# Effect of Composition on the Drug Release Behaviour and Properties of Hydrogels for Contact Lenses

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**Abstract**

Many efforts have been done in order to overcome the problems of conventional ocular treatments. Therapeutic soft contact lenses have gained special attention and different strategies to obtain controlled drug release profiles have been followed.

In this work, the effect of changing the composition of hydrogels for contact lenses, on their properties, especially the drug release behaviour, was evaluated. The hydrogels produced were based on the following components: monomethacryloxypropyl-terminated Polydimethylsiloxane (mPDMS) and 3-[tris(trimethylsiloxy)silyl]propyl methacrylate (TRIS) (hydrophobic silicone compounds); N,N-Dimethylacrylamide (DMA) and 2-hydroxyethyl methacrylate (HEMA) (hydrophilic compounds); N-vinylpyrrolidone (NVP), 3-methacryloxy-2-Hydroxypropoxy(propylbis(trimethylsilyloxy)methylsilane (SiGMA), and ethylene glycol dimethacrylate (EGDMA) (crosslinker). The release profiles of diclofenac and dexamethasone from hydrogels were investigated. Some properties, relevant for the contact lenses performance, such as, transmittance, ionic permeability, swelling capacity, wettability, surface energy, surface morphology, mechanical properties, water states in hydrogels and porosity were determined.

Hydrogels with higher amounts of EGDMA showed smaller pores, which in turn decreased the cumulative diclofenac release, ionic permeability and swelling, and increased the Young's modulus and tension at break. NVP increases the water content, leading to higher amounts of drug released, in contrast with SiGMA which decreases swelling and drug release. Unexpectedly, the substitution of TRIS by mPDMS (super hydrophobic) lead to an increase in the swelling and drug release. DMA proved to be more hydrophilic than HEMA, and seems to be an excellent hydrophilic component, increasing the swelling and diclofenac release, while keeping adequate mechanical properties and ionic permeability. Dexamethasone was released in much lower amounts than diclofenac, for all hydrogels.

**Key words:** ophthalmic drug delivery, hydrogels, hydrophilic and hydrophobic monomers, drugs, properties, soft contact lenses.

## INTRODUCTION

A variety of options are available to treat eye diseases, including drugs administration, laser procedures, and surgery. The most used is drug administration. Due to the eye complexity, all drug delivery strategies should meet some key requirements, such as biocompatibility, ease of use, comfort, do not affect the vision or produce side effects. In order to achieve all these requisites, over the years, drug ocular therapy has been considered a major challenge for scientists. Nowadays, topical administration in the form of solutions, emulsions, suspensions and ointments is the most common therapy for the treatment of ocular diseases located in the anterior segment. These forms of administration have the great advantage of being essentially non-invasive [1–4]. However, the bioavailability of the topical administration is very low, which only 5% of the dose administered in the eye is adequately absorbed through the cornea [2]. The problems addressed by the topical administration led the researchers to investigate other ways of delivering the drugs in the eye more effectively. Since 1965, contact lenses ($CL_s$) have been increasing their importance as a new revolutionizing drug delivery vehicle. $CL_s$ can provide higher drug bioavailability, comfort, mechanical support and protection, maintenance of corneal epithelial hydration, safety and higher patient compliance. Another benefit is the improvement of the pharmacokinetics; $CL_s$ can deliver the drug at a more controlled rate and prevent the achievement of toxicity levels [1,4–6]. Many strategies are being used in order to control the drug release through $CL_s$. The drug soaking method is the most well-known; however, presents some disadvantages, such as low drug loading and low residence time[1,5]. To surpass these problems more strategies are arising, such as molecular imprinting, nanotechnology-based formulations, and others [7]. Currently, $CL_s$ are generally made of hydrogels. Hydrogel's materials are composed of chains of several monomers linked among them, which form a

polymer network with a high capacity to absorb water [8]. The monomers used in CLs polymers can be hydrophilic, when containing parts that interact with water, or hydrophobic, which have no affinity for water but increase the mechanical strength. Cross-linking agents can be used to increase both mechanical strength and thermal stability [9]. In the hydrogel CLs' field, there are two important groups: conventional hydrogel CLs and silicone hydrogel CLs. Conventional hydrogel CLs have the problem of the corneal hypoxia that have been addressed in many ways, highlighting the incorporation of hydrophilic monomers [10]. On the other hand, silicone hydrogel CLs combine the best characteristic of silicone (hydrophobic material), high oxygen permeability, and the properties of hydrophilic materials, such as the ease of the fluid transport and high wetting capacity [10]. However, the combination of these two materials can result in phase-separation due to the low miscibility of the silicone materials with the hydrophilic materials. The result is an opaque polymer that is unsuitable for the use as CLs [10]. The addition to the mixture of macromers that are intended to ensure the solubilization of the silicone with the hydrophilic monomer, like 3-methacryloxy-2-Hydroxypropoxy(propylbis(trimethylsilyloxy)methylsilane (SiGMA), is one of the solutions that can be used to prevent this problem [11]. In this work, hydrogels of different compositions were prepared and characterised in order to find optimised formulations which combine good drug release profiles with adequate characteristics as contact lens materials.

Many properties can be studied in order to know if the hydrogels can meet the requirements when applied for therapeutic purposes. In this work, several hydrogel properties were studied: transmittance, ionic permeability, swelling capacity, wettability, surface energy, surface morphology, mechanical properties, water states in hydrogels and porosity. Transmittance is an important pre-requisite that hydrogels have fulfil to provide a clear vison for the wearer [10]. Ionic permeability is responsible for the lens motion preventing CLs from adhering permanently to the cornea [12]. Swelling capacity is the capacity of the different hydrogels to retain aqueous solvents (e.g. water) in their inside [13]. The hydrogel can contain in their network three types of water: free water (water molecules that do not directly interact with the polymer matrix, freezing at 273 K), loosely bound water (interacts weekly with the polar groups of the polymer matrix through hydrogen bonding, freezing between 180 and 273 K), and the tightly bound water (strongly bonded to the polar groups of the polymer matrix by hydrogen bonding or is linked to the ionic residues of the network, freezing below 180 K) [14]. The study of the pore-size dimensions is also of extreme importance, since they affect the swelling capability, water states and the mechanical properties of hydrogels as well as the diffusion of an eventual solute through the matrix [15]. Wettability is described as the capability of a liquid to spread on a solid surface and it is related to the lens ability to support a stable tear layer; otherwise, it can affect the visual performance giving rise to the increase of debris accumulation and discomfort for the patient [16]. The surface energy can be determined through the wettability and can give an insight on the surface properties of hydrogels. With the surface energy values, it is possible to understand the interactions between the liquid and the solid surface, as well as the nature of the surface (hydrophilic or hydrophobic) [17]. Also, the mechanical properties of hydrogels are important to be studied because they give important information about the comfort that the hydrogels can offer when used as CLs.

## MATERIALS & METHODS

### Materials

3-[Tris(trimethylsiloxy)silyl]propyl methacrylate (TRIS) (98%), 2-Hydroxyethyl methacrylate (HEMA) (≥ 98%), N,N-Dimethylacrylamide (DMA) (≥ 99.5%), ethylene glycol dimethacrylate (EGDMA) (98%), and 2,2′-Azobis(2-methylpropionitrile) (AIBN) (98%) were all purchased from Sigma-Aldrich®. N-Vinylpyrrolidone (NVP) (≥ 98%) was obtained from Merck®. Monomethacryloxypropyl terminated Polydimethylsiloxane (mPDMS) (Bisomer® Bu-PDMS) and 3-Methacryloxy-2-Hydroxypropoxy(propylbis(trimethylsilyloxy)methylsilane (Bisomer® SiGMA) (96.9%) were kindly provided by GEO Specialty Chemicals®. The drugs diclofenac sodium salt (> 99%) and dexamethasone (>96%) were purchased from Sigma-Aldrich® and Carbosynth®, respectively.

Dichlorodimethylsilane (99.5%) was obtained from Fluka®. Carbon tetrachloride (99.9%), dichloromethane and diiodomethane (99%) were purchased from Sigma-Aldrich®. A Millipore Milli-Q water purification system was used to prepare distilled and deionized (DD) water.

**Hydrogels Preparation**

***TRIS/NVP/HEMA hydrogels.*** 5 mL solutions containing TRIS, NVP and HEMA in the appropriate volume percentages, and a fixed concentration of the crosslinker EGDMA (4.7 mM) were prepared. Then, the solutions were degassed by ultra-sounds for 5 minutes and after that, they were bubbled with a gentle stream of nitrogen for 15 minutes. Afterwards, a fixed quantity (6.7 mM) of the polymerization initiator, AIBN, was added and then, the resulting mixtures were magnetically stirred for about 10 minutes, in order to obtain homogeneous solutions. The mixtures were then injected into a mould composed by two silanized glasses (5x10 cm) separated by a Teflon spacer, with a thickness of approximately 0.3-0.6 mm. The mould was placed in the oven and the polymerization reaction occurred at 60ºC for 24 hours.

The glasses were silanized following the protocol described by Vazquez et al. [18], where the glasses were immersed in a 2% solution of dichlorodimethylsilane in carbon tetrachloride, for 1 hour. After that, the glasses were rinsed with dichloromethane and dried with nitrogen. The preparation of other hydrogels differing only in the amount of crosslinker, followed the same protocol outlined above.

***TRIS/NVP/SiGMA/DMA/HEMA hydrogels.*** The preparation of this type of hydrogels followed the same protocol as above; the only difference was the polymerization process, which occurred through ultraviolet radiation for 120 minutes. A UV lamp (UV-Exposure box 2; with a wavelength of 350 nm and a power of 15 W) was used and the moulds were placed approximately 10 cm from the lamp. In this type of hydrogels, it was performed the polymerization reaction by ultraviolet radiation because in the first attempts, it was used the oven (at 60ºC for 24 hours) and they became opaque.

***TRIS/mPDMS/NVP/SiGMA/HEMA and mPDMS/NVP/SiGMA/DMA hydrogels:*** Depending on the type of hydrogel, TRIS, mPDMS, NVP, HEMA or DMA were added in the necessary volume percentages one at a time, to prepare 5 mL solution. Degassing by ultra-sounds for 5 minutes was carried out between the adding of each material. After that, the mixtures were bubbled with gentle stream of nitrogen, for 15 minutes, and, at the same time, magnetically stirred at 50ºC. This step was needed in order to eliminate all the air bubbles and to prevent the phase separation. EGDMA (4.7 mM) and AIBN (6.7 mM) were added after cooling the solutions because these agents can precipitate with the heat. After that, the mixtures were magnetically stirred (10 minutes) and then, they were injected into the mould described above. In this case, the polymerization process occurred through ultraviolet radiation for 120 minutes.

**Hydrogels Characterization**

***Transmittance.*** For the optical transparency analysis hydrogel samples with 10 mm of diameter were used in their swollen state. The absorbance, in the range of the visible light (400 to 700 nm), was measured using the UV-Vis spectrophotometer (Multiskan™ GO Microplate Spectrophotometer from Thermo™ Scientific). The hydrogels were mounted on one side of the outer surface of the cuvette and it was placed in the UV-Vis spectrophotometer and the absorbance values were obtained. This procedure was held, at least, in triplicate for each type of hydrogel and in different regions of the hydrogel.

***Ionic Permeability.*** For the ionic permeability studies, a home-made PMMA horizontal diffusion cell, with two compartments, the donor and the receiver chamber, was used. The hydrogel, hydrated in DD water, was mounted between the two compartments, and 24 mL of NaCl solution (130 mM) and 32 mL of DD water were inserted into the donor and receiver compartment, respectively. This experiment was held in triplicate for each type of hydrogel at 36ºC. For these measurements, hydrated hydrogels were cut in discs with 12 mm of diameter in order to seal the aperture between both compartments of the cell. The conductivity, in μS $cm^{-1}$, was measured hour by hour for at

least ten hours using a conductivity meter (Handheld meter Cond 340i from WTW). The conductivity data acquired were then converted into NaCl concentration (in mg $mL^{-1}$) through a calibration curve previously obtained. The NaCl concentration in the receiver compartment was plotted as a function of time and the rate of ion transport (F) was obtained from the slope of the linear regression. The ionic permeability (also referred as $D_{ion}$) was then calculated solving the following equation:

$$\frac{F.V}{A} = D_{ion}\left(\frac{dC}{dx}\right) \quad \textbf{(1)}$$

where $F$ = rate of the ion transport, $V$= volume of the receiver solution, $A$= area of the silicone hydrogel lens, and $\left(\frac{dC}{dx}\right)$ = initial NaCl concentration gradient across the hydrogel [19].

***Swelling.*** Hydrogels, with 10 mm of diameter, were dried for in the oven for 24 hours. Then, the hydrogels were weighted, and immersed in 3 mL of DD water at 4ºC or 60ºC, depending on the experience carried. During the assay, the hydrogels were taken out of the solution, gently blotted with absorbent paper, weighted and then immersed in the same DD water solution at 4ºC or 60ºC. This procedure was done at 2, 4, 6, 8, 24, 48, and 72 hours. The last measurement varied according to the time needed for the sample to achieve the equilibrium swelling. The swelling capacity was then estimated using the following equation:

$$SC = \frac{W_t - W_0}{W_0} \times 100 \quad \textbf{(2)}$$

where $W_0$ is the weight of the dry hydrogel and $W_t$ is the weight at time t [19].

***States of Water in Hydrogels and Thermoporometry.*** It was used a differential scanning calorimeter, DSC 200 F3 Maia from NETZSCH, and the Proteus® Software for the data analysis. The samples were disks of hydrogels hydrated in DD water with 2 mm of diameter, in order to fit the crucible. For the experiments, the samples were taken out of DD water and carefully blotted with wet absorbent paper to prevent the hydrogel from losing water. After that, it was registered the weight of the crucible + lid (pan) and then the weight of pan + sample. The set pan + sample was then hermetically sealed with a sealing press and placed in the heating block of the equipment. The samples were initially kept at 20ºC for 10 minutes in order to stabilize the temperature inside the heating block. After that, the samples were subjected to a cooling step where the temperature decreased at the rate of 2ºC/min until -60ºC and then, another isothermal step occurred for 10 minutes. Afterwards, the heating step started at a rate of 2ºC/min until 20ºC. Then, an isothermal step occurred and the experiment ended. These tests were done in triplicate for each type of hydrogel analysed. The obtained data were then analysed with the Proteus® Software, which displayed a graphic, for each sample, relating the heat flow (rate at which thermal energy is supplied to reference and to the sample) with the temperature. With this software it was possible to access the onset and peak temperatures of the peaks corresponding to both free and loosely bound water, which are important for the calculations of the pore-size of hydrogels. Also, the software gave the values for enthalpy of both free and loosely bound water, by the integration of each peak, which were used for further calculations of the states of water in each type of hydrogel. In order to have an idea of the quantity of tightly bound water present in the hydrogel, a little hole was made with a needle in the lid, after the DSC measurements, and then the pans were placed in the vacuum oven at 50ºC for 24 hours to remove as much as possible the free and loosely bound water of the hydrogel's matrix. After that, the sample was weighted. From the difference between the weight of the dried sample and that of the fully hydrated sample, the amount of tightly bound water was estimated. To access to the pore-size dimensions of hydrogels, it was used two models proposed by Brun et al.[20] and Landry[21] (equations shown respectively):

$$r_p(nm) = -\frac{32{,}33}{\Delta T(K)} + 0{,}68 \quad \textbf{(3)}$$

$$r_p(nm) = -\frac{19{,}082}{\Delta T(K) + 0{,}1207} + 1{,}12 \quad \textbf{(4)}$$

Where, $\Delta T(K)$ is the melting temperature depression (difference between the maximum of each peak obtained from DSC measurements). Through the resolution of both equations, it was possible to obtain the pore-size dimensions of the hydrogels. A comparison was then made to compare the two methods applied.

***Wettability.*** For the wettability studies, the contact angle was measured, at room temperature, using two methods: sessile drop and captive bubble. For the sessile drop method, dry hydrogel disks with 10-12 mm diameter were used. The hydrogels were carefully dried in the oven at 50ºC for 72 hours, in order to remove as much water as possible. After that, the contact angle was measured, placing drops of 3-5 µL of DD water with a micrometric syringe, on the surface of the hydrogel. For further calculations of hydrogels' surface energy, it was necessary to measure the contact angle of a non-polar liquid. Diiodomethane was the chosen liquid and it was followed the same procedure referred above. For the contact angle determination using the captive bubble, hydrogels in their swollen state were glued to a plastic support and then placed downwards in a liquid cell with quartz windows, which was full of DD water. Then, with the help of a micrometric syringe with an inverted needle, an air bubble of approximately 3-5 µL was placed on the hydrogel's inferior surface. After placing the drop on the hydrogel's surface in both techniques, a set of images was recorded. A video camera (JAI CV-A50) attached to a microscope (Wild M3Z) was used for the image acquisition and the video signal was transmitted to a frame grabber (Data Translation DT3155).

***Morphology.*** To access the hydrogels' surface morphology, SEM images were taken. Initially, the samples were hydrated in DD water and then carefully cleaned with an absorbent paper and then dried at 36ºC for 3 days, to take out the water of the hydrogel as much as possible. After drying the samples, they were coated with a thin gold layer using the equipment Q150T ES from Quarum Technologies. The samples were then analysed using a Field Emission Gun (FEG) SEM JEOL JSM-7001, and images from the different types of hydrogels were obtained with various magnifications: 3 000x, 10 000x, and 20 000x.

***Mechanical Properties***. The mechanical tests were done using a TA.XT*plus* Texture Analyser equipment and the software *Exponent* for data collection. The hydrogels were cut in strips with: 5 mm of width, ≈10 mm of gauge length and 0.4-0.6 mm of thickness. These strips were maintained in their swollen state during the whole experiment. For the measurements, each strip was fixed between two clamps in the sample testing area, at the top and at the bottom, with sandpaper to prevent the hydrogel from slipping during the test. The test conditions were introduced in the software *Exponent*: test speed = 0.3 mm $s^{-1}$ and trigger force = 0.005 N. Then, the test started and the data were collected until the hydrogel broke. These experiments were performed at room temperature (≈20ºC). Six strips of each type of hydrogel were tested. The data analysis was done using the software *Excel*. A stress-strain graphic was drawn, using the data from *Exponent* and the dimensions of each hydrogel (width, gauge length and thickness). For the determination of stress, it was used the measured force, F, in N, and the values of width and thickness of the hydrogels to calculate the initial area, $A_0$. For the determination of the strain, it was used the gauge length, $L_0$, of each hydrogel and the length variation of the sample at each instant, from the Exponent. Then, from the first part of the graphic (elastic region) it was taken the slope of the curve, which corresponds to the Young's modulus. The average of the values obtained for the different samples of each type of hydrogel was calculated. From this experiment, it was also possible to obtain the tension at break, elongation at break and toughness. To obtain the values of tension and elongation at break, it was necessary to identify the last point before the break in the stress-strain plot. The x coordinate of that point corresponds to the elongation at break and the y coordinates corresponds to the tension at break. From the values obtained in independent experiments, the average tension at break and elongation at break for each type of hydrogel studied was calculated. For the determination of the toughness, which corresponds to the area under the stress-strain graphic, the software *TableCurve 2D 5.0* was used. With this software it was possible to adjust an appropriate equation to each curve and then to integrate this equation. Again, the average toughness for each type of hydrogel was calculated.

**Drug Loading/Release**

The hydrated hydrogels were cut with 10 mm diameter and then they were dried at 36ºC for 24 hours. After that, the weight of hydrogels was measured for further calculations. The drug

loading was performed using the drug soaking method, where the hydrogels were immersed in 3 mL of drug solution for 38 hours at 4ºC. In some cases, the loading was also carried out at 60ºC for comparison purposes. For the drug release tests using diclofenac, the loading was performed in a NaCl solution (130 mM) with a drug concentration of 1 mg $mL^{-1}$. For dexamethasone release experiments, the hydrogels were loaded in NaCl solution with a drug concentration of 0.08 mg $mL^{-1}$ or in an ethanol solution with a drug concentration of 1 mg $mL^{-1}$. After the drug incorporation, the drug release experiments were performed. The loaded hydrogels were removed from the drug solution, dipped in DD water and blotted with dry absorbent paper. This procedure is important to remove the excess of drug that is on the surface of the hydrogel. Then, the hydrogels were immersed in 3 mL of NaCl solution (to mimic the lacrimal fluid) and placed in a shaker (Incubating Mini Shaker from VWR) at 36ºC and 180 rpm.

Aliquots of 0.2 mL were collected during the release experiments and replaced with 0.2 mL of fresh NaCl solution (130 mM). This procedure was done each hour, in the first 8 hours, and then each 24 hours until the point at which no more drug is released from the hydrogels. The absorbance of each aliquot was determined by a UV-Vis spectrophotometer (Multiskan™ GO Microplate Spectrophotometer of Thermo™ Scientific), using the appropriate wavelength for each drug. For diclofenac, it was used a wavelength of 276 nm, whereas for dexamethasone it was used a wavelength of 240 nm. The drug concentration was then determined by converting the absorbance into concentration of drug, using Beer's Law.

## RESULTS AND DISCUSSION

### *The Effect of the Amount of the Crosslinker*

It was studied the role of the crosslinker EGDMA on the hydrogels' properties. TRIS-based hydrogels with the composition TRIS/NVP/HEMA (36.8/41.8/21.5, V/V/V %), were prepared varying only the quantity of the crosslinker in the mixture: 0.64 (V/V %), 1.28 (V/V %), 2.56 (V/V %) and 5.13 (V/V %) for 1x, 2x, 4x and 8x EGDMA respectively.

From the drug release experiments, it was concluded that the increase of the amount of EGDMA leads to a decrease in the cumulative diclofenac release (Figure 1). This is an expected result because with the increase of the amount of crosslinker, the hydrogels' mesh becomes tighter, making more difficult the entry and exit of the drug [22]. Despite the increased amount of crosslinker in the hydrogels 2x EGDMA and 4x EGDMA, no significant differences are seen between the two cumulative diclofenac releases. However, in 8x EGDMA the hydrogel's mesh was so tight that the loading and the release were much reduced.

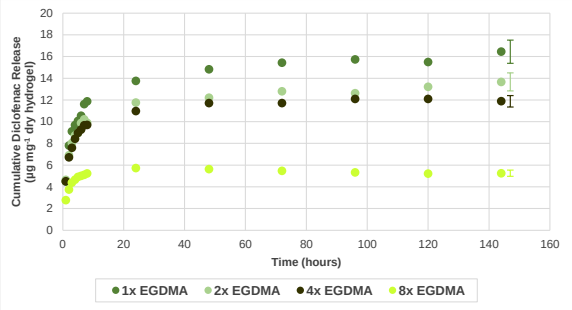


**Figure 1 -** Cumulative diclofenac release from TRIS-based hydrogels with different amounts of crosslinker (EGDMA). The error bars correspond to the mean standard deviation.

All hydrogels showed transmittance values above the minimum accepted value, 90% [10].The ionic permeability and swelling are directly related with the drug release results. When the amount of crosslinker increases, the ionic permeability as well as the swelling percentage decrease.

### *Study of Different Compositions of TRIS-based Hydrogels*

The goal was to try different compositions of TRIS-based silicone hydrogels in order to understand better the role of each component. In order to achieve that, several hydrogels were prepared by varying the amount of the components TRIS, HEMA, and NVP (Table 1). Some hydrogels became opaque, after the polymerization reaction, suggesting that phase separation had occurred. It was concluded that it is necessary to have a minimum amount of NVP to have transparent hydrogels, which is 40 (V/V %).

**Table 1 -** Compositions, in V/V %, of the TRIS-based hydrogels.

| Material / Name | TRIS | NVP | HEMA |
|---|---|---|---|
| TRIS 34 50 16 | 34 | 50 | 16 |
| TRIS 37 45 16 | 37 | 45 | 18 |
| TRIS 38 43 19 | 38 | 43 | 19 |
| TRIS 36.8 41.8 21.5 | 36.8 | 41.8 | 21.5 |
| TRIS 50 40 10 | 50 | 40 | 10 |

Figure 2 shows that the cumulative diclofenac release increases with the amount of NVP. An explanation for this result is the fact that NVP is a super water absorbent material, leading to high quantities of drug loaded into the hydrogel [23].

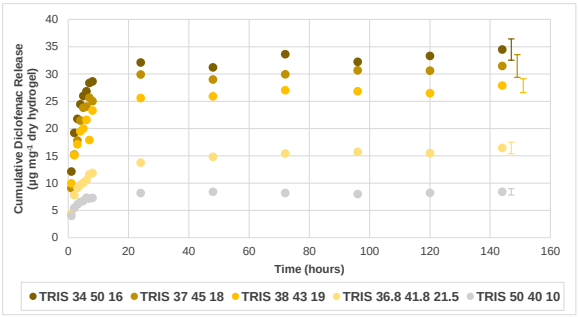


**Figure 2 -** Cumulative diclofenac release of the TRIS-based hydrogels. The error bars correspond to the mean standard deviation.

The transmittance in all hydrogels is above 90%. The results obtained for the TRIS-based hydrogels showed a relationship between the cumulative diclofenac release, ionic permeability and swelling capacity. The increase in the amount of NVP induces an increase in the three parameters aforementioned; however, these variations are not directly proportional. For example, the increase in the cumulative diclofenac release when the amount of NVP increases from 41.8 to 43 (V/V %), corresponds to a negligible variation in the swelling percentage.

### *The Role of the Hydrophobic Materials (TRIS and mPDMS)*

The goal was to compare the effect of two different hydrophobic compounds (TRIS and mPDMS) on the hydrogels' properties and drug release behaviour. In these formulations the amounts of TRIS and mPDMS were inversely changed, keeping constant (≈40%) the total amount of these hydrophobic components (Table 2). It was added a new material, SiGMA, for the solubilisation of the hydrophilic monomers with the hydrophobic compounds to prevent the phase separation.

**Table 2 -** Compositions, in V/V %, of the different hydrogels by varying the amount of the hydrophobic components (TRIS and mPDMS).

| Material / Name | TRIS | mPDMS | SiGMA | NVP | HEMA |
|---|---|---|---|---|---|
| mPDMS 36.7 | - | 36.7 | 40 | 5 | 18.3 |
| TRIS 10 mPDMS 30 | 10 | 30 | 40 | 5 | 15 |
| TRIS 20 mPDMS 20 | 20 | 20 | 40 | 5 | 15 |
| TRIS 30 mPDMS 10 | 30 | 10 | 40 | 5 | 15 |
| TRIS 35 mPDMS 5 | 35 | 5 | 40 | 5 | 15 |

Looking at Figure 3, it is possible to conclude that despite the low differences, with the increase in the amount of mPDMS, the cumulative diclofenac release also increases. Surprisingly, the substitution of TRIS by mPDMS, which is more hydrophobic [24] leads to a higher drug loading and, consequently, drug release. This demonstrates that the behaviour of the hydrogels is not only determined by the hydrophilicity/hydrophobicity of the monomers. Comparison with data in Figure 2 relative to TRIS-based hydrogels reveals that, more important than the ratio PDMS/TRIS is the use of SiGMA instead of NVP: even with low quantities of mPDMS (5%), the presence of SiGMA in high quantities (40%) decreases significantly the diclofenac release.

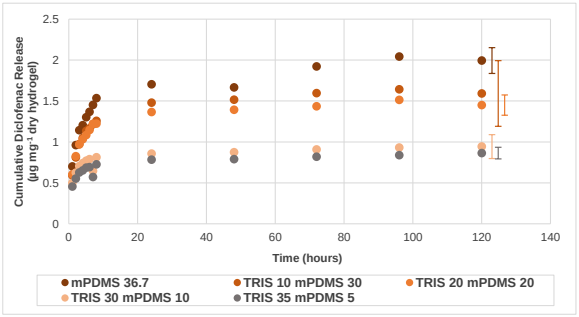


**Figure 3 -** Cumulative diclofenac release of the hydrogels where the amount of the hydrophobic materials (TRIS and mPDMS) was varied. The error bars correspond to the mean standard deviation.

From the transmittance results obtained, it is possible to conclude that all the hydrogels have values above 90%. The ionic permeability and swelling results obtained show that a correlation may be established between the amount of mPDMS and cumulative diclofenac release, ionic permeability (except in mPDMS 36.7) and swelling: when the amount of mPDMS increases, the values of these properties also increase.

### *The Role of the Hydrophilic Materials (DMA and HEMA)*

In this part, the goal was to study two different hydrophilic compounds: DMA and HEMA. Table 3 shows the hydrogels composition; in one hydrogel half of the amount of NVP was substituted by SiGMA in order to compare the role of these two components.

**Table 3 -** Compositions, in V/V %, of the hydrogels where mainly the amount of the hydrophilic materials (DMA and HEMA) was varied.

| Name \ Material | TRIS | SiGMA | NVP | DMA | HEMA |
|---|---|---|---|---|---|
| DMA 20 | 40 | - | 40 | 20 | - |
| SiGMA 20 DMA 20 | 40 | 20 | 20 | 20 | - |
| DMA 10 HEMA 10 | 40 | - | 40 | 10 | 10 |

Figure 4 shows that, when the amount of DMA decreases, being partially substituted by HEMA, the cumulative diclofenac release also decreases. Also, the substitution of half of NVP by SiGMA in SiGMA 20 DMA 20 decreases approximately three times the cumulative diclofenac release, which may be attributed to the significant reduction in the content of the hydrophilic monomer NVP. Comparison of the hydrogels with composition DMA 20 and TRIS 36.8 41.8 21.5 (Figure 4 and Figure 1), shows that the cumulative diclofenac release is much higher in the former, suggesting that DMA might be more hydrophilic than HEMA, which favours drug loading and release. This conclusion is in accordance with the literature [25] which says that polymers prepared with DMA are considered super water absorbent, absorbing several times their weight in water.

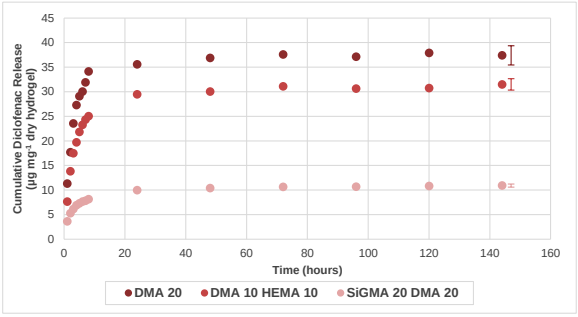


**Figure 4 -** Cumulative diclofenac release of the hydrogels where mainly the amount of the hydrophilic materials (DMA and HEMA) was varied. The error bars correspond to the mean standard deviation.

All hydrogels showed transmittances above 90%. Again, ionic permeability and swelling capacity followed the same tendency of the cumulative diclofenac release.

### *mPDMS/DMA-based Hydrogels*

The goal in this part of the work was to investigate if hydrogels using mPDMS, as the hydrophobic monomer, and DMA, as the hydrophilic monomer, instead of TRIS and HEMA, have a different behaviour concerning drug release among other properties. Also, a large part of NVP was replaced by SiGMA, needed to guarantee the solubilisation of the silicone with the hydrophilic monomer, and avoid phase separation (Table 4).

**Table 4 -** Compositions, in V/V %, of the hydrogels using mPDMS as the silicone monomer and DMA as the hydrogel monomer.

| Name \ Material | mPDMS | SiGMA | NVP | DMA |
|---|---|---|---|---|
| mPDMS 36.7 DMA 18.3 | 36.7 | 40 | 5 | 18.3 |
| mPDMS 36.7 DMA 28.3 | 36.7 | 30 | 5 | 28.3 |

Figure 5 shows that the increase in the amount of DMA together with the decrease in the amount of SiGMA lead to a higher cumulative diclofenac release. DMA, being highly hydrophilic, favours the drug release from the hydrogels. Unexpectedly, the cumulative diclofenac release of mPDMS 36.7 DMA 18.3 was approximately the same comparing to the hydrogel mPDMS 36.7 (Figure 3) which has the same composition, except that DMA was substituted by HEMA. In these cases, the differences in the hydrophilicity of DMA and HEMA do not have consequences on the drug release behaviour.

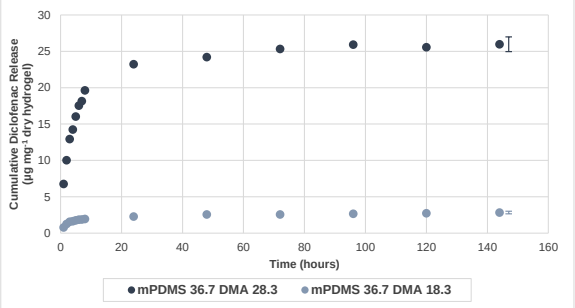


**Figure 5 -** Cumulative diclofenac release of mPDMS/DMA-based hydrogels. The error bars correspond to the mean standard deviation.

However, analysing the swelling results the hydrogels mPDMS 36.7 DMA 18.3 and mPDMS 36.7 revealed a difference in the equilibrium swelling percentages: ≈15% and ≈4.5%, respectively. Although, there is no significant difference between the drug release behaviour of these two hydrogels the use of DMA instead of HEMA results in a significant increase on the swelling percentage. Moreover, the mPDMS 36.7 DMA 28.3 showed a higher swelling percentage and ionic permeability than mPDMS 36.7 DMA 18.3 due to the increase in the DMA content and decrease in the SiGMA content. The transmittance values in both hydrogels are above 90%.

### ***Study of Other Properties for the Most Relevant Hydrogels' Types***

*Drug Release with Dexamethasone*

From the results of the release of dexamethasone it was possible to conclude that lower amounts of drug were released from the hydrogels compared with diclofenac. Two possible explanations for this result could be the low solubility of this drug in aqueous mediums and its hydrophobic nature, which hampers the drug loading and release.

*Wettability and Surface Morphology*

Wettability was measured using two different techniques: captive bubble and sessile drop. All hydrated hydrogels studied showed a hydrophilic surface (contact angles obtained with the captive bubble method around 40º). On the other hand, dry hydrogels showed a hydrophobic surface. Wettability measurements carried out on the dry hydrogels also allowed to estimate its surface energy. The low surface energy values and the predominance of the dispersive component, proved again the lower hydrophilicity of the hydrogels in the dry state. This characteristic, which was observed even when a high percentage of hydrophilic monomers was present, may be attributed to the surface roughness of the dry hydrogels, according to the Cassie-Baxter model. This result also leads to the conclusion that the hydrophilicity/hydrophobicity of the hydrogels could not be directly correlated with the hydrophilicity/hydrophobicity of their components, but should be mostly determined by the morphology/topography of the surfaces. Unfortunately, this could not be confirmed by the SEM analysis which did not reveal significant differences among the hydrogels.

*Mechanical Properties*

The mechanical properties of the hydrogels were found to depend sharply on the amount of crosslinker: the hydrogel 8x EGDMA presented the largest Young's modulus (Figure 6) and tension at break and the lowest value of toughness. This result proves that the increase in the amount of crosslinker in hydrogels could bring comfort issues for the $CL_s$ wearers. The hydrogels containing DMA have the lowest Young's modulus (Figure 6), but the values of toughness depended on the monomers present. This result also proves that the water content influences the mechanical properties on hydrogels: higher water contents, lower Young's modulus and higher elongation at break. Also, the values obtained for the Young's modulus of the hydrogels containing DMA (last two bars in Figure 6) are similar to those of commercial lenses with similar compositions [26].

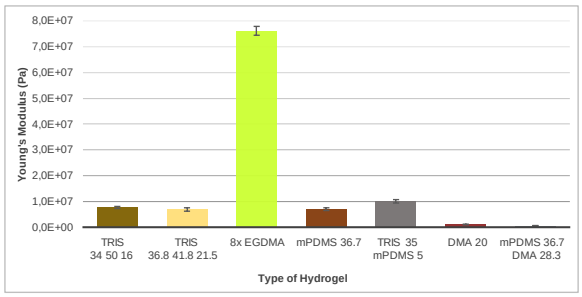


**Figure 6 -** Young's modulus of the different hydrogels. The error bars correspond to the standard deviation.

*Water States in Hydrogels and Pore-size Distribution*

The water states in the hydrogels vary with the amount of crosslinker, the amount of hydrophilic monomers and also with the pore-size dimensions, according to Figure 7. The increase in the crosslinker leads to smaller pore-size dimensions, which in turn leads to higher amount of tightly bound water in the hydrogel, such as in the hydrogel 4x EGDMA. The increase of the hydrophilicity of the hydrogel's monomers leads to larger pore-size dimensions and consequently higher amount of free and loosely bound water, as shown by the hydrogel DMA 20. Also, a direct relationship between the cumulative drug released and the pore-size dimensions was found (larger pore-size dimensions lead to a higher cumulative drug release); DMA 20 and mPDMS 36.7 DMA 28.3 show the largest pore-size dimensions and high cumulative diclofenac releases.

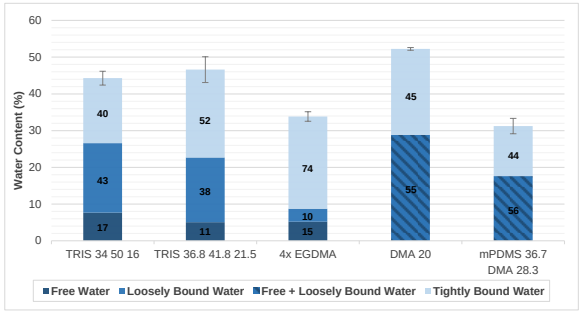


**Figure 7 -** Equilibrium water content and the relative portions of the different water states presented in each hydrogel. The error bars correspond to the standard deviation.

*Release Profiles Vs Therapeutic Windows*

The efficiency of the drug delivery of the hydrogels was assessed through the comparison of the concentration of the drugs released with the therapeutic windows of two commercially available ophthalmic drugs, Voltaren® (diclofenac) and Ronic® (dexamethasone). The therapeutic window is defined by two limits: the lower limit corresponds to the therapeutic needs of the cornea for the two drugs and the upper limit corresponds to the limit of toxicity for both drugs. All hydrogels showed to efficiently deliver diclofenac and dexamethasone within the therapeutic window, being the hydrogel TRIS 36.8 41.8 21.5 the most efficient for the two drugs tested, with 70 hours and 40 hours of release, respectively for each drug.

## CONCLUSIONS

Analysing all the results obtained during this work, it is possible to draw some conclusions about the monomers to be used as well as the relative amounts of each of them. DMA showed to be an excellent hydrophilic monomer capable of increasing the drug release while keeping the adequate mechanical properties, ionic permeability and transmittance. Moreover, the replacement of NVP by SiGMA seems not to be a good alternative, since it decreases the water content of the hydrogels and, consequently, decreases the drug release, ionic permeability and compromises the mechanical properties of the hydrogels. Another aspect that is necessary to take into account is the quantity of the crosslinker because, in high amounts, it can compromise not only the drug release behaviour but also the hydrogels' properties. In this work, it was possible to point out some hydrogels that have potential to be used as new drug carriers to the eye: TRIS 34 50 16, TRIS 36.8 41.8 21.5, DMA 20, and mPDMS 36.7 DMA 28.3. However, more important than proposing alternative formulations was the attempt to better understand the role that each component of the hydrogel formulation plays in the hydrogels' properties.

In the future, more properties of these hydrogels should be studied, such as oxygen permeability and surface roughness. Additionally, more drugs as well as other materials commonly associated with commercial $CL_s$ should be tested. Finally, *in vivo* tests should be performed to confirm the adequacy of the best hydrogels as therapeutic contact lens materials.

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