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Controlled drug delivery of ciprofloxacin from ultrasonic hydrogel

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Abstract: Ciprofloxacin is an antibacterial fluoroquinolone that stops the DNA synthesis, after penetration into the bacterial cells. This drug is applied in the curing of bacterial infections, as well as in antibiotics to treat urinary infections in women, infectious diarrhea and typhoid fever. The objective of the present work is to study controlled release of ciprofloxacin by hydrogel prepared by ultrasound. For this, first the swelling properties of hydrogel and then the absorption of drug were evaluated. The swollen hydrogel was dried in oven (50°C) and was ready for release experiments. During release, the loaded powder of the hydrogel was added to a buffer solution of pH 7.4, similar to human body condition. Then drug concentration was measured using a UV-visible (UV-Vis) spectrophotometer and a calibration curve. The results showed that the hydrogel is sensitive to pH, which makes it a good candidate for ciprofloxacin delivery in intestine. In addition, it was shown that the drug absorption is proportional with the swelling content of the hydrogel and the drug concentration in the loading process. The chemical structure and morphology of the hydrogels and loaded drug were characterized using Fourier transform infrared, UV-Vis, scanning electronic microscopy and thermal gravimetric analysis spectroscopy. According to the results presented here, acrylic-based hydrogels can be used in biomedical fields, especially for controlled drug release.

Keywords: antibacterial; ciprofloxacin; drug delivery; hydrogel; ultrasound.

1 Introduction

The effect of ultrasound on chemical processes is not the direct effect of the sound field on chemicals at the molecular level but is the result of cavitation, namely, the creation of small cavities in a liquid as due to strong negative pressure. The most important effects of this phenomenon include accelerating a reaction, milder conditions in reaction, more economical process than using raw reagents, reviving old techniques excluded from the developing reactivity, reducing the required steps, setting up hard reactions, reducing activation time, promoting the catalytic efficiency and development of radical reactions (1, 2).

Hydrogels containing ionizable groups such as carboxyl or amine are sensitive to charge changes in the environments and may swell during ionization. In fact, the electrostatic repulsion causes network swelling and then water diffusion. Such hydrogels that have rapid and clear response to minor changes in environmental factors (as change in the swelling properties) are called intelligent, sensitive or responsive hydrogels (3–5).

Katchalsky (1949) prepared the first polymeric gel responsive to the environment via networking of water-soluble polyelectrolytes, which swell or gather in response to changes in solution (5). The importance of hydrogels in medical applications was revealed in 1950, in manufacturing soft contact lenses by using 2-hydroxyethyl methacrylate gel. Since mid-1980, field of research was focused on the smart hydrogel, particularly temperature-sensitive hydrogels (6). pH-sensitive hydrogels are the most suitable candidates for guided drug delivery systems, in which the intended drug is released in response to the needs of the body (7–15).

The pores in the hydrogel let the drug be easily placed inside them and be used as a drug delivery system. Drug delivery hydrogels are used in the form of pieces, microparticles, nanoparticles, coatings or films (6, 7). Hydrogels can be used for delivery in both hydrophilic and hydrophobic drugs and can place both hydrophilic and hydrophobic drugs into the hydrogel concurrently. For example, the temperature and pH-sensitive hydrogel oligo β-aminoesteruratan is used to control drug release hydrophilic doxorubicin (8), and the chitosan networked by light is used for loading hydrophobic paclitaxel (9), and the glycol/chitosan and polyethylene glycol hydrogel are used to release both paclitaxel and doxorubicin simultaneously (10).

Great water diffusion in hydrogel causes the drug release faster, especially for hydrophilic drugs used for

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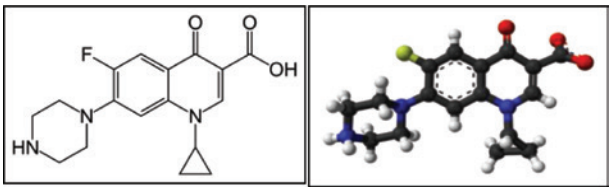

Cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-quinoline-3-carboxylicacid

Figure 1: Chemical structure and IUPAC name of ciprofloxacin.

delivery from hydrogel. A set of strategies have been used to delay the release of drugs from hydrogels. One that increases the duration of drug delivery is the hydrogel-drug interaction, which can be physical or chemical (11). Hydrogels are hydrophilic and can absorb large amounts of water. It is expected that the mechanism of drug release from these carriers is completely different from that of the hydrophobic cases. A variety of simple and complex models has been used for the study of the active agents delivery from hydrogels. The release diagram shows three control mechanisms: diffusion, swelling and chemical (12, 13).

Ciprofloxacin, $C_{17}H_{18}FN_3O_3$ with the commercial name "Siloxane Cipro Neofloxin" and the molecular structure shown in Figure 1, is a fluoroquinolone antibacterial that stops the DNA synthesis after penetrating the cell membrane. When DNA is opened for copying, it lacks the necessary enzyme to turn and twist again and would be destroyed. Ciprofloxacin is used in the treatment of infections caused by gram-negative and sometimes gram-positive bacteria (14), as well as in antibiotics to treat urinary tract infections, bladder infections in women, chronic bacterial prostatitis, lower respiratory tract infections, chronic sinusitis, skin infections, bone and joint infections, infectious diarrhea and typhoid fever.

In this study, acrylic hydrogels synthesized in the presence of ultrasound were studied to evaluate the controlled delivery of ciprofloxacin. The new system, namely, pH-sensitive drug delivery, was introduced in which drug or any other active ingredient release is done only by pH stimulants. If the drug release kinetics is known, it would be easy to inform the amount of the medication and treatment based on the amount of drug released into the environment. In general, the required amount of drug released into the environment must be determined by considering medical conditions and needs of patients. Based on such information and drug release kinetics curves, we can decide on the system design conditions. The important benefits of the technique used in this study are as follows:

1. This hydrogel was used to load for drugs that are often harmful to other organs in the body. In such systems, loaded drug is released with gel swelling.
2. Drug release is controlled as needed, which prevents sudden increases or decreases of drug during use.
3. The use of this method is highly valuable for the preparation of drugs having a fast metabolism or short half-life in the body (as a bodyguard).
4. The use of hydrogels as drug carrier is an appropriate method for poison or nonbiodegradable material control.

2 Materials and methods

2.1 Material and devices

Sodium hydroxide, pure glycerin and acrylic acid were purchased from Merck (Germany). Acrylamide and methylene bis-acrylamide were purchased from Fluka (Germany). Analytical methylene bis-acrylamide was used without further purification. Acrylic acid was used after vacuum distillation, and double-distilled water was used as solvent. Table 1 shows the characteristics of the devices used in this project.

2.2 Ultrasonic hydrogel synthesis

Hydrogel synthesis was optimized using the classical method (15): 14 g 75% (w/w) glycerin as solvent and mixed monomer containing 0.75 g acryl amid and 0.75 g of acrylic acid neutralized 30% by NaOH were mixed with 0.1 g methylene bis-acrylamide cross-linker. Then the mixture was exposed to an ultrasonic probe with 80% (56 W) power and a pulse 8. At the end of the reaction, the obtained hydrogel was weighed and washed three times with water and ethyl alcohol and then dried in the oven 60°C for 8 h. The dry product was kept in a container away from light, heat and humidity.

Table 1: Specifications of devices used.

No	Unit	Model/Company
1	Balance ± 0.001 g	TE124S/Sartorius (Germany)
2	Ultrasonic probe	Sonoplus HD2070/Bandelin (Germany)
3	UV-Vis	UV-visible 1650 PC/Shimadzu (Japan)
4	FT-IR	FT-IR, 4200/Jasco (Japan)
5	TGA	Pyris Dimmand/TG/DTA
6	Stirrer	RZR 2102 Control/Heidolph (Germany)
7	pH meter	827/Metrohm (Swiss)
8	SEM	XL30 Scanning/Philips (Netherlands)
9	Oven	INB 400/Memmert (Germany)

2.3 Product analysis

The hydrogel samples were dried in vacuum at 60°C for 12 h to a constant weight. The dried hydrogels were analyzed in potassium bromide discs by Fourier transform infrared (FT-IR). In addition, UV-visible (UV-Vis) was used for the preparation of UV-Vis spectra. Scanning electron microscopy (SEM) was used to study the morphology of the hydrogels surfaces. Thermogravimetric analysis (TGA) was performed under nitrogen atmosphere.

2.4 The extinction coefficient measuring

To access the calibration curve, a 2.9×10^{-3} M drug solution in water was prepared, and then solutions with concentration of 39, 79, 159, 238 and 318 mg/L were prepared via step dilutions of this solution. Ultraviolet absorption of these solutions was recorded in 271 nm. Extinction coefficient was calculated from the slope of the calibration curve (absorbance vs. concentration).

2.5 Swelling measurements

The method of tea bag was used to measure the speed of water absorption by hydrogel (16). This method is one of the most common and suitable criteria to measure the water absorption methods. Gel powder (0.2 g) was put in a tea bag and was suspended in 200 ml double-distilled water. Tea bag was hung after 3 h swelling of the hydrogel (10 min) to remove excess water, and the swelling capacity (g/g) was calculated using equation [1], where W_S and W_D are swollen and dry hydrogel, respectively.

$$W.A. = \frac{(W_S - W_D)}{W_D} \quad [1]$$

2.6 Drugs loading in hydrogel

In order to investigate ciprofloxacin loading in hydrogel, its 2.1×10^{-3} M solution was prepared, and 0.02 g of hydrogel was added to 20 ml of this solution in ambient temperature. Periodically, sampling was done from the upper part of the solution, and then it was analyzed with UV. After drug loading, the hydrogel containing the drug was filtered and washed with distilled water and was dried in an oven at 50°C for 8 h. Then dried hydrogel was washed with pure ethanol and was passed through filter, and the substrate solution was analyzed. Finally, the hydrogel was dried at room temperature and was ready for drug delivery. To study the effect of drug concentration, 0.02 g hydrogel was added to the samples mentioned in Section 2.4. Solutions were filtered after 30 min stirring and drug loading in the hydrogel, and the UV absorbance of each solution was measured.

2.7 Drug release from hydrogel

Due to the complexity of the human body simulation, the phosphate buffer in pH 7.4 was used to study drug delivery. To prepare the solution, 3.6 g of KH_2PO_4 and 5.79 g of Na_2HPO_4 were added to 1 L of volumetric flask with distilled water using the reference standard United States Postal. For drug delivery, the loaded hydrogel was put in a beaker containing 20 ml of buffer solution. The beaker was placed in a water bath at 37°C, the body temperature. Then the solution was analyzed at intervals of 30 min.

2.8 Effect of temperature and pH on drug release

To study the effect of the temperature, 20 ml of buffer solution was placed in a water bath with temperatures 5, 20, 37 and 45°C, respectively, and 0.02 g of gel containing the drug was added to each beaker. Then the solution was characterized by UV after each 15 min for 1 h. To study the effect of pH, some solutions at pH 2 and 8 (the stomach and intestines, respectively) and pH 10 were prepared. The solutions of sodium hydroxide and hydrochloric acid (0.1 M) were used to set the pH of the solution. Having adjusted the pH, 0.02 g of loaded hydrogel was added to each solution. The mixture was stirred each 15 min for 2 h, and the solution was characterized by ultraviolet.

2.9 Repeating experiments

Drug loading and release experiment were repeated in a different concentration of ciprofloxacin (2.9×10^{-3} M) to confirm the obtained results and effects of the drug concentration.

3 Results and discussion

Hydrogel based on acrylic acid and acryl amide was synthesized by ultrasound, and its swelling behavior was studied in different environments. Moreover, drug

loading and release of ciprofloxacin and the effect of various factors such as time, pH and temperature on this loading and release were studied too. After determining optimal conditions, the capacity of drug absorption was determined.

3.1 Gel formation

Figure 2 shows the preparation steps of ultrasonic hydrogel from the formation to obtaining a dry sample. Method details are given in Section 2. After the gel formation, its swelling was studied as the most important property (17–19).

3.2 FT-IR and TG spectroscopy and structural analysis

The infrared spectrum was used to characterize and evaluate the functional groups. For this purpose, FT-IR spectra of the drug-loaded hydrogel, hydrogel and ciprofloxacin alone were recorded (Figure 3). In IR spectrum of ciprofloxacin, a broad peak in the area 3300–3500 cm^{-1} related to the hydroxyl group O-H and an amino group NH in chain and the symmetric stretching vibration of methyl 2926 cm^{-1} introduced a peak of moderate intensity and bending vibration in the area of 1451 cm^{-1} CH_3 group, respectively. In addition, stretching vibration in the area of 1705–1725 cm^{-1} belongs to the group C=O of ketones. Peak of the C-F vibrations was seen at 1000–1400 cm^{-1}. A peak with moderate intensity was seen in the 1600–1660 area, which is related to C=C double-bond vibration on the ring.

Comparison of IR absorptions shows that the frequency of 1624–1708 cm^{-1} in loaded gel is related to two peaks, the first carbonyl group of drug C=O 11708 cm^{-1} and the second C=C peak of the hydrogel.

Thermal gravimetric analysis diagram of prepared hydrogel has been shown in Figure 4. According to this diagram, thermal degradation starts with achieving temperature at 100°C and violent degradation at 600°C, and a significant reduction has occurred in the product mass. This destruction has continued up to 700°C with less intensity, and then no more changes were observed in product mass with increasing temperature. In addition, this figure shows the DTA charts (temperature vs. the symbols of reaction) in which we observed thermal analysis of two peaks, one minimum and another maximum. In this figure, the minimum peak shows dehydration process of components, as a result of an endothermic process, and the maximum peak can be the beginning of the crystallization and the formation of the first crystal, which is an exothermic process.

3.3 Effects of various factors on hydrogel swelling

In this section, the effects of several factors such as time, temperature and pH were studied on hydrogel swelling to be compared with the effects of these factors on the drug release process in the next part.

Table 2 and Figure 5 show the changes in hydrogel water absorption with time. As it can be seen, hydrogel swelling increases over time to about 60 min, and maximum water absorption is seen. It shows that the hydrogel synthesized by ultrasound has faster water absorption due to great pores.

Table 3 and Figure 6 show the water absorption changes of the hydrogel with temperature. As expected, hydrogel swelling has been reduced with increasing temperature. We can see maximum water absorption at 5°C and the lowest at 45°C; swelling lessens also at higher than 45°C. This behavior is due to a change in the lattice structure of the prepared hydrogels causing the flexibility of hydrogel structure to decrease with increasing temperature and water influence leading to decline gel swelling (20).

Due to the use of hydrogel in the pharmaceutical industry, it is important to study the behavior of its swelling with pH. Table 4 and Figure 7 show changes in the

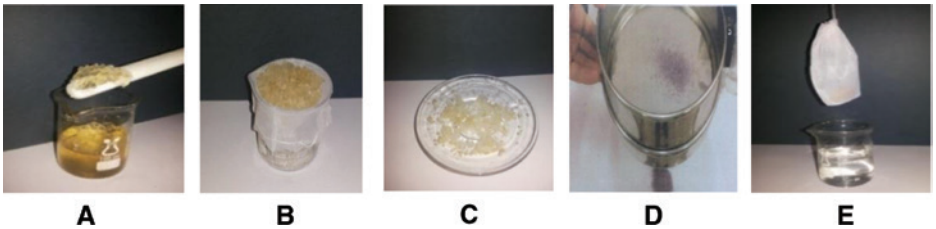

Figure 2: Steps of processing of ultrasonic hydrogel preparation.
(A) synthesis, (B) filtering, (C) drying, (D) grinding and (E) swelling.

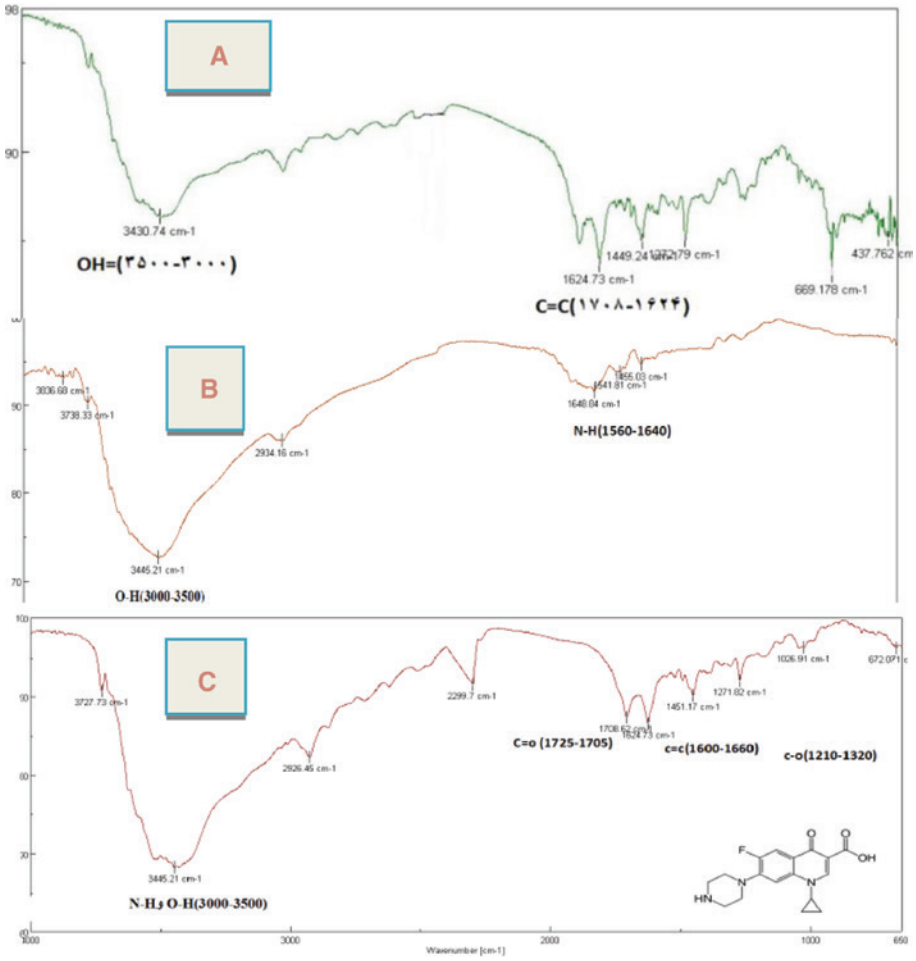

Figure 3: Comparing of FT-IR spectra of drug absorbed on the hydrogel (A), hydrogel (B) and ciprofloxacin (C).

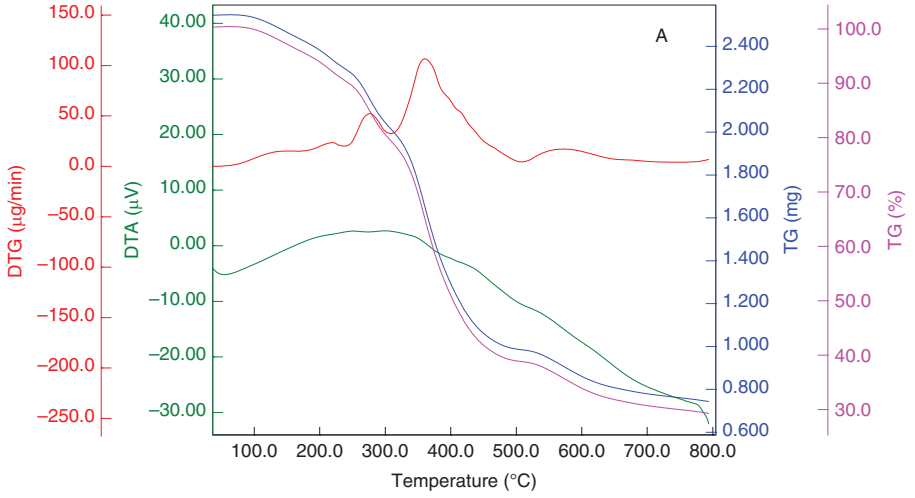

Figure 4: TGA and DTA graph of hydrogel synthesized by ultrasound.

synthetic hydrogel swelling with pH. We can observe that swelling reaches its maximum (764.68) at pH 8 and then drops again. Ammonium groups (NH_3^+) are formed in an acidic medium and the carboxyl ion (COO^-) in basic environment. At pH 7 and above, water absorption and swelling increases with increasing ionization of carboxylic

Table 2: Hydrogel swelling changes over time.

Time (min)	15	30	45	60	75	90	120
Swelling (g/g)	345.2	654.2	789.9	895.4	896.5	898.6	898.9

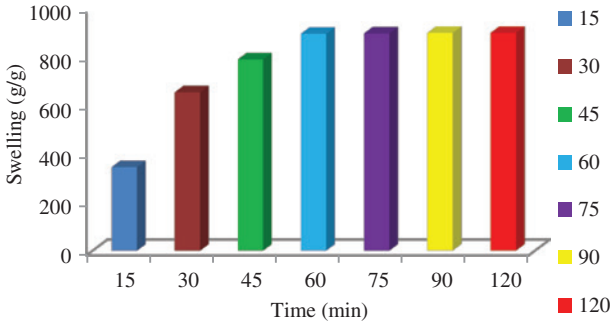

Figure 5: Hydrogel swelling changes over time.

Table 3: Changes of the hydrogel swelling verses temperature.

Temperature (°C)	5	15	30	45
Swelling (g/g)	898.9	783.2	653.8	342.1

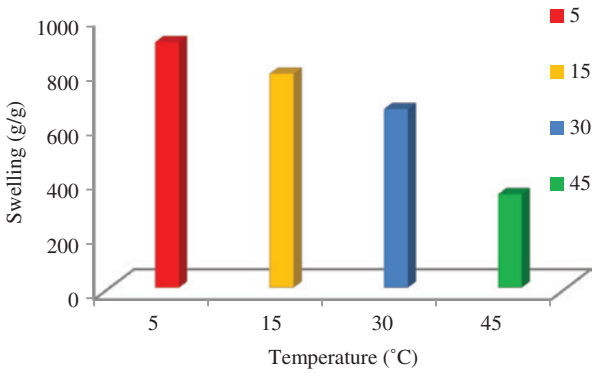

Figure 6: The effect of temperature on the water absorbed by the hydrogel.

acid groups (COOH). However, at pH 10 and 4, swelling decreases due to charge overlap effect (3).

3.4 Drug selection

In the selection of medical model to assess the loading and release, the intended drug should not react with hydrogel components or solvent. This interaction can be specified by shift in λ_{max}. This drug is a good case because no change was observed in the amount and location of λ_{max} over time. At first, its calibration curve was prepared at wavelength 271 nm (Figure 8). Extinction coefficient was

Table 4: Changes of the hydrogel swelling verses pH.

pH	2	4	6	7	8	10
Swelling (g/g)	116.42	512.06	560.82	651.31	764.68	589.03

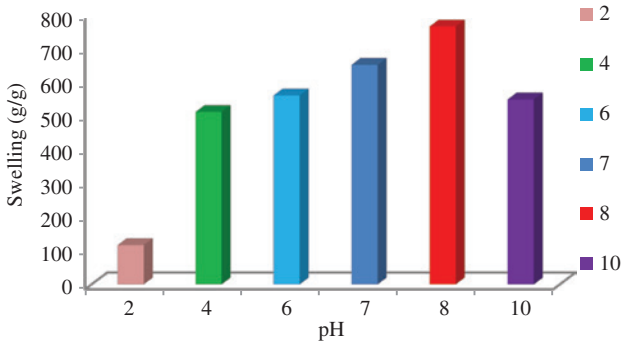

Figure 7: Effect of pH on the water absorption of hydrogel (environments: acidic, basic and neutral).

obtained 0.008, equal to the slope of the curve (absorption vs. concentration). In addition, there was no interference between the drug and hydrogel spectra.

3.5 Drug loading and the concentration effects

A 20-ml solution of ciprofloxacin (2.1×10^{-3} M) was mixed with 0.02 g hydrogel at ambient temperature. Then hydrogel solution containing the drug was characterized by ultraviolet every 15 min, and its graph was plotted (Figure 9). It was observed that the highest absorption rate was at the beginning of drug loading on the hydrogel, and the drug was absorbed by the hydrogel and rate of absorption (drug concentration) reduced gradually over time

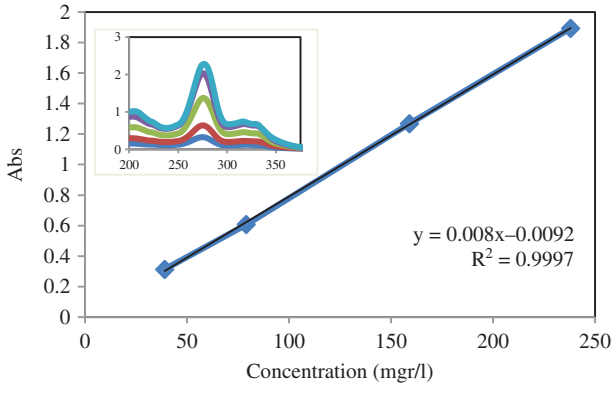

Figure 8: Ciprofloxacin calibration curve (UV absorption vs. concentration).

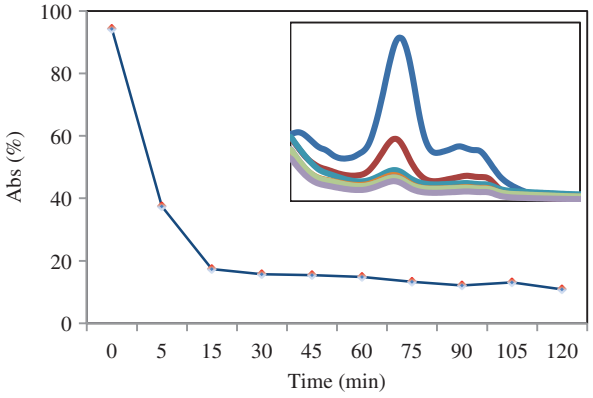

Figure 9: Plot of percent drug loading by hydrogel with time.

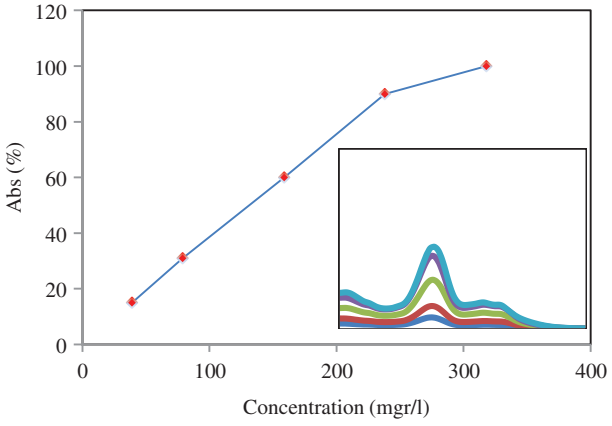

Figure 10: The effect of drug concentration on the drug loading into hydrogel.

(21–25). Drug absorption was complete approximately at 60 min, and then the absorption is fixed. This indicates that drug is loaded in the gel within a short time due to the large number of pores devised in the hydrogel.

Ciprofloxacin has a maximum absorption in 271 nm, and absorption has a direct relationship with concentration (in less than 0.01 M), so we can use absorption changes in λ_{max} versus its concentration during loading in the hydrogel. Figure 10 shows the effect of drug concentration on the drug loading in the hydrogel. As we see, the amount of drug loaded in hydrogel increases with increasing drug concentrations, although the increase is not linear.

3.6 Drug release and factors affecting it

3.6.1 Drug release as a function of time

Drug release is conducted so that water penetrates the hydrogel network. Therefore, the release time of the drug

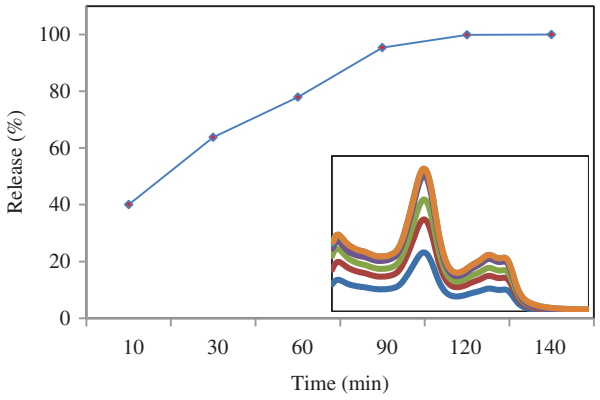

Figure 11: Diagram of the hydrogel drug release over time.

is shortened by increasing the penetration rate of water into the hydrogel network. Accordingly, the drug releases from hydrogels, and its concentration increases in the buffer drastically over time (26–28). Figure 11 shows drug release changes from the hydrogel over time.

3.6.2 Drug release as a function of temperature

In order to evaluate the effect of temperature according to Section 2.8, the magnitude of drug release was studied in different temperatures with time (Figure 12). Drug release is reduced as the temperature increases, and the least drug release is observed in the temperature of 45°C. As temperatures rises, the hydrogel network is undermined and its flexibility decreases. Thus, water penetration and hydrogel swelling reduces; thus, the lower buffer solution diffuses into hydrogel, and subsequently lower drug is released from the hydrogel. Low swelling and low release are desirable near the body temperature. On the other

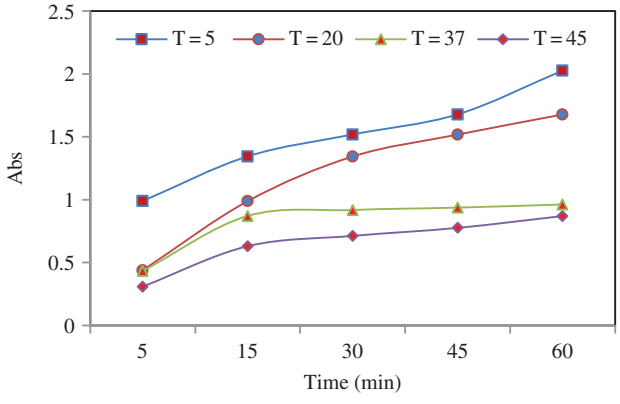

Figure 12: Drug release over time at different temperatures.

hand, gel occupies a smaller volume in intestine, and drug releases more slowly too and consequently has more opportunities to be absorbed. Also, in the residence time of the gel in gut (1 h or more), every loaded drug will be released and absorbed by blood.

3.6.3 Drug release as a function of pH

Most of the drugs lose their structures upon entering the stomach (affect the gastric acid), and only a small amount of the drug absorbed through the intestines enters the blood. As a result, the effective amount of the drug needs to be increased as the drug enters the blood circulation, and this causes some side effects. pH sensitivity and biodegradability are very important for oral drugs. Because the swelling ratio of the drug-loaded hydrogels differs under the various pH values in the human digestive tract, the hydrogel can prevent drug release in the stomach (low pH), whereas the drug can be selectively released in the small intestine or colon (high pH) (29). Therefore, ciprofloxacin drug delivery is studied with time at pH 2 and 8, equivalent to the acidity of the human stomach and small intestines, respectively. As seen in Figure 13, drug release is greater at pH 8 rather than pH 2. This behavior is reasonable with the swelling pattern of hydrogel (Section 3.3) (3). Here, the highest drug release was observed at pH 8.

Comparing the simultaneous effects of temperature and pH on drug release, we conclude that all the required conditions are preferred for the slow release of the drug in the gut, and this leads to the highest absorption of drug (30). It should be noted that the temperature is almost constant throughout the path of the drug, whereas the pH has many changes from the mouth to the anus.

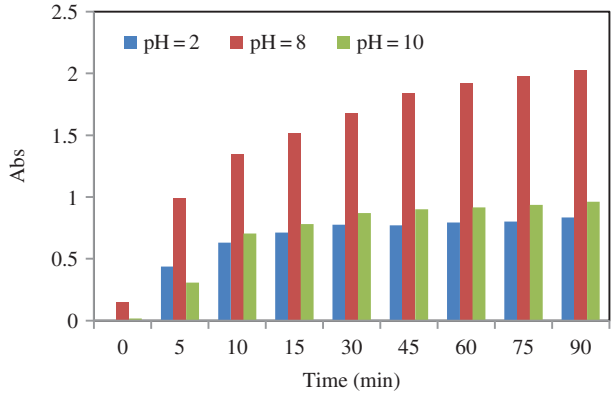

Figure 13: Diagrams of drug release from the hydrogel at different pH levels.

3.7 Repeating loading and releasing experiments

In order to ensure the reproducibility of loading and delivery experiments, the entire process of loading and release of ciprofloxacin was repeated in another different concentration (2.9×10^{-3} M). Other conditions were the same as mentioned before. The results were repeated here, similar to the previous concentration. The only difference was more absorption of drug due to more concentration. Data have not been shown here because of the high similarity and proximity to previous results.

4 Conclusion

It can be concluded that programed methods may be devised for drug delivery to control drug release in accordance with changes in acidity. These methods have essential roles for the development of targeted therapy. In this study, the hydrogel prepared by ultrasound was studied for its effect on ciprofloxacin, and the capabilities of synthetic hydrogel for the absorption and release of this drug were demonstrated. The results showed that the drug absorption was rapid and the release rate from hydrogel was acceptable (less than 1 h). The important point in hydrogel application is that the increase in the rate of water penetration and buffer solution into hydrogel reduces drug loading time and the time of drug release from the hydrogel; thus, it can be used in applications where rapid release is intended. Hydrogels synthesized by ultrasound can be used in special intestinal drug delivery, drug dose modification, making dressings, local drug delivery as ointments, cartilage repair, tissue engineering, cosmetic applications and Botox due to good swelling properties, flexibility and controllability by external stimuli. This method can be extended to other medicine systems and its broad domain. The use of these hydrogels is highly valuable in providing drug carriers for poison control or environmental incompatibility and also in providing drugs having fast metabolism or short half-life in the body because hydrogel can act as a support.

Conflict of interest statement: The authors declare that there is no conflict of interests regarding the publication of this paper.

References

1. Pokhrel N, Vabbina PK, Pala N. Sonochemistry: science and engineering. Ultrason Sonochem. 2016;29:104–28.
2. Ebrahimi R, Sadeghi Niyaraki F, Bolouri Jirandeh A. Ultrasonic irradiated synthesis of acrylic acid-co-acrylamide as pH and salt sensitive hydrogel. J Polym Mat. 2014;31:159–67.
3. Wan T, Xiong J, Zhao Q, Wu D, Tang L, Liao L, Chen Q. Crosslinker effects on swelling and gel properties of pH- and temperature-responsive poly (NIPAM/IA/AM) hydrogels. Polym Bull. 2016;73:1447–58.
4. Wu C, Wang D, Wu H, Dan Y. Synthesis and characterization of macroporous sodium alginate-g-poly(AA-co-DMAPMA) hydrogel. Polym Bull. 2016;73:3255–69.
5. Katchalsky A, Gillis J. Theory of the potentiometric titration of polymeric acids. RECUEIL 1949;68:879–97.
6. Kim JK, Basavaraja C, Yamaguchi T, Huh DS. Preparation and characterization of smart hydrogel nanocomposites sensitive to oxidation–reduction. Polym Bull. 2013;70:207–20.
7. Hamidi M, Azadi A, Rafiei P. Hydrogel nanoparticles in drug delivery. Adv Drug Deliv Rev. 2008;60:1638–49.
8. Huynh CT, Nguyen MK, Lee DS. Biodegradable pH/temperature-sensitive oligo(β-amino ester urethane) hydrogels for controlled release of doxorubicin. Acta Biomat. 2011;7:3123–30.
9. David Betts M, Suh A, Bui K, Doyoung Kim L, Cho H. Hydrogel-based drug delivery systems for poorly water-soluble drugs. Mol. 2015;20:20397–408.
10. Zhao L, Zhu L, Liu F, Liu C, Shan-Dan, Wang Q, Zhang C, Li J, Liu J, Qu X, Yang Z. pH triggered injectable amphiphilic hydrogel containing doxorubicin and paclitaxel. Int J Pharm. 2011;410:83–91.
11. Ganji F, Vasheghani-Farahani E. Hydrogels in controlled drug delivery stems. Iran Polym J. 2009;18:63–88.
12. Ayres E, Regina Ferreira C, Henrique Lima T, Martins GS, Villanova JCO, Orefice RL. Self-crosslinkable complexes based on poly(ethylene glycol) (PEG), poly(itaconic acid) (PIA) and N-methylol acrylamide (NMA) as pharmaceutical hydrophilic matrices. Polym Bull. 2016;73:75–95.
13. Chang A. pH-sensitive starch-g-poly(acrylic acid)/sodium alginate hydrogels for controlled release of diclofenac sodium. Iran Polym J. 2015;24:161–9.
14. Drusano GL, Standiford HC, Plaisance K. Absolute oral bioavailability of ciprofloxacin. Antimicrob Agents Chemother. 1986;30:444–6.
15. Ebrahimi R, Ebrahimi M. The stimuli-response characters of the hydrogels prepared from ultrasound. J Polym Eng. 2014;34:625–32.
16. Turan E, Caykara T. Swelling and network parameters of pH-sensitive poly(acrylamide-coacrylic acid) hydrogels. Appl Polym Sci. 2007;106:2000–7.
17. Anbarasan R, Jayaseharan J, Sudha M, Gopalan A. Sonochemical polymerization of acrylic acid and acrylamide in the presence of a new redox system. Appl Polym Sci. 2003;89:3685–92.
18. Isık B, Kıs M. Preparation and determination of swelling behavior of poly(acrylamide-co-acrylic acid) hydrogels in water. Appl Polym Sci. 2004;94:1526–31.
19. Teo BM, Prescott SW, Ashokkumar M, Grieser F. Ultrasound initiated miniemulsion polymerization of methacrylate monomers. Ultrason Sonochem. 2008;15:89–94.
20. Bromberg LE, Ron ES. Temperature-responsive gels and thermos gelling polymer matrices for protein and peptide delivery. Adv Drug Deliv Rev. 1998;31:197–221.
21. Amin S, Rajabnezhad S, Kohli K. Hydrogels as potential drug delivery systems. Sci Res Essay 2009;3:1175–83.
22. Hoare TR, Kohane DS. Hydrogels in drug delivery: progress and challenges. Polymer 2008;49:1993–2007.
23. Isıklan N, Kucukbalcı G. Synthesis and characterization of pH and temperature sensitive materials based on alginate and poly(Nisopropylacrylamide/acrylic acid) for drug delivery. Polym Bull. 2016;73:1321–42.
24. Lin WJ, Chen YC, Lin CC, Chen CF, Chen JW, Lin CC, Metters AT. Hydrogel in controlled release formulations: network design and mathematical modeling. Adv Drug Del Rev. 2006;58:1379–408.
25. Yadav I, Shaw G, Nayak SK, Banerjee I, Shaikh H, Al-Zahrani SM, Anis A, Pal K. Gelatin and amylopectin-based phase-separated hydrogels: an in-depth analysis of the swelling, mechanical, electrical and drug release properties. Iran Polym J. 2016;25:799–810.
26. Obara K, Ishihara M, Ozeki Y, Ishizuka T, Hayashi T, Nakamura S, Saito Y, Yura H, Matsui T, Hattori H, Takase B, Ishihara M, Kikuchi M, Maehara T. Controlled release of paclitaxel from photocrosslinked chitosan hydrogels and its subsequent effect on subcutaneous tumor growth in mice. Control Release 2005;110:79–89.
27. Zarzycki R, Modzejewska Z, Nawrotek K. Drug release from hydrogel matrices. Ecolog Chem Eng. 2010;17:2.
28. Ichikawa H, Fukumori Y. Design of nanohydrogel-incorporated microcapsules for appropriate controlled-release of peptide drugs. Yakugaku Zasshi. 2007;127:813–23.
29. Suna XF, Wang HH, Jing ZX, Mohanathas R. Hemicellulose-based pH-sensitive and biodegradable hydrogel for controlled drug delivery. Carbohydrate Polym. 2013;92:1357–66.
30. Deligkaris K, Tadele TS, Olthuis W. Berg van den A. Hydrogel based devices for biomedical application. Sens Actuators. 2010;147:765–74.