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SYNTHESIS AND CHARACTERIZATION OF CO-POLYMER AND SUBSTITUTED WITH AMINO DRUG

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ABSTRACT

In this research the structural modification of starch was carried out with methyl nadic anhydride (H) as a spacer by using ceric ammonium nitrate (CAN) as an initiator, and grafted copolymer was substituted with amino drug procaine (HB) , 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 non toxic, biodegradable and slow digesting nature, the new drug copolymer was characterized by FTIR, ^{1}H-NMR and UV Spectroscopes, Thermal analysis was studied. The prepared drug copolymer was analyzed in different pH values at (37 ^{0}C) as in vitro study and controlled drug release was compared at zero time and after four days..

KEYWORDS: starch, methyl nadic anhydride, Procaine, Copolymer, Drug Copolymer.

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 on to natural polymers such as starch (starch-graft-copolymers), the side chains of a given monomer are attached to the main chain of 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 procaine as antibiotics.

Procaine is a white powder with Molecular formula ($C_{13}H_{20}N_2O_2$), and molecular weight (236.3 gm/mole), it like other local anesthetics such as tetra caine acts as a nerve block, halting the generation and conduction of nerve impulses signal pain, it has four to six times less toxic than cocaine, it is also used in obstetrics and some times for relief pain in the lower back and tooth extraction[11], and it is useful for treating bacterial (as an antibacterial drug) and parasitic infections.[12] 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 procaine to gain combinatorial and new properties of natural polymer. This work aimed to preparation of new procaine 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, ^{1}H-NMR spectra were measured with a bruker spectrophotometer model ultra-shield at 300.13 MHz in DMSO-d6, 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.

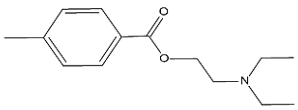
A- Preparation of starch grafted methyl nadic anhydride (H)

(1.0 gm) of starch dissolved in (25ml) of acetone, (0.1gm) (1ml) of ceric ammonium nitrate solution (CAN), (1gm) of methyl nadic anhydride (MNA) was added, the mixture was introduced in polymerization bottle, the mixture was heated about (30) minutes at (60 ^{0}C), using water bath, the green color product was produced (90%), S.P (86-92 ^{0}C).

B-Substituted of (H) with procaine

(0.2 gm) of starch- g-methyl nadic anhydride (H) was dispersed in (5ml) of acetone, (0.1 gm) of procaine 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 ^{0}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 ^{0}C) in a vacuum, conversion (92%). S. p. (210-220 ^{0}C). all physical properties were listed in table (1).

Table 1: Physical properties of prepared Polymer (HB).

Pol.	-Drugs	Color	Softening point ^{0}C	Conversion ratio %
HB	 Procaine	Light brown	210-220	92

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 cerous (Ce^{+3}) ion.[14] and glucose radicals created by hydrogen abstraction from glucose .Thus, The radical formation on the glucose backbone occur 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:

$$\text{Starch—OH} + \text{Ce(IV)} \rightleftharpoons \{\text{Starch—OH—Ce(IV)}\} \longrightarrow \text{Starch—O}^{\bullet} + \text{Ce(III)} + \text{H}^{+} \quad (1)$$

$$\text{Starch—O}^{\bullet} + \text{M} \longrightarrow \text{Starch—O—M}^{\bullet} \quad (2)$$

* Propagation:

$$\text{Starch—O—M}^{\bullet} + \text{M} \longrightarrow \text{Starch—O—M}_2^{\bullet} \quad (3)$$

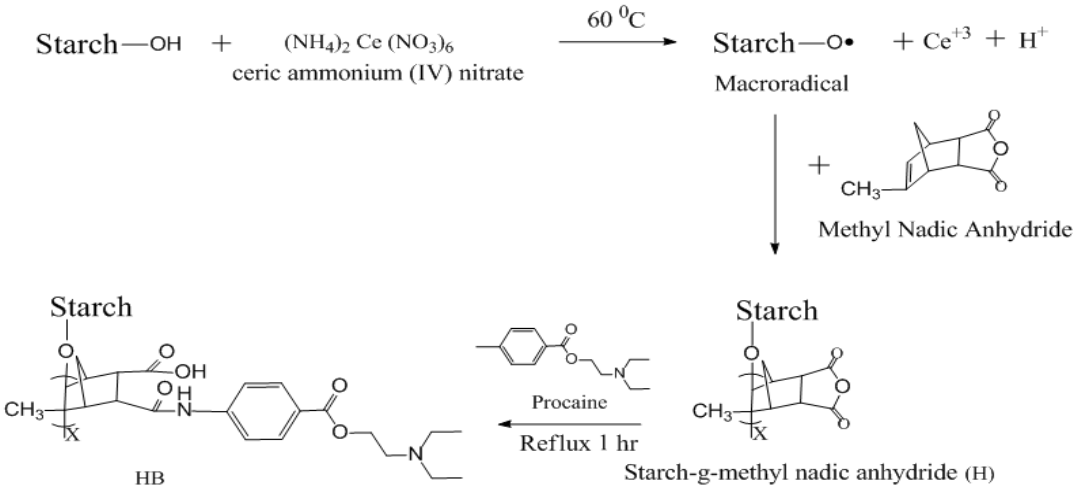
$$\text{Starch—O—M}_n^{\bullet} + \text{M} \longrightarrow \text{Starch—O—M}_{n+1}^{\bullet} \quad (4)$$

* Termination:

$$\text{Starch—O—M}_n^{\bullet} + \text{Starch—O—M}_n^{\bullet} \longrightarrow \text{graft copolyme} \quad (5)$$

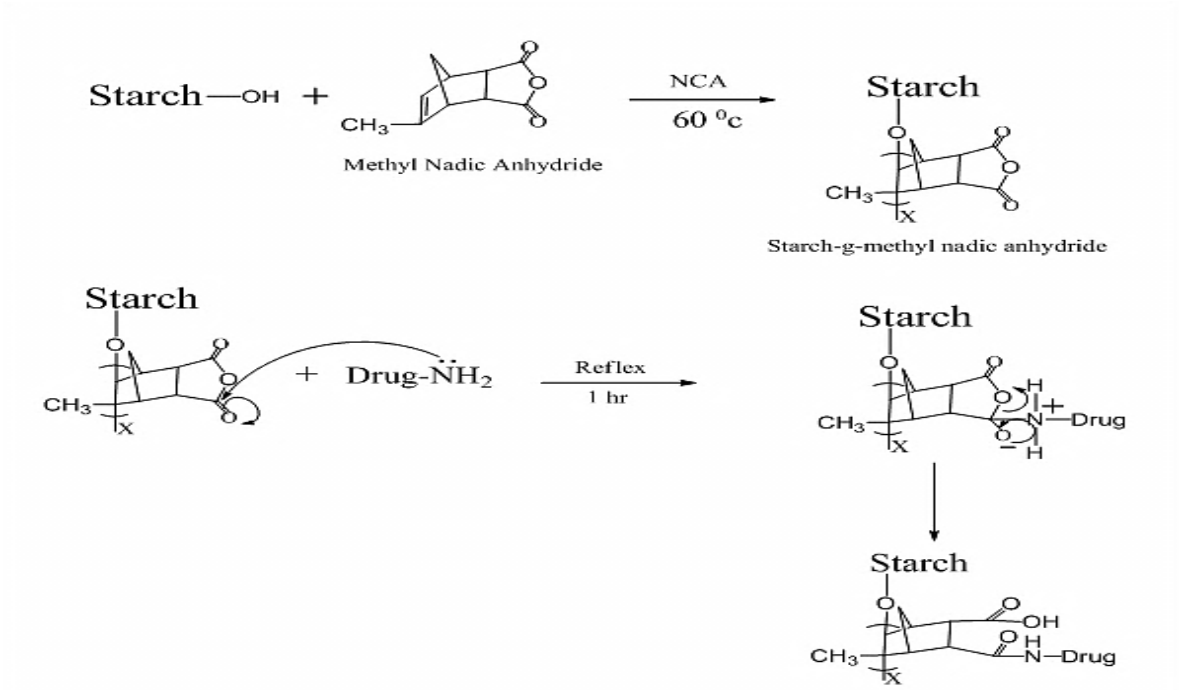
Scheme (1): The mechanism of grafting reaction of monomer onto starch by CAN.

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 procaine in reaction below.



Scheme (2): starch-g- methyl nadic anhydride and Substituted it with procaine.

The presence of $-NH_2$ group in the drug, which acts as strong nucleophile attack on the C=O group of methyl nadic anhydride produced N-drug substituted, the mechanism of reaction was described as shown bellow.[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 cm^{-1}) of (O-H) group and (C-O-C) ether absorption peak at (1012-1149 cm^{-1}), peak at (2928) cm^{-1} due to (C-H aliphatic) stretching.

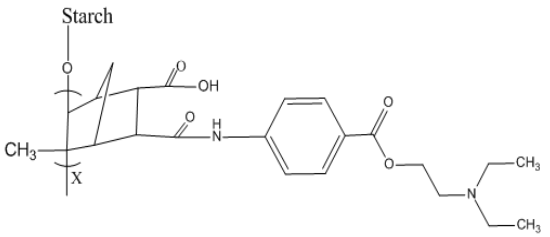
Figure (2) FTIR spectrum of (H) starch grafted Methyl nadic anhydride gave the characteristic absorption of carbonyl group of anhydride peak was appeared at (1776 and 1855 cm^{-1}) in addition to the starch backbone absorptions.

Figure (3) FT-IR spectrum of prepared compound[HB] showed absorption band at (3227) cm^{-1} due to (NH) stretching, and (1651) cm^{-1} due to (C=O amide) stretching, and (1602) cm^{-1} due to (NH) bending, peak at (1705) cm^{-1} correlated 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 (Procaine).[HB]

Comp No.	υ (O-H) cm^{-1} alcohol	υ(N-H) cm^{-1} amide	υ(C=O) cm^{-1} amide	υ (C=C) cm^{-1} Aromatic	υ (C-H) cm^{-1} Aromatic	υ (C-O) cm^{-1} acid	υ(C=O) cm^{-1} carboxylic	υ (O-H) cm^{-1} carboxylic	υ (C-N) cm^{-1}	υ (C-O-C) cm^{-1} Ether	υ (C-H) cm^{-1} aliphatic	υ other band cm^{-1}
starch	3290 broad	–	–	–	–	–	–	–	–	1012 -1149 Strong	2928, 2852	–
H	3180	–	–	–	–	–	1703	2400-3500 Very broad	–	1080-1217 Strong	2968, 2872	Anhydride 1776-1855 Strong
HB	3354	3227	1651 Strong	1519	3086	1271 Strong	1705	2400-3500 Very broad	1311 medium	1001-1170 Strong	2874, 2933	1602 -NH bending

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

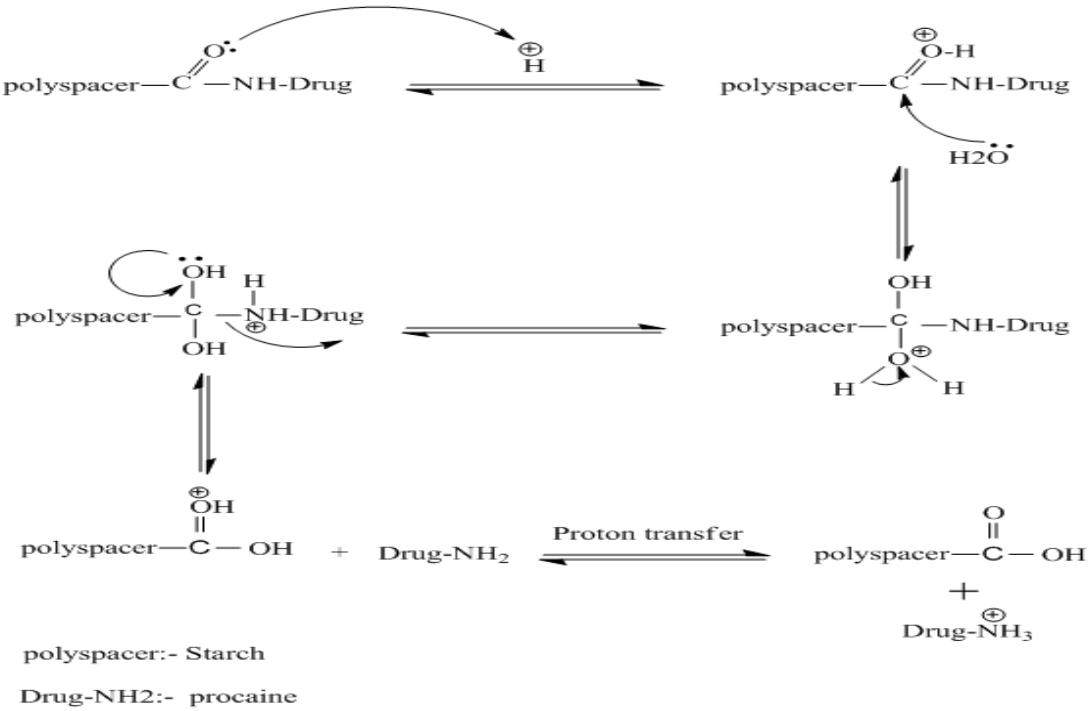


Structure of HB

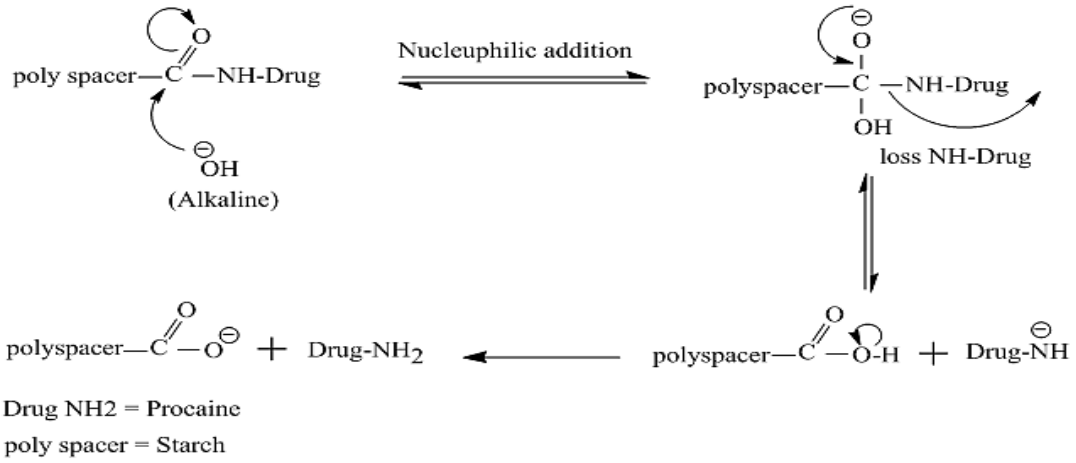
0.85 ppm (Singlet, 3H, CH_3) for ring methyl nadic, 1.24 ppm (Triplet, 6H, $2CH_3$), 1.4 ppm (Triplet, 2H, CH2) for ring methyl nadic, 2.2 ppm (Triplet, 2H, CH_2-N), 3.19 ppm (quartet, 4H, $2CH_2$), 3.5 ppm (doublet, 1H, CH-O-starch), 4.5 ppm, (Triplet, 2H, COO-CH_2), 5.7 ppm (Singlet, 1H, OH for starch), 6.5-7.7 ppm (Multiple, 4H, Ar-H), 8 ppm (Singlet,1H, CO-NH amide), 12.0 ppm (Singlet, 1H, COOH).

Controlled drug release

Release of (HB) was studied, (100 mg) was added continuously in (100 ml) buffer solution at (37 ^{0}C). the wave length of λ_{max} was measured at different periods and different pH values (1.1 –7.4) by using UV spectrometer. These samples were analyzer by 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 as shown in the scheme (4,5).



Scheme (4): Mechanism of hydrolysis drug polymer in acidic medium.



Scheme (5): Mechanism of hydrolysis drug polymer in basic medium.

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

Thermal Properties of polymer drug[14]

Thermal stability of prepared polymers were investigated by (TGA and DSC) Table (3) TGA showed the results of some prepared drug polymers which indicated the high thermal resistance and showed their steps of weight loss-temperature. This high thermal resistance indicated the high interaction between amide hydrogen bonding through the polymer chains and led to best sustain drug release**.** Several thermal stability parameters were determined from TGA curve as shown in table (3).

Table (3): TGA Analysis of some polymer drugs.

No. drug polymer	Temperature	Losses weight%
H	123, 318, 404	3, 58, 38
HB	212, 283, 480	13, 26, 48

It was concluded that the thermal stability of drug polymer was more than the drug alone this cause more expire date and more protection of the drug satiability.

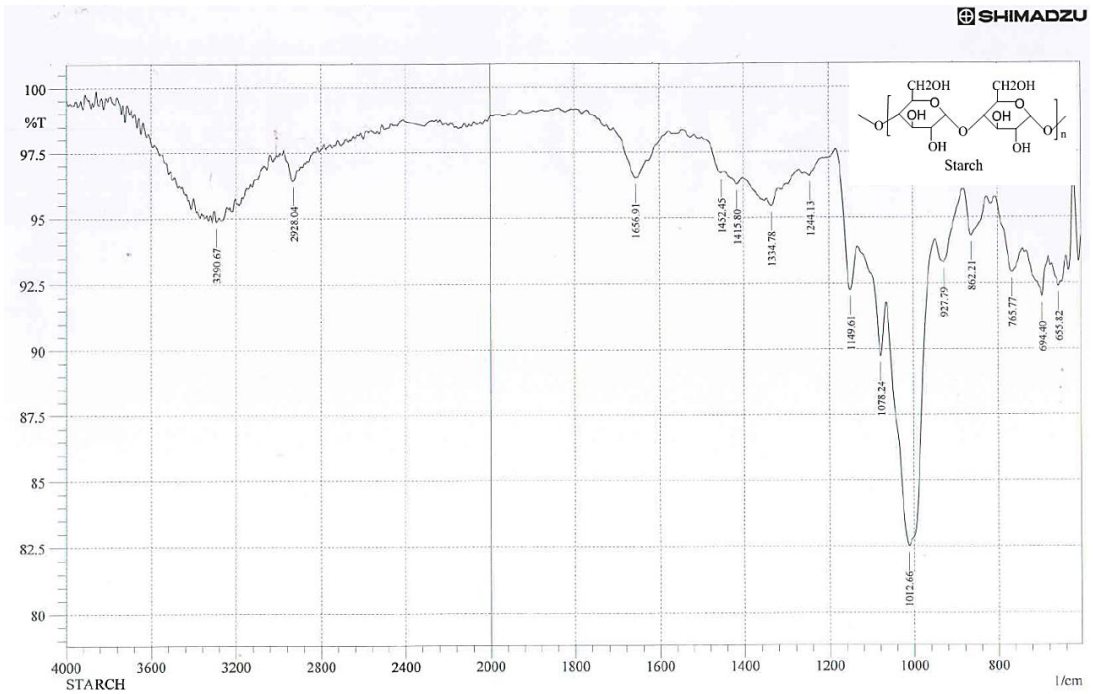


Figure (1): FTIR spectrum of starch.

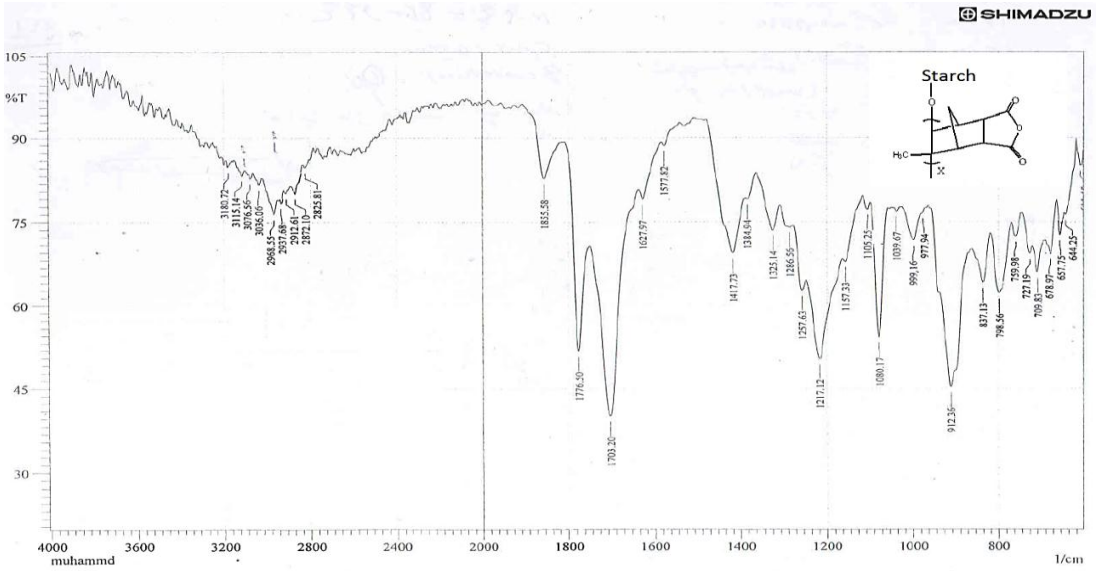


Figure (2): FTIR spectrum of starch-g-methyl nadic anhydride (H).

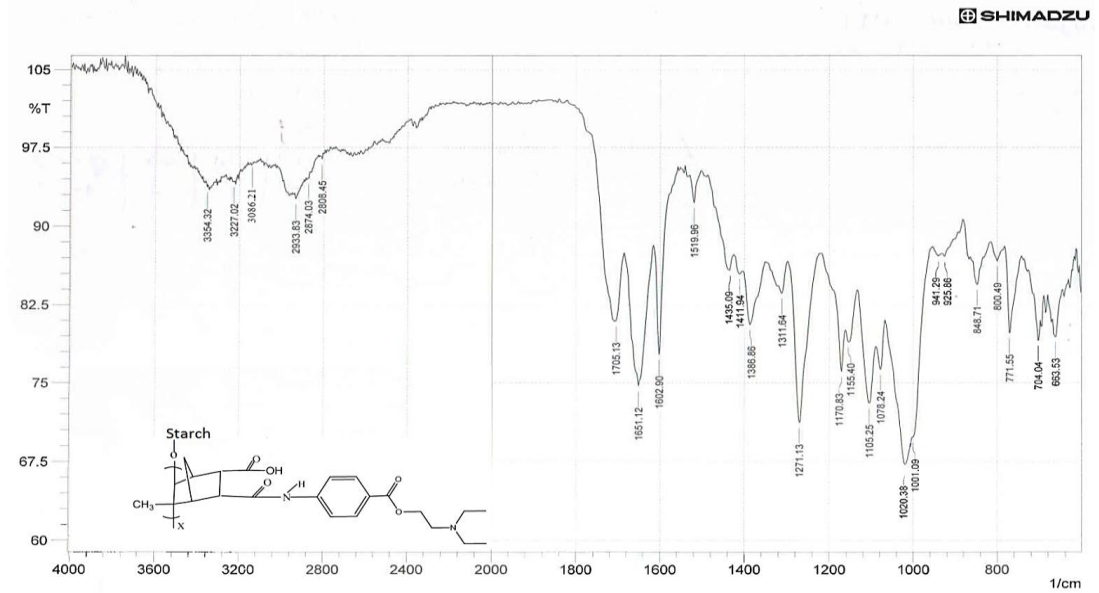


Figure (3): FTIR spectrum of starch-g-methyl nadic anhydride (HB).

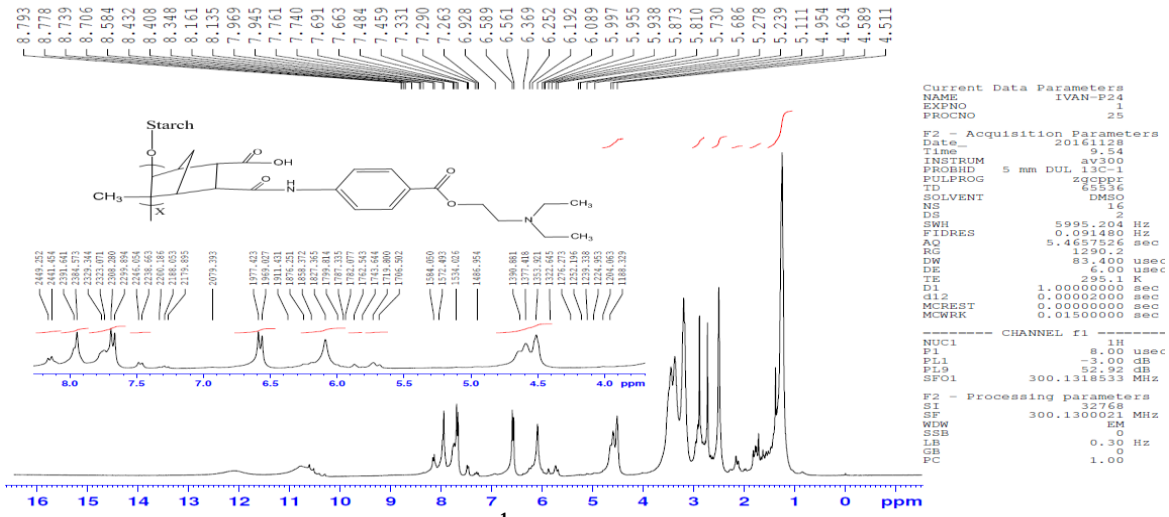


Figure (4): ^{1}H-NMR Spectrum of HB.

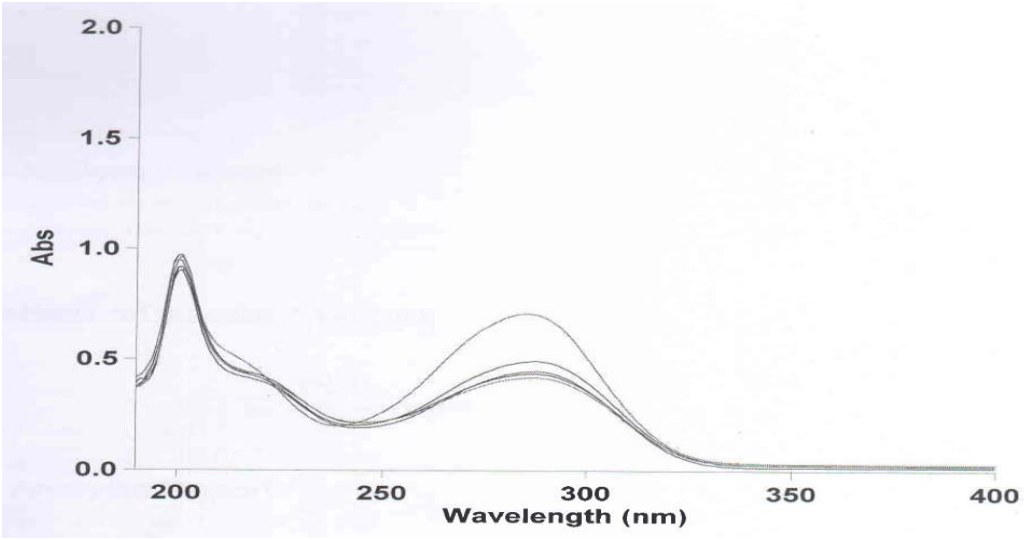


Figure (5): UV Spectra hydrolysis of HB in pH7.4.

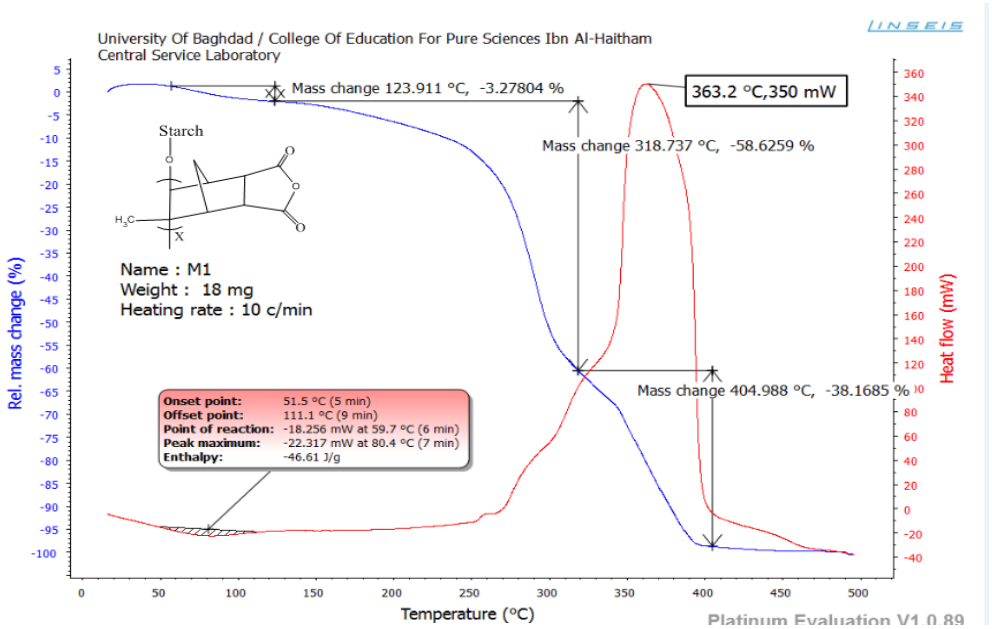


Fig (6): DSC and TGA Analysis of H.

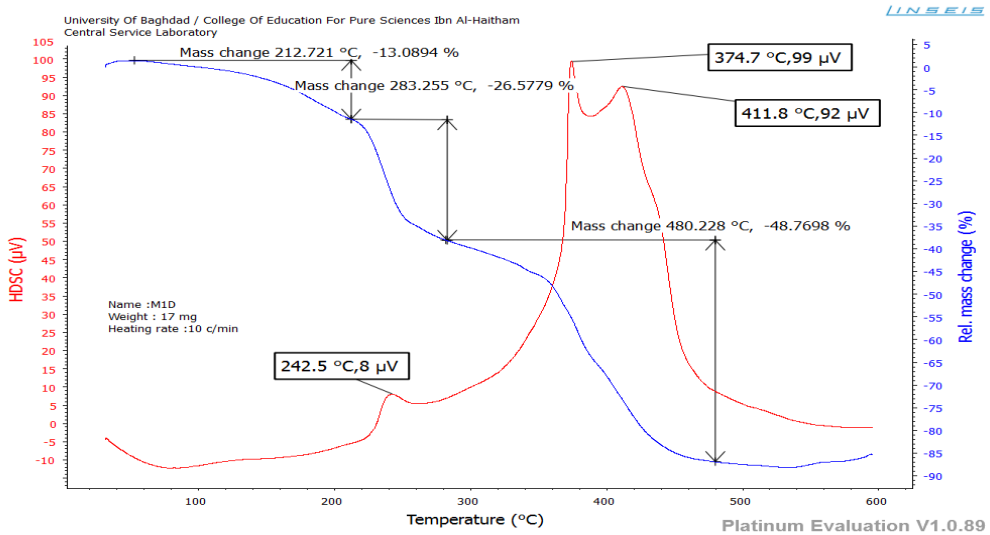


Fig (7): DSC and TGA Analysis of HB

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