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Chloramphenicol controlled release from Poly(acrylic acid-co-methyl methacrylate)hydrogels

Mohammed A. Mutar
Department of Chemistry, College of Education, University of Al-Qadissiya
mohammeddw@yahoo.com
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Abstract

In the present work methyl methacrylate-co-acrylic acid (MMA-co-AA) hydrogels were synthesized by free radical copolymerization of methyl methacrylate (MMA) and acrylic acid (AA) using methylene bisacrylamide (MBA) as crosslinker, potassium persulfate (KPS) and sodium metabisulfite (SMBS) as a type of mixed redox initiators. Selected samples were loaded with model drug chloramphenicol. For the chloramphenicol release, the effect of pH, monomeric compositions, degree of crosslinking were investigated. The release of chloramphenicol was studied for 11 day period in phosphate buffer solutions of different pH 2, 4, and 7.2. The swelling ratio (Rs) was measured for all the hydrogel structures, in three different media (pH=2), (pH=4) and (pH=7.2), and three different temperatures (37, 45, 50) ^{0}C as function of time. The results showed that drug release increased by decreasing (MMA) content in the hydrogels

Keywords*:* Methyl methacrylate-co-acrylic acid, pH Sensitive hydrogels, chloramphenicol , Controlled release.

Introduction

Hydrogels are highly swollen, hydrophilic polymer networks that can absorb large amounts of water and drastically increase in volume. It is well known that the physicochemical properties of the hydrogel depend on the molecular structure, the gel structure, and the degree of crosslinking, but also on the content and state of the water in the hydrogel. Hydrogels have the inherent ability to swell in aqueous media because of their thermodynamic compatibility with water. In water they swell to an equilibrium volume, but preserve their shape. The utility of hydrogels as biomaterials lies in their permeability to small molecules, a soft consistency, and a low interfacial tension between the gel and aqueous solutions. Their physical properties are very similar to those of living tissues [1-4]. These materials can be used as contact lenses, membranes for biosensors, blood oxygenators, materials for artificial prosthesis, artificial corneas, bone cements, soft tissue substitutes, suture coatings, and have been widely used in controlled drug release systems. Of the several possible routes of introducing release medication into the body, the oral administration of single medicinal dose is one of the simplest and safest, since it does not pose the sterility problem and the risk of damage at the site of administration is minimal. The systems developed to control drug release have been designed to maintain the concentration of the biochemical active substance inside an optimum therapeutic interval. These polymers have been used as vehicles to release many substances in a controlled way. Hydrogels represent an important group of biomaterials used for the controlled release of bioactive agents. They are polymeric networks that can absorb large amounts of water without the dissolution of the network. [5-12]

Equilibrium water content in hydrogels is one of their basic properties. A hydrogel with high water content is generally more advantageous. However, this fact adversely affects its mechanical properties, for example hydrogels with high equilibrium hydration degrees, show poor mechanical properties at ambient temperature, showing low resistance to traction and tear. The copolymerization of different monomers in order to obtain the desired properties is a way of solving this problem. Generally a hydrophilic monomer is mixed with a more hydrophobic monomer to improve

mechanical properties in the resulting hydrogel[13].

Chloramphenicol is an antimicrobial agent with restricted use, because it causes blood dyscrasia. It is used to combat serious infections where other antibiotics are either ineffective or contraindicated. It can be used against gram-positive cocci, bacilli and gram-negative aerobic and anaerobic bacteria (DFC 2000). Chloramphenicol also has been used in veterinary medicine as a highly effective and well-tolerated broad-spectrum antibiotic. Because of its tendency to cause blood dyscrasia in humans, its use in food-producing animals is now prohibited. Chloramphenicol is still used in cats, dogs, and horses to treat both systemic and local infections .[14]

Different hydrogels have been synthesized through copolymerizing of acrylic acid with different methacrylates in order to find how the methacrylate side group can affect the hydrophilic characteristics of the network and therefore it can influence on the swelling properties of the network and the release of Chloramphenicol.

The aim of this work the study of different applied conditions on controlled release of chloramphenicol from poly(acrylic acid–co–methyl methacrylate) hydrogel crosslinked with methylene bisacrylamide(MBA).

Experimental

Materials

Acrylic Acid (AA, HIMEDIA), methyl methacrylate (MMA, Aldrich), was separated from the inhibitor. chloramphenicol (BDH), N,N-methyl bis acryl amide (MBA, BDH), potassium Persulfate (KPS, MERCK), sodium metabisulfite (SMBS, MERCK), sodium Hydroxide (BDH), phosphate buffer saline (HIMEDIA), buffer solution pH= 2, 7 (BDH), hydrochloric acid (BDH), and deionized water (Iraqi local product).

Apparatus

1- pH meter, HANNA, Romania.

2- FTIR 8400S,Fourier Transform infrared spectrophotometer, SHIMADZU ,Japan.

3-UV-1650PC, Ultra violet-visible spectrophotometer, SHIMADZU, Japan. was used for the analysis of chloramphenicol solution.

4- Fume Hood, K &K Scientific suppler, Korea.

5- Hot plate stir, BIBBY STRILINTD.UK.

6- Oven ,TRIVP International CORP. Italy.

Crosslinked Of Polyacrylic acid With Methyl methacrylate (MMA) (A1-A5)

Acrylic acid (AA) (5 gm) was dissolved in 50 mL de-ionized water and neutralized by NaOH to the neutralization degree of 50%, and then the solution was added into a triple-necked flask, which was equipped with a stirring apparatus and a reflux condenser, The solution was stirred for 20 min and heated in a water bath of 70 °C under nitrogen protection. Then, different amounts of methyl methacrylate (MMA) are given in Table(1), and 0.05gm of N,N-methyl bis acryl amide (MBA) were added into the flask and then the solution was stirred incessantly. An amount of 0.45gm potassium persulfate (KPS), dissolved in 30 mL de-ionized water, and 0.32gm of sodium metabisulfite (SMBS), dissolved in 20ml de-ionized water were dropped within 2 min into the reactant solution as initiator four hours later the reaction was stopped the product was stopped after 4 h. The prepared hydrogel was poured into a Petri dish of 90×10 mm and then was dried in oven at 50 °C for 24 h.

Table (1) Amounts of reaction parameters for synthesis of PAA-MMA crosslinked hydrogels

Sample No.	Monomer (MMA) (gm)	Monomer (AA) (gm)	Initiator	
			KPS(gm)	SMBS(gm)
A1	0.5	5	0.45	0.32
A2	1.0	5	0.45	0.32
A3	1.5	5	0.45	0.32
A4	2.0	5	0.45	0.32
A5	2.5	5	0.45	0.32

Drug Loading

Chloramphenicol is soluble in water and because the prepared gels are swell extensively in water, the drug was loaded through immersing the dry gel discs in the saturated solution (0.1,0.2 and 0.3)gm of Chloramphenicol for 11days at 37ºC in order to achieve a high drug loading in the gels. After the discs were reached max. Swelling, takes out, washed and the excess water on samples equilibrating the drug solution, the discs were washed with water in order surfaces were wiped with tissue paper and dried in vacuum at room temperature.

Swelling Measurement

Dried hydrogel samples were used to determine the swelling ratio(Rs). The swelling ratio (Rs) was determined by immersing the hydrogel samples (0.1gm) in100 ml of different pH buffer solutions pH (2, 4 , 7.2) and was allowed to swell for 11 days at different temperatures (37, 45, and 50) ^{0}C. Every 24 hr, the samples were removed from swollen solution, wiped with filter paper and weighted and (Rs) was calculated using the following Equation

$Rs = (Ws-Wd)100 / Wd$

Where Ws and Wd are the weights of swollen and dried hydrogel samples, respectively.

Deswelling Measurement

The deswelling of the hydrogel samples was measured gravimetrically at 60 ^{0}C. The samples were shrieked and the excess water on samples surfaces were wiped with tissue paper. Before deswelling measurement, the hydrogels were allowed to swell and reached their equilibrium as in, deionized water and at 25 ^{0}C. The change in weight after deswelling were recorded at regular time intervals. Water retention (W_R) is defined as follows:

$W_R = (Wt – Wd)100 / Ws$

Where Ws and Wd are the weight of water in the swollen gel and the weight of dry gel, respectively. Wt, represent total weight of the shrink gel at a certain time interval.

Preparation Of Standard Calibration Curve

A standard curve of chloramphenicol as model drug was carried out in the range of 0.001 to 0.04g.L^{-1} Deionized water was used for preparation of stock solution. The absorbance of different prepared concentrations were measured at λ_{max} 278 nm using Shimadzu UV-1650PC spectrophotometer. The standard curve was plotted, and The regression analysis showed a linear relationship between the concentration of the chloramphenicol and instrument response (R^2 = 0.9988) and the intercept was very low. The molecular structure of chloramphenicol is shown in figure (1).

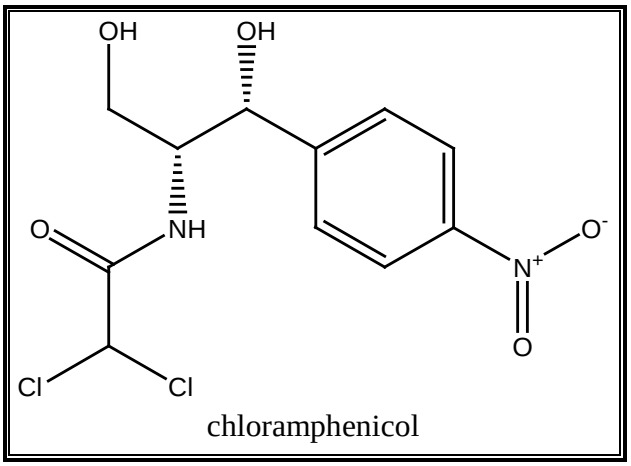


Figure (1) Molecular structure of Chloramphenicol

Drug(Chloramphenicol) Release

A loaded hydrogel sample is used in order to determine the amount of Chloramphenicol released from the hydrogel network. The sample was dried and 0.1gm was immersed in 100 ml solution of different pH (2,4 and 7.2) and the study was carried out at different temperatures(37 , 45 and 50) ^{0}C.

The amount of chloramphenicol release was evaluated using UV-spectrophotometer at λ_{max} 278 nm each 24h and for 11 days.

Results and Discussion

Synthesis Crosslinked of Copolymer Acrylic acid with Methyl methacrylate (MMA) and Spectral Characterization

N,N-methyl bis acryl amide (MBA) crosslinked (0.05)gm copolymer of acrylic acid with methyl methacrylate (MMA) was synthesized by free radical solution polymerization using potassium persulfate as initiator and sodium metabisulfite as accelerator, the polymer matrix become more rigid as the degree of crosslinking increase and hence its swelling in water will decrease . as in figure (2).

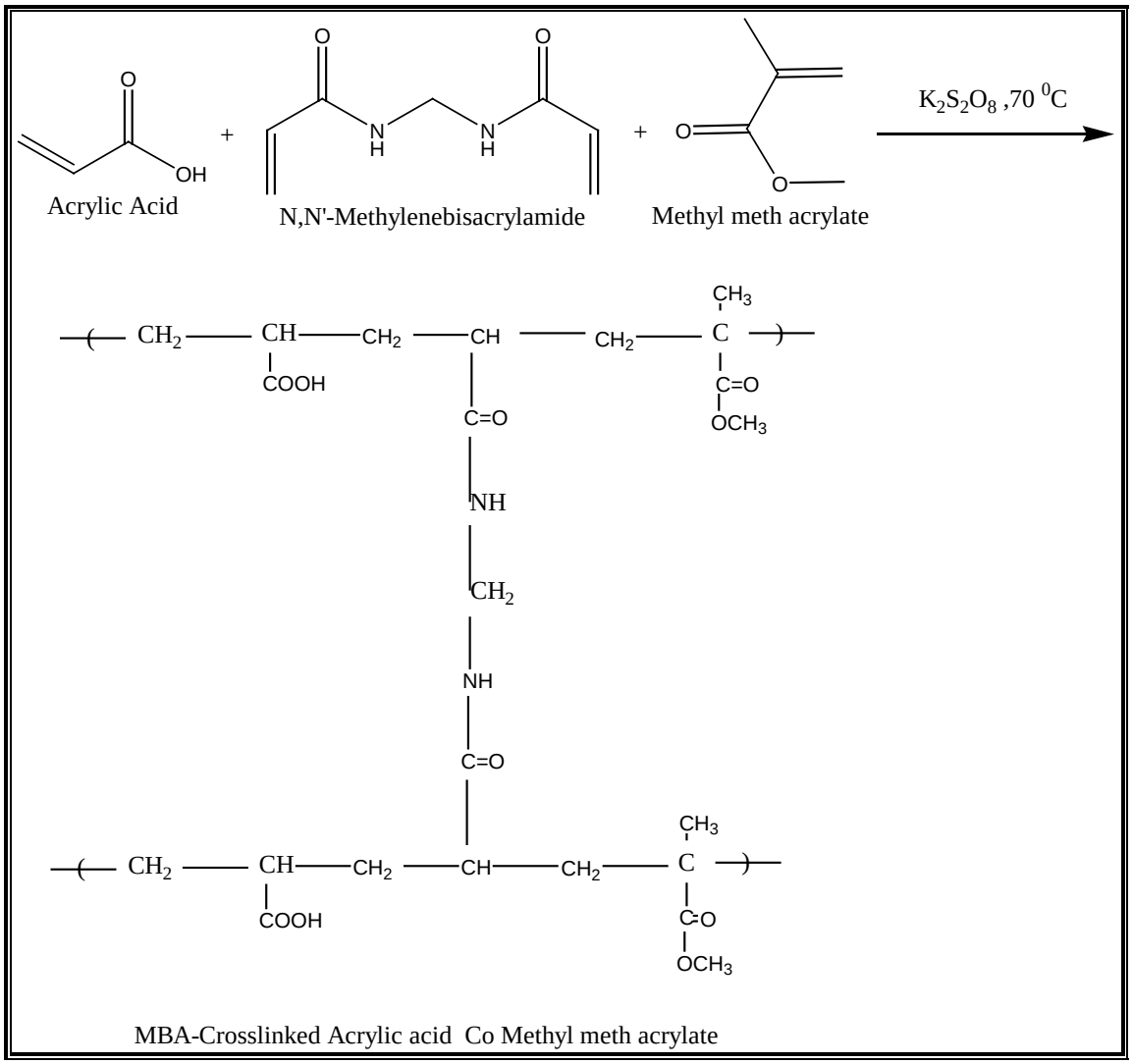


Figure (2) Synthesis of Crosslinked Copolymer AA-MMA

The FT-IR spectrum in figure (3) showed a strong peak at 1712cm^{-1} is due to the presence of C=O group stretching vibration .The broad band ranged 3000-3500cm^{-1} is due to stretching vibration of carboxyl groups , The band at 3200cm^{-1} represents stretching vibration of N-H the peak at 2920cm^{-1} is due to C-H stretching of polymer back bone ,and the peak at 1000-1320cm^{-1} is due to C-O group .The peak at 1557cm^{-1} indicates the stretching vibration of C=O in carboxamide functional groups of crosslinked agent MBA [15].

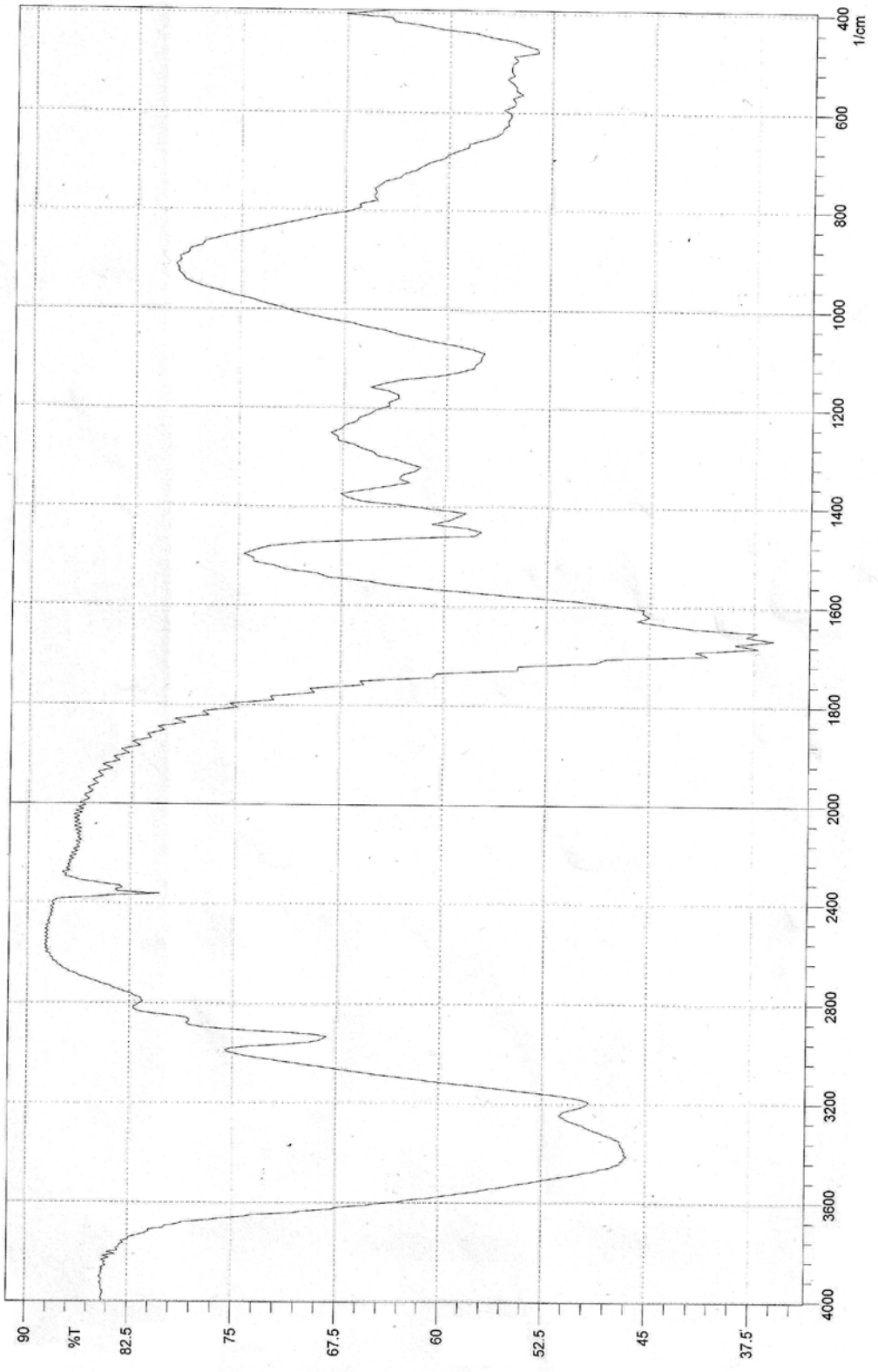


Figure (3) FTIR spectrum of polyacrylic acid crosslinked with MMA

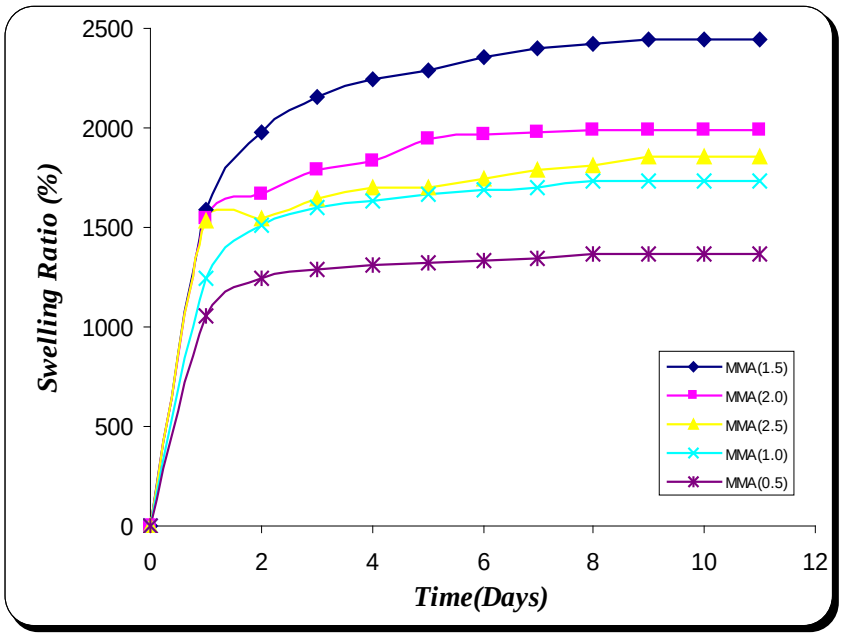
Swelling Characterization of Copolymer Acrylic acid with Methyl methacrylate (MMA))

The swelling ratio behaviors of Poly(acrylic acid –co-methyl methacrylate) hydrogels was studied as a function of time and pH at 37^0C. The ability of a polymer network to absorb water was significantly hindered by the degree of crosslinking . The swelling behavior of polyacrylic –co – methyl methacrylate hydrogels was depended on the pH of the swelling medium, because of the hydrogel carboxylic groups. At higher pH carboxylic groups on hydrogel became progressively more ionized and due to the repulsion between counter ions, swelling ratio of the hydrogel will increase [16].

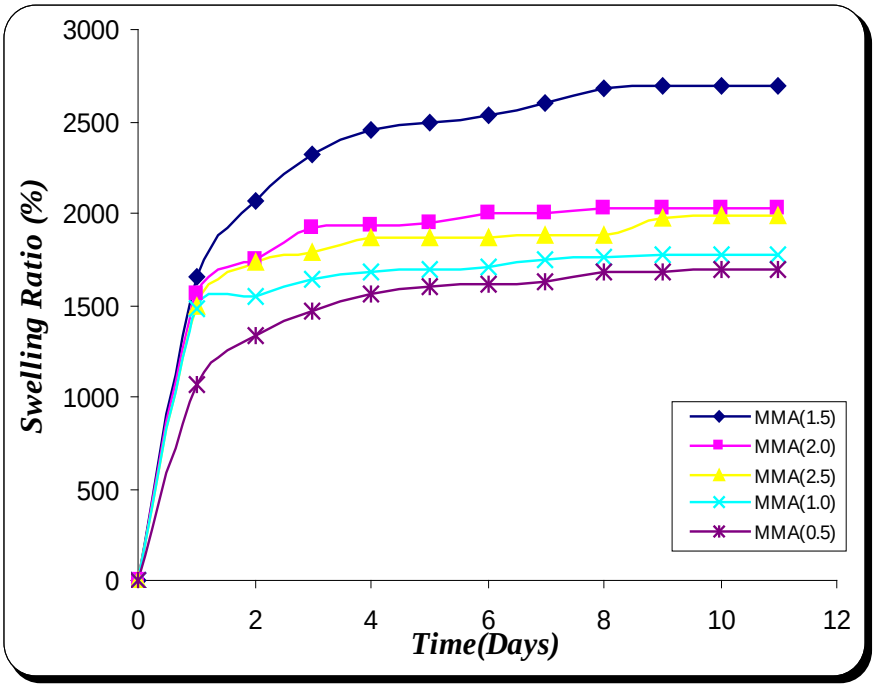
The presence of methyl methacrylate in the hydrogel decreases the swelling due to the hydrophobic character of this monomer, as the content of hydrophobic comonomers (0.5-1.5)gm in the hydrogel increases the swelling inside the hydrogel structure will be slower. It is possible that the swelling degree is affected by the presence of high percentage of hydrophobic comonomers (methyl methacrylate) (2.5gm, 2gm), because retarded the mobility of the chain in the hydrogel present.

Figures (4),(5) and (6) show the swelling ratio of an initially dry hydrogels at different time intervals in at known pH.

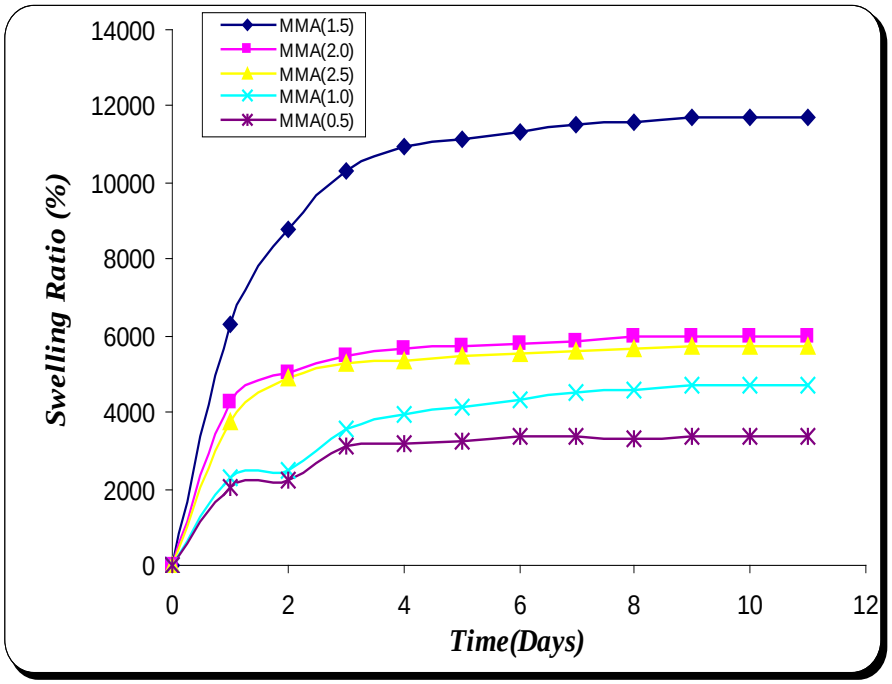
The results concluded from figures (4),(5) and (6) were shows that maximum swelling ration of the hydrogels increased with increasing molar ratio of MMA monomer in prepared hydrogel to some extent (0.5 , 1.0 , 1.5 gm) because of hydrogen bonding while decreased at higher ratios due to competitive reaction occur between acrylic acid and MMA and as acrylic acid in hydrogel decrease its degree of swilling would decreased. [17].



Figure(4) swelling ratio (Rs) of Poly(acrylic acid –co-methyl methacrylate) hydrogels vs. time at pH=2



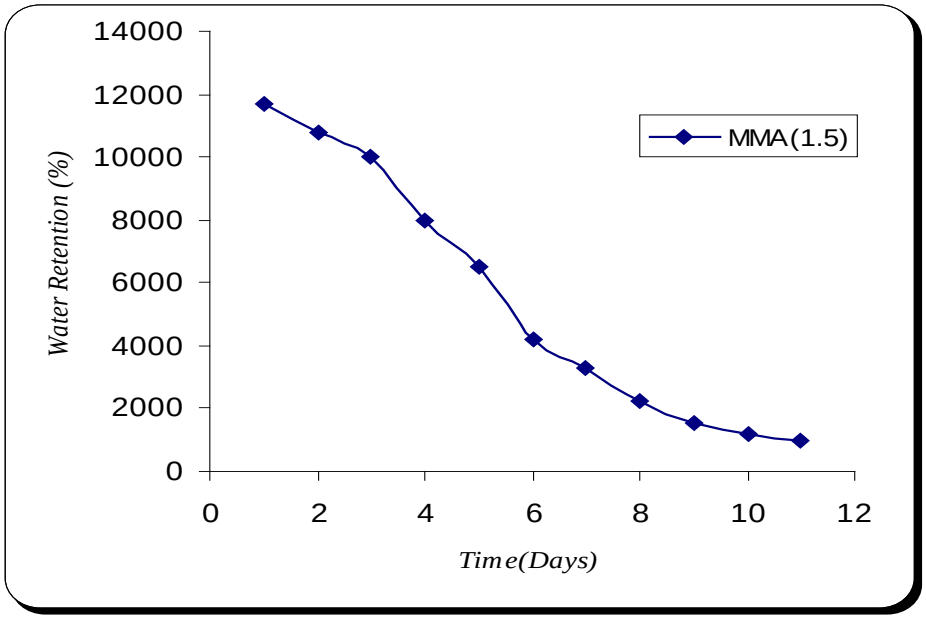
Figure(5) swelling ratio (Rs) of Poly(acrylic acid –co-methyl methacrylate) hydrogels vs. time at pH=4



Figure(6) swelling ratio (Rs) of Poly(acrylic acid –co-methyl methacrylate) hydrogels vs. time at pH=7.2

Deswelling of Hydrogels Poly(acrylic acid –co-methyl methacrylate)

The deswelling of the hydrogels polymers with 1.5gm of MMA, after a temperature jump from the equilibrium swollen state at 25 ^{0}C to the hot water at 60 ^{0}C are illustrated in Figure(7).



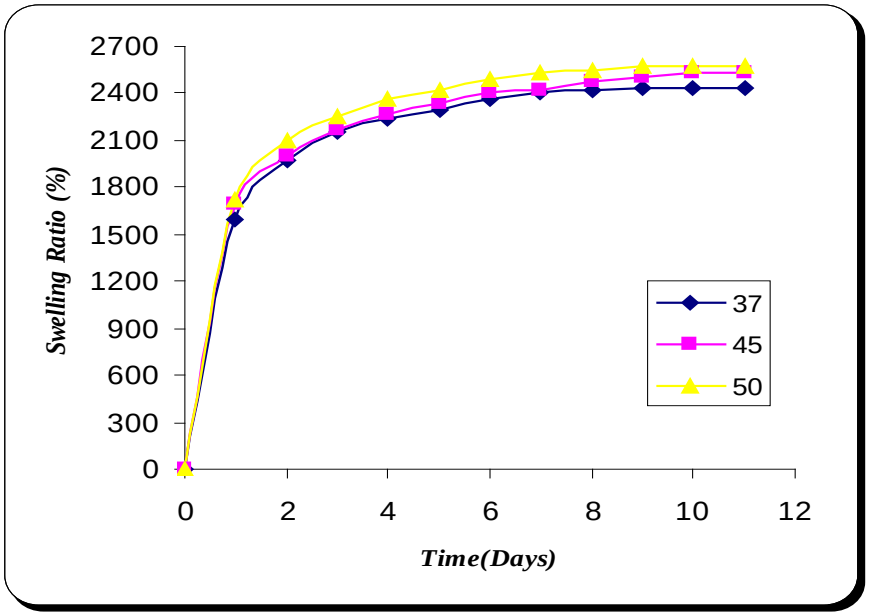
Figure(7) Deswelling of hydrogels Poly(acrylic acid –co-methyl methacrylate)

From Figure (7), it can be seen that the sample lose water dramatically. When a hydrogel is placed in water above its shrinking immediately starts at the gel surface due to the free mobile nature of the surface and the collective

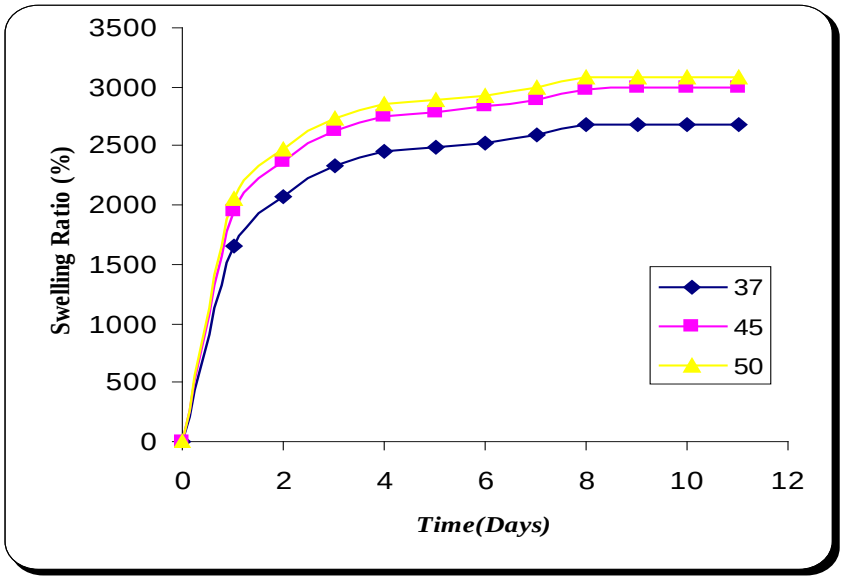
diffusion of the polymer network in water. [18]

Effect of Temperature on Swelling Ratio

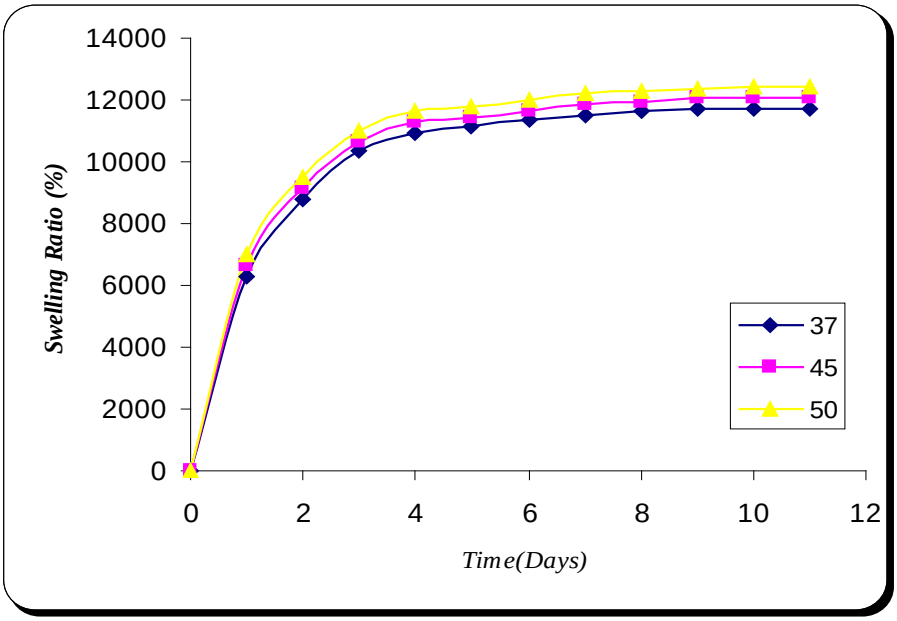
The figures (8), (9) and (10) shows the effect of storage temperature and time on swelling ratio of hydrogels at different pH. It was observed that at higher temperature (45,50) ^{0} C the swelling ratio of formulations was increased, whereas at low temperature 37 ^{0}C, it was decreased. The increase in the swelling ratio of formulations stored at higher temperature may account for the more solution loss and the dehydration of formulations at low temperature. This greater loss or dehydration on storage at higher temperature had resulted to in more solution uptake by the hydrogel during swelling and hence increase in the numerator value used in the formula for the calculation of swelling ratio [19].



Figure(8) Effect of Temperature on the Swelling Ratio vs. time at pH(2)



Figure(9) Effect of Temperature on the Swelling Ratio vs. time at pH(4)



Figure(10) Effect of Temperature on the Swelling Ratio vs. time at pH(7.2)

Effect of MMA Molar Ration on the Release of Chloramphenicol

The release of chloramphenicol from Poly(acrylic acid –co-methyl methacrylate) hydrogels was studied by varying MMA concentration at different pH.

Figures (11),(12) and (13) show the effect of MMA molar ration on the chloramphenicol release behavior of hydrogels in different pH media. The results indicate that the release of active agent depends obviously on the MMA molar ration .

The high entrapment efficiency of hydrogel formulation is observed because of hydrophobic and low molecular weight of chloramphenicol. When the molar ration of MMA was increased, loading efficiency of hydrogel decreases, this might be due to the hydrophobic character of this monomer, as the content of the hydrophobic comonomers(MMA) in the hydrogel increases, the drug will be more retained inside the hydrogel structure and its release will be slower. The fast release of chloramphenicol is due to the higher swelling behavior of hydrogel with low the molar ration of MMA [20].

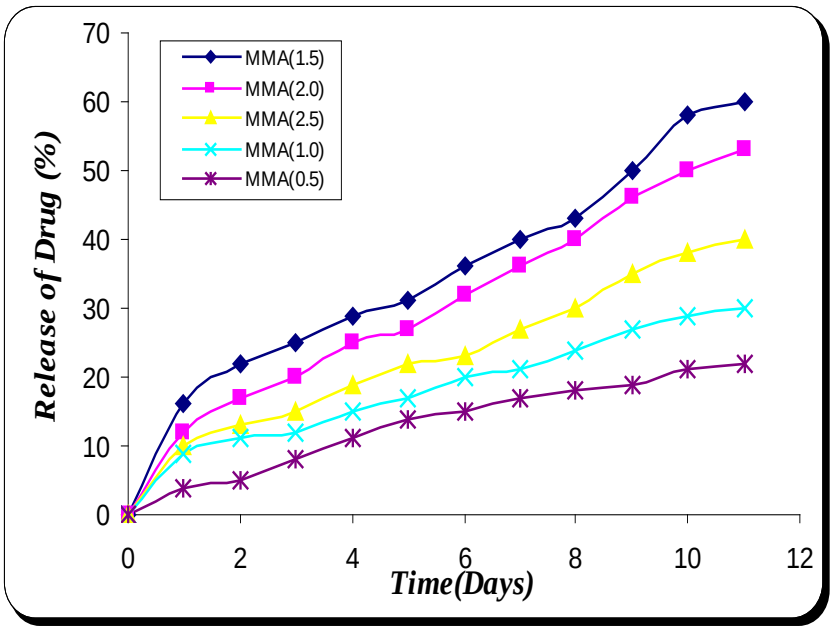


Figure (11) Effect of MMA Concentration on the Release of Chloramphenicol at pH(2)

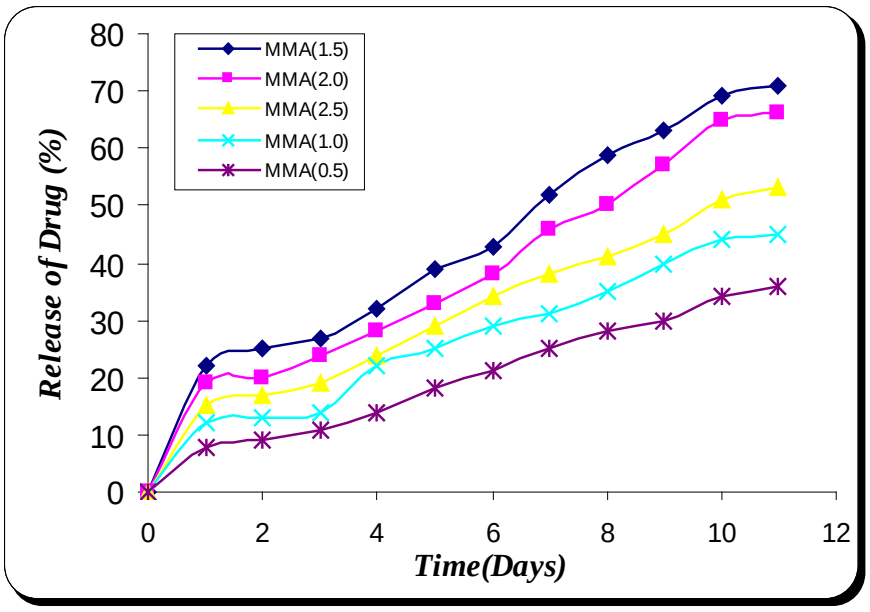


Figure (12) Effect of MMA Concentration on the Release of Chloramphenicol at pH(4)

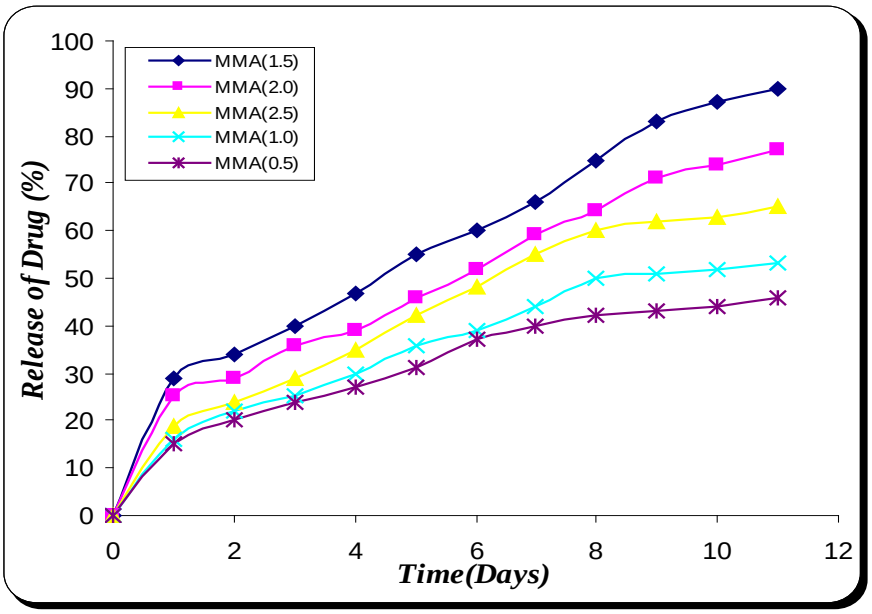


Figure (13) Effect of MMA Concentration on the Release of Chloramphenicol at pH(7.2)

Effect of amount of loading on release of Chloramphenicol

The release profile of chloramphenicol from the porous Poly(acrylic acid –co-methyl methacrylate) hydrogel loaded with various amounts of the chloramphenicol was studied in different pH(2 ,4 and 7.2). The results are shown in figures (14), (15) and (16), that the loading increased with increasing the chloramphenicol concentration in loading medium .The release profiles indicate that the amount of released chloramphenicol increases with increasing loading of active agent. It is attributed to the larger amount of loading, the faster the movement of the solvent front penetrating the surface of the loaded hydrogel, This may be attributed to the factor that free volume spaces are available in the matrix. [21]

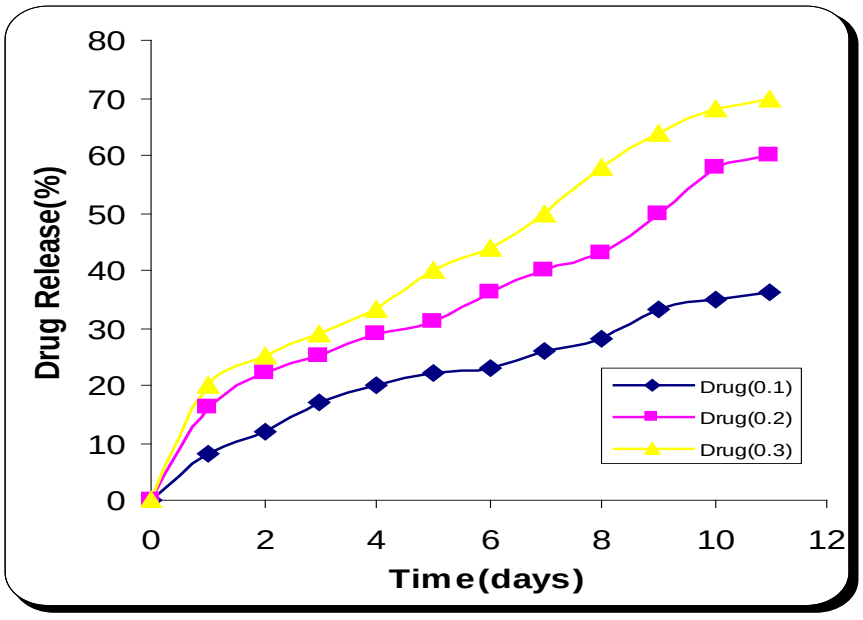


Figure (14)Effect of amount of loading on release of Chloramphenicol at pH 2

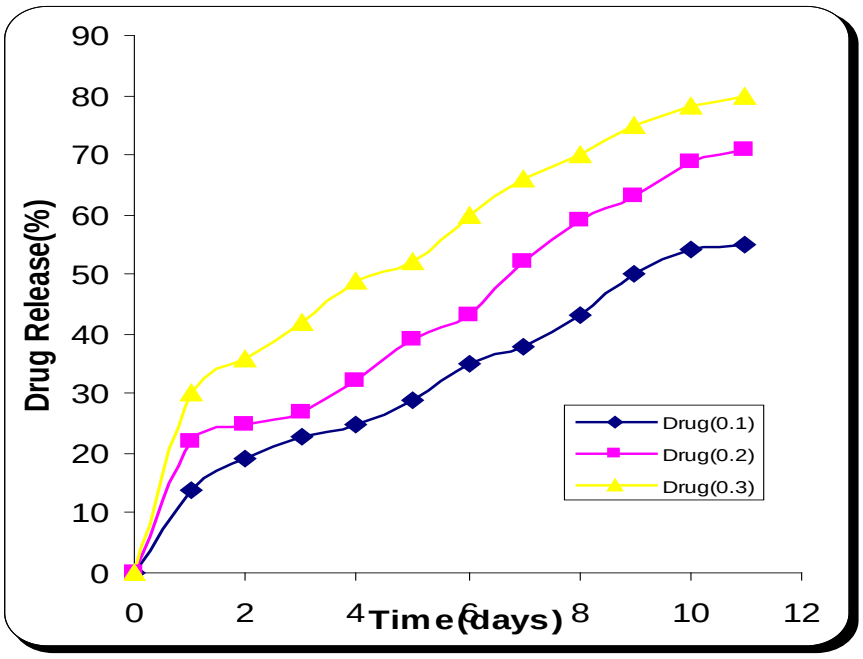


Figure (15)Effect of amount of loading on release of Chloramphenicol at pH 4

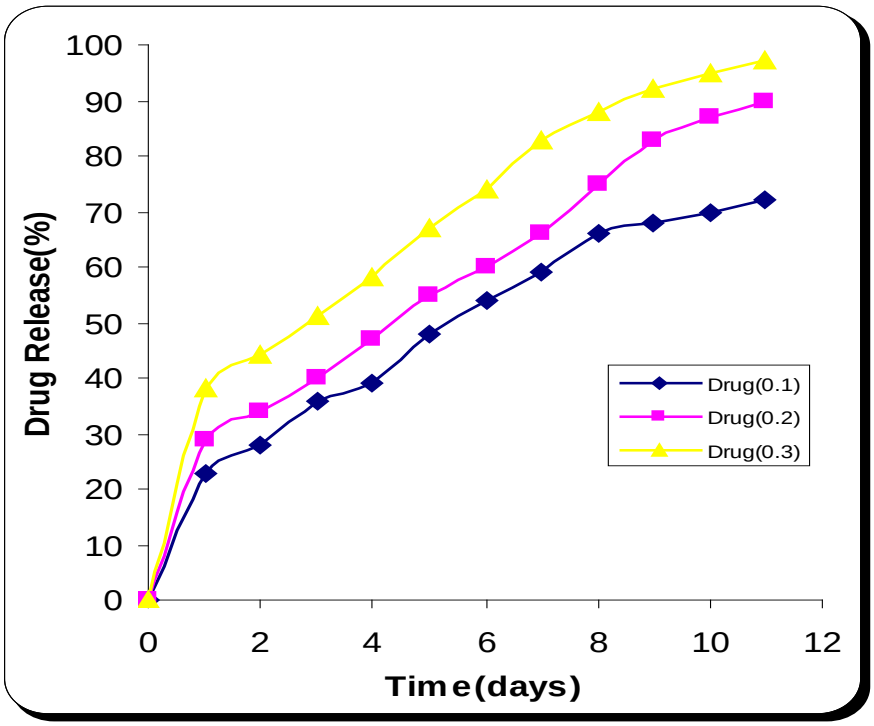


Figure (16)Effect of amount of loading on release of Chloramphenicol at pH 7.2

Effect of pH on the Release of Chloramphenicol

The chloramphenicol release rates from the Poly(acrylic acid –co-methyl methacrylate) hydrogels have been measured at pH 2,4 and 7.2, See figure (17), the chloramphenicol release rate at pH 7.2, is higher release rate may be related to the higher swelling ratio of the hydrogels, and the weak H-bonding interaction between drug and polymer network, the carboxylic groups of acrylic acid present along the macromolecular chains in the drug-

loaded device are almost completely ionized, thus causing the polymeric chains to undergo extensive relaxation due to electrostatic repulsion among the charged carboxylic groups. This the finally results in the higher swelling ratio.

While in pH 2 and 4, the amount of chloramphenicol released is decrease may be related to the lower swelling ratio of the hydrogels, and unionized carboxylic groups do not induce the chain relaxation process. The drug molecules were protonated and unable to form strong hydrogen bonds like at pH 7.2 with the gel matrix. Additionally, carboxylic groups in the matrix were fully protonated to give –COOH , which could form hydrogen bonds with the structure of hydrogel [22].

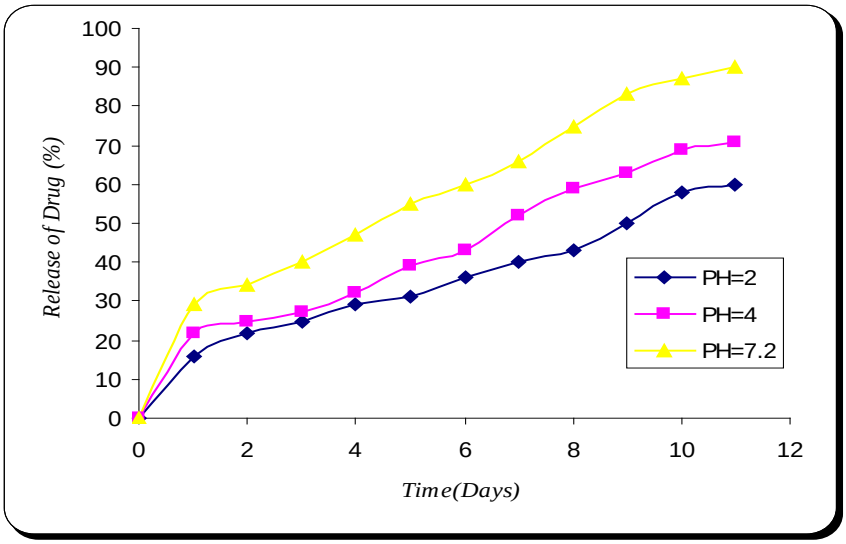


Figure (17)Effect of pH on The Release of Chloramphenicol at 37^0C

Effect of Temperature on the Release of Chloramphenicol

The effects of temperature on the release rate of chloramphenicol has also been examined in this search. As shown in figures (18),(19) and (20), the higher release rate was observed at 50,45 ºC, while the release rate of chloramphenicol at 37ºC was found to be much lower, which can be attributed to the decreased H-bonding by increasing the temperature, which accelerated the drug release, and the increase of the diffusivity as well as the solubility of loaded Chloramphenicol molecules inside the superabsorbent. Meanwhile, Chloramphenicol release rate as the temperature is increased [22,23].

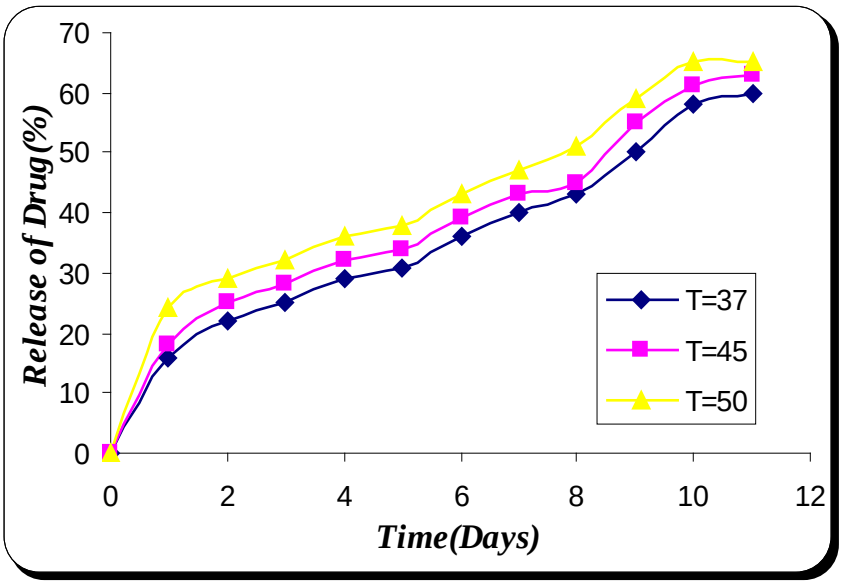


Figure (18) Effect of Temperature on The Release of Chloramphenicol at pH(2)

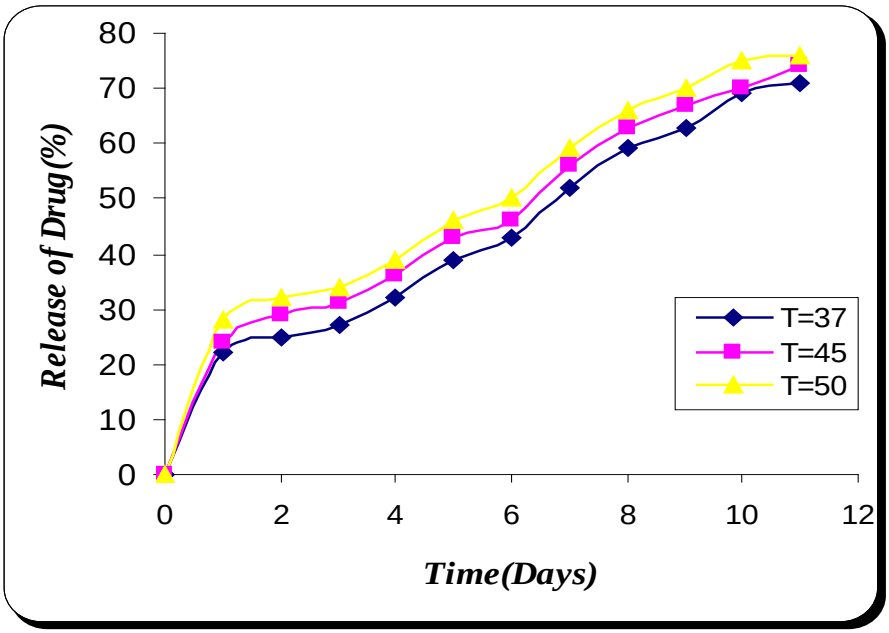


Figure (19)Effect Of Temperature On The Release Of Chloramphenicol at pH(4)

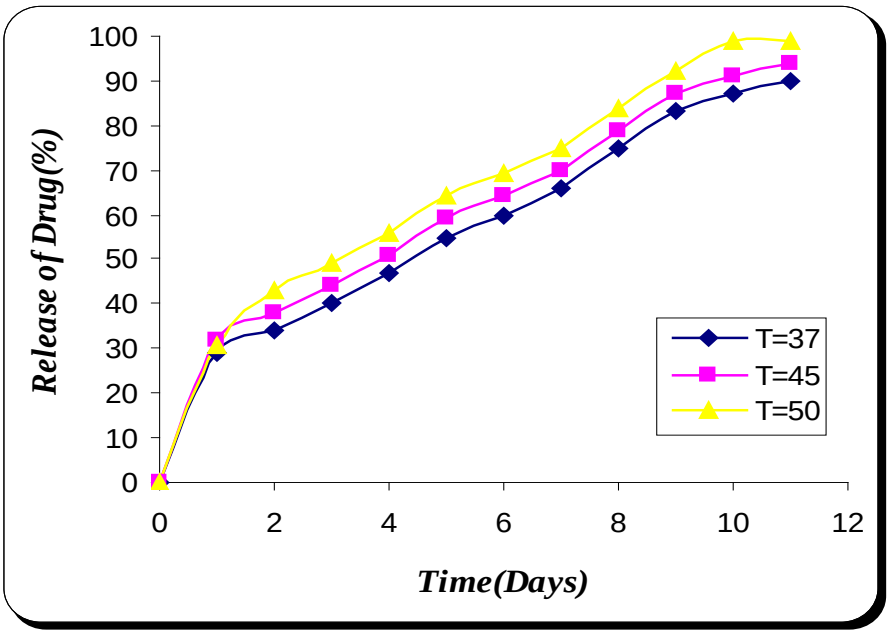


Figure (20)Effect Of Temperature On The Release Of Chloramphenicol at pH(7.2)

Conclusion

A new class of hydrogels has been synthesized by free radical copolymerization of MMA with AA in the presence of crosslinking agents MBA. These pH sensitive gels respond to small change of pH to much sharper extant than other pH-sensitive gels, which may be due to the presence carboxylic groups of AA in the hydrogels. chloramphenicol was loaded as model drug. The effect of monomeric composition, degree of MMA and natural monomer on drug release were investigated. Hydrogels with 1.5gm content of MMA showed more drug release than those gels with other contents of MMA. When the concentration of MMA was increased, the loading efficiency of hydrogel decreases, this might be due to the hydrophobic character of this monomer, as the content of the hydrophobic comonomers(MMA) in the hydrogel increases. The chloramphenicol release rate at pH 7.2, is higher release rate may be related to the higher swelling ratio of the hydrogels, and the weak H-bonding interaction between drug and polymer network. The higher release rate was observed at 50,45 ºC, while the release rate of Chloramphenicol at 37ºC was found to be much lower, which can be attributed to the decreased H-bonding by increasing the temperature.

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التحرر المسيطر علية لكلورام فينيكول من هلاميات كوبوليمرات الاكريلك والميثايل ميثااكريليت

محمد علي مطر
قسم الكيمياء/ كلية التربية / جامعة القادسية
mohammeddw@yahoo.com

الخلاصة

في هذا البحث تم تحضير هلاميات مائية للمونومرات المتشابكة methyl methacrylate–co–acrylic acid حيث خلقت باستخدام البلمرة المتشابكة لجذور الحرة لمونمرات مثيل ميثااكريليت بنسب وزنيه مختلفة وحامض الاكريلك باستخدام مثلين بس اكريل امايد كعامل مشابك وبيرسلفات البوتاسيوم وصوديوم ميتابيسلفات كمواد بادئة للجذور الحرة حيث تمت دراسة نسبة الانتفاخ لجميع التراكيب البوليمرية المحضرة.وكذلك تم تحميل دواء الكلورام فينكول على البوليمر ودراسة الإطلاق ألبطي له وكذلك دراسة تأثير الدالة الحامضية بأوساط مختلفة (PH=4), (PH=2)و (PH=7.2). ثم دراسة تأثير درجة الحرارة بدرجات حرارية مختلفة (37, 45, 50) م^0. فقد لوحظ أن زيادة سرعة التحرر تزداد بنقصان محتوى ميثايل ميثا اكريليت في البوليمرات الهلامية.