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CONTROLLED DRUG DELIVERY FROM HYDROGEL SYNTHESIZED BY ULTRASOUND

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Abstract— **Concentration of drugs in blood might exceed toxicity level or come below effective level. In addition, side effects of some drugs are not negligible. The present study is an attempt to propose a simple, easy, and environmental friendly method to survey controlled absorption and desorption of medicine using ultrasonic hydrogels and to survey controlled delivery of medicine in pseudo-human body environments [1]. Hydrogels have been used as a base for rectal and vaginal drug delivery. Modern controlled drug delivery systems also greatly rely on hydrogels. Drug loading of hydrogel was carried out by 20 ml of ciprofloxacin (0.0021mol/l) in a beaker for 5 min at ambient temperature. Afterward, 0.2gr of synthesized hydrogel powder was added to the solution and homogeneity of the solution was ensured. Having the drug completely absorbed, the swelled hydrogel was processed in oven (50°C) and prepared for delivery step. To this end, the loaded powder of the gel was added to buffer solution (PH=7.4; resembling acidity of the stomach and large intestine); then the delivery was measured using UV-meter for 4 hours at 37 °C (body temperature). There is no need for chemical initiator – toxic in some cases – and higher temperature when ultrasonic hydrogel polymerization is used [2] as the ultrasonic-based gel is more porous than non-ultrasonic gels. Therefore, faster absorption and delivery of drug is expected with ultrasonic gel. In addition, the results showed that the hydrogel is responsive to pH, which makes it a good candidate for ciprofloxacin delivery. The results also indicated that the higher the swelling of the hydrogel, the higher the loading time and concentration of drug. Furthermore, increase of the water diffusion rate to the hydrogel led to more drug delivery. Moreover, biodegradability and environmental friendly features of this system makes it a good candidate to be used in pharmaceutical industry as a way to control rate, time, and place of drug delivery and minimize side effects.**

Index Terms— **ciprofloxacin, drug delivery, hydrogel, pH sensitive, polymerization, ultrasound.**

INTRODUCTION

Ultrasound has been used for the initiation of many different polymerization reactions. These include polymerization of acrylic acid and acrylamide, butyl acrylate [1,2] and soon. An area where ultrasound can be used is the preparation of hydrogel. However, to the best of our knowledge, we only found a few reports on hydrogel synthesis in the presence of ultrasonic irradiation[3]. To put the present research into perspective, a review of the studies which synthesized hydrogel in the absence of ultrasound seems necessary. This study found that increasing temperature, power output, and sodium dodesyl sulfate concentration and also decreasing monomer concentration results in reduced induction period and enhances polymerization rate[4,5].

Most of ionic hydrogels usually undergo volume changes in response to a little change in environmental conditions such as heat, pH, electric field, chemical environments, etc. The hydrogels sensitive to external stimuli are often referred to as intelligent and smart hydrogels. They have important applications in the field of medicine, pharmacy, and biotechnology. Among these, pH-sensitive hydrogels have been extensively investigated for the potential use in the site-specific delivery of drugs to specific regions of the gastrointestinal tract and have been prepared for the delivery of protein drugs with low molecular weight. Such observed sensitivity to pH variations is in agreement with the results published by Mohy Eldin et al., in which they studied the effect of pH variation on the swelling of pH-sensitive polyacrylamide-grafted carboxymethyl cellulose hydrogel system composed of acrylamide and carboxymethyl cellulose. These gels exhibited a fair pH-dependent swelling behavior as the pH of the swelling medium varied from 1.0 to 11.

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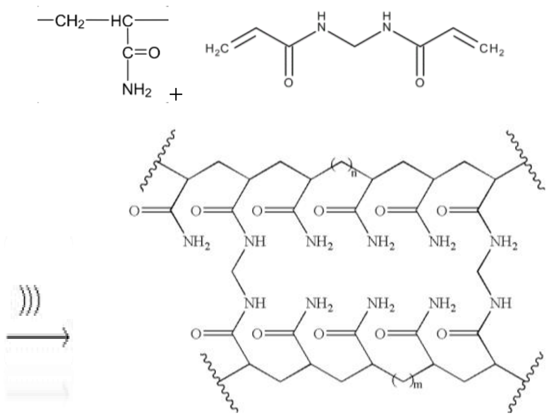

Fig. 1 Chemical reaction of synthesizing acrylamide hydrogel via ultrasound

METHODS

A. Chemicals

In preliminary runs of the experiment, optimum parameters were obtained as;
monomer concentration = 3.02M, MBAAm = 0.6 %; crosslinker = 1.3 mol %, AAc = 7.3 to 29.1 mol %. The mass ratio of AA and AM is 6 : 1, Total mass percent of both monomers is 25%, the neutralized degree of AA is 70%, Mass percentages of the cross-linker = 0.01%, with respect to the total mass of the monomers.

B. Drug tests

Drug loading of hydrogel was carried out by 20 ml of ciprofloxacin (0.0021mol/l) in a beaker for 5 min at ambient temperature. Afterward, 0.2gr of synthesized hydrogel powder was added to the solution and homogeneity of the solution was ensured. Having the drug completely absorbed, the swelled hydrogel was processed in oven (50 °C) and prepared for delivery step. To this end, the loaded powder of the gel was added to buffer solution (PH=7.4; resembling acidity of the stomach and large intestine); then the delivery was measured using UV-meter for 4 hours at 37 °C (body temperature).

RESULTS AND DISCUSSION

Fig. 1 is a schematic representation of the reaction involved in the synthesis of hydrogel in the presence of ultrasonic irradiation. There is no need for chemical initiator – toxic in some cases – and higher temperature when ultrasonic hydrogel polymerization is used as the ultrasonic-based gel is more porous than non-ultrasonic gels. Therefore, faster absorption and delivery of drug is expected with ultrasonic gel. In addition, the results showed that the hydrogel is responsive to pH, which makes it a good candidate for ciprofloxacin delivery.

A. ultrasonic synthesis

Fig. 2 shows the changes which took place during ultrasonic irradiation. As can be seen, hydrogel formation started 20 sec after ultrasonic irradiation commenced. The reaction then accelerated and was complete after 25 sec. It is worth noting that hydrogel formation was also observed before and after these times, but the amount was just negligible.

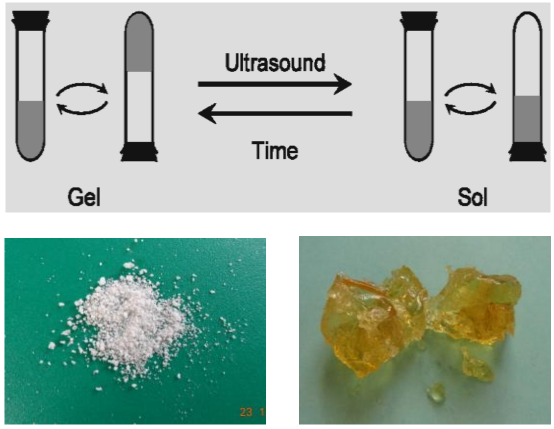

Fig. 2. Monomer conversion during ultrasonic irradiation and produced hydrogel

We studied the effect of the amount of the reagents and the solvent on reaction time. Table 1 shows the reaction times as a function of varied percents of monomers (Acrylic acid and Acrylamide), the crosslinker (methylene bisacrylamide), and the solvent (glycerol and water).

TABLE I THE IMPACT OF THE AMOUNT OF MONOMERS, CROSSLINKER, AND SOLVENT ON REACTION TIMES

No. EXP	AA (gr)	AAm (gr)	MBA (gr)	Glycerol (gr)	H_2O (gr)	starting and ending reaction times (min:sec)
1	*0.25*	*0.25*	*0.05*	*10.5*	*3.5*	*11:45-18:40*
2	*0.25*	*0.25*	*0.05*	*12*	*2*	*2:55-7:07*
3	*0.5*	*0.5*	*0.1*	*10.5*	*3.5*	*9:15-10:02*
4	*0.5*	*0.5*	*0.1*	*12*	*2*	*2:00-2:48*
5	*0.75*	*0.75*	*0.1*	*12*	*2*	*1:25-2:17*

B. Drug loading and releasing character

Faster absorption and delivery of drug is expected with ultrasonic gel. The results showed that the hydrogel is responsive to pH, which makes it a good candidate for ciprofloxacin delivery. The results also indicated that the higher the swelling of the hydrogel, the higher the loading time and concentration of drug. Furthermore, increase of the water diffusion rate to the hydrogel led to more drug delivery. Moreover, biodegradability and environmental friendly features of this system makes it a good candidate to be used in pharmaceutical industry as a way to control rate, time, and place of drug delivery and minimize side effects.

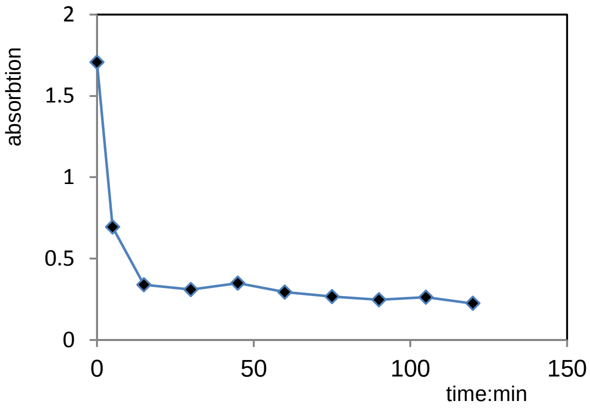

Fig. 3 ciprofloxacin drug loading on hydrogel prepared from ultrasound

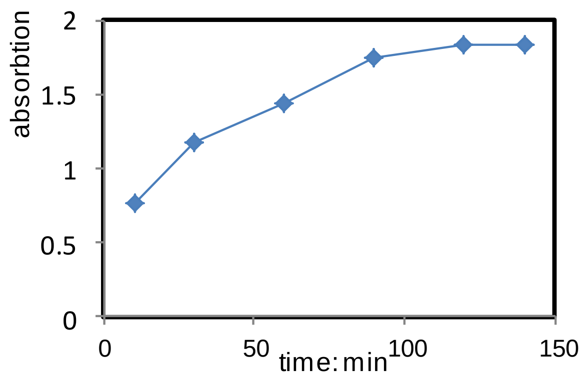

Fig. 4 ciprofloxacin drug releasing from hydrogel prepared from ultrasound

I. Conclusion

We compared the synthesis of hydrogel using conventional synthesis. experiments were performed at a constant temperature of 37 °C. hydrogel formation is faster in the presence of ultrasound than in its absence. It was also discovered that hydrogel formation speeds up at higher quantities of glycerol. The paper deals with ultrasound assisted synthesis of hydrogel and reports expected results in terms of better product, which has been established by so many earlier studies. The paper discussed on mechanism by which ultrasound improves the product properties. Also there is much of sonochemistry content such as understanding effect of ultrasound parameters such as power dissipation or frequency. Calorimetric measurements were shown.

The results also indicated that the higher the swelling of the hydrogel, the higher the loading time and concentration of drug. Furthermore, increase of the water diffusion rate to the hydrogel led to more drug delivery. Moreover, biodegradability and environmental friendly features of this system makes it a good candidate to be used in pharmaceutical industry as a way to control rate, time, and place of drug delivery and minimize side effects.

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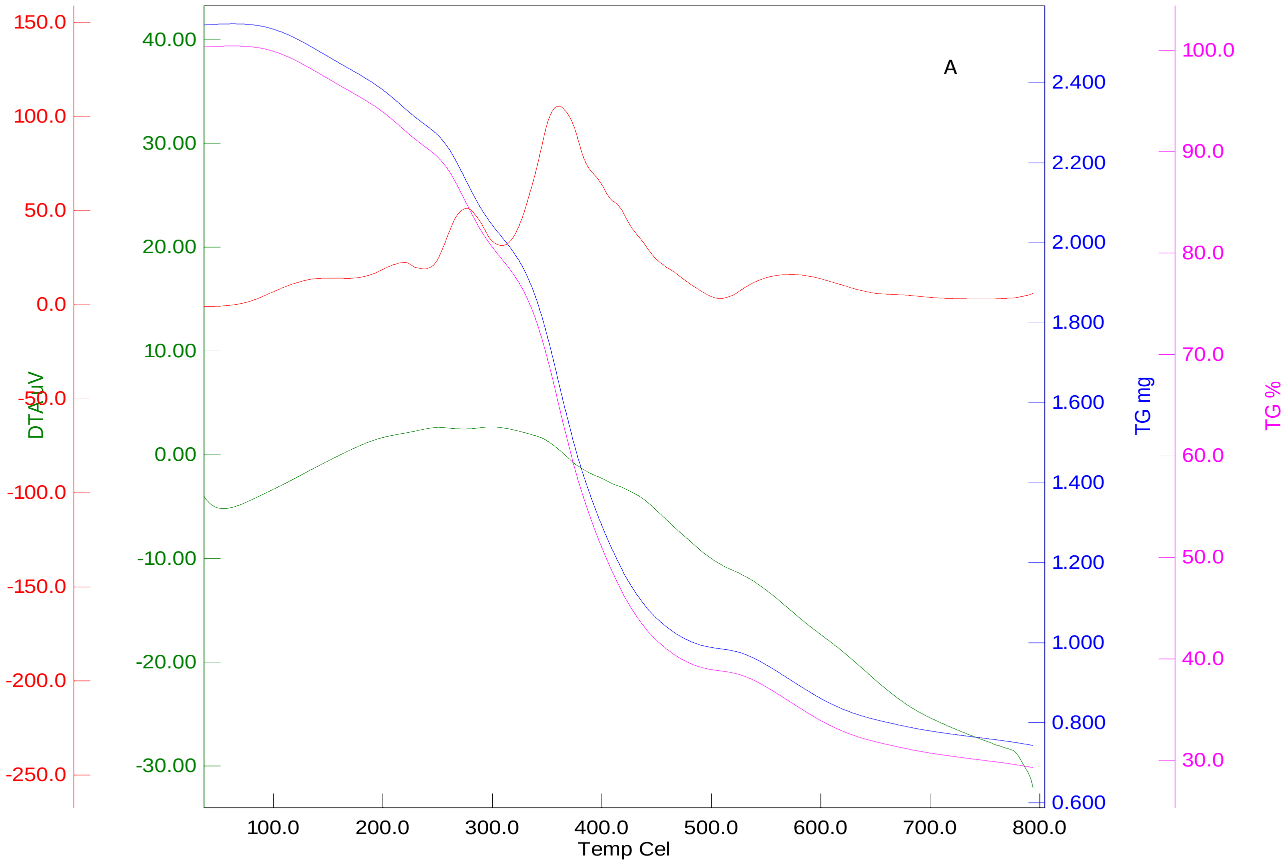
Appendix: *TG analysis of hydrogel produced by ultrasound*



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