



# Synthesis and Characterization of Substituted Starch Grafted Methyl Nadic Anhydride and Substituted with 4-Aminoantipyrine

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## Abstract

In this research the structural modification of starch was carried out with methyl nadic anhydride (M1) as a spacer by using ceric ammonium nitrate (CAN) as an initiator, and grafted copolymer was substituted with amino drug such as 4-aminoantipyrine (M1B), this design of carries for controlled delivery of therapeutic agent which could release the entrapped drug over an extended period of time, due to its nontoxic, biodegradable and slow digesting nature, the new drug copolymer was characterized by FTIR, <sup>1</sup>H-NMR and UV Spectroscopes. The prepared drug copolymer was analyzed in different pH values at (37°C) as in vitro study and controlled drug release was compared at zero time and after four days.

## 1. Introduction

Starch is a valuable ingredient in the food industry, it serves not only as a nutrient source for food, but also as a thickener, a binding agent, a texturizer, a filler and a film forming agent in the food industry. A selection of starch varieties for different food products depends on starch functional properties, including viscosity, shear resistance, gelatinization properties, textures, solubility, tackiness and gel stability. These functional properties are determined by the chemical structures of starch [1]. Grafted copolymerization of unsaturated monomer onto natural polymers such as starch (starch-graft-copolymers), the side chains of a given monomer are attached to the main chain of

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starch. Acrylic/vinyl monomers are usually used for grafting onto starch, which include acrylamide, acrylic acid, acrylonitrile, methacryl amide, methacrylic acid, vinyl acetate, methacrylonitrile [2, 3], to add new properties and more attention tissue engineering and tissues adhere [4-6]. It can be used for the production of biocompatible materials in the pharmaceutical and medical applications [7]. The hydrophilic monomers which grafted on surface of polymers are biodegradable and sensitive to stimuli pH and temperature [8]. The biodegradable property makes it possible to implant them into the body without the need of subsequent removal by the surgical operation. Drugs formulated with these polymers can be released in a controlled manner, by which the drug concentration in the target site is enhanced. The release rates of the drugs from biodegradable polymers can be controlled by a number of factors, such as biodegradation kinetics of the polymers [9, 10], grafted copolymer was substituted with 4-aminoantipyrine as antibiotics. Molecules with 4-aminoantipyrine nucleus are known to possess analgesic, anti-inflammatory (temperature reducing), anticancer, antibacterial, antiviral, and antifungal, properties [11].

4-aminoantipyrine has also been used for the protection against oxidative stress as well as prophylactic of some diseases including cancer, and these are important directions in medical applications. Several derivatives of antipyrine were also evaluated as analgesic, anti-inflammatory, antimicrobial, and anticancer activity [12].

The main objective of the research is to modify and study starch which was grafted with methyl nadic anhydrides, then the grafted anhydride was substituted by 4-aminoantipyrineto gain combinatorial and new properties of natural polymer. This work aimed to preparation of new 4-aminoantipyrine copolymer to enhance the sustained release throw long period, also to minimize the some side effect of this drug.

## **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, <sup>1</sup>H-NMR spectra were measured with a bruker spectrophotometer model ultra-shield at 300.13 MHz in DMSO-d<sub>6</sub>, U.V-Visible double beam scanning spectrophotometer VARIAN (UV-Vis)-100 Conc, at room temperature. All chemicals were purchased from Fluka and BDH; all the available chemical reagents were used without further purification.

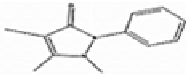
### A. Preparation of starch grafted methyl nadic anhydride (M1)

(3.0 gm, 0.018 mole) of starch dissolved in (25 ml) of acetone, (0.1 gm) (1 ml) of ceric ammonium nitrate solution (CAN), (3 gm, 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 4-aminoantipyrine

(0.6 gm) of starch-g-methyl nadic anhydride (M1) was dispersed in (5 ml) of acetone, (0.3 gm) of 4-aminoantipyrine dissolved in (5 ml) 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 black product was washed with di ethyl ether two times and dried at (50°C) in a vacuum, conversion (80%), S.P. (115-125°C). All physical properties were listed in Table 1.

**Table 1.** Physical properties of prepared polymer (M1B).

Pol.	-Drugs	Color	Softening point °C	Conversion ratio %
M1B	 4-Aminoantipyrine	Black	60 - 75	70

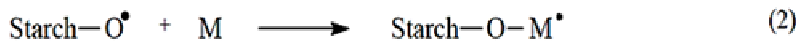
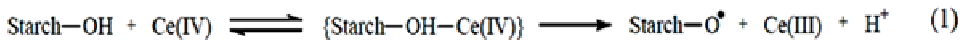
## Result and Discussion

Starch can be grafted as main chain of backbone of polymer, it was polymerized and initiated by various initiators [13]. Among the various types of initiators, ceric ion offers many advantages because of its high grafting efficiency. When ( $Ce^{+4}$ ) salts such as cerium ammonium nitrate (CAN) is used as initiator in the grafting of vinyl monomers onto glucose, at first a ceric ion-glucose complex occurs, and then it decomposes to ( $Ce^{+3}$ ) ion [14] and glucose radicals created by hydrogen abstraction from glucose. Thus, the radical formation on the glucose backbone occurs on the oxygen atom [15, 16]. The

-OH group present on the backbone of starch polymer acts as the active sites for the graft copolymerization.

The mechanism of grafting monomer onto starch as shown below in equations (1)

\* Initiation:



\* Propagation:

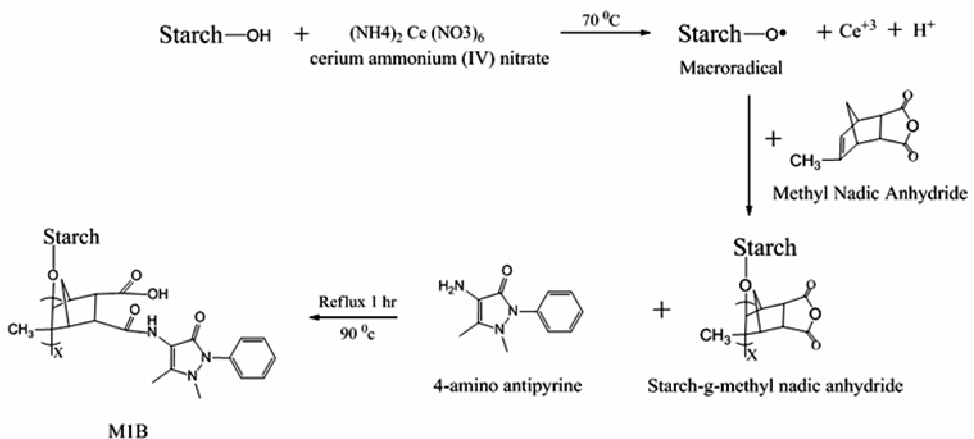


\* Termination:



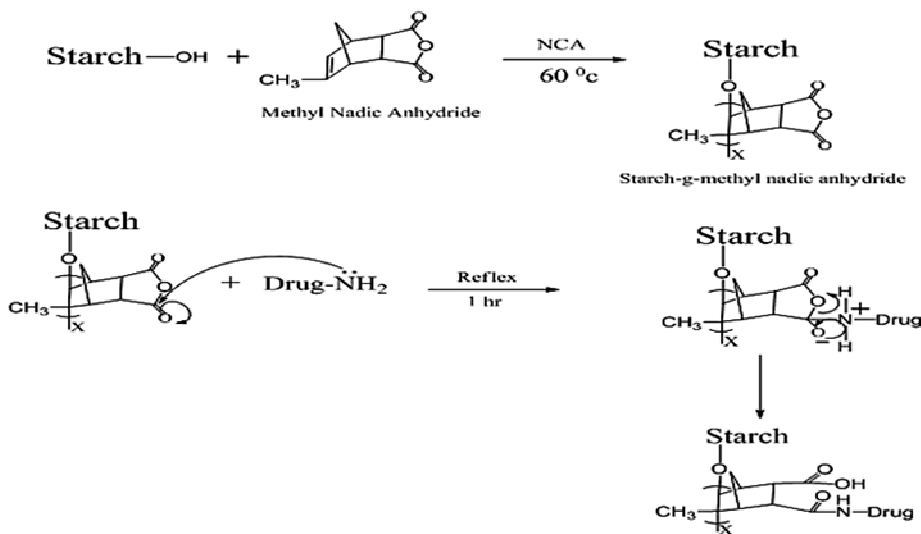
**Scheme 1.** The mechanism of grafting reaction of monomer onto starch by CAN.

Graft copolymer 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 4-aminoantipyrene in reaction below:



**Scheme 2.** Starch-g-methyl nadic anhydride and substituted it with 4-aminoantipyrene.

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 below [17]:-



**Scheme 3.** Mechanism of ring opening reaction of starch-g-methyl nadic anhydride by nucleophilic reaction.

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 ( $1012\text{-}1149\text{ cm}^{-1}$ ), peak at ( $2928\text{ cm}^{-1}$ ) due to (C-Haliphatic) stretching.

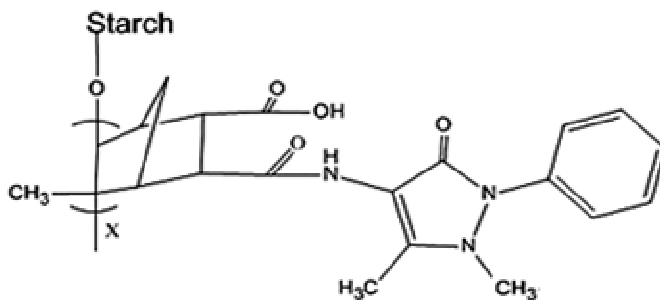
Figure 2: FTIR spectrum of (M1) starch grafted methyl nadic anhydride gave the characteristic absorption of carbonyl group of anhydride peak was appeared at ( $1776$  and  $1855\text{ cm}^{-1}$ ) in addition to the starch backbone absorptions.

Figure 3: FT-IR spectrum of prepared compound [M1B] showed absorption band at ( $3261\text{ cm}^{-1}$ ) due to  $\nu(\text{OH})$  stretching vibration, and at ( $3200$ ) due to the  $\nu(\text{NH})$  stretching, band at ( $1660\text{ cm}^{-1}$ ) due to ( $\text{C}=\text{O}$ ) stretching vibration of amide, and ( $1714\text{ cm}^{-1}$ ) due to ( $\text{C}=\text{O}$ ) 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 (4-aminoantipyrine) [M1B]

Comp No.	$\nu(\text{O-H})$ $\text{cm}^{-1}$ alcohol	$\nu(\text{N-H})$ $\text{cm}^{-1}$ amide	$\nu(\text{C=O})$ $\text{cm}^{-1}$ amide	$\nu(\text{C=C})$ $\text{cm}^{-1}$ Aromatic	$\nu(\text{C-H})$ $\text{cm}^{-1}$ Aromatic	$\nu(\text{C-O})$ $\text{cm}^{-1}$ acid	$\nu(\text{C=O})$ $\text{cm}^{-1}$ carboxylic	$\nu(\text{O-H})$ $\text{cm}^{-1}$ carboxylic	$\nu(\text{C-N})$ $\text{cm}^{-1}$	$\nu(\text{C-O-C})$ $\text{cm}^{-1}$ Ether	$\nu(\text{C-H})$ $\text{cm}^{-1}$ aliphatic	$\nu$ other band $\text{cm}^{-1}$
starch <sup>1</sup>	3290 broad	-	-	-	-	-	-	-	-	1012 -1149 Strong	2928, 2852	-
M1	3180	-	-	-	-	-	1703	2400-3500 Very broad	-	1080-1217 Strong	2968, 2872	Anhydride 1776-1855 Strong
M1B	3261	3200	1660 Strong	1541-1591	3043	1296	1714	2400-3500 Very broad	1384 medium	1001 - 1253 Strong	2852, 2962	-

<sup>1</sup>H-NMR spectra of [M1B] polymer was obtained using DMSO-d<sup>6</sup> as a solvent with TMS as internal standard. The <sup>1</sup>H-NMR spectrum of drug polymer [M1B] showed in Figure 4 indicated the signal assignments in the corresponding formula, which showed the following signals:-

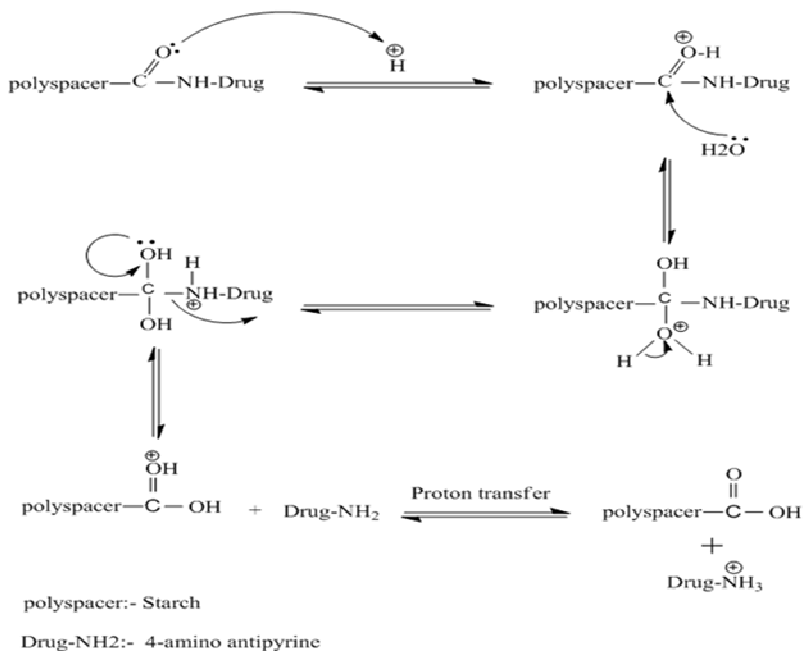
**Structure of M1B**

0.85 ppm (singlet, 3H, CH<sub>3</sub>) for ring methyl nadic, 2.2 ppm (singlet, 6H, Ar-CH<sub>3</sub>), 3.0 ppm, (doublet, 2H, CH<sub>2</sub>) for starch, 6.8-7.5 ppm (multiple, 5H, Ar-H), 8.1 ppm (singlet, 1H, CO-NH amide).

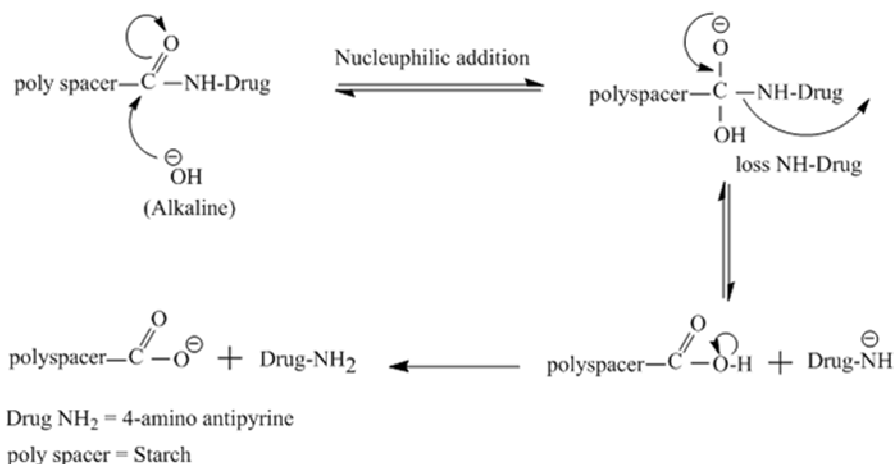
### Controlled Drug Release

Release of (M1B) was studied. (100 mg) was added continuously in (100 ml) buffer solution at (37°C). The wave length of  $\lambda_{\text{max}}$  was measured at different periods and different pH values (1.1-7.4) by using UV spectrometer. The sample was analyzed by UV-spectroscopes periodically withdrawn everyday. The sustained release measured by

the mole fraction constructed from UV spectra indicated that the rate of hydrolysis in basic medium is higher than acidic medium. Mechanism of this drug polymer was illustrated as shown in Schemes 4 and 5.

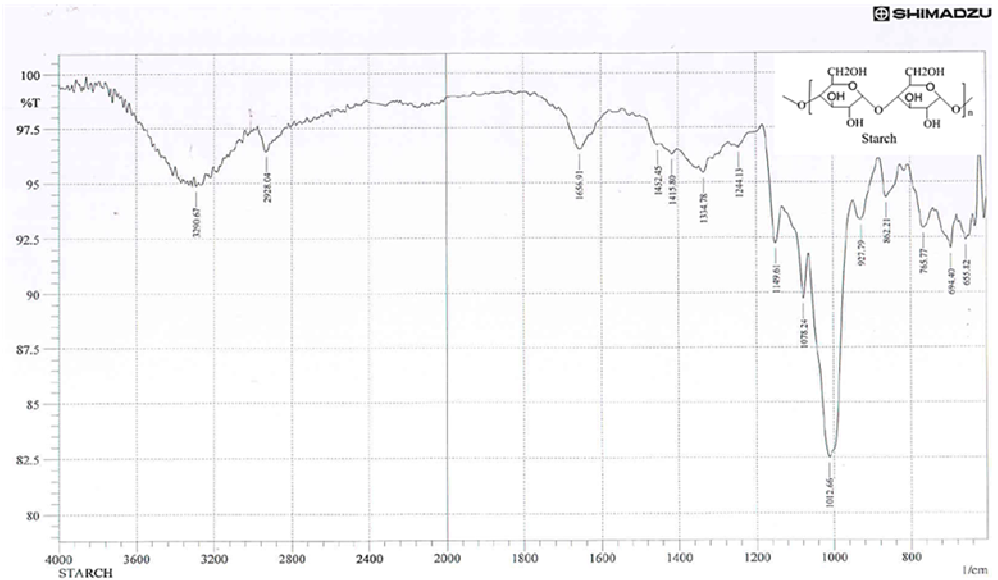


**Scheme 4.** Mechanism of hydrolysis drug polymer in acidic medium.

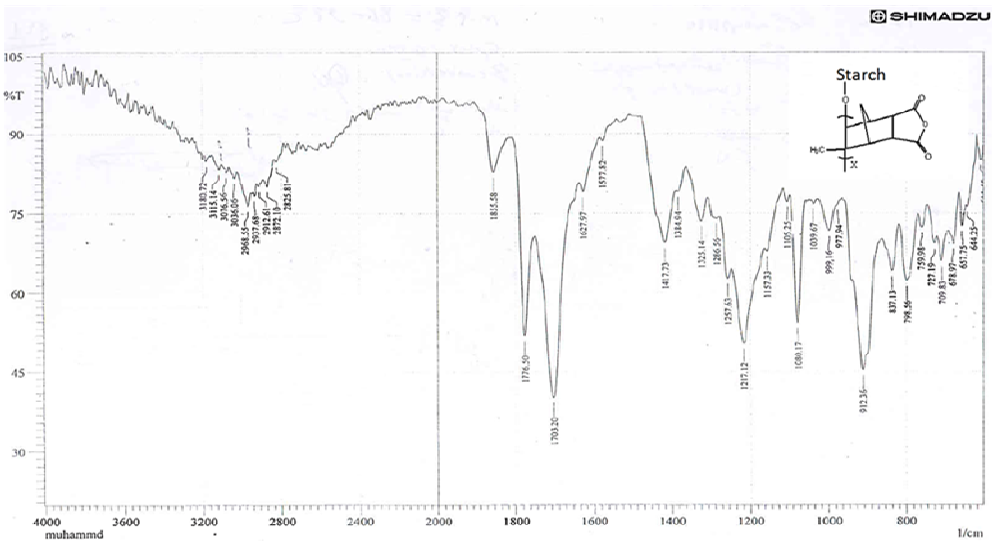


**Scheme 5.** Mechanism of hydrolysis drug polymer in basic medium.

It was found that the controlled drug release was hydrolysis of amide group over four days in basic medium, but it was higher hydrolysis in basic medium than acidic medium.



**Figure 1.** FTIR spectrum of starch.



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



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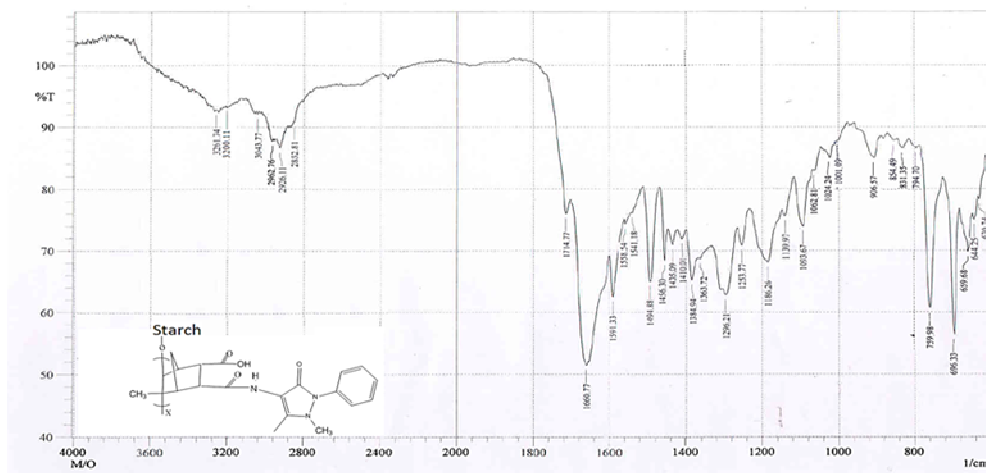


Figure 3. FTIR spectrum of starch-g-methyl nadic anhydride (M1B).

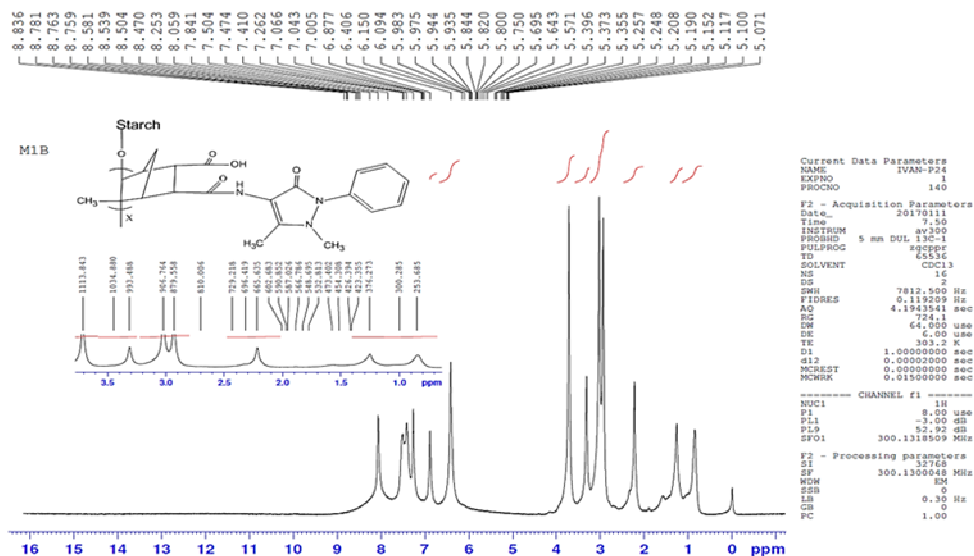
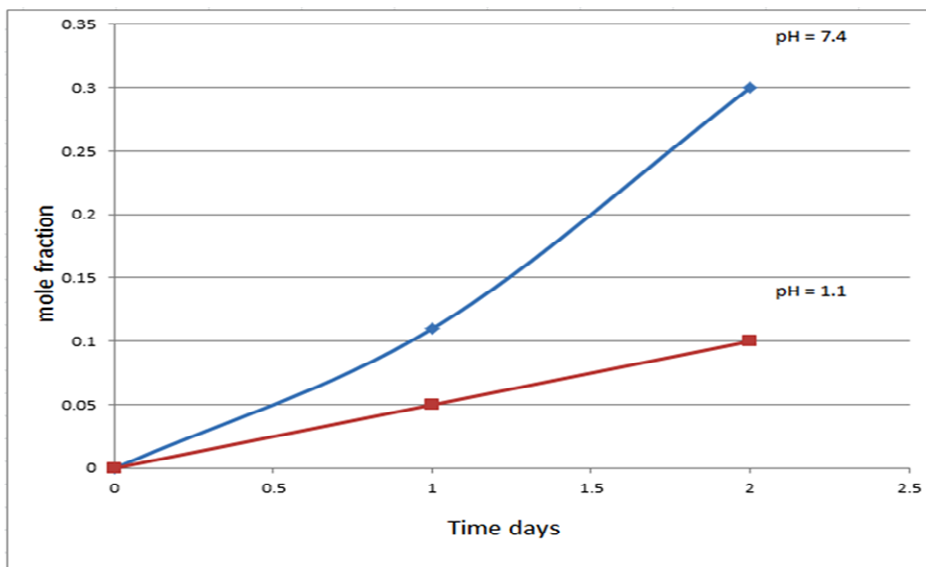


Figure 4. <sup>1</sup>H-NMR Spectrum of M1B.



**Figure 5.** UV Spectra hydrolysis of M1B in pH 7.4 and pH 1.1.

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