Controlled Release From Crosslinked Polyacrylic acid As Drug Delivery Theophylline

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Abstract

In this search polyacrylic acid (PAA) hydrogels were synthesized by radical polymerization in solution with N,N'-Methylene bis acryl amide (MBA), as crosslinking agents and potassium persulfate (KPS), sodium metabisulfite (SMBS) as type of mixed redox initiators, poly acrylic acid hydrogel structures were prepared by using N,N'-Methylene bis acryl amide (MBA) as crosslinking agent (0.05, 0.1, 0.15, 0.2, 0.25)g. at temperature 70^0C for 4 hr. 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. Theophylline was loaded into polymeric matrix during in situ polymerization, The concentration of theophylline released was measured on UV-Vis spectrophotometer. The drug release studies from the theophylline loaded hydrogel was studied in three different media (pH=2 ,4 and 7.2),and three different temperature (37, 45 and 50) ^{0}C as function of time. The results showed that the samples involving the highest release of theophylline were arranged as follows :

$$PAA\text{-}MBA_{0.05} > PAA\text{-}MBA_{0.1} > PAA\text{-}MBA_{0.15} > PAA\text{-}MBA_{0.2} > PAA\text{-}MBA_{0.25}$$

الخلاصة

في هذا البحث تم تخليف الهلاميات المائية لـ Polyacrylic acid بواسطة البلمرة بالجذور الحرة باستخدام N,N-methyl bis acrylamide(MBA) كعامل مشابك، metabisulfite(SMBS), Potassium Persulfate (KPS) Sodium كمواد بادئة للجذور الحرة. وتم قياس نسبة الانتفاخ (R_S) لجميع التراكيب الهلامية المحضرة في ثلاث أوساط مختلفة من المحاليل pH=2 , pH = 4 , pH =7.2 وبدرجات حرارة مختلفة ^{0}C 37 , 45 , 50 كدالة للزمن، وكذلك تم دراسة سلوك فقدان الماء الممتص من التراكيب الهلامية في درجة حرارة الغرفة كدالة للزمن ، تم تحميل الدواء (الثيوفيلين) داخل الشبكة البوليمرية من خلال عملية البلمرة حيث يمزج الدواء مع المونمر والعامل المشابك والبادئ وينقل الى تفاعل البلمرة. تم دراسة سرعة تحرر الدواء (الثيوفيلين) المحمل على البوليمرات الهلامية في ثلاث أوساط مختلفة من المحاليل pH=2 , pH = 4 , pH =7.2 وبدرجات حرارة مختلفة ^{0}C 37 , 45 , 50 كدالة للزمن، ومن ثم تمت دراسة تأثير الدالة الحامضية pH على سرعة تحرر الثيوفيلين للتراكيب الهلامية المحضرة، وأخيراً تم دراسة تأثير تركيز الدواء على سرعة التحرر حيث لوحظ عند زيادة تركيز الدواء يؤدي الى زيادة في عملية التحرر.

Introduction

Hydrogels are water swollen polymer matrices, with a huge tendency to absorb water. Their ability to swell, under physiological conditions, makes them an ideal material for biomedical applications [1]. The hydrophilicity of the network is due to the presence of chemical residues such as hydroxylic, carboxylic, amidic, primary amidic, sulphonic and others that can be found within the polymer backbone or as lateral chains [2-7]. It is also possible to produce hydrogels containing a significant portion of hydrophobic polymers, by blending or copolymerizing hydrophilic and hydrophobic polymers, or by producing interpenetrating networks (IPN) or semi-interpenetrating polymer networks (s-IPN) of hydrophobic and hydrophilic polymers[8,9].

Hydrogels can be classified as neutral or ionic, based on the nature of the side groups. In neutral hydrogels, the driving force for swelling is due to the water-polymer thermodynamic mixing contribution to the overall free energy, along with elastic polymer contribution[10,11]. Hydrogels can be classified as affine or phantom, based on their mechanical and structural characteristics[12].Hydrogels are also classified as homopolymers or copolymers, based on the methods of preparation[13].Additionally, they can be classified based on the physical properties of the network as amorphous, semi-crystalline, hydrogen bonded structures, super-molecular structures and hydrocolloidal aggregates [14].An important class of hydrogels is the stimuli responsive gels. These gels show swelling behaviour dependent on their physical environment, allow for usage in a number of applications[15].

The present work investigate the possibility of applying PAA-based hydrogels crosslinked by N,N'-Methylene bis acryl amide (MBA), for retarded drug release.

Experimental

Materials

Acrylic Acid (AA, HIMEDIA), Theophylline (BDH), N,N'-Methylene 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), Hydrochloride Acid (BDH), 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 theophylline solution
4- Fume Hood, K &K Scientific suppler, Korea
5- Hot plate stir, BIBBY STRILINTD.UK
6- Oven ,TRIVP International CORP. Italy

Synthesis Of Polyacrylic acid Hydrogel

Acrylic acid (5g.) was dissolved in 50 ml de-ionized water and neutralized by NaOH to 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. An amount of 0.45g. potassium persulfate (KPS), dissolved in 30 ml de-ionized water, and 0.32g. of sodium metabisulfite (SMBS), dissolved in 20ml de-ionized water were dropped into it with 2 min of interval, added into the flask to initiate the polymerization process after 30 min.

The reaction was stopped after 4 h. The prepared hydrogel was poured into a Petri dish of 90×10 mm and was then dried in the oven of 50 °C for 24 h.

Crosslinked of Polyacrylic acid with N,N'-Methylene bis acryl amide (MBA) (A1-A5)

Acrylic acid (AA) (5g.) was dissolved in 50ml de-ionized water and neutralized by NaOH to 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 N,N'-Methylene bis acryl amide (MBA) are given in Table(2.1), were added into the flask and then solution was stirred incessantly. An amount of 0.45g. potassium persulfate (KPS), dissolved in 30 ml de-ionized water, and 0.32g. of sodium metabisulfite (SMBS), dissolved in 20ml de-ionized water were dropped into it with 2 min of interval, added into the flask to initiate the polymerization process after 30 min. The reaction was stopped after 4 h. The prepared hydrogel was poured into a Petri dish of 90×10 mm and was then dried in the oven of 50 °C for 24 h.

Table (2.1) Amounts of reaction parameters for synthesis of MBA crosslinked hydrogels

Sample No.	Crosslinked agent (MBA)(g.)	Monomer AA(g.)	Initiator	
			KPS(g.)	SMBS(g.)
A1	0.05	5	0.45	0.32
A2	0.1	5	0.45	0.32
A3	0.15	5	0.45	0.32
A4	0.2	5	0.45	0.32
A5	0.25	5	0.45	0.32

Drug Loaded(B1-B5)

The synthesis of loaded hydrogels is similar to that of the unloaded ones. The difference is, The drug loaded polymer networks based on PAA were obtained by dissolving the drug in a mixture of crosslinking agent MBA, and PAA in various mass ratios (70 °C under nitrogen protection). The reaction was carried out until a constant mass of reaction mixture. The drug content in the obtained polymer network was 0.1g. ,0.2g. and 0.3g., are given in table(2.2).

Table (2.2) Amounts of drug loaded in different amounts of crosslinking agent in Polyacrylic Acid hydrogels

Sample No.	B1	B2	B3	B4	B5
Monomer AA(g.)	5.0	5.0	5.0	5.0	5.0
MBA(g.) Crosslinked agent	0.05	0.1	0.15	0.2	0.25
Drug loaded (g.)	0.1	0.1	0.1	0.1	0.1
	0.2	0.2	0.2	0.2	0.2
	0.3	0.3	0.3	0.3	0.3

Swelling Measurement

Dried hydrogel pieces were used to determine the swelling ratio(Rs). The swelling ratio (Rs) was determined by immersing the hydrogels (0.1g.) in 100ml of different pH (pH=2, pH=4 and pH=7.2) and was allowed to soak for 11 days at different temperatures (37, 45, and 50) ^{0}C. After every 24h, they were removed from the water, blotted with filter paper to remove surface water, weighted and the (Rs) was calculated using Equation

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

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

Deswelling Measurement

The deswelling of the hydrogels was measured gravimetrically at 60 ^{0}C after wiping off the excess water from the gel surface using moistened filter paper. Before the measurement, the hydrogels were allowed to swell to equilibrium in deionized water at 25 ^{0}C. The mass changes of hydrogels 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 weight of dry gel, respectively. And Wt equals to total weight of the gel at a certain time interval.

Preparation of Calibration Curve

A standard curve for theophylline was constructed in the range of 0.001 to 0.04g.L^{-1} The Solutions Were prepared from stock solution using deionized water as solvent. The absorbance of the resulting solutions was measured at λmax 272.0 nm using distilled water as a blank on Shimadzu UV-1650PC spectrophotometer. The standard curve was plotted in the range of 0.001-0.04g.L^{-1},and The regression analysis showed the linear relationship between the concentration of the theophylline and the absorbance. the plot is shown in figure (2.1).

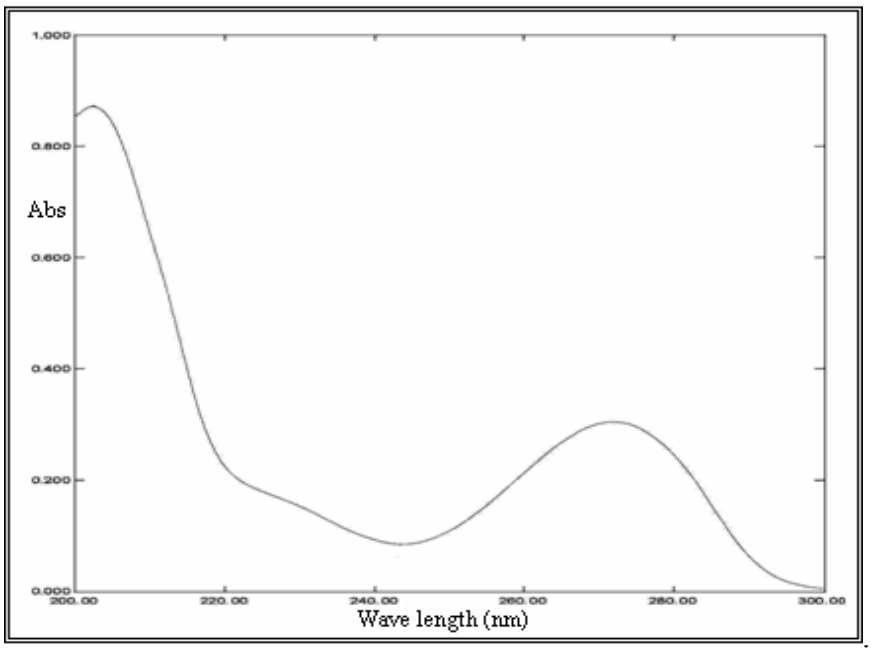


Figure (2.1)UV spectra of Theophylline

Similarly, the calibration curve was plotted in phosphate buffer saline (pH 4.0). The absorbance was taken at *λmax* 272.0 nm using UV-1650PC Shimadzu spectrophotometer.

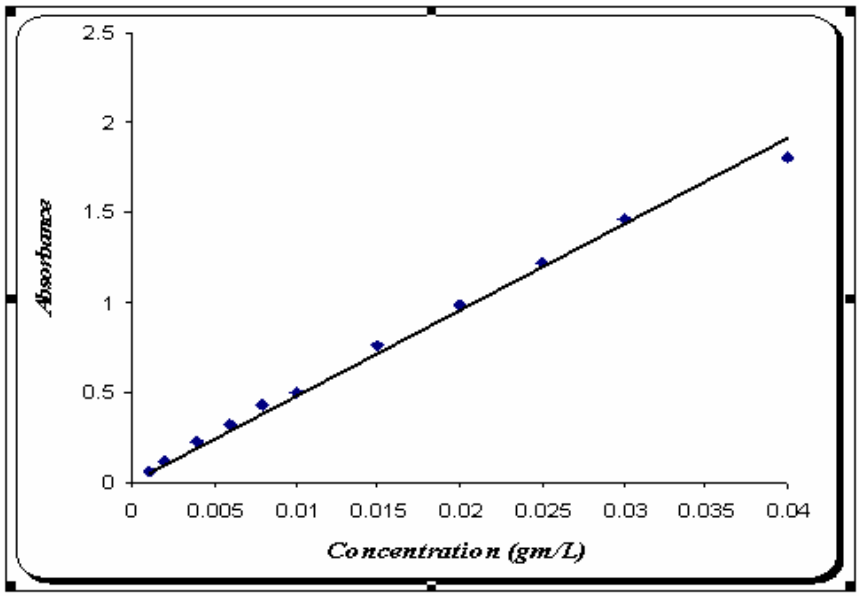
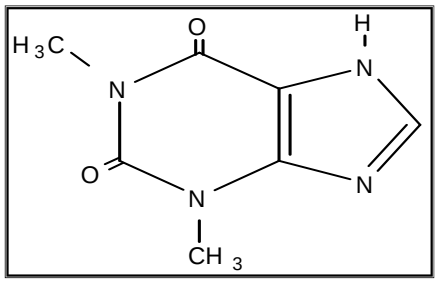


Figure (2.2) The working calibration curve for the data of theophylline (the absorbance in 1 cm cell)at λmax 272.0 nm

Drug(Theophylline) Release

Theophylline,1,3-dimethyl xanthine, thin monoclinic tablets from water, m.p (270-274) ^{0} C, soluble in water, in alkali hydroxide, dil.HCl. is widely described for the treatment of asthma and chronic obstructive pulmonary disease (COPD). For pharmaceutical usage, theophylline can be manufactured to produce many forms including tablets, capsules, and syrup.



Figure(2.3) Structure Of Theophylline

A loaded hydogel sample is used in order to determine the amount of theophylline released from the hydrogel network. The sample is dried and weighted (0.1g.), and then immersed in 100 ml from different pH(2,4 and 7.2) and temperatures(37 , 45 and 50) ^{0}C.

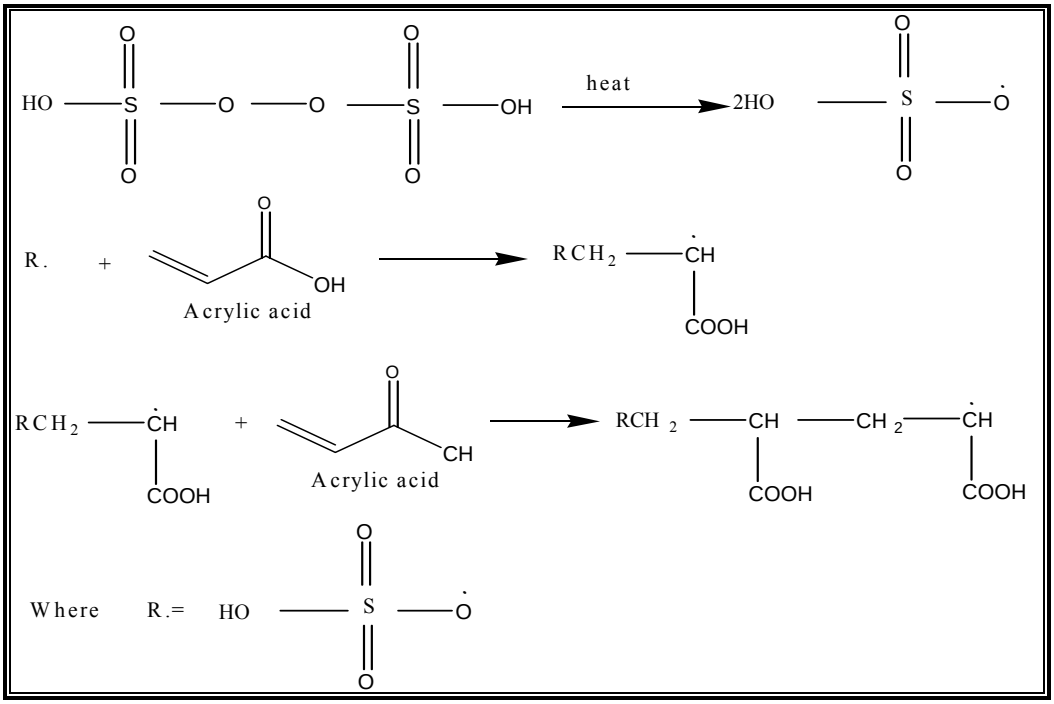
The amount of theophylline release was evaluated using UV-spectrophotometer at λmax 272nm each 24h for 11 days.

Result and Discussion

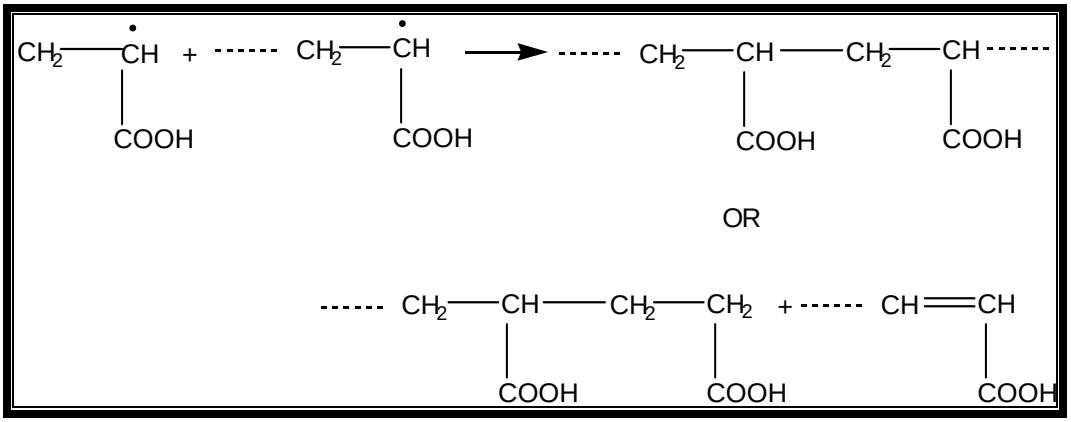
Synthesis of Polyacrylic acid and Spectral Characterization

A wide variety of synthetic polymers are used in the design of hydrogels for drug delivery. Synthetic hydrogels can be reliably produced in large quantities and are amenable to many structural variations. Moreover, the properties of synthetic hydrogels can be controlled by their composition, crosslinking density, and degradable linkages [16].

The reaction is a vinyl addition polymerization initiated by potassium persulfate and sodium metabisulfite free radicals convert acrylic monomers to free radicals which react with unactivated monomers to begin the polymerization chain reaction, Figure (3.1)and Figure (3.2), show Initiation, propagation and Termination steps of the polymerization reaction.



Figure(3.1) Initiation and propagation steps of the polymerization reaction.



Figure(3.2) Termination step of the polymerization reaction

Figure (3.3) Represents FTIR spectra of PAA scanned in the range 400-4000 cm^{-1}.The characteristic peak at 1690 cm^{-1} is due to the presence of C=O stretching vibration ,and the peak observed at 3400 cm^{-1} is due to the OH stretching vibration .The peak at around 2930cm^{-1} is due to C-H stretching of polymer backbone while the peak C-O stretching absorbed at 1150 cm^{-1}[159] .These observed peaks indicated that the polymer was obtained.[17].

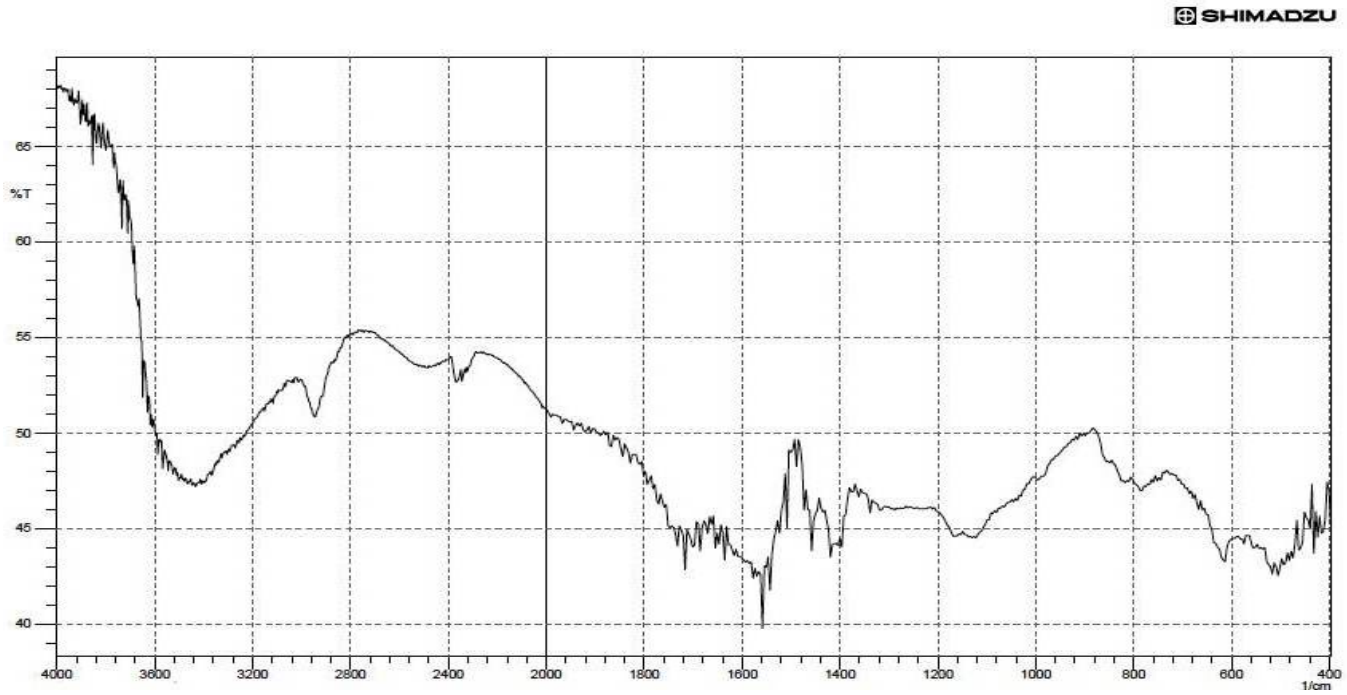


Figure (3.3) FTIR spectra of polyacrylic acid

Synthesis of Polyacrylic acid with crosslinking N,N'-Methylene bis acryl amide e(MBA) and Spectral Characterization

N,N'-Methylene bis acryl amide (MBA) crosslinked (0.05-0.25)g. polyacrylic acid were synthesis by free radical solution polymerization of the monomer acrylic acid and tetrafunctional crosslinking agent (MBA) using potassium persulfate as the initiator and sodium metabisulfite as accelerator, the polymer matrix become more rigid with increasing crosslinking and hence the swelling in water also decreased .The polymerization reaction See figure

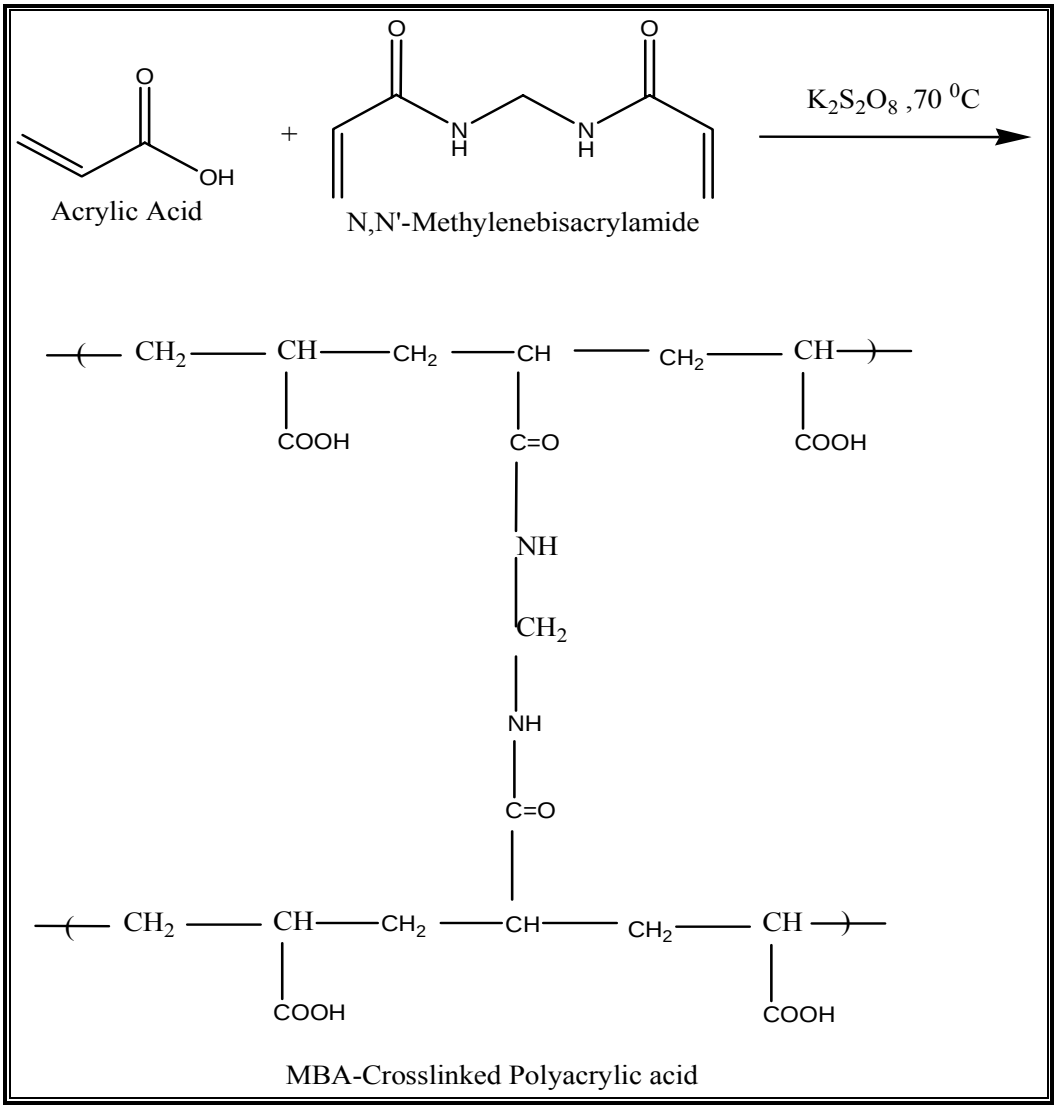


Figure (3.4) Synthesis of MBA-Crosslinked polyacrylic acid

The FTIR spectrum in figure (3.5) shows a peak at 1690 cm^{-1} is due to the presence of C=O stretching vibration .The broad band at 3400cm^{-1} is due to stretching vibration of –OH groups , the peak at 2920cm^{-1} is due to C-H stretching of polymer back bone ,and the peak at 1100cm^{-1} is due to C-O .The peak at 1590cm^{-1} is due to the stretching band of C=O in carboxamide, the peak at 3320cm^{-1} is due to the stretching band of NH functional groups of crosslinked agent MBA [18].

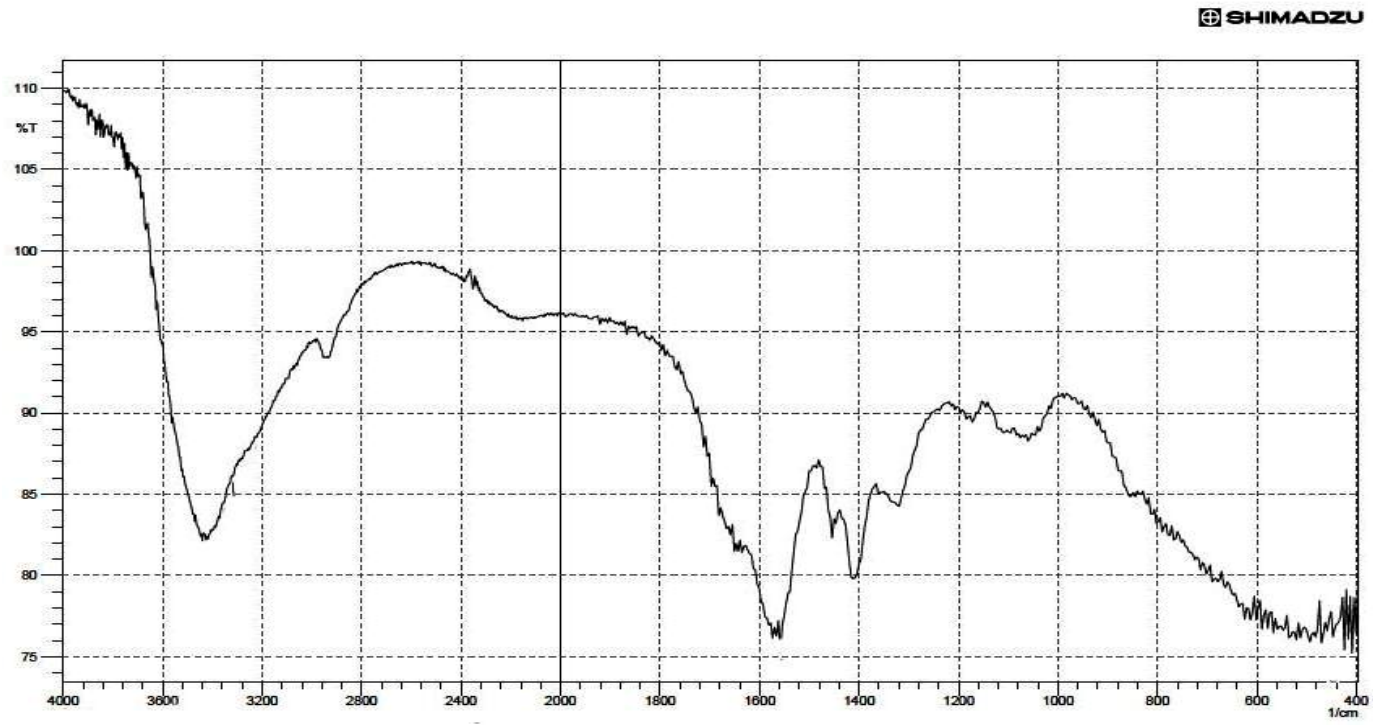


Figure (3.5) FTIR spectra of polyacrylic acid crosslinked with MBA

Swelling Characterization Of the Crosslinking Polyacrylic acid With N,N'-Methylene bis acryl amide (MBA)

The swelling ratio behavior of PAA hydrogels were 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 presence of cross-links. Because of the carboxylic acid side groups, the swelling behavior of the poly acrylic acid hydrogels is highly dependent on the pH of the surrounding medium. In higher pH medium the carboxylic acid groups on the PAA became progressively more ionized. In these cases, the hydrogels swelled more rapidly due to a large swelling force created by the electrostatic repulsion between the ionized acid groups and the osmotic pressure resulted from different concentrations of free ions within ionic network and the surrounding solution [19].

The pH was adjusted by preparation of buffers (2 ,4 and 7.2). Dried hydrogels were left to swell in a solution of desired pH. Swollen gels removed from the solution at regular intervals and weighed. The measurement was continued until a constant weight was repeated for each sample.

Figure (3-6),(3-7) and (3-8) show the typical swelling ratio of an initially dry hydrogels at times in the known pH values. This weight was used to calculate the swelling ratio:

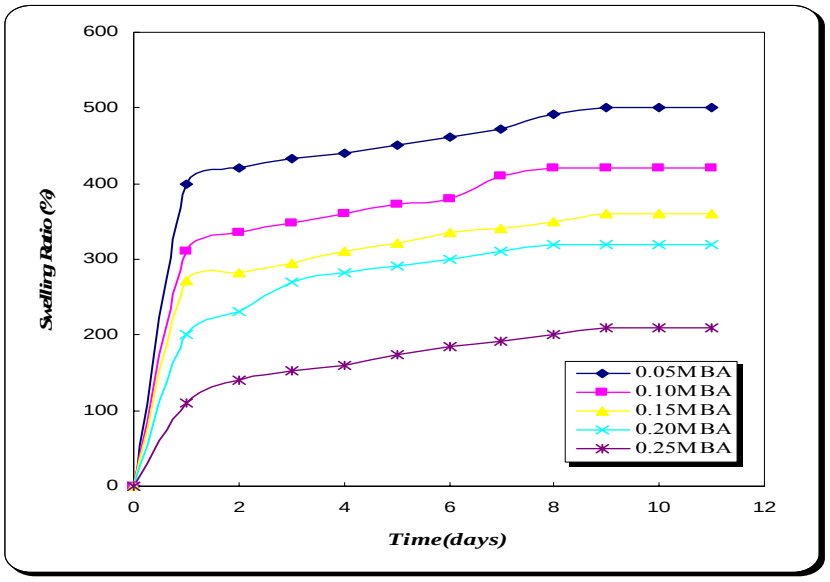
$$Rs = (Ws-Wd)100 / Wd$$

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

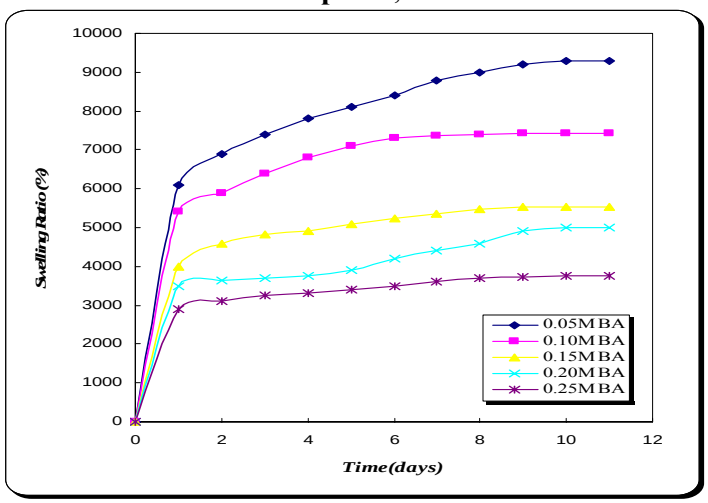
The observed that the time taken to achieve swelling ratio of the hydrogels decreased with increasing molar proportion of cross-linking agent (0.05-0.25) g. .

Figure (3.6),(3.7) and (3.8) it was obvious that the rate of solution uptake was significantly faster for the polymer network in solutions with pH=7.2 than for the network in lower pH. Since pKa of acrylic acid is

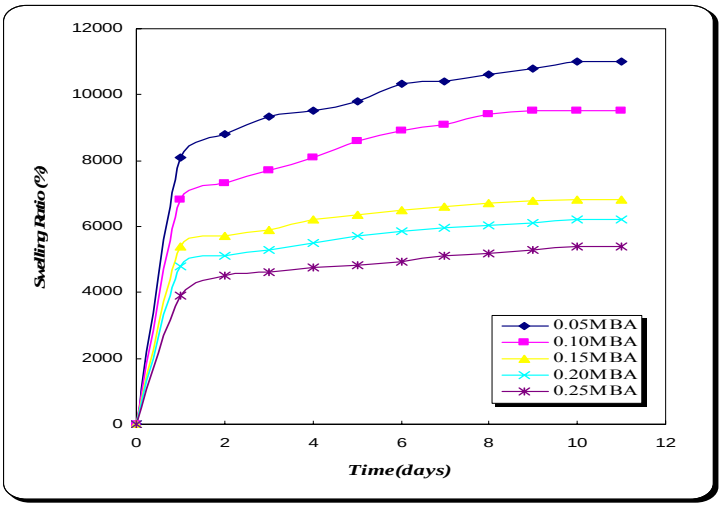
between 4.7, PAA hydrogels swell significantly at pH=7.2. However, they very low swell significantly at pH=2 and 4 [20].



Figure(3.6) swelling ratio (Rs) of cross-linking PAA hydrogels with (MBA) vs. time at pH=2, T=37^0



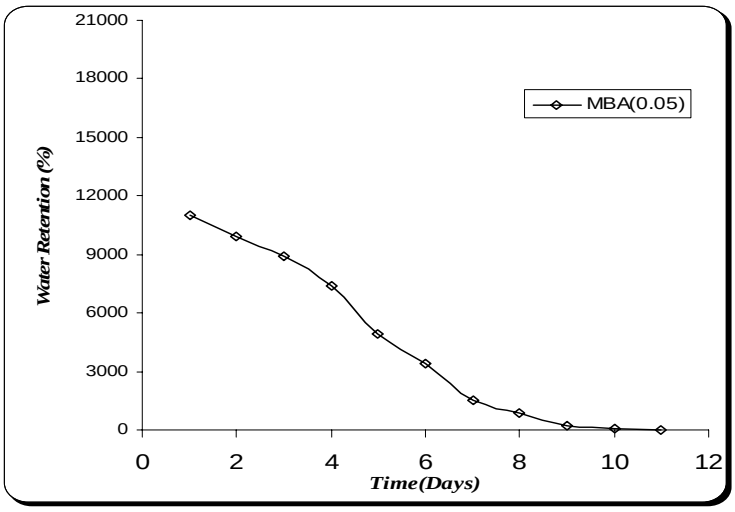
Figure(3.7) swelling ratio (Rs) of cross-linking PAA hydrogels with(MBA) vs. time at pH=4, T=37^0



Figure(3.8) swelling ratio (Rs) of cross-linking PAA hydrogels with(MBA) vs. time at pH=7.2, T=37^0

Deswelling Of Hydrogels PAA-MBA

The deswelling of the hydrogels polymers with different amounts MBA, 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(3.9).



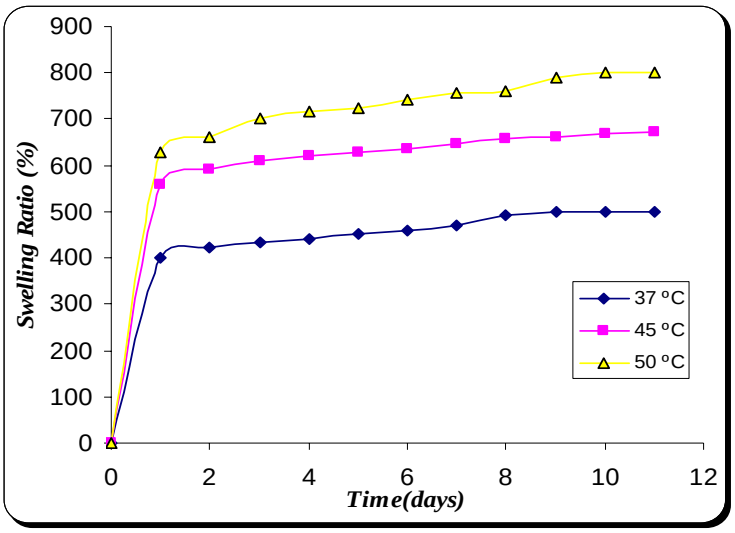
Figure(3.9) Deswelling of hydrogels PAA-MBA

From Figure (3.9), it can be seen that all the samples 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. Then a dense polymer skin layer at the surface of the gel is formed, preventing water to flow out of the gel. As different composition was incorporated into hydrogel, the surface of the hydrogels was quite uneven compared to that of the pure PAA hydrogel, which would weaken or destroy the dense skin layer

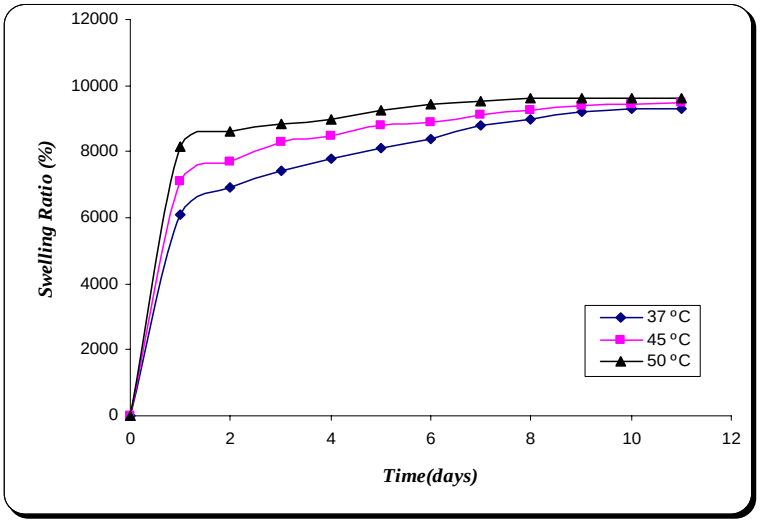
of hydrogel. Therefore, water molecules pass through the surface layer more easily, and the shrinking rate is improved [21].

Effect Of Temperature On Swelling Ratio

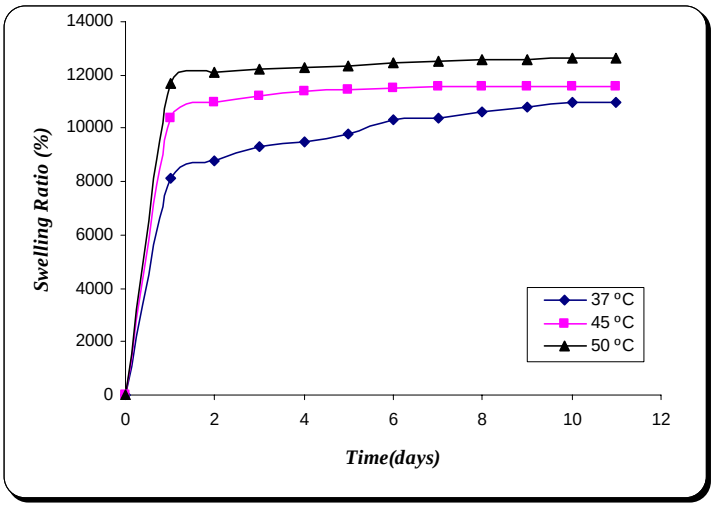
In the figure (3.10), (3.11) and (3.12) shows the effect of storge temperature and time on swelling ratio of hydrogels at different pH. It was observed that at higher temperature (45,50) ^{0}C the swelling ratio of formulations was increased, whereas at low temperature 37 ^{0}C, it was decreased. The increased in swelling ratio of formulations stored at higher temperature may be accounted for the more solution loss and dehydration of formulations that at low temperature. This greater loss or dehydration on storge at higher temperature had resulted in to more solution uptake by the hydrogel during swelling and hence increase in the numerator value used in the formula for calculation of swelling ratio [22].



Figure(3.10) Effect of Temperature on the Swelling Ratio vs. time at pH(2)



Figure(3.11) Effect of Temperature on the Swelling Ratio vs. time at pH(4)



Figure(3.12) Effect of Temperature on the Swelling Ratio vs. time at pH(7.2)

Effect Of MBA Concentration On The Release Of Theophylline

The release of theophylline from PAA hydrogels was studied by varying MBA concentration at different pH.

Figure (3.13),(3.14) and (3.15) shows the effect of MBA concentration on the theophylline release behavior of hydrogels in different pH media. The results indicate that the release of active agent depends obviously on the crosslinker concentration.

The high entrapment efficiency of hydrogel formulation is observed because of hydrophilicity and low molecular weight of theophylline. When concentration of MBA was increased, loading efficiency of hydrogel decreased, this might be due to increase in the density of polymer and less free space available for the entrapment of drug. Therefore, the resulted highly crosslinked rigid structure can not be expended and hold a large quantity of buffer solution. As the amount of MBA increases from 0.05 to 0.25 g., the drug release rate decreased because of the increase crosslinking density. The fast release of theophylline is due the higher swelling behavior of hydrogel with low concentration of MBA [23].

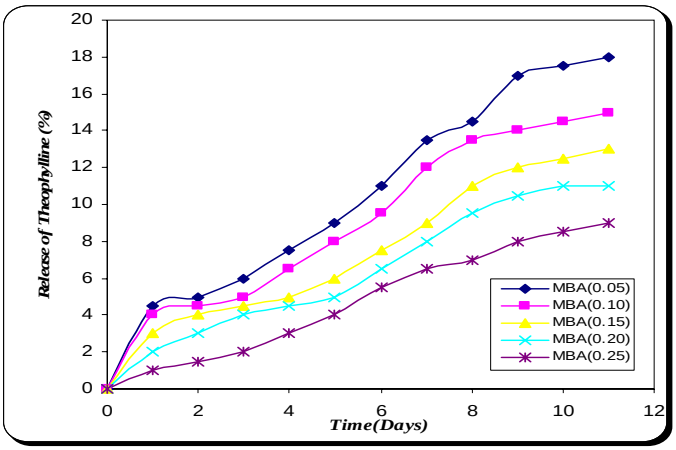


Figure (3.13) Effect Of MBA Concentration On The Release Of Theophylline at pH(2), T=37^0, at λmax 272.0 nm

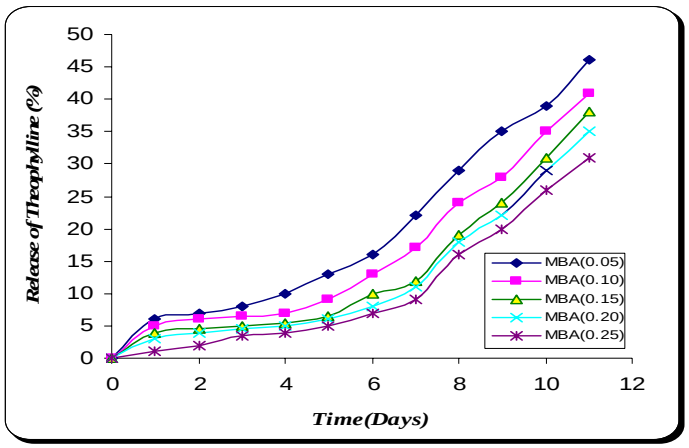


Figure (3.14) Effect Of MBA Concentration On The Release Of Theophylline at pH(4), T=37^0, at λmax 272.0 nm

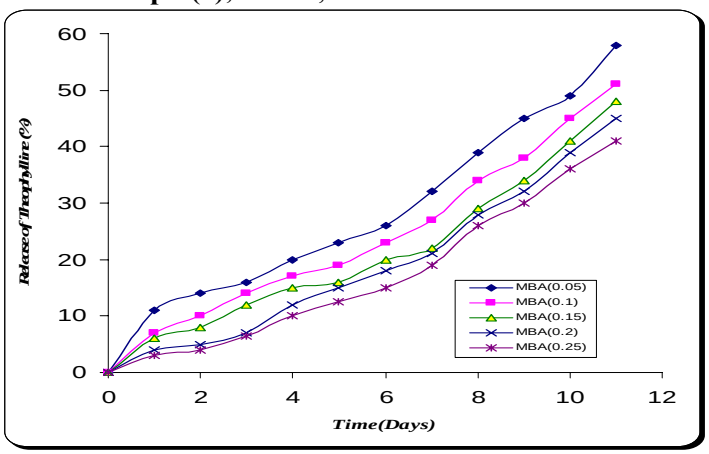


Figure (3.15) Effect Of MBA Concentration On The Release Of Theophylline at pH(7.2, T=37^0, at λmax 272.0 nm)

Effect of amount of loading on release of Theophylline

The release profile of theophylline from the porous PAA hydrogel loaded with various amounts of the theophylline was studied in different pH(2 ,4 and 7.2). The results are shown in figure (3.16), (3.17) and (3.18), that the loading is increased with increasing the theophylline concentration in loading medium .The release profiles indicate that the amount of released theophylline 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 through which, a lesser number of theophylline molecules would transport showing. Generally, drug release through microspheres depend upon the particle size, polymer crystallinity, surface character, molecular weight, polymer composition, swelling ratio, degradation rate, drug binding affinity, rate of hydration [24].

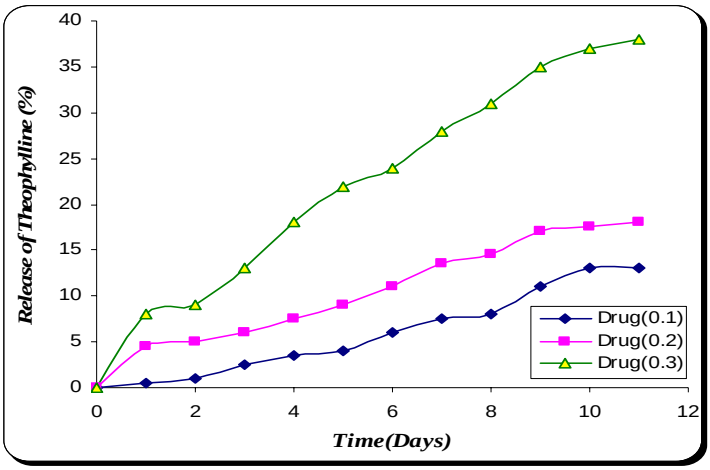


Figure (3.16)Effect of amount of loading on release of Theophylline at pH 2, T=37^0, at λmax 272.0 nm

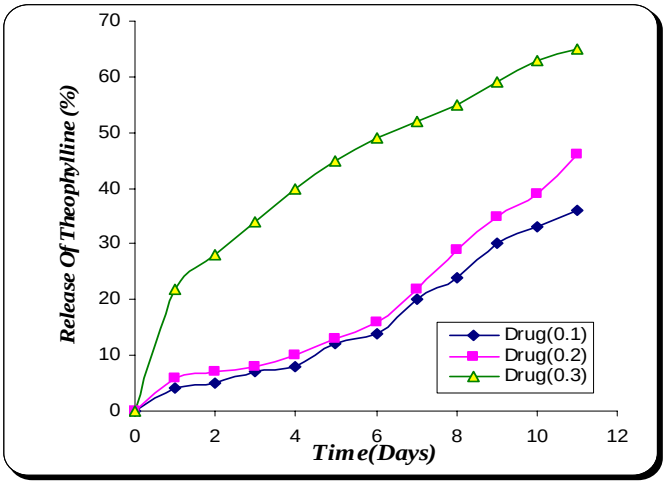


Figure (3.17)Effect of amount of loading on release of Theophylline at pH 4, T=37^0, at λmax 272.0 nm

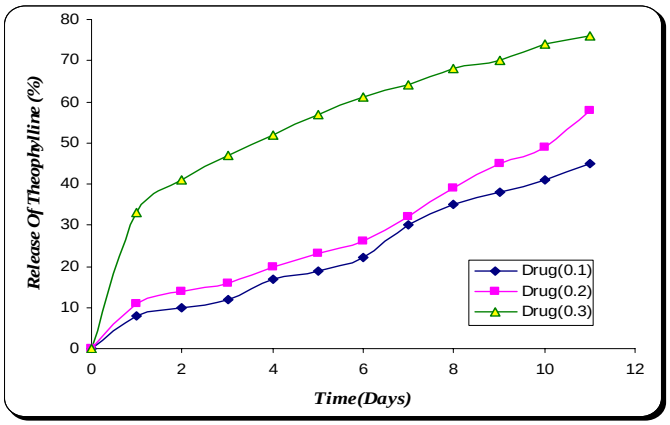


Figure (3.18)Effect of amount of loading on release of Theophylline at pH 7.2, T=37^0, at λmax 272.0 nm

Effect Of pH On The Release Of Theophylline

The theophylline release rates from the PAA hydrogels have been measured at pH 2,4 and 7.2, See figure (3.19), the theophylline 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 carboxylate groups. This finally results into the higher swelling ratio.

While in pH 2 and 4, the amount of theophylline 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 composition of hydrogel [25].

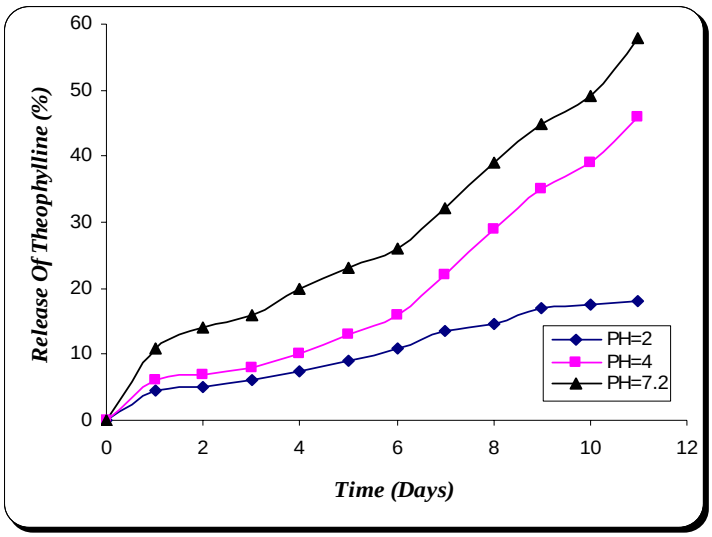


Figure (3.19)Effect Of pH On The Release Of Theophylline at 37 ^{0}C , λmax 272.0 nm

Effect Of Temperature On The Release Of Theophylline

Effects of temperature on the release rate of theophylline have also been examined in this search. As shown in Figure(3.20),(3.21) and (3.22), the higher release rate was observed at 50,45 ºC, while the release rate of theophylline 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 theophylline molecules inside the superabsorbent. Meanwhile, the swelling ratio of the superabsorbent as a result of temperature increases may also be at least partly responsible for the increase of theophylline release rate through enlarging the diffusion pathways throughout the superabsorbent. Both two factors are believed to contribute to the increase of theophylline release rate as the temperature is increased [25].

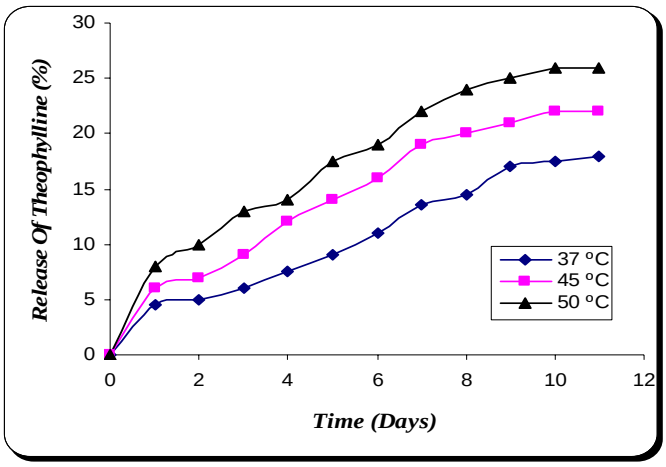


Figure (3.20)Effect Of Temperature On The Release Of Theophylline at pH(2), λmax 272.0 nm

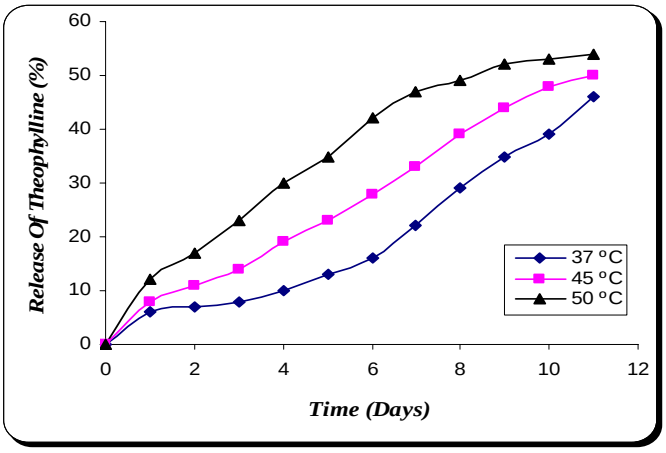


Figure (3.21)Effect Of Temperature On The Release Of Theophylline at pH(4), λmax 272.0 nm

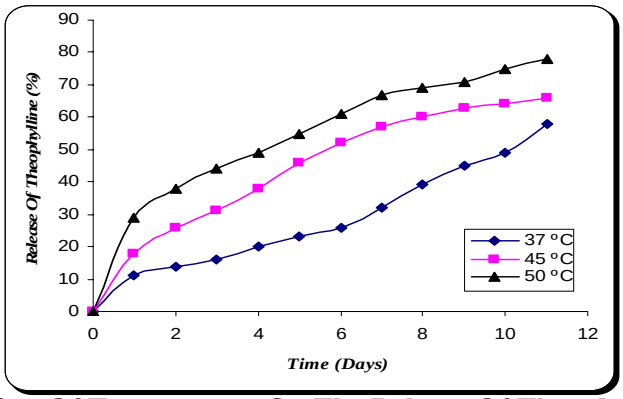


Figure (3.22)Effect Of Temperature On The Release Of Theophylline at pH(7.2), λmax 272.0 nm

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