Nr 1 (1–72) STYCZEŃ 2025 Tom LXX

POLIMERY

Synthesis and characterizations of poly(hydroxybenzyl methacrylate-*co*-acrylamide) based hydrogel as drug delivery system

Fatima Hekmat Assal[1)], Ameen Hadi Mohammed[1), *)] (0000-0003-2323-198X)

DOI: https://doi.org/10.14314/polimery.2025.1.1

Abstract: The aromatic/hydrophilic monomer, hydroxybenzyl methacrylate (HBM), was synthesized by reaction of 4-hydroxy benzyl alcohol with acrylic acid and then copolymerized with acrylamide (AAM) in various proportions. Potassium persulfate (PPS) was used as the initiator. The copolymer (3HBM/1AAM), selected based on the swelling results in water, was crosslinked using different concentrations of ethylene glycol dimethyl acrylate (EGDMA). The chemical structure of the monomer and copolymers was confirmed by Fourier transform infrared spectroscopy (FT-IR) and proton magnetic resonance (1H-NMR). The effect of the crosslinker concentration on the swelling, mechanical and thermal properties of the copolymers was investigated. The equilibrium water content (EWC) increased with the increase in the amount of crosslinker. The mechanical and thermal properties were also improved. The ability of the obtained copolymers to incorporate and release the drug (ciprofloxacin) was investigated based on swelling in the drug solution. A higher proportion of HBM in the copolymer resulted in a higher efficiency of the copolymer as a drug carrier.

Keywords: hydrophilic monomer, copolymerization, crosslinking, mechanical and thermal properties, ciprofloxacin.

Synteza i charakterystyka hydrożelu na bazie polihydroksybenzylometakrylanu-*co*-akrylamidu jako układu dostarczania leków

Streszczenie: W reakcji alkoholu 4-hydroksybenzylowego z kwasem akrylowym otrzymano aromatyczny/hydrofilowy monomer, hydroksybenzylometakrylan (HBM), który następnie kopolimeryzowano z akrylamidem (AAM) w różnych proporcjach. Jako inicjator stosowano nadsiarczan potasu (PPS). Wybrany na podstawie wyników pęcznienia w wodzie kopolimer (3HBM/1AAM) poddano sieciowaniu przy użyciu różnych stężeń dimetyloakrylanu glikolu etylenowego (EGDMA). Strukturę chemiczną monomeru i kopolimerów potwierdzono metodą spektroskopii w podczerwieni z transformacją Fouriera (FT-IR) i protonowego rezonansu magnetycznego (1H-NMR). Zbadano wpływ stężenia środka sieciującego na pęcznienie, właściwości mechaniczne i termiczne kopolimerów. Wraz ze wzrostem ilości środka sieciującego zwiększała się równowagowa zawartość wody (EWC). Poprawiły się również właściwości mechaniczne i termiczne. Zdolność otrzymanych kopolimerów do wprowadzania i uwalniania leku (ciprofloksacyna) zbadano na podstawie pęcznienia w roztworze leku. Większy udział HBM w kopolimerze skutkował większą wydajnością kopolimeru jako nośnika leku.

[1)] Department of Chemistry, College of Science for Women, University of Baghdad, 10071 Baghdad, Iraq.

[*)] Author for correspondence: ameenhadi80@yahoo.com

Słowa kluczowe: monomer hydrofilowy, kopolimeryzacja, sieciowanie, właściwości mechaniczne i termiczne, ciprofloksacyna.

The last decade has seen a rise in interest in the synthesis of multifunction polymers that are prepared from aromatic or aliphatic acrylate monomers due to their importance in different medical and industrial applications [1-4]. This type of polymer possesses diverse characteristic properties such as super-absorbency, flexibility, transparency, rubbery, oil and heat resistance among other polymers [5-8]. Therefore, these polymers are widely used in various industrial and medical applications such as adhesives, paints, lubricant additives, oil/water separation, textiles, bone cements, diapers, contact lenses, cosmetics, drug delivery, coatings, and orthopedics [9-13]. Numerous techniques might be used to overcome the drawbacks of these polymers, for instance, copolymerization with other monomers could improve their mechanical and thermal properties [14, 15]. In addition, using crosslinking agents could also enhance their properties due to their role in restricting the mobility of polymers chains [16]. However, the comonomer reactivity ratio values should be considered and determined using accurate procedures due to their direct impact on the properties of produced copolymers [17, 18].

During the last decades, poly(methyl methacrylate) (PMMA), in the form of beads known as spacers, has been widely used in the treatment of infections during orthopedic surgeries [19]. However, the inserted beads in the infection region can cause a reduction in mobility, joint stiffness, and pain [20]. On the other hand, the potential use of polymers, based on hydrophilic monomers as drug carriers has gain more attention due to their high water holding capacity and three-dimensional structural network which supports the controlled release of drugs, the high--water content of hydrogel allows in the encapsulation of hydrophilic drugs [21]. Based on this fact, several types of hydrogels have been used by researchers as drug carriers. Moreno *et al*. have used aqueous ethanol, aqueous dioxane and water as solvents in the synthesis of poly (acrylamide-co-methyl methacrylate) for use as drug carriers. Only polymers synthesized in aqueous dioxane showed satisfactory performance in the loading and releasing of ciprofloxacin drug [22]. Begam *et al*. have also prepared the same copolymer using *N*,*N*-methylene-*bis*-acrylamide as crosslinker. The effect of used crosslinker amount on properties of polymers in addition to their ability for use in controlled release of model drugs such as *p*-nitroaniline, salicylic acid and benzoic acid was investigated [23].

The aim of this study is to synthesize hydroxybenzyl methacrylate (HBM), copolymerize the prepared monomer with acrylamide AAM in different proportions using cross-linker (ethylene glycol dimethyl acrylate, EGDMA), and study the thermal and mechanical properties of the cross-linked polymers. The performance of the prepared polymers as drug carriers is also evaluated in this work.

EXPERIMENTAL PART

Materials

All chemicals used in this work including acrylamide, 4-hydroxy benzyl alcohol, acrylic acid, potassium persulfate, paratoluenesulfonic acid, hydroquinone, aluminum oxide, stannous chloride, hydrochloric acid, benzene, ethanol, xylene, toluene, and isopropanol were purchased from Aldrich-OMA Chemical Co (Germany). To purify acrylamide monomer and potassium persulfate, they were recrystallized from methanol and ethanol, respectively, and then dried at 40°C.

Methods

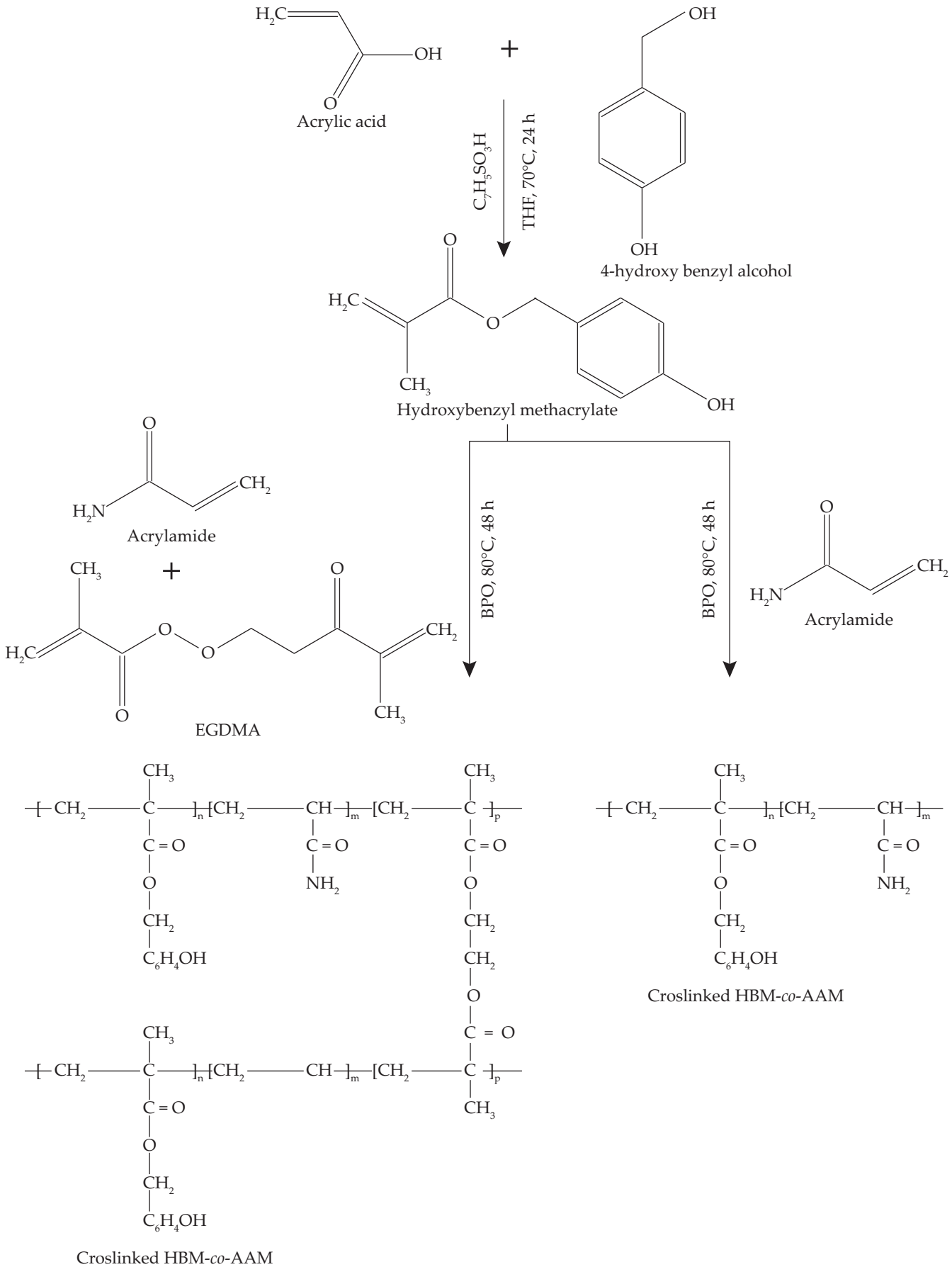
The Perkin Elmer-1650 spectrophotometer (Shelton, Connecticut, USA) was used to characterize the synthesized monomer and copolymers at a wave number of 400-4000 cm-1. 1H-NMR of the monomer was recorded using a JOEL JMTC-500/54/SS spectrometer (500 MHz) (Akishima, Tokyo, Japan). The tensile mechanical properties were evaluated using an Instron 3366 tensile testing machine (Illinois Tool Works Inc., Glenview, Illinois, USA), the dimensions of the samples were 20 mm in length, 4 mm in width, and 3 mm in thickness. Perkin Elmer SDT 650 (Shelton, Connecticut, USA) was used as a TGA analyzer, the temperature range was 0–800°C. The drug concentration was determined using a double-beam UV-Vis spectrophotometer at 270 nm.

Synthesis of hydroxybenzyl methacrylate

Hydroxybenzyl methacrylate (HBM) monomer was synthesized using the direct esterification method. Equimolar amounts of acrylic acid and 4-hydroxybenzyl alcohol and 1 wt% of paratoluenesulfonic acid as a catalyst were dissolved in 100 mL of toluene. After adding 0.5 wt% of hydroquinone as a polymerization inhibitor, the mixture was heated under reflux at 70°C for 24 h. Toluene was removed from the reaction mixture by rotary evaporation after water separation using a Dean-Stark apparatus. A mixture of distilled water and ethanol was used to wash the crude product three times and remove the unreacted acrylic acid and catalyst and then dried in a vacuum oven at 40°C for 24 h [24].

Copolymerization of HBM with AAM

Three different compositions of hydroxybenzyl methacrylate-co-acrylamide (HBM-co-AAM) were synthesized at high conversion by changing the molar fraction of HBM and AAM in the feed mixture to 3/1, 1/1 and



Scheme 1. Synthesis of HBM, HBM-*co*-AAM, and crosslinked HBM-*co*-AAM

1/3. The polymerization process was carried out in quick-connect tubes, which were previously siliconized with a dichloro-dimethyl silane solution to avoid the adhesion of the produced polymer to the tube walls. The dissolved mixture in 25 mL of benzene was bubbled with nitrogen gas for 20 min to reduce the inhibition effect of oxygen. Then, the process was continued in a thermostatic water bath at 80°C for two days and one day in an oven at 90°C. After the completion of the polymerization process, the polymer rods were taken out of the quick-connect tubes and washed three times with ethanol to remove any impurities and unreacted monomers. To obtain perfect drying, the polymer rods were first placed in a vacuum oven at 40°C for 24 h and then left in the laboratory for a week. The preparation process of 2-ethylhexyl acrylate and its copolymer with acrylamide is shown in Scheme 1 [25].

Swelling procedure

After cutting polymers rods as disks with 1 cm diameter and 3 mm thickness, the dried and weighted disks W_0 were submerged in 100 mL of deionized water at 30°C. Tweezers were used to remove the disk from water and put between two pieces of edge of filter paper to remove the excess of water. The swollen disks were weighed each one hour and after fully hydrated W_s to calculate water content *WC* and equilibrium water content *EWC* (Eq. 1), respectively. After reaching equilibrium water content, the polymeric disks were dried again in an oven at 40°C for 48 h and weighted W_d to calculate the weight loss during swelling *WL*, as presented in Equation 2 [26].

$$EWC\ \% = \frac{W_s - W_d}{W_s} \cdot 100 \quad (1)$$

$$WL = \frac{W_0 - W_d}{W_0} \cdot 100 \quad (2)$$

Loading and releasing of ciprofloxacin drug

100 mg of dried and polished polymeric discs were submerged in 100 mL of ciprofloxacin drug solution which was prepared by dissolving 1000 mg of drug in 100 mL of water at 37°C. By following the swelling procedure, the polymeric discs were weighed each hour until reaching the equilibrium water content EWC. The discs were then dried at 40°C for 48 h until reaching to constant weight. The difference between the loaded disc weight and the original disc weight represents the weight of loaded ciprofloxacin drug in the polymer.

To measure the amount of released drug from the polymer, the loaded disc was immersed with stirring in 250 mL of saline solution at 37°C and pH 7.3. The drug concentration at various times was determined by withdrawing 1 mL of the solution each one hour, diluting, and analyzing using a UV-Vis spectrophotometer at 270 nm, the withdrawn solution was replaced with the same volume of fresh saline solution. The amount of the released drug was then obtained by comparing the absorbance of each aliquot with the calibration curve of the drug.

RESULTS AND DISCUSSION

Characterization of chemical structure

The structure of hydroxybenzyl methacrylate and its copolymer with acrylamide was characterized by FT-IR. As shown in Figure 1, the success of hydroxybenzyl methacrylate synthesis was confirmed by appearing the absorption bands of O-H at 3400 cm^{-1}, alkane C-H stretching at 2931 cm^{-1}, ester C=O at 1712 cm^{-1}, weak aliphatic C=C at 1616 cm^{-1}, aromatic C=C at 1410 cm^{-1}, methyl CH_3 at 1200 cm^{-1}, and ester C-O at 1006 cm^{-1}. In Figure 2, FT-IR spectrum of HBM-*co*-AAM shows many absorption bands which belong to the stretching vibration in different functional groups of corresponding monomers, HBM and AAM: O-H at 3500 cm^{-1}, amide N-H at 3250 cm^{-1}, ester C=O at 1710 cm^{-1}, amide C=O at 1635 cm^{-1}, and ester C-O at 1064 cm^{-1}. In addition, no absorption bands were observed at the region of aliphatic C=C (1600–1620 cm^{-1}) which proves the completion of polymerization process.

^{1}H-NMR spectroscopic analysis of the HBM monomer is shown in Figure 3. The signals at about 7.2 ppm to 7.5 ppm could be assigned to the protons of CH in the benzene ring. The protons of CH_3 attached to the main

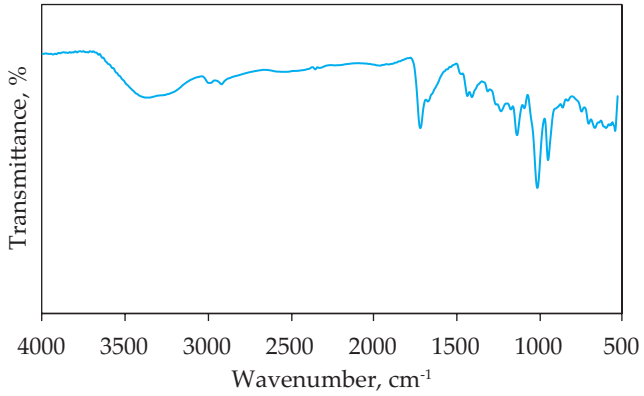


Fig. 1. FT-IR spectrum of HBM monomer

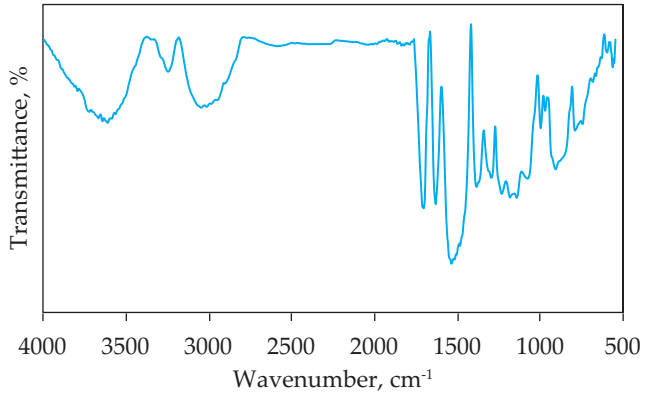


Fig. 2. FT-IR spectrum of HBM/AAM copolymer

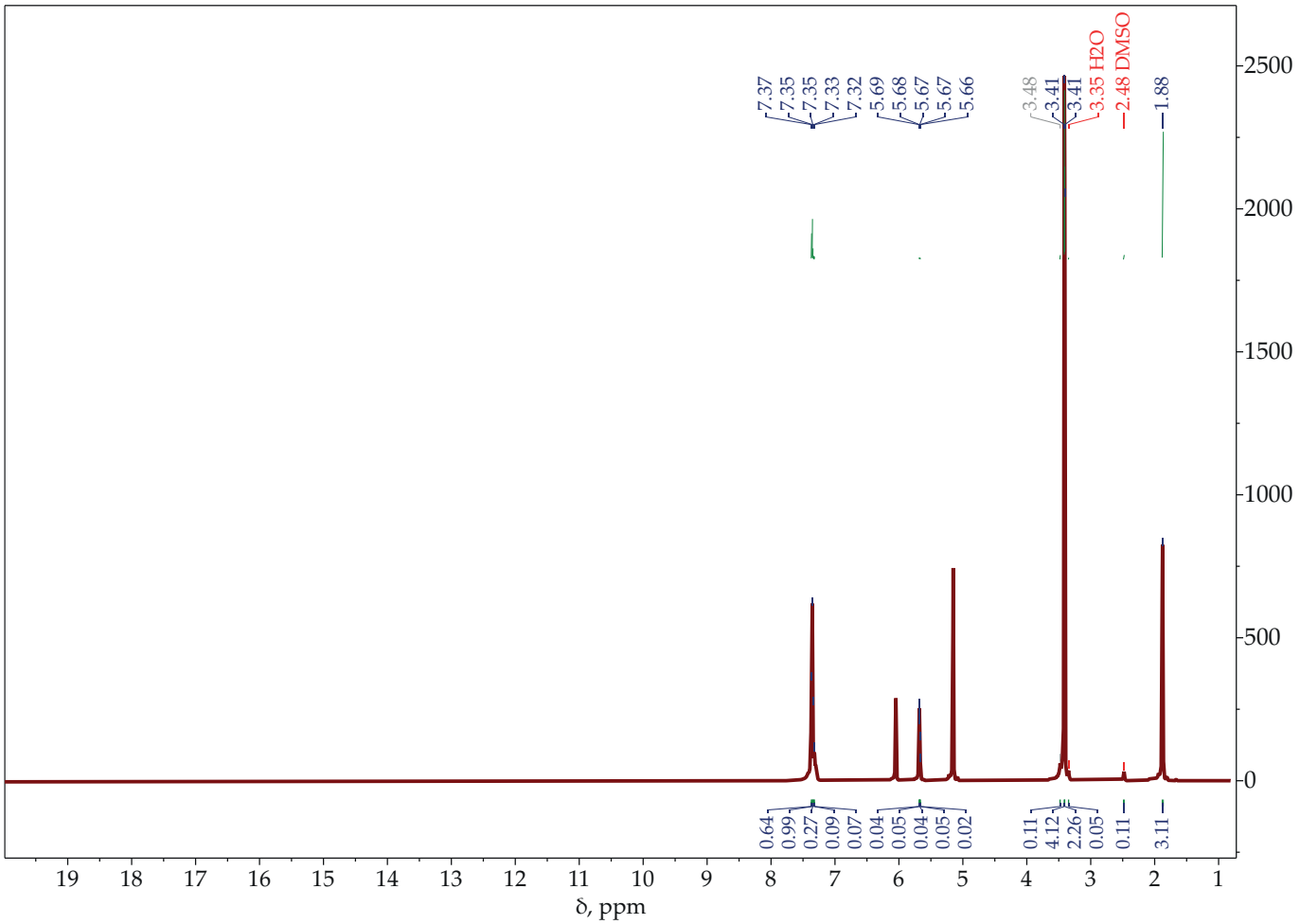


Fig. 3. ^{1}H-NMR spectrum of HBM monomer

chain backbone resonate at 1.96 ppm. The signals at 5.6 ppm and 6.2 ppm are assigned to the methylene group of the main chain backbone. The protons of CH_2 groups attached to benzene ring resonate at about 5.2 ppm.

Swelling

Figure 4 shows the results of equilibrium water content ECW and weight loss WL for C1, C2 and C3. The results reveal that with the increase of the concentration of hydroxybenzyl methacrylate monomer in the polymerization mixture, the equilibrium water content ECW and weight loss WL increase. Thus, C1 has the highest EWC and WL values, 87% and 13%, respectively. These results can be explained by the fact that the hydrophilicity of the hydroxyl group is higher than that of the amid group. Moreover, the low cross-linking density between the polymer chains, due to the lack of cross-linking agent, is another explanation for the obtained results [27]. The increase in WL of the polymers during swelling is attri-

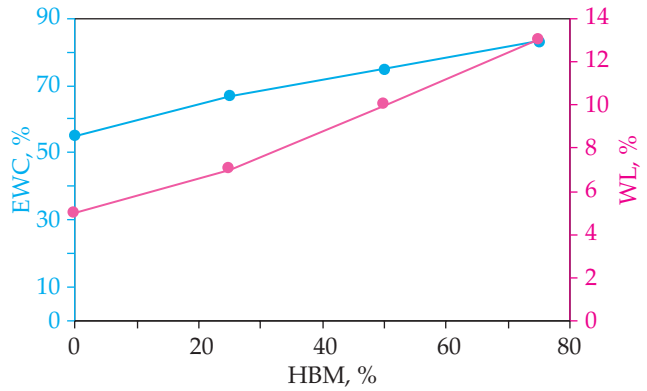


Fig. 4. Effect of HBM concentration on EWC and WL of HBM-*co*-AAM

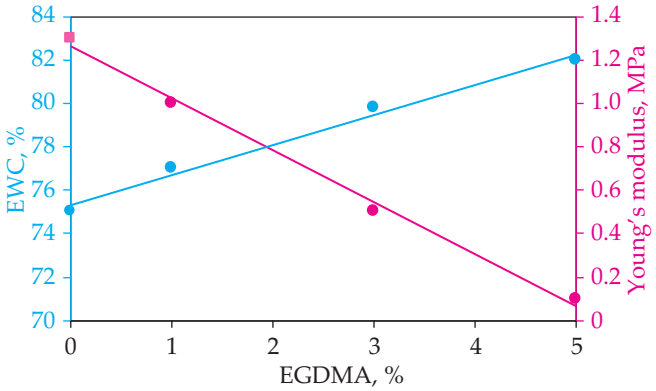


Fig. 5. Effect of EGDMA amount on mechanical properties of C1 polymers

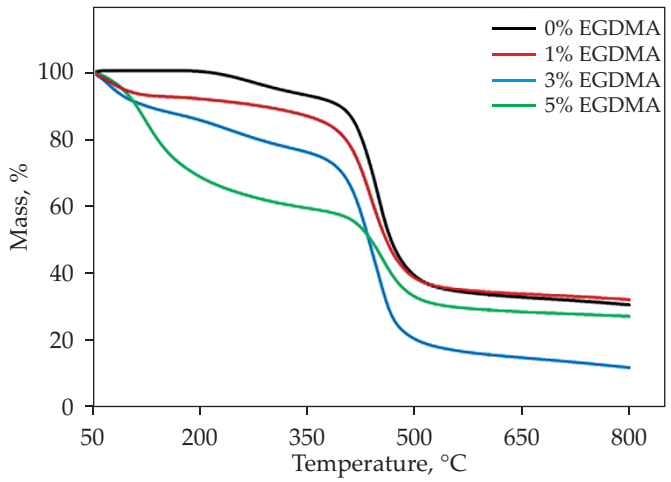


Fig. 6. Effect of EGDMA content on thermal stability of C1 polymers

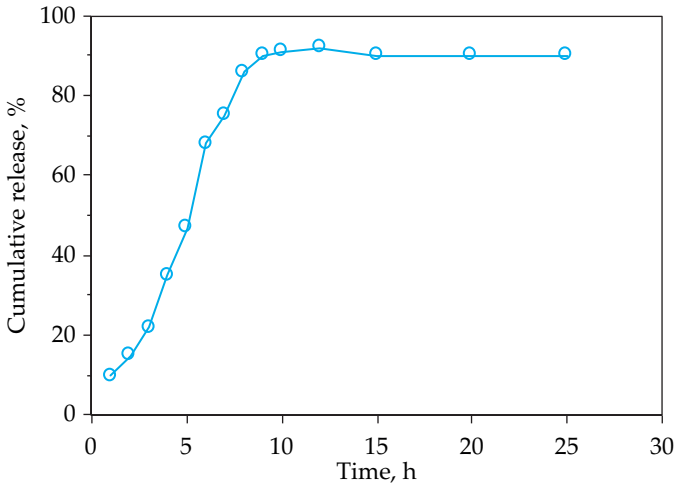


Fig. 7. Release behavior of 1HBM/3AAM copolymer on ciprofloxacin release

buted to the possibility of forming polyhydroxy benzyl methacrylate as a homopolymer. Based on these results, polymer C1 was selected to investigate the effect of cross-linking agent concentration on the thermal and mechanical properties as well as the performance of these polymers as drug carriers.

Tensile properties

Tensile strength testing is one of the most important methods for studying the mechanical properties of polymers. Figure 5 shows the results of tensile strength tests of C1 polymers containing different concentrations of EGDMA. As expected, polymers containing low concentration of EGDMA as a crosslinker exhibit poor mechanical properties at higher water content compared to polymers containing high concentration of EGDMA at lower water content. Thus, increasing the EGDMA concentration from 0 to 5 leads to an increase in the Young's modulus of the polymers from 0.5 to 2.1 and a decrease in EWC from 83 to 71. Abdallah and Mohammed [28] observed similar behavior when they studied the mechanical properties of crosslinked poly(hydroxy butyl acrylate-*co*-acrylamide) [28].

Thermal properties

The effect of EGDMA concentration on thermal properties of obtained polymers was also studied. Figure 6 shows TGA diagrams of C1 polymers containing 0–5 wt% of EGDMA. In all cases, the sharp increase in weight loss started at about 350°C. Polymers before adding crosslinker are less stable than polymers containing crosslinkers with 40% weight loss of C1/0 EGDMA at about 400°C, which is lower than 450°C, 575°C, and 590°C of C1/1 EGDMA, C1/3 EGDMA, and C1/5 EGDMA, respectively. In addition, the residue weight of C1 with 0%, 1%, 3%, and 5% of EGDMA at about 800°C are 30%, 13%, 34, and 39%, respectively. The obtained results could be explained in terms of crosslinkers restricting the mobility of polymer chains and this leads to an increase in the rigidity of polymers. The effect of crosslinkers in enhancement thermal stability of polymers is well known and already discussed by other researchers [29].

Loading and releasing of drug

The performance of polymers series 1 and series 2 in loading and releasing ciprofloxacin drug was also examined to study the effect of hydroxybenzyl methacrylate and

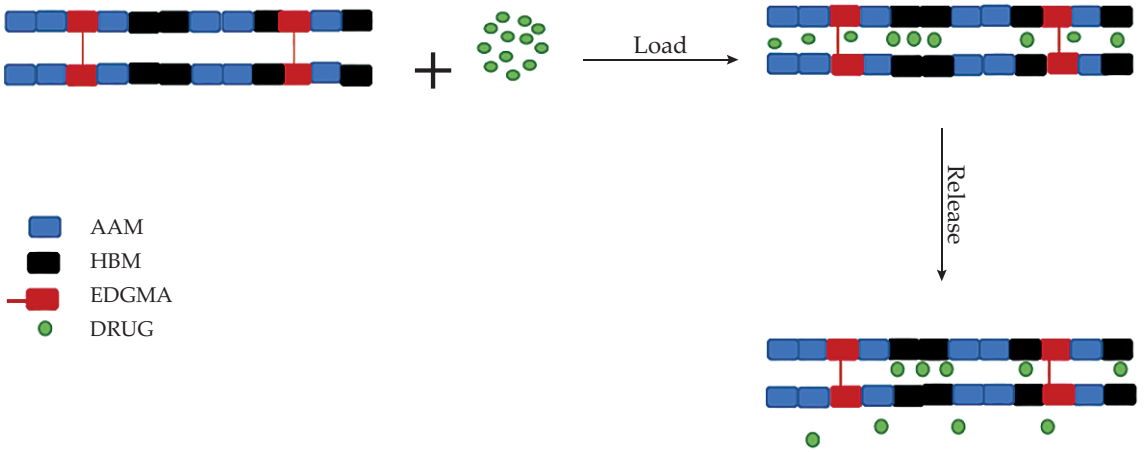


Fig. 8. Loading and releasing of ciprofloxacin drug from HBM/AAM copolymer

EGDMA concentrations on the loaded amount of ciprofloxacin drug. It can be concluded that with the increase of hydroxybenzyl methacrylate concentration in the copolymerization feed mixture, the loaded amount of ciprofloxacin drug increases. 10, 8 and 5 mg of ciprofloxacin drug were loaded on 3HBM/1AAM, 1HBM/1AAM and 1HBM/3AAM copolymers, respectively. The ability of hydroxybenzyl methacrylate to interact with ciprofloxacin drug rather than acrylamide is attributed to the difference between the solubility parameter values of ciprofloxacin/polyacrylamide and ciprofloxacin/poly hydroxy benzyl methacrylate pair [30].

As shown in Figure 8, ciprofloxacin drug prefers to interact with poly(hydroxybenzyl methacrylate) rather than with the solvent itself. On the other hand, the released amount of ciprofloxacin drug increases as the concentration of acrylamide increases in the copolymerization mixture feed. The maximum amount 91% was released from 1HBM/3AAM copolymer indicates that ciprofloxacin drug has been completely released after 8 hours (Figure 7). On the other hand, the incomplete release was recorded for 3HBM/1AAM and 1HBM/1AAM copolymers which released about 63% and 45% of the loaded ciprofloxacin drug, respectively.

No change has been observed in the loaded and released amount of ciprofloxacin drug, when 3HBM/1AAM copolymer, containing 0-5% of crosslinker, was used as drug carrier. 5 % of EGDMA decreases about 2% and 1% of the loaded and released amount of ciprofloxacin drug, respectively. These results could be explained in terms of EGDMA decreased water content of polymers which directly affected the capacity of polymer for loading ciprofloxacin drug.

CONCLUSIONS

The synthesized hydroxybenzyl methacrylate was successfully copolymerized with acrylamide to prepare two series of polymers, without and with cross-linking agent. Based on the swelling test of series 1, the polymer with high content of hydroxybenzyl methacrylate was selected to investigate the effect of cross-linking agent on its thermal and mechanical properties, which showed improvement with the increasing amount of cross-linking agent. All the obtained polymers were evaluated as drug carriers, but the polymer with high content of hydroxybenzyl methacrylate showed better performance in drug loading, while no effect of cross-linking agent was observed in the loaded and released amount of drug.

Authors contribution

F.H.A – research concept, methodology, investigation, validation, visualization, writing; A.H.M. – research concept, methodology, investigation, validation, visualization, writing.

Funding

No funding/no source of financing.

Conflict of interest

The authors declare that they have no known competing commercial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

[1] Lai H., Peng X., Li L.*et al.: Progress in Polymer Science* **2022**, *128*, 101529. https://doi.org/10.1016/j.progpolymsci.2022.101529
[2] Buss B.L., Lim C.H., Miyake G.M.: *Angewandte Chemie International Edition* **2020**, *59(8)*, 3209. https://doi.org/10.1002/anie.201910828
[3] Kizhakidathazhath R., Nishikawa H., Okumura Y. *et al.: Polymers* **2020**, *12(8)*, 1625. https://doi.org/10.3390/sym13050772
[4] Mohammed A.H., Ahmad M.B., Ibrahim N.A. *et al.: Polimery* **2018**, *63*(9), 577. https://doi.org/10.14314/polimery.2018.9.1
[5] Kostić M., Igić M., Gligorijević N. *et al.: Polymers* **2022**, *14*(21), 4511. https://doi.org/10.3390/polym14214511
[6] Fiosina J., Sievers P., Drache M. *et al.: ACS Polymers Au* **2024**, *4*(5), 438. https://doi.org/10.1021/acspolymersau.4c00047
[7] Veith C., Diot-Néant F., Miller S.A. *et al.: Polymer Chemistry* **2020**, *11*(47), 7452. https://doi.org/10.1039/D0PY01222J
[8] Abbas N.N., Mohammed A.H., Ahmad M.B.: *Egyptian Journal of Chemistry* **2022**, *65*(9), 293. https://doi.org/10.21608/ejchem.2022.112096.5091
[9] Droesbeke M.A., Aksakal R., Simula A. *et al.: Progress in Polymer Science* **2021**, *117*, 101396. https://doi.org/10.1016/j.progpolymsci.2021.101396
[10] Akbulut G., Bulbul Sonmez H.: *Journal of Coatings Technology and Research* **2022**, *19*(5), 1421. https://doi.org/10.1007/s11998-022-00616-y
[11] Soleymani Eil Bakhtiari S., Bakhsheshi-Rad H.R., Karbasi S. *et al.*: *Polymer International* **2021**, *70*(9), 1182. https://doi.org/10.1002/pi.6136
[12] Mohammed A., Dhedan R.M., Mahmood W.A. *et al. Egyptian Journal of Chemistry* **2021**, *64*(8), 4271. https://doi.org/10.21608/ejchem.2021.61665.3327
[13] Abbas N.N., Mohammed A.H.: *Egyptian Journal of Chemistry* **2022**, *65(132)*, 719. https://doi.org/10.21608/ejchem.2022.142847.6239

[14] Mohammed A.H., Mousa E.F., Hamed A.H. *et al*.: *Baghdad Science Journal* **2023**, *20(6)*, 2467. https://doi.org/10.21123/bsj.2023.9095
[15] Wang H., Cao M., Zhao H.B. *et al*.: *Chemical Engineering Journal* **2020**, *399*, 125698. https://doi.org/10.1016/j.cej.2020.125698
[16] Abed N.A., Mohammed A.H., Musa A.M.: *Egyptian Journal of Chemistry* **2021**, *64*(4), 1981. https://doi.org/10.21608/ejchem.2021.44316.2900
[17] Wang W., Zhou Z., Sathe D. *et al*.: *Angewandte Chemie International Edition* **2022**, *61(8)*, e202113302. https://doi.org/10.1002/anie.202113302
[18] Ameduri B.: *Progress in Polymer Science* **2022**, *133*, 101591. https://doi.org/10.1016/j.progpolymsci.2022.101591
[19] Van Vugt T.A., Arts J.J., Geurts J.A.: *Frontiers in Microbiology* **2019**, *10*, 1626. https://doi.org/10.3389/fmicb.2019.01626
[20] Hasandoost L., Rodriguez O., Alhalawani A. *et al*.: *Journal of Functional Biomaterials* **2020**, *11(2)*, 25. https://doi.org/10.3390/jfb11020025
[21] Lusina A., Cegłowski M.: *Polymers* **2022**, *14(3)*, 640. https://doi.org/10.3390/polym14030640
[22] Moreno R.O., Penott-Chang E.K., de Gáscue B.R. *et al*.: *European Polymer Journal* **2017**, *88*, 148. https://doi.org/10.1016/j.eurpolymj.2017.01.005
[23] Begum R., Farooqi Z.H., Khan S.R.: *International Journal of Polymeric Materials and Polymeric Biomaterials* **2016**, *65(16)*, 841. https://doi.org/10.1080/00914037.2016.1180607
[24] Siwan G.Q., Mohammed A.H.: *Polimery* **2024**, *69(4)*, 229. https://doi.org/10.14314/polimery.2024.4.3
[25] Al-Mokaram A.M.A.A., Mohammed A.H., Ghani H.A.: *Polimery* **2022**, *67(10)*, 489. https://doi.org/10.14314/polimery.2022.10.3
[26] Zhang K., Feng W., Jin C.: *MethodsX* **2020**, *7*, 100779. https://doi.org/10.1016/j.mex.2019.100779
[27] Trabbic-Carlson K., Setton L.A., Chilkoti A.: *Biomacromolecules* **2023**, *4(3)*, 572. https://doi.org/10.1021/bm025671z
[28] Abdallah Z.S., Mohammed A.H.: *Polimery* **2023**, *68(2)*, 86. https://doi.org/10.14314/polimery.2023.2.2
[29] Krumova M., Lopez D., Benavente R. *et al*.: *Polymer* **2000**, *41(26)*, 9265. https://doi.org/10.1016/S0032-3861(00)00287-1
[30] Abed N., Mohammed A.: *Egyptian Journal of Chemistry* **2021**, *64(9)*, 5175. https://doi.org/10.21608/ejchem.2021.70441.3552

Received 3 XI 2024.
Accepted 16 XII 2024.

Rapid Communications

Przypominamy Autorom, że publikujemy artykuły typu **Rapid Communications – prace oryginalne wyłącznie w języku angielskim** (o objętości 4–5 stron maszynopisu z podwójną interlinią, zawierające 2–3 rysunki lub 1–2 tabele), którym umożliwiamy szybką ścieżkę druku (do 3 miesięcy od chwili ich otrzymania przez Redakcję). Artykuł należy przygotować wg wymagań redakcyjnych zamieszczonych we wskazówkach dla P.T. Autorów.

* * *

We remind Authors that we publish articles of the **Rapid Communications** type **– the original papers, in English only** (with a volume of 4-5 pages of double-spaced typescript, containing 2–3 figures or 1–2 tables), which allow a fast print path (up to 3 months from when they are received by the Editorial Board). The article should be prepared according to the editorial requirements included in the Guide for Authors.