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Preparation of Poly (N-Cephalexin Amic Acids) as Drug Polymers

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الخلاصة:

حضر في هذا البحث المونومرات N– سيفالكسين حامض المالي اميك M_1 و N– سيفالكسين حامض الستراكونيك M_2 من تفاعل السيفالكسين مع حامض الماليئك او الستراكونيك اللامائي وبدرجة حرارة الغرفة باستخدام الدايوكسان مذيبا.

بلمر المونيمران المحضران M_1 وM_2 بالجذور الحرة باستخدام AIBN بادئا, الى البوليمرات المقابلة P_1و P_2, ثم حولت الى املاح الصوديوم للبوليمرات المحضرة P_3 وP_4 لتسهيل قابلية الإذابة بالماء.

درست الصفات الفيزيائية للمونمرين المحضرين والبوليمرات المقابلة، ثم شخصت بواسطة استخدام أطياف الأشعة تحت الحمراء والرنين النووي المغناطيسي والأشعة فوق البنفسجية ووتم قياس اللزوجة الجوهرية باستخدام استوالد فسكوميتر بدرجة 30 م واستخدام DMF مذيبا، كما تم قياس سرع التحرر الدوائي للسيفالكسين وكانت في الوسط القاعدي أعلى من الوسط ألحامضي.

درجة التلين للبوليمر P_1 تساوي ^0C 130.23–138.35 والطاقة المصروفة لقياس درجة التلين هي 190.17mj ودرجة التلين للبوليمر P_2 تساوي ^0C 207–220.

Abstract:

In this work new monomers have been prepared such as N-Cephalexin maleamic acid M1 and N-Cephalexin citriconamic acid M_2, from reaction of Cephalexine with maleic anhydride and citraconic anhydride at room temperature using dioxane as a solvent.

The new prepared monomers $M_1$and M_2 were polymerized free radically with AIBN as initiator to their corresponding poly amic acids P_1 and P_2. Which were converted to their sodium salt polymers P_3 and P_4 to enhance their solubility in water.

The physical and chemical properties were studied; the prepared monomers and polymers were characterized by FTIR, ^{1}H-NMR and UV. Spectroscopy, the intrinsic viscosity was measured by Ostwald viscometer at 30 ^{0}C with DMF as a solvent; the drug release rate was studied. Experimental results showed that the hydrolysis of Cephalexin in alkaline medium was higher than acidic medium.

The softening point of the prepared P_1 drug polymer was 130.23-138.35^{0}C with −190.17mJ as used to need in softing point, and softening point of the prepared P2 was 207-220^{0}C.
Keywords: Cephalexine; Amic Acids; Drug Polymers

Introduction:

Cephalexin is chemically 7-[(amino-phenyl acetyl) amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid Fig.-1, belongs to the first generation cephalosporins, intended for oral administration. With the brand names of Ceporex (or Keflex) in the US, Novolexin in Canada, and many others outside North America, cephalexin is one of the top 20 drugs used in prescriptions worldwide. The first-generation cephalosporins have the highest activity against gram-positive and gram-negative bacterias [1].

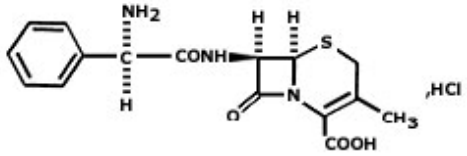
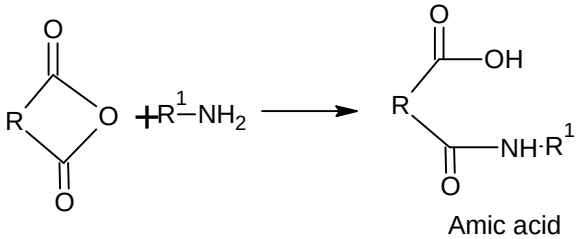


Figure 1: Structure of Cephalexin

Mechanism of action of Cephalexin is same as that of beta-lactam antibiotics (such as penicillins). It acts by binding to specific penicillin-binding proteins located inside the bacterial cell wall and inhibits the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins; it is possible that it interferes with an autolysin inhibitor. Cephalexin inhibits mucopeptide synthesis in bacterial cell wall, causing cell death [2,3].

The polyamides were prepared from reaction of acid anhydride such as phthalic anhydride, maleic anhydride or naphthalic anhydride with different amines, the reaction is as follow [4,5,6]:

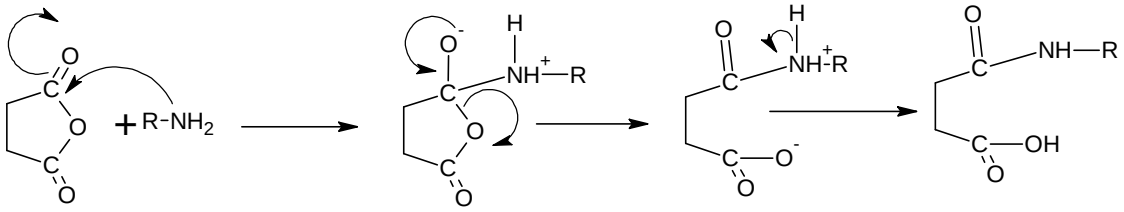


Amic acid

R = alkyl , aryl

R^1 = H , alkyl , aryl

Amic acids were prepared according to literature procedures from reaction of cyclic anhydrides with aromatic or aliphatic primary amines. Different solvents were used such as benzene, acetone, dioxane, tetrahydrofurane, diethylether or dimethyl formamide, the mechanism of the reaction is as the follows [7,8]:



Material and Methods:

Cephalexin was obtained as a gift sample from Samarra Drug Company, Maleic anhydride and Citraconic anhydride were purchased from Fluka and Merck.

All other chemicals used in the study were of analytical grade.

FTIR spectra were recorded on a Shimadizu spectrophotometer. Ultra violet spectra was recorded using Shimadizu UV-VIS. ^{1}H-NMR spectra was recorded on a Fourier transform Varian spectrometry, company Bruker, model, Ultra shield 300MHZ, origin: Switzerland,with titra methyl silane as internal standard in DMF measurements were made at the Chemistry Department, AL-Yarmouk University, Jordan. Differential Scanning Calorimeter (DSC) study was carried out on a Shimadzu 60 instrument (Japan) at a heating rate of $10C^{0}$ min^{-1},under air (normal), not vacuum, temperature range from -140 ^{0}C temperature up to 600 ^{0}C. The detector type K for the furnace temperature as shown in Fig.-2. C.H.N analysis was determined by analyzer type 1106 Carlo Irba.

Preparation of N-Cephalexin maleamic acid M_1 and N- Cephalexin citriconamic acid M_2:

To solution of maleic anhydride or citraconic anhydride (0.01 mole) was dissolved in dioxane was added Cephalexin powder (0.01mole) dissolving in dioxane was drop wise.

The mixture of solution was stirred 1hr at room temperature, until the yellowish –white product of monomer was obtained; the yield was recrystillized from ethanol. Table-1 shows the physical properties of M1 and M2 monomers.

No.	m.p ^{0}C	Color	Yield %
M1	70-71	Yellowish-white	90
M2	68-69	Yellowish-white	85

Table-1: physical properties of prepared amic acid monomers

Polymerization of M_1&M_2 to P_1&P_2

In a screw capped polymerization bottle, 3g. of N-Cephalexin maleamic acid or N- Cephalexin citriconamic acid were dissolved in 15 ml of dioxane, 0.05% of the monomer weight of azobisisobuteronitrile was added. The bottle was flushed with nitrogen for few minutes inside a glove and firmly stopped. The solution was refluxed for 1h. At 70 ^{0}C .The pale-yellow solid that separated out was filtered washed with ether and dried, it was recrystallized from ethanol. The brown residue of polymer was obtained, washed three times with ether, dried in a vacuum oven. Table-2 shows the physical properties of prepared polyamic acids P_1&P_2.

No.	Softening point ^{0}C	Color	Conversion%	Swelling % in hexane	Intrinsic viscosity $[h]_{in}$=dl/g
P_1	130.23-138.35	pale-yellow	80	6	0.77
P_2	207-220	pale-yellow	84	10	0.81

Table-2: Physical properties of prepared Cephalexin amic acid P_1&P_2.

Conversion of P_1&P_2 to their corresponding sodium salts P_3&P_4:

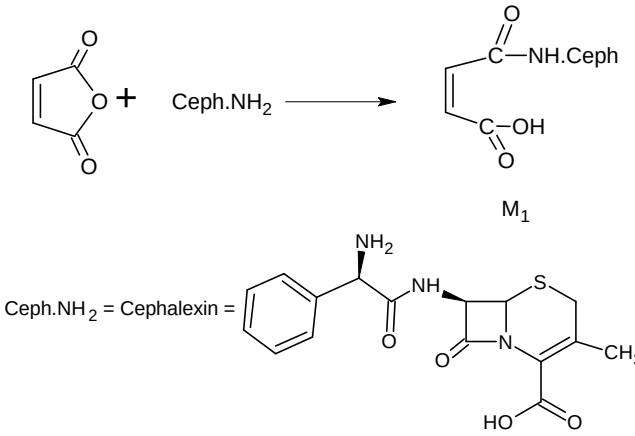
The new prepared polymer P1&P2 (2g) was dissolved in 10 ml of (5% of NaOH solution). The reaction mixture was then concentrated and the residue was washed with ethanol, filtered and dried.

Studying of Controlled release of drug polymer: (9,10)

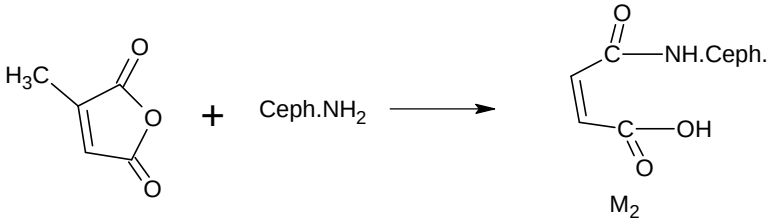
A mixture of 50:50ml of dioxane and solution in (pH4, pH 10) was kept in a cylinder 100 mg of P_1 or P_2 wad added, kept at 37C^0 with out stirring, release sample was periodically drown with an analysis by UV spectra at 300 nm to determine the amount of release Cephalexin. A calibration curve was constructed with soft ware built in the computerized UV photometer and the controlled release polymer were carried out in different pH value (pH4, pH 10) at 37 ^{0}C.

Result and Discussion:

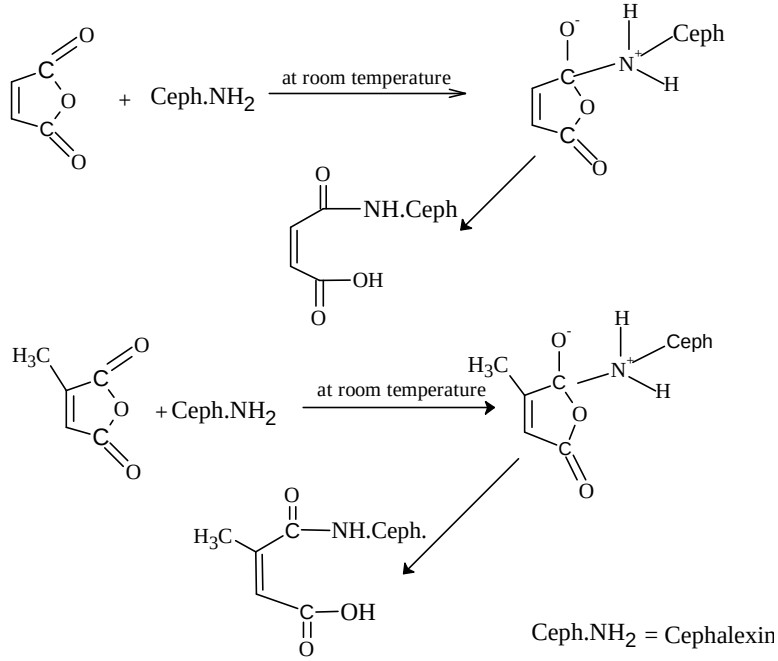
The objectives of the present work was to prepare new drug polymers and studying their controlled release of free drug units gradually at different pH values in order to prolong the steps of a hydrolysis of drug polymer through amide groups. Advances in polymer science have led to the development of several novel drug delivery systems. A proper consideration of gradually hydrolysis in the designing of polymers for various drug delivery applications. Biodegradable drug delivery to non-toxic monomers[6]. M1 monomer was prepared from reaction of maleic anhydride with cephalexin producing N-Cephalexin maleamic acid monomer, as shown in the following equation:



and M_2 was prepared from reaction of citraconic anhydride with cephalexin as illustrated in the following equation:



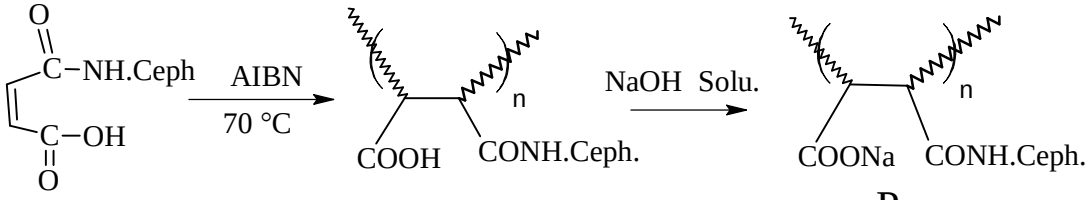
The mechanism of ring opening of acid anhydride was illustrated as in scheme [7].



Scheme-2: Shows the ring opening reaction of acid anhydride by nucleophilic reaction.

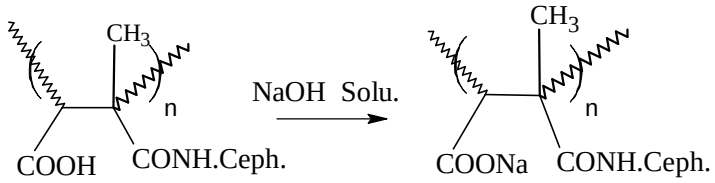
The FT-IR spectra of prepared monomer M_1 and M_2,shows the disappearance of the characteristic bands of the primary amine υ (NH_2) have two bands in the range 3500-3300cm^{-1}, and disappearance of the characteristic bands of the anhydride bands near 1820 and 1750 cm^{-1} and the appearance of secondary amides have one band υ (-NH) at about 3300cm^{-1} and υ (C=O) at 1700cm^{-1} and the appearance of carboxylic acid very broad of υ(-OH) at 3400-2400cm^{-1}.

The prepared drug polymers P_1 and P_2 were prepared from polymerization of M_1&M_2 freeradically using AIBN as initiator at 70C^0 as described in the following equation :



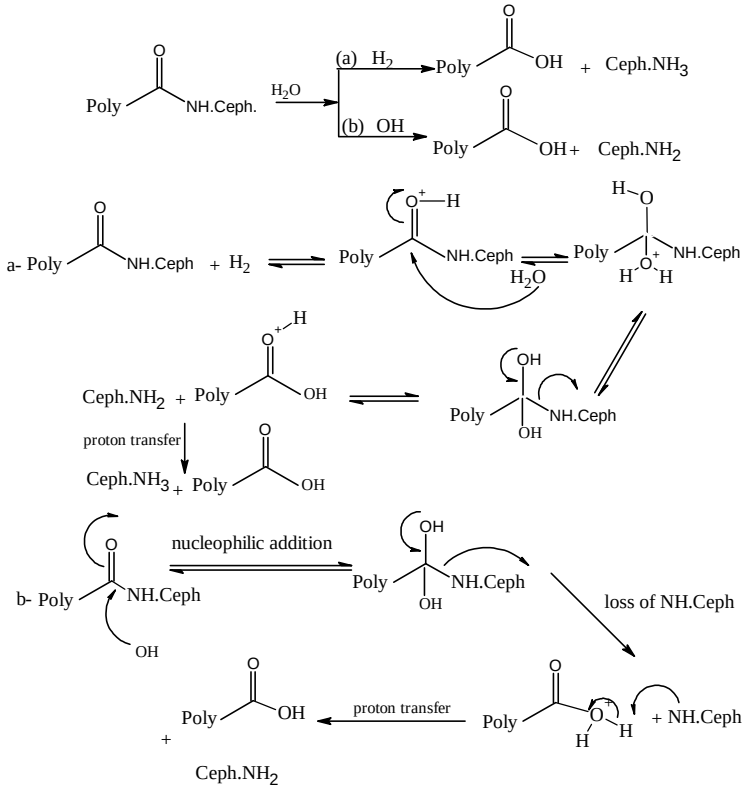
P_1 P_3

The P_2 was prepared and its sodium salt to enhanced the drug solubility as in P_2 to P_4



P_2 P_4

These biodegradable polymers offer a novel drug delivery system which is convenient to patient. Fig-2 and 3 shows the effect of pH 4 and pH 10 values at 37 ^{0} C on rate of release and the profiles of mole fraction of cephalexin ratio to total moles present in the sample versus time at pH 4and 10 at 37 ^{0} C, an analysis was determined by UV. Spectra and 290nm .and the calibration curve was constructed with soft ware built in the computerized UV photometer. The controlled release cephalexin as antibiotic which released from hydrolysis of polymer as shown in the following mechanism[8]:



The main key advantages of polymeric drug are sustained delivery of drug; stabilization of the drug, release rate is less dependent of the drug properties and steadier release rate with time.

The ^{1}H-NMR spectrum of amide polymer was shown in (Fig-5) indicating the signal assignments in the corresponding formula, which shows the following peaks:

δ -CH_3 at 1.1ppm , δCH_2- 1.9ppm , δCH at 2.1ppm , δ CH=CH aromatic ring at 8 ppm,
δ -NH at4ppm, δ CO-NH- amide 7.5ppm, δ –$COOCH_2$ at 4.8ppm. for δ –COOH of 10ppm.

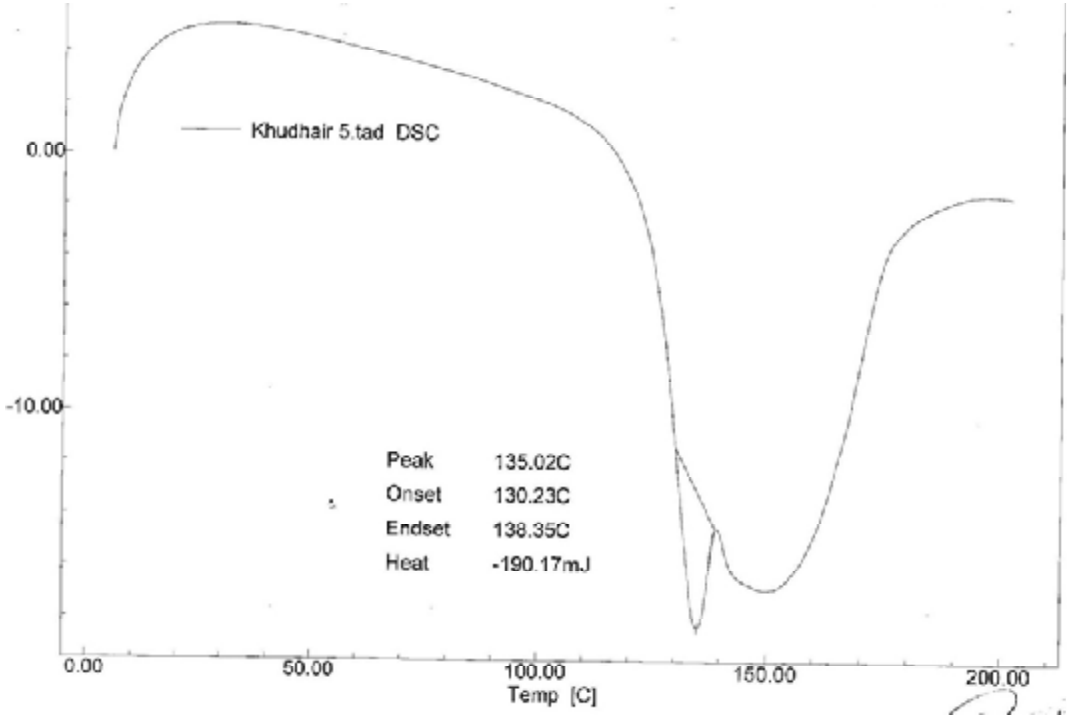


Figure-2: Thermal Analysis (DSC) Result of P2 polymer

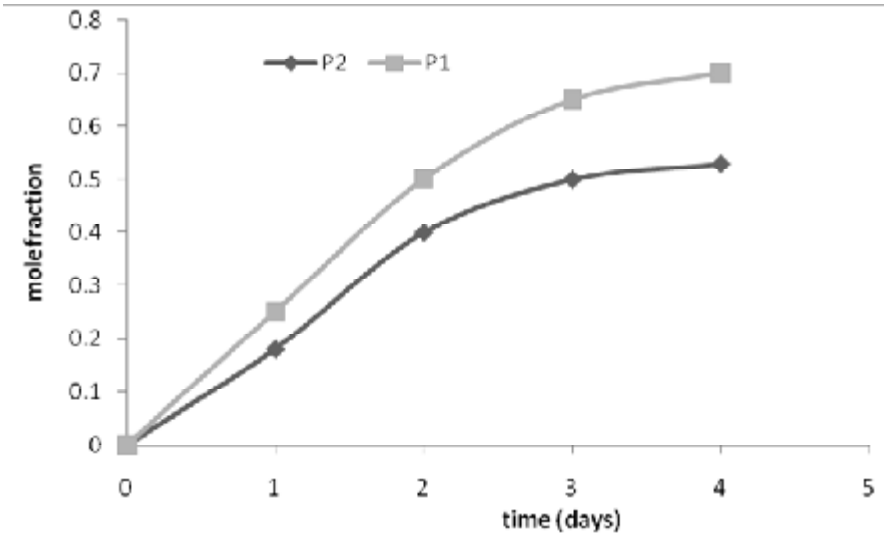


Figure-3: Controlled release of P1& P2 in pH10

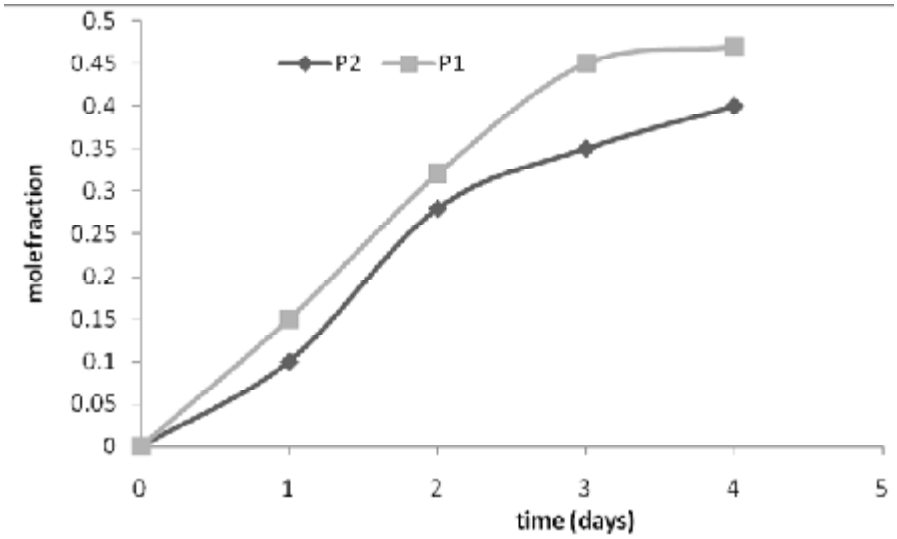


Figure-4: Controlled release of P1& P2 in pH4

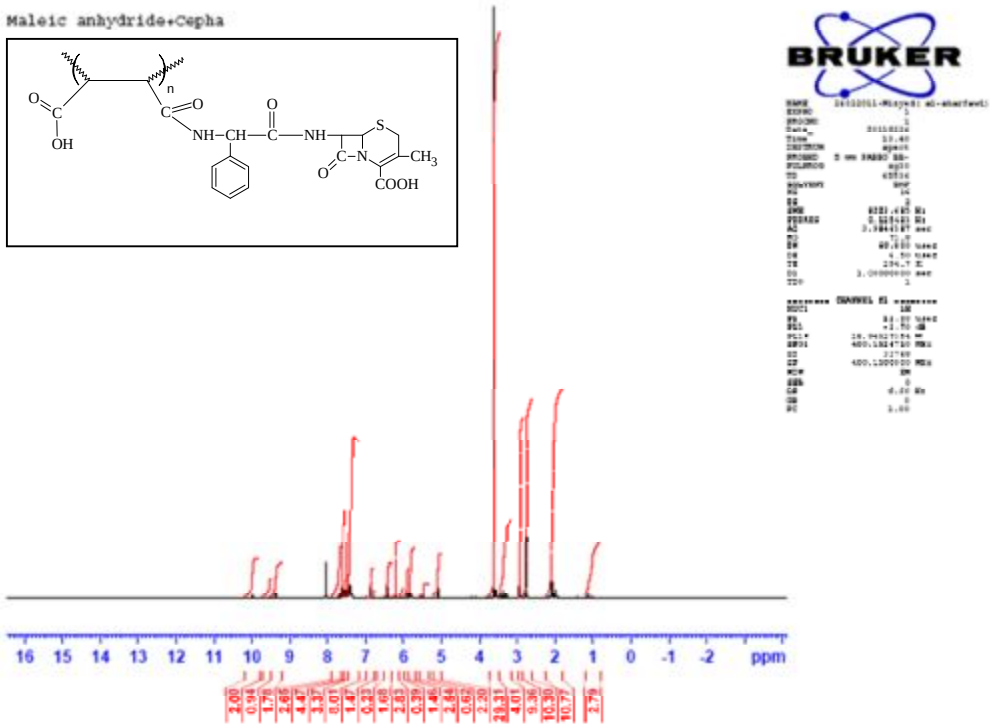


Figure-5: ^{1}H-NMR spectra of N-Cephalexin maleamic acid

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