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# Biocompatible Phosphorus Containing Photopolymers

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## 1. Introduction

Radical photopolymerization is the key technique to prepare films and coatings in an environmentally friendly way within the fraction of a second. During the last decade this technique has found access to many other categories, as for example rapid prototyping, manufacturing of printed circuits boards, dental filling materials and other biomedical applications. Photopolymers display several advantages compared to classical thermally cured materials like polylactic acid (PLA). Their most important features are: easy processability and implantation; it is possible to perform the photopolymerization *in vivo* and *ex vivo*, which allows for minimal invasive surgery; preparation of complex shaped polymeric scaffolds; spatial and temporal control of the polymerization process; versatility of the formulations and good storage stability of the formulations under the most appropriate conditions until use.

Considering these many advantages, photopolymerized networks have found a broad application spectrum in drug delivery (Liat & Seliktar 2010; Censi et. al. 2009; Clapper et. al. 2007) tissue engineering (Schuster et. al. 2009; Ma et. al. 2010) cell encapsulation (Nuttelman et. al. 2008; Declerq et. al. 2008), biomimetic coatings (Naik et. al. 2003), contact lenses (Xu et. al. 2010), and dental restorative materials (Anseth et. al. 1996). In current biomedical research, great efforts are undertaken to obtain superior materials for tissue restoration, because the loss of tissue by an accident or disease as well as bone defects are crucial topics for our aging society. The human body as a complex and sensitive biological system provides a great challenge for the development of appropriate materials in the field of tissue engineering. Therefore, the requirements for such biocompatible materials are high: they must display proper mechanical strength, they should be degradable after cells initiate the re-growth of tissue and last but not least these materials, respectively their degradation products, must be safe concerning human health. This chapter will provide a general review on the photopolymerization technology, discuss some biomedical application fields, emphasize still open potentials or challenges and report some of the work that has been carried out so far to further develop this technology, for example the use of monomers based on phosphorus containing vinyl esters.

## 2. Radical photopolymerization

A simple photopolymerizable system consists of a monomer, a photoinitiator and a light source. To fulfil the targeted application, such a formulation can be amended with other

additives, e.g. other type of monomer, crosslinkers, bioactive molecules, drugs etc. Upon irradiation with UV or visible light, light-sensitive compounds, so-called photoinitiators, are able to decompose into free radical species, that can initiate polymerization in a monomer formulation to deliver crosslinked networks.

### 2.1 Photoinitiators

The key component of a photopolymerizable formulation is the photoinitiator. It should show a high absorption at a specific wavelength of light, thus generating the radical initiating species. For biomedical applications also the biocompatibility, the water solubility, stability and cytotoxicity of a photoinitiator should be considered (Fouassier 1995). There are three major classes of photoinitiators depending on the cleavage mechanism: radical formation can occur by photocleavage, hydrogen abstraction and cationic polymerization. Cationic photoinitiators are generally not applicable for tissue engineering due to the formation of protonic acids. A complete list of photoinitiators would be beyond the scope of this review, but it is worth mentioning at least a few of them: e.g. eosin Y (Desai et. al. 2010) 2,2-dimethoxy-2-phenyl acetophenone, (Nijst et. al. 2007; Niu & Bhatia 2002), Irgacure 2959 (Leach & Schmidt 2002), Irgacure 651 (Peng et. al. 2007), camphorquinone/ amine, where the amine is triethylamine, triethanolamine or ethyl 4-*N,N*-dimethylamino benzoate. They have been used as photoinitiators for tissue engineering, drug delivery and cell encapsulation.

### 2.2 Photopolymerizable materials

While photopolymerization with UV/Vis light works well for many applications, there are some difficulties for the use in tissue engineering. The main problem is, that most of the monomers are cytotoxic and one cannot rule out, that some residual (meth)acrylate groups remain unreacted in the cured polymer. To circumvent this problem, macro-monomers, or macromers are in use (Figure 1a and 1b). Monomers, that have been investigated extensively are (di)methacrylic or (di)acrylic derivatives of poly(ethylene glycol), PEG (Liu et. al. 2008; Polizzotti et. al. 2008; Lavanant et. al. 2010) poly(vinyl alcohol) and its derivatives (Martens et. al. 2003; Mawad et. al. 2006), ethylene glycol-lactic acid copolymers (Shah et. al. 2006), poly(anhydrides) (Shi et. al. 2010; Burkoth), urethanes (Werkmeister et. al. 2010), polysaccharides (Matsuda & Magoshi, 2002), like dextran (Liu & Chan-Park, 2010), collagen (Gonen-Wadmany et. al. 2007), hyaluronic acid (Baier et. al. 2003; Burdick, 2005), diethyl fumarate (Hou et. al 2009; Sharifi et. al. 2009) and many others. PEG has been used for long as biomaterial due to its high hydrophilicity, thus reducing the adsorption of proteins and allowing to alter the interaction of materials with tissues and cells. For the synthesis of methacrylate end-capped oligo esters like ethylene glycol lactic acid a PEG chain is used as initiator for the ring opening polymerization of D,L lactide, glycolide or  $\epsilon$ -caprolactone (Sawhney et. al. 1993; Davis et. al. 2003). Anhydrides such as carboxyphenoxy propane with methacrylic groups have been described as injectable materials for bone regeneration (Burkoth et. al. 2000)

Furthermore, photopolymerizable monomers are able to deliver partially degradable or non-degradable polymer networks. However, polyacrylates and polymethacrylates are unable to undergo full degradation due to the formation of a non-degradable hydrocarbon backbone. To control the degradation process, it is possible to add easily hydrolyzable chemical bonds to the monomer (e.g. esters, anhydrides, amides), or to decrease the molecular weight of the monomer, or to change the hydrophilic/hydrophobic nature of the

monomer. The molecular weight (MW) determines whether the network is loosely (high MW) or dense (low MW). In a dense network, degradation is slowed down as the cleavage of the bonds is hindered.

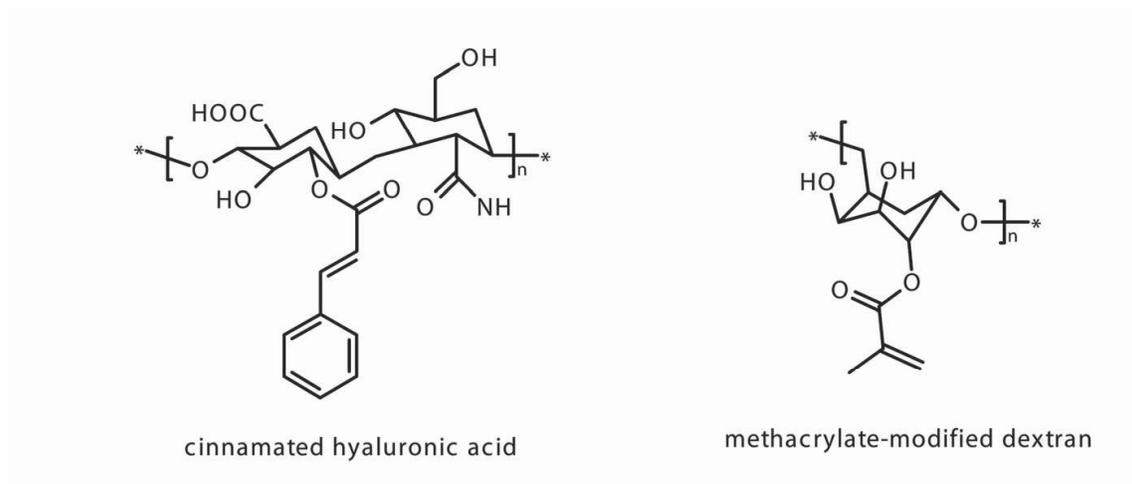


Fig. 1. a. Chemical structures of photopolymerizable glycomonomers for tissue engineering

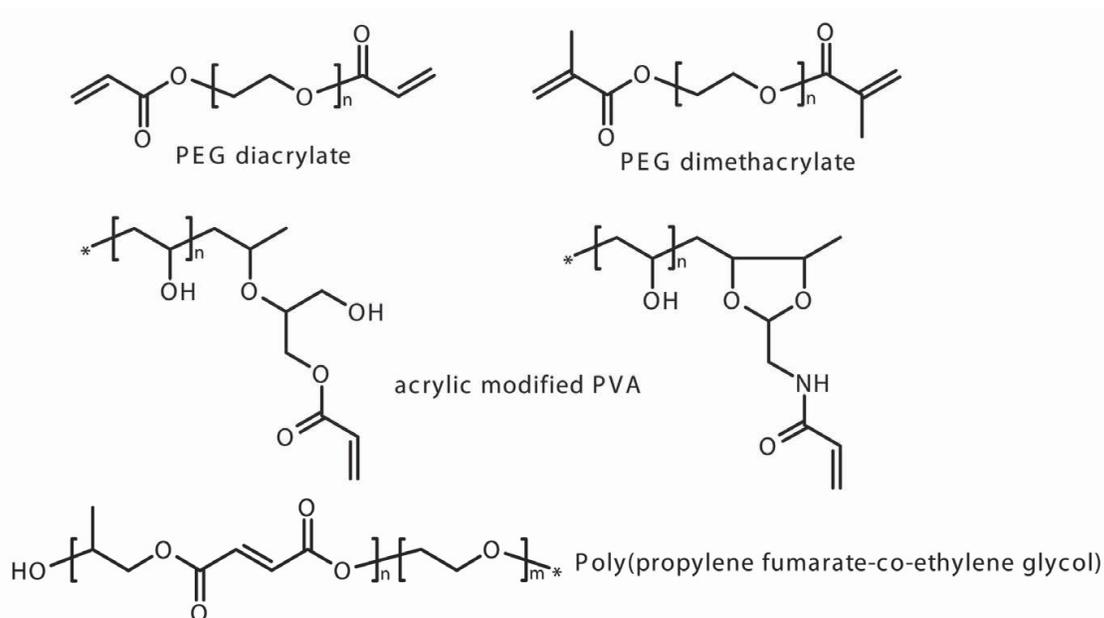
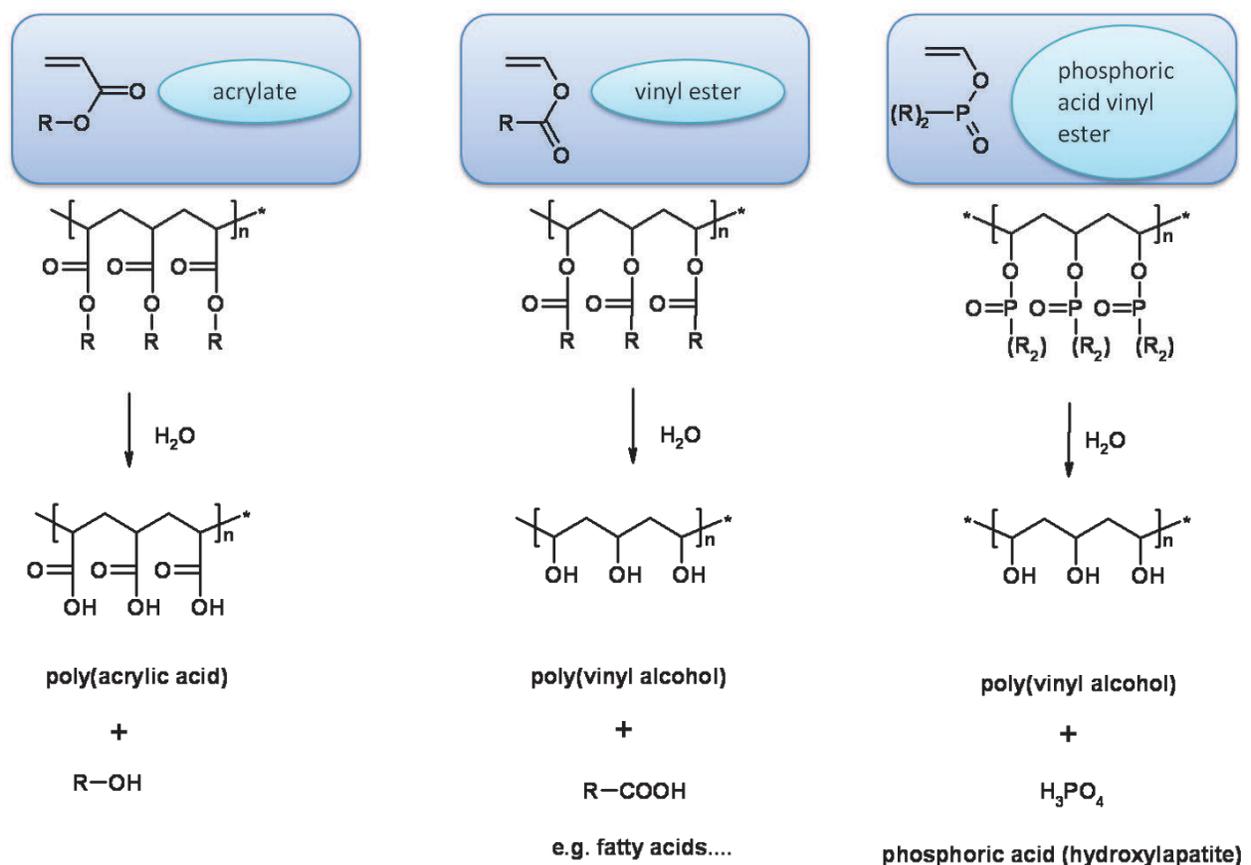


Fig. 1. b. Chemical structures of photopolymerizable monomers for tissue engineering

For example, Sawhney et. al. prepared photopolymerizable, bioerodible hydrogels based on PEG-co-poly( $\alpha$ -hydroxy acid) diacrylate macromers (Sawhney et. al. 1993). A more detailed overview is given by Ifkovits & Burdick (2007). Such materials are suitable as injectable biomaterials, although certain challenges must be met. As already stated before, unreacted monomer can significantly influence the mechanical properties as well as the biocompatibility and should therefore be avoided. However, full double bond conversion is almost never achieved due to limited mobility of the polymerizing molecules. Another

restricting condition is the exothermic reaction of the radical polymerization, resulting in an elevated temperature in vivo. Nevertheless, of some materials reports of successful curing in vivo without severe damage on the surrounding tissue have been obtained (Hill-West, 1994). Another major issue of tissue engineering apart from curing in vivo is the delivery of living cells to the injured tissue. Therefore, water-soluble macromers, which give highly hydrated polymers upon curing, are used for the photoencapsulation of living cells (Burkoth et. al. 2000).

In comparison to thermoplastics, photocured polymers display several outstanding advantages, especially easy processing and tailor made mechanical properties due to the formation of crosslinked networks. However, there are also some disadvantages to be accepted. For example, the toxicity and skin irritancy of (meth)acrylate based monomers limit their application in biomedicine. The reason for such drawbacks can be found within the high reactivity of the acrylate double bond towards Michael Addition reaction with amino or thiol groups of biologic molecules like proteins or DNA. Monomers based on diethyl fumarate (Figure 1b) display less toxicity, but also less photoreactivity. Another approach is the use of thiol-ene chemistry (Rydholm 2008), which offers the possibility to tune the mechanical properties of photopolymerizable formulations, in order to control the cell-material interactions. To obtain lower molecular weight fragments also radical ring opening polymerization can be applied, which leads to the formation of ester groups in the polymer backbone (Hiraguri et. al. 2006).



Scheme 1. Degradation of polymers

In summary, there exists only a limited number of reactive groups, that are applicable as biocompatible photopolymers. Therefore, the focus of photopolymers for biomedical research switches to alternative polymerizable groups. It is well known, that vinyl acetate delivers an easily cured polymer with low cytotoxicity, that finds wide-spread use in food industry. However, there are only few vinyl ester monomers commercially available and most of them are monovinyl esters. Recently, Heller et al (2009) synthesized a large number of vinyl esters to study their hence unknown photoreactivity, mechanical properties and their behaviour towards biological systems. In a further step it seemed of interest to prepare a series of monomers based on phosphorus containing vinyl esters (Dworak et. al; 2010), as many of the most important biochemicals, including DNA and RNA, are organophosphates. Another major drawback of crosslinked acrylates is their main degradation product: polyacrylic acid. It is stable towards biodegradation and its transport within the human body is quite difficult. The local decrease of the pH by the presence of the polyacid might also provoke adverse effects on cells. As a remedy poly(vinyl esters) can form non-toxic poly(vinyl alcohol) as degradation product, which is widely applied in drug, food and cosmetic industry (Scheme 1).

### 3. Biocompatible phosphorus containing photopolymers

Basically, vinyl esters of phosphoric acid, which resemble the monomer type II (Figure 1) own a broad application spectrum as insecticides (Zhang & Casida, 2000) and pharmaceutical industry (Kumpulainen et. al., 2005), but they are also able to undergo radical photopolymerization. Acrylate and methacrylate based phosphoesters are mainly in use as flame-retardant materials. Unfortunately, scaffolds made of poly(meth)acrylates might result in polyacid degradation products, which are rather stable towards biodegradation and furthermore cannot be transported easily within the human body as already discussed in the previous chapter. In contrast to that, monovinyl and divinyl esters of phosphoric acid provide linear, respectively crosslinked polymers, that can undergo hydrolyzation (Hayashi, 1978). Thus, from such polymer types it can be expected, that they form non-toxic polyvinyl alcohol based degradation products and phosphates.

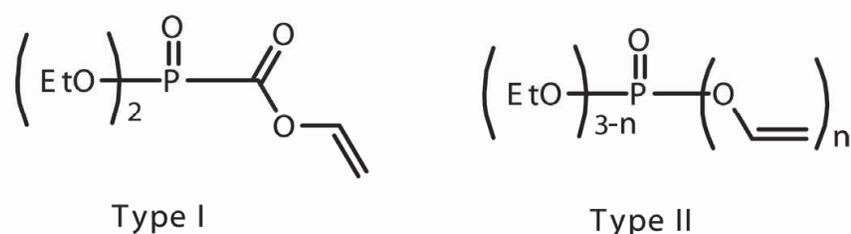
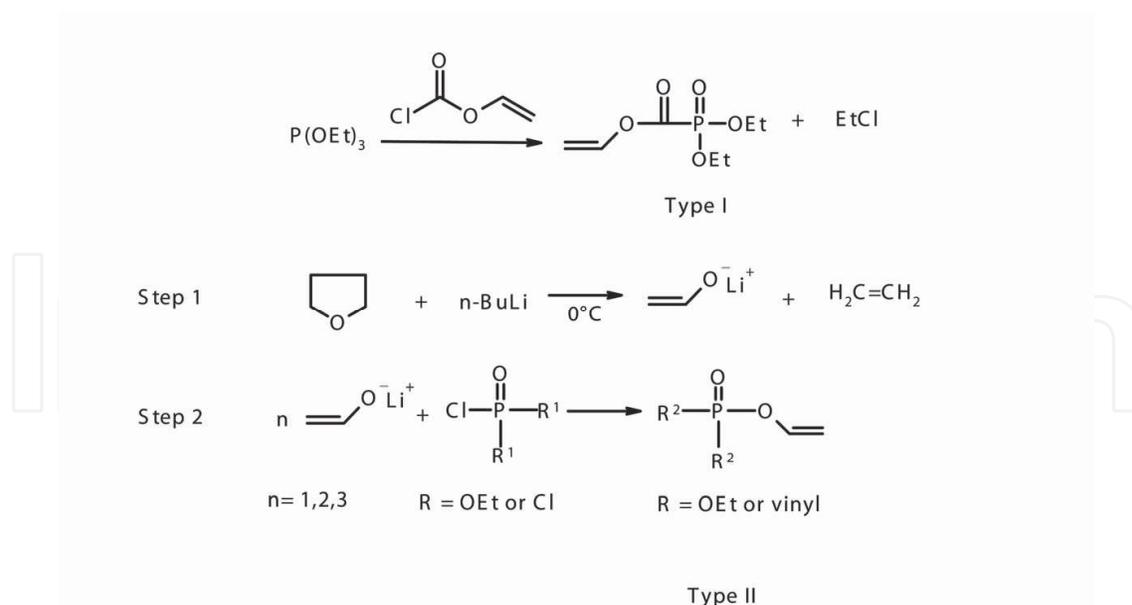


Fig. 2. Monomers based on phosphorus containing vinyl esters

Synthesis of such phosphorus-based vinyl esters is simple and straight forward. For type I a Michaelis-Arbuzov reaction can be applied, starting from triethyl phosphate and chlorovinyl formate. The second type of vinyl esters of phosphoric acid is prepared in a two-step synthesis. First the lithium enolate of vinyl alcohol is prepared by the cycloreversion reaction of THF with n-butyl lithium at room temperature (Bates et. al., 1972). The enolate is then converted with a mono-, di- or trichloride of phosphoric acid to the corresponding vinyl ester of phosphoric acid.



Scheme 2. Synthesis of vinyl esters Type I and Type II

Suitable reference compounds are classical acrylates and methacrylates; poly ( $\epsilon$ -caprolactone), PCL, and PLA as representatives for biocompatible thermoplastics.

### 3.1 Photoreactivity

One of the most important requirement for such new monomers is their photoreactivity. By photo-differential scanning calorimetry (DSC) experiments it is possible to determine the performance of a formulation. The reactivity can be derived from the time, which is needed to reach the maximum polymerization heat ( $t_{\max}$ , s). The double bond conversion (DBC) and the maximum rate of polymerization ( $R_{P_{\max}}$ , mol L<sup>-1</sup> s<sup>-1</sup>) give additional information on the performance of a photo-curable system.  $R_{P_{\max}}$  is calculated from the height of the maximum ( $h$ , mW mg<sup>-1</sup>), and the density of the monomers ( $\rho$ , g L<sup>-1</sup>) using equation 1.

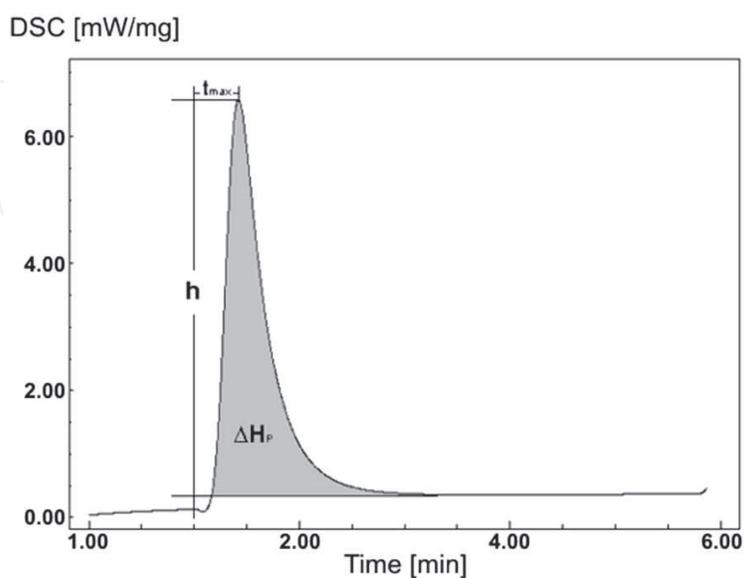


Fig. 3. Example for a photo-DSC plot and the parameters, that can be obtained

$$R_{P_{\max}} = \frac{h \times \rho}{\Delta H_{0,P}} \quad (1)$$

To obtain knowledge on the photoreactivity of a monomer it is also essential to know the theoretical polymerisation heat ( $\Delta H_{0,P}$ , J mol<sup>-1</sup>). A well established method (Hoyle et. al., 1999) to determine this value is to cure monomer formulations by photo-DSC. Thus the actual heat of polymerization ( $H_P$ , J g<sup>-1</sup>) evolved under this conditions is determined. In combination with the DBC obtained from ATR-IR analysis of the sample after curing by photo-DSC it is possible to calculate the theoretical polymerization heat using equation 2, where  $M_M$  (g mol<sup>-1</sup>) is the molecular weight of the monomer.

$$\Delta H_{0,P} = \frac{H_P \times M_M}{DBC} \quad (2)$$

For evaluation of the monomer reactivity and in terms of calculating their  $\Delta H_{0,P}$  peak fitting can be used (PeakFit V4.12, SSI) to determine the DBC of the polymers. This method has already been established by Lemon et. al. (2007) for the investigation of hydrogen bonding in methacrylate-based monomers and polymers. In case of vinyl esters the decrease of the C=C stretching vibration at 1640 cm<sup>-1</sup> in the monomer and the polymer spectrum, for (meth)acrylates the vibration at 1660 cm<sup>-1</sup> is applicable. The P=O vibration at 1265 cm<sup>-1</sup> served as reference for the phosphorus-based compounds, whereas for acrylates, methacrylates and common vinyl esters the C=O bond at 1740 cm<sup>-1</sup> is suitable for this purpose.

The DBC of the phosphorus-containing vinyl monomers, obtained by peak fit analysis of the ATR-IR spectra, is rather high (~90%) - as expected. Also  $t_{\max}$ , the time to reach the maximum polymerization rate, was in the range of the reference methacrylates. Generally, vinyl esters showed higher values for the  $\Delta H_{0,P}$  than the reference acrylates and methacrylates, which is also in good accordance with experiments already stated in literature (Roper et. al. 2006).

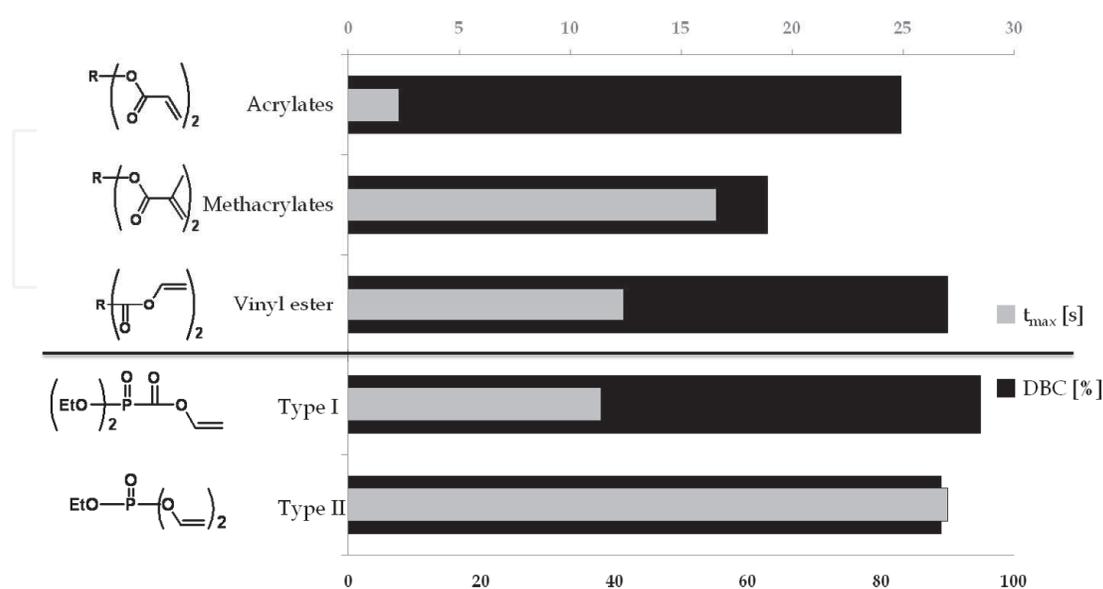


Fig. 4. Photo-Differential Scanning Calorimetry data for the phosphoronomers, Type I and II, as well as for reference acrylates and methacrylates

### 3.2 Cytotoxicity

Generally, photopolymers are well known to release several components into the environment after curing. These compounds might be residual monomer, molecules derived from the photoinitiator or similar products of degradation processes. With respect to their application in medicine and tissue regeneration, it is absolutely necessary to evaluate the influence of such compounds on cell proliferation and differentiation. Cell viability and multiplication as well as alkaline phosphatase (ALP) activity of osteoblasts are sensitive indicators of any substance for their compatibility with the biological tasks of the cells. Especially the ALP-activity is an important indicator whether osteoblasts proceed in their cell differentiation process or are blocked by a reagent. To compare the toxicity of the monomers, MC3T3-E1 cells were incubated with increasing amounts of the monomers. Then the concentration was approximated at which half of the cells survived. This concentration was denominated as LC<sub>50</sub>. Although, some differences between cell viability and cell number were found, both parameters were comparable for all investigated monomers (Table 1). In this match vinyl esters with/without phosphorus moieties had the least influence on cell multiplication. Compared to methacrylates, which are already in use as biomaterials (e.g. poly(methyl methacrylate) as component in dental filling formulations), ALP activity was significantly better for the vinyl ester-based monomers. It could be demonstrated, that some of the vinyl ester compounds even stimulated the cell differentiation process, visible by an increase of ALP activity over 100% compared to the control group. Short chain fatty acids differentially regulate proliferation and differentiation of cultured cells. Most studies are based on butyrate and the tumor drug valproate (Oki & Issa, 2006). Both regulate proliferation and differentiation by inhibiting histone deacetylase activity, which is an important regulator of gene expression and cell differentiation. It might be speculated, that the increase of ALP activity of the vinyl esters is the result of a similar mechanism.

	phospho vinyl esters	vinyl esters	methacrylates
Viability [LC <sub>50</sub> ]	3-12 mM	3-10 mM	1-3 mM
Cell number [LC <sub>50</sub> ]	5-16 mM	2-10 mM	0.8-2 mM
ALP-activity [% of control group]	60-123	40-135	6

Table 1. Influence of the monomers on cell multiplication, viability and ALP activity of osteoblast-like cells

### 3.3 Mechanical testing

Mechanical properties of a material can be easily screened by the nanoindentation method. It allows a very fast and material-saving comparison of some basic mechanical properties of the investigated polymers. From the recorded load versus displacement data the indentation modulus (YM<sub>IT</sub>) and indentation hardness (H<sub>IT</sub>) can be extracted (Schiffmann, 2007; Oliver & Pharr, 2007). H<sub>IT</sub> is calculated starting from the maximum force F<sub>max</sub> by applying equations 3 and 4:

$$H_{IT} = \frac{F_{max}}{24.5 \times h_c^2} \quad (3)$$

$$h_c = h_{max} - \varepsilon(h_{max} - h_r) \tag{4}$$

where  $F_{max}$  is the maximum force,  $h_{max}$  is the penetration depth at maximum force,  $h_r$  is the intersection of the tangent of the unloading curve at maximum load with the x-axis, and  $\varepsilon$  is the indenter constant.

$YM_{IT}$  is calculated starting from the slope of the unloading curve's tangent at the maximum load as shown in equations 5 and 6.

$$YM_{IT} = \frac{1 - (\nu_s)^2}{\frac{1}{YM_r} - \frac{1 - (\nu_s)^2}{YM_i}} \tag{5}$$

$$YM_r = \frac{\sqrt{\pi} \times s}{2 \times \sqrt{A_p}} \tag{6}$$

With  $\nu_s$  being the Poisson's ratio of the indenter tip,  $YM_r$  the reduced modulus of the indentation contact in [MPa],  $YM_i$  the modulus of the indenter tip in [MPa],  $S$  the contact strength in [N/m] (defined as the resistance of two particles against their mutual displacement) and  $A_p$  the projected area in [m<sup>2</sup>].

As shown in Figure 5, the mechanical properties of all investigated photopolymers materials superseded the reference material PCL which is used as biodegradable polymer for various biomedical applications, e.g. bone replacement or tissue engineering. Astonishingly, the highly crosslinked Type II polymer with  $n=3$  exhibited even better mechanical properties than the semicrystalline reference PLA which finds also wide-spread use as biodegradable material. Moreover, the IM of this polymer already approached that of human bone (Lewis & Nyman, 2008) and also an extraordinary high hardness was found for this compound.

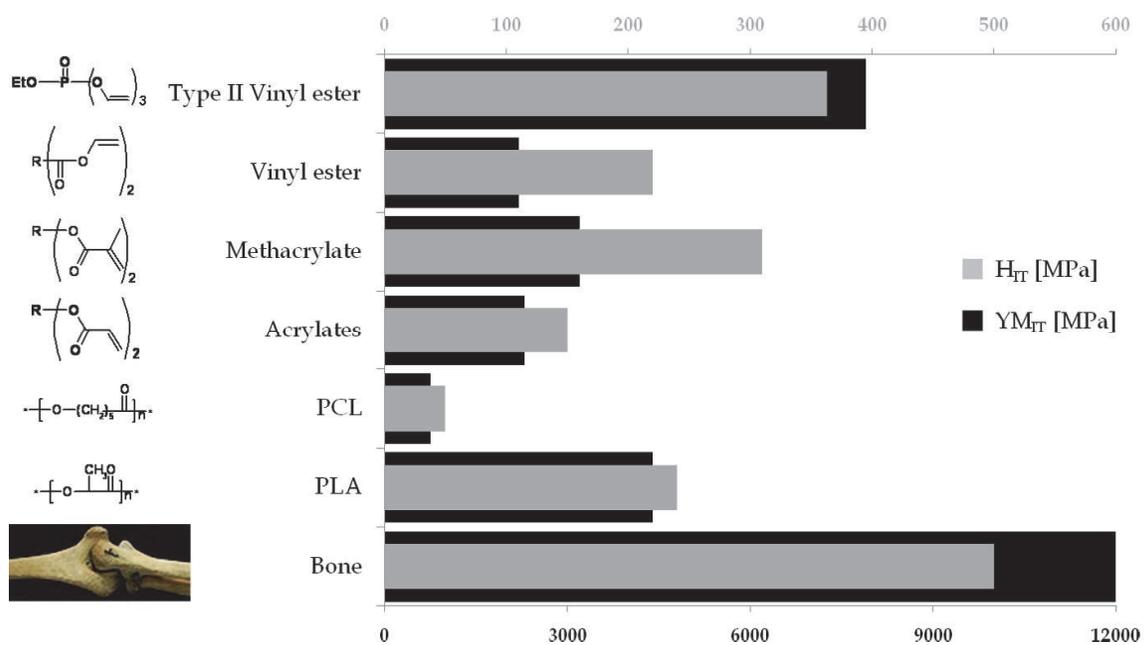


Fig. 5. Mechanical Properties of the phosphorus containing polymers determined by nanoindentation experiments

### 3.4 Degradation behaviour

Hydrolytic degradation of polymers is a desired feature especially for bone replacement materials. In the ideal case, the polymeric material will start degradation after the cultivation with bone cells and the initiation of bone re-growth. An important point is also the nature of the degradation products, which should of course be non-toxic towards the human body. From the degradation of polyphosphoesters it is known, that the breakdown of such polymers by hydrolytic or enzymatic cleavage delivers finally phosphates and alcohol derivatives (Wang et. al. 2001; Wachiralarpphaithoon et. al. 2007). Several other phosphorus based degradation products could be expected as it was shown in another study dealing with the hydrolytic degradation mechanisms of polyphosphoesters (Baran & Penczek 1995). However, it can be assumed in the case of the vinyl ester based phosphopolymers that during the surface erosion and/or degradation process non-toxic polyvinyl alcohol is released from such materials.

Recent studies (Heller et. al. 2011) have proven that degradation rates of cross-linked vinyl esters are significantly higher than for PLA, PCL or their acrylate counterparts under acidic conditions (Figure 6). This was confirmed in model experiments with low molecular polymer-analogous compounds. An explanation could be given by the less sterically hindered C=O group of polyvinyl esters compared to polyacrylates. Surprisingly, the polymers of Type II phosphoric acid vinyl esters showed almost similar degradation times under acidic and alkaline conditions, exceeding the other investigated materials at low pH values. This rather fast degradation under acidic hydrolysis might be favourable for its use as bone replacement material, as the bone-destroying cells, the osteoclasts also form an acidic milieu during the bone-resorption process.

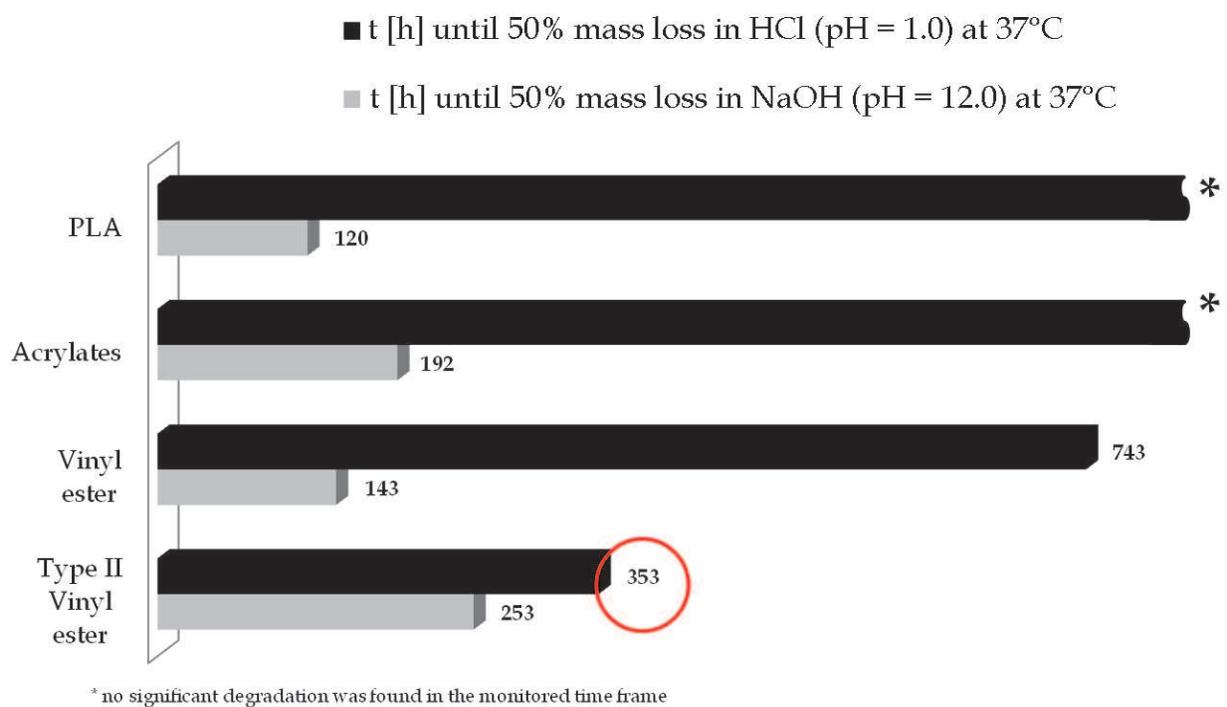


Fig. 6. Data for erosion behaviour of the phosphorus-containing photopolymers compared to PLA

#### 4. Conclusion

Biocompatible photopolymerizable polymers with a polyvinyl alcohol backbone are promising alternatives to common thermoplastic materials like PLA, as photopolymerization offers a wide range of processing technologies. Besides, vinyl esters show great advantages compared to acrylates and methacrylates, which are standard materials for soft tissue replacement. In contrast to non-toxic vinyl esters, scaffolds based on classical polyacrylates proved to be harmful because of their residual functional groups, that provoke adverse effects on the cells already adhered to the scaffolds surface by Michael addition to amino or thiol containing groups in proteins or DNA. To further improve biocompatibility of the monomers, polymers and degradation products, aiming at future applications in bone replacement surgery, a phosphorus moiety can be introduced onto these vinyl esters. The advantage of such polymers is clear: the products of hydrolytic degradation are phosphoric acid or phosphates and non-toxic polyvinyl alcohol, which finds widespread use as glue on stamps, as component of chewing gums and also as additive in medical drugs. By Photo-DSC experiments good photoreactivity was found for the phosphorus-containing monomers, comparable to common vinyl esters. With respect to their use as medical implants, the cytotoxicity, hydrolytic degradation and mechanical properties of the obtained polymers were tested. Cell viability and measurements on the development of alkaline phosphatase-activity revealed a low cytotoxicity. Surprisingly, some phosphorus containing vinyl esters exhibited even a stimulatory effect on the osteoblast cells' differentiation process. By nanoindentation measurements the hardness and elastic modulus of the polymers was determined. These showed mechanical stability almost in the range of human bone, actually without the addition of any filling material.

#### 5. Acknowledgment

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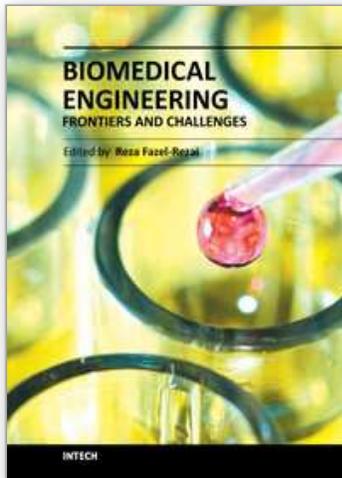
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In all different areas in biomedical engineering, the ultimate objectives in research and education are to improve the quality life, reduce the impact of disease on the everyday life of individuals, and provide an appropriate infrastructure to promote and enhance the interaction of biomedical engineering researchers. This book is prepared in two volumes to introduce recent advances in different areas of biomedical engineering such as biomaterials, cellular engineering, biomedical devices, nanotechnology, and biomechanics. It is hoped that both of the volumes will bring more awareness about the biomedical engineering field and help in completing or establishing new research areas in biomedical engineering.

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