Synthesis and characterization of new (N-Ethyl Acrylamide Mefenamate)

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Abstract

In this research, a new carrier polymer was prepared through two steps, which included modification of polyacrylic acid (P_1) with ethanol amine producing N-ethanol acrylic amide polymer (P_2) then reacting it with mefenamic acid would give mefenamate ester polymer (P_3) as a new drug carrier polymer. Ethanol amine was used as spacer between polyacrylic acid and mefenamic acid, which could have a potential use as a carrier for drug delivery system due to extended pendant drug. The evaluation of sustained release of mefenamic acid was studied through hydrolysis of ester attachment bond by invitro drug release, using different pH values at 37℃. The prepared prodrug polymer was characterized by FTIR and ^{1}H−NMR spectra physical properties and intrinsic viscosity were determined. It was concluded that the spacer group acts as an extended group to be easy hydrolysised during controlled release.

Key words: Mefenamic acid, Polymer; Acrylamide.

الخلاصة

في هذا البحث تم تحضير بوليمرات حاملة للدواء في خطوتين تتضمن تحوير البولي أكريلك مع الايثانول أمين ليعطي amide N olyP−acrylicEthanol، بعد ذالك تمت مفاعلتة مع namicefeM ليعطي بوليمر أستر ميفانيسيت كبوليمر جديد حامل للدواء. الأيثانول أمين أستخدم كجسر رابط بين بولي اكريلك أسد مع ميفانيميك أسيد والتي تستعمل كنظام ناقل للدواء. تمت دراسة عمليه تحرير الميفينياميك اسيد من خلال تحلل الاصرة الاسترية الذي يساعد على تحرير الدواء داخل الجسم، حيث تم ذلك باستخدام قيم pH مختلفة عند درجة حرارة الجسم 37℃. شخصت البوليمرات المحضرة بتقنية FTIR و H−NMR بالاضافة الى الخواص الفيزياوية الاخرى. المجموعة الجسرية المستخدمة هي للمساعدة في كلية التحرير لسهولة تحللها (كسرها).

الكلمات المفتاحية: الميفينياميك اسيد، بوليمر، اكرليمايد.

Introduction

The action of polymeric drugs invivo usually depends on hydrolytic on enzymatic cleavage of the drug moiety from the polymer [Gebelein *et al.,* 1981]. This gives an advantage of delayed and sustained release of drug over long time with corresponding decrease of side effects [Rang *et al.,* 1995]. It is potentially possible to make a polymer drug with specific required solubility rate of diffusion and increased or decreased the activity by the appropriate choice of the polymer and the drug. These include situation requiring the slow release of water-soluble drugs, the fast release is of the low solubility drugs [Luten *et al.,* 2008]. Mefenamic acid (MF), N-(2,3-Xylyl) anthranilic acid, is a non-steroidal drug. It has analgesic and antipyretic properties. mefenamic acid is used in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis [Tayyebeh *et al.,* 2009]. The compound is almost insoluble in water but is readily soluble in organic solvents such as dioxane, alcohols and dimethyl form amide [Sakhare *et al.,* 2012]. Acrylic acid (AA) is deemed to form a super absorbent polymer which can absorb very large amount of water and retain it even under high pressure. As a result of this unique characteristic, it has been used in various controlled drug delivery systems [Talib *et al.,* 2013]. Some of the most common functional groups that are amenable to prodrug design include carboxylic, hydroxyl, amine, phosphate/phosphate and carbonyl groups. Prodrugs typically produced via the modification of these groups include esters, carbonates, carbonates, amides, phosphates and oximes. However, other uncommon functional groups have also been investigated as potentially useful structures in prodrug design. For example, thiols react in a similar manner to alcohols and can be derivatives to thio ethers and thio

esters [Majumdar and Sloan, 2006]. Amines may be derivatives into imines [Jarkko *et al.*, 2008] and N‑ Mannich bases [Simplicio *et al.*, 2006]. Polymer-drug conjugates of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and indomethacin have become important as polymeric prodrugs [Cecchi *et al.*, 1981]. These systems have been developed in order to minimize delivery problems and reduce gastrointestinal side effects by controlling the rate, duration, and site of release. These kind of polymeric prodrugs have been designed for localized and prolonged duration of drug action by parenteral administration [Iansen and Johansen 1995], or as a dermal prodrug [Bonina *et al.*, 1995]. The purpose of this research is to synthesis of polymer based smart prodrug polymer with extended pendent side chain and investigation the efficient drug release.

Experimental

Materials and Instruments

Mefenamic acid was purchased from Samarra Company. Thionyl chloride was obtained from Fluka. Hydroxyl amine and acrylic acid were obtained from Aldrich. Dimethylformamide was purchased from Merck. ^{1}H-NMR spectra were recorded on a Shimadzu spectrophotometer in Dimethylsulphoxide ($DMSO^{6}$). The FTIR spectra were recorded by ($4000\text{-}400cm^{-1)}$ on a Shimadzu spectrophotometer. Melting points were determined on callenkamp MF B-600 Melting point apparatus. Electronic spectra measurement using CINTRA5-UV.Visble spectrophotometer.

Polymerization of Acrylic acid. [Soudabeh D. and Ali A.].

In a screw capped polymerization bottle (3g , 0.041 moles) of acrylic acid was dissolved in 10 ml of DMF, 0.05% of the monomer weight of di benzoyl peroxide was added as an initiator. The bottle was flashed with nitrogen for few minutes inside a glove and firmly stopped. The solution was maintained at 90℃, using water bath for 1 hr. The solvent was evaporated under vacuum; the product was obtained, washed three times with ether. Dried in a vacuum oven at 50℃, produced 95% of polymer, and the intrinsic viscosity was 0.46 dL /g.

Modification of polyacrylic acid with ethanol amine. [Sameaa J.K.]

(3g , 0.041 moles) acrylic acid and (2.5g , 0.04 moles) of ethanol amine were dissolved in 10ml of DMF. The mixture was stirred vigorously at room temperature for 1 hr. The solvent was evaporated, washed with ether and dried at room temperature and the viscous product was obtained. The hydroxyl ethyl acrylamide polymer (P_2) was obtained with 70% as a yellow viscous polymer.

Substitution of Poly [N-(2-hydroxyethyl)-2-methylbutanamide] with Mefenamic acyl chloride(P_3) . [Al-Lami, 2006]

Polymer (P_2) (1.5g , 0.01 moles) was dissolved in 5ml of DMF, and (3.1g , 0.01 moles) of prepared mefenamic acyl chloride was added, the mixture was refluxed with stirring for 1hr. The solvent was evaporated under vacuum and the product was washed with water three times, dried in vacuum oven. The yellowish Brown polymer (P_3) was obtained with 69%. The softening point of the drug polymer (P_3) was (110-115) ℃.

Determination of degree of Mefenamic acid substitution. [Mahammad R. S. et al.]

Prodrug polymer (P_3) at 5 mg was dissolved in 2 ml of 0.1 N NaOH, the solution was heated to 70℃, for 15min in a water bath, cooled and the resulting solution was titrated with 0.1N HCL to determine the excess of NaOH solution.

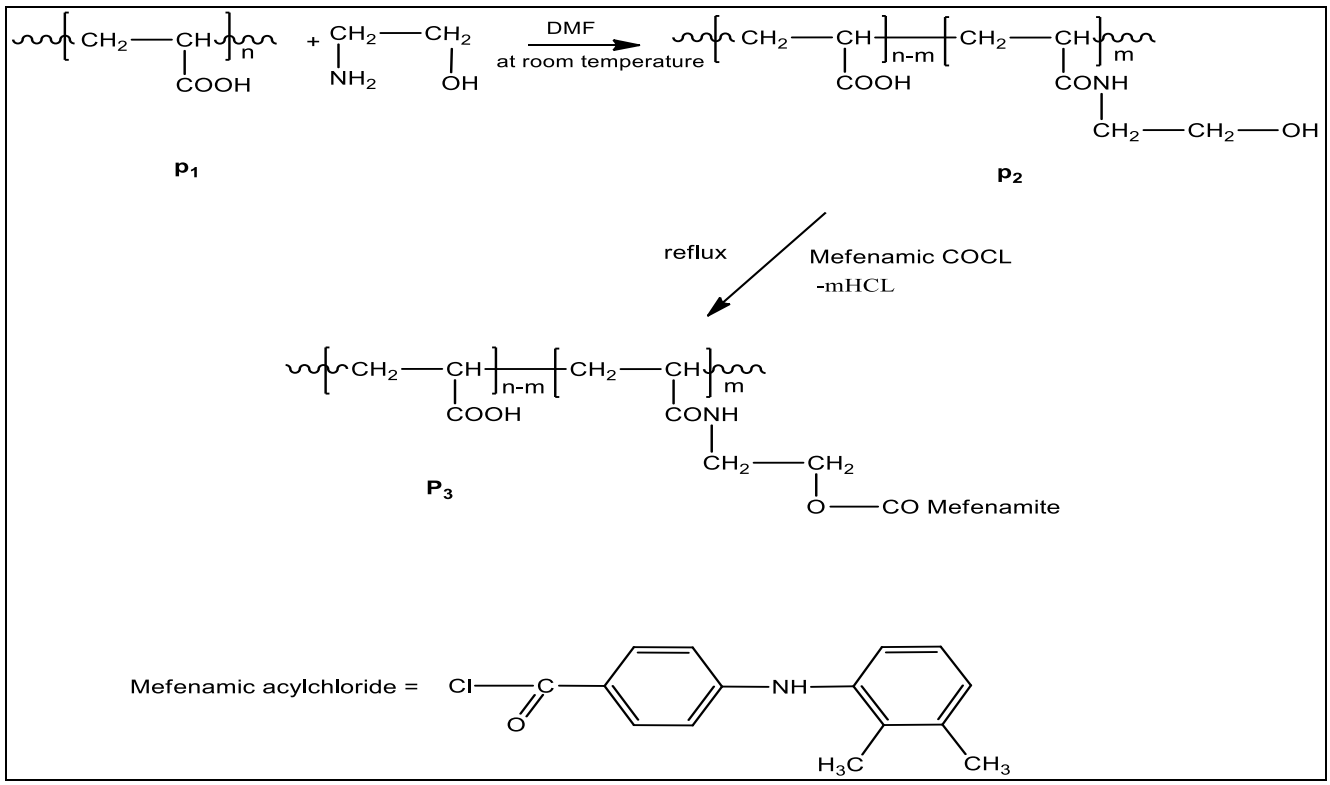
Controlled Drug Release. [Fang *et al.*, 2011]

Prodrug polymer (P_3) (0.1g , 0.003 mole) was poured in 100 ml of aqueous buffer solution such as (phosphate buffer pH 7.4) or acidic (solution pH 1.1). The buffer solution

maintained at 37℃. with continuously stirred and 3ml of sample was analyzed by UV spectrophotometer and compared with calibration curve which was obtained and computerized under similar medium. Fig. (5). Showed controlled mefenamic acid release in different pH values at 37℃.

Results and discussion

The prodrug was prepared using di functional spacer groups such as ethanol amine which was inserted between the mefenamic acid and polyacrylic acid. The carboxylic acid groups were reacted with amino groups of ethanol amine, produced amide attachment group, and the other hydroxyl groups were reacted with prepared mefenamic acyl chloride which could produce ester arm groups. This work aimed to extend the drug pended units to be easy hydrolysis through polymer chains. The high yield was obtained by reaction of polyacrylic acid and ethanol amine as spacer arm units as shown below :(scheme 1)



Scheme (1) Synthesis of P_3

The modified polymer (P_2) and (P_3) were characterized. by FTIR spectrum, Fig(1) showed the peak around 3416 cm^{-1} assigned to the –OH carboxylic group as exhibit a broad at 3200-3500 cm^{-1} of poly acrylic acid, and N-H stretching from an amide group, 3350cm^{-1} due to the hydroxyl group of substituted ethanol group, 2949 cm^{-1} of C-H aliphatic. Peak around 1700 cm^{-1} represents stretching vibration of C=O from carboxylic groups, the new absorption was appeared at 1651cm^{-1} represented the amide carbonyl. Fig(2) ^{1}H−NMR spectrum of P_2 showed the signals at δ: 2.9 ppm and 2.1 ppm assigned to the (CH−CO, 1H, T) chain, (CH_2−CH, 2H, d) chain of poly acrylic acid, δ: 2.7 ppm and 2.3 ppm assigned to the (CH−CO, 1H, T), (CH_2−CH, 2H, d) , δ: 5.0 ppm of (2H−OH, 2H, T), δ: 3.4 ppm due to (CH_2−N, 2H, T) of ethanol amide, δ: 4.2 ppm of (OH, 1H, S), δ 8.0 ppm of (NH, 1H, S) of amide, δ 10.5 ppm of (COOH, 1H, S) of carboxylic acid for poly acrylic acid.

Fig (3) shows the FTIR spectrum of mefenamic acryl amide polymer P_3 peak 3460 cm^{-1} of OH carboxylic and 3255 cm^{-1} as shoulder peak due to NH amide, 3053 cm^{-1} of C−H aromatic, the new absorption was appeared at 1718 cm^{-1} is attributed to carbonyl-ester and the other absorption appeared at 1672cm^{-1} is for carbonyl amide. Fig (4) shows the ^{1}H−NMR spectrum of polymer (P_3) signals 2.3 ppm of (2CH−CO, 4H, d), 2.6 ppm of (CH−CO, 1H, T) polymer, 2.8 ppm of (CH−CO, 1H, T), δ: 3.6 ppm of ($2CH_3$, 6H, S), δ: 3.8 (CH−NH, 2H, T), δ: 4.0 ppm (CH_2−O, 2H, T), δ: 7.0 - 7.9 ppm of M-Ring aromatic (7-H) m. for mefenamate, δ: 8.0, 8.3 ppm (NH, 1H, S), δ: 10.2 ppm (COOH, 1H, S).

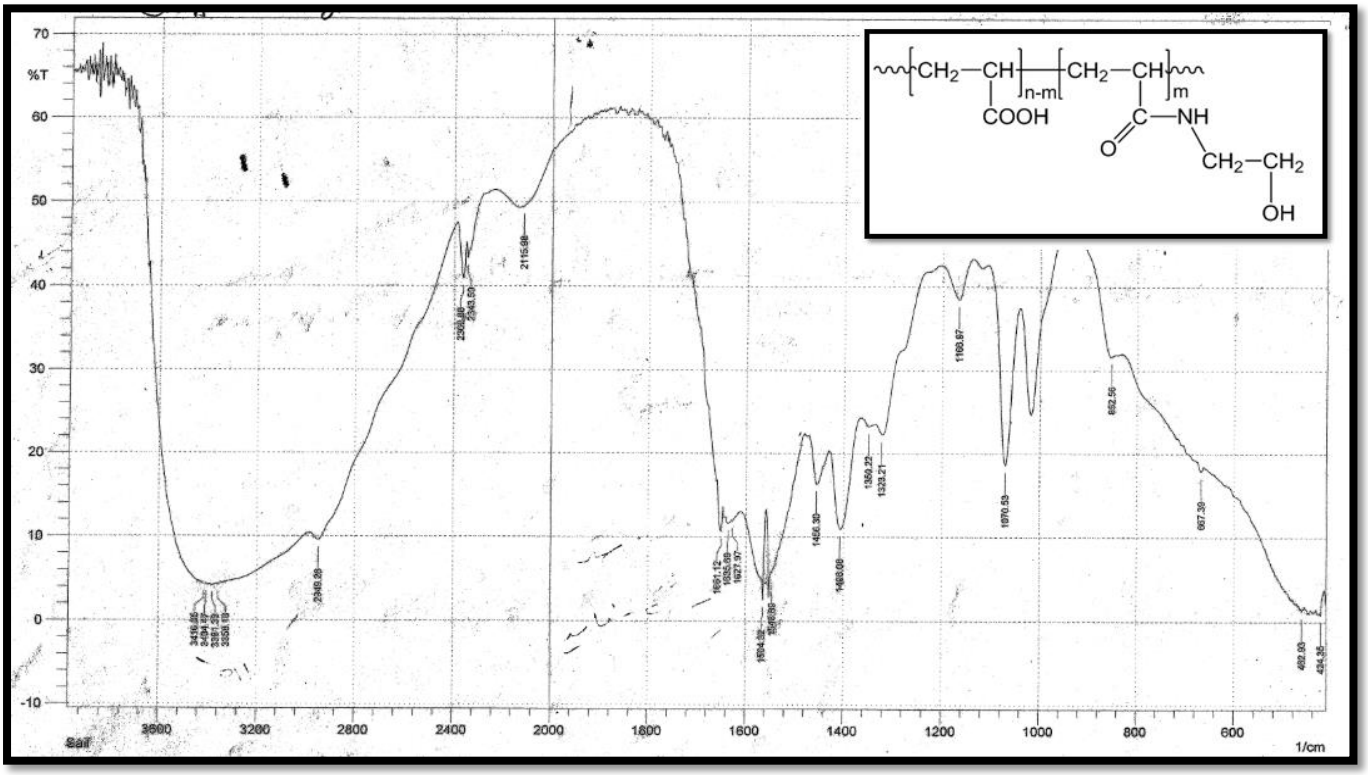


Fig (1) FTIR spectrum of ethanol acryl amide polymer (P_2)

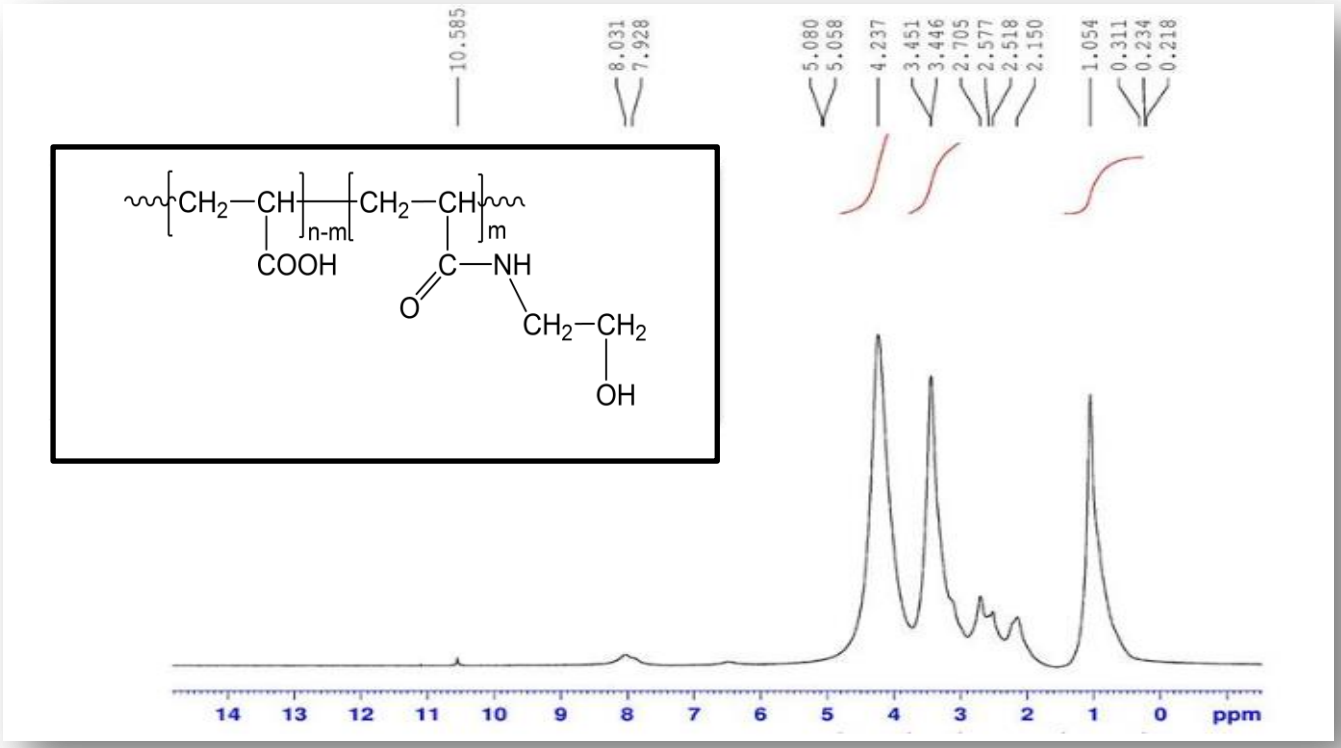


Fig (2) ^{1}H-NMR spectrum of ethanol acryl amide polymer (P_2)

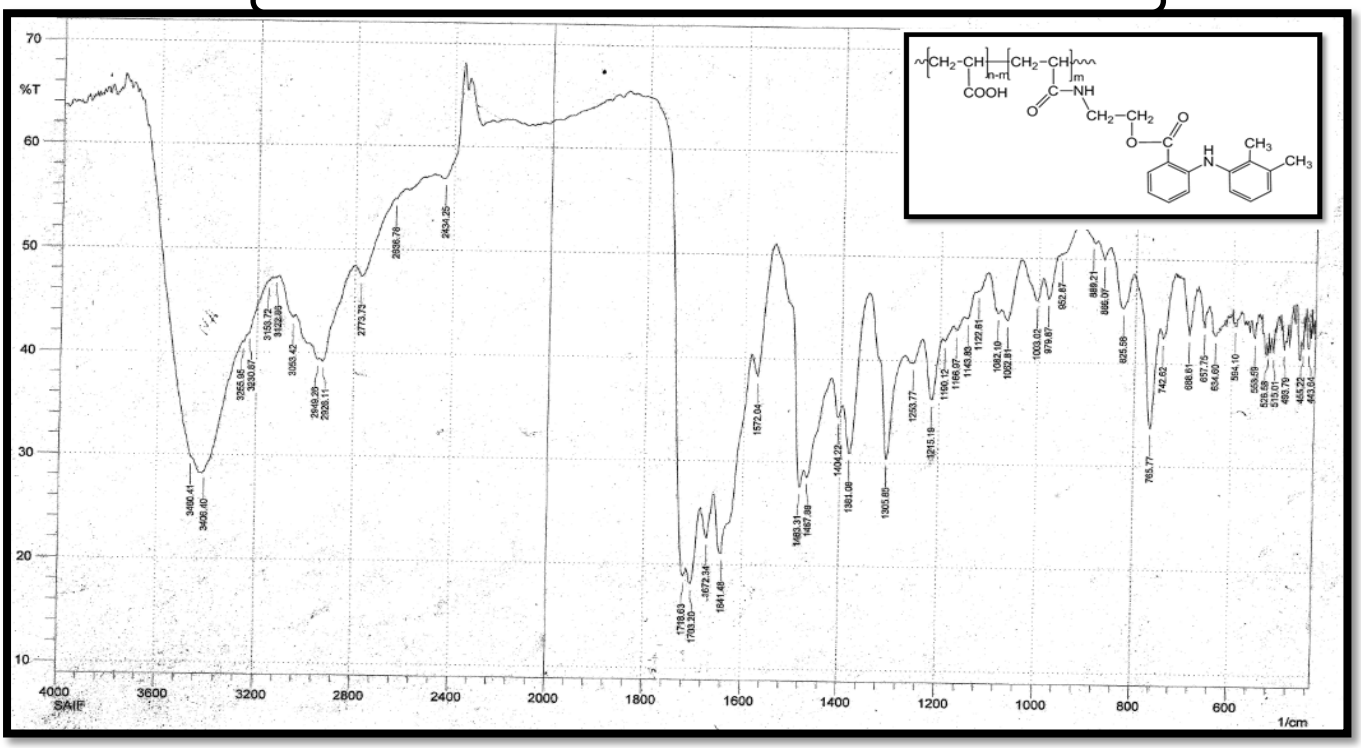


Fig (3) FTIR spectrum of mefenamic ethyl acryl amide polymer (P_3)

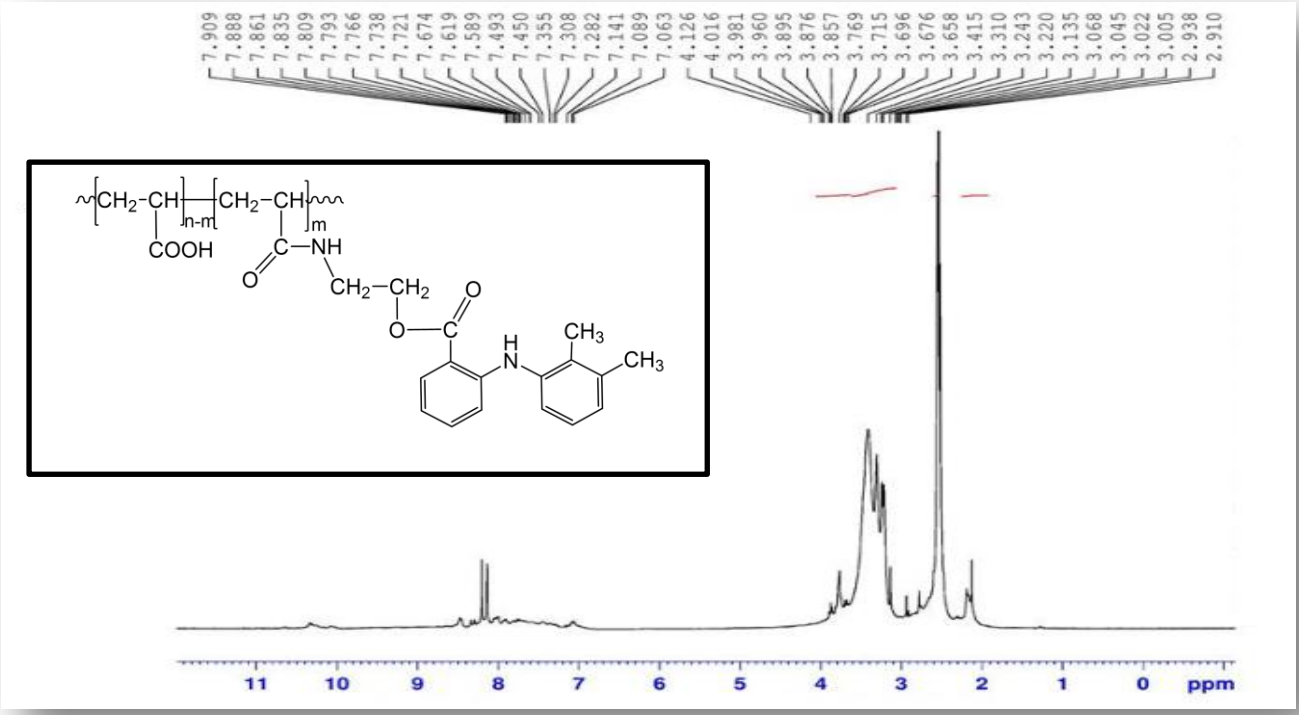


Fig (4) ^{1}H-NMR spectrum of mefenamic ethyl acryl amide polymer (P_3)

The remained carboxylic acid was 32% that was tested by titration of polymeric sample with 0.1N of NaOH in the presence of phenolphthalein as an indicator. The concept of polymeric drug has been subjected with medicine chemists as long consideration synthetic polymers. The polymer which is substituted by mefenamic acid groups enhanced for the using as prodrug polymers. The UV. Spectra of polymer (P_3) gave absorptions at 200 and 400 nm due to. (n-π*) and (π-π*) due to electron transition for drug conjugation structures.

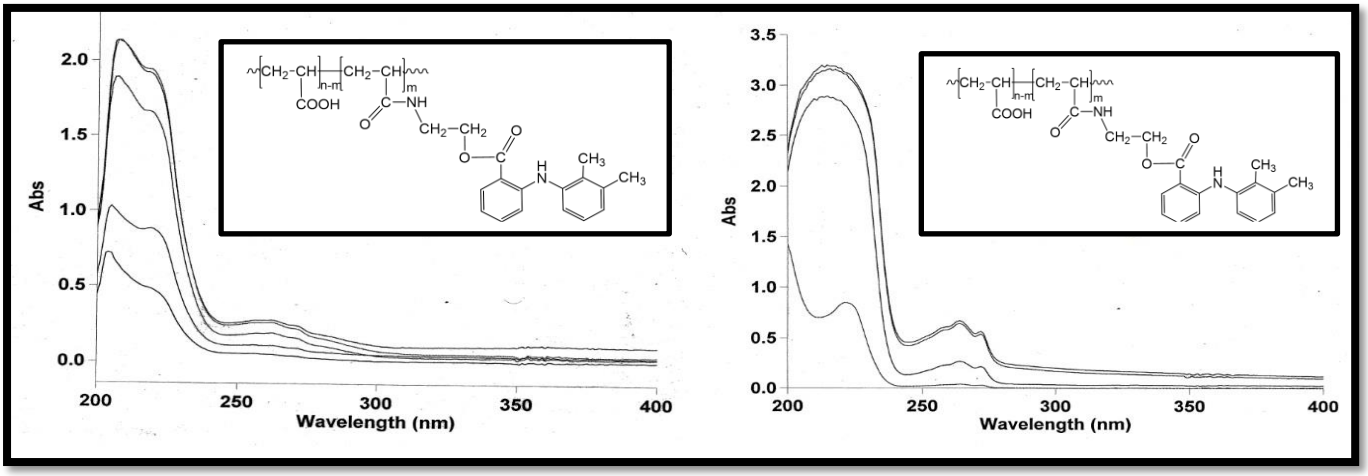


Fig (5) (A) Drug release of (P_3) in pH 1.1 and 7.4

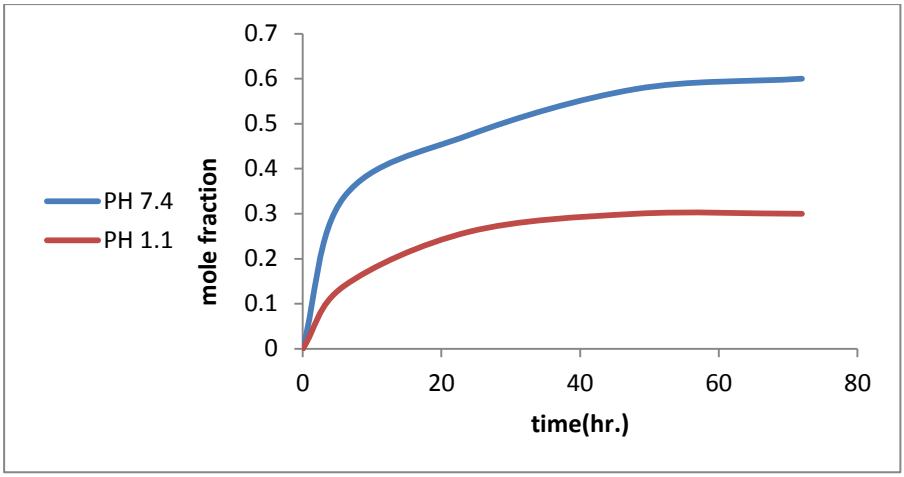
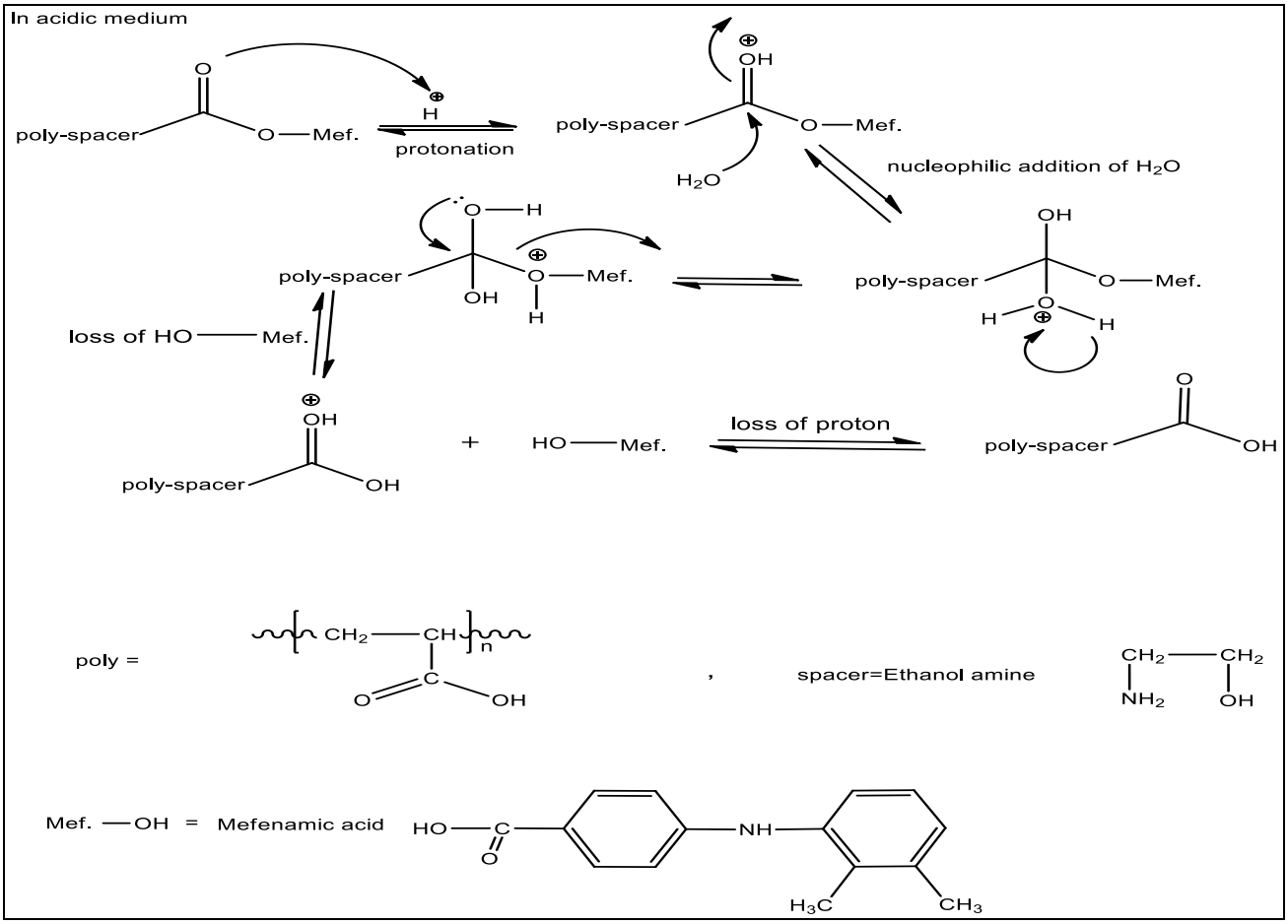
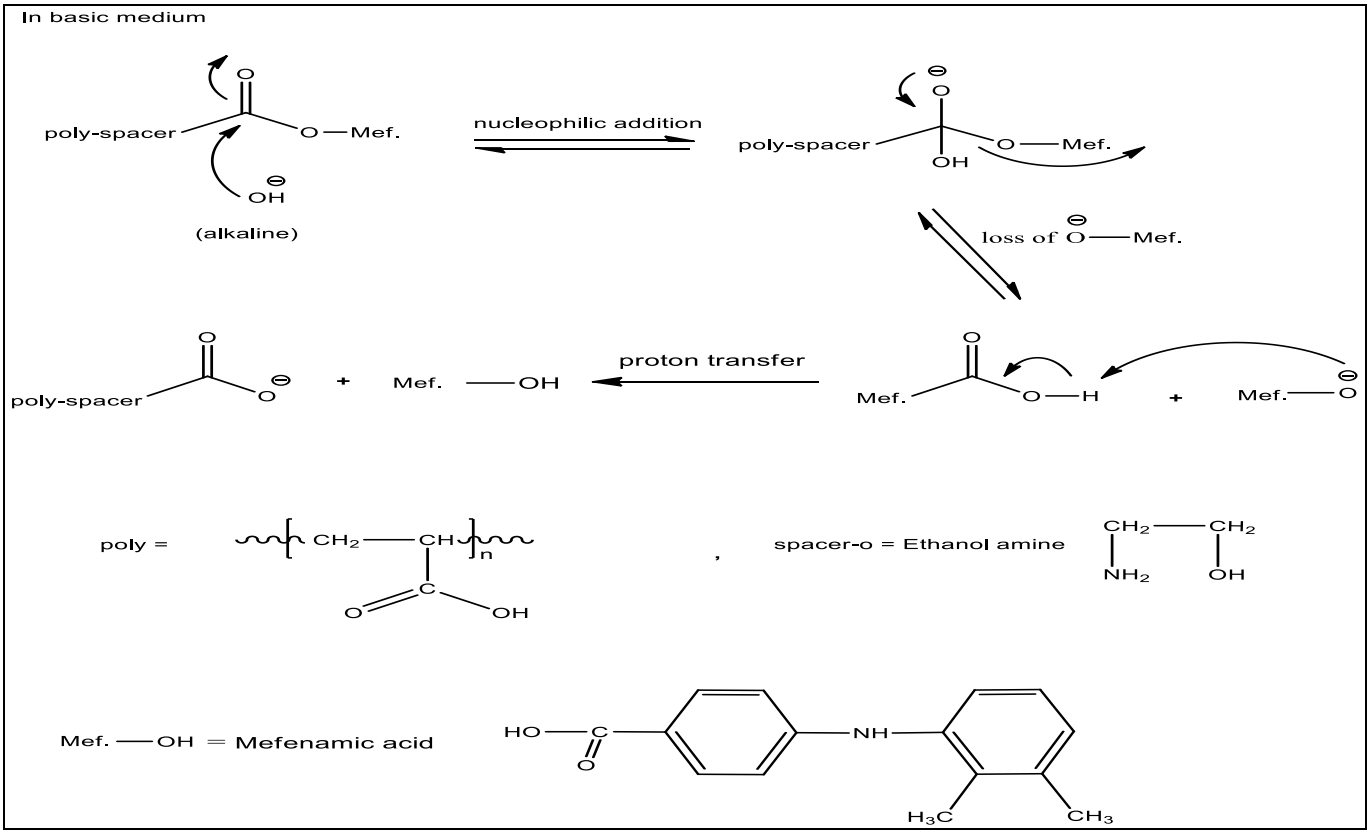


Fig (5) (B) Drug release of (P_3) in pH 1.1 and 7.4 at 37°C

The controlled release rates were studied as drug polymers which could be hydrolyzed in basic and acidic medium due to ester bonds as shown in the following mechanism:- [Firyal and Emad, 2010].



Scheme (2) Hydrolysis of (P_3) in acidic medium



Scheme (3) Hydrolysis of (P_3) in basic medium

Conclusion

In conclusion, in basic medium, the rate of hydrolysis is higher than acidic medium, due to the presence of OH^- in alkaline, which acts as a stronger nucleophilic with respect to water, the hydrolysis by water is faster than acidic medium, whene H^+ is bonded to oxygen atom of ester as shown in [Scheme (3)].The spacer effect appeared more enhancement in hydrolysis of ester or amide groups. Fig (5) showed the release profile of drug release (mole fraction) versus time. A swelling percentage of the prepared polymer was studied which equaled to 12% .The swelling% was calculated according to the following equation [Ameen, 2004].

$$\Delta m = m_1 - m_\circ / m_\circ \times 100$$

When:-

$m_\circ$ is the weight of dry drug polymer.

m_1 is the swallowed polymer in water.

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