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RESEARCH ARTICLE

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Investigation of the antimicrobial effects of niclosamide, furosemide and nifedipine drugs released from a modified hydrogel structure

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Abstract

HEMA-based hydrogels were also developed and they were characterized for a few drugs including nifedipine, furosemide and niclosamide. The HEMA hydrogels were synthesized by functionalizing with methacrylated β−cyclodextrin monomer and then were tested in drug release studies. Antimicrobial study against bacteria: The pathogen was studied using disc diffusion and microdilution methods for the drug released from HEMA-based hydrogels. The hydrogel synthesized was found to have a very high capacity for absorption of water and it was also found that depending on this, the potential of drug absorption was also very high. In vitro, cumulative drug release studies on nifedipine, furosemide and niclosamide were carried out using hydrogel under various time and pH conditions. The released drug was adjustable as we obtained data on drug release profiles. Nifedipine, furosemide and niclosamide release percentages were 68.9±3.8%, 75.2±3.6% and 58.7±4.2%, respectively. Additionally, all three drugs exhibited marked activity against bacteria. These findings indicate that the synthesized hydrogels are a promising basis for bio-medical applications.

Keywords: Methacrylated β-Cyclodextrin; Niclosamide; Furosemide; Nifedipine; Antimicrobial activity

1. Introduction

Recently, the field of biomaterials has been drawing more and more attention in the research community. This process has been followed by an increase in research activities concerning drug delivery systems which are a successful method in the application of biomedical drugs [1, 2]. Drug delivery means that the active substance is released from the system in a controlled manner, at a desired time, with a certain velocity and a certain amount [3]. There are two main components in drug delivery: the active substance and the polymeric support material. Support

material controls the release of active substances. When a polymer (either natural or synthetic) is used in drug delivery, the active substance is released as planned [4,5]. Typically, in drug delivery systems, three-dimensional, network-structured, and cross-linked hydrogels are used [6]. Hydrogels are highly hydrophilic polymers that can swell significantly in water without dissolving, and they are flexible with high mechanical stability [7]. The degree of hydrophilicity of hydrogels depends on the presence of polar groups in their structure, and due to the advantages, they provide, they show excellent biocompatibility [8, 9]. Hydrogels are three-dimensional hydrophilic structures with the ability to adsorb large amounts of water. Because of their variable network structure, high water content, and soft texture, they are used not only in drug delivery systems but also as biomaterials [10]. These structures, in their hydrated form, have mechanical properties and water content similar to those of soft tissues, which is why they exhibit high biocompatibility. Hydrogels also exhibit swelling behavior depending on the external environment [11, 12].

Antimicrobial studies play a crucial role in drug delivery systems. These studies are essential in the fight against various infectious diseases. However, there are challenges such as bacterial resistance and some side effects with current treatment options [13,14]. In the treatment of such pathologies, the choice and application of drugs with various mechanisms of action become crucial in developing effective options [15, 16]. Niclosamide, nifedipine, and furosemide have the most pronounced and positive action in this respect [17, 18].

The current study focused on the encapsulation, protection, and release of such drugs using HEMA-based hydrogels [19,20]. It also provided an in-depth discussion on the release patterns of these antimicrobial agents. Nifedipine, niclosamide and furosemide are broad-spectrum drugs. These drugs are widely used in the treatment of bacterial and antimicrobial infections [21, 22]. HEMA-based hydrogels improved the effectiveness of these drugs, controlled the release, and ensured more reliable and successful treatments. [23, 24] Antimicrobial effectiveness of these drugs was fully investigated in this study to determine their effectiveness [25]. Results obtained will be helpful in supporting the future clinical application of these drug molecules.

2. Experimental

2.1. Materials

All chemical utilized in the research was acquired from Sigma-Aldrich and Merck. In the trials, purchased substances were utilized as such.

2.2. Synthesis process for preparing HEMA-based hydrogels with GMA-bound β-cyclodextrin monomer

HEMA was mixed with the prepared monomer and subjected to polymerisation to form gels. Two hydrogels were prepared for each drug. Then, two more hydrogels were prepared to provide negative and positive control groups. GMA-bound β-cyclodextrin was dissolved in 5 mL of pure water and mixed with HEMA polymer. MBAAm crosslinker was dissolved in 10 mL of pure water in another beaker. The two solutions obtained were mixed and the mixture was placed in an ice bath for 10 minutes and transferred to the mixer. APS was then added to the mixture in the ice bath to act as a radical initiator. TEMED was added to this mixture to accelerate polymerization. The resulting mixture was then transferred to empty containers, making sure that no air bubbles remained. The empty containers were placed in the freezer to remain in this bath. These containers were placed in a freezer at -20°C and kept there for 24 hours. After 24 hours, it was removed from -20 °C. It was left at room conditions for approximately 2 hours to replace the ice crystals in the voids in the hydrogel with empty compartments. The resulting hydrogel was washed with pure water to ensure the adhesion of the drugs to be immobilized [26].

2.3. FT-IR analysis

FT-IR spectroscopy was used to investigate the structure of drug-doped HEMA hydrogels and pure 2-hydroxyethyl

methacrylate (HEMA). The Fourier transform infrared spectra were measured between 4000 and 400 cm^{-1} using a Bruker Vertex 70 ATR-FTIR spectrophotometer [17, 27].

2.4. Morphological studies

The structural nature of the GMA-bound β-CD doped HEMA hydrogel was examined using scanning electron microscopy and the results are presented. The SEM images of the GMA-bonded β-CD doped HEMA hydrogel samples coated with 5 nm gold (Au) were examined at approximately 1 μm [27].

2.5. Swelling measurement

Free hydrogels' equilibrium swelling (ES) was determined in distilled water and different buffer solutions. The maximum swelling of HEMA hydrogels was used to calculate the ES ratio. For this, they were put in 50 mL of the solution prepared at 25 °C for 20 hours. The equilibrium swelling percentage was computed using the following formula, as shown in Equation (1).

$$ES = W2 - W1 / W1 \otimes 100 \quad (1)$$

According to this formula, W1 is the initial weight of the prepared hydrogels after drying, and W2 is the weight of the prepared hydrogels after swelling for 20 h. The swelling capacities of all prepared hydrogels were obtained using different pH buffers. The pH values of these buffers were calculated as 2, 4, 7, 9 and 12. Three or four repetitions of each experiment were performed [27].

2.6. Antimicrobial activity test method

2.6.1. MIC dilution

The broth microdilution method determined the antibacterial activity of the drugs used in the study. In the antibacterial test, different concentrations of these drugs (0.1-10 mg/ml) were used to determine the minimum inhibitory concentration (MIC) values on *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacteria. In this investigation, buffer solution was used to replace the negative control, and chloramphenicol was used to replace the positive control. The lowest drug concentration that inhibited bacterial growth was calculated and reported as the MIC [28].

2.6.2. DISC diffusion

In this study, an agar diffusion test was conducted to test the antimicrobial activity of the drug-loaded hydrogel disks. During the test, 1-1.5 mm-thick hydrogel samples for each group were positioned on agar plates, to which 0.1 ml cultures of *Staphylococcus aureus* ATCC 25923 and *Pseudomonas aeruginosa* ATCC 10145 bacteria were added. This subject was focused on because drug-loaded hydrogel systems play a very important role in developing effective antimicrobial agents. The present study was performed to investigate the antimicrobial efficacy of 2-hydroxyethyl methacrylate (HEMA) hydrogel discs eluted by different drug solutions. The incubation of the tests was performed at 37 °C after 24 hours, and then measurements were taken around each specimen on the created areas of inhibition. Therein obtaining the numerical quantitative values of such activity. The prepared hydrogel disks were loaded with drug solution concentrations of 6, 12, 18, 30 and 50 mg/g HEMA hydrogel disk structure, respectively. In such a way that the influence of different drug loading could be investigated on the antimicrobial activities of the prepared drug-loaded discs. Drug-free hydrogel discs were used as a control, which exhibited no inhibition, proving the inhibition

by the drug effect alone. To enhance the reliability of the experiments, all the tests were repeated three times, and their average results were statistically accurate. It is a very strict method that gives scientific validity to the obtained results and reproducibility. These results demonstrated that the antimicrobial properties of HEMA-based drug delivery systems can be improved and were a very important step towards improving the usability of the systems discussed in clinical applications, including the treatment of wound healing and infections. This research provides an important basis for improving drug delivery formulations [29].

3. Results and discussion

3.1. Nuclear Magnetic Resonance Spectroscopy analysis

Figure 1 shows the proton from the methacrylate group, a part of GMA, around 6.2 ppm. This signal is due to the vinyl protons of the methacrylate group of GMA. The chemical shift at approximately 6.2 ppm is characteristic for protons attached to a carbon-carbon double bond, confirming the presence of the methacrylate functionality in the GMA-β-CD complex. Methyl protons-CH_3 are detected at about 1.8 ppm. This signal points to protons on a methyl group, which is part of the GMA structure. A chemical shift value of about 1.8 ppm may be indicative of a methyl substitution in a relatively electron-rich environment, such as that linked to the methacrylate part of GMA. It has been proved from the 1H-NMR spectra that GMA-β-CD forms with its molecular structure, one GMA molecule covalently attached to the β-CD through a methacrylate group. The complexation so formed will further confirm the hypothesis on successful synthesis that could be further characterized or used for various applications involving drug delivery or material science [30, 31].

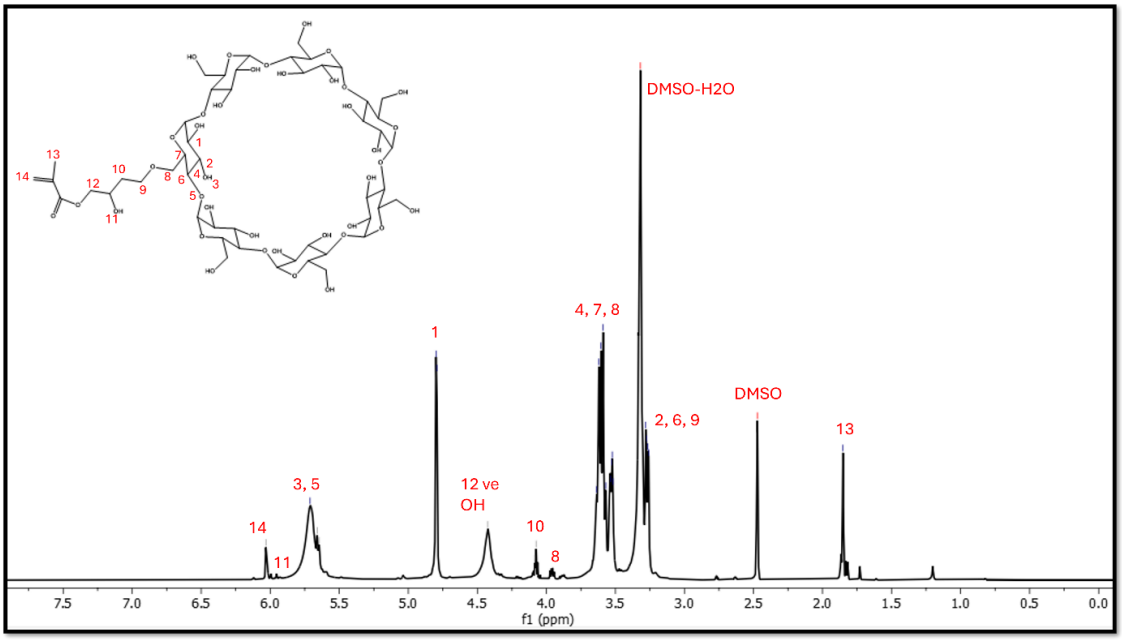

Fig. 1. NMR Graph of the synthesized GMA+ β-CD monomer

3.2. Fourier-transform infrared spectroscopy analysis

The distinctive spectra of the β-CD monomer attached to GMA were visible in the acquired FTIR spectrum. Figure 2 shows that the stretching vibrations of the carbonyl group (C=O) and the double bond C=C of the methacrylate structures are observed in the HEMA spectrum at about 1716 cm−1 and 1633 cm−1, respectively. In the β-CD spectrum, the vibrations of C-O-C (ether group) and -OH (hydroxyl group) were found between 1000-1200 cm^{-1} and 3300-3500 cm^{-1}. The interactions between β-CD and HEMA, which indicate cross-linking, appeared as changes in the 1100-1300 cm^{-1} range. This suggests that HEMA and β-CD have successfully bonded to form a network structure. The FTIR spectra of the drugs also showed characteristic peaks for functional groups. For nifedipine, peaks for C=O and -NO_2 groups appeared at about 1740 cm^{-1} and 1320 cm^{-1}, respectively. Niclosamide exhibited peaks for amide groups and aromatic rings at approximately 1630 cm^{-1} and 1650 cm^{-1}, while furosemide had peaks for carbonyl groups and sulfonamide at about 1300 cm^{-1} and 1650 cm^{-1}. The shifting, broadening, or disappearance of some peaks in the FTIR spectra of the drugs indicates the interaction between the drugs and the HEMA-β-CD hydrogel network. Of importance are changes in the -OH peaks, which may indicate interactions between the drugs and the hydroxyl groups in the network. These results show that the pharmaceuticals under investigation have been successfully added to the β-CD-HEMA and GMA-β-CD-HEMA hydrogels and that the drug release properties of the hydrogel may be influenced by these copolymer structures. The effective preparation of HEMA-based hydrogels made with GMA-coupled β-CD interacting with the drugs under study was confirmed by the resulting FTIR spectra. Drugs are absorbed into the network, as indicated by changes in their FTIR peaks, which may impact regulated release. The study constitutes an important step in designing drug delivery systems and in understanding the interaction of drugs with hydrogel matrices [5, 17].

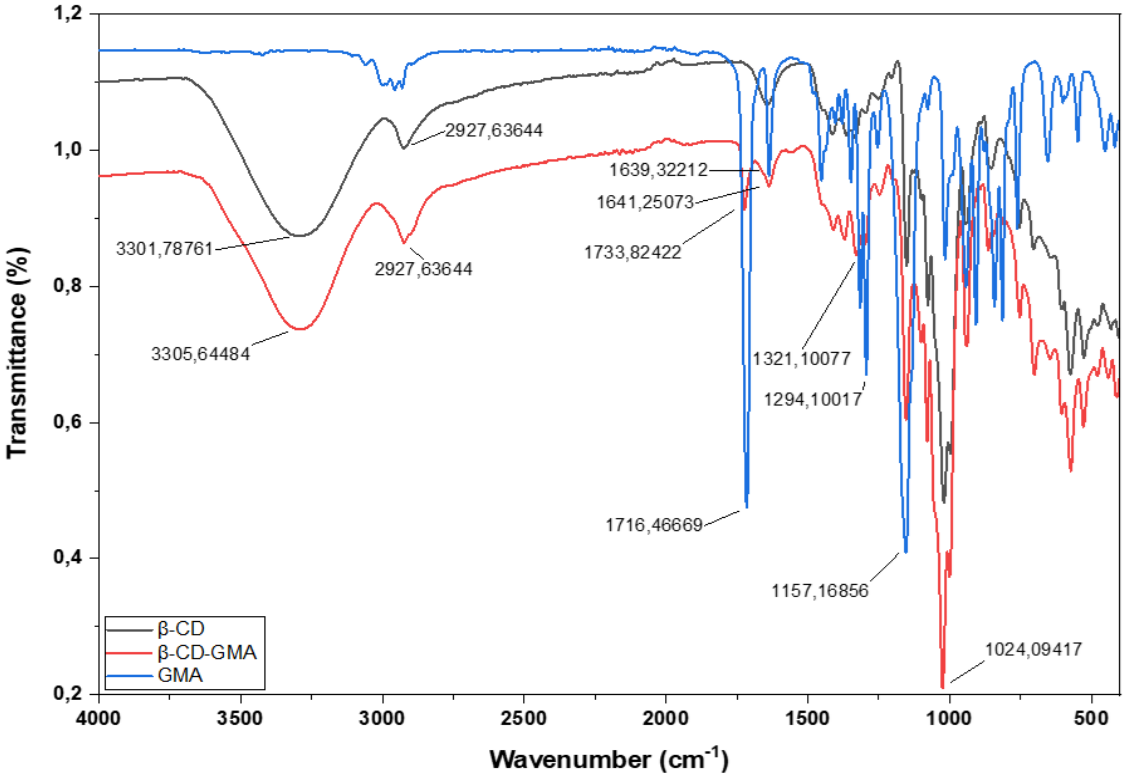

Fig. 2. FTIR spectra of the obtained HEMA+GMA+β-CD hydrogel

3.3. Scanning electron microscope analysis

Figure 3 shows SEM images of the surface, pore structure, and network in HEMA hydrogels modified with methacrylated GMA+β-CD monomer. The homogenous and consistent nature of the pores is critical for drug transport to be supported, as is their controlled release in these hydrogels. The images show that the methacrylate samples exhibit a sharply curved structure. At the same time, the pronounced hollow structure helps the medicines to be transported easily. The smooth surface and continuous network structure may help improve hydrogel efficacy and stability for biomedical applications. The SEM images show that the HEMA hydrogels made of copolymer with GMA-bonded β-CD were effectively created and have the appropriate properties [17].

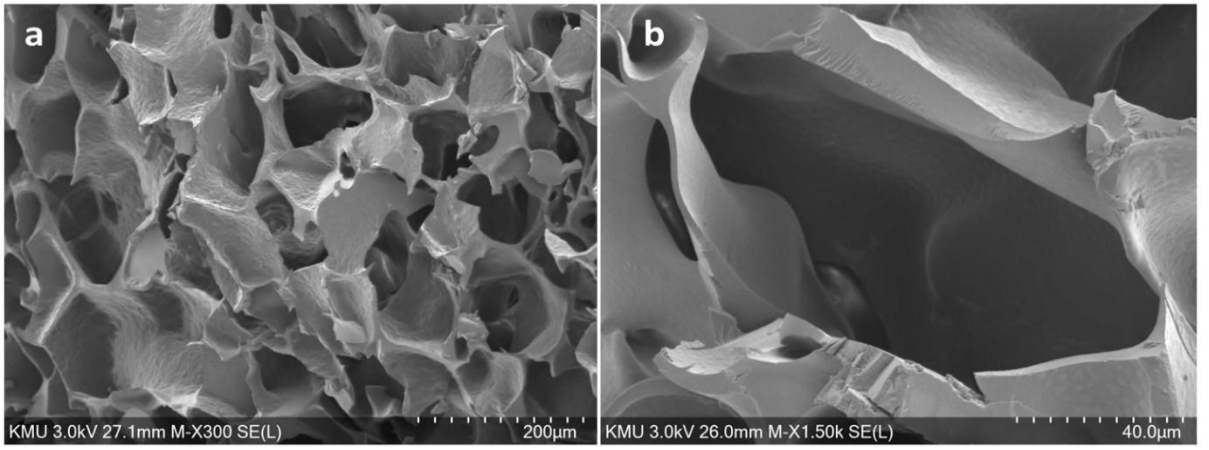

Fig. 3. SEM images of produced GMA-bound β-CD HEMA hydrogel (a) 200 µm (b) 40.0 µm size

3.4. Hydrogel's swelling and cumulative release

The swelling behaviour of HEMA hydrogels copolymerized with GMA-bound β-CD was studied in different buffers with pH values of 2, 4, 7, 9, and 12, and the results are shown in Figure 4. The hydrogel absorbed the most water at pH 7. The swelling of the hydrogel depends on the pH of the surrounding solution, with higher pH values generally leading to more swelling. However, when the pH went above 7, the swelling ratio of the HEMA hydrogel decreased. This is because the hydrogen bonds between the oxygen atoms in the ether groups and the carboxylic acid groups of MBA were broken, causing MBA's carboxyl groups to ionize. Since the ideal pH for the hydrogel is around 7, it does not cause any issues for its biological properties. Drug release from hydrogel was achieved using the homogeneous matrices technique in Diffusion-Based Matrix Systems. The release of drugs was rapid in the first hours, then slowed down over the next 10 hours and finally stabilized (Figure 4). After 10 hours, the release percentages of nifedipine, furosemide and niclosamide were 68.9 ± 3.8%, 75.2 ± 3.6% and 58.7 ± 4.2%, respectively [27].

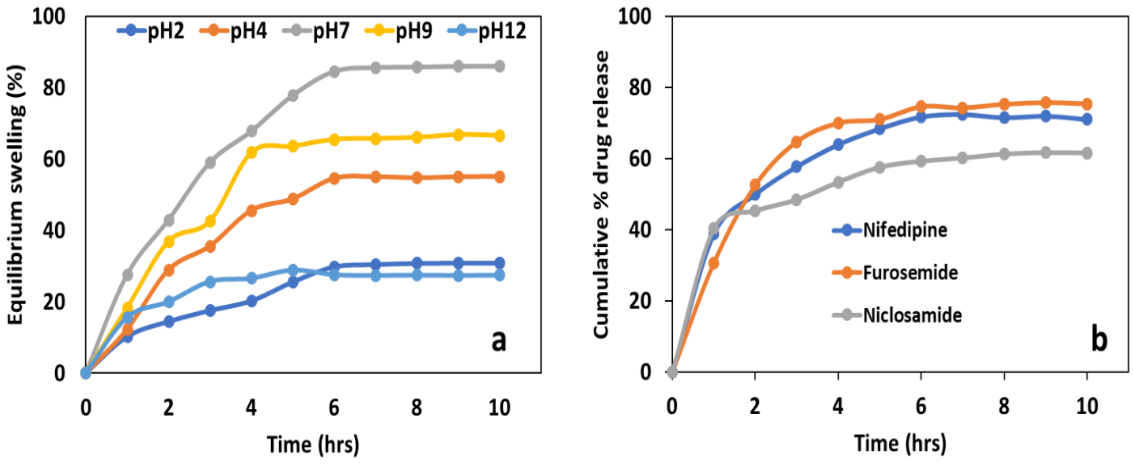

Fig. 4. As time depends, (a) Equilibrium swelling behaviour of hydrogels at different pHs (b) Total drug release from HEMA hydrogel

3.5. Results of antimicrobial tests

3.5.1. Minimum inhibitory concentration dilution

MIC dilution test was used to determine the smallest concentration of drugs needed to stop bacterial growth. The findings indicate that GMA-linked β-CD monomer-based hydrogels based on HEMA can be a useful material for antimicrobial drug testing (Figure 5). The low MIC values obtained from niclosamide among the tested drugs indicate that it is a potent antimicrobial agent. It thus infers that the drug has retained its effectiveness even upon loading into the hydrogel. Niclosamide maintains its antimicrobial property during effective transport and release by the hydrogels. It provides evidence that HEMA hydrogels are to be exploited in drug release applications as well as in assessing the effectiveness of anti-microbial drugs. Therefore, such information leads to the use of the hydrogel system towards assessing other varieties of drugs besides drug delivery mechanisms and methodologies improvement.

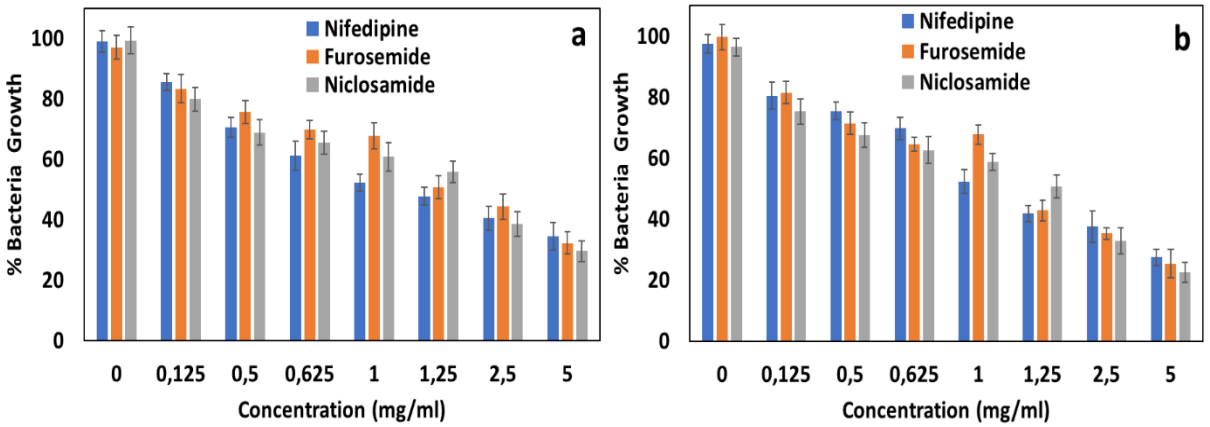

Fig. 5. The lowest amount of drug that inhibits bacterial cultures when removed from the HEMA hydrogel and administered to bacteria of (a) *Pseudomonas aeruginosa* (P A) and (b) *Staphylococcus aureus* (S A)

3.5.2. Disc diffusion

Antimicrobial activity testing of drug-loaded hydrogel samples was done using a disk diffusion method. To this end, hydrogels at five different drug concentrations, such as 6, 12, 18, 30, and 50 mg/g polymer, were prepared. The measured diameter of the inhibition zone in Figure 6 has been presented. After incubation for 24 hours, the drug-loaded hydrogels showed clear antimicrobial effects. Figure 5 shows the lowest amounts of drug that inhibited the growth of Pseudomonas aeruginosa and Staphylococcus aureus bacterial cultures upon release in the hydrogels. Activity was concentration-dependent and depended on the type of microorganism. In particular, the inhibition zones were larger for the Gram-negative *P. aeruginosa* compared to the Gram-positive *S. aureus*. Niclosamide was found to exhibit enhanced antimicrobial activity when released from a HEMA hydrogel matrix containing methacrylated β-CD. The diameters of the inhibition zones emphasize that niclosamide is active against both bacteria. Interestingly, hydrogel molds with drug concentrations of 30 – 50 mg showed similar results to hydrogels with drug concentrations of 6 – 18 mg. Larger inhibition zones were the outcome of lower medication concentrations.

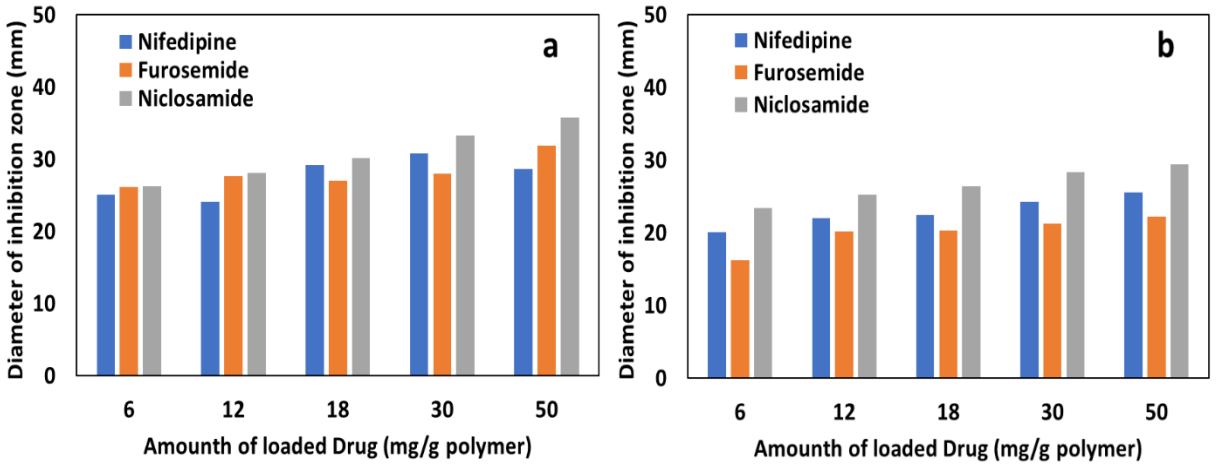

Fig. 6. pHEMA hydrogel disks' inhibition zone diameters with bacterial cultures (37°C, 24 hours) (a) *Staphylococcus aureus* (S A) and (b) *Pseudomonas aeruginosa* (P A)

4. Conclusion

In this study, HEMA-based hydrogels were prepared and the hydrogels were functionalized with GMA-linked β-cyclodextrin monomer. The drug release profiles of the developed hydrogels were assessed for drugs like nifedipine, niclosamide and furosemide and the outcomes were stated. The potency of the drug molecules that are released was assessed on the antibacterial activity against the Gram-positive and Gram-negative bacteria by the disk diffusion and microdilution methods. The findings show that they will provide significant benefits for such studies. From these data, it is also seen that these hydrogels will be highly useful as drug delivery systems. Especially, it has been observed that these hydrogels have high drug carrying capacity and hence are effective in infection therapy. The research also found that the hydrogels that were prepared from the combination of HEMA and β-CD effectively controlled the drug release and produced favourable results. The drug release profiles of nifedipine, niclosamide, and furosemide from the gels also presented pH and time-dependent release profiles. This indicates that the embedding of GAM-linked β-CD into the HEMA network is capable of delivering the drug in a controlled and specific manner. Thus, the drug release can be constant and extended during the whole period of treatment. This may enable better control of the dosage. The assay of the antimicrobial test has revealed that the drug molecules have an excellent antibacterial effect against the indicated bacterial strains. especially niclosamide shows high antibacterial activity against the Gram-negative bacteria. It has been noticed that the HEMA-based hydrogels synthesized in the present work with methacrylated β-CD have high potential and offer strong evidence for their use in various biomedical applications. In addition, these hydrogels can be applied in various fields with their remarkable ability to absorb water and release drugs. Future studies will examine the interactions of these hydrogels with different drugs and biological systems and create new opportunities for clinical research.

Appendix A.

This study is presented as a part of Mukaddes Keskinates' doctoral thesis. Conflict of Interest The authors declare that they have no conflict of interest.

Acknowlegde

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Author Contribution

All authors contributed to the conceptualization and design of the study. Material preparation, method research and implementation, data collection and analysis were carried out by Mukaddes Keskinates. Bahar Yılmaz played an important role in research, methodology, data editing, writing the original draft and verification. Mevlüt Bayrakcı contributed as a supervisor to research, methodology, data editing, writing the original draft and verification. All authors read and approved the final draft.

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