; MDPB; Hydrophilic aliphatic dimethacrylate; water; initiators; accelerators; dyes. *Bond:* Bis-GMA; HEMA; sodium fluoride; 10-MDP; Hydrophobic aliphatic dimethacrylate; colloidal silica; CQ; Initiators; accelerators.	*Primer:* <2.5 *Bond:* Not Determined
	Cleafill SE Bond 2	Kuraray Noritake Dental Inc, Tokyo, Japan	*Primer*: HEMA; 10-MDP; hydrophilic aliphatic dimethacrylate; CQ; accelerators; water; dyes. *Bond*: Bis-GMA; HEMA; 10-MDP; hydrophobic aliphatic dimethacrylate; colloidal sílica CQ; Initiators; accelerator.	*Primer:* < 2.5 *Bond:* Not Determined
	AdheSE	Ivoclar Vivadent, Schaan, Liechtenstein	*Primer*: phosphonic acid acrylate; bis-acrylamide derivative. *Bonding*: Bis-GMA; HEMA	*Primer:* Not Determined *Bonding:* Not Determined
	Clearfil SE Bond	Kuraray Noritake Dental Inc, Tokyo, Japan	*Primer*: HEMA; 10-MDP; hydrophilic aliphatic dimethacrylate; CQ; accelerators; water; dyes; others. *Bond*: Bis-GMA; HEMA; 10-MDP; hydrophobic aliphatic	*Primer:* 2 *Bond:* Not Determined

			dimethacrylate; colloidal sílica; CQ; Initiators; accelerator.	
One-step self-etch adhesives	ONE-UP BOND F Plus	Tokuyama Dental Corporation, Tokyo, Japan	*Agent A*: MAC-10; Bis-MPEPP; BHT;BIS-EMA ; MMA. *Agent B*: DMAEMA; HEMA; BHT; MMA.	*Agent A:* < 7 *Agent B:* Not Determined
	EE-Bond	Tokuyama Dental Corporation, Tokyo, Japan	Bis-GMA; HEMA-Phosphate; HEMA ; TEGDMA; CQ; BHT; Lucirin TPO; Mequinol.	2.3
	Optibond All-in-one	Kerr, Orange, CA, USA	acetone; HEMA; ethanol; glycerol 1,3-dimethacrylate	Not Determined
	Tokuyama Bond Force	Tokuyama Dental Corporation, Tokyo, Japan	HEMA; CQ; Bis-GMA; BHT; Lucirin TPO; mequinol; BIS-EMA; 2 Propanol; TEGDMA.	2.3
Multi-Mode or "Universal" adhesives	Scotchbond Universal	3M ESPE, St Paul, MN, USA	Bis-GMA; HEMA,; P205; ethanol; water; 2-Propenoic acid, 2-methyl-,3-(trimethosysilyl)propyl ester, reaction products with vitreous sílica; copolymer of acrylic and itaconic acid; CQ; Parbenate; DMAEMA.	Not Determined
	Tetric N-Bond Universal	Ivoclar Vivadent, Schaan, Liechtenstein	HEMA; Bis-GMA; ethanol; 1,10-decandiol dimethacrylate; 10-MDP; CQ; DMAEMA	Not Determined
	All-Bond Universal	Bisco Inc, Schaumburg, IL, USA	Bis-GMA; ethanol; 10-MDP; HEMA;	2.5 - 3.5
	Peak Universal	Ultradent Products Inc; S. Jordan, UT, USA	ethyl alcohol, HEMA, methacrylic acid, chlorhexidine diacetate	Not Determined
	Futurabond U	VOCO, Cuxhaven, Germany	Bis-GMA; HEMA; HDDMA;acidic adhesive monomer; UDMA; Catalyst.	2.3
	Optibond Universal	Kerr, Orange, CA, USA	Acetone; Ethanol; HEMA; GPDMA; GDMA	Not Determined
	Optibond eXTRa Universal	Kerr, Orange, CA, USA	*Primer:* Acetone; Ethanol; HEMA; GPDMA. *Adhesive: Ethanol; HEMA; GPDMA; GDMA; Sodium hexafluorosilicate.*	*Primer:* 2.2 *Adhesive:* Not Determined
	Ambar Universal	FGM; Joinville, SC, Brasil	UDMA; HEMA; methacrylate hydrophilic monomers; methacrylate acid monomers; ethanol; water; silanized silicon dioxide; CQ; parbenate; surfactant; sodium fluoride.	2.6 - 3.0
	ZIPBond Universal	SDI, Bayswater, Australia	Ethanol; acrylic monomer.	3.0

All information presented in this table was obtained from the Material Safety Data Sheet (MSDS) provided by each manufacturer.

HEMA: 2-hydroxyethyl methacrylate; **Bis-GMA**: bisphenol A diglycidyl methacrylate; **MMEP**: 2-[2-(methacryloyloxy)ethoxycarbonyl]benzoic acid; **GPDM**: glycerol phosphate dimethacrylate; **CQ**: Camphorquinone; **BHT**: Butylated hydroxytoluene; **MEMO**: 3-trimethoxysilylpropyl methacrylate; **TEGDMA**: Triethylene glycol dimethacrylate; **2MEM**: maleic-acid-mono-2-methacryloyl-ethylester; **Lucirin BDK**: 2,2-dimethoxy-1,2-diphenylethan-1-one; **Parbenate**: Ethyl-4-Dimetylamino Benzoate; **DPI**: Diphenyliodonium Hexafluorophosphate; **UDMA**: urethane dimethacrylate; **PENTA**: dipentaerythritol pentaacrylate phosphate; **GDMA**: glycerol dimethacrylate; **GPDMA**: glycerol phosphate dimethacrylate; **Climacel**: 2-Ethylhexyl 4-(dimethylamino)benzoate; **BHT**: 2,6-Di-tert-butyl-4-methylphenol; **MEMO**: gamma – methacryloxypropyltrimethoxysilane; **10-MDP**: 10-methacryloyloxydecyl dihydrogen phosphate; **MDPB**: 12-Methacryloyloxydodecylpyridinium bromide; **MAC-10**: 11-methacryloxy-1,1-undecanedicarboxylic acid; **Bis-MPEPP**: bisphenol A polyethoxy dimethacrylate; **BIS-EMA**: methacryloxyalkyl acid phosphate; **MMA**: methyl methacrylate;

DMAEMA: 2-dimethylaminoethyl methacrylate; **HEMA-phosphate**: 2-propenoic acid, 2-methyl-, 2-hydroxyethyl ester, phosphate; **TEGDMA**: 2,2'-ethylenedioxydiethyl dimethacrylate; **Lucirin TPO**: diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide; **P205**: 2-propenoic acid, 2-methyl-, reaction products with 1,10-decanediol and phosphorous oxide; **Parbenate**: dimethylaminobenzoat(-4); **HDDMA**: 1,6 Hexanediylbismethacrylate.