An overview on low cytotoxic alternatives to (meth)acrylates: vinyl esters and vinyl carbonates

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Abstract

Vinyl esters and vinyl carbonates have been shown to be promising alternatives to (meth)acrylates due to significantly lower cytotoxicity. Their reactivity is lower than those of acrylates. By addition of thiols, the reactivity may exceed the acrylates. These materials are suitable for biomedical application as well as for coatings.

1. Introduction

Currently, acrylates and methacrylates are the state-of-the-art monomers for UV polymerizable formulations.[1] A large variety of mono-, di-, and multifunctional (meth)acrylates of low and high molecular weight are present in the market today. They are generally used as protective and decorative coatings and have found applications as paints, coatings, printing inks, resists, etc. Some selected methacrylates are also used as biocompatible materials, such as bone cements or dental filling materials. (Meth)acrylates possess many attractive properties, such as good storage stability, fast curing rates, tunable mechanical properties, and allow solvent free processing. However, higher price of these monomers in comparison with other common monomers (*e.g.* styrene) has to be accepted due to their preparation from (meth)acrylic acid. Furthermore, some methacrylates and especially acrylates and acrylamides exhibit some specific unattractive properties regarding their toxicology profile.[2] Skin irritancy or toxicity of some monomers will be a serious reason to limit their use due to health and environmental legislation. These drawbacks can be mainly addressed to the reactivity of the acrylate double bond towards Michael addition reactions with amino- or thiol-groups of proteins.

There are not many alternatives if one wants to sustain the excellent performance profile of (meth)acrylates and the polymers thereof along with lower irritancy or cytotoxicity of the monomers. Vinyl esters might be a good substitute. However, currently there are only few monofunctional, one difunctional, and no multifunctional vinyl esters commercially available. Vinyl carbonates are practically absent on the market.[3] The reason is a difficult synthesis of this type of monomers. The

availability of these novel monomers might be expanded in the future since they can be prepared in high yields from cheap starting material in the presence of metal complex catalyst as recently claimed in two BASF's patents.[4,5] Therefore, the purpose of this conference paper is to show that these monomers have a surprisingly high photoreactivity and low cytotoxicity and thus could be a suitable alternative to (meth)acrylates.[6,7,8] Here we compare two series containing acrylate, methacrylate, vinyl ester, and vinyl carbonate with either short hydrophobic spacer or tetraethylene glycol spacer (Figure 1).

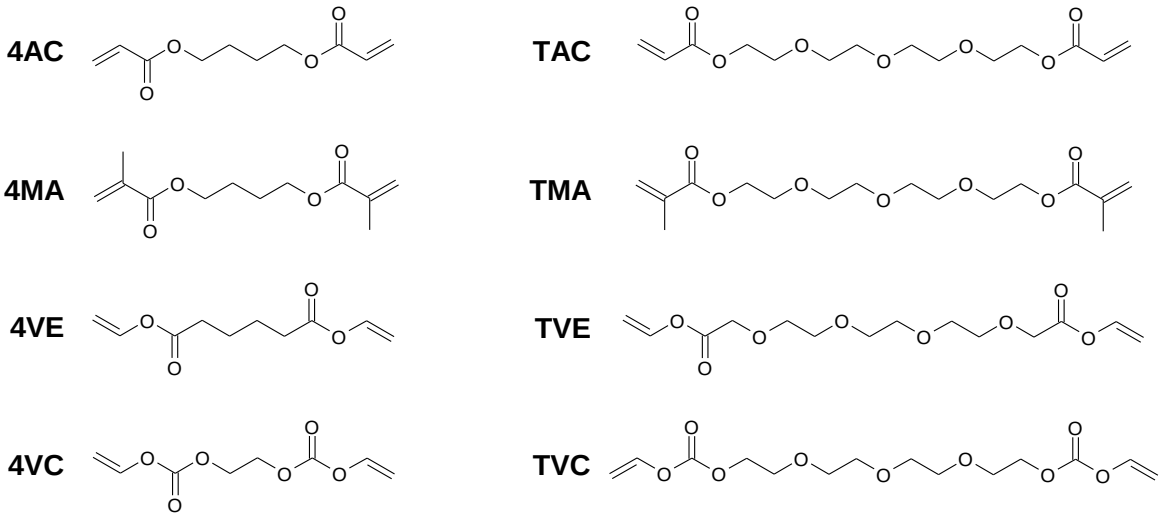


Figure 1: Monomers used in this study

2. Synthesis

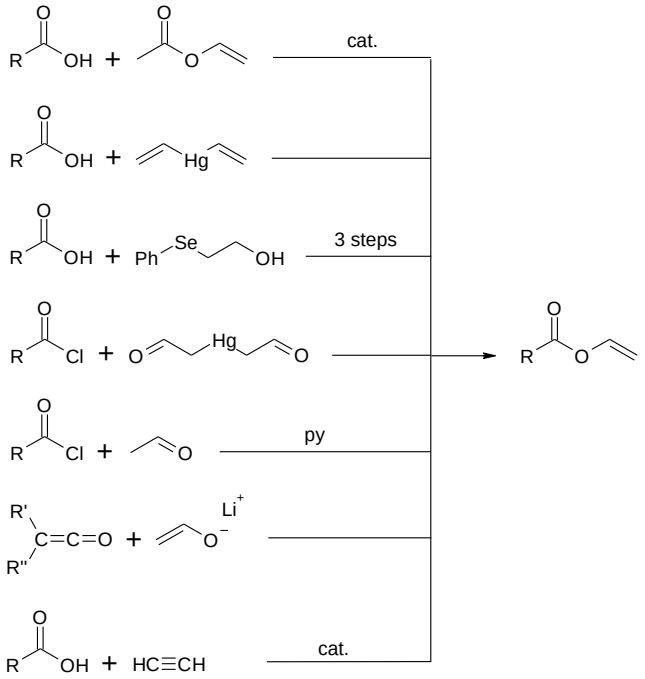
2.1 Synthesis of vinyl esters

Only one divinyl ester and a few monovinyl esters are commercially available. For the synthesis of vinyl esters (Scheme 1), vinyl acetate is used in most cases as a vinyl group donating agent in the presence of Hg(II)[9] or a Pd(II)[10] salt catalyst to afford vinyl esters in mediocre yields. Carboxylic acids can be esterified using divinyl mercury in 41–86% yield.[11] Another synthetic route to obtain vinyl esters is a three-step reaction using phenylselenium ethanol under mild conditions.[12] Reaction of acyl chlorides with mercuric diacetaldehyde gave vinyl esters in 88–90% yields.[13] Acyl chlorides can be also converted to vinyl esters with acetaldehyde in presence of pyridine.[14] Nucleophilic addition to ketenes by acetaldehyde lithium enolate followed by hydrolysis gave vinyl esters in 40–47% yields.[15] An industrially promising method is vinylation of carboxylic acids with acetylene in the presence of various Re, Mn, Mo, Fe catalysts in high yields (87–99%).[4]

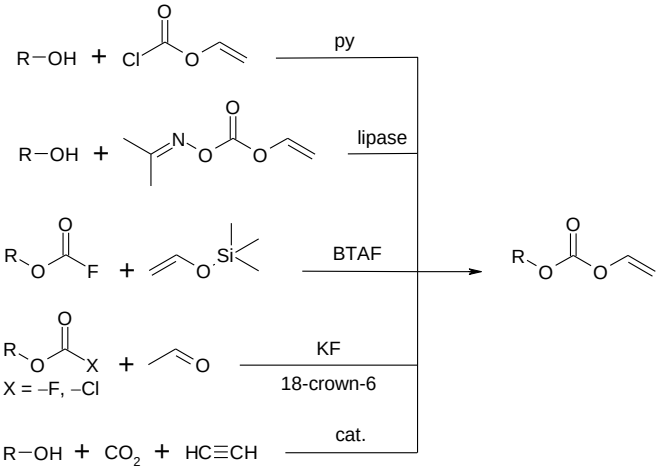
2.2 Synthesis of vinyl carbonates

Vinyl carbonates are practically commercially unavailable with few exceptions available in limited quantity. Few synthetic pathways were described for the preparation of vinyl carbonates in literature (Scheme 2). The most frequently used method is the simple conversion of alcohols with vinyl chloroformate as vinyloxycarbonyl (VOC) group donating reagent using pyridine as an acid scavenger giving vinyl carbonates in high yields.[16] However, this commercially available reagent is rather expensive. Acetone *O*-(vinyloxy)carbonyl oxime is a selective VOC donating agent synthesized from

vinyl chloroformate.[17] Treatment of trimethylvinyloxysilane with fluoroformates in THF with a catalytical amount of benzyltrimethylammonium fluoride gives vinyl carbonates in 70–97% yield.[18] This reaction does not work with chloroformates, and traces of chloroformate impede the reaction. Acetaldehyde can be converted to vinyl carbonates by treatment with chloro- or fluoro- formates, KF, and 18-crown-6 or by reaction of fluoroformates with KF in DMSO without any catalyst in 56–92% yields.[19] The only industrially applicable procedure is reaction of corresponding alcohol with CO_2 and acetylene as claimed in BASF's patent.[4]



Scheme 1: Synthetic pathways to vinyl esters



Scheme 2: Synthetic pathways to vinyl carbonates

3. Photoreactivity

Undoubtedly, the most important characteristic of photoreactive monomers is their photoreactivity here expressed by time to reach the maximum polymerization heat flux (t_{max}). Double bond conversion (DBC) is another important factor for the practical application. Low values do not only lead to a significant amount of leachable monomers but also reduce mechanical properties of the photopolymer. Photo-DSC is an efficient method that provides much information within one simple measurement and therefore this technique was selected to evaluate the monomers.

For the comparison of photoreactivity of vinyl esters and vinyl carbonates with (meth)acrylates, monomers with the same spacer have been chosen (Figure 2). In case of hydrophobic series (**4AC**, **4MA**, **4VE**, **4VC**) the concentration of photoinitiator (Irgacure 819) was only 0.5 wt% in order to emphasize the differences between the polymerizable groups. Tetraethylene glycol-based monomers (**TAC**, **TMA**, **TVE**, **TVC**) were cured with 5 wt% of photoinitiator due to lower reactivity.

Among the low molecular weight monomers, photoreactivity was found to be in the following order: acrylate (**4AC**) > vinyl carbonate (**4VC**) ≈ vinyl ester (**4VE**) > methacrylate (**4MA**) as indicated

by t_{max} (Figure 2, left). Values for DBC decrease in the same order, giving conversions up to 75% for the new monomers. DBC in that range is a typical value for highly crosslinked photopolymers due to limited diffusion at higher conversions.

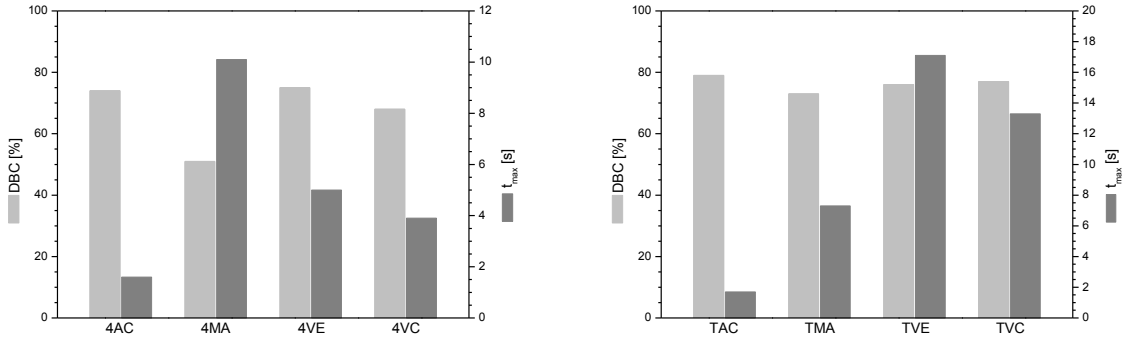
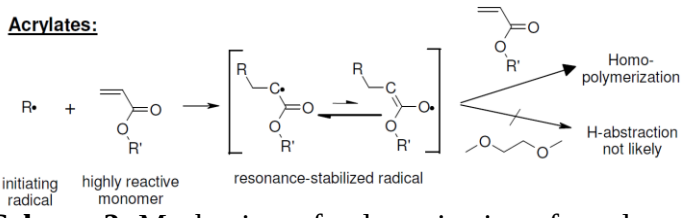


Figure 2: Double bond conversion and time to reach the maximum polymerization heat flux (t_{max})

In contrast to the results obtained for low molecular weight counterparts, the photoreactivity of the tetraethylene glycol-based monomers decreased in the order of acrylate (**TAC**) > methacrylate (**TMA**) > vinyl carbonate (**TVC**) ≈ vinyl ester (**TVE**) (Figure 2, right). Significantly lower reactivity compared to (meth)acrylates might be explained by well-known chain transfer reactions of vinyl ester based monomers, which are favored in the presence of hydrogen abstractable domains like ethylene glycols.

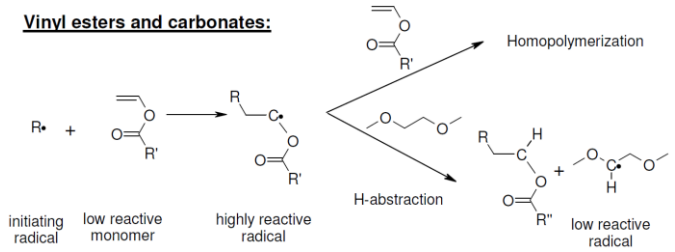
4. Improved photoreactivity of thiol-ene formulation

The general differences in reactivity might be explained by the way the different kinds of monomers react with radicals. Acrylates are highly reactive monomers as the formed radical is well resonance stabilized. Due to the resonance stabilization of the formed radical side reactions such as hydrogen abstraction reactions are not likely. Nevertheless, because of the high reactivity of the acrylate monomer homopolymerization occurs to a great extent (Scheme 3).



Scheme 3: Mechanism of polymerization of acrylates

If one looks at vinyl esters or carbonates the picture is completely different. Vinyl ester or carbonate monomers are of relatively low reactivity as the formed radicals lack resonance stabilization (Scheme 4).[20,21] Conversely, the low resonance stabilization can also explain the high reactivity of the formed vinyl ester or carbonate radicals. Therefore these radicals are rather prone to side reactions like H-abstractions as the monomer itself has low reactivity. If hydrogen abstraction occurs, *e.g.* from ethylene glycol units, radicals of low reactivity, denoting de facto termination of the reaction, are formed.



Scheme 4: Mechanism of polymerization of vinyl esters and vinyl carbonates

In order to circumvent these side reactions, trifunctional thiol **TMP700** (Figure 3) has been employed. Thiols contain easily abstractable hydrogens. The thiyl radical generated through this reaction is highly reactive towards different kinds of monomers leading to a thiol-ene polymerization. Thus propagation reactions exceed termination reactions. The effect of thiols on photoreactivity of vinyl esters and vinyl carbonates was tested by photo-DSC, too. The thiols were added in 0, 10, 20, and 40 mol% based on functional groups. Irgacure 2959 (2 wt%) was used as a photoinitiator. Formulations were stabilized with pyrogallol (0.1 wt%). Due to the mixed polymerization mode (thiol-ene vs. ene homopolymerization), the DBC and rate of polymerization cannot be determined from these experiments.

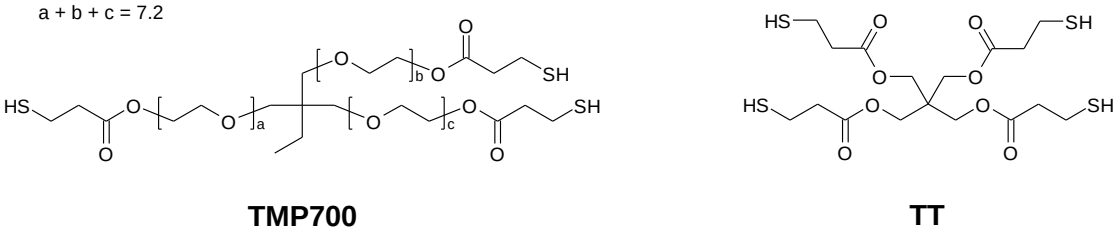


Figure 3: Structure of trithiol **TMP700** and tetrathiol **TT**

As follows from Figure 4 (left), for the short aliphatic acrylate **4AC** there is a slight decrease in the photoreactivity noticeable when adding trithiol **TMP700**. **TMP700** itself contains abstractable hydrogens, which slightly influence the thiol-ene polymerization that is based on hydrogen abstraction reactions, too. The reactivity of the **4MA** is significantly decreased. The most interesting result is that of the **4VE** and **4VC**. Even though there is not a high concentration of abstractable hydrogens present in this system, the reactivity is significantly increased. In fact, t_{max} is even shorter than that for acrylates. This is due to formation of a highly reactive radical, which is capable of increasing the reactivity due to presence additional chain transfer process caused by **TMP700**.

While for **TAC** there is hardly any difference noticeable, the loss in reactivity of the **TMA** is surprisingly high as seen in Figure 4 (right). Addition of **TMP700** to **TVE** boosts the photoreactivity by a factor of 3. In contrast to the result for the **4VE** with CH_2-spacers, t_{max} for **TVE** with longer spacers is not as low as that of acrylates, although still lower than that of methacrylates. Surprisingly, **TVC** is able to exceed the reactivity of pure acrylates with the help of **TMP700**.

Moreover, the addition of thiols helps to reach higher double bond conversion. In Figure 5, the conversion of **4VE** and mixtures with 40 and 100% of tetrathiol **TT** (based on functional groups) is followed by means of real time FTIR with formulations containing 0.1 wt% pyrogallol and 2 wt%

Irgacure 2959. Polymerization was monitored using the peak of the double bond (C=C bending peak at 1645 cm^{-1}).

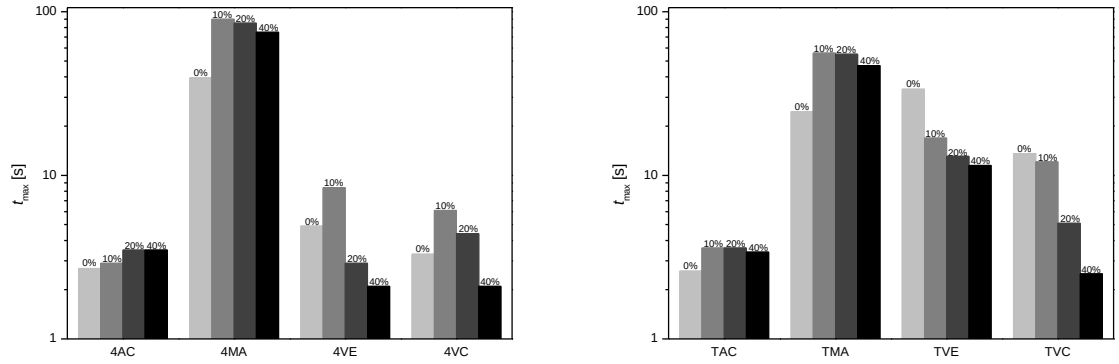


Figure 4: Time to reach the maximum polymerization heat flux (t_{max}) of formulations containing 0, 10, 20, and 40% of **TMP700**

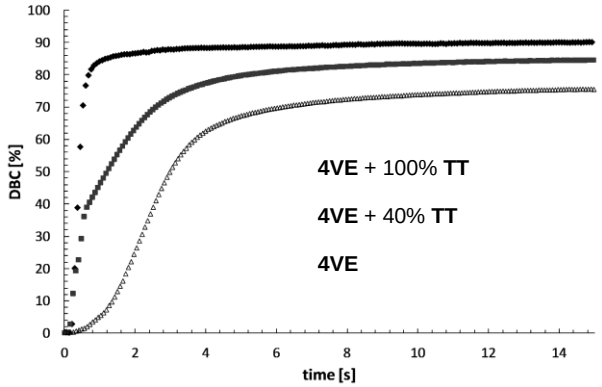


Figure 5: Real time FTIR curves of **4VE** containing 0, 40, and 100% of **TT**

As seen from real time FTIR curves, not only the reaction speed of the vinyl esters is increased, also the ultimate double bond conversion (DBC) is increased. While only 75% DBC is achieved for pure **4VE**, addition of increasing concentration of **TT** increases DBC to almost 90% for formulations with equal numbers of vinyl ester and thiol groups. This can be explained through sterical considerations. **4VE** itself is a rather small molecule, which makes it hard for every double bond to be reacted simply due to steric effects. Together with **TT**, **4VE** is undergoing preferably a step growth polymerization forming a network, in which a higher fraction of vinyl ester double bonds are able to be reacted. Similar result was observed with **TVE**. While curing of pure **TVE** gave 70% DBC after 60 s, **TVE** with equimolar amount (based on functional groups) of **TT** reached 93% DBC. The effect is less pronounced when vinyl carbonates are cured with thiols.

5. Storage stability

A very important aspect in the applicability of the new monomers is their storage stability. Sufficient stabilization of acrylates can be achieved by adding up to 1000 ppm of hydroquinone

monomethylether. Methacrylates are significantly less sensitive to thermal gelation. Thermal stability of the monomers has been assessed by a DSC experiment with a heating rate of 10 °C min^{-1}. While (meth)acrylates **4AC** and **4MA** showed an onset for the thermally induced polymerization already at ≈135°C, the new monomers were significantly more stable. Thermal polymerization of vinyl ester **4VE** was induced at 171 °C and vinyl carbonate **4VC** even at 182 °C. These results lead to the assumption that vinyl esters and vinyl carbonates can be expected to exhibit a longer storage stability than (meth)acrylate references without the use of any inhibitor.

6. Cytotoxicity

Manipulation with photoreactive resins presents a safety hazard for the workers. Also photopolymers are known to potentially release residual monomers thus presenting a health risk of the consumers. Here we present cytotoxicity data addressed by measuring cell viability of the calcaria derived MC3T3-E1 mouse cell line. In culture this cell line differentiates from proliferating preosteoblasts into mature osteoblasts forming a tissue like structure. The used assay determines the conversion of an uncolored tetrazolium salt into a formazan dye by the mitochondria of living cells and resembles. MC3T3-E1 cells were incubated at various concentrations of the monomers up to 10 mM and approximated the concentration LC_{50}, at which 50% of the cells survived after one week (Table 1).

Table 1: Cytotoxicity data of the monomers expressed by viability of MC3T3-E1 cells6

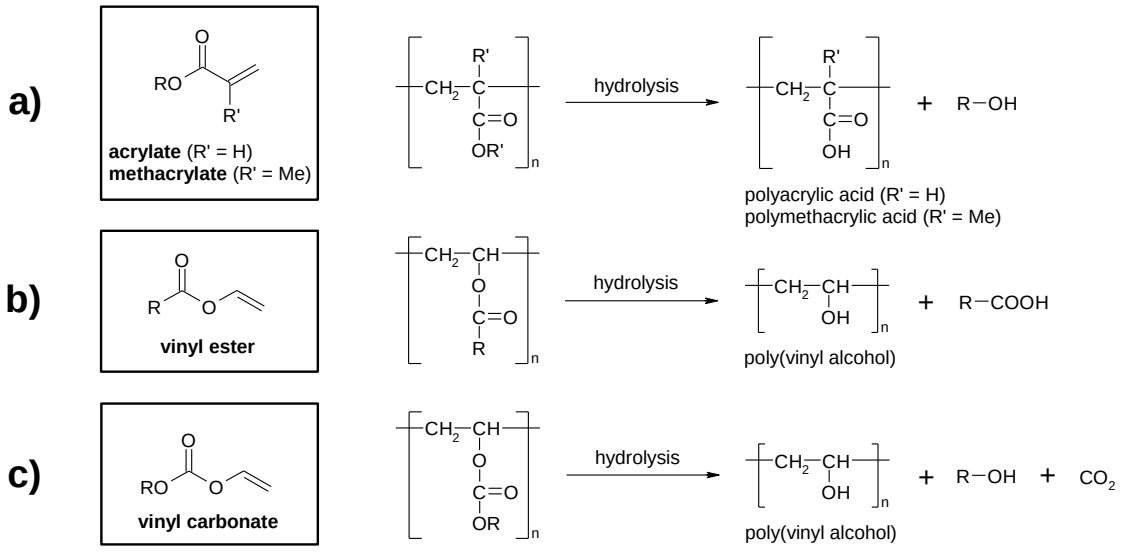
Monomer	Viability LC_{50} [mM]	Monomer	Viability LC_{50} [mM]
4AC	0.023	**TAC**	0.035
4MA	0.68	**TMA**	0.49
4VE	4.4	**TVE**	4.1
4VC	6.7	**TVC**	1.7

As seen from Table 1, most cells died after treatment with the methacrylates and especially with acrylates. Their toxicity is due to electron-withdrawing carbonyl group adjacent to vinyl group thus making (meth)acrylates prone to Michael addition of amino and thiol groups of proteins. Compared to the methacrylate **4MA** and especially to the acrylate **4AC** reference, vinyl ester **4VE** and vinyl carbonate **4VC** demonstrated significantly better tolerance as demonstrated by cell viability. Hydrophilic tetraethylene glycol-based series showed similar cytotoxic behavior.

7. Prospect in medical use

(Meth)acrylates are more than often the first option for photopolymerizable monomers used in tissue engineering. However, they are not fully biocompatible since they have some adverse effects on surrounding tissue, such as irritancy and sometimes cytotoxicity. It is impossible to avoid residual reactive groups and monomers that can migrate, while irritancy and toxicity result from Michael addition reactions of the double bonds with free amino and thiol groups in proteins. Moreover, degradation gives rise to high molecular poly(meth)acrylic acid (Scheme 5a) that leads to a local decrease in pH and might have an adverse effect on the surrounding tissue as this polymer cannot be easily transported within the human body. The cytotoxicity profile of vinyl esters, vinyl carbonates, and harmless degradation products of polymers thereof designate them as biopolymers for medical use.

Poly(vinyl ester)s and poly(vinyl carbonate)s hydrolytically degrade to FDA approved polyvinyl alcohol well-known from its use as a pharmaceutical additive and in medical implants (Scheme 5b,c).



Scheme 5: Hydrolysis of poly(meth)acrylates, poly(vinyl ester)s, and poly(vinyl carbonate)s

In the literature, these monomers are predominantly used in biomedical applications such as materials for soft contact lenses.[22] In pharmacy, they found application as drug carriers, which release the active substance upon hydrolysis.[23,24] 3D cellular structures made of vinyl esters and vinyl carbonates with good mechanical properties were printed by digital light processing and implanted in rabbit's femoral bone.[6,7] No inflammatory round cells and excellent osseointegration were shown after 4 and 12 weeks.

Conclusion

Radiation curable decorative and protective coatings are mainly based on (meth)acrylate-based monomers. While acrylates are generally preferred due to the higher reactivity, irritancy and sometimes cytotoxicity are some serious disadvantages. Due to environmental issues it could be expected that legislation will restrict the use of such monomers in consumer applications. Therefore, alternative polymerizable groups are of interest. Actual synthetic routes to vinyl esters/carbonates are expensive and only suitable for laboratory scale preparation, and therefore have been excluded from extensive industrial use. Nevertheless, two recent patents from BASF describes a high yield synthesis from cheap reagents applicable on an industrial scale, which may afford even cheaper monomers than (meth)-acrylates. Vinyl esters/carbonates have reactivities between those of acrylates and methacrylates, especially when polymerized at room temperature under UV-vis irradiation. Due to the highly reactive radicals and the comparable low reactivity of the monomers one has to keep in mind that for highly reactive formulations, monomers containing abstractable hydrogens such as PEG should be avoided. With cytotoxicity 1–3 orders of magnitude lower than (meth)acrylates, they are good candidates as alternatives for coatings if these will be subjected to regulations in the future. Furthermore, poly(vinyl ester)s and poly(vinyl carbonate)s form FDA approved poly(vinyl alcohol) as a degradation product that makes these materials suitable for biomedical applications.

Acknowledgement

The support by the European Commission in the framework of Marie Curie Intra-European Fellowships (IEF) through the project "VINDOBONA" (No. 297895) is gratefully acknowledged.

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