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Poly(methyl vinyl ether-co-maleic acid) hydrogels containing cyclodextrins and Tween 85 for potential application as hydrophobic drug delivery systems.

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Abstract: Hydrogels have been extensively investigated as a platform for drug delivery. However, their use for the delivery of hydrophobic drugs has been limited by their incompatibility with hydrophobic drug molecules. The chemical modification of the structure of the hydrogels to include hydrophobic moieties has been proven to be a good alternative to increase the stability and solubility of hydrophobic drugs in the polymer matrix of the hydrogel. The inclusion of hydroxypropyl- β -cyclodextrins (HPBCD) and Tween[®] 85 (T85) within hydrogel matrices has the potential to improve hydrophobic drug loading and release. HPBCD have the ability to host hydrophobic drug molecules in their cone-like structure, forming inclusion complexes through host-guest interactions. On the other hand, T85 is an amphiphilic molecule and, consequently, has the potential to increase hydrophilic drug loading within the hydrogels. In the present work, a new type of hydrogel made from poly(methyl vinyl ether-co-maleic acid) (GAN) and poly(ethylene glycol) (PEG) containing T85 and HPBCD was synthesized for hydrophobic drug release. Hydrogels were based on GAN crosslinked (PEG) and HPBCD and/or T85 via an esterification reaction in the solid state (solvent free). The synthesised hydrogels were characterised using Fourier transform infrared (FTIR) spectroscopy, swelling studies and contact angle measurements. The hydrogels showed swellings ranging from 140 to 180%. The inclusion of T85 in the hydrogels improved the wettability of the materials. On the other hand, the inclusion of HPBCD within the hydrogels decreased the wettability as the contact angle between the hydrogels and water increased with the HPBCD content. Finally, the materials were loaded with an ophthalmic drug, dexamethasone (DX). HPBCD-containing hydrogels showed a higher DX uptake and, consequently, they showed a higher capacity of DX release. On the other hand, T85 containing hydrogels did not show any improvement over the hydrogels containing only GAN and PEG. The hydrogels were able to provide sustained DX release over periods of 6 hours.

Keywords: hydrogels; hydrophobic drug delivery; dexamethasone; cyclodextrin; polysorbate

1. Introduction

Hydrogels are three dimensional, hydrophilic networks of cross-linked polymers with a high capacity to absorb and retain water and other biological fluids (1-6). They can be made from virtually any water-soluble polymer, and can be formulated in a number of different physical forms including: microparticles; nanoparticles; and films (1-6). Crosslinking between polymeric chains can be achieved by chemical bonds (chemical hydrogels) (2, 7) or by non-covalent interactions (physical hydrogels) (7-11). Both types of hydrogels have been extensively used for drug delivery applications (1-4). However, the majority of the described applications are restricted to the delivery of small, hydrophilic molecules (12-14). The hydrogels used for these purposes are formed by hydrophilic polymer matrices. Consequently, the compatibility of these materials with hydrophobic drugs are limited (12-14). This is a huge limitation as it is estimated that around 40% of the marketed drugs and up to 60% of potential new drugs have low water solubility (14, 15).

Researchers have used various methods to improve the loading and homogeneity of hydrophobic drugs in hydrogels, including the incorporation of hydrophobic drug-containing moieties such as surfactants, micelles and/or hydrophobic molecules (12-14, 16-19). Surfactants provide micellar and/or hydrophobic domains within the hydrogel structure, thus, improving the loading of

hydrophobic drugs (20). Another approach to improve hydrogel compatibility with hydrophobic drugs is the incorporation of molecules which have the ability to form inclusion complexes, such as cyclodextrins (CDs) (18, 21). CDs are cyclic oligosaccharides formed by 6, 7 or 8 dextrose units (α , β and γ -CD respectively), which have a truncated cone structure with a hydrophilic outer surface and a hydrophobic inner cavity (21-24). The hydrophobic cavity has the ability to host hydrophobic molecules, which results in the formation of an inclusion complex (21-23).

In the present work, a simple solvent-free strategy to prepare hydrogels containing cyclodextrins and/or surfactants is described. These hydrogels will be characterised and tested for hydrophobic drug delivery. For this purpose, poly(methyl vinyl ether-alt-maleic acid), also known as Gantrez[®] (GAN), was covalently crosslinked with poly(ethylene glycol) (PEG). Two different compounds were added to the hydrogel structure to improve their compatibility with hydrophobic drugs: hydroxypropyl- β -cyclodextrin (HPBCD); and a surfactant (Tween[®] 85) (T85). The main novelty of the process is that these hydrogels can be synthesised in solid phase using a solvent-free process. The hydrogels were characterised and evaluated as drug delivery systems using dexamethasone (DX) as a model hydrophobic drug molecule.

2. Materials and Methods

2.1. Materials

GAN (acid form of methylvinylether and maleic anhydride copolymer) ($M_w = 1.2 \times 10^6$ Da) and HPBCD (Cavitron[®] W7 HP7) were provided by Ashland (Tadworth, UK). T85 was obtained from Croda (Snaith, United Kingdom). DX was purchased from Bufa (Hilversum, the Netherlands). PEG ($M_w = 200$ Da) was obtained from Sigma-Aldrich (Steinheim, Germany)

2.2. Preparation of the hydrogels

Aqueous solutions containing different ratios of HPCD/GAN/PEG and T85/GAN/PEG (Table 1) were poured into 5x5 cm moulds, ensuring they were all spread evenly. Films were dried at room temperature for 48 hours and subsequently crosslinked at 80°C for 24 hours. A 1 cm diameter cork-borer was then used to cut the films into discs.

Table 1. Composition of the aqueous blends used to prepare the hydrogels

Hydrogel Name	Composition of the aqueous solution (%)				
	GAN	PEG	HPBCD	T85	Water
Control	20.0	20.0	0.0	0.0	60.0
B5	20.0	20.0	5.0	0.0	55.0
B10	20.0	20.0	10.0	0.0	50.0
T5	20.0	20.0	0.0	5.0	55.0
T10	20.0	20.0	0.0	10.0	50.0
T5B5	20.0	20.0	5.0	5.0	50.0

2.3. Hydrogel characterisation

Hydrogels were characterised by measuring their fluid uptake capacity. Film discs were weighed (m_o), placed in pH 7 phosphate buffer solution (PBS) and left to swell for 24 hours at room temperature. Subsequently, the discs were removed, blotted dry and weighed (m_t). Equation 1 was used to calculate the percentage of swelling of the hydrogels. This process was repeated to study the swelling of the hydrogels in ethanol.

$$\% \text{ Swelling} = 100 \cdot (m_t - m_o) / m_o \quad (1)$$

Attenuated total reflectance (ATR)-FTIR spectroscopy (IR-4100 Series, Jasco, Essex, UK) was used to confirm the esterification reaction between GAN and PEG had taken place after crosslinking. The IR

Spectra were recorded at room temperature with the MIRacle software between 4000-800 cm^{-1} , with a resolution of 4.0 cm^{-1} . An average of 64 repeat scans was taken to obtain each spectra. The contact angle of water with the surface of the dry hydrogels was also studied. For this purpose, an Attension Theta equipment (Attension Theta, Biolin Scientific, Gothenburg, Sweden) was used. OneAttension software analysed results to give an indication of the wettability of the surface. Finally, the morphology of the synthesized hydrogels was evaluated by using scanning electronic microscopy (SEM) (Hitachi TM3030; Tokyo, Japan).

2.4. Dexamethasone loading and release

Hydrogels were loaded with DX by placing the dry films in 10 mg/mL DX dissolution in ethanol. They were left in solution for 24 hours in a dark place to prevent drug degradation. The films were then removed, blotted dry with tissue paper to remove excess drug solution and set aside for 24 hours to dry. The loading capacity of hydrogels was then evaluated by cutting loaded films into fragments, placing in 5 mL ethanol and leaving them on a rotator for 96 hours to allow all of the DX to be released. The resulting concentration of DX in Ethanol was measured using a UV-visible plate reader (FLUOstar Omega Microplate Reader, BMG LABTECH, Ortenberg, Germany) at wavelength 241 nm. Films loaded with DX were analysed using a TA Instruments DSC Q100 differential scanning calorimeter (DSC Q100). The temperature range was from 30 to 300°C at a heating speed of 10°C/min.

DX loaded hydrogels were used to test drug release. They were placed in glass vials containing 15 mL of PBS/Ethanol 20% to maintain sink conditions. Glass vials placed in shaking incubator, (40 rpm and 37°C) to mimic physiological conditions, for 24 hours. At specified times samples were taken and the concentration of DX was evaluated using a UV-visible plate reader at a wavelength of 241 nm.

3. Results

3.1. Hydrogel synthesis and characterisation

GAN is a biocompatible polymer (25) that contains a high concentration of carboxylic acid groups in its structure (Figure 1). The combination of GAN with molecules containing alcohol groups via an esterification reaction has been used in the past to prepare different types of materials for biomedical applications (26-29). In the present work GAN was crosslinked using PEG. Moreover, T85 and HPBCD were incorporated into GAN chains to improve the hydrogel capacity for hydrophobic drug loading. The chemical structure of these molecules can be seen in Figure 1.

The hydrogel synthesis took place in solid state. This type of process presents several advantages over conventional solution reactions. The obvious one is that no solvent is required. This simplifies the process and reduces the potential environmental impact of the synthesis (30). Additionally, using this process, hydrogels can be prepared using defined shapes. This can be especially beneficial for medical materials.

Figure 1 shows schematic of the hydrogel networks. PEG was used as a crosslinker. HPBC molecules contain a high amount of OH groups that can crosslink GAN chains. However, GAN/HPBCD hydrogels were discarded because they fracture during the swelling process. Consequently, PEG was added to the structure to prevent this.

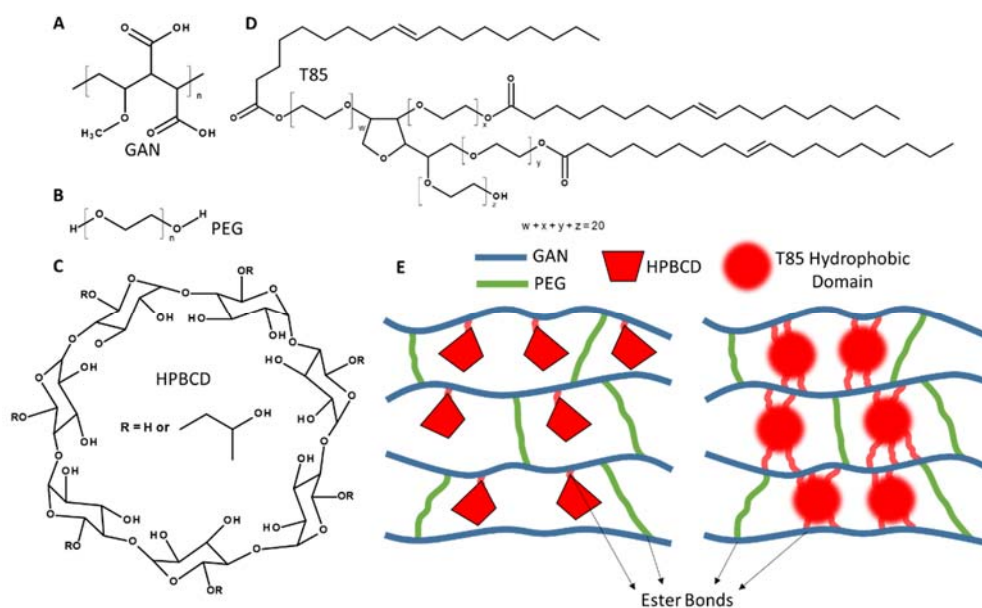


Figure 1. Chemical structures of GAN (A), PEG (B), HPBCD (C) and T85 (D). Structure of the prepared hydrogels containing HPBCD or T85 (E).

The crosslinking reaction was ascertained by using FTIR spectroscopy. Figure 2 shows the IR spectra of representative hydrogels before and after the crosslinking process. The esterification reaction between GAN and PEG or GAN and T85/HPBCD can be observed by having a close look at the carbonyl peak (ca. 1725 cm^{-1}) and to the C-O stretches (ca. 1070 cm^{-1}). The formation of new ester bonds has been reported in the past for GAN-based materials as a shift in the carbonyl peak (20). The reported peak shift indicates the presence of a new ester peak that is overlapping with the previous acid peak (31).

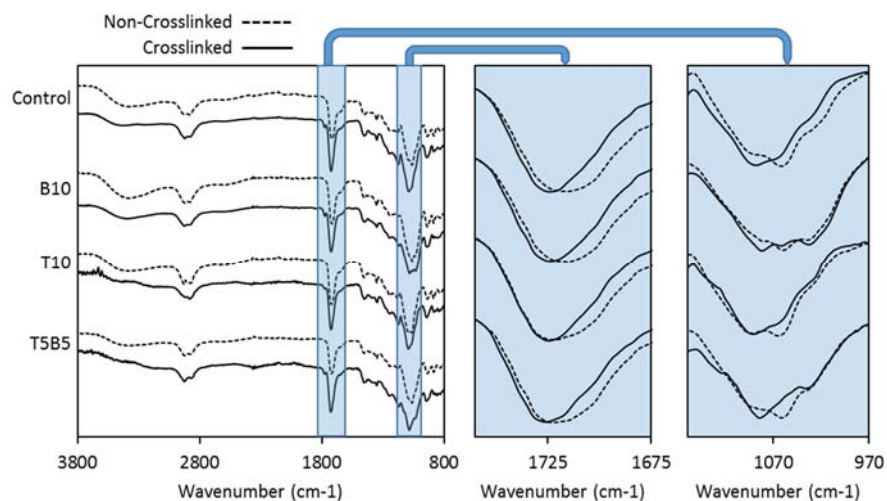


Figure 2. FTIR spectra of control, B10, T10 and T5B5 hydrogels before and after crosslinking

Additionally, the bands at around 1070 cm^{-1} showed some changes after crosslinking. These bands can be attributed to C-O stretching. Consequently, the materials present new C-O bonds after esterification. It is important to note that GAN can react with PEG and with T85/HPBCD and the FTIR results do not distinguish between these two types of esterification. However, further results will show that T85 and HPBCD were incorporated into the hydrogel structure as the swelling capacities, surface properties and drug loading/release capacities were affected by the composition of the hydrogel.

After the thermal treatment the resulting hydrogels were capable of absorbing fluids. PBS was used for the swelling experiments as simulant of physiological media. Figure 3A shows the maximum swelling capacity of the prepared hydrogels. It can be seen that hydrogels containing T85 showed slightly lower swelling capacity than the hydrogels containing HPBCD. Figure 3B show the influence of HPBCD or T85 in the swelling capacity of the hydrogels. The presence of T85 did not modify the swelling capacity of the hydrogels as T5 and T10 present equivalent swelling capacities to the control hydrogels. On the other hand, the presence of HPBCD increased the swelling capacity of the hydrogels. B5 showed the highest swelling capacity. Interestingly, when the amount of HPBCD was increased the swelling capacity decreased to levels similar to the control hydrogels. A possible explanation for this phenomenon is that small amounts of HPBCD yield a more expanded structure and PEG cannot crosslink the structure as efficiently. On the other hand, HPBCD can contribute to crosslink the structure. Therefore, higher concentration of the cyclodextrin derivative will increase the crosslinking degree of the material. Interestingly, the hydrogel containing both T85 and HPBCD showed swelling between that of B5 and T5.

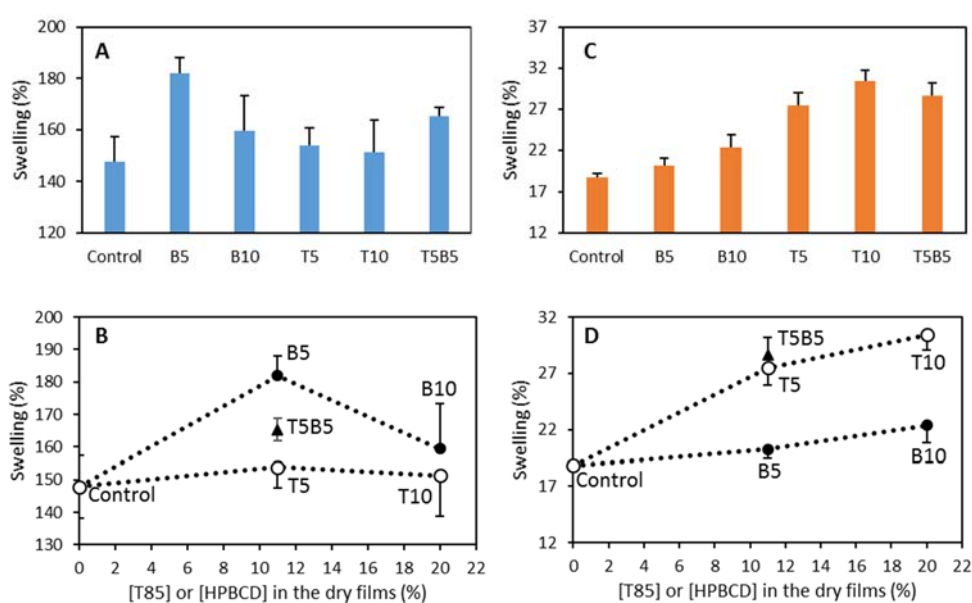


Figure 3. Maximum swelling obtained for all the hydrogels in PBS (A). Swelling capacity in PBS of the hydrogels as a function of the T85/HPBCD content in the films (B). Maximum swelling obtained for all the hydrogels in ethanol (C). Swelling capacity in ethanol of the hydrogels as a function of the T85/HPBCD content in the films (D).

Due to the amphiphilic nature of T85, the swelling capacity of the hydrogels in ethanol was evaluated (Figure 3C). The swelling capacities of the materials in this solvent were lower than in PBS. As expected, T85 showed higher swelling degrees in this solvent than the other hydrogels. Figure 3D shows the influence of the composition of the hydrogels in their swelling in ethanol. In this case, adding HPBCD or T85 to the hydrogel contributes to an increased ethanol uptake. However, the effect is more obvious in T85 based hydrogels. In this case T5B5 hydrogels showed equivalent swelling to T5 hydrogels. The ethanol swelling capacity was evaluated because DX was loaded by soaking the hydrogels in an ethanol solution of the drug. Consequently, the swelling capacity of the material for this solvent can influence the drug loading and should be considered.

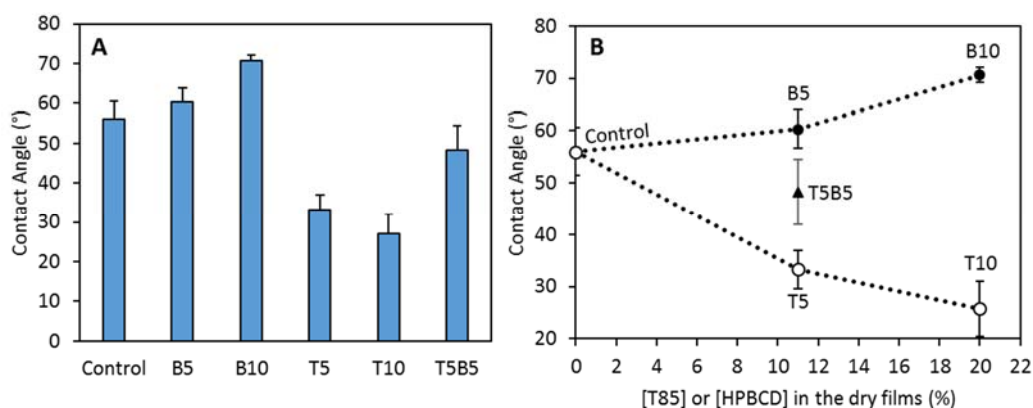


Figure 4. Static contact angles of the hydrogels (A). Static contact angles of the hydrogels as a function of the T85/HPBCD content in the material (B).

The hydrogels described in the present manuscript were designed as drug delivery systems. A key parameter for a medical material and drug delivery systems is wettability. The wettability of the material will influence the kinetics of drug release and the biocompatibility of the material (32, 33). This is especially important if the hydrogels are designed as contact lenses for drug delivery (33). Figure 4A shows the static contact angles obtained for all the different hydrogels. T85 based hydrogels showed a better wettability as the contact angles were lower. This is not surprising as T85 is a surfactant, the hydrophilic moieties of the hydrogel will be exposed in the surface while the hydrophobic sections will be forming hydrophobic domains within the interior of the material (20, 34). The influence of the composition of the hydrogels on the contact angle can be seen in Figure 4B.

The presence of HPBCD decreased the wettability of the material. This is an interesting result as in the past it has been reported that the presence of cyclodextrins in hydrogels improves the wettability (reduces contact angle) of the materials (35, 36). This can be explained by looking at the structure of the surface. In further sections it will be seen that HPBCD hydrogels present a surface with a high content of pores that can explain this result. Finally, T5B5 hydrogels showed a better wettability than B5, however, the presence of HPBCD in the hydrogel reduced the wettability of the material when compared to T5.

SEM microscopy was used to evaluate the surface morphology of the hydrogels (Figure 5). It can be seen that the addition of T85 and HPBCD has an impact in the surface morphology. Control hydrogels show flat surfaces while B10, T10 and T5B5 showed porous surfaces. B10 hydrogels showed higher porosity than T10 and this can explain the higher contact angle values obtained for the HPBCD hydrogels. T10 present pores in the surface but its wettability is better due to the presence of the surfactant. The presence of T85 in hydrogels has been reported to increase the porosity of the surface in previous work (20). Interestingly, T5B5 presents a high degree of porosity in the surface similar to the one obtained in T10.

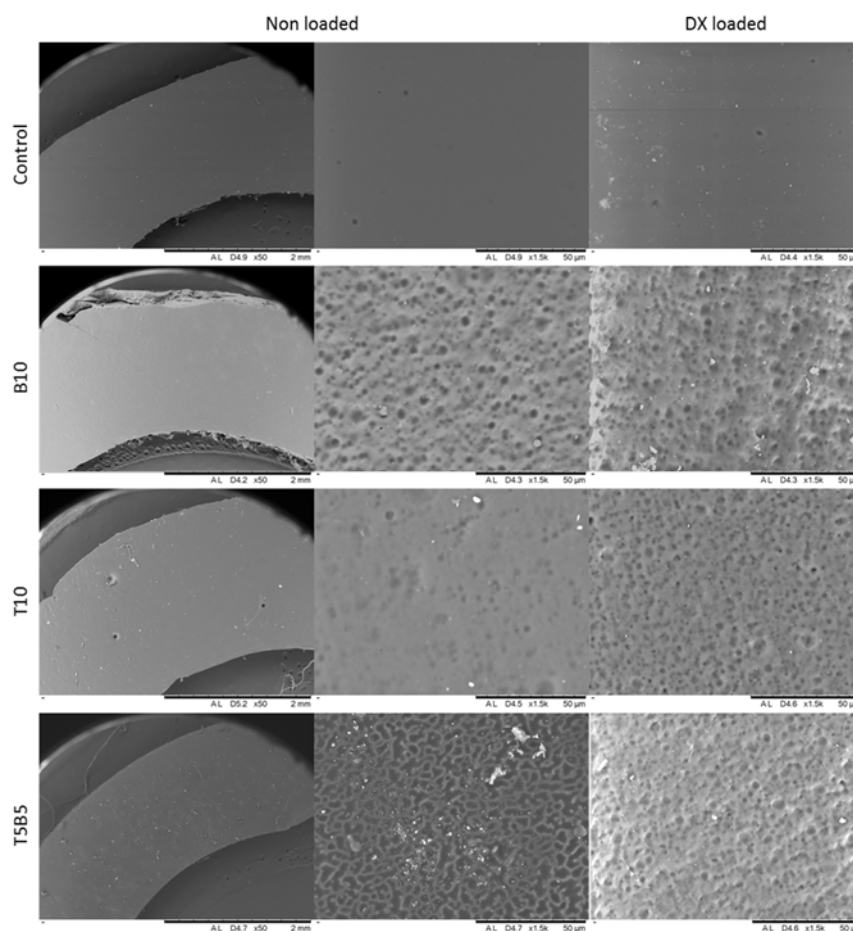


Figure 5. SEM microscopy images of representative hydrogels and DX containing hydrogels. The scale bars represent 2 mm in the first column and 50 μm in the second and third column.

3.2. DX loading and release

DX was selected as a model hydrophobic drug. The hydrogels were placed in DX solutions to be loaded. By using SEM the morphology of the hydrogels was studied. Figure 5 shows the surface of DX loaded hydrogels and no DX crystals can be observed in these materials. Similar behavior has been observed in the past for several hydrophobic drugs loaded in GAN/T85 based hydrogels (20) and β -cyclodextrin containing hydrogels (37). Figure 6A shows the loading of DX for all the synthesized hydrogels. It is obvious that the highest loadings were obtained for the hydrogels containing HPBCD. Additionally, T85 containing hydrogels showed drug loadings similar to the control ones and in some cases lower. When comparing the concentration of T85/HPBCD (Figure 6B) in the hydrogel with the loading it can be seen that there is no clear correlation with the T85 content. However, higher contents of HPBCD in the hydrogels lead to higher DX loadings. This is not surprising as the capacity of cyclodextrins to increase the solubility of hydrophobic DX molecules has been reported in the past (38, 39). The reason for this solubility increase is the formation of inclusion complexes between the drugs and cyclodextrin molecules (21, 40, 41). It has been reported previously that DX forms a 1:1 inclusion complex with HPBCD and its binding constant has been determined by several authors ranging between 2000 and 2500 M^{-1} (42, 43). Stability constant values ranging between 100 and 1000 M^{-1} are considered ideal (44). Smaller values indicates weak interactions between the cyclodextrin and the drug while values higher than 1000 M^{-1} suggest that incomplete release of the drug from the inclusion complex will take place (44). The complex formed between HPBCD and DX fulfill all this requirements.

T85 has been used to increase hydrophobic drug loading in GAN hydrogels in the past (20). However, it was reported that the loading was heavily influenced by the ethanol swelling capacity. In this case the ethanol swelling was limited and, consequently, the DX loading was similar to the one obtained for the control hydrogels. Interestingly, T5B5 hydrogels again showed drug loading between that obtained for B5 and T5. In this case the presence of T85 limits the loading of DX within the hydrogels. Figure 6C shows the DSC curves of pure DX and DX loaded hydrogels. It is important to note that the drug showed a defined melting peak at around 260°C. This peak cannot be observed in the loaded hydrogels. Consequently, this suggests that the drug is dispersed within the hydrogel matrix and is not in crystalline form.

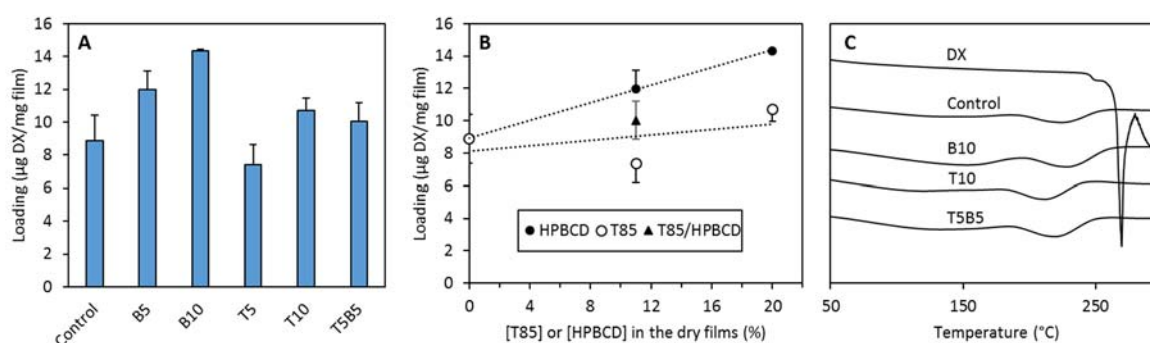


Figure 6. DX loading obtained for all the prepared hydrogels (A). DX loading as a function of the T85/HPBCD content in the hydrogels (B). DSC curves for DX and representative DX loaded hydrogels (C).

The release of DX from the hydrogels was studied by placing DX loaded hydrogels in 15 mL of PBS with 20% of ethanol to maintain sink conditions. Figure 7A shows the cumulative DX release from the hydrogels. As expected, HPBCD-containing hydrogels released higher amounts of DX. B10 showed the highest capacity to deliver DX, followed by B5 and T5B5. T85 containing hydrogels showed similar or even lower quantities of released DX than the control hydrogels. This indicates that T85 limits DX release. This can be explained by the presence of hydrophobic domains within the hydrogel matrix that will interact DX molecules preventing their release (20).

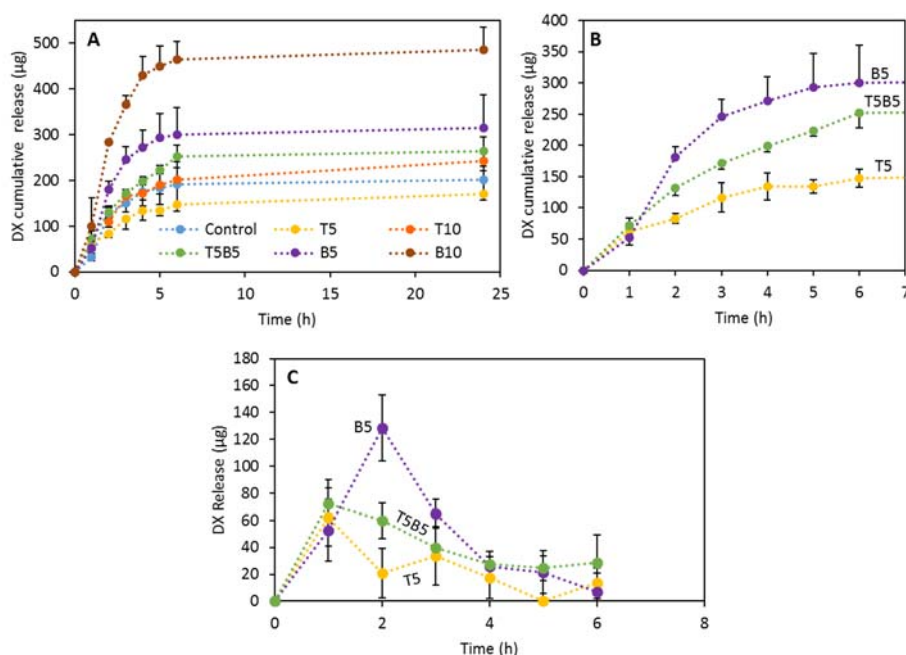


Figure 7. DX cumulative release as a function of time for all the prepared hydrogels (A). DX cumulative release (B) and DX release (C) as a function of time for B5, T5 and T5B5 hydrogels.

All the hydrogels were capable of releasing DX during a period of 6 hours. However, by looking at the curves, it can be seen that T5B5 showed a more sustained release profile than the other hydrogels. This type of material combines the higher DX loading capacities of the hydrogels containing HPBCD and the sustained delivery of T85 containing hydrogels (Figure 7B). This can be seen in more detail in Figure 7C that shows the DX release as a function of the time for B5, T5 and T5B5. It can be seen that B5 provided a quick release of DX with a maximum after 2 hours. However, after this time the amount released decreases rapidly. On the other hand, T5 and T5B5 presented a lower DX release but in a more sustained way. These hydrogels provided a peak at around 1 hour and then the release decreased gradually over the next hours. This is particularly noticeable for T5B5 that presents more sustained drug release profiles.

4. Conclusions

Hydrogels containing cyclodextrins and other moieties capable of incorporating hydrophobic drugs have been extensively described in the literature (12, 21, 37, 45, 46). However, this manuscript describes a simple method to synthesize GAN and T85/HPBCD hydrogels. The method is quick and simple as it does not require the use of solvents or toxic reagents. The main byproduct of esterification is water. Consequently, it is ideal for biomedical and pharmaceutical applications as no toxic byproducts or reagents are used. Additionally, the process can be considered environmental-friendly.

The addition of T85 and HPBCD to GAN hydrogels could potentially improve the loading and release of hydrophobic drugs. T85 has been incorporated into hydrogels in the past to improve curcumin loading and to provide sustained release over 30 days (20). However, in this case the addition of T85 did not influence the loading of DX. However, the surfactant showed strong affinity for DX as it prevents the release of this molecule from the hydrogel. On the other hand, cyclodextrins have been extensively incorporated into hydrogels for drug delivery purposes. The use of cyclodextrin containing hydrogels for DX release has been described in the past (47). This is due to the inclusion complex that is formed between HPBCD and DX (43).

The described hydrogels present potential applications in different scenarios. These hydrogels can be easily applied as contact lenses for DX delivery. Ophthalmic drug delivery by contact lenses is more efficient than conventional eye drop formulations as it extends release of drug while increasing the residence time in the tear film (48-51). DX is an ideal candidate as it is used to relieve eye inflammation caused by severe allergies (48, 52). However, the hydrogels described in the present paper should be modified as the normal ocular dose required per day is around 10 μg (53) and these hydrogels provided release of up to 450 μg of DX in 5 hours. Additionally, the formulation should be modified to allow a more sustained drug release over a prolonged time to replace the continuous administration of DX eye drops.

There are other potential applications for hydrogels for localized delivery of DX, such as the treatment of osteoarthritis (54) or the prevention of restenosis using DX eluting vascular stents (55). However, the hydrogels should be modified to allow sustained release of DX for this type of application. The release profile of the hydrogels seems to be more applicable as an oral or topical DX release system (56, 57). The release profile over a few hours will be ideal to provide a sustained oral delivery of the drug. DX has been previously loaded into hydrogels achieving drug loadings ranging from 5 to 10 mg/g (56, 58). On the other hand, the hydrogels described in the present study are capable of loading up to 14 mg/g.

The present study was a proof of concept describing how GAN can be easily combined with surfactants and cyclodextrins to yield hydrogels for hydrophobic drug delivery. Further work should be performed to optimize the drug release process. However, the materials described here have potential as systems for local delivery of DX.

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