In Vitro Study of MefenamateStarch as Drug Delivery System

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Abstract:

Mefenamic acid was esterified with starchwith[1:1] Molar ratio, as drug substituted with natural polymer, to prolongthe period of hydrolysis of drug polymer with other advantages. The new prodrug starch was characterized by FT-IR and UV-Visible and ^{1}H-NMR spectroscopies. The physical properties were studied and controlled drug release was studied in different pH values at 37^{o}C. The stability of drug was carried out by measuring the absorbance of mefenamic starch which hydrolyzed in HCl solution of pH 1.1 (artificial gastric fluid) and phosphate buffer of pH 7.4 (simulating intestinal fluid SIF) at 37^{o}C for several days. The thermal analysis such as DSC was studied.

Key words: Mefenamic acid, Starch, natural polymers, esterfication

Introduction

The action of polymeric drugs in vivo usually depends on hydrolytic on enzymatic cleavage of the drug moiety from the polymer [1, 2], this give advantage of delayed and sustained release of drug over long time with corresponding decrease of side effects [3]. It is potentially possible to make a polymer drug with specific required solubility rate of diffusion and increased or decreased 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 [4].

Poly (Vinyl Alcohol) is almost completely resistant to fungi and bacteria in dry state. Aqueous solutions are susceptible to microbial degradation [5]. In these systems, the drug molecule is chemically bonded to a polymer backbone and the drug released approach provides an opportunity to target the drug to a particular cell type or tissue affinity [6, 7].

Mefenamic acid is a non-steriodal anti-inflammatory drug used to treat pain, including menstrpain [8]. The side effects of the mefenamic acid include headache, nervousness, vomiting, diarrhea, hematemesis (blood urine), skin rash and swelling [9, 10].

Cell immobilization by means of biomass entrapment [11] within

various hydrogels is one of the progressive approaches, for the creation of immobilized biocatalyst [12, 13]. Many diverse gel matrices have been proposed as possible carriers. In these cases, ether natural biopolymers (polysaccharides such as aliginate, carrageenan, agar, …etc. or proteins such as gelatin collagen and others) or synthetic polymers (polyacrylate, polyurethanes and polyethers) can be used as the gel-forming agent.

Materials and Methods:

Materials :

Mefenamic acid was obtained from Pharmacy College, starch, dioxand, DMF and ether were purchased from Fluka.

Synthesis of Starch-Mefenamate :

In a (100 ml) round bottom flask provided with magnetic bar was introduced (5 g., 0.025 mole) of starch with 15 ml of dioxin, the prepared mefenamic acid chloride was added (g., 0.025 mole) with vigorous stirring, the mixture was refluxed for about 1 hr. the precipitate was filtered and then washed with ether for several times and the product was dried.

Table (1): The Physical Properties of StarchMefenamate

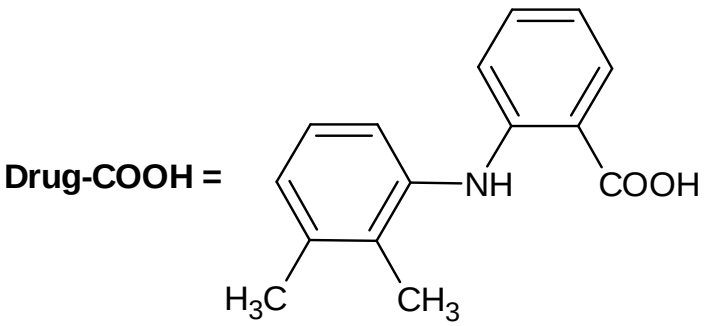
No.	Color	Softening Point ^{o}C	UV. Absorption nm	Conversion %	Δ H J/g
P_1	Brown	283.38	280- 330	80	190.9

Controlled Drug Release :

(0.1 g) of the prepared starch-drug P_1 was placed in 50 ml of buffer solution with pH 1.1 or 7.4 at 37^{o}C. At periodic intervals 2 ml of solution with tested at 280nm using UV. Spectrophotometer. The amount of the released mefenamic acid was quantified using appropriate calibration curve and figure 3 shows the mole fraction of drug release through many days.

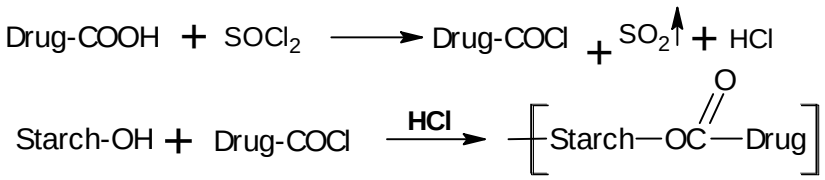
Results and Discussion

The formula of mefenamic acid is $C_{15}H_{15}NO_2$ its structure is as shown :



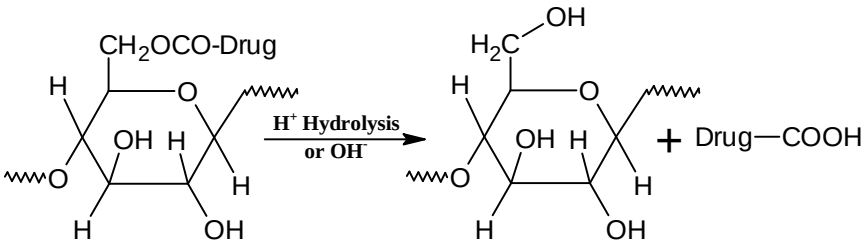
2-(2,3-dimethyl phenyl) aminobenzoic acid mol. mass 241

The acid chloride-drug was bonded with starch by esterification reaction with 1:1 molar ratio according to the following reaction:



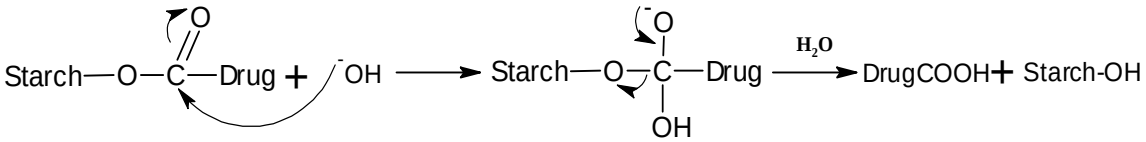
The modified starch which is bonded with drug; this polymer has been investigated in this study, using FT-IR spectrum, figure 1 of the blank sample and figure 2 of drug bonded polymer reveals the existence of peaks at 3311 and 2980 cm^{-1}, which are due to –NH of mefenamateand C-H stretching of methyl groups, respectively, the υC=O absorption was observed at 1668 cm^{-1} of ester group, these peaks confirm the polymer formation. The presence of the drug in the polymer is confirmed by the fact that peaks in the rang 3100 cm^{-1} due to C-H stretching of aromatic groups appear in the spectrum of both blank and drug bonded polymer sample; the aromatic C-H and out-of-plane peaks appear at 900-700 cm^{-1}, and C=C streatching appears at 1600 cm^{-1} in both spectra. Also, the remained OH starch have been observed at 3450 cm^{-1}.

The conventional controlled release dosage form is the inability to increase its residence time for example in pH 1.1 of small intestine, resulting in an improved and bioavailability of the basic drug and to prolong the presences of dosage form in the stomach until all the drug is released in the desired period of time, figure (3) shows the controlled drug release in different pH values at 37^{o}C, and the following equation shows the hydrolysis of drug bonded polymer through ester:



The amount of drug released was determined spectrophotometrically, the total volume of release medium was kept constant by addition of the drawal sample every time.

The hydrolysis of ester group in acidic medium was lower than alkalinmedium, this was attributed to attack OH^- as nucleophilic to carbonyl group. The mechanism is illustrated as shown below :



This study of the drug elution with time evidence that only a fraction of the total amount of the initially adsorbed drug is released and the eluted amount depends on the strength of the drug-polymer interaction and the ester group was observed as a good hydrolysis through basic medium.

The present paper aimed at developing drug-polymer models able to prevent infections associated with the use of medical devices. The drug-polymer possessing long-term drug activity, which is hydrolyzed gradually in specific site, in suitable pH values. Also, we aimed in this paper to use natural polymer such as starch to prevent any toxicity or any side effect.

The natural drug-polymer plays a significant role, in fact, high specificity of interaction together.

Swelling Behavior:

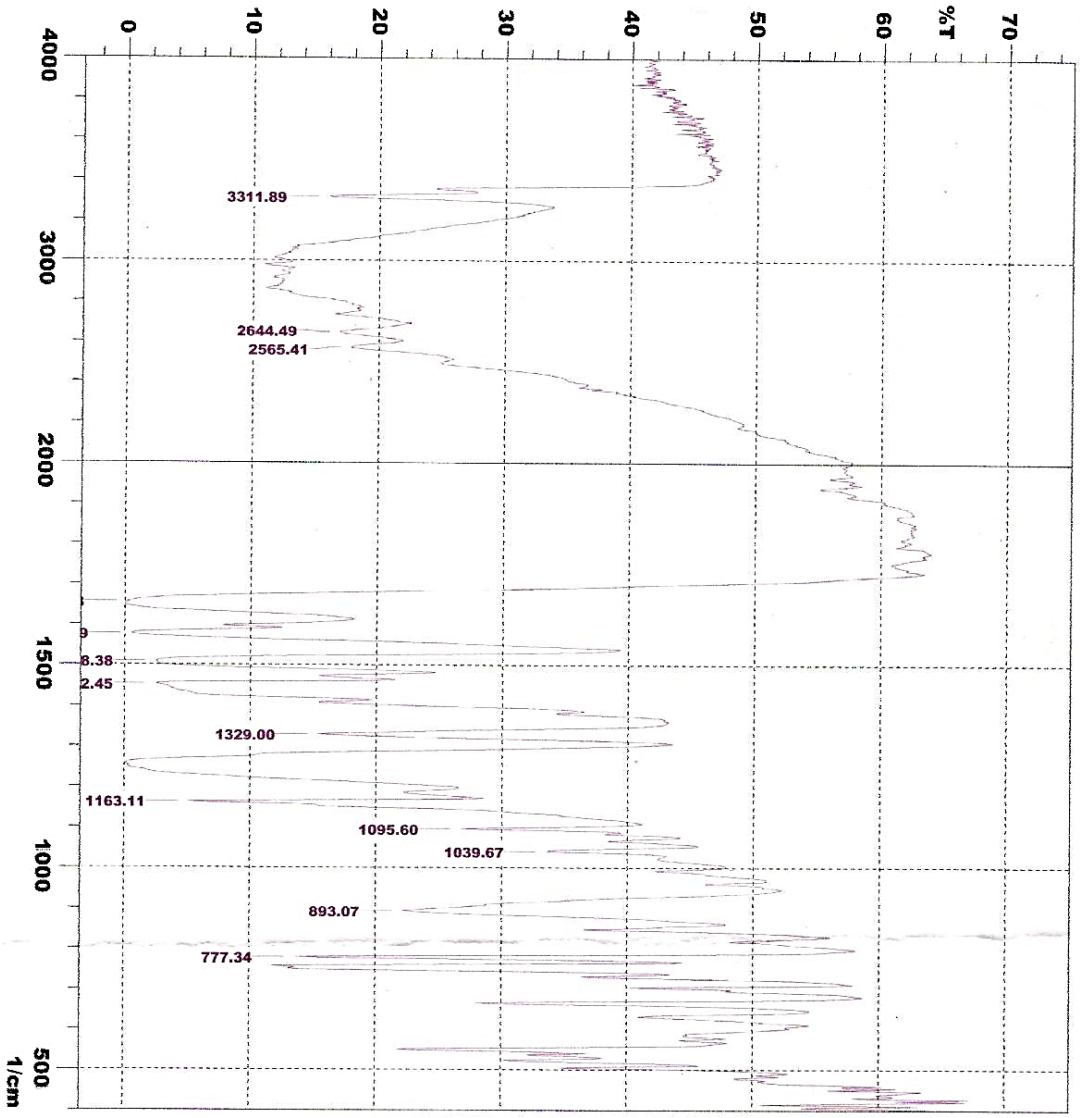
In order to study the swelling behavior 0.05g of the sample was immersed in water as swelling solution and the weight of the swollen sample was measured against time after the excess surface water was removed by gently tapping the surface with a drug pieces of filter paper. The degree of swelling was calculated using the following equation:

$$\Delta_m = \frac{m_1 - m_0}{m_0} * 100$$

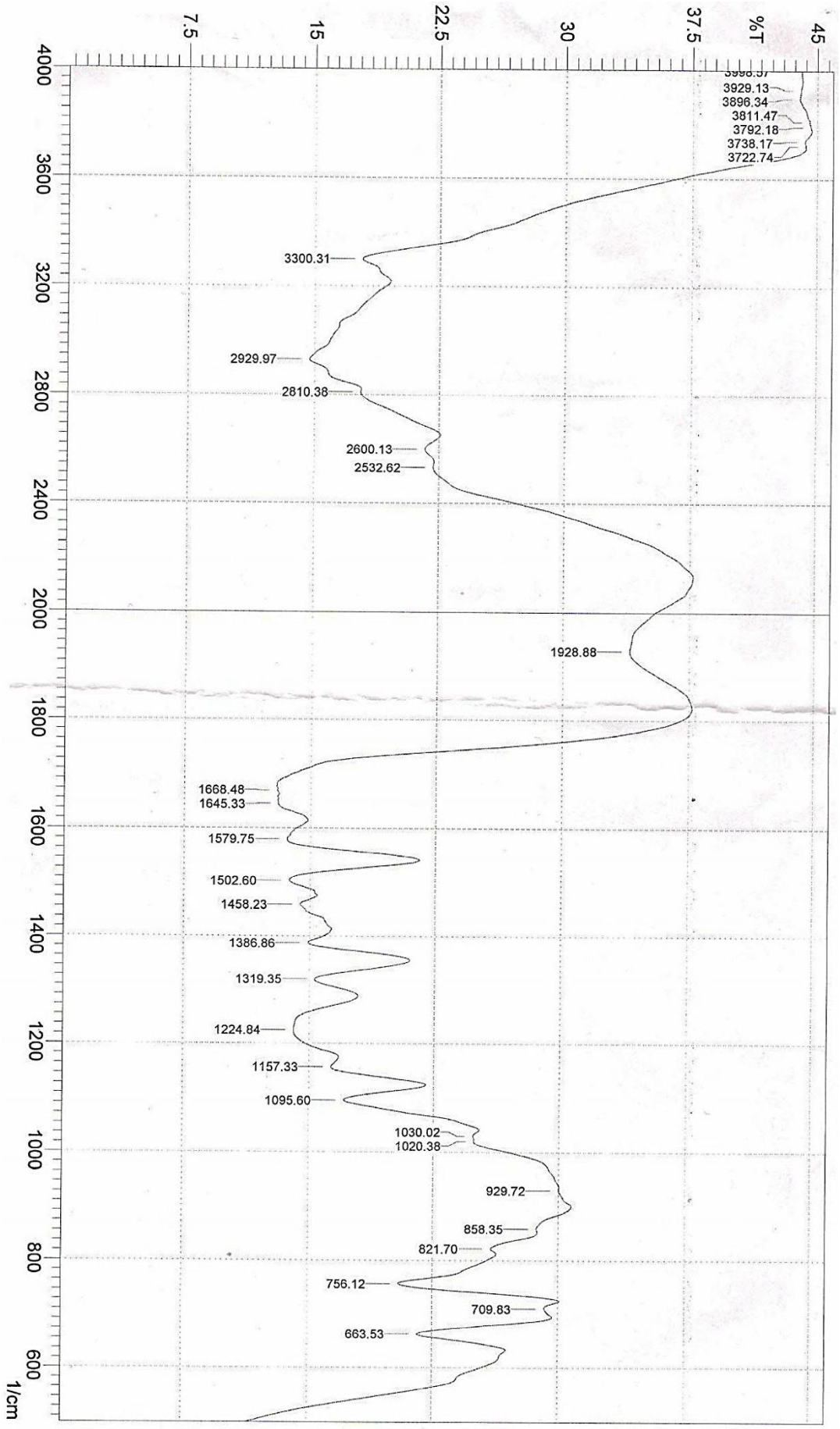
Where, m_0 is the mass of a dry polymer at t=0

m_1 is the swallowed polymer at time t.

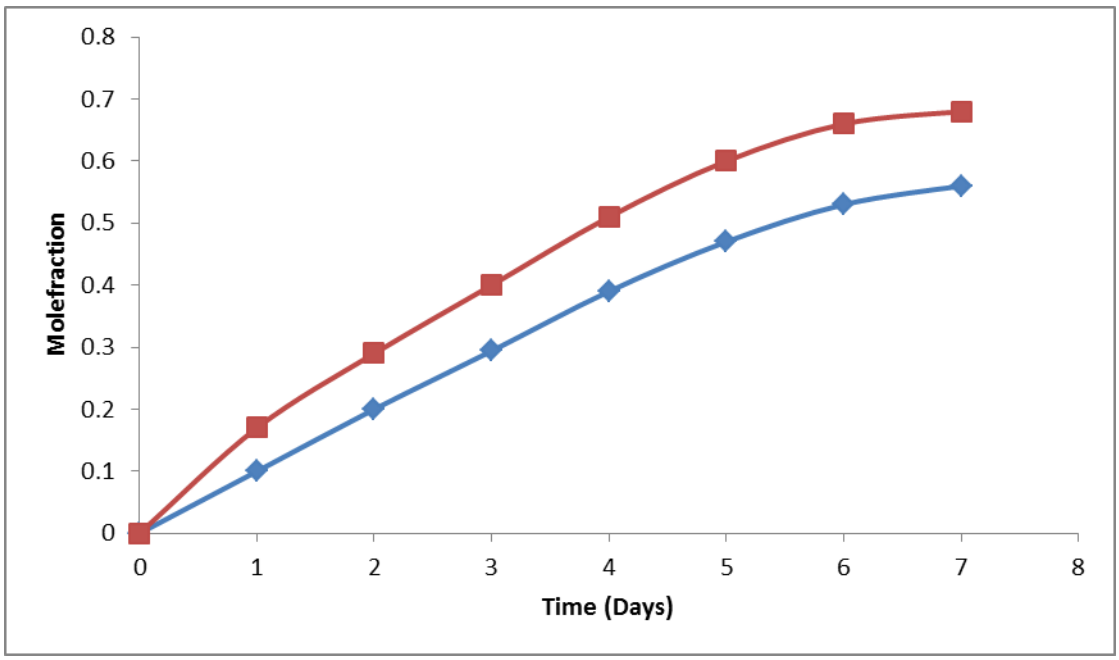
it appears that high swelling% was obtained for the prepared drug polymer through 1 hr.



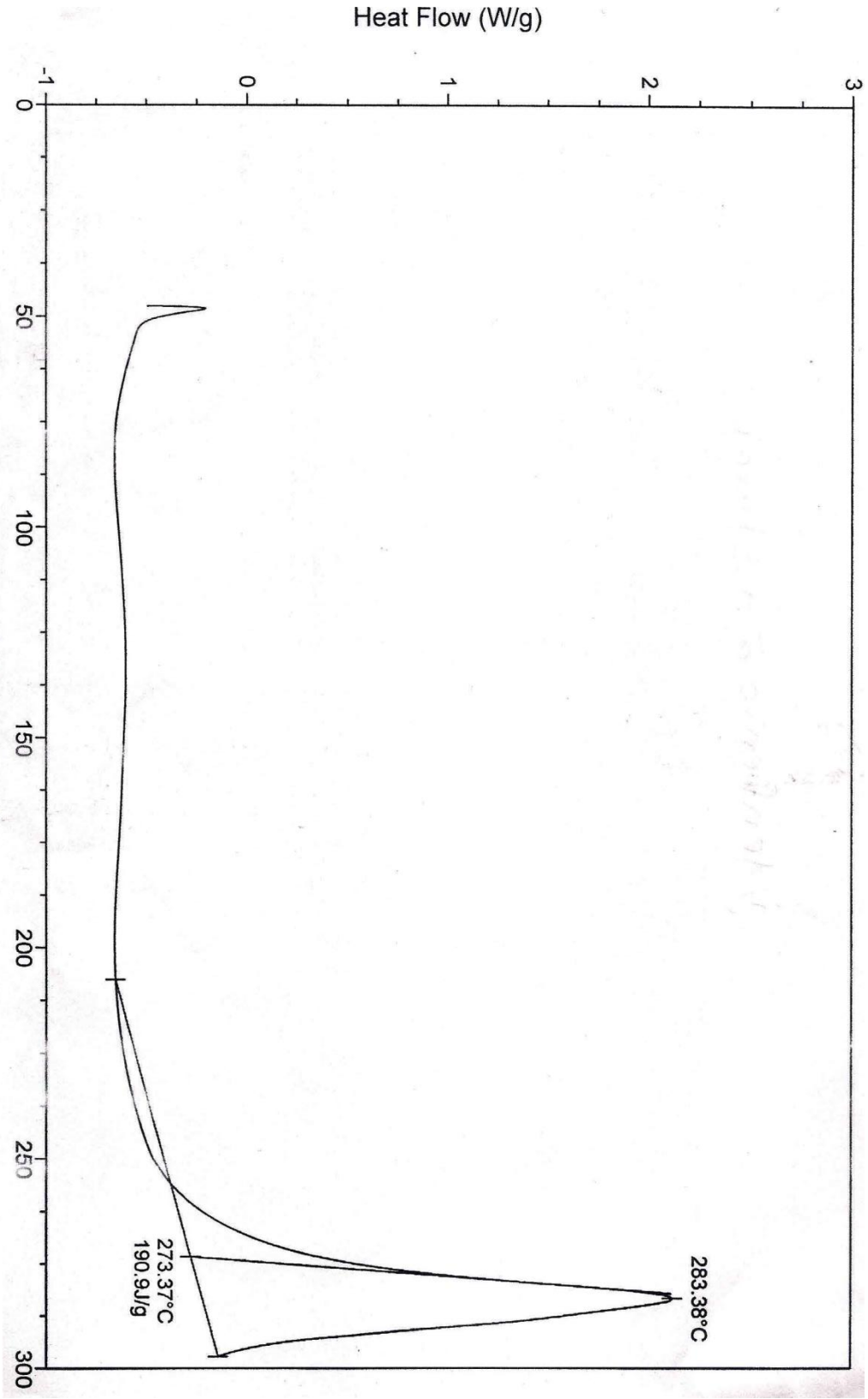
Fig(1): FT-IR Spectra of Mefenamic Acid



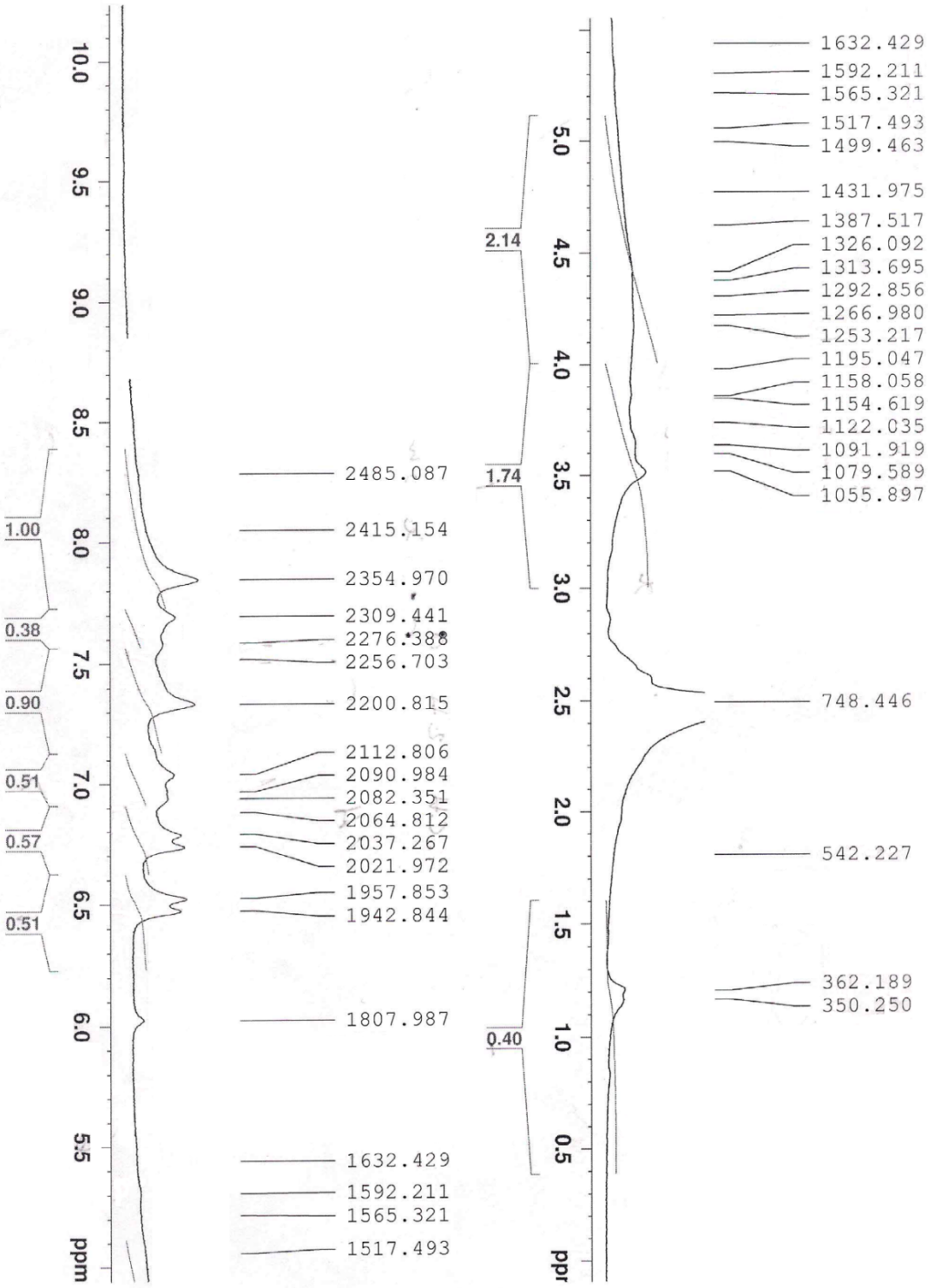
Fig(2): FT-IR Spectra of Starch-Mefenamate



Fig(3): Controlled Drug Release of Mefenamic Acid in pH 7.4 and 1.1 at 37^{o}C



Fig(4): DSC Analysis of Drug Polymer P_1



Fig(5) ^{1}H-NMR Spectrum of Drug Polymer P_1

Figure 4 shows the DSC analysis, which recorded the softening point=28338^{o}C and ΔH=190.9J/g for the prepared drug polymer P_1.

Figure 5 shows the ^{1}H-NMR spectrum, which indicated the signals were observed of the following:

Part 1 indicated the menfenic aromatic rings δ6-7.8ppm included 4CH, 4H

and 3CH, 3H d.d. and $2CH_3$ s. at 2.5ppm, the NH, s. signal was observed at 4.5ppm.

Part 2 included 5 CH-O 5H d-d and CH_2-O 2H d. (δ3.5-4.0)ppm and some unreacted –OH group at δ4.5ppm as a broad signal.

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دراسة حيوية لبوليمر المفينـاميت – النشا كنظام دوائي جديد

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الخلاصة:
تم أسترة حامض المفينامك مع النشا بنسبة مولية [1:1] كتعويض دواء على بوليمر طبيعي لغرض إطالة فترة التحرر الدوائي ولفوائد أخرى. شخص البوليمر الدوائي الجديد بواسطة طيف الأشعة تحت الحمراء والأشعة فوق البنفسجية وطيف الرنين النووي المغناطيسي. قيست الصفات الفيزيائية ودرست سرع التحرر الدوائي المحكم بدوال حامضية 1.1 و7.4 للمعدة والأمعاء وبدرجة 37^{o}م.