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Article

# Synthesis of 4-Acryloylmorpholine-based Hydrogels and Investigation of their Drug Release Behaviors

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Neste trabalho, hidrogéis baseados em um derivado de acrilamida anfifílico, solúvel em água, bissubstituído e biocompatível, a saber 4-acriloilmorfolina (4-AcM), foram preparados. Hidrogéis baseados em 4-AcM com diferentes composições foram sintetizados por fotopolimerização de misturas de polietilenoglicol diacrilato (PEG-DA) e poli(2-hidroxietil metacrilato) (HEMA), e caracterizados por espectroscopia no infravermelho com transformada de Fourier (FTIR). As porcentagens de gel e razões de entumescimento no equilíbrio foram determinadas. Imagens obtidas por microscopia eletrônica de varredura (SEM) confirmaram a estrutura porosa dos hidrogéis. Ciprofloxacino.HCl foi escolhido como fármaco modelo para entender os comportamentos de carga e liberação de fármacos dos hidrogéis. Com o aumento da quantidade de 4-AcM, observou-se maior liberação do fármaco. Por outro lado, o aumento na densidade de reticulação devido ao conteúdo de PEG-DA resultou na diminuição do entumescimento do hidrogel e reduziu a difusão do medicamento.

In this study, hydrogels based on an amphiphilic, water soluble, bisubstituted and biocompatible acrylamide derivative, namely 4-acryloylmorpholine (4-AcM), were prepared. 4-AcM based hydrogels with different compositions were synthesized by photopolymerization from the mixtures of poly(ethylene glycol) diacrylate (PEG-DA) and poly(2-hydroxy ethyl methacrylate) (HEMA), and characterized by Fourier transform infrared spectroscopy (FTIR). Gel percentage and equilibrium swelling ratios were determined. Images obtained by scanning electron microscopy (SEM) confirmed porous structure of the hydrogels. Ciprofloxacin.HCl was chosen as a model drug in order to understand the drug loading and release behaviors of the hydrogels. As 4-AcM content increased, higher drug release was observed. On the other hand, the increase in crosslinking density due to PEG-DA content resulted in the swelling decrease of the hydrogel and reduced the diffusion of the drug.

**Keywords:** hydrogel, photopolymerization, drug release, 4-acryloylmorpholine, ciprofloxacin

## Introduction

Hydrogels are of great interest in the biomedical area because of their hydrophilic and biocompatible nature as well as mechanical strength.[1] They are widely used in controlled release systems, contact lenses, tissue barriers, artificial blood vessels, bioactive protein separation membranes and artificial muscular systems.[2,3] The research on hydrogels with respect to drug delivery devices has been extensive over the last few decades because of their biocompatibility and easy control of solute transport.[4,5]

Hydrogels with additional functions such as the ability to swell or shrink in response to a signal (temperature or pH) are often called "smart" hydrogels. They are also known as environment-sensitive hydrogels.[6,7]

Negative temperature sensitive gels possess a lower critical solution temperature (LCST).[4,6,8] Polymers with LCST decrease their water solubility as the temperature increases.[8] The adjustment of LCST to near body temperature is required especially for "smart" drug delivery applications.[6,7]

Interpenetrating polymer networks (IPN) are the preferred devices in drug delivery.[9,10] Another preferred method is the incorporation of hydrophobic components into hydrophilic hydrogels through copolymerization. In this way, the active agent is involved within the hydrogel system to ensure that the solute remains in the hydrogel by the presence of sufficient crosslinking. Peppas *et al*.[6] studied the potential use of hydrogels and encapsulated

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drugs into gels in order to investigate changes in the level of drug release.

4-Acryloyl morpholine (4-AcM) and its high molecular weight polymers have been studied for many years.[11] P-AcM derivatives have a wide range of use in peptide synthesis, enzyme immobilization, membranes for blood plasma separation and drug release applications.

4-AcM derivatives serve as an acceptor to make a hydrogen bond since they have a disubstituted amide group. 4-AcM is soluble in water and other ordinary organic solvents (insoluble in hexane). 4-AcM also acts as a solvent for organic materials containing resin, dye, wax, varnish and casein.[12] 4-AcM is a hydrophilic and non-ionic monomer. These properties make it ideal to increase the swelling ratio of hydrogels facilitating water penetration into the polymeric network.[13]

Ciprofloxacin (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, $C_{17}H_{18}FN_3O_3$), a member of the fluoroquinolone antibiotic family, is often used to treat and prevent infections caused by bacteria such as enteric, respiratory and urinary tract infections, gastrointestinal surgery and septicemia. Ciprofloxacin inhibits bacterial enzymes, such as DNA gyrase.[14,15] The solubility of ciprofloxacin is low in the range of pH 6-9. On acidic pH 4-5 and basic pH 10-11 scales, the solubility is sensitive to changes in pH. Ciprofloxacin gains a cationic nature below pH 6, whilst it is anionic above pH 9. Ciprofloxacin solubility in water is high. It creates an ionic surface with chloride in water, increasing solubility. Temperature is another factor to increase the solubility.[16,17]

In this study, copolymeric hydrogels based on 4-AcM, 2-hydroxyethyl methacrylate (HEMA) and poly(ethylene glycol) diacrylate (PEG-DA) in the presence of a photoinitiator (Irgacure® 184) were synthesized by the UV curing technique. Ciprofloxacin (CFX).HCl was used as a model drug in order to evaluate hydrogels as drug carriers. In the literature, there is no study which involves ciprofloxacin.HCl drug release of hydrogels based on 4-AcM prepared by UV curing technique.

Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM) and thermogravimetric (TGA) analyses were applied. Gel percentages and equilibrium swelling ratios of the hydrogels were determined. pH sensitivity experiments of the hydrogels were also performed. The equilibrium swelling ratios increased with the increase of the 4-AcM content and decreased with the increase of PEG-DA. As the 4-AcM content increased, higher drug release was observed. On the other hand, the increase in crosslinking density due to the PEG-DA content resulted in the swelling decrease of the hydrogel and reduced the diffusion of the drug.

## Experimental

### Materials

4-Acryloyl morpholine (4-AcM) and poly(ethylene glycol) diacrylate (PEG-DA, $M_n$: 258 g $mol^{-1}$) were purchased from Aldrich and used as received. 2-Hydroxyethyl methacrylate (HEMA) was obtained from Fluka and used as received. Irgacure® 184 (IRG-184) was kindly supplied by Ciba Company and used without purification. Ciprofloxacin.HCl was generously provided by Atabay Pharmaceutical. Buffer solutions were prepared as follows:

Solution A: 1/15 mol $L^{-1}$ $KH_2PO_4$ 9.073 g $L^{-1}$ in distilled water;

Solution B: 1/15 mol $L^{-1}$ $Na_2HPO_4.2H_2O$ 11.87 g $L^{-1}$ in distilled water;

For pH 6.9, 534 mL of solution A and 413 mL of solution B were mixed and then completed to 1 L.

For pH 5, 992 mL of solution A and 8 mL of solution B were mixed;

For pH 2, solution a: 2.1014 g $C_6H_8O_7$ *per* 100 mL in distilled water;

Solution b: 20 mL of 1 mol $L^{-1}$ NaOH;

Solution c: (a + b);

Solution d: 250 mL of 0.1 mol $L^{-1}$ HCl;

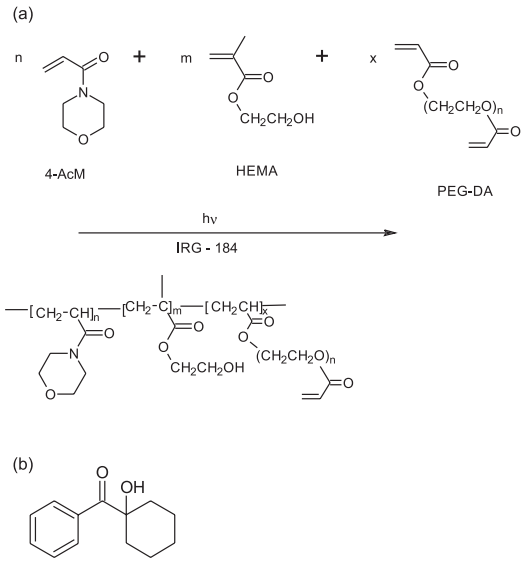
75.5 mL of solution c were completed with 174.5 mL of solution d to 250 mL;

50 ppm (mg $L^{-1}$) ciprofloxacin.HCl were dissolved in pH 6.9 buffer solution;

### Synthesis of 4-AcM based hydrogels

Various hydrogel formulations based on 4-AcM, HEMA and PEG-DA (Scheme 1a) in the presence of a photoinitiator (IRG-184, Scheme 1b) were prepared, as shown in Table 1.

The prepared formulations were poured onto Teflon® molds (diameter of 10 mm, depth of 2 mm). In order to prevent the inhibitory effect of oxygen, the mixture in the mold was covered with a 25 μm thick Teflon transparent film before irradiation with a high pressure UV-lamp (OSRAM 300 W, $\lambda_{max}$ at 365 nm; the distance between the lamp and the sample was 25 cm). Then, photopolymerization was performed under UV irradiation for 180 s. The obtained polymer samples were extracted with distilled water to remove unreacted parts and the photoinitiator.




**Scheme 1.** (a) 4-AcM-based hydrogel and (b) the chemical formula of Irgacure® 184.

**Table 1.** Formulation details of the hydrogels

| Hydrogel[a] | 4-AcM / mol% | HEMA / mol% | PEG-DA / mol% |
|---|---|---|---|
| AcM-1 | 0 | 90 | 10 |
| AcM-2 | 10 | 80 | 10 |
| AcM-3 | 20 | 70 | 10 |
| AcM-4 | 20 | 75 | 5 |
| AcM-5 | 20 | 65 | 15 |
| AcM-6 | 20 | 60 | 20 |
| AcM-7 | 30 | 60 | 10 |

[a]All formulations contain 3 wt.% IRG-184 as photoinitiators and 20 wt.% of $H_2O$.

### Characterization of hydrogels

#### Determination of gel percentage

The samples were freeze-dried after irradiation, and then they were immersed in distilled water for one week to remove the unreacted monomers, photoinitiator and impurities. The water was refreshed every two days. One week later, the gels were removed and freeze-dried. The gelation (%) was calculated by the following equation 1:

$$\text{Gelation} = \frac{w_d}{w_o} 100 \quad (1)$$

where $w_d$ is the weight of the gel after freeze drying and $w_o$ is the weight of the gel after polymerization.

#### Swelling studies

The equilibrium mass swelling of the hydrogels was measured in deionized water and in various pH media ranging from 2 to 6.9. The pre-dried hydrogel samples ($w_o$) were placed in vials filled with 25 mL of deionized water or different buffer solutions. The vials were placed in a temperature-controlled bath at 20.0 ± 0.1 °C for one week until reaching constant weight. The swollen hydrogels were removed from the medium, gently wiped with filter paper and weighed ($w_s$). The swelling ratio of the hydrogels was calculated from the following equation.

$$\text{Equilibrium swelling ratio} = \frac{w_s - w_o}{w_o} 100 \quad (2)$$

#### Drug-loading and release

Ciprofloxacin.HCl was used as a model drug for loading and release experiments. The dried hydrogels were kept in a 50 ppm (mg $L^{-1}$) ciprofloxacin.HCl aqueous solution at 4 °C for 2 days. After incubation, the gels were removed from the solution and rinsed in cold distilled water. The CFX.HCl release experiments were carried out by transferring previously incubated drug-loaded gels into 20 mL of phosphate buffer, pH 6.9 at 37 °C at a constant shaking rate. At various time intervals, 3 mL of the drug solution were taken to measure the drug concentration by using a Shimadzu UV-spectrophotometer (λ at 270 nm) and refreshed by adding 3 mL of phosphate buffer each time. The calibration curve based on different concentrations was plotted, then, the weight $w_t$ at time t and the total weight ($w_{total}$) were calculated.

The amount of the release (%) of CFX.HCl was calculated from the following equation:

$$\text{Release} = \frac{w_t}{w_{total}} 100 \quad (3)$$

where $w_t$ is the weight of released CFX.HCl at time t and $w_{total}$ is the total adsorbed CFX.HCl in the gel structure.

#### Equipments

FTIR spectrum was recorded on a Perkin Elmer Spectrum 100 FTIR spectrophotometer. TGA analyses were performed using a Perkin-Elmer Thermogravimetric analyzer Pyris 1 TGA model, under $N_2$ atmosphere, 10 °C $min^{-1}$ from 30 to 700 °C. SEM images of the films were performed on a Philips XL30 ESEM-FEG/EDAX microscope.

## Results and Discussion

### Compositions and swelling properties of hydrogels

In this work, 4-AcM-based hydrogels were prepared by the UV curing technique. Scheme 1a shows the synthesis of the 4-AcM-based hydrogels.

The chemical structures of the hydrogels were characterized by the FTIR technique. Figure 1 displays the FTIR spectrum of AcM-3 hydrogel. As seen in Figure 1, the broad absorption band around 3388 $cm^{-1}$ is ascribed to the peaks of –OH groups. The absorption bands observed at 1715 $cm^{-1}$ are characteristic of the carboxylic C=O group in HEMA. The band at 1615 $cm^{-1}$ displays the shift of C=O vibration of the AcM structure due to hydrogen bonding interactions. The peaks at 1387 and 1448 $cm^{-1}$ are attributed to $–CH_3$ groups. Also, the ring stretching vibration (mainly asymmetric ν(C–O–C)) in morpholine is observed at 1112 $cm^{-1}$.[12,17,18]

## Thermal properties

Thermal properties of the 4-AcM-based hydrogels were characterized by TGA analyses. Table 2 shows the evaluated results for TGA analysis.

**Table 2.** TGA analyses of the hydrogels

| Hydrogel | Temperature / °C, 10% weight loss | Temperature / °C, 50% weight loss | Char / % |
|---|---|---|---|
| AcM-1 | 275 | 357 | 0.0 |
| AcM-3 | 336 | 410 | 0.3 |
| AcM-6 | 349 | 411 | 3.0 |

When the temperatures at which a 10 wt.% loss occurs are compared, it can be seen that AcM-3 and AcM-6 hydrogels are more stable than the AcM-1 hydrogel (without 4-AcM monomer). The incorporation of 4-AcM monomer increased the decomposition temperature. The char yield increased with an increasing PEG-DA amount.

## Morphological behavior

Secondary electron image mode was applied in SEM. The specimens were prepared for SEM by freeze fracturing in liquid nitrogen and applying a gold coating of approximately 300 Å. In Figure 2a, the SEM image reveals that the ACM-1 hydrogel was rather dense and homogenous. This result indicated that the hydrogel without 4-AcM is a highly cross-linked structure. Previously, it was reported that the addition of PEG chains would influence the pore-size distribution of membranes.[19] As seen from the SEM image (Figure 2a), this morphology can cause limitation in the drug diffusion.

However, porous interconnected morphology (Figures 2b and 2c) was observed for AcM-3 and AcM-6 hydrogels, respectively. The incorporation of morpholine molecules can exert a steric hindrance against the orientation of polymer segments. Suitable pore channels of AcM-containing hydrogels lead to efficient drug release.

## Gel percentage and equilibrium swelling results

The synthesized hydrogel compositions are given in Table 1. The values of gel percentages of hydrogels were ranged between 93 and 95% (Table 3). High gel percentages denote almost complete conversion of monomers to polymer.

Table 3 also exhibits the equilibrium swelling ratio of the hydrogels in water at 20 °C. From the data in

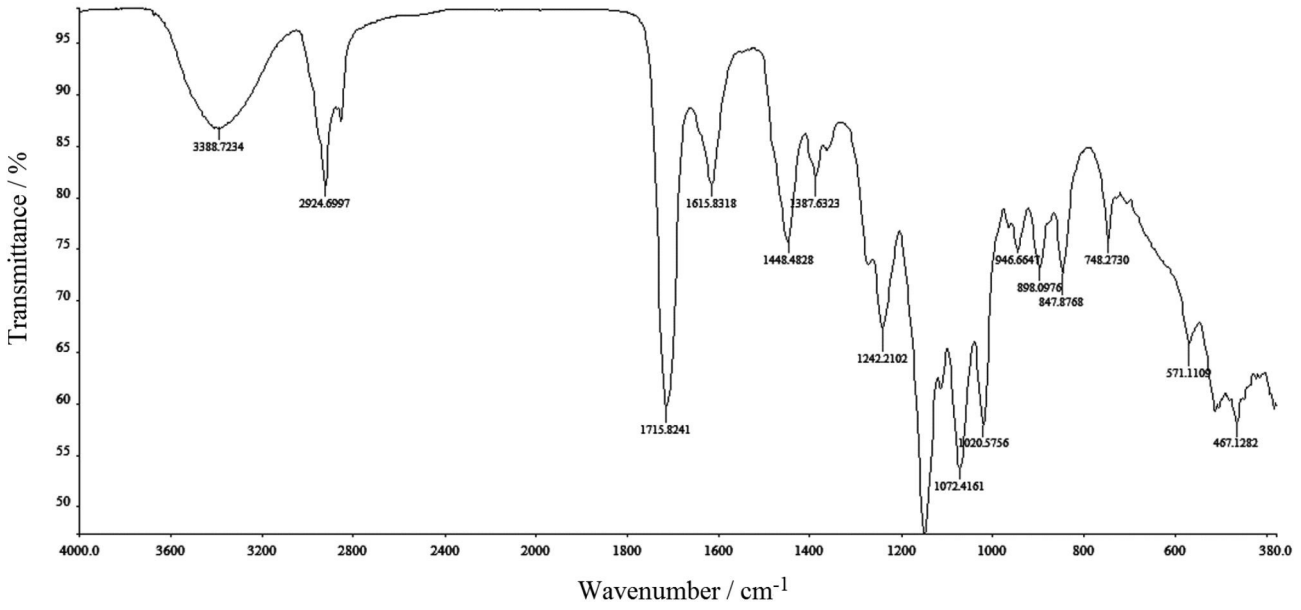



**Figure 1.** FTIR spectrum of AcM-3.

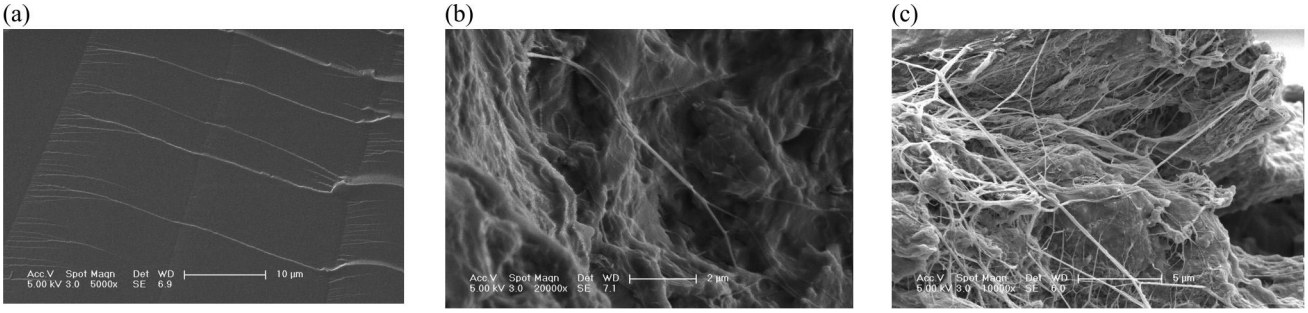



**Figure 2.** SEM images of (a) ACM-1, (b) AcM-3 and (c) AcM-6 hydrogels.

**Table 3.** Gel percentages and equilibrium swelling ratios of the hydrogels

| Hydrogel | Gel / % | Equilibrium swelling ratio in water / % |
|---|---|---|
| AcM-1 | 93.0 | 35 |
| AcM-2 | 93.5 | 38 |
| AcM-3 | 94.0 | 43 |
| AcM-4 | 95.0 | 55 |
| AcM-5 | 93.0 | 38 |
| AcM-6 | 93.0 | 32 |
| AcM-7 | 95.0 | 50 |

Table 3, it can be seen that the equilibrium swelling ratio of 4-AcM-based hydrogels gradually increased with the increasing 4-AcM content in the corresponding hydrogel at a constant crosslinking monomer (PEG-DA) content. For instance, AcM-1 presented the lowest equilibrium swelling ratio, 35% at 20 °C, while the equilibrium swelling ratios of AcM-2, AcM-3 and AcM-7 were 38, 43 and 50%, respectively. The equilibrium swelling ratio of hydrogels is also affected by the PEG-DA content. AcM-4 with 5 wt.% PEG-DA content presented the largest equilibrium swelling ratio (55%). Further increase in the PEG-DA content of the hydrogels (AcM-5 and AcM-6) decreased the equilibrium swelling values because of the increased crosslinking density.

## The pH dependency of swelling

The pH dependency of the equilibrium swelling percentage of the hydrogels produced with different 4-AcM contents is shown in Figure 3. The concentration of total co-monomer and crosslinker in the polymerization medium is fixed. At pH 2, the swelling ratio of the hydrogel increased with the increasing 4-AcM content.

As pH increases, the swelling ratio of the hydrogels decreased slightly. Since AcM has amide and ether groups, these groups can be classified as soft acids;[20] at low pH values, the enolate structure of 4-AcM will probably be protonated. Therefore, higher swelling ratios at low pH is expected. Based on the hard and soft acid and base (HSAB,

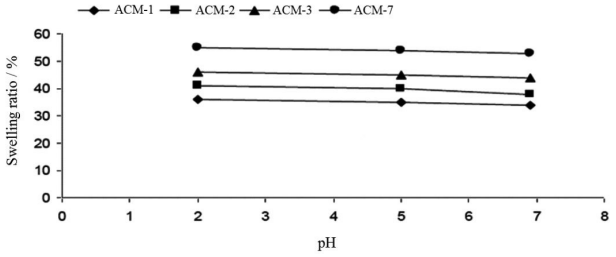



**Figure 3.** Equilibrium swelling percentages of ACM-1, ACM-2, ACM-3 and ACM-7 hydrogels in buffer solutions, pH 2, 5 and 6.9.

by Pearson) principles, the structures in which 4-AcM (soft acid) is involved will interact with soft bases and borderline bases. A weak or no interaction with hard bases can be observed. The soft acids and bases are easily polarized. They show low electronegativity. The C atom is less electronegative than other atoms (N, O). Carbon atom is soft in the enolate anion. Thus, the other reaction (between enolate and 4-AcM) can proceed via this atom (shown in Figure 4). In the case of protonation, oxygen (a more electronegative atom) would probably accept a hydrogen to give the enol form ($R_1$–C(OH)=CH–$R_2$), which is converted to the keto form ($R_1$–C(O)–$CH_2$–$R_2$).

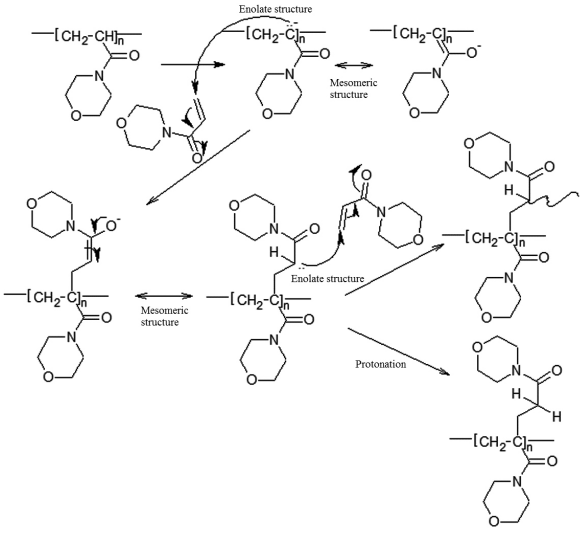



**Figure 4.** The estimated mechanism between 4-AcM and its enolate anion.

In the copolymerization experiments, the concentration of crosslinker PEG-DA was also changed by fixing the total monomer content. Figure 5 demonstrates the pH dependence of the equilibrium swelling ratio of hydrogels with different concentrations of crosslinker. As seen in Figure 5, regardless of pH, the hydrogels had similar swelling behaviors as a function of the crosslinker content. It is observed that the equilibrium swelling ratio of the hydrogels was significantly decreased with increasing PEG-DA content.

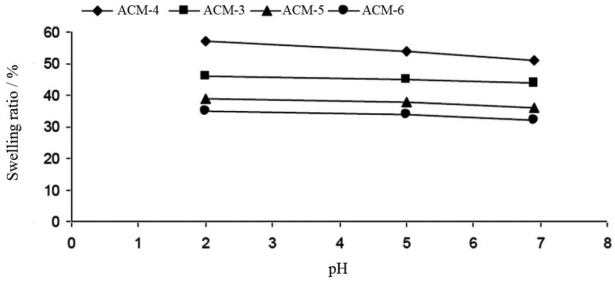



**Figure 5.** Equilibrium swelling percentages of ACM-3, ACM-4, ACM-5 and ACM-6 hydrogels in buffer solutions, pH 2, 5 and 6.9.

## Drug loading and drug release

In Table 4, the total drug uptake and equilibrium release amounts for the hydrogels can be seen.

**Table 4.** Total drug uptake and equilibrium release results

| Hydrogel | Total uptake / (mg $g^{-1}$ dry gel), pH 6.9 | $m_{nonreleased}$ / (mg $g^{-1}$ dry gel) | Release / % |
|---|---|---|---|
| AcM-1 | 41.81 | 11.28 | 73 |
| AcM-2 | 43.59 | 9.15 | 79 |
| AcM-3 | 45.29 | 6.79 | 85 |
| AcM-4 | 61.61 | 6.16 | 90 |
| AcM-5 | 37.88 | 10.64 | 72 |
| AcM-6 | 34.21 | 13.68 | 60 |
| AcM-7 | 49.63 | 0.99 | 98 |

Drug loadings were performed in buffer at pH 6.9 and 4 °C. As seen in Table 4, the drug loading increased with increasing AcM content and decreased with increasing PEG-DA content of the hydrogels. Drug release from a hydrogel is closely related to many factors such as swelling behavior of the hydrogel, drug affinity for the polymer structure and solubility of the drug in water.[21] Figures 6 and 7 depict the *in vitro* release profile of CFX.HCl from hydrogels at pH 6.9 and 37 °C.

Generally, all hydrogels showed an initial burst release within the first 15 min with an amount of 5-20%. The explanation for this sudden release is possibly due to the drug absorbed at the gel surface.[22] The CFX.HCl release increased rapidly at first and then gradually reached the equilibrium value in approximately 7 h. The release percentage increased with an increase in the 4-AcM content and a decrease in the PEG-DA content in the hydrogel structure. This can be explained by the increase in the diffusional path due to the high swelling of hydrogels. While 73% of CFX.HCl was released from the hydrogel without AcM, this value increased to 98% with the increase of the AcM content to 30 wt.% in the gel structure.

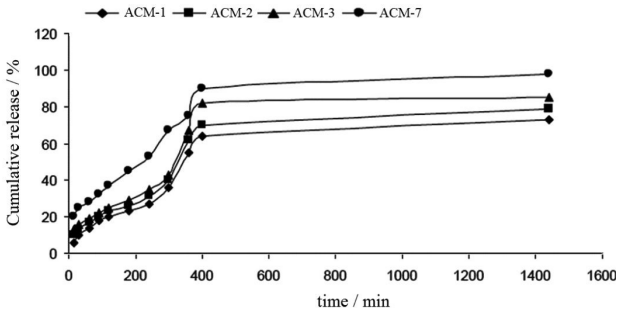



**Figure 6.** Release of CFX.HCl from ACM-1, ACM-2, ACM-3 and ACM-7 hydrogels.

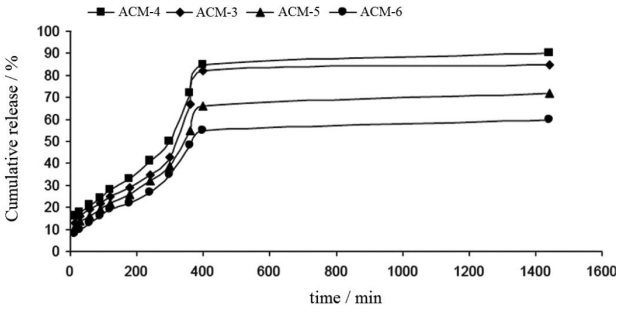



**Figure 7.** Release of CFX.HCl from ACM-3, ACM-4, ACM-5 and ACM-6 hydrogels.

On the other hand, the release is also affected by the crosslinking density of the hydrogel. While 90% of CFX.HCl were released from the hydrogel with 5% of PEG-DA content, this value decreased to 60% with increasing PEG-DA content to 20 wt.% in the gel structure. Since the mesh sizes of the 4-AcM hydrogel with low PEG-DA content are larger, the CFX.HCl diffusivity will be easy.

## Conclusions

Hydrogels are of specific interest in biomedical applications, such as promising devices in drug delivery systems because of their high water content and biocompatibility. In this work, CFX.HCl release from 4-AcM hydrogels was studied. 4-AcM-containing hydrogels are a suitable matrix for drugs dissolved in water because of its hydrophilic nature.

The hydrophilic nature of 4-AcM containing hydrogels can develop the quality of drug therapy. The gel percentages of hydrogels varied between 93 and 95%. The equilibrium swelling ratios increased with the increase of the 4-AcM content and decreased with the increase of PEG-DA. Moreover, loading trends are in conformity with the swelling behavior of hydrogels. As the 4-AcM content increased, higher drug release was observed. On the other hand, the increase in crosslinking density due to PEG-DA content results in the swelling decrease of the hydrogel and the reduced diffusion of the drug.

## Acknowledgement

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