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DEPARTMENT OF MATERIALS SCIENCE AND TECHNOLOGY

Photodegradable polyacetal-based cross-linkers and polymer hydrogels

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Abstract

Photodegradable polymers constitute an emerging class of materials that finds numerous applications in biotechnology, biomedicine, and nanoscience [1]. Photodegradable polymers in the form of hydrogels are of particular interest, because of their excellent adaptation in cell cultures allowing also the spatiotemporal control of their gelation behavior by an external stimulus such as light irradiation.

In this work, we have synthesized photodegradable cross-linkers based on a photodegradable acetal oligomer decorated with acrylate terminal groups. The photodegradable acrylate terminated oligomers were synthesized via a two-step process. In the first step, 1,4benzene dimethanol was reacted with an excess of cyclohexanol divinyl ether in mildly acidic conditions to obtain a photo-cleavable acetal oligomer with vinyl ether terminal groups. For the second step, hydroxyethyl acrylate was added in the reaction to convert the vinyl ether terminal groups of the oligomer into acrylate functionalities. The progress of the reaction was monitored by gel permeation chromatography and proton nuclear magnetic resonance spectroscopy.

The synthesis of the gel was achieved using radical polymerization. Poly (ethylene glycol) methyl ether methacrylate was reacted with the crosslinker under nitrogen at 70^{o}C with Azobisisobutyronitrile as initiator. The gel purified, and the swelling degree was calculated in both water and THF. To demonstrate the degradation and the release of substances, first, malachite green dye was encapsulated in the gel. Then, after the irradiation of the gel, the release of the dye in a solution was measured by UV/Vis spectroscopy.

1. Introduction

1.1. Polymers

Polymers are large molecules, composed of many repeated subunits called monomers. These monomers are covalently bounded and form chains. [2] Degree of polymerization (n) is defined as the number of repeated units or monomers in a polymer molecule. Molecular weight of polymer chains is calculated by multiplying its degree of polymerization with molecular weight of each monomer or repeated unit. Polymers may be natural, such as cellulose or DNA, or synthetic, such as nylon or polyethylene.

Categories of polymers

Based on different architecture:

- Linear polymers, which have the form of a long chain. (fig. 1a)
- Star-polymer, in which many polymer chains are connected to a central core (fig. 1c).
- Branched polymers, in which polymer chains are attached to a main backbone chain (fig. 1d).
- Polymer gels, in which polymer chains are linked together forming a network (fig. 1e).
- Ring polymers, which consist of a linear polymer that has its ends bounded together (fig. 1f).

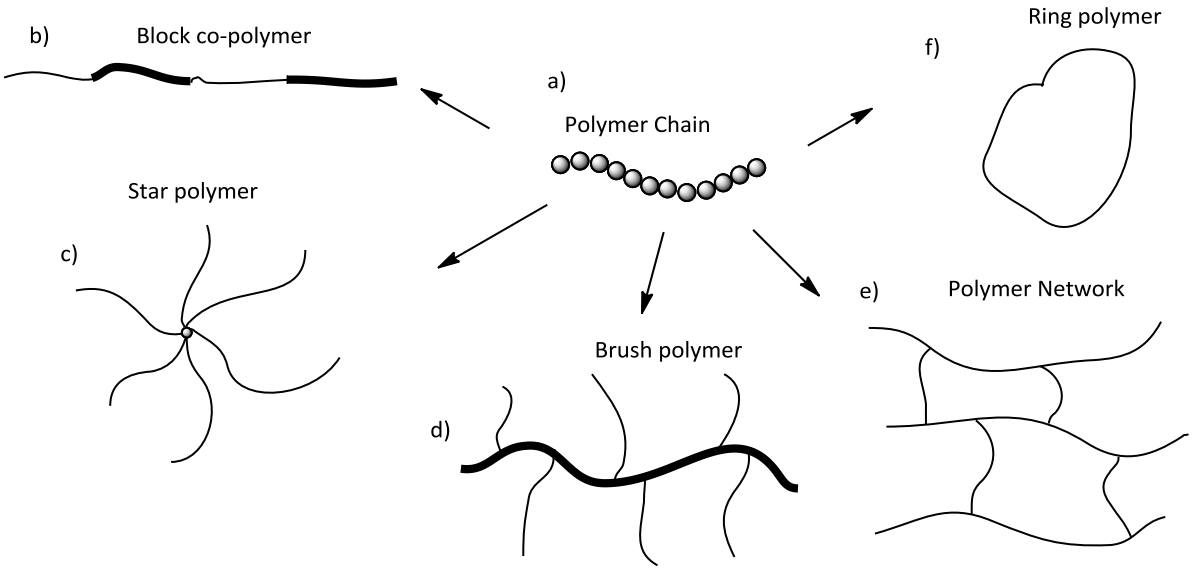

Figure 1: Different polymer architectures

Based on composition:

- Homo-polymers, which are composed by one kind of monomer.
- Copolymers, which consist of two or more different kind of monomers.

Copolymers can be categorized further, based on how monomers are arranged along the chain.

- Random copolymers, in which monomer A and monomer B are randomly arranged.
- Alternating copolymer, in which monomer A is always followed by monomer B.
- Block copolymers, in which two or more homopolymer subunits linked together.
- Graft copolymers, which is a special type of branched copolymer in which the side chains are structurally distinct from the main chain.

1.2. Polymer gels

Polymer gels consist of macromolecular polymer chains which are bound together, at both ends, either physically or chemically. By increasing concentration of polymer chains in a solution, a physical polymer network will be formed through the physical aggregation of the polymer chains, caused by hydrogen bonds or crystallization. This network of course is not stable and will dissolve by increasing the solvent concentration.

A chemical or covalent polymer network can be formed by crosslinking polymer chains. To achieve this we can use some molecules that are called crosslinkers. These crosslinkers are usually bifunctional molecules that can be covalent bound to polymer chains and create a polymer network.

The main characteristic of these three-dimensional networks is that they don't dissolve in solvents but can swell in them. Depending on the type of polymer and solvent, some gels can absorb multiple times their weight in solvent. To measure the ability of gel to swell, we have the swelling degree, which is the ratio of the swollen mass of the gel to the dry mass of polymer network.

$$Swelling\ Degree = \frac{Mass\ of\ Swollen\ Gel\ (Gel + Solvent\ absorbed)}{Mass\ of\ Dry\ Gel}$$

Due to their high absorbance of solvents, polymer gels, have found many applications, from diapers and incontinence garments, to security services, as fire-retardant gel [3], in agricultural sector as water retention for supplying water to plants [4] or soil moisture control [5], as protection against humidity for electronic devices and cables, or to filtration applications as gel filtration chromatography.

1.3. Hydrogels in Biotechnological Applications

Polymer networks in which the swelling agent is water are known as hydrogels. Hydrogels are highly absorbent, they can contain over 90% water. Due to their significant water content, hydrogels possess a degree of flexibility very similar to natural tissue and consider to be, a great mimic of the extracellular matrix.

Due to this, hydrogels have been extensively used for in 3D cell cultures for tissue engineering [6] and organ reconstruction [7]. Another, well know use of hydrogels is in the fabrication of contract lenses [8]. Hydrogels, also, are widely used as debriding agents, moist dressings, and components of pastes for wound care [9]. Finally, hydrogel recently have been studied as potential drug delivery systems [10] [11].

1.4. Photodegradable polymers

The degradable polymers are an emerged category that needs to be studied. Degradable polymers being developed for many of applications from biomedical materials, to sensors and actuators, to packaging and waste management, and photolithography.

The majority of degradable materials are designed in a way that the degradation could be triggered by an external stimulus, which is usually of (bio) chemical or physical nature such as temperature, pH, enzymes, but also ultrasound and light. [12]

1.5. Photodegradable polyacetal

Polyacetal is a polymer which has been extensively studied the past years, as a suitable platform for developing external stimuli responsive materials. This is mainly because, polyacetal have shown degradation both at acidic conditions and ultraviolet light irradiation. These conditions, however, are not suitable for an in vivo application.

In recent literature, we have seen studies suggesting, that by inserting a chromophore group into a polyacetal chain, we can change the photosensitivity of the polymer. This strategy, allows the fabrication of tunable polymers that exhibit degradation at both higher and less harmful wavelengths, but also complete degradation at very low energy doses [12].

1.6. Current Study

External stimuli-responsive degradable hydrogels for drug delivery applications and other biomedical uses, is a class of polymers that constantly develops. In recent works, we have seen cross-linkers cleavable under thermolysis or alkaline conditions hydrolysis [13]. These conditions, caused by high temperature (130 ^{o}C) or the addition of NaOH, are not suitable for an in vivo application. Light seems to be the most suitable for a drug delivery application. The method in which a drug is delivered have a significant effect on its efficiency. Using light, we can adjust precisely the intensity and the duration of the irradiation to control the degradation of a polymer matrix thus the release of the drug [14].
The aim of this is project is to provide a facile and simple procedure to synthesize a polymer hydrogel with a photodegradable cross-linker that could be use in such applications. Polyacetal, is a simple polymer to synthesize, which can be easily cleaved by UV irradiation [15]. Followed proposed synthesis [13], we can synthesize a crosslinker that decomposes under irradiation of light around of 250nm, and the producing products are not cytotoxic (Fig. 2).

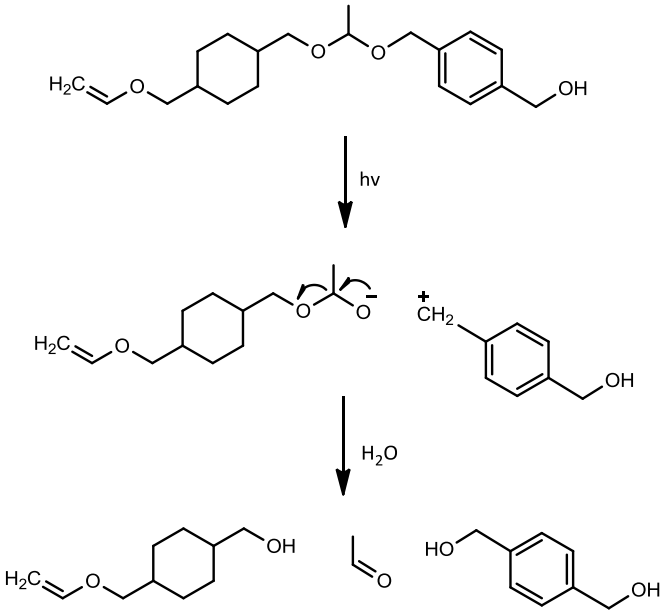

Figure 2: Photodegradation Mechanism

However, the longer wavelengths cause less damage to the healthy cells, so the need of a crosslinker that can be cleaved by irradiation from a cytocompatible light source is urgent. An acetal oligomer with a nitrobenzene moiety, which absorbs up to 400nm, seems to be a suitable candidate for this purpose.

The terminal groups of this acetal oligomer were convert into acrylate groups, so it could form a polymer network via radical polymerization with the addition of poly (ethylene glycol) methyl ether methacrylate.

In order to show the substance release, dye molecules were encapsulate in the hydrogel. Then, by irradiating the hydrogel, we measure the increasing concentration of the dye in the supernatant via uv/vis spectroscopy.

Our novel photo-cleavable cross-linker is a potentially versatile and convenient material used for the development of photodegradable hydrogels for biomedical applications. Their degradation upon visible light irradiation at very low dosages is envisaged [12].

This work, also, includes a study of hydrogels that synthesized with a crosslinker which didn't contain a nitro group but had similar structure to the one mentioned. This crosslinker was photo-degradable at lower, non cytocompatible, wavelengths, but the aim of this study was to optimize the synthesis procedure of the crosslinker, as well as, to investigate how the ratio of crosslinker to monomers affects the swelling degree of the hydrogels.

2. Experimental

2.1. Materials

The materials used in this project are listed below:

- **Solvents:** Tetrahydrofuran (THF), Nano pure Water(H_2O), Hexane
- **Initiator:** Azobisisobutyronitrile (AIBN)
- **Catalyst:** Pyridinium p-toluenesulfonate (PPTS)
- **Monomers:**
  - **a.** 2Nitroresorcinol, 2Nitrobenzene dimethanol, 1,4Benzene dimethanol
  - **b.** 1,4Cyclohexane dimethanol divinyl ether
  - **c.** Hydroxyethyl acrylate (HEA)
  - **d.** Poly(ethylene glycol) methyl ether methacrylate (PEGMA)
- **Dye:** Malachite Green
- **Other reagents:**
  - **a.** THF-Borane complex
  - **b.** 2-Nitroterephthalic Acid
  - **c.** Nitrogen Gas
  - **d.** Petroleum Ether
  - **e.** Ethyl Acetate
  - **f.** Deuterated Chloroform
  - **g.** Triethylamine

2.2. Synthesis of cross-linkers and hydrogels

In the first part of the project, photodegradable cross-linkers were synthesized and characterized, while in the second part, we synthesized a hydrogel, using those cross-linkers, and we studied the photodegradation of the cross-linkers.

2.2.1. Cross-linker synthesis

- Synthesis of the crosslinker without the nitro group

The photodegradable acrylate terminated oligomers were synthesized via a simple two-step polycondensation reaction. Initially, we used 1,4benzene dimethanol as our monomer to synthesize

the crosslinker. This molecule doesn't absorb in the desired area of 400nm, but in lower wavelengths around 250nm. The point of this work, was to optimize the crosslinker, and later the hydrogel, synthesis recipe, with a low cost and available commercially monomer.

In the first step, 1,4benzene dimethanol (diol) (0.5 g) was added in tetrahydrofuran (THF) solution (3.6ml 1M) in a 20ml vial with a stir bar. Subsequently, 1,4cyclohexane dimethanol divinyl ether (0.92ml) was added in excess 20%mol to diol. The excess of the divinyl ether provided, that we will obtain an oligomer with low molecular weight, since the reaction will not propagate after the "consumption" of all the diol monomers. Catalyst PPTS (0.009 g 1%mol to dimethanol) was added to create mildly acidic conditions for the reaction of diols and vinyl ether groups (fig. 3). The solution was left under stirring for 2 hours.

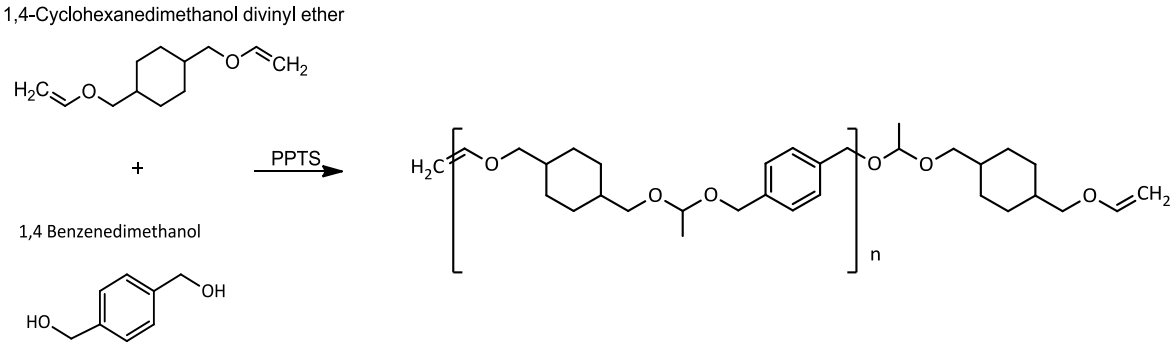

Figure 3: First step of the cross-linker synthesis

In the second step, hydroxyethyl acrylate (HEA) (0.52ml 1:1 ratio to divinyl ether) and another 1% PPTS (0.005g) were added to convert the vinyl ether terminal groups of the acetal oligomer, into acrylate terminal groups (fig. 4). Subsequently, 2 hours after the addition of HEA, a few drops of Triethylamine (TEA) were added to the solution. TEA used as an acid neutralizer to prevent degradation due to the present mildly acid conditions. Then, a few minutes after the addition of TEA, the solution was poured in a cold petroleum ether (PE) solution for precipitation. The solution was placed in the freezer overnight to achieve better precipitation. The next day, unreacted monomers and catalyst, which were dissolved in the supernatant, were removed with it. The precipitate, a turbid viscous liquid, was collected and placed under vacuum for 2 hours to remove residues of THF or PE. A clear and more viscous liquid was obtained. The crosslinker was placed in 22ml vial and stored in the refrigerator.

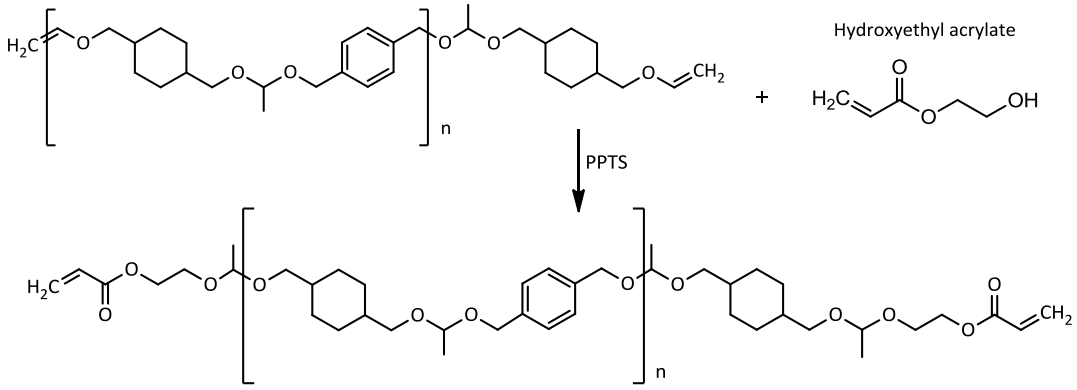

Figure 4: Second step of the cross-linker synthesis

- 2-Nitroresorcinol experiments

After the successful synthesis of the benzene dimethanol based crosslinker, we proceed to synthesize a crosslinker using 2nitroresorcinol as monomer.

However, and after several adjustments to the synthesis recipe, 2-Nitroresorcinol did not polymerize properly, probably due to steric effects. To overcome that setback we chose to use a slightly different monomer but with the same functionalities (fig. 5). That monomer, 2Nitrobenzene dimethanol wasn't commercially available at the time, so we had to synthesize it.

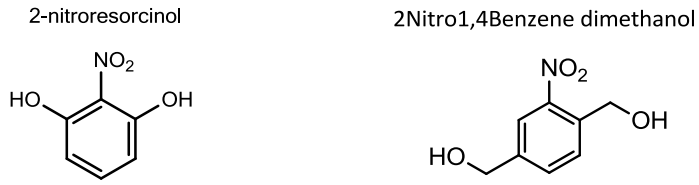

Figure 5: 2-Nitrorecorsinol and 2-Nitro 1,4 benzene dimethanol

- 2-Nitro 1,4 benzene dimethanol synthesis

To synthesize 2-Nitro 1,4 benzene dimethanol, the procedure of Piggott and Karuso [16] was followed (fig. 6). A solution of borane-THF complex in THF (1 M, 50 mL) was added dropwise, with vigorous stirring, to a solution of 2-nitroterephthalic acid (2.0 g) in THF (25 mL) at 0 °C under nitrogen. The solution was allowed to warm to room temperature over 1 h and was then stirred at 40 °C for 18 h. Excess borane was destroyed by dropwise addition of ice-cold water (50 mL) to the reaction mixture. The THF was removed in vacuum and the remaining aqueous solution was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate and reduced to dryness in vacuum, yielding a pale-yellow solid that was recrystallized from chloroform to give the pure diol as white feathery needles.

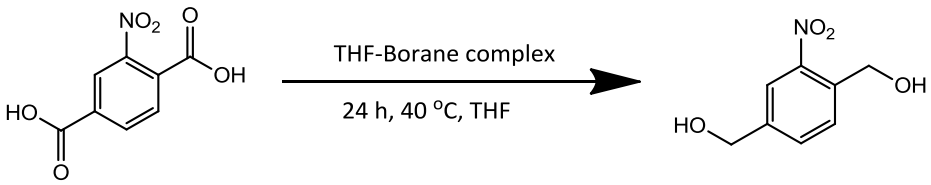

Figure 6: 2-Nitro 1,4 benzene dimethanol synthesis

- Synthesis of the o-nitrobenzene based cross-linker

We follow the successful synthesis procedure of the 1,4 benzene dimethanol based crosslinker, with a few minor changes to quantities, due to the different molecular mass of the 2 nitrobenzene dimethanol (fig.7-fig.8).

Also, we had cover the vial with aluminum sheet during reaction to prevent degradation, due to susceptibility of nitrobenzene at low, visible light, wavelengths.

The crosslinker was again a high viscous liquid but with a yellowish color. It was placed in a 22ml vial and stored in the refrigerator.

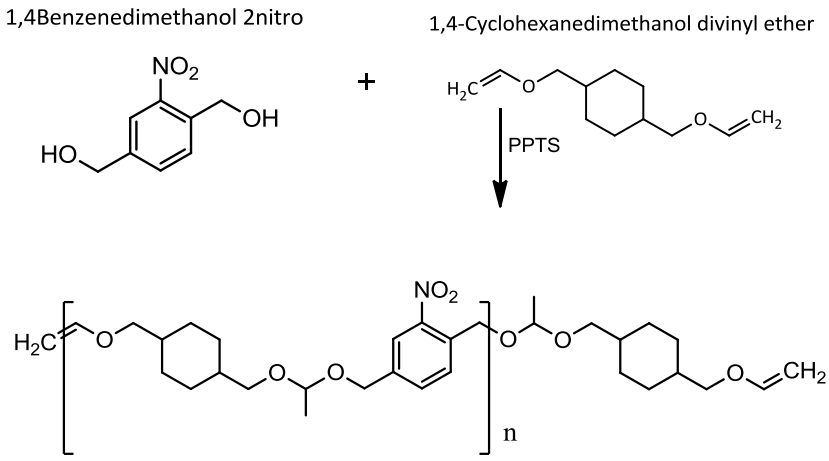

Figure 7: First step of the cross-linker synthesis

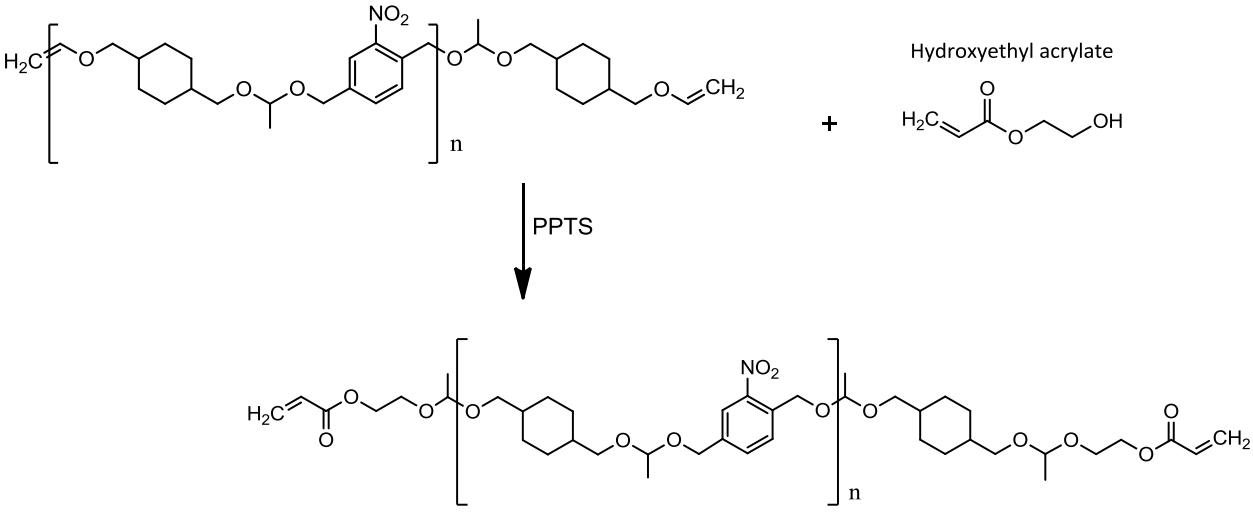

Figure 8: Second step of the cross-linker synthesis

2.2.2. Gel synthesis

- Hydrogel with nitrobenzene crosslinker.

The synthesis of the gel was achieved using radical polymerization. Poly (ethylene glycol) methyl ether methacrylate (PEGMA) (0.50g) placed in a 22ml vial with THF solution (2ml). Crosslinker in different concentration from 2% to 10%mol with respect to monomer and 1%ww initiator azobisisobutyronitrile (0,005g) were added to the solution. A stir bar was added and the vial sealed. Oxygen acts as inhibitor to radical polymerizations, so, nitrogen flow used to substitute the oxygen inside the vial. After 10 minutes of degasification, the vial was placed in a water bath at 65^{o}C under stirring. The temperature will cause the decomposition of the initiator, producing two free radicals, which will initiate the

polymerization. Gelation was observed around 40min, but the gel was left in water bath for at least another 2 hours in order to obtain fully polymerized hydrogel. Gelation time differs depending of the crosslinkers concentration.

2.3. Instruments

2.3.1. Gel Permeation Chromatography (GPC)

GPC is a type of size exclusion chromatography that separates analytes on the basis of size. GPC was used to determine the molecular weight of the acetal oligomers.

GPC operate based on columns with porous material, which columns have a range of molecular weights that can be separated. A pump keeps a solvent flow thought the instrument. Samples are dissolved in the same solvent, and using an injection, are introduced into the flow. As the solution flows through the column, small size molecules enter the porous and therefore spend more time in the column while large size molecules can't enter the porous and spend less time in the column. A detector at the end of the column monitors the exit of molecules.

2.3.2. Nuclear Magnetic Resonance (NMR)

^{1}H NMR spectroscopy was used in order to identify the chemical composition of synthesized cross-linker and whether the reaction was complete.

NMR is a physical phenomenon in which nuclei in a magnetic field absorb and re-emit electromagnetic radiation and allows the observation of specific quantum mechanical magnetic properties of the atomic nucleus. In this case we observe the absorbance and re-emit of the hydrogen nucleus.

2.3.3. Ultra Violet/Visible Spectroscopy (UV/Vis)

UV/Vis spectroscopy was used to measure the increasing dye concentration of a supernatant solution during a hydrogel photodegradation.

During the measure, electromagnetic radiation passes through the sample which is held in a cuvette. Radiation across the whole ultra violet-visible range is scanned, through the sample and a reference cuvette containing only solvent. The transmitted radiation is detected and the absorption is calculated by comparing the difference between the intensity of the radiation passing thought the sample and the reference.

3. Results

3.1. Cross-linker Characterization and Degradation

The synthesis of the crosslinkers was monitored by nuclear magnetic resonance (NMR) spectroscopy and gel permeation chromatography (GPC).

Samples were taken, from both of the crosslinkers, and dissolved in deuterated chloroform. Deuterated solvent was used because the deuterium does not exhibit a large interfering peak in the spectra of ^{1}H NMR.

For the GPC measurements, samples of the cross-linkers were dissolved in THF which was appropriate for high-performance liquid chromatography.

3.1.1 Benzene based crosslinker

GPC results (fig.9) shown that we managed to obtain a low molecular weight oligomer (Mn 1419). Also, we can calculate that the number of repeated units in our oligomer is 3 (fig. 10).

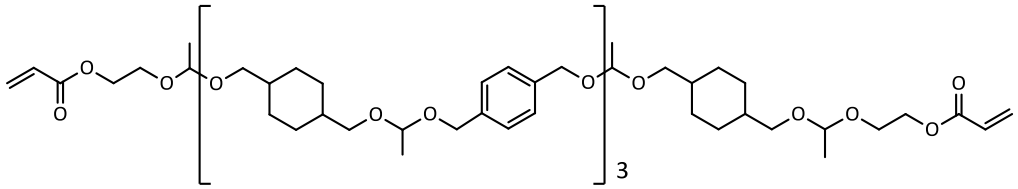

Figure 9: Chemical structure of the benzene based cross-linker

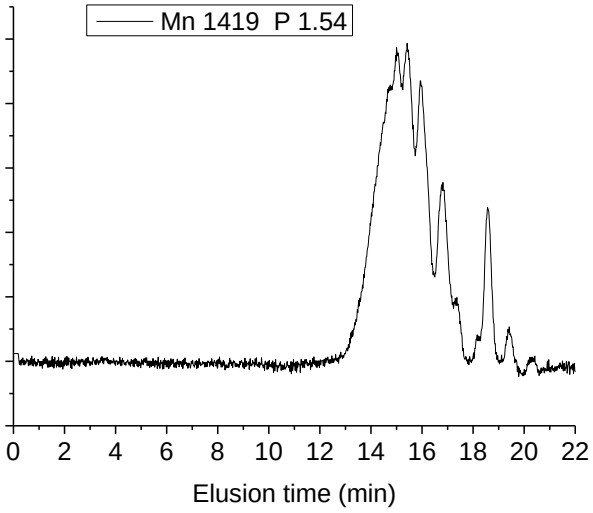

Figure 10: GPC result of benzene based cross-linker

The successful synthesis of the crosslinker was confirmed by NMR spectroscopy (fig.11). Each proton of the cross-linker structure corresponds to a characteristic peak, which was marked below. We know from literature, that the vinyl ether peaks appear around 4.10, so the absence of this peak suggest that all acetal oligomers have end capped with acrylate groups. Also, by calculating the integrals of the peaks we can again confirm the successful synthesis of the cross-linker. For example, the sum of protons of a and b, which correspond to the acrylate terminal group is 3. The sum of the protons of the benzene (m) is 4. Each oligomer though, has two acrylate groups, one at each end, which give us 2*3=6 protons and three benzenes, as we calculate from GPC results, which give us 3*4=12 protons. So the ratio is 6 to 12, which is the same ratio of the integral of the peaks a+b to peak m (3 to 6).

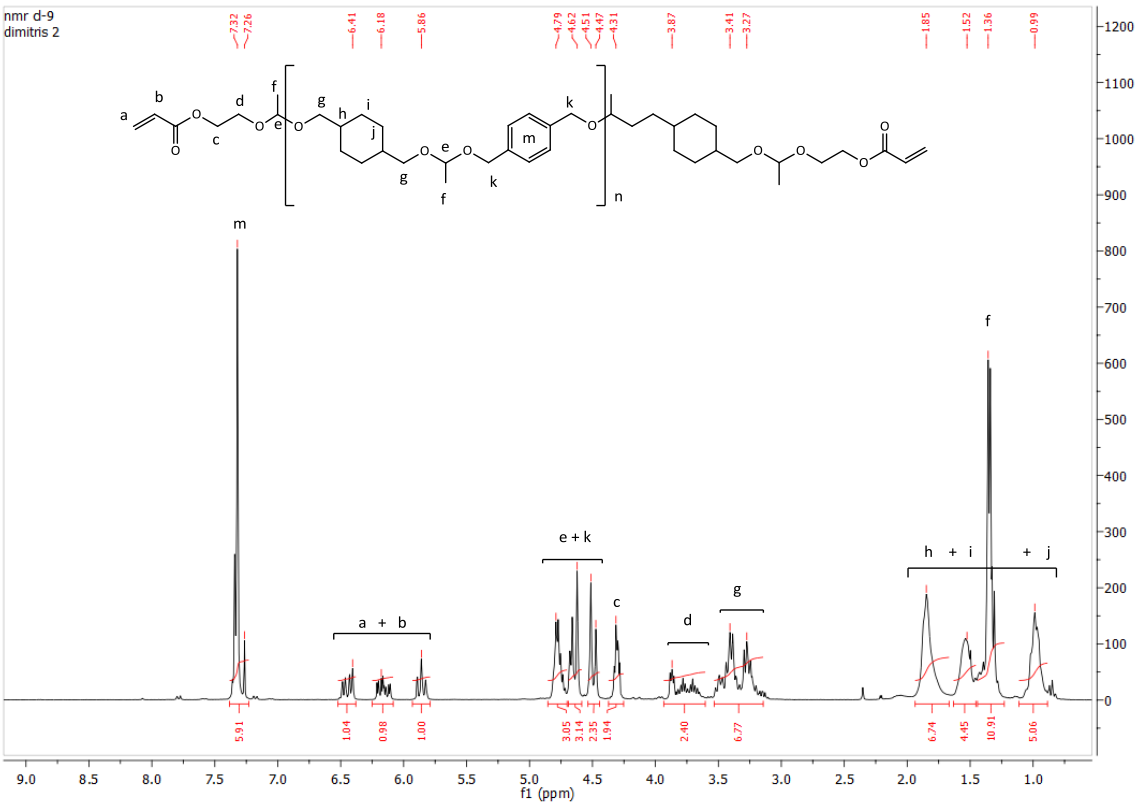

Figure 11: ^{1}H NMR spectrum of the benzene based cross-linker

To examine the photodegradation, a sample of the crosslinker was irradiated by UV light at 254 nm for 30 min. After the irradiation, again with NMR spectroscopy (fig. 12), we confirmed the degradation of the crosslinker. The shifted characteristic peaks that are marked (c, d, e, f), correspond to the protons that were close to the acetal bond that was cleaved. Finally, we have the appearance of two new peaks (a, b), which both correspond to acetaldehyde, the product that was expected after the photodegradation.

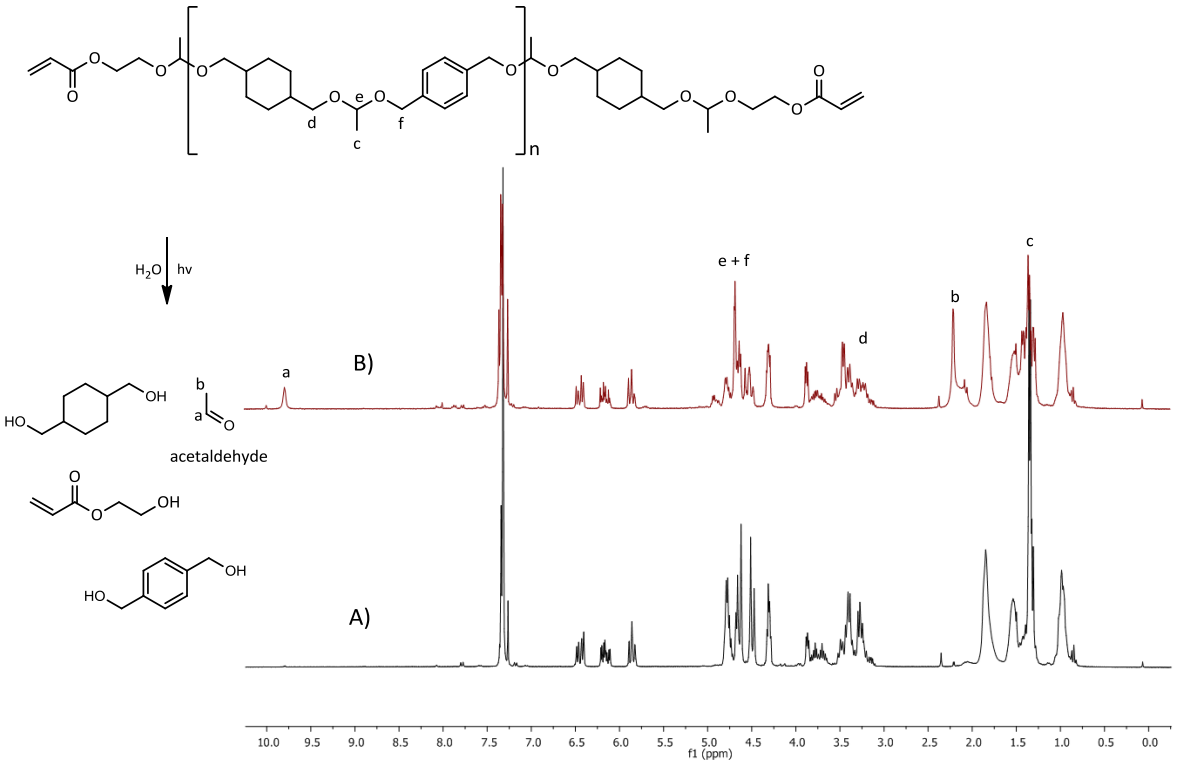

Figure 12: ^{1}H NMR spectra of the benzene based cross-linker A) Before irradiation B) After 30min irradiation at 254nm

3.1.2 Nitrobenzene based cross-linker

We obtain similar GPC results (fig. 14) that show low molecular weight crosslinker (Mn 1487) and we estimate that the number of repeated unit of the oligomer is 3 (fig. 13).

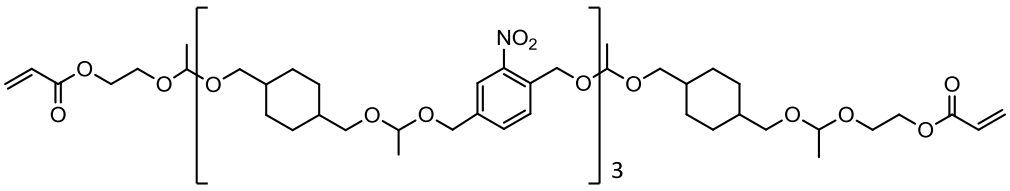

Figure 13: Chemical structure of the nitrobenzene based cross-linker

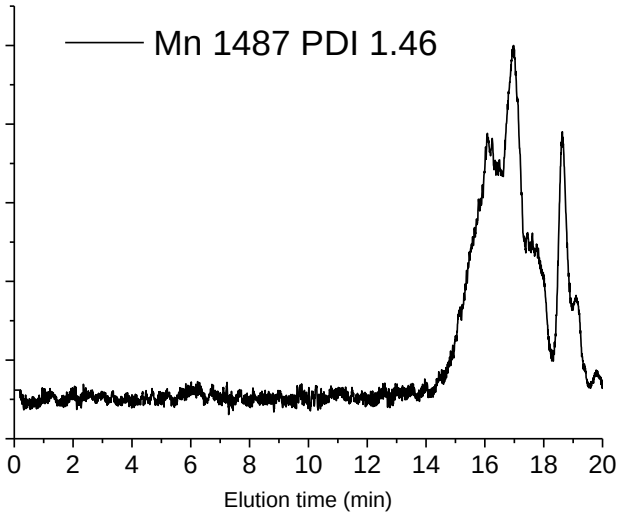

Figure 14: GPC results of the nitrobenzene based cross-linker

The successful synthesis of the crosslinker was, again, confirmed by NMR spectroscopy (fig. 15). Each proton of the cross-linker structure corresponds to a characteristic peak, which was marked below.

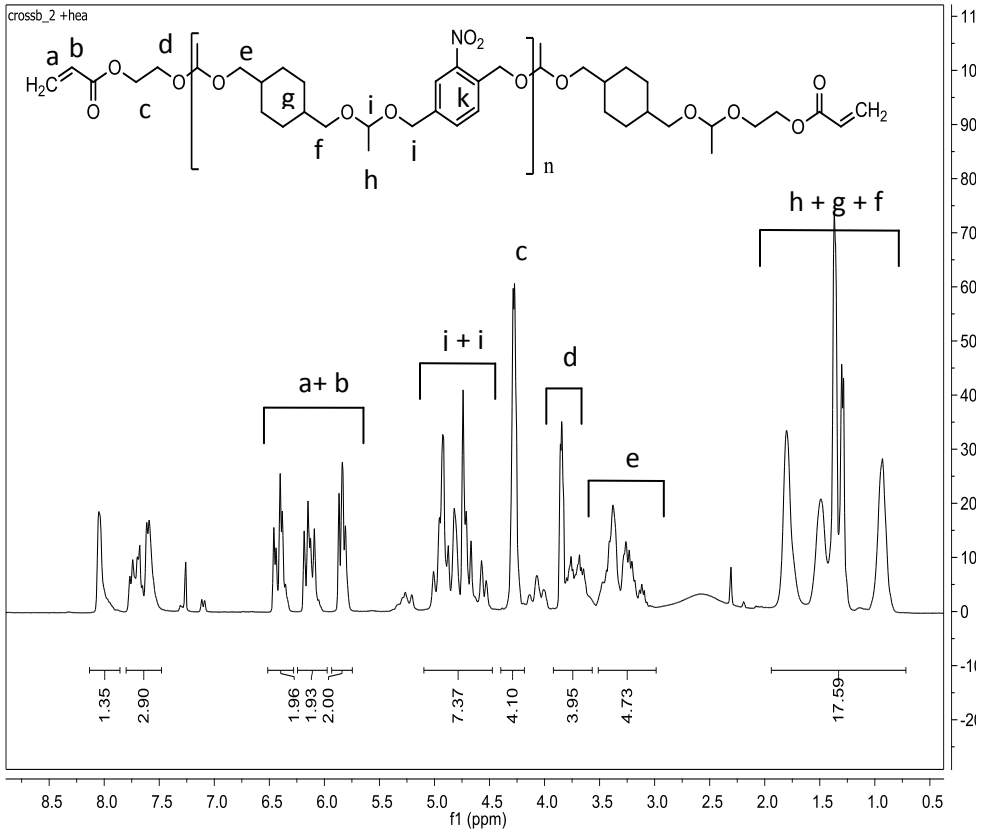

Figure 15: ^{1}H NMR spectrum of the nitrobenzene-based cross-linker

Again, the photodegradation was confirmed by NMR spectroscopy (fig. 16). The shifted characteristic peaks that are marked (c, d, e, f), correspond to the protons that were close to the acetal bond that was cleaved and the appearance of two new peaks (a, b), which both correspond to acetaldehyde, the product that was expected after the photodegradation.

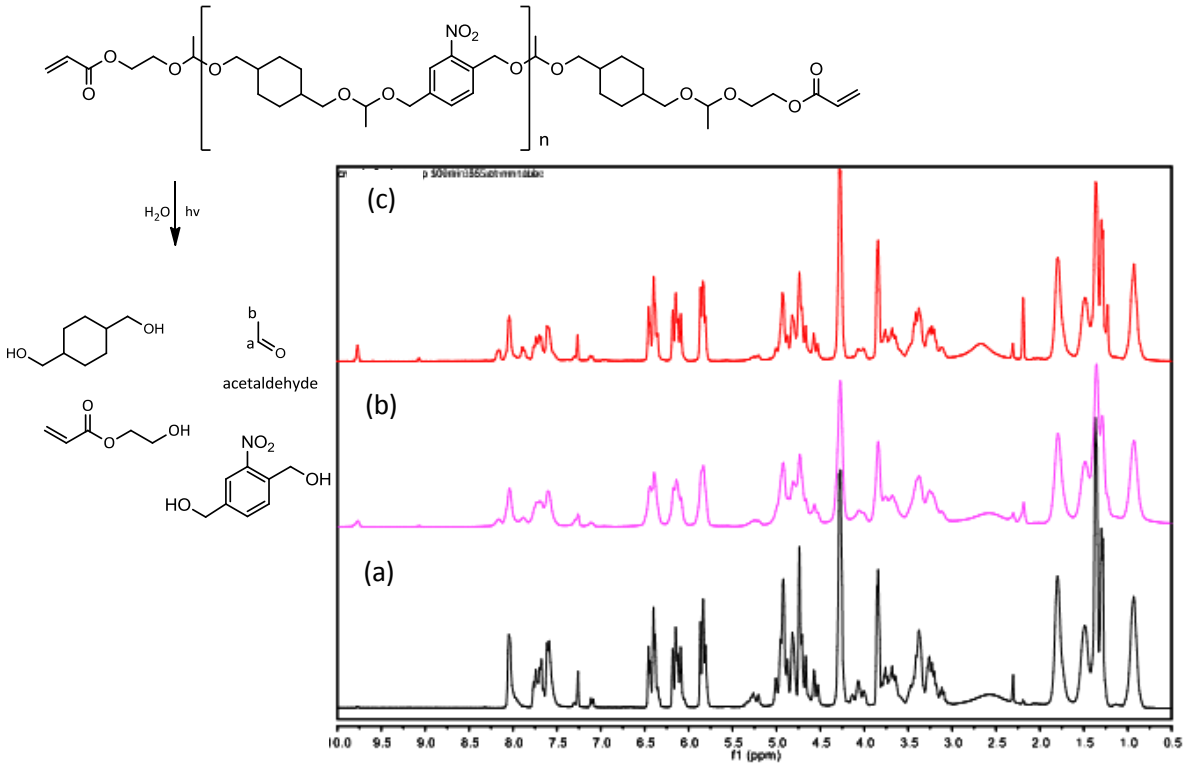

Figure 16: ^{1}H NMR spectra of the nitrobenzene-based cross-linker before irradiation (a), after 10 mins irradiation at 365 nm (b) and after 20 mins irradiation at 365 nm (c)

3.2. Hydrogel Synthesis, Characterization and Photodegradation

3.2.1 Degree of Swelling

A dry piece of the PEGMA hydrogel with 5% mole of the benzene-based cross-linker was placed in a vial with nanopure water for 48 h to measure the equilibrium swelling. As we can see (fig. 17), the hydrogel reaches the maximum swelling degree in about 3 hours.

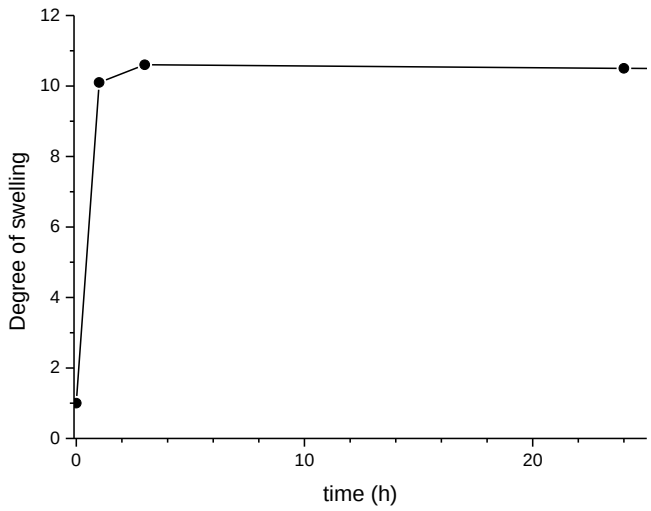

Figure 17: Degree of swelling as a function of time for the PEGMA hydrogel using 5 mole% of the benzene-based cross-linker

- Effect of crosslinker concentration on the degree of swelling

Hydrogels were also synthesized using different concentrations of the benzene-based cross-linker, at 2.5%, 5% and 10 mole% with respect to the monomer.

As expected, the increase of the cross-linker concentration causes a decrease in the degree of swelling of the hydrogel (fig.18). This is because, the more cross-links we have in a hydrogel, the shorter are the elastic chains of the gel and therefore it adsorbs less solvent.

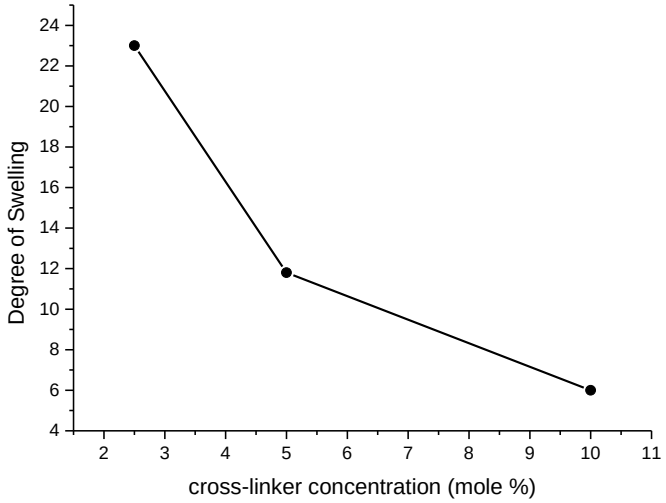

Figure 18: Degree of swelling as a function of PEGMA hydrogel using different concentrations of the benzene-based cross-linker

- Effect of the cross-linker concentration on the gelation time

During the synthesis of the hydrogels at different cross-linker concentrations we also observed different gelation times (fig. 19). The gelation time decreased as the cross-linker concentration increased, which was also expected. This is because the branching and finally cross-linking of the polymer requires a minimum gel point to be reached.

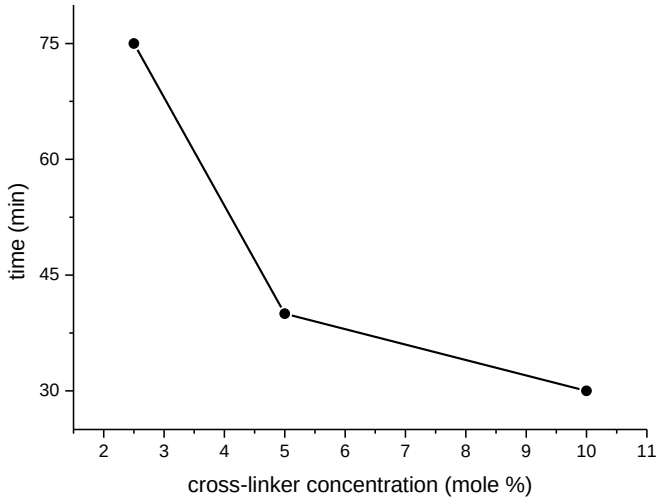

Figure 19: Gelation time as a function of PEGMA hydrogel using different concentrations of the benzene-based cross-linker

3.2.2 Photo-degradation Study

- Dye encapsulation and release

A water-soluble dye (malachite green) was encapsulated in hydrogels, in order to study the release of active substances from the photodegradable system.

Two identical dry pieces of hydrogel (Fig. 20a) were placed in two 1 mM aqueous solution of Malachite Green (Fig. 20b). They were left to reach equilibrium for 48 hours. Subsequently, they were removed and placed in two vials containing nanopure water (Fig. 20c).

(a) (b) (c)

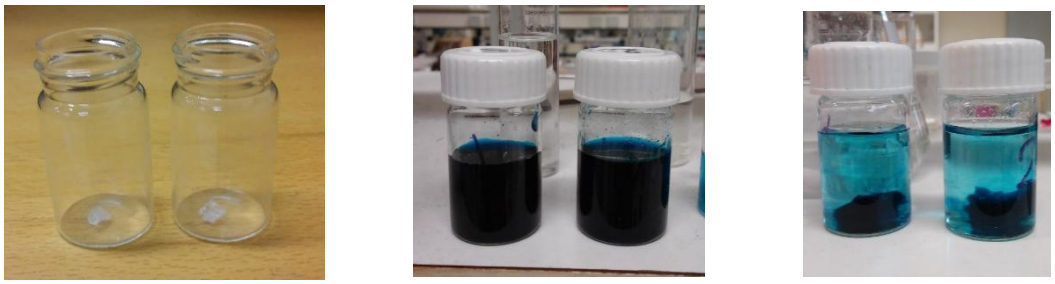

Figure 20: The procedure of dye encapsulation

Next, one of the vials was irradiated with a lamp at 254 nm while the second served as a control. When following the release of the dye at 250 nm from the two samples we found that both samples exhibited a similar trend in the dye release which increased with time (fig. 21). Only in the first 30 minutes of irradiation we found a higher release of the dye for the irradiated sample. This is attributed to the release of the dye in the supernatant after 30 minutes irradiation which adsorbed the light and prevented it from reaching the hydrogel in the bottom of the vial (fig. 22). Therefore, the increase in dye concentration from that time and on is only due to simple dye diffusion, similar to the control sample, and not the degradation of the dye.

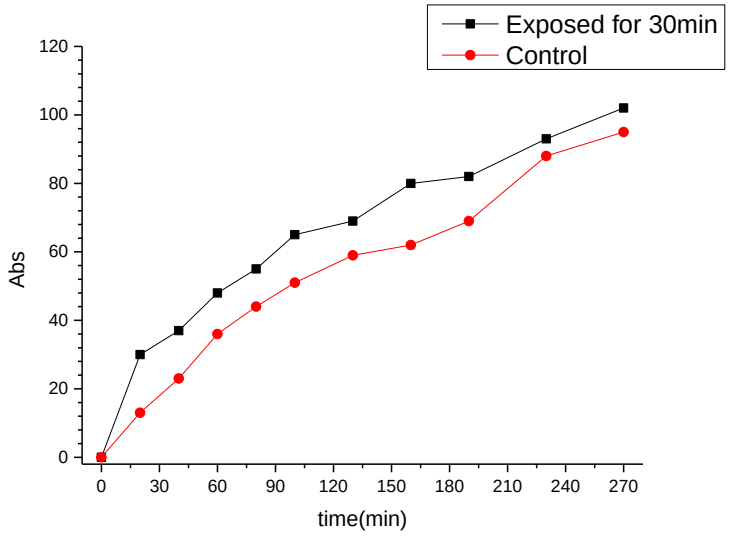

Figure 21: Release of the dye over time

Figure 22: Released dye in vial

To confirm this result we run the experiment in a different setup, where the exposed hydrogel was placed in a petri dish (fig.24) with a small amount of water which was at the level of the gel. This allowed the dye to diffuse in the surrounding supernatant while the gel remained exposed to the irradiation source. The results of this experiment shown a slow release of the dye from the control sample due to diffusion which level off at around 210 min. On the other hand, the exposed sample exhibited a three times higher release of the dye at the same time and the release continued to increase (Fig.23).

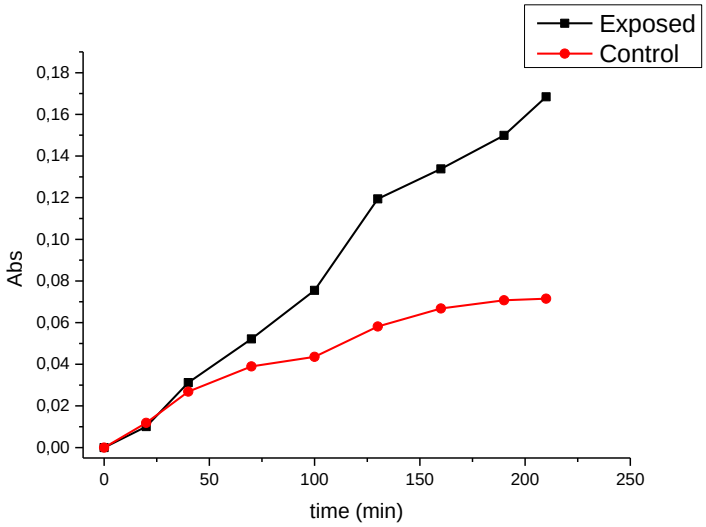

Figure 23: Dye release over time

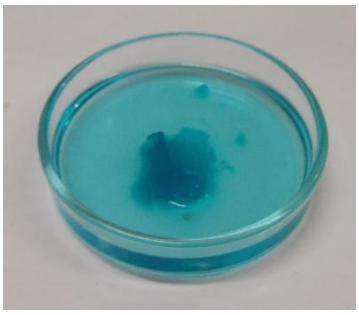

Figure 24: Dye released in petri dish

- Hydrogel degradation

Finally, a PEGMA hydrogel was prepared using the nitrobenzene-based cross-linker at 5 mole %. The hydrogel was irradiated with UV light at 365 nm for three 10 minutes sessions. After each session, we observed a partial collapse of the hydrogel, which is confirmed by the change of the color of the supernatant solution (fig. 23) due to the color of the photodegradation products, that is the original 2-Nitro 1,4 benzene dimethanol monomer, which has a reddish-yellow color and doesn't dissolve in water.

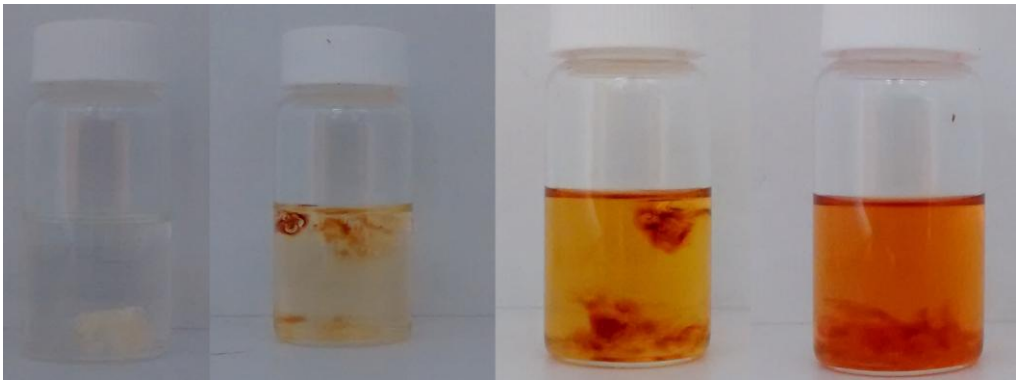

Figure 25: Hydrogel Degradation after three 10 minutes irradiation sessions at 365nm

4. Conclusions

We successfully synthesized and characterized two different photodegradable polyacetal-based cross-linkers, which degrade at low wavelength UV irradiation (256nm) but also in the near visible light region at 365 nm. These cross-linkers were synthesized in two steps using a polycondensation reaction of a diol with a divinyl ether followed by the capping of the vinyl ether ends of the polyacetal oligomers with 2-hydroxylethyl methacrylate. The successful synthesis of the cross-linkers was verified by GPC and ^{1}H NMR.

These cross-linkers were used of the synthesis of hydrogels using PEGMA as the monomer. The hydrogels were characterized in terms of their degrees of swelling and their decomposition was studied in water following irradiation at two different wavelengths.

The release of active compounds (dyes) from the hydrogels after irradiation was also demonstrated.

Future work will include the synthesis of cross-linkers which can degrade at longer wavelengths as well as to improve the degradation profile of the hydrogels upon irradiation.

5. References

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