

**Preparation of Starch Grafted Methyl Nadic Anhydride and Substituted  
with Amino Drug**

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**Abstract**

The aim of this work is to improve pharmaceutical and therapeutic drugs to enable delivery to the right place, this format of carries for controlled delivery of therapeutic agent which could Release a small amount of drug over a long period of time, by graft copolymerization of methyl nadic anhydride (MNA) onto starch (M1) ,due to its biodegradable, not harmful, and slow digesting nature . It was carried out by using ceric ammonium nitrate (CAN) as an initiator, the graft copolymer was substituted with trimethoprim (M1C) as amino drug, the new prepared drug copolymer was characterized by FTIR, 1H-NMR and UV Spectroscopes. The physical properties were measured. The drug copolymers were prepared, analyzed in various pH values at (37 OC) as in vitro study and the release of controlled drugs was compared through many days analysis.

**Keywords:-** Starch, methyl nadic anhydride, Trimethoprim, Copolymer, Drug Copolymer.

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تحضير نشأ مطعم بالمثل نادك انهريد وتعويضه بالتريميثوبريم

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الخلاصة

يهدف هذا العمل على تحسين الخاصية العلاجية للدواء لإيصاله الى المكان الصحيح، ان تصميم هذا البوليمر الحامل للدواء يستخدم لإيصال الدواء بحيث يحرر كمية منه بفترة زمنية أطول، من خلال تطعيم المثل نادك انهريد على النشا MI، بالإضافة الى كونه غير سام، قابل للتحلل، وبطيء الهضم. وتم التطعيم باستخدام نترات سريك امونيوم كبدئ مولد للجذور الحرة على الهيكل البنائي للنشأ، والبوليمر المطعم المحظر تم تعويضه بالدواء الاميني مثل تريميثوبريم MIC، البوليمر الدوائي الجديد تم تشخيصه بواسطة طيف الرنين النووي المغناطيسي، طيف الاشعة تحت الحمراء، وكذلك بطيف الاشعة فوق البنفسجية. وقيست صفاته الفيزيائية، تم تحليل البوليمر الدوائي المحظر في اوساط حامضية مختلفة بدرجة حرارية (37) درجة مئوية خارج جسم الكائن الحي وسجلت كمية التحرر الدوائي عند الزمن صفر لحد 4 ايام .  
**الكلمات المفتاحية:** - النشأ، مثل نادك انهريد، تريميثوبريم، البوليمر المشترك، الدواء البوليميري.

Introduction

Development of polymers, by changing their structures and characteristics in response to environmental motivate such as pH, temperature and sun light, has attracted a large interest.<sup>[1,2]</sup> Starch as comparatively inactive structures, which are composed of macromolecules coordinated in a polycrystalline state.<sup>[3]</sup> Starch is obtainable of all natural polymers. It is a high polymer consist of repeating (anhydrous glucose units) and, mostly, a mixture of stringy and branched components.<sup>[4]</sup> Graft copolymerization Is a mechanism to modify the chemical and physical characteristic of synthetic and natural polymers.<sup>[5]</sup> Chemical modification for the glouose molecules via vinyl graft copolymerization led to add new properties and more tissue engineering interest [6-8] . It can be applied to product biocompatible materials in

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pharmaceutical and medical implementation<sup>[9]</sup> firstly, free radical-initiated methods could achieve starch graft copolymers. affirmation is placed on high-energy ionization radiation and redox systems<sup>[10]</sup> Grafting is Which are generally considered the result of proliferation by radical sites generated on the polymer substrate. many studies investigated the graft copolymerization of vinyl monomers such as N-vinyl pyrrolidone onto gelatin, methyl methacrylate (MMA) onto curdlan, methyl acrylate (MA) onto potato starch, methacrylic acid onto starch, acrylic acid on to starch, (MA) onto sago starch, and vinyl pyrrolidone onto chitosan.<sup>[11-13]</sup> In this article we report on the grafting of methyl nadic anhydride onto starch using ceric ammonium nitrate (CAN) then substituted with amino drug such as Trimethoprim. Drugs work out with these polymers can be released in a specific side, by which the drug concentration in The targeted location is enhanced. The rates of drug release can be controlled from biodegradable polymers by biodegradation kinetics of the polymers.<sup>[14]</sup> Trimethoprim was first used in 1962.<sup>[15]</sup> It is mainly used in the treatment of bladder infections, other uses include for travelers' diarrhea and middle ear infections, it is always used in the treatment of urinary tract infections,<sup>[16]</sup> so it has a broad spectrum of antimicrobial activity. it is active with against Gram-positive, aerobic bacteria such as Staphylococcus epidermis's, Gram-negative, aerobic bacteria such as most E. coli, Common side effects include nausea, changes in taste, and rashes. This rarely leads to blood problems such as insufficient platelets or white blood cells, May cause sun sensitivity.<sup>[3]</sup> it makes to undermine the folate metabolism of some bacteria<sup>[17]</sup>. The aim of this research is to improve the drug delivery which can release a small amount of drug over a long period of time, and to decrease the other side effect.

### Experimental

#### **Instrumentation**

Melting points were measured using Thermal Microscope (Kofler-method), and Reichert thermovar, Stuart SMP 30. Infrared spectrophotometer measurements were performed using Shimadzu FT-IR 8400 series Fourier Transform, U.V-Visible double beam scanning spectrophotometer VARIAN (UV-Vis)-100 Conc, at room temperature. All chemicals were

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purchased from Fluka and BDH; all the available chemical reagents were used without further purification.

**A- Preparation of starch grafted methyl nadic anhydride (M1):-**

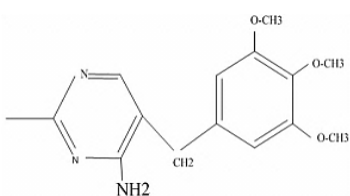
(3.0 gm, 0.018 mole) of starch dissolved in (25ml) of acetone, (0.1gm) (1ml) of ceric ammonium nitrate solution (CAN), (3gm, 0.016 mole) of methyl nadic anhydride (MNA) was added, the mixture was introduced in polymerization bottle, the mixture was heated about (30) minutes at (60 °C), using water bath, the green color product was produced (90%), S.P (86-92 °C).

**B-Substituted of (M1) with trimethoprim:-**

(0.60 gm, 0.0017 mole) of starch- g-methyl nadic anhydride (M1) was dispersed in (5ml) of Acetone, (0.50 gm, 0.0017 mole) of trimethoprim dissolved in (5ml) of dioxane, (0.5 ml) of DMF was added to the mixture, the mixture was refluxed with stirring about 1 hour at (90 °C), the colored solution was filtered, the filtrate was isolated and the solvent was evaporated, the Light green product was washed with di ethyl ether two times and dried at (50 °C) in a vacuum, conversion (55%).

S. p. (94-102 °C). all physical properties were listed in table (1).

**Table (1) Physical properties of prepared Polymer (M1C)**

Pol. No	-Drugs	Color	Softening point °C	Conversion %
M1C	 <p style="text-align: center;"><b>Trimethoprim</b></p>	Light green	94-102	55



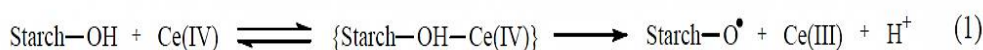
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**Result and Discussion**

The main objective of the research is to modified and study starch which was grafted with methyl nadic anhydrides, then the grafted anhydride was substituted by trimethoprim to get combinatorial and new properties of natural polymer. Chemical modification of natural polymers by grafting has wide variety of monomers available<sup>[18]</sup>. The group –OH that present on the starch polymer acts as the active sites for the graft copolymerization of methyl nadic anhydride onto starch. Starch can be grafted as main chain of backbone of polymer, it was polymerized and initiated by various initiators<sup>[19]</sup>. Among the several types of redox initiators, ceric ion offers many advantages due to its high grafting efficiency. when (Ce<sup>+4</sup>) salts such as cerium ammonium nitrate (CAN) is used as initiator in the grafting of vinyl monomers onto glucose, primary a ceric ion–glucose complex occurs, and then it disband to cerous (Ce<sup>+3</sup>) ion, and glucose radicals created by hydrogen remove from glucose .Thus, the initiation sites for grafting are formed on the glucose molecules. The radical that formed on the glucose molecules occur on the oxygen atom [20, 21]. The mechanism of grafting reaction of monomer on to starch initiated by CAN, as shown in equations (1).

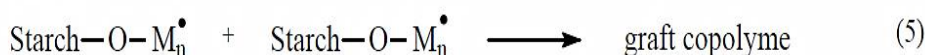
\* Initiation:



\* Propagation:



\* Termination:

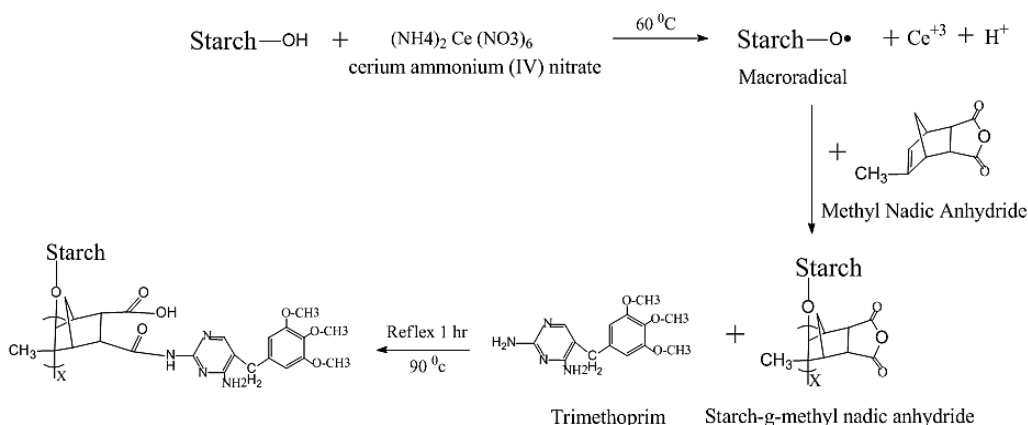


**Scheme (1) the mechanism of grafting reaction of monomer onto starch initiated by  
CAN**

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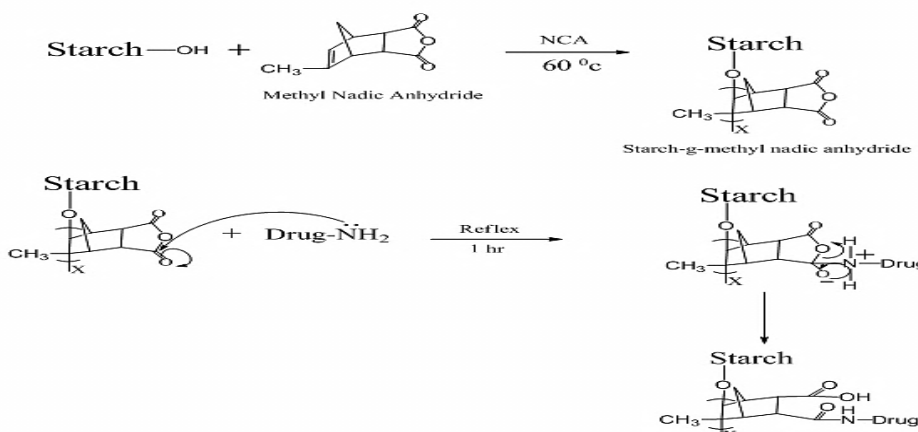
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Graft co polymer was prepared by the reaction of starch with methyl nadic anhydride by using ceric ammonium nitrate as a radical initiator. new drug polymer was prepared by the reaction of starch with methyl nadic anhydride and substituted with trimethoprim in reaction below



### Scheme (2) starch-g- methyl nadic anhydride and Substituted it with trimethoprim.

The presence of  $-\text{NH}_2$  group in the drug, which acts as strong nucleophile attack on the  $\text{C}=\text{O}$  group of methyl nadic anhydride produced N-drug substituted, the mechanism of reaction was described as shown bellow<sup>[21]</sup> :-



### Scheme (3) Mechanism of Ring opening reaction of Starch -g- Methyl nadic anhydride by nucleophilic reaction

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Figure (1) FTIR spectrum of natural polymer (starch) showed absorption peaks at (3290  $\text{cm}^{-1}$ ) of (O-H) group and (C-O-C) ether absorption peak at (1012-1149  $\text{cm}^{-1}$ ), peak at (2928)  $\text{cm}^{-1}$  due to (C-H aliphatic) stretching. Figure (2) FTIR spectrum of (M1) starch grafted Methyl nadic anhydride show the characteristic absorption of carbonyl group of anhydride peak was appeared at (1776 and 1855  $\text{cm}^{-1}$ ) in addition to the starch backbone absorptions. Figure (3) FT-IR spectrum of prepared compound [M1C] is showed the absorption at (3375)  $\text{cm}^{-1}$  due to (OH) stretching vibration, and (3171) due to the (NH) stretching, peak at (1647)  $\text{cm}^{-1}$  due to (C=O) stretching vibration of amide, and (1716)  $\text{cm}^{-1}$  due to (C=O) stretching vibration of acid. other bands of the compounds are listed in Table (2)

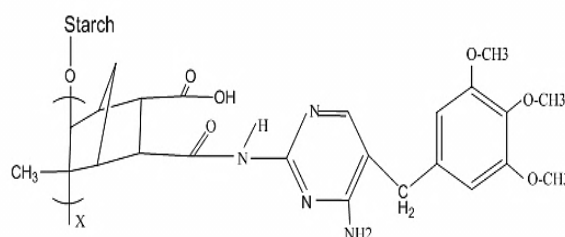
**Table (2) FT-IR absorptions of grafted Natural polymers (Starch) with anhydrides and substituted with drug Compound (amoxicillin) [M1C]**

Comp No.	Starch	M1	M1C
$\nu$ other band $\text{cm}^{-1}$	-	Anhydride 1776-1855 Strong	-
$\nu$ (C-H) $\text{cm}^{-1}$ aliphatic	2928	2968, 2872	2939
$\nu$ (C-O-C) $\text{cm}^{-1}$ Ether	1012 - 1149 Strong	1080-1217 Strong	1003-1190 Strong
$\nu$ (C-N) $\text{cm}^{-1}$	-	-	1329 medium
$\nu$ (O-H) $\text{cm}^{-1}$ carboxylic	-	2400-3500 Very broad	2400-3500 Very broad
$\nu$ (C=O) $\text{cm}^{-1}$ carboxylic	-	1703	1716
$\nu$ (C-O) $\text{cm}^{-1}$ acid	-	-	1236 Strong
$\nu$ (C-H) $\text{cm}^{-1}$ Aromatic	-	-	3055
$\nu$ (C=C) $\text{cm}^{-1}$ Aromatic	-	-	1500-1591
$\nu$ (C=O) $\text{cm}^{-1}$ amide	-	-	1647 Strong
$\nu$ (N-H) $\text{cm}^{-1}$ amide	-	-	3171
$\nu$ (O-H) $\text{cm}^{-1}$ alcohol	3290 broad	3180	3375

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$^1\text{H-NMR}$  spectra of polymer (M1C) was obtained using TMS as internal standard with  $\text{DMSO-d}^6$  as a solvent. The  $^1\text{H-NMR}$  spectrum of drug polymer [M1C] showed in Figure (4). Indicated the signal assignments in the corresponding formula, which showed the following signals:-



**Figure (4) Structure of M1C**

3.74 ppm (Singlet, 3H, -O-CH<sub>3</sub>), 6.5 ppm (Singlet, 1H, Ar-H), 6.2 ppm (Singlet, 1H, CO-NH amide), 2.6 ppm (Singlet, 2H, CH<sub>2</sub>), 7.4 ppm, (Singlet, 2H, Ar-NH<sub>2</sub>).

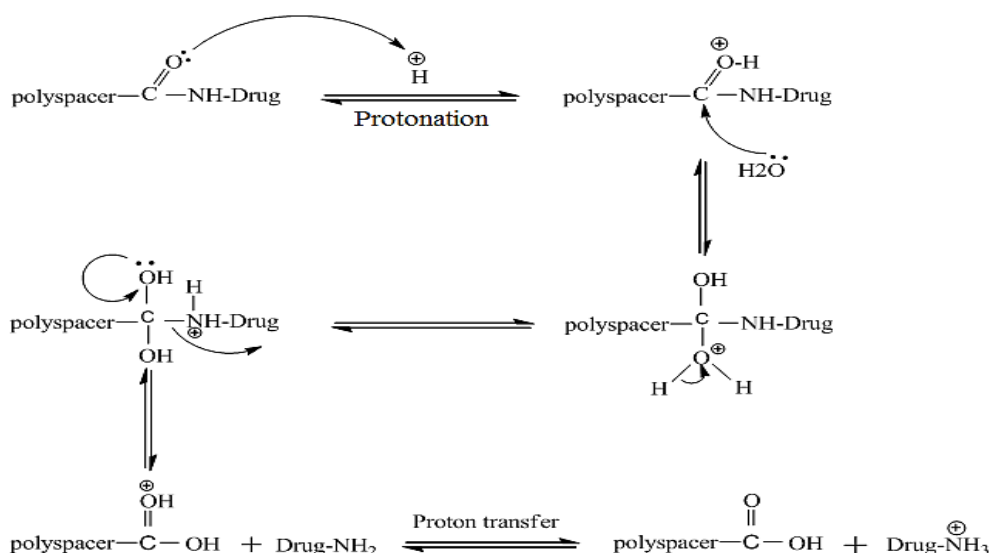
**Controlled drug release:-**

drug polymers (M1C) was studying release (50 mg) was added continuously in (100 ml) buffer solution at (37 °C). the wave length of  $\lambda_{\text{max}}$  was measured at different times and different pH values (1.1 –7.4) by using UV spectrometer. These samples were analyzer b UV-spectroscopes periodically withdrawn for every days, it was appeared the sustained release by measuring the mole fraction were constructed from UV. indicated the rate of hydrolysis in basic medium is higher than acidic medium. Mechanism of these drug polymer were illustrated in the following equations :-



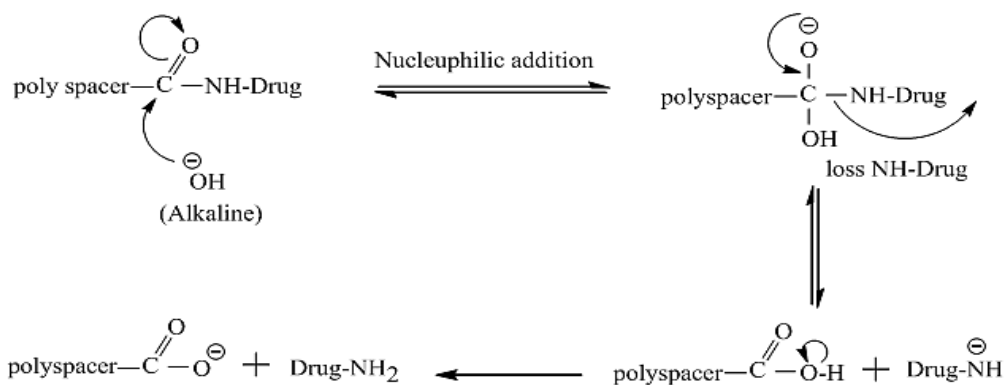
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polyspacer:- Starch  
 Drug-NH2:- Trimethoprim

Scheme (4) Mechanism of Hydrolysis drug polymer in acidic medium



Drug NH2 = Trimethoprim  
 poly spacer = Starch

Scheme (5) Mechanism of Hydrolysis drug polymer in basic medium

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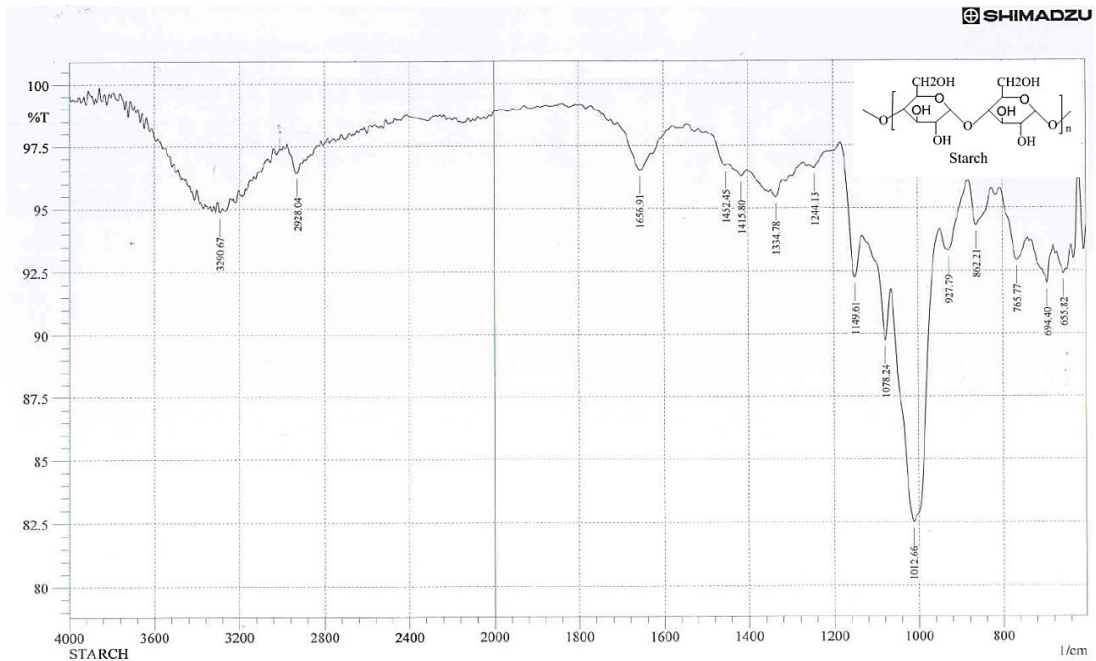


Figure (1) FTIR spectrum of starch

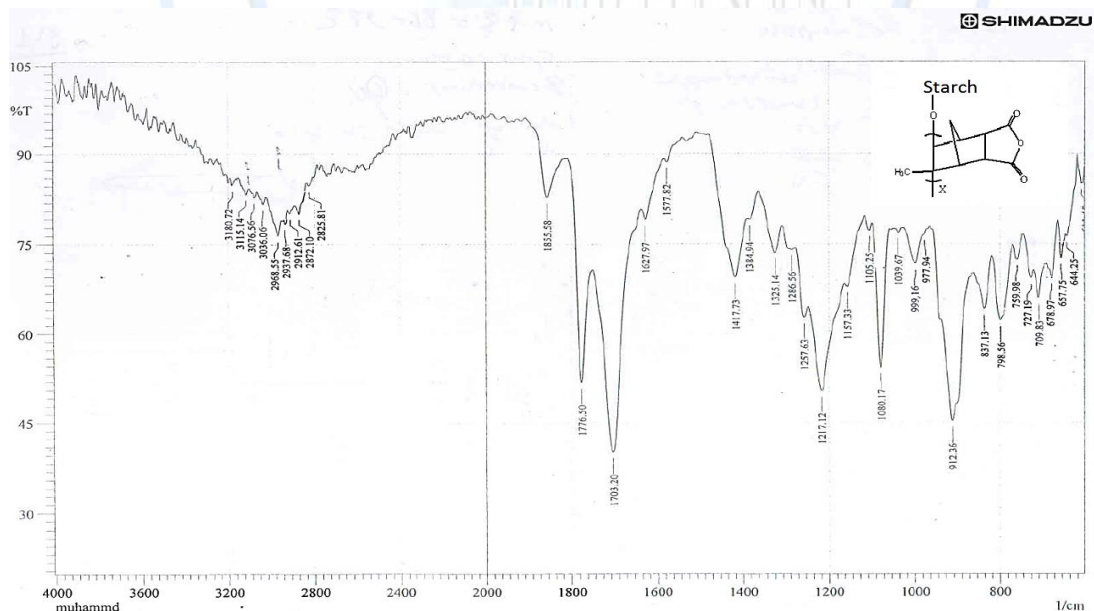


Figure (2) FTIR spectrum of starch-g-methyl nadic anhydride (M1)

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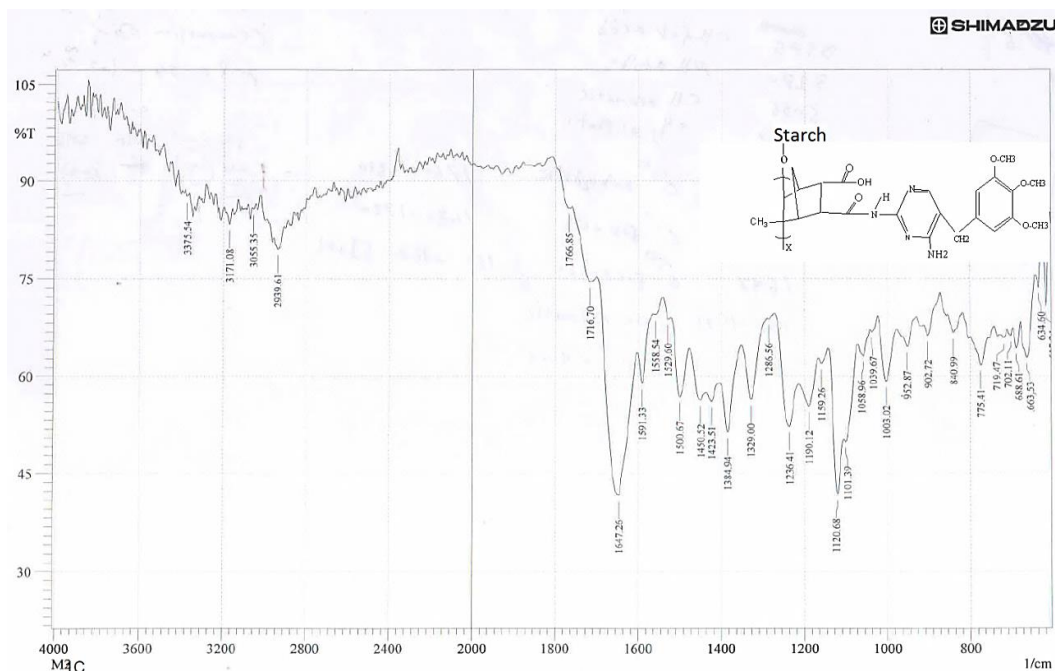


Figure (3) FTIR spectrum of starch- g-[N-Trimethoprimyl amic acid] (M1C)

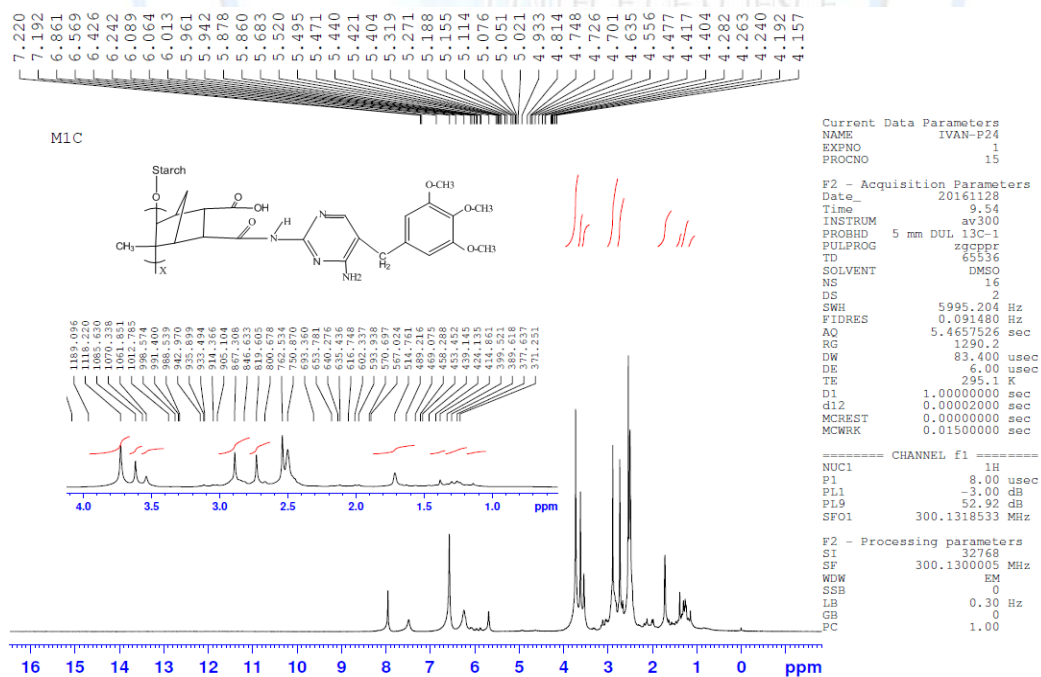
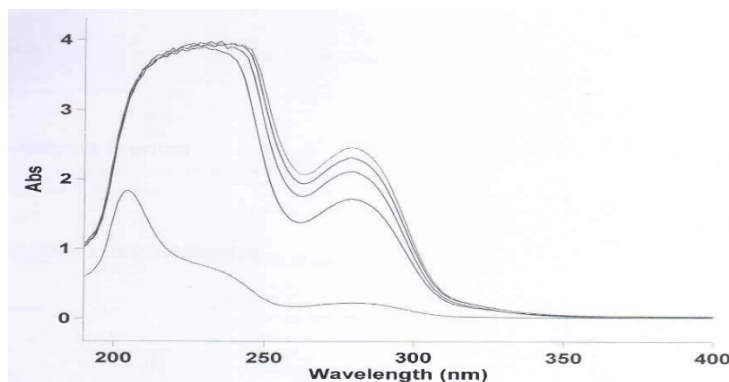


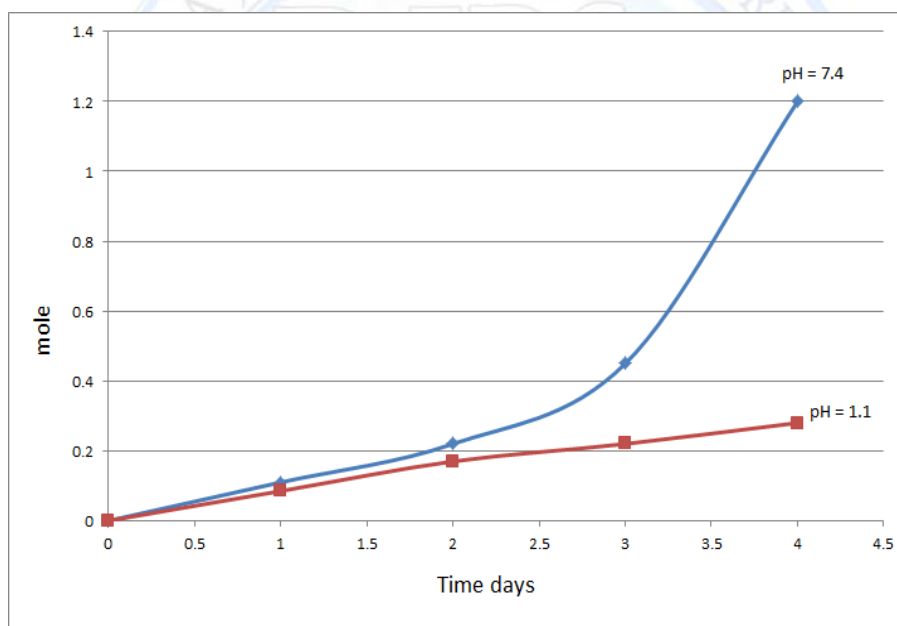
Figure (4) H-NMR Spectrum of M1C

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**Figure (5) UV Spectrum hydrolysis of (M1C) in PH7.4**



**Figure (6) UV Spectra hydrolysis of M1C in pH7.4 and pH 1.1**

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