Development of Novel Polymer Technology for a New Class of Restorative Dental Materials

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Purpose: The aim of this review article was to provide an overview of the scientific and patent literature on the different synthesis pathways of modified polyacids suitable for application in a new class of restorative dental materials.

Methods: The literature based on patents and publications from 2009 to 2018 of Dentsply Sirona in cooperation with Heinrich Heine University, Düsseldorf, was reviewed and summarized.

Results: Multiple approaches towards the development of polymerizable acid polymers have been introduced and their strength and weaknesses were discussed. A target structure and the respective synthesis were developed allowing the formulation of a restorative dental material with unique properties, such as high mechanical strength paired with good adhesion properties.

Conclusion: From a variety of hydrolytically stable acidic polymers, the most promising versions were selected and used for the product development of Surefil one (Dentsply Sirona).

Keywords: additive coupling, copolymerization of acrylic acid with amine derivatives, modified polyacrylic acid, polymer-analogous modification, restorative materials.

Polymers are widely used in dental applications and in the field of materials for restorative dentistry. Some of the special polymers frequently used include acidic polymers, such as polyacrylic acid or copolymers of acrylic acid with other acidic monomers, eg, itaconic or maleic acid. These acidic (co-)polymers are used, for instance, in glass ionomers, resin-modified glass ionomers, adhesives, or cavity conditioners. One of the main functions of these polyacids is facilitating or supporting adhesion to dental hard tissue, while also contributing to the setting reaction in certain materials. These unique properties and features make polyacids an interesting topic for technology research to further improve restorative dental materials.

This article intends to summarize the research in the field of polymerizable polyacids which was conducted in our labs in cooperation with an academic partner to create a novel polymer technology for a new class of restorative dental materials.

The focus of this work was to develop polymers and respective synthetic approaches to facilitate the incorporation of the polyacids in an overarching polymer network by radical copolymerization with matrix monomers. To this end, three general approaches were pursued:

1. Additive coupling or copolymerization
2. Polymer-analogous modification of polyacids with monomers having amino-terminated or amino-protected groups and polymerizable moieties
3. Copolymerization of acrylic acid or its derivatives with monomers having amino-terminated or amino-protected groups as well as polymerizable moieties and subsequent polymer-analogous modification

1. Additive Coupling or Copolymerization

Additive coupling requires polyacids that have either thiol groups or allylic moieties on the backbone. Allylic moieties can be incorporated by a 2- or 3-step synthesis as depicted in equations 1 and 2 of Fig 1. According to eq 1 in Fig 1, acrylic acid and acrylic acid tert-butyl ester are copolymerized, followed by polymer-analogous reaction with allylic amine and deprotection of the carboxylic acid ester.

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Alternatively, acrylic acid and itaconic acid anhydride can be copolymerized and modified in a second step with allylic amine (Fig 1, eq 2).

The copolymer acids according to Fig 1 (eqs 1 and 2) comprise hydrolytically stable allylic amide moieties. These can undergo post-crosslinking by reaction with di- or polythiols (Fig 2, eq 3).[1,2] Further, they make post-crosslinking by copolymerization possible with di- or polyfunctional (meth)-acrylates (Fig 2, eq 4).[1,2,11]

Especially the dithiol route (Fig 2, eq 3) has significant disadvantages, such as the relatively weak crosslinking with di- or poly-thiols, as well as the unpleasant odor of the di- or poly-thiols.
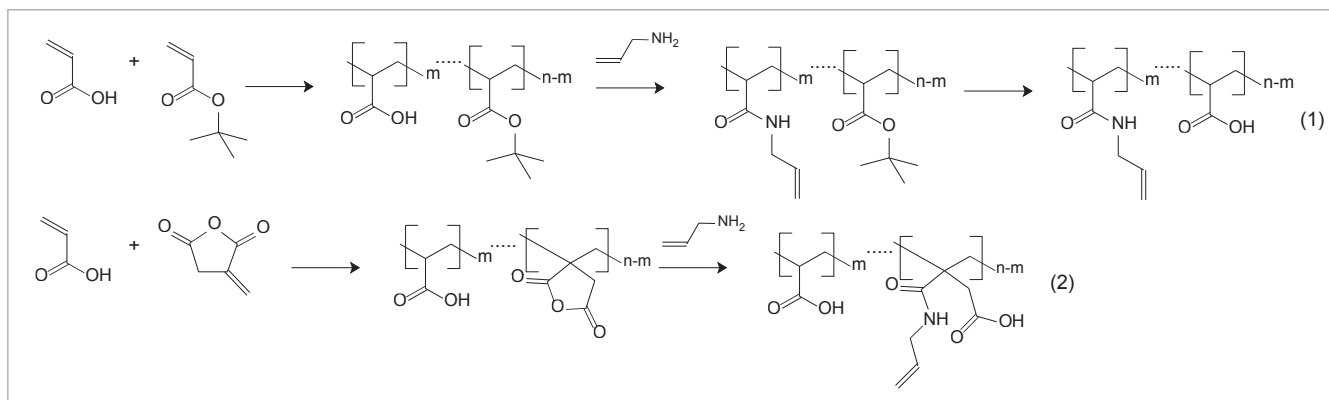

Fig 1 Reaction scheme of copolymerization of acrylic acid and acrylic acid tert-butyl ester, followed by polymer-analogous reaction with allylic amine, deprotection of the carboxylic acid ester (eq 1), copolymerization of acrylic acid and itaconic acid anhydride, and modification with allylic amine (eq 2).
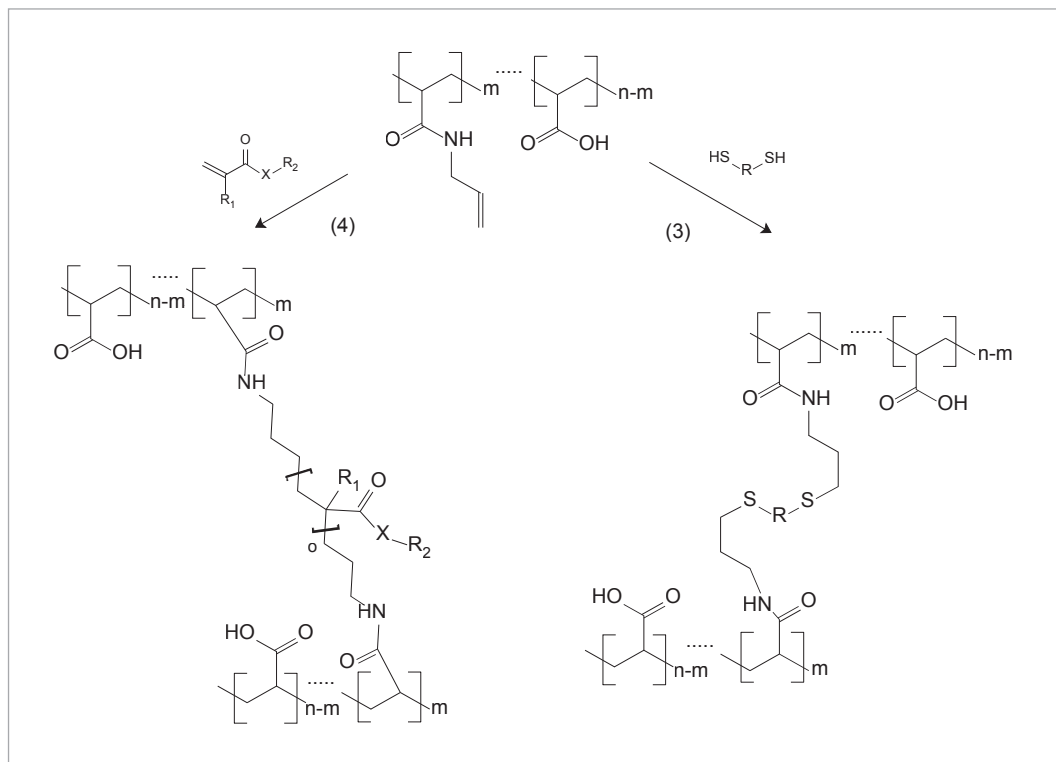

Fig 2 Reaction scheme of post-crosslinking reaction of allylic polymers with di- or polythiols (eq 3) or with di- or polyfunctional (meth)acrylates.

2. Polymer-analogous Modification of Polyacids with Monomers Having Amino-terminated or Protected Amino Groups and Polymerizable Moieties

In general, this approach deals with the synthesis of reactive acidic polymers as intermediates, which, in a second step, are modified in a polymer-analogous reaction with molecules bearing polymerizable double bonds.

a. Synthesis of polyacids with double bonds

By copolymerization of acrylic acid and itaconic acid anhydride, a reactive polymer is formed which is transferred by subsequent modification with hydroxy-methyl acrylic acid or amino-methyl acrylic acid (Fig 3, eq 5).[12-14] This leads to a polymer in which the content of carboxylic acids is unchanged compared to pure polyacrylic acid, and which has C-C double bonds suitable for polymerization with matrix monomers.

It must be mentioned that the synthesis of the amine is challenging and therefore expensive, and of limited industrial applicability.
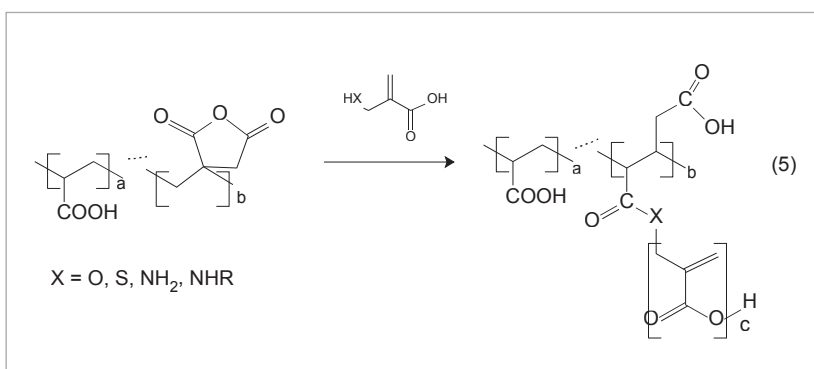

Fig 3 Reaction scheme of modification of copolymer with hydroxy-methylacrylic acid or amino-methylacrylic acid.

b. Inverse system generating carboxylic acids by reaction with polyethylene imine or polyvinyl alcohol

A completely new concept that upends the previous syntheses starting from acrylic acid or polyacrylic acid consists of the use of polyvinyl alcohol or polyethyleneimine as a precursor polymer.[6]

Their modification with unsaturated carboxylic anhydrides leads to polyacids with polymerizable double bonds (Fig 4, eq 6). Both polymer types can be copolymerized using (meth)acrylates.

In fact, this approach is limited by the interaction of carboxylic acid groups with unreacted amino functions and/or tertiary amino groups. In addition, a high degree of polymer modification is necessary, because it determines the number of necessary acid groups. To avoid compelling their number to be directly related to that of the double bonds, non-functional cyclic anhydrides can be used as well, eg, succinic acid or phthalic anhydride. Furthermore, it is known that the copolymerization of acrylates and maleic acid or itaconic acid double bonds is limited. Therefore, the obtained polymers are not ideal candidates for use in a restorative dental material.
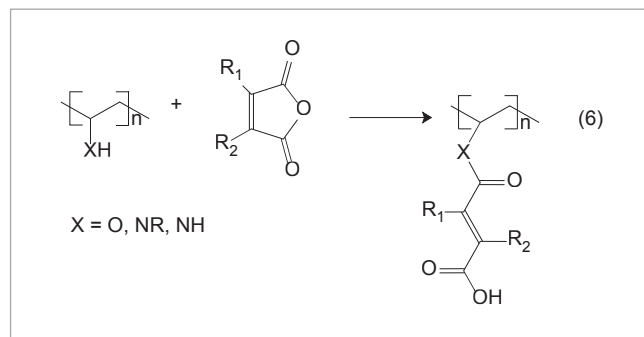

Fig 4 Reaction scheme of modification of polyvinyl alcohol or polyethyleneimine with unsaturated carboxylic anhydrides.

c. Cyclopolymerization

Cyclopolymerization of divinylether (DIVE) and maleic anhydride (MSA) leads to polymers with anhydride moieties (DIVEMA), which can be opened by oxygen or nitrogen nucleophiles, such as HEMA (hydroxyethyl-methacrylate) or amino-methylacrylate, to polycarboxylic acids having free-radical polymerizable double bonds (Fig 5, eq 7).[3-5]

Due to the cycloaliphatic rings, these polymers are expected to be more rigid compared to the aliphatic polyacrylic acid (PAA).

Attention must be drawn to the toxicity of divinyl ether and its challenging handling (boiling point of 28.3°C) at a possible scale-up.
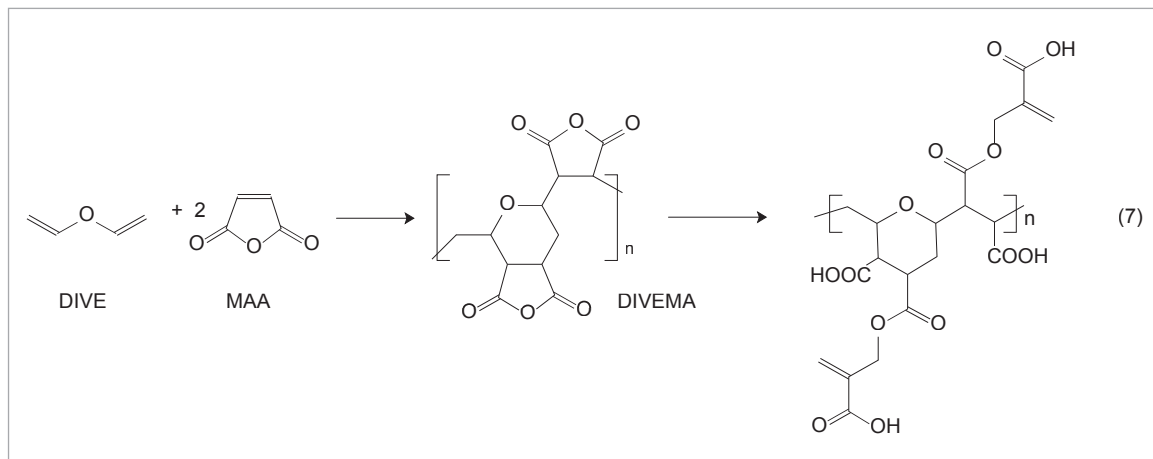

Fig 5 Reaction scheme of polymerization of DIVE and MAA (maleic anhydride) to DIVEMA, which can be opened by oxygen or nitrogen nucleophiles, such as HEMA or amino-methylacrylate to polycarboxylic acids.

d. Synthesis and investigation of hyperbranched PAA and graft-on PAA and their application in GI formulation

Easy access to hyperbranched polyacids and graft-on polyacids was found by polymerization of acrylic acid onto amino ethyl thiol (Fig 6, eq 9).[10]

One goal is the synthesis and comparison of hyperbranched structures to linear PAA. Furthermore, these polymers must be modified and cross linked, as outlined in eqs 1 and 2 above.

Unfortunately, only strongly discolored products were obtained with that synthesis, making them of limited use only for dental material development.
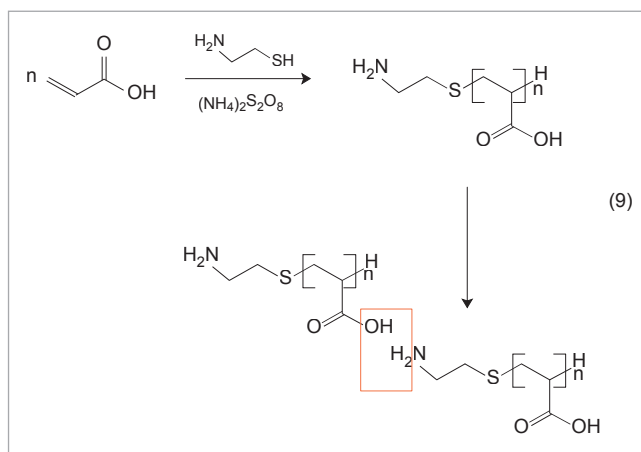

Fig 6 Reaction scheme of the synthesis of hyperbranched PAA and graft-on PAA by polymerization of acrylic acid onto amino ethyl thiol.

e. Hydroxy methylene acrylamide polyacrylic acid (HMAA-PAA)

The following pathway starts with the electrophilic substitution of phenol with hydroxy methylene acrylamide, followed by polymerization of the obtained substituted phenol with acrylic acid. Subsequent polymer-analogous modification with hydroxy methylene acrylamide leads to a polymerizable polyacid (Fig 7, eq 11).[7] Due to the aromatic moieties, the solubility of the obtained polymer is significantly impaired compared to purely aliphatic polyacids; hence, the potential use in aqueous formulation is limited.
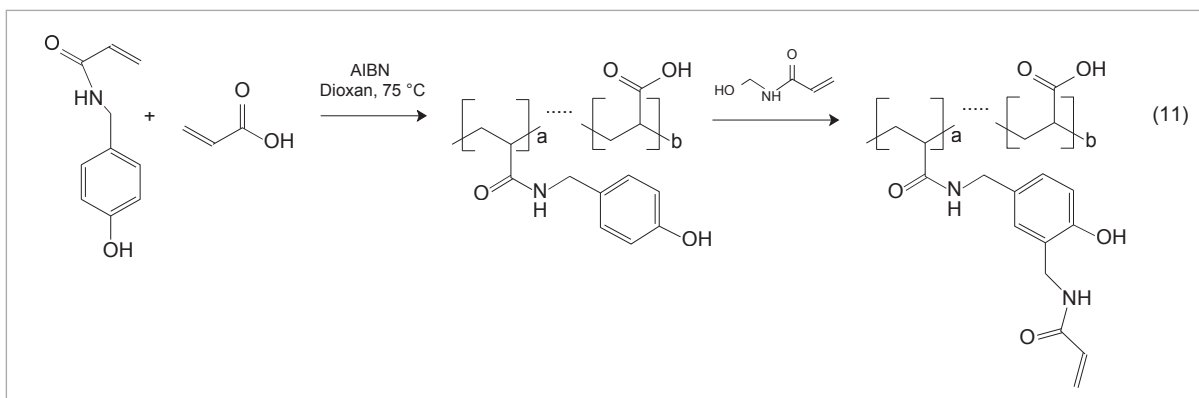

Fig 7   Reaction scheme of synthesis of hydroxy methylene acrylamide polyacrylic acid (HMAA-PAA).

f. Reaction of monoacrylamides to PAA

One of the easiest means of producing polymerizable polyacids is the polymer-analogous modification of polyacids with mono(meth)acrylamido alkylene amines or with the corresponding isocyanates (Fig 8, eqs 12 and 13).[16] However, the synthesis of the mono(meth) acrylamido alkylene amines or the corresponding isocyanates is challenging and therefore limits the industrial applicability of this approach. Depending on the synthesis strategy, it is also possible to use polyacid anhydrides (see Fig 3, eq 5) for the polymer-analogous reaction or polyacid ester copolymers.
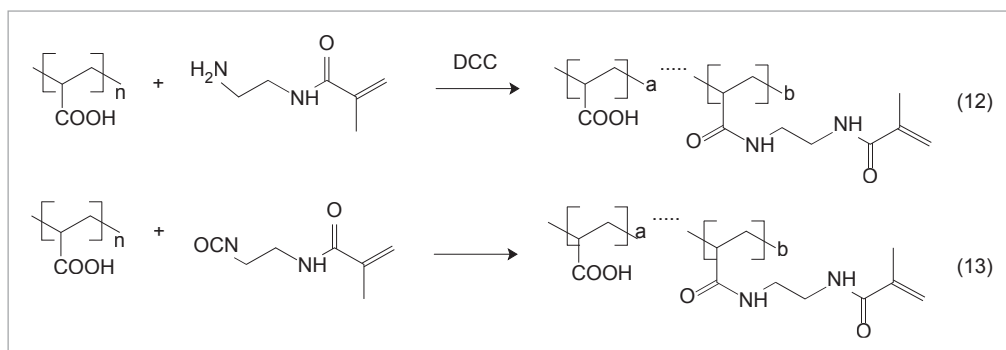

Fig 8   Reaction scheme of polymer-analogous modification of polyacids with mono(meth)acrylamido alkylene amines (eq 12) or with the corresponding isocyanates (eq 13).

3. Copolymerization of Acrylic Acid with Monomers Having Amino-terminated or Protected Amino Groups and Polymerizable Moieties and Subsequent Polymer-analogous Modification

The fundamental idea of this approach is the copolymerization of acrylic acid or protected acrylic acid with an α,ω-amino vinyl component which bears a free or protected amino moiety (Fig 9, eq 14). In the following synthesis steps, the amino

group can be deprotected if necessary and modified by (meth)acrylic acid or its derivatives.[8,9]

The following amines or suitable N-compounds are available as shown in Fig 10. They include allylamine, acrylonitrile, (meth)acrylamido alkyl amines, itaconic amido alkyl amines, ω-carboxylic aminoalkylene acrylamides, aminomethylen acrylic acid, N-vinyl formic amide (NVFA) and amino alkyl vinyl ethers.
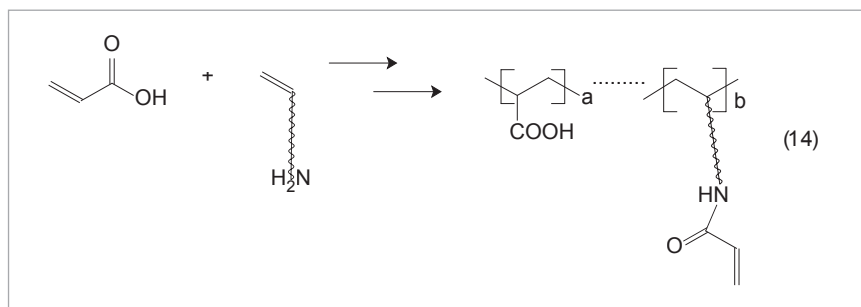

Fig 9 Reaction scheme of copolymerization of acrylic acid with an α,ω-amino vinyl component.
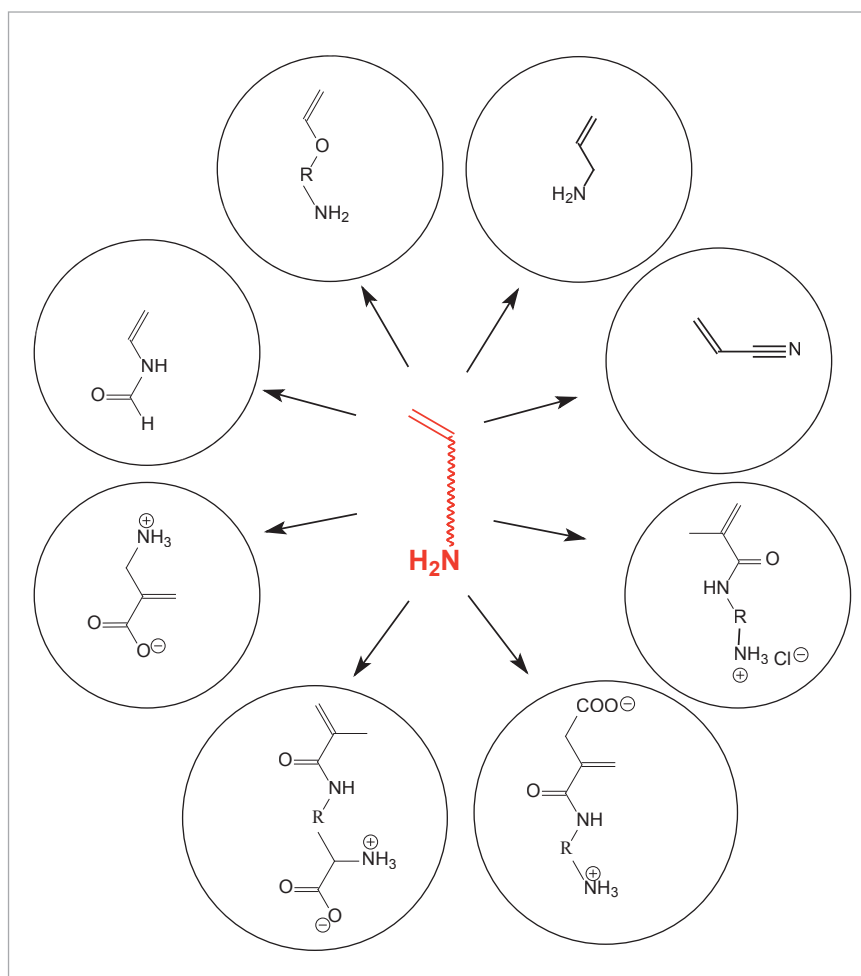

Fig 10 Amines, protected amines, and N-containing molecules which can be used for copolymerization with acrylic acid or its derivatives, followed by amine deprotection if necessary and a subsequent conversion into polymer bonded (meth)acrylamides.

a. Allylamine and (meth)acrylic acid

An obvious possibility is the copolymerization of acrylic acid and allylic amine (Fig 11, eq 15).[8,9] However, detours will be necessary, and either the acid function or the amino group must be protected, because otherwise an acid-base reaction or aza-Michael reaction occurs.

A disadvantage of this route is the limitation of copolymerization of acrylic groups with allyl moieties, leading to a low percentage of double-bond modification using large access of allylic amine. Furthermore, the relatively short and non-flexible chain between the polymer backbone and acrylic moiety could be a disadvantage. Indeed, relatively low mechanical properties were found when using this in a restorative dental formulation.
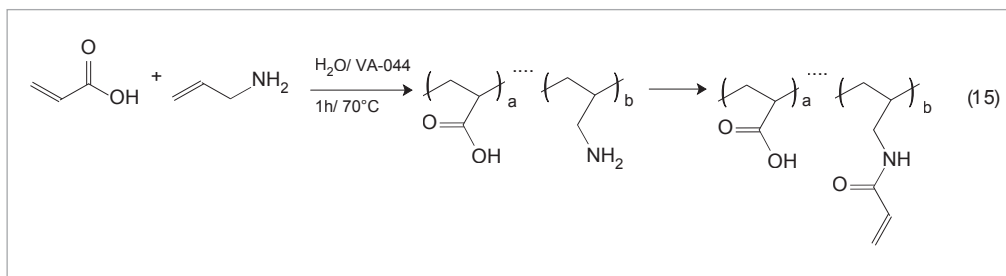

Fig 11 Reaction scheme of copolymerization of acrylic acid and allylic amine.

b. Acrylonitrile and (meth)acrylic acid

The copolymerization of acrylonitrile and (meth)acrylic acid seemed to be a straightforward strategy (Fig 12, eq 16).[8,9] The good copolymerization of the two monomers is advantageous. However, for industrial applicability, protection of the carboxylic acid would be needed to overcome internal salt formation due to the acid-base reaction after reduction, which makes large scale handling difficult and limits the subsequent polymer-analogous modification. Again, the relatively short and non-flexible spacer length represents a disadvantage.
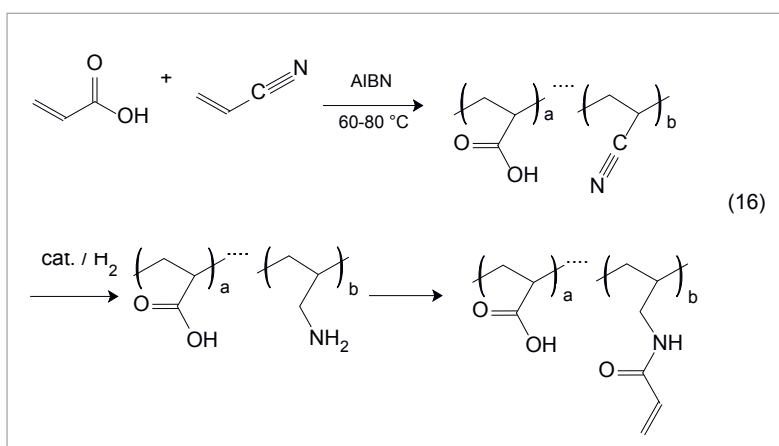

Fig 12 Reaction scheme of copolymerization of acrylonitrile and acrylic acid.

c. (Meth)acrylamido alkylamine and (meth)acrylic acid

The copolymerization of acrylic acid and (meth)acrylamido alkylamines may prove to be an effective strategy (Fig 13, eq 17), as it leads to an amino-functionalized polyacid.[8,9] The chain length of the (meth)acrylamido alkylamines is variable and allows adjustment to the requirements.

However, the synthesis of the mono(meth)acrylamido alkylene amines is challenging. Traces of dimethacrylated amine lead to crosslinking of the polymer during synthesis, making this approach suboptimal for large scale manufacturing. Depending on the synthesis strategy, it is appropriate to use acrylic acid t-butyl ester instead of acrylic acid to avoid an acid base reaction after neutralisation of the ammonium salt.
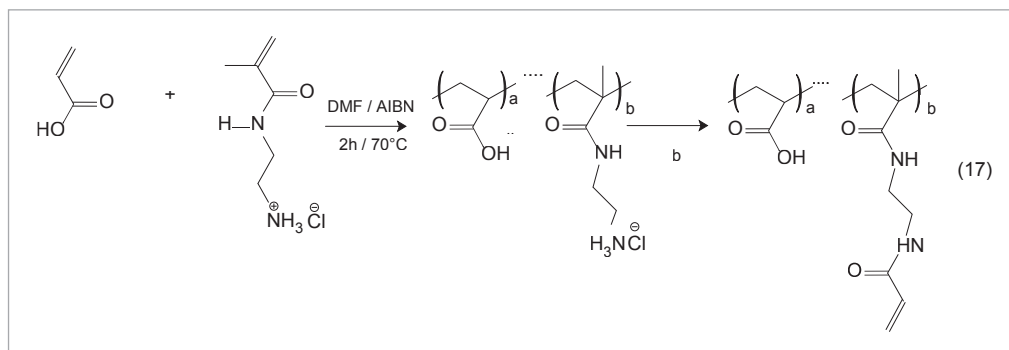

(17)

Fig 13 Reaction scheme of copolymerization acrylic acid and (meth)acrylamido alkylamines.

d. Itaconic amido alkyl amine

In the same manner as (meth)acrylamido alkylamines and their hydrochlorides, itaconic acid amido alkylamines react in a free-radical polymerization with acrylic acid (Fig 14, eq 18).[8,9] It may be advantageous that with each polymerizable group a further acid group is introduced into the copolymer at the same time.

In this case as well, a limitation of the copolymerization acrylic groups with itaconic moieties exists. Besides the limitations mentioned above for the similar approach in Fig 13, eq 17, the copolymerization of the itaconic acid derivative with acrylic acid is not favorable. Therefore, the expensive itaconic-acid derivative would need to be used in excess, limiting the industrial applicability of this approach.
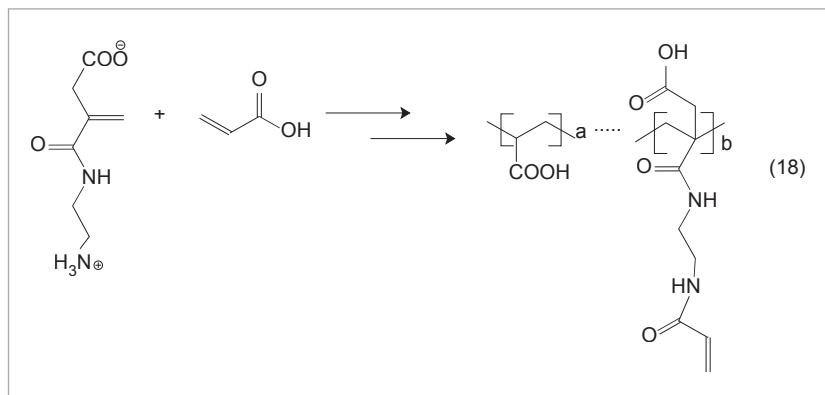

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Fig 14 Reaction scheme of copolymerization of itaconic acid amido alkylamines with acrylic acid.

e. ω-carboxylic aminoalkylene acrylamide (lysine)

The following pathway (Fig 15, eq 19) shows the copolymerization of lysine acrylamide with acrylic acid.[8,9] Here the spacer length is fixed to five carbon atoms. Since lysine acrylamide also has a free carboxylic acid group in addition to a polymerizable group, the number of acid groups is not reduced compared to polyacrylic acid.

As in the previous synthesis strategy, the use of an acrylic acid ester is also recommended, although it requires an additional step in the release of free carboxylic acid. It avoids side reactions and makes possible scale-up more convenient. Unfortunately, the access to the selectively mono-acrylated lysine derivative is challenging, making this approach less attractive.
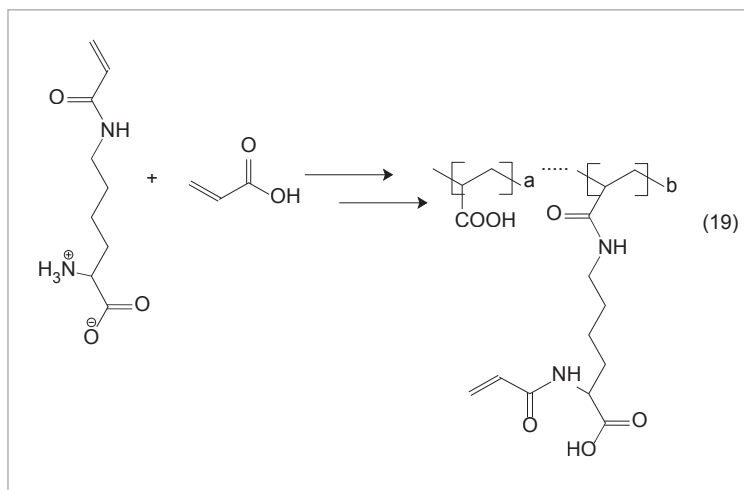

Fig 15 Reaction scheme of copolymerization of lysine acrylamide with acrylic acid.

f. Aminomethylen acrylic acid

Aminomethylen acrylic acid and acrylic acid polymerize to a copolymer with amino groups and acidic moieties. In a subsequent reaction, the amino groups are converted to a (meth)acrylic group (Fig 16, eq 20).[8,9]

As discussed in section 2a, the synthesis of the amine is challenging and therefore relatively expensive. Furthermore, a steric hindrance may appear due to the close proximity of the polymerizable groups and the polymer backbone.
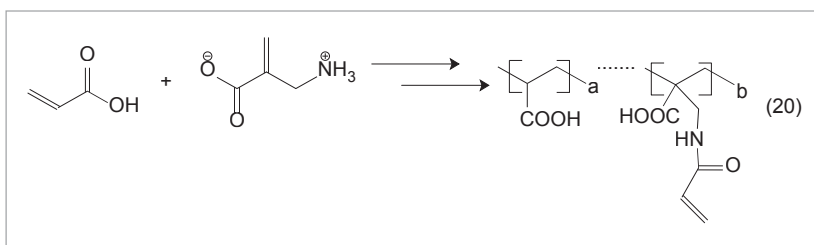

Fig 16 Reaction scheme of copolymerization of aminomethylen acrylic acid and acrylic acid.

g. N-vinylformamide (NVFA) and (meth)acrylic acid

NVFA is a commercially available, protected polymerizable amine suitable for achieving the desired structures. It copolymerizes very well with acrylic acid and its derivatives (Fig 17, eq 21).[8,9] The subsequent amine release and (meth)acrylation lead to a copolymer of the desired structure.

A limitation of the scale-up of this route is the toxicity of NVFA. In the same manner as describe above (3f), a steric hindrance may appear due to the close proximity of the polymerizable groups and the polymer backbone.
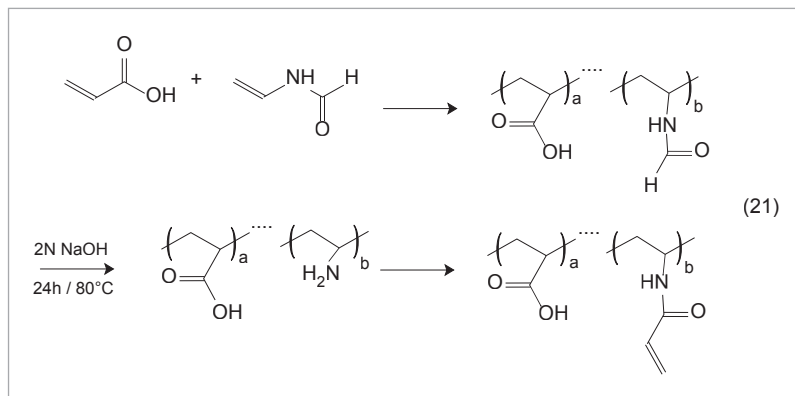

(21)

Fig 17 Reaction scheme of copolymerization of N-vinylformamide and acrylic acid.

h. Amino alkyl vinyl ethers

Based on the drawbacks of the different approaches discussed above, we have developed an approach and synthesis leading to a target structure in a scalable, efficient manner: t-butyl acrylate is copolymerized with amino-propylvinylether, leading to an amine-functionalized protected polymer. In a one-pot reaction, the copolymer is functionalized using methacrylic anhydride followed by deprotection of the t-butylester under acidic conditions (Fig 18, eq 22).[8,9,15]
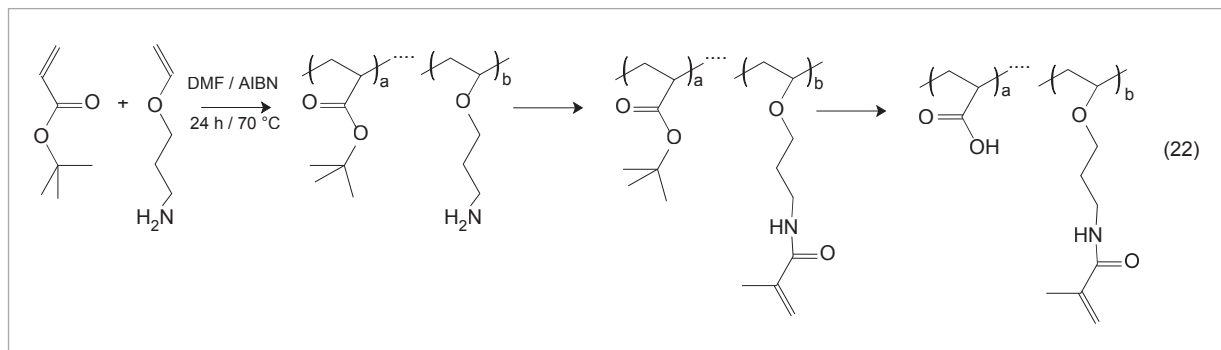

(22)

Fig 18 Reaction scheme of copolymerization of t-butyl acrylate with amino-propylvinylether followed by modification with methacrylic anhydride and deprotection of t-butylester.

Besides the conversion of the amino group in a methacrylamide function, the reaction with derivatives of acrylic acid, itaconic acid or maleic acid are also possible (Fig 19).

This target structure allows the development of a new class of restorative dental materials with unique properties.

Among those properties are high mechanical strength paired with good adhesion to dental hard tissue, yielding a truly self-adhesive restorative dental material for load-bearing permanent restorations.
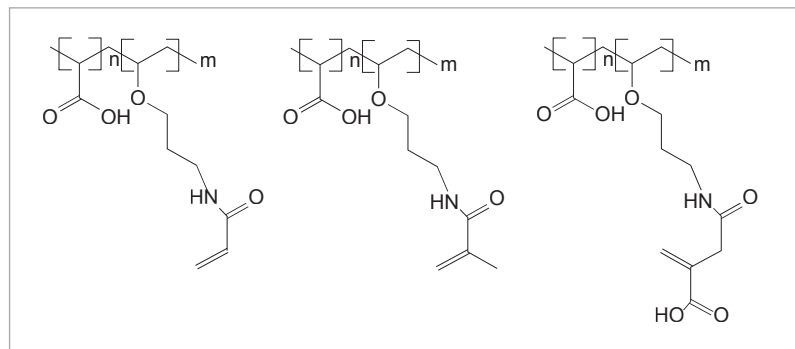

Fig 19 Alternative modification of amino moieties with acrylic, methacrylic, and itaconic moieties.

SUMMARY AND CONCLUSION

Multiple approaches towards the development of polymerizable acid polymers have been introduced and their strength and weaknesses discussed. A target structure and the respective synthesis were developed, allowing the formulation of a restorative dental material with unique properties such as high mechanical strength paired with good adhesion properties.

REFERENCES

1. Klee JE, Brugger S, Ritter H, Weber C, Elsner O, Bardts M, Facher A, Pohle S. Dental composition. EP 2228049 (09.11.2016).
2. Klee JE, Brugger S, Ritter H, Weber C, Elsner O, Bardts M, Facher A, Pohle S. Dental composition. US 9289360 (22.03.2016).
3. Klee JE, Elsner O, Pohle S, Ritter H, Bernert D. Dental composition. EP 2316407 (30.10.2009).
4. Klee JE, Elsner O, Pohle S, Ritter H, Bernert D. Dental composition. US 9682019 (20.06.2017).
5. Klee JE, Elsner O, Pohle S, Ritter H, Bernert D. Dental composition. US 9999576 (20.06.2017).
6. Klee JE, Fik CP, Maier M, Ritter H. Dental composition. EP 12 003 764.3 (11.05.2012).
7. Klee JE, Renn C, Szillat F, Elsner O, Scheufler C, Lampe U, Ritter H. Polymer for a Glass Ionomer Cement. EP 3141567 (15.03.2017).
8. Klee JE, Ritter H, Maier M, Gansel J, Facher A, Elsner O, Pohle S. Polymer for a Glass Ionomer Cement. EP 2 655 427 (22.12.2010).
9. Klee JE, Ritter H, Maier M, Gansel J, Facher A, Elsner O, Pohle S. Polymer for a Glass Ionomer Cement. US 9993395 (31.10.2013).
10. Klee JE, Ritter H Pohle S, Bezdushna E, Elsner O. Process for the preparation of a composition comprising hyper-branched compounds. EP 2272487 (08.07.2009).
11. Klee JE, Ritter H, Pohle S, Elsner O. Dental composition. EP 2329807 (08.06.2011).
12. Klee JE, Ritter H, Pohle S, Elsner O, Bardts M. Dental composition. EP 2460507 (17.04.2013).
13. Klee JE, Ritter H, Pohle S, Elsner O, Bardts M. Dental composition. EP 2470153 (28.08.2013).
14. Klee JE, Ritter H, Pohle S, Elsner O, Bardts M. Dental composition. US 10123948 (13.11.2018).
15. Maier M, Dollendorf C, Ritter H, Klee JE. Radically Crosslinkable Poly(acrylic acid)s From Poly((tert-butyl acrylate)-co -(3-aminopropyl vinyl ether)): Synthesis and Rheological Properties. Macromolecular Chemistry and Physics 2012;213:2598-2605.
16. Scheufler C, Renn C, Maier M, Klee JE. Preparation process of a dental resin-modified glass ionomer composition. EP 3339335 (27.06.2018).

Clinical relevance: The chemistry reviewed in this publication allows the development of a new type of restorative dental material, simplifying restorative treatment. Not needing a separate etching or adhesive step, such self-adhesive restorative materials can also be successfully applied in cases where either patient compliance or the clinical situation requires fast and efficient treatment steps.