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Naproxen Sodium Release from Poly(acrylic acid-co- N-vinyl-2-pyrrolidone) Hydrogels

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Abstract

Copolymer hydrogels of acrylic acid (AA) and N-vinyl-2-pyrrolidone (NVP), crosslinked with 1,4-butanediol dimethacrylate (BDDMA), were prepared by radical copolymerization. The chemical structures of copolymer hydrogels were analyzed by Fourier transform infrared spectrometer (FTIR) and H NMR spectroscopy. The swelling ratio (Rs) was measured for four types of hydrogels structures, in three different media pH 1.2 , 4 and 7.4 at 37^0C as a function of time. A Naproxen Sodium is used as a model drug to investigate the drug release profile of the hydrogels. The concentration of drug released was measured on UV-Vis spectrophotometer. Results indicated that the swelling ratio and drug release is increase concentration decrease of crosslinked agent and pH increase.

Keywords: hydrogels, acrylic acid, N-vinyl-2-pyrrolidone, swelling ratio, Naproxen Sodium, drug release

Comical **Classification** QD241-441

1- Introduction

Polymer hydrogels, that are three-dimensional polymeric networks produced from highly hydrophilic monomers caused to become insoluble through hydrogen bond, electrostatic or covalent crosslinking [1]. A result of the super-hydrophilicity characteristics and porous structure networks, they are able to swell quickly in the aqueous solution. Copolymerization is one of the important techniques adopted in effecting systematic changes in the properties of the commercially important polymers. [2]

The chemical structure of copolymer depends not only on the monomer units forming the macromolecule but also how such units are distributed along macromolecular chains. This distribution is a direct consequence of each monomer's reactivity in the copolymer molecule [3,4]. Reactivity ratios are the most important parameters for a composition equation of copolymers and they offer information about the reactivity of monomer pairs. However, the copolymer composition is important in evaluating its own utility. The copolymer composition and its distribution are dependent on their reactivity ratios, which can be evaluated either by employing linear and nonlinear methods or by using other copolymer composition equations [5,6].

N-vinyl-2-pyrrolidone (VP) is a water-soluble, nonionic monomer that can be used to prepare hydrogels[7]. N-vinylpyrrolidone (NVP) has been widely investigated for applications in various fields, as these are known to exhibit good biocompatibility due to their hydrophilic nature and low cytotoxicity [8,9]. The amide group of NVP has a high binding affinity for several small and large molecules that are known as good hydrogen-bond acceptors and has been copolymerised with a variety of monomers [10]. Dilek Solpan et al. Synthesized copolymer N-Vinyl Pyrrolidone – Methylmethacrylate and they studied the swelling property of these hydrogels [11]. Polyacrylic acid is known to be a good mucoadhesive and may increase the transit time of formulation, in drug delivery systems [12].

Polyacrylic acid (PAA) and its copolymers have often been used as carriers in drug release systems, because of their multifunctional nature, unique properties and good biocompatibility[13]. The copolymer hydrogels have been shown to display properties ranging between those of the two homopolymers

and reported that the extent of swelling depends on the copolymer composition and crosslink density[14]. The swelling and drug release properties of the hydrogels also vary depending on the sorbent temperature, pH and ionic strength. Besides studies on the release of low molecular weight drugs, the release kinetics of large protein molecules from both charged[15].

2. Experimental

2.1. Materials

Acrylic Acid (AA, HIMEDIA), N-vinyl-2-pyrrolidone (NVP) (Merck, Germany), 1,4-butanediol dimethacrylate (BDDMA)(Sigma-Aldrich), potassium Persulfate (KPS, Merck, Germany), Naproxen Sodium supplied by Samara Drug Industry (SDI), sodium Hydroxide (BDH), phosphate buffer saline (HIMEDIA), buffer solution pH= 4, 1.2 (BDH), hydrochloric acid (BDH).

2.2.Instrumental

1- pH meter, HANNA, Romania.
2- FTIR 8400S,Fourier Transform infrared spectrophotometer, SHIMADZU ,Japan.
3-UV-1650PC, Ultra violet-visible spectrophotometer, SHIMADZU, Japan.
4- Fume Hood, K &K Scientific suppler, Korea.
5- Hot plate stir, BIBBY STRILINTD.UK.
6- Oven ,TRIVP International CORP. Italy.

2.3. Preparation of crosslinked PAA-PVP copolymer hydrogels

As both the monomers are soluble in water, the copolymerization is carried out in the presence of water. Known amounts of monomer NVP, AA (5 g) was dissolved in 100 ml de-ionized water are taken in a three necked 250 ml round bottom flask. When the mixture is heated up to 45°C under nitrogen protection. Then, different amounts (BDDMA) are given in Table (1), were added into the flask and then the solution was stirred incessantly. 0.02 g Potassium persulfate, dissolved in 10 ml de-ionized water, polymerization process after 30 min. The reaction was stopped after 2 h. The prepared hydrogel dried in the oven of 50 °C for 24 h. The gels were soaked in distilled water for one day to remove any possible residual monomers and dried in vacuum at 80 °C for 5 h to form crosslinked PAA-PVP copolymer hydrogels with constant weights[16].

Table (1) Amounts of reaction parameters for Preparation of crosslinked PAA-PVP copolymer hydrogels

Sample No	Monomers		Crosslinked agent (BDDMA)(g)	Initiator (g)
	AA(g)	NVP(g)		
1	5	5	0.1	0.02
2	5	5	0.2	0.02
3	5	5	0.3	0.02
4	5	5	0.4	0.02

2.4. Drug Loaded

Powdered samples (1-4) (0.1g), with average particle sizes between 40-60 mesh (250-420 μm), were accurately weighted and immersed in an aqueous solution of Naproxen Sodium (10 mg dissolved in 50 ml distilled water) at room temperature for 1 day. Preliminary tests revealed that 1 day was the minimum time to ensure maximal drug loading. After that time, the hydrogels were removed from the drug solution and left to dry to constant weight. The Naproxen Sodium content was determined UV-visible spectrophotometer [17] .

2.5. Equilibrium swelling studies

(0.1g) of the dried hydrogel samples were soaked in solutions of pH 1.2 , 4 and 7.4 for 8 hrs at 37°C. After every 1h, they were removed from the water, blotted with filter paper to remove surface water, weighted and the swelling ratio (SR) was calculated as equation 1:

$$SR = (Ws-Wd)100 / Wd \quad .....(1)$$

Where Ws and Wd are the weights of swollen and dried hydrogels, respectively.[18]

2.6. Preparation of Calibration Curve

A standard curve for Naproxen Sodium was constructed in the range of 1 to 2 ppm The Solutions were prepared from 100 ppm stock solution was prepared by dissolving 10 mg of Naproxen sodium in 100 ml deionized water. From this stock solution, aliquots of 0.1, 0.12, 0.14, 0.16, 0.18 and 0.2 ml were withdrawn in 10 ml volumetric flasks and diluted to volume with distilled water to obtain standard solutions of the concentrations 1, 1.2, 1.4, 1.6, 1.8 and 2 ppm respectively. The absorbance of the resulting solutions was measured at λmax 231 nm using distilled water as a blank. As shown in the Figure (2), the linear relationship between the concentration of the Naproxen Sodium and the absorbance. The plot is shown in figure (3).

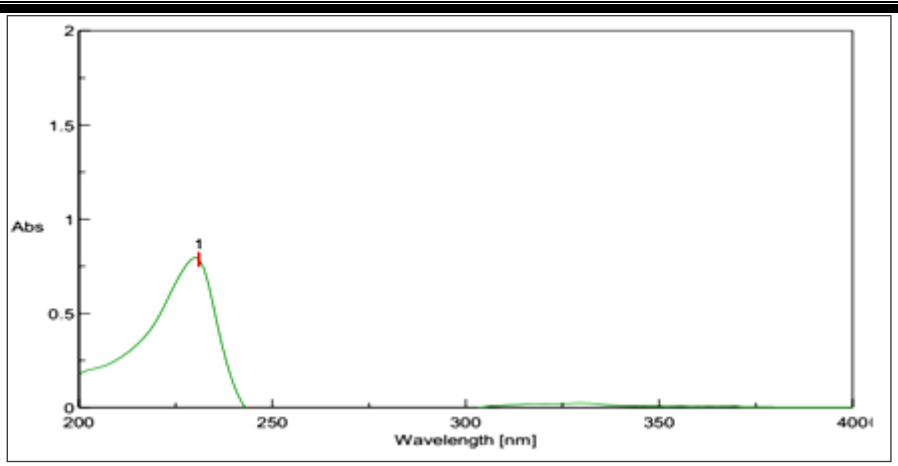


Figure (2): UV spectrum of Naproxen Sodium (Conc.)

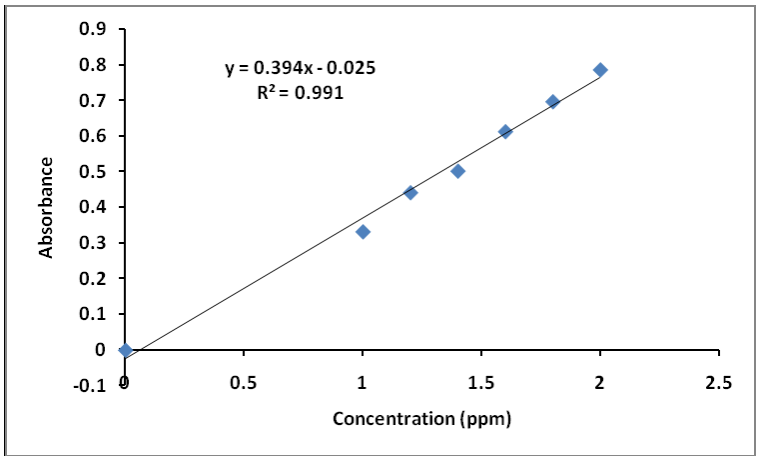


Figure (3): The working calibration curve for the data of Naproxen Sodium (the absorbance in 1 cm cell)at λmax 231 nm

2.7. Drug Release Studies

The chemical name for naproxen sodium is (S)- 2-naphthalene acetic acid, 6-methoxy-a-methyl-sodium salt, Molecular Formula: C14H13NaO3,Molecular Weight: 252.24, odorless crystalline powder, white to creamy in color. It is soluble in methanol and water. Member of the aryl acetic acid group of nonsteroidal anti-inflammatory drugs, the following structural formula.

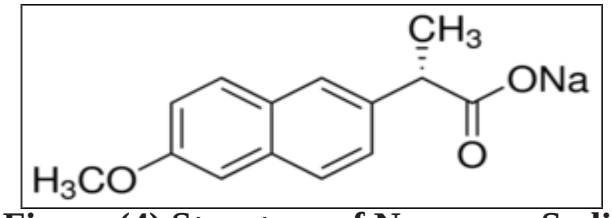


Figure (4) Structure of Naproxen Sodium

The drug release properties of the hydrogels were evaluated under the normal physiological pH conditions of the gastrointestinal tract, as the method used should simulate the environment to which the hydrogen will be exposed in the gastrointestinal tract. Thus sequential drug release method was used by continuously changing the pH of the dissolution media [19] .

Drug loaded hydrogels samples are used in order to determine the amount of naproxen sodium released from the hydrogel network. Drug loaded hydrogel with known amount of drug was placed in 50 ml from different pH 1.2 , 4 and 7.4 at temperature 37°C and taking out aliquots of 3 ml at particular time intervals. The withdrawn aliquots were replenished with equal volumes of fresh buffer solution to simulate physiological conditions. The concentration of naproxen sodium released was estimated by UV spectroscopy at the wavelength of maximum absorption (231 nm).

3. Results and Discussion

3.1. Preparation of crosslinked PAA-PVP copolymer hydrogels

In the present work (AA) , (NVP) and (BDDMA) undergoes free radical crosslink copolymerization in water. During free radical polymerization three acrylic monomers copolymerize with three vinyl (CH_2=CH-) functional groups of one (BDDMA) monomer and thus a three dimensional network of crosslink copolymer gel is formed as shown in the Fig. (5) [20].

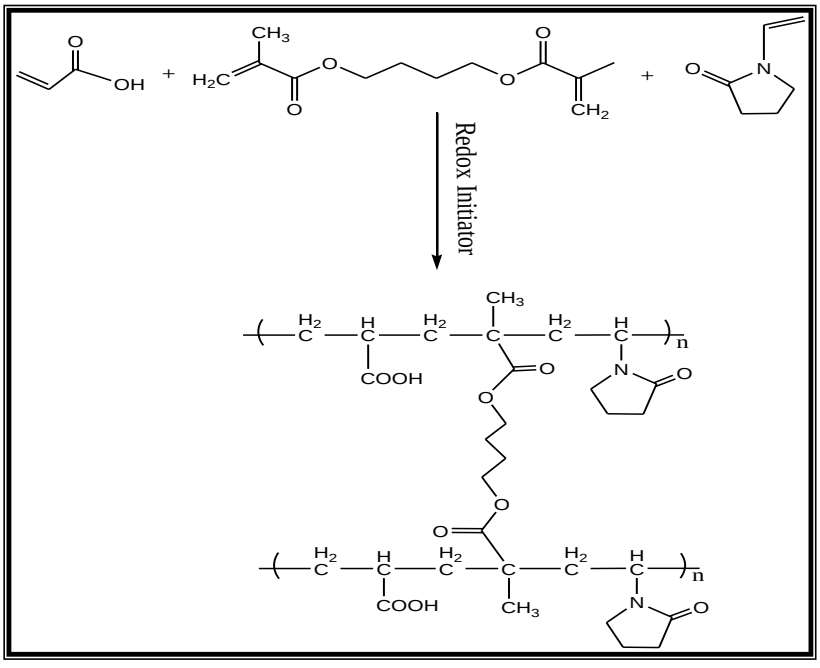


Fig.(5) Crosslinked PAA-PVP copolymer hydrogels

The FT-IR spectrum of crosslinked AA-NVP copolymers showed the characteristic absorption of an amide carbonyl (>C=O) of NVP at 1739 cm^{-1} A band found at 2818-2955 cm^{-1} range is attributed to -C-H stretching of the polymeric back bone. A band at 3273cm^{-1} region was due to the O-H vibration The carboxyl group of the AA-NVP copolymer showed a strong absorption band at 1642cm^{-1} and weak one at 1494 cm^{-1} corresponding to >C=O group [21].

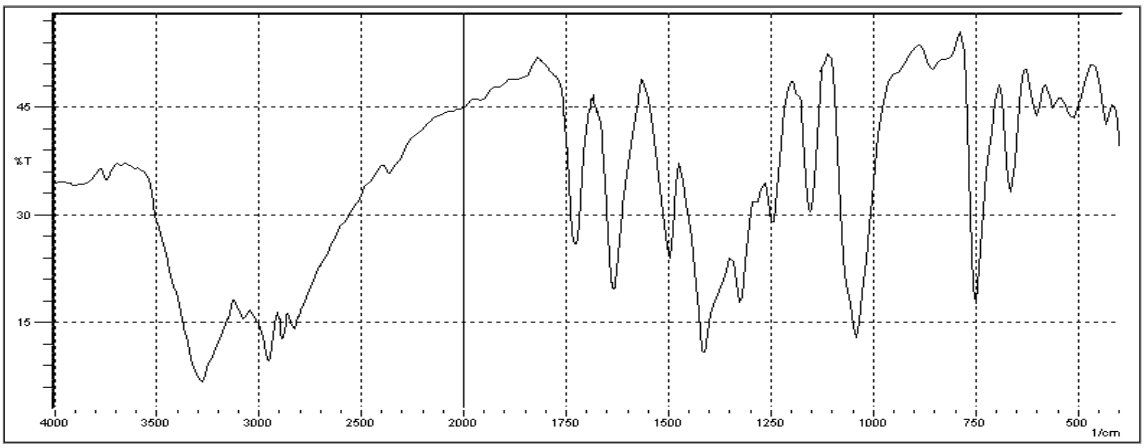


Figure (6) FTIR spectrum of crosslinked PAA-PVP copolymer ydrogels

The crosslinked copolymer AA-NVP is also confirmed by NMR spectrum.The main chain methylene proton of both NVP and AA units resonate at δ 4.12, 3.35 and 2.61 ppm. The –CH group of NVP appears at δ 4.81 ppm. The ring methylene proton in NVP are assigned at δ =2.32, δ = 1.52 and δ = 2.82 ppm respectively. The proton present in carboxylic group of AA resonates at δ = 11.34 ppm [22].

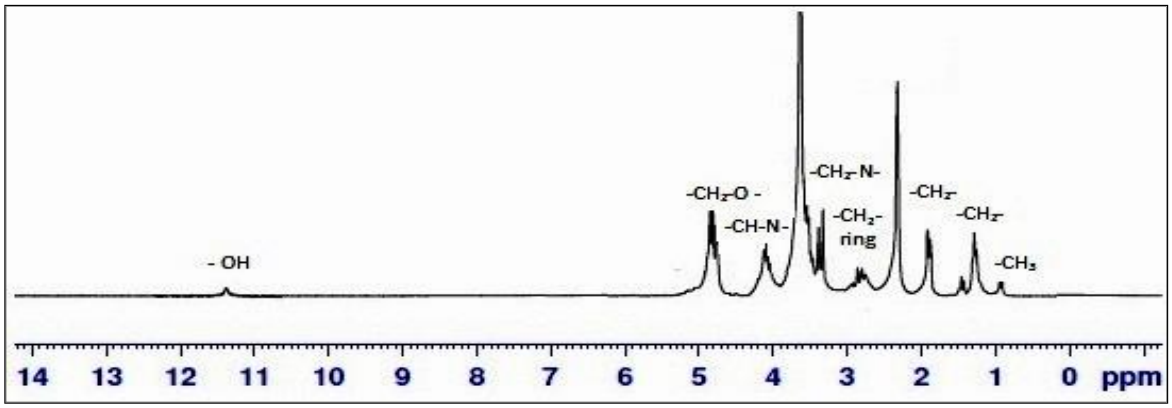


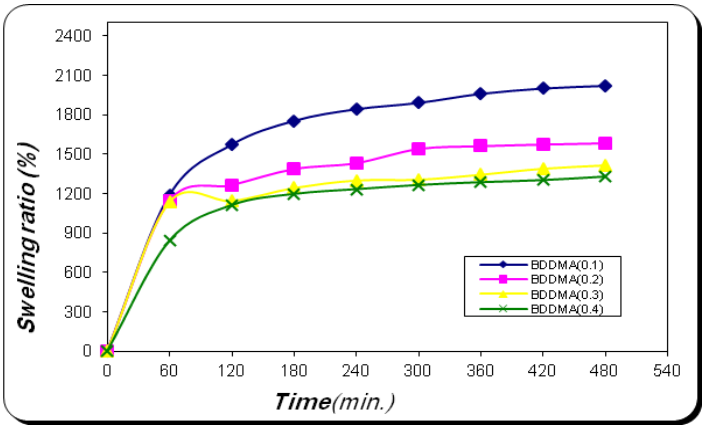
Figure (7) H1 NMR spectrum of crosslinked PAA-PVP copolymer hydrogels

3.2. Effect of variation of pH and cross-linker on swelling ratio

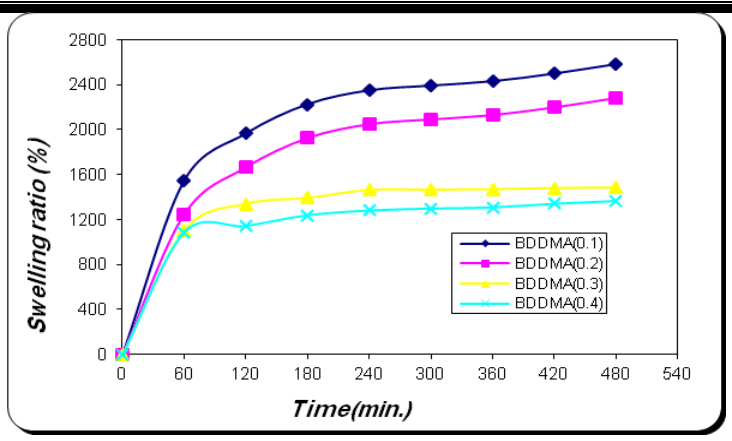
The swelling behaviour of hydrogels plays an important role in controlled drug release behaviour. Therefore, it was important to investigate various factors affecting the swelling. The nature of pH-sensitive hydrogels strongly depends on the pH of the medium[23].

To study this effect, 0.1 g of the dried hydrogel samples(1-4) were soaked in solutions of pH 1.2 , 4 and 7.4. Effect of pH on dynamic and equilibrium swelling of various samples containing different amounts crosslinking agents are given in figure(8),(9)and(10).

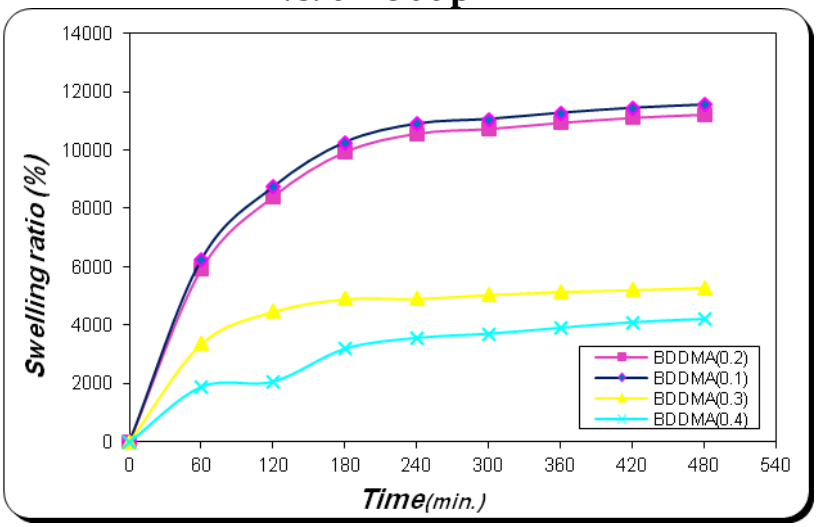
From these results, it is obvious that there is a significant variation in the degree of swelling at different pH values. These hydrogels show low swelling at acidic pH is due to a high content of carboxylic acid groups that remain un-ionized at this pH, while the degree of swelling increases as the pH of medium increases due to availability of more carboxyl groups for ionization[24]. As a result, electrostatic repulsion increases along the chain, which causes an expansion of the chain. After confirming the swelling effect at low and high pH, we were further interested to see the swelling as a function crosslinking agents concentration. swelling decreases with increasing concentrations of cross-linker due to the increase in the degree of cross-linking between polymer chains, which prevents their expansion [25].



Figure(8) Swelling ratio of cross-linking PAA-PVP copolymer hydrogels vs.time at pH=1.2



Figure(9) swelling ratio of cross-linking PAA-PVP copolymer hydrogels vs. time at pH=4



Figure(10) Swelling ratio of cross-linking PAA-PVP copolymer hydrogels vs.time at pH=7.4

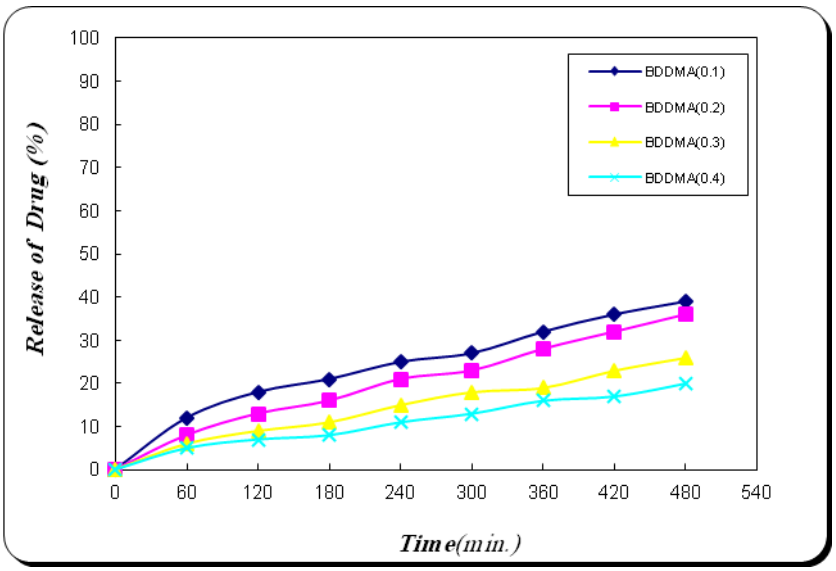
3.3. Effect of variation of pH and cross-linker on Drug Release

The release of naproxen sodium from all the four hydrogels was studied by varying BDDMA concentration at different pH. Figure (11),(12) and (13) shows the effect of BDDMA concentration on the naproxen sodium release behavior of hydrogels in different pH media. Similar to swelling ratio, The release of naproxen sodium is also observed to increase with decrease in crosslinker BDDMA wt%, and increase in solution pH from 1.2 to 7.4 From all of these figures it is observed that an initial burst release of the drug is followed by a sustained rate of release for all of these hydrogels [26] .

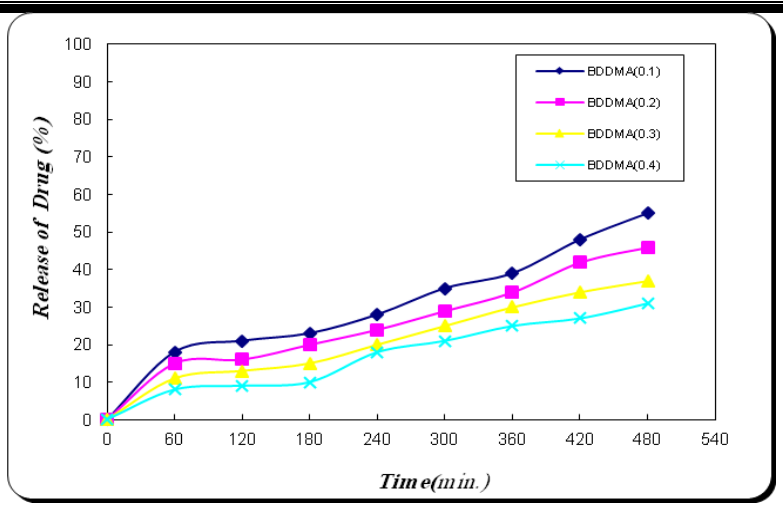
When concentration of BDDMA was increased, loading efficiency of hydrogel decreased, this might be due to increase in the density of polymer and less free

space available for the entrapment of drug. Therefore, the resulted highly crosslinked rigid structure cannot be expended and hold a large quantity of buffer solution [27] .

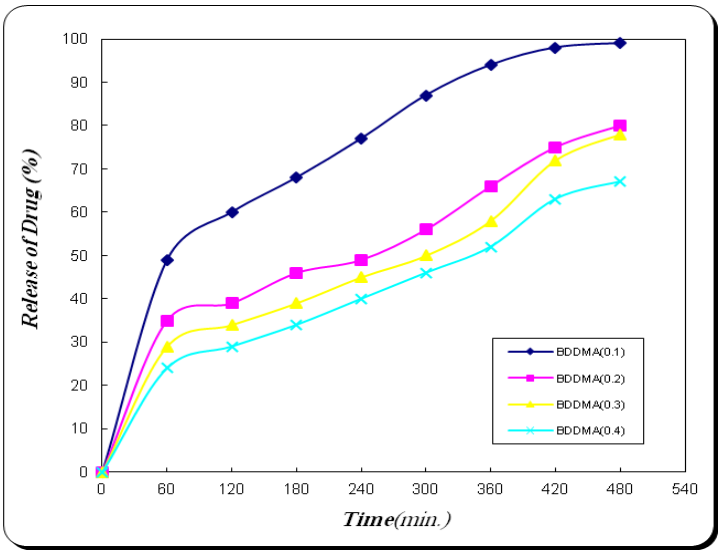
In solutions of low pH, carboxylic groups of AA remain unionised and hydrogen bonding of PVP and AA also remain intact, resulting in decreased swelling and drug release. On increasing pH value of the medium above the pKa value, i.e. 4.26 of AA, carboxyl groups dissociate to form carboxylate ions, which also result in the destruction of hydrogen bonds between PVP and AA. It also results in a decrease in the cross-linked density. Additionally, charge repulsion results in an increased swelling, which originates from a higher concentration of COO^- groups. These effects ultimately lead to increased drug release[28] .



Figure(11) Drug release of cross-linking PAA-PVP copolymer hydrogels vs.time at pH=1.2



Figure(12) Drug release of cross-linking PAA-PVP copolymer hydrogels vs.time at pH=4



Figure(13) Drug release of cross-linking PAA-PVP copolymer hydrogels vs. time at pH=7.4

CONCLUSIONS

PAA-PVP copolymer hydrogels were prepared free radically using BDDMA as a cross-linker. The chemical structures of copolymer hydrogels were analyzed by (FTIR) and (H NMR.). The variations in swelling (%) with time and pH were determined for each type of hydrogel. The swelling for PAA-PVP, which was the most swollen hydrogel, was 11541% at pH 7.4 and 37^0C. The drug release from naproxen sodium loaded PAA-PVP copolymer

hydrogels was followed at pH 7.4, 37^0C for 8 h. The release from the 0.1gm crosslinked
hydrogel was faster than other hydrogels.

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التحرر البطئ لدواء نابروكسين صوديوم من البوليمرات الهلامية المشتركة لمتعدد (حامض الاكريليك- فينل البايروليدين)

تاريخ الاستلام 2015/3/12 تاريخ القبول 2015/5/25

ناظر ضمان راضي - جامعة القادسية / كلية الصيدلة / فرع الكيمياء الصيدلانية

الخلاصة

في هذا البحث تم تحضير هلاميات مائية لبوليمرات مشتركة من حامض الاكريليك وفنيل بايرولدين باستخدام تراكيز مختلفة من العامل المشابك 1و4-بيوتان ثنائي الكحول ثنائي ميثااكريليت باستخدام البلمرة المشتركة للجذور الحرة .حيث تم تشخيص البوليمرات المحضرة باستخدام تقنية فوريرلطيف الاشعة تحت الحمراء وتقنية الرنين النووي المغناطيسي .تمت دراسة نسب الانتفاخ لاربعة من البوليمرات المحضرة في ثلاث اوساط حامضية مختلفة وهي (4, 1.2 و7.4) عند درجة حرارة 37م كدالة للزمن .تم دراسة الاطلاق اليطيئ لدواء الصوديوم نابروكسين المحمل على البوليمرات المحضرة ,حيث تم دراسة تركيز الدواء المتحرر باستخدام تقنية الاشعة فوق البنفسجية .اضهرت النتائج المستحصلة ان نسب النتفاخ وتحرر الدواء تزداد بزيادة الاوساط الحامضية ونقصان تركيز العامل المشابك.

الكلمات المفتاحية:

حامض الاكريليك ، ن- فنيل-2- بايرولدين ، الهلاميات المائية ، نسبة الانتفاخ ، اطلاق الدواء