

**SYNTHESIS AND CHARACTERIZATION OF CELLULOSE GRAFTED MALEIC ANHYDRIDE AND SUBSTITUTED IT WITH AMOXICILLIN**<sup>1</sup>\*Mohammed A. Farhan, <sup>2</sup>Hiba B. Dheyab and <sup>3</sup>Assmaa A. Hasan<sup>1,2</sup>Diyala University, College of Science, Department of Chemistry, Diyala, Iraq.<sup>3</sup>Diyala University, College of Science, Department of Biology, Diyala, Iraq.**\*Corresponding Author: Mohammed A. Farhan**

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**ABSTRACT**

In this research the structural modification of cellulose was carried out with maleic anhydride (H) as a spacer by using ceric ammonium nitrate (CAN) as an initiator, and grafted copolymer was substituted with amino drug such as amoxicillin (HA), 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 biodegradable, non toxic and slow digesting nature, the new drug copolymer was characterized by FTIR and UV Spectroscopes. Differential scanning calorimetry (DSC) and thermo gravimetric analysis (TGA). The physical properties were measured. 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.

**KEYWORDS:** Cellulose, maleic anhydride, amoxicillin, Copolymer, Drug Copolymer.**INTRODUCTION**

Cellulose is the most widely found natural polymer in nature, it is found in wood, cotton, hemp and other plant-based materials. It consists of repeating an hydro glucose units joined by  $\beta(1-4)$  linkages, forming the basic repeating unit. It is the structural component of the primary cell wall of green plants and many forms of algae. Cellulose is biocompatible and non-toxic, what makes it a good material candidate for medical applications e.g.: wound dressings, scaffolds for tissue engineering, soft tissue replacement and artificial blood vessels.<sup>[1]</sup> Cellulose is highly crystalline and generally insoluble, due to the intramolecular hydrogen bond networks extending from the O(3<sup>-</sup>)-H hydroxyl to the O(5) ring oxygen of the next unit across the glycosidic linkage and from the O(2)-H hydroxyl to the O(6<sup>-</sup>) hydroxyl of the next residue.<sup>[2]</sup>

Natural polymers are preferable due to low toxicity, renewability, flexibility to modification, biodegradability and low cost.<sup>[3]</sup> Natural polymers such as polysaccharides are hydrophilic, enzymatically degradable and are able to retain the stability of protein drugs incorporated in them as well as increase their (proteins) therapeutic effects.<sup>[4]</sup> Polysaccharides exhibit good haemo compatibility and interaction with living cells.<sup>[5]</sup> making them compatible and suitable biomaterials for long systemic circulation and targeting. Modification of natural polymers are a means to overcome their setbacks such as drop in viscosity, microbial degradation, and partial or low solubility. In

addition, modification of natural polymers enhances their drug delivery properties and versatility. Modification should be undertaken such that the natural polymers do not lose their biological properties. Methods of modification include grafting, crosslinking, derivative formation and polymer-polymer blending.<sup>[6]</sup> Amoxicillin is a white powder, Soluble in water with molecular formula (C<sub>16</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>S) maintained the broad-spectrum activity of Ampicillin, but with increased bioavailability . It is dissolve fast, has a high solubility and a good stability if the pH can be buffered at 8. Amoxicillin is one of the most important commercial antibiotics due to its high bacterial resistance and large spectrum against a wide variety of microorganisms.<sup>[7]</sup> It is effective against a wide range of infections caused by wide range of Gram -positive and Gram- negative bacteria in both human and Animals.<sup>[8]</sup> It act by inhibiting enzymes involved in bacterial cell wall synthesis. Drugs may also act by inhibiting extracellular reactions.<sup>[9]</sup> Graft polymerization of cellulose can be initiated by various initiator system such as potassium per sulfate, redox pair of Fe<sup>2+</sup>/H<sub>2</sub>O<sub>2</sub>, KMnO<sub>4</sub>/organic acid, transition metal ions/organic redactors, and also irradiation initiation, of the redox systems investigated so far the Ce (IV) ion has received considerable interest, because of its high graft yield and very low homo polymer formation<sup>[10]</sup> In this research the structural modification of cellulose was carried out with malic anhydride as a spacer by using ceric ammonium nitrate (CAN) as an initiator<sup>[11]</sup>, and grafted copolymer was substituted with amino drug such as amoxicillin (HA).

**EXPERIMENTAL****Instrumentation**

Melting points were measured using digital melting point, Stuart SMP 10. Infrared spectrophotometer measurements were performed using perkin elmer spectrum 65, U.V-Visible double beam scanning spectrophotometer V-650, at room temperature. Differential scanning calorimetry (DSC) and Thermo gravimetric analysis (TGA) were recorded using Shimadzu, Japan.

**A-Preparation of cellulose graft maleic anhydride (H)**

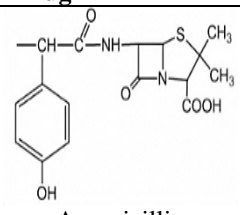
(2 gm) of cellulose dissolved in (10 ml) of acetone, (0.1gm) (1ml) of ceric ammonium nitrate (CAN), (2gm) of maleic anhydride (H) was added, the mixture was

introduced in polymerization bottle, and heated about (30) minutes at (60 °C), using water bath, the white color product was produced (92%), S.P (122-132 °C).

**B-Substituted of (H) with amino drugs (HA)**

(0.30 gm) of cellulose - g-maleic anhydride (H) was dispersed in (5ml) of Acetone, (0.50 gm) of amoxicillin 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 solution was filtered, the filtrate was isolated and the solvent was evaporated, the pink product (HA) cellulose-g-[N-Amoxicillinyl maleic acid] was dried at (50 °C) in a vacuum, conversion (80%), S.p. (135-138 °C). all physical properties were listed in table (1).

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

Pol. No	-Drug	Conversion %	Softening point °C	Color
HA	 <p>Amoxicillin</p>	80	135-138	Pink

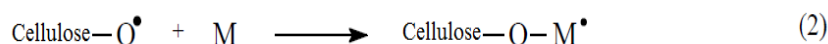
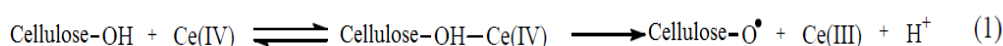
**RESULT AND DISCUSSION**

Chemical modification of cellulose by grafting with maleic anhydride. cellulose can be grafted as main chain of backbone of polymer, it was polymerized and initiated by various initiators.<sup>[12]</sup> Among the various types of redox initiators, ceric ion offers many advantages because of its high grafting efficiency. when (Ce<sup>+4</sup>) salts such as cerium ammonium nitrate (CAN) is used as

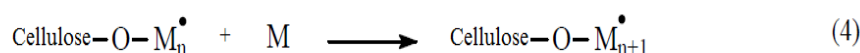
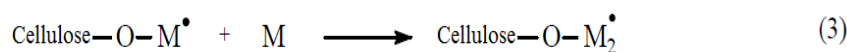
initiator in the grafting of vinyl monomers onto glucose, at first a ceric ion-glucose complex occurs, and then it decomposes to cerous (Ce<sup>+3</sup>) ion.<sup>[13]</sup> and glucose radicals created by hydrogen abstraction from glucos. Thus, The radical formation on the glucose backbone occur on the oxygen atom.<sup>[14,15]</sup> The -OH group present on the backbone of cellulose polymer acts as the active sites for the graft copolymerization.

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

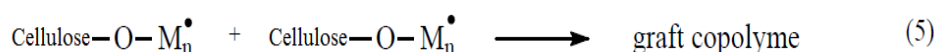
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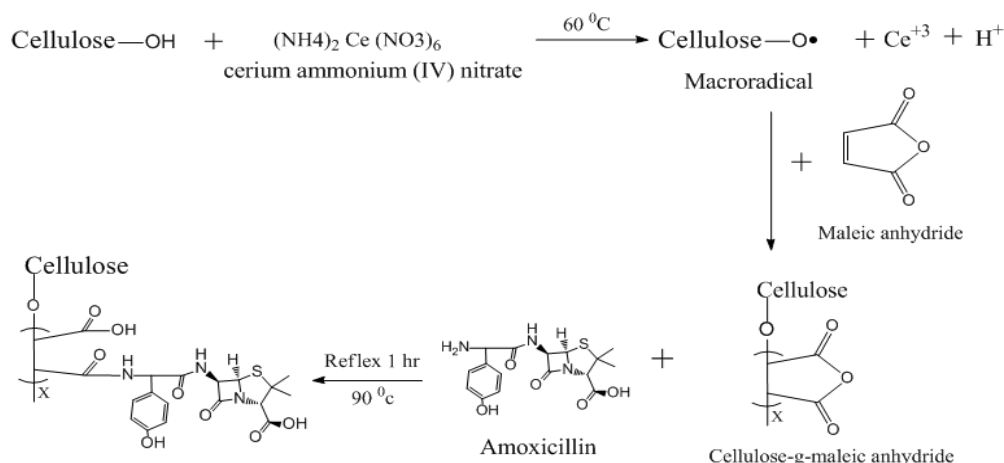
\* Propagation:



\* Termination:

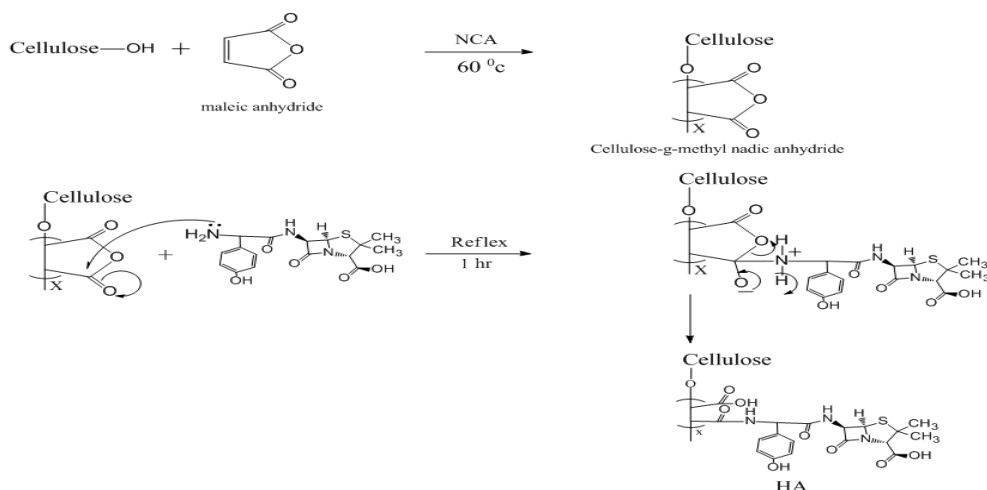
**Scheme (1) The mechanism of grafting reaction of monomer onto cellulose by CAN**

Graft co polymer was prepared by the reaction of cellulose with maleic anhydride by using ceric ammonium nitrate as a radical initiator. New drug polymer was prepared by the reaction of cellulose with maleic anhydride and substituted with amoxicillin in scheme below.



### Scheme (2) cellulose-g- maleic anhydride and Substituted it with amoxicillin.

The presence of  $-\text{NH}_2$  group in the drug, which acts as strong nucleophile attack on the  $\text{C}=\text{O}$  group of maleic anhydride produced N-drug substituted, the mechanism of reaction was described as shown below.<sup>[16]</sup>



### Scheme (3) Mechanism of Ring opening reaction of cellulose -g- Maleic anhydride by nucleophilic reaction.

Figure (1) FTIR spectrum of natural polymer (cellulose) showed absorption bands at  $(3345\text{ cm}^{-1})$  of (O-H) group and (C-O-C) ether absorption band at  $(1025-1117\text{ cm}^{-1})$ , band at  $(2904)\text{ cm}^{-1}$  due to (C-H aliphatic) stretching.

Figure (2) FTIR spectrum of (H) cellulose grafted maleic anhydride gave the characteristic absorption of carbonyl group of anhydride band was appeared at  $(1740-1775\text{ cm}^{-1})$  in addition to the cellulose backbone absorptions.

Figure (3) FTIR spectrum of (HA) Cellulose-g-[N-Amoxicillinyl male amic acid] copolymer containing (-NH amide) as characteristic absorption was appeared at  $(3283\text{ cm}^{-1})$  in addition absorption for carbonyl of amide (CONH) appeared at  $(1658\text{ cm}^{-1})$ , band at  $(1720)\text{ cm}^{-1}$  due to (C=O) stretching vibration of acid. Other bands of the compounds are listed in table.<sup>[2]</sup>

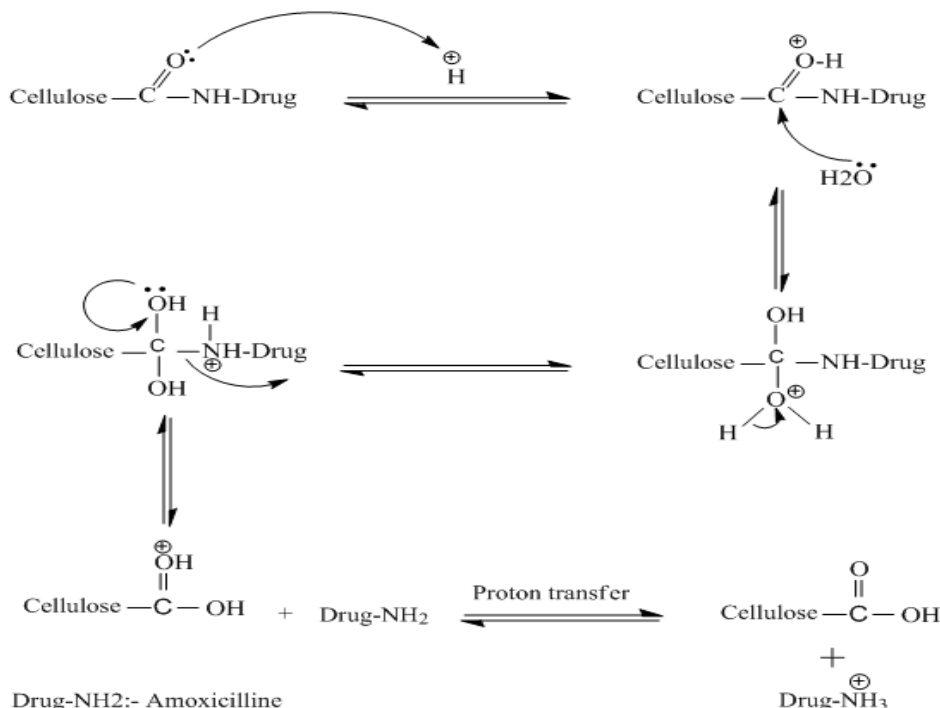
**Table (2): FT-IR absorptions of grafted natural polymers (cellulose) with maleic anhydrides and substituted with drug compound (amoxicillin) [HA]**

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	$\nu(\text{C=O})$ $\text{cm}^{-1}$ carboxylic	$\nu(\text{O-H})$ $\text{cm}^{-1}$ carboxylic	$\nu(\text{C-O-C})$ $\text{cm}^{-1}$ Ether	$\nu(\text{C-H})$ $\text{cm}^{-1}$ aliphatic	$\nu$ other band $\text{cm}^{-1}$
Cellulose	3345 broad	-	-	-	-	-	-	1025-1117 Strong	2904	-
H	3345	-	-	-	-	1709	2400-3500 Very broad	1082-1113 Strong	2896	Anhydride 1740-1775 Overlap
HA	-	3283	1658 Strong	1519	3056	1720 Overlap	2400-3500 Very broad	1003 - 1105 Strong	2932	-

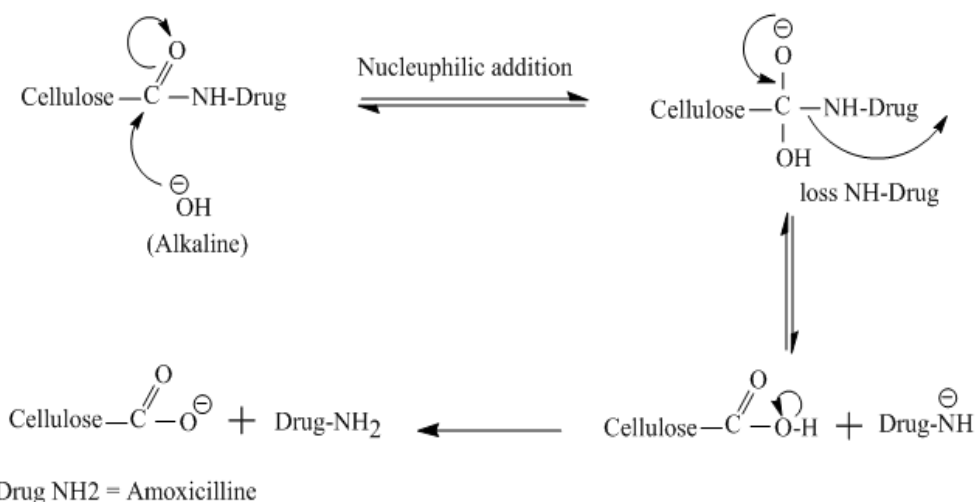
**Controlled drug release**

Release of (HA) was studied, (100 mg) was added continuously in (100ml) buffer solution at (37°C). the wave length of  $\lambda_{max}$  was measured at different periods and different pH values (1.1 –7.4) by using UV spectrometer. These samples were analyzed 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.<sup>[16]</sup> Mechanism of these drug polymer were illustrated as shown in the scheme.<sup>[4,5]</sup>



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



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

**Thermal Properties of polymer drug<sup>[13]</sup>**

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 and DSC curves as shown in table (3) and table (4).

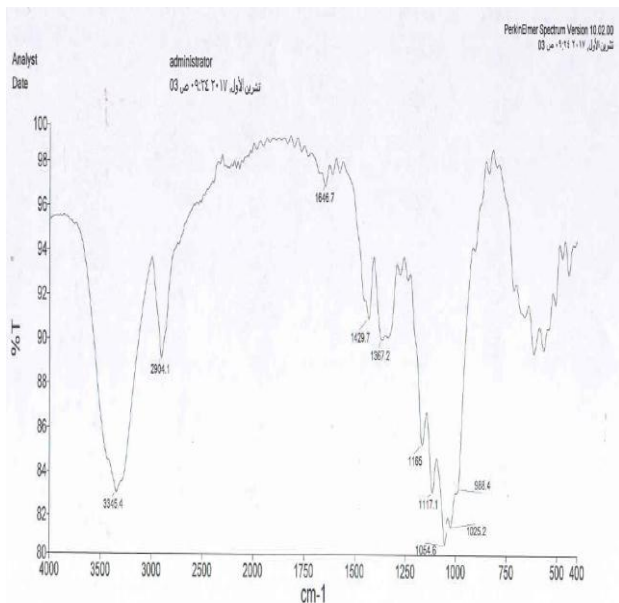
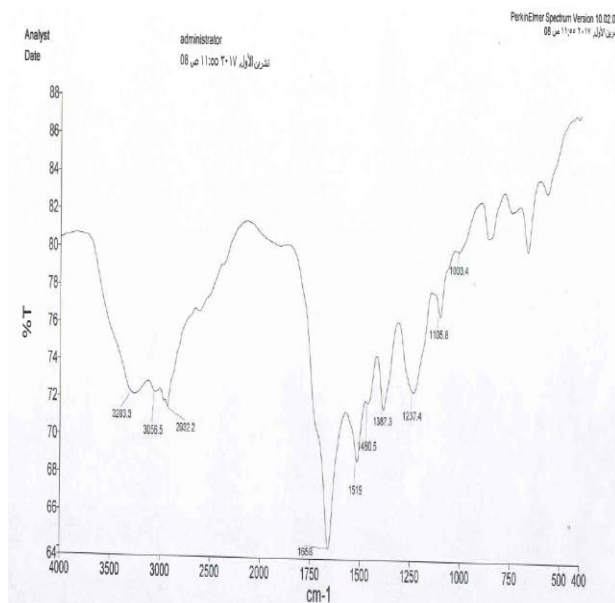
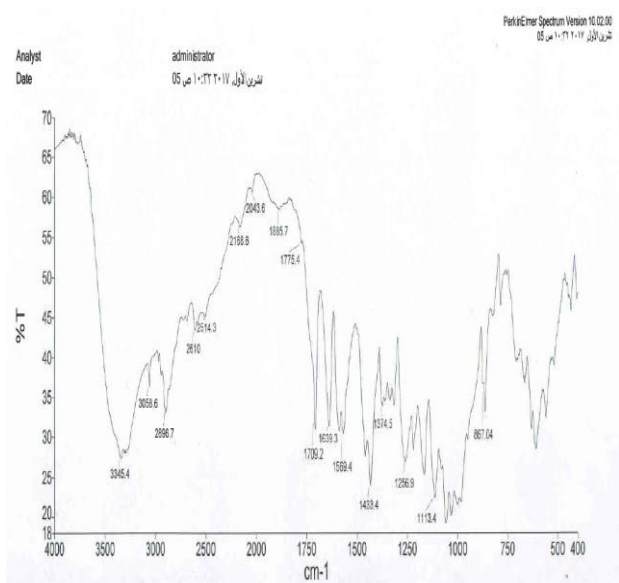
**Table (3) TGA Analysis of some polymer drugs**

No. drug polymer	Temperature	Losses weight%
H	219, 372, 594	37, 53, 8
HA	457, 593	71, 28

**Table (4) DSC Analysis of some polymer drugs.**

No. drug Polymer	Onset Temp. °C	End set Temp. °C	Peak Temp. °C	ΔH J/g
H	132.2	173	140.2	292.2
HA	122	175.3	130	64.1

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 cellulose.****Figure (3) FTIR spectrum of cellulose-g-[N-Amoxiclinyl male amic acid] (HA).****Figure (2): FTIR spectrum of cellulose-g-maleic anhydride (H).**

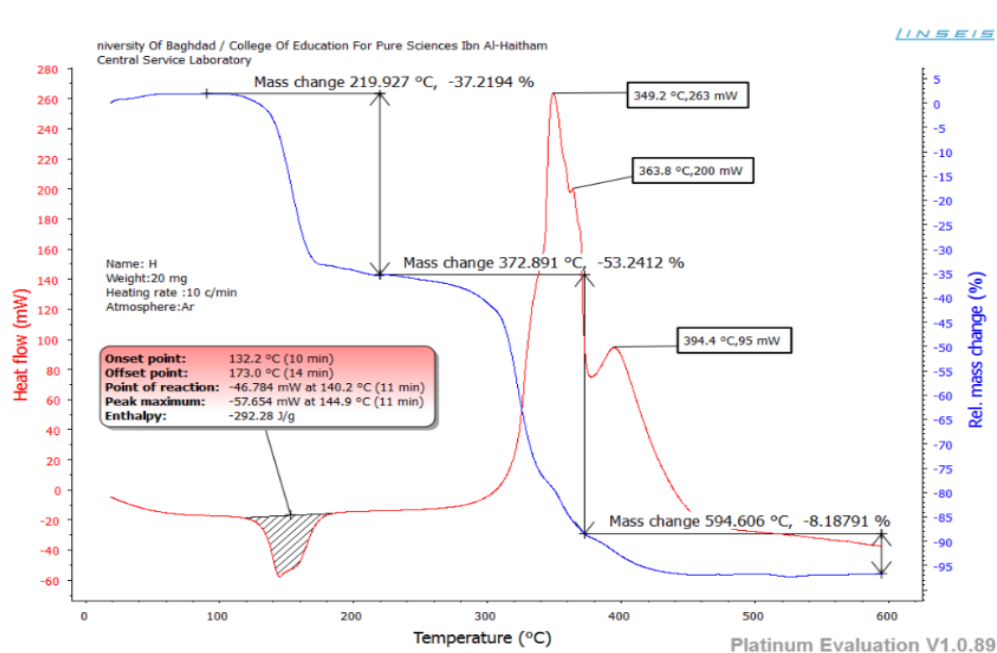


Figure (4) DSC and TGA Analysis of H.

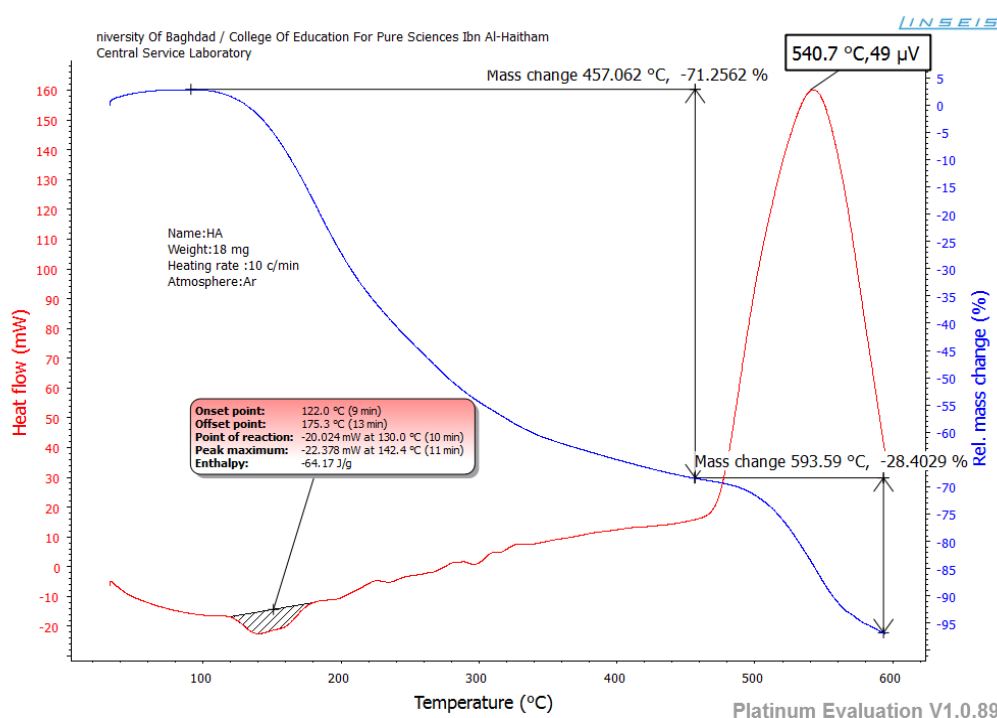


Figure (5) DSC and TGA Analysis of HA.

## REFERENCES

1. Justyna Kucińska-Lipka<sup>1</sup>, Iga Gubańska<sup>1</sup>, Helena Janik<sup>1</sup>, Polyurethanes modified with natural polymers for medical application. Part II. Polyurethane/gelatin, polyurethane/starch, polyurethane/cellulose, polymer, 2014; (195—276).
2. Hongliang Kang, Ruigang Liu, Yong Huang, Graft modification of cellulose: Methods, properties and applications, polymer, Polymer, 2015; 70: A1-A16.
3. Ngwuluka, N.C.; Akanbi, M.; Agboyo, I.; Uwaezuoke, O.J. Characterization of gum from Sesamum indicum leaves as a suspending agent in a pediatric pharmaceutical suspension. WJPR, 1, 909–924, 2012.
4. Sonia, T.A.; Sharma, C.P. An overview of natural polymers for oral insulin delivery. Drug Discov. Today, 2012; 17: 784–792.
5. Malafaya, P.B.; Silva, G.A.; Reis, R.L. Natural-origin polymers as carriers and scaffolds for biomolecules and cell delivery in tissue engineering applications. Adv. Drug Deliv. Rev., 2007; 59: 207–233.

6. Ndidi C. Ngwuluka, Nelson A. Ochekepe 1 and Okezie I. Aruoma, *Naturapolyceutics: The Science of Utilizing Natural Polymers for Drug Delivery*, *Polymers*, 2014; 6: 1312-1332.
7. A thesis, Sana H. Awad, *Synthesis and Characterization of Some New Drug Derivatives of Natural Polymers*, University of Baghdad, Iraq, 2016.
8. SIMAR PREET KAUR, REKHA RAO, SANJU NANDA., (Amoxicillin, a Broad Spectrum Antibiotic), *International Journal of Pharmacy and Pharmaceutical Sciences*, 2011; 3(3): 30-37.
9. Denise R. Ferrier, PhD, *Lippincott's Illustrated Reviews: Biochemistr, SixthEdition*, Drexel University College of Medicine, New York, 2014.
10. Nguyen T., Nguyen V., kinetics and mechanism of graft polymerization of acrylic acid on to starch initiated with ceric ammonium nitrate, *Journal of Chemistry*, 2010; 48(5): 621-626.
11. Kaviani neelam, sharma vijay, singh lalit, various techniques for the modification of starch and the applications of its derivatives, *International research journal of pharmacy*, 2012; 3(5).
12. Isam Y. M., Fakhru<sup>1</sup>- Razi A., Suleyman A., Mansor B., Rahman A., Yunus W. M. Z., (Preparation and characterization of poly(methylmethacrylate) grafted sago starch using potassium persulfate as redox initiator), *Journal of Applied Polymer Science*, 2004; 94(5): 1891-1897.
13. A thesis, Ahlam Ahmed Frayyih AL-Shihani, *Synthesis and Characterization of Graft Copolymers as Fillers of Dentistry*, Al-mustansiriyah University, Iraq, 2016.
14. Susheel Kalia<sup>1</sup>, M.W. Sabaa<sup>2</sup>, *Polysaccharide Based Graft Copolymers*, <sup>1</sup>Dept. of Chemistry, Bahra University, India, <sup>2</sup>Faculty of Science Cairo University, Egypt, New York, 2013.
15. Nguyen T.T, nguyen V., KINETICS AND MECHANISM OF GRAFT POLYMERIZATION OF ACRYLIC ACID ONTO STARCH INITIATED WITH CERIC AMMONIUM NITRATE, *Journal of Chemistry*, 2010; 48(5): 621-626.
16. Firyal M.Ali Sana .H.Awad\* Mena. M. Hamid, *Synthesis of Substituted Gelatine Grafted Maleic Anhydride as Drug Copolymer*, *Chemistry and Materials Research*, 2015; 7(5): 1-8.