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# Synthesis and Characterization of Starch Grafted Maleic Anhydride and Substituted With Ampicillin

**Firyal Mohammed Ali[1], Mohammed Alwan Farhan[2*]**
[1]Department of Chemistry, College of Science, Al-Mustansiriyah University, Baghdad, Iraq
[2]Department of Chemistry, College of Science, Diyala University, Diyala, Iraq
***Corresponding author: E-Mail: alshamary_198840@yahoo.com**

**ABSTRACT**

In this research the structural modification of starch was carried out with maleic anhydride (M2) as a spacer via ceric ammonium nitrate (CAN) as an initiator, and grafted copolymer was substituted with amino drug such as ampicillin (M2E), this design of carries for controlled delivery of therapeutic agent which can release the drug over a long period of time, due to its biodegradable, non-toxic and slow break down nature, the characterization of new drug copolymer was achieved by FTIR, $^1$H-NMR and UV Spectroscopes. The physical properties were measured. 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.

**KEY WORDS:** Starch, Maleic anhydride, Ampicillin, Copolymer, Drug Copolymer.

## 1. INTRODUCTION

Natural sugars and their derivatives represent a group of polymers widely used in pharmaceutical and biomedical fields for the release of controlled drugs. The advantages of control systems for controlled drugs delivery are mainly to optimize concentration, usually for long periods of time, to enhance the activity of risk drugs, and to reduce the side effects of reduction of high initial blood concentration. Natural polymer do the advantages over synthetic polymers, generally because they are non-toxic, cheaper, biodegradable, and freely offered (Sabyasachi, 2010). Starch is a polysaccharides which occurs naturally, is an inexpensive polymer with an expanded application in the food processing industry because of its integrity, and biodegradability (Hui, 2008) and specific technological properties, such as gelling, thickening, film forming (Durdica, 2015). Starch is formed by all green plants as an energy store and is a important energy source for humans. It is found in potatoes, wheat, rice, and other foods, and it varies in appearance, depending on its source (Abbas, 2010).

The modification of natural polymers as a way to overcome their reversals such as low viscosity, microbial degradation, and partial or low melting. In addition, the modification of natural polymers enhances the properties of drug delivery and ingenuity. Modification should be accepted such that the natural polymers do not lose their biological properties. Techniques of modification include grafting, crosslinking, derivative formation and polymer-polymer blending (Ololade, 2016). The chemical modifications of natural polymers like starch grafting of vinyl monomers onto it by using initiators, seems to be promising modification to impart desirable properties (Susheel, 2013). Ampicillin is a white powder with molecular formula ($C_{16}H_{19}N_3O_4S$), it is a semi synthetic antibiotic, a member of the penicillin family of antibiotics, it is synthesized to extent the usefulness of the penicillin to the treatment of infection caused by gram-negative (Essack, 2001) and Gram-positive , intestinal bacilli, salmonella, shigella, enterococci, listeria, and a few strains of hemophilic bacilli. Ampicillin is the preferred medicine for infections caused by beta-lactamase negative types of Haemophilus influenza, Listeria monocytogenes, and enterococci. It is used for bronchitis, pneumonia, dysentery, salmonella, whooping cough, pyelonephritis, endocarditis, sepsis, and so on (Vardanyan, 2006). Ampicillin acts as inhibitor of the enzyme transpeptidase, which is required by bacteria to make their cell_walls. Therefore, ampicillin is usually bacteriolytic (Petri, 2011). In this research the structural modification of starch was carried out with malic anhydride (M2) as a spacer by using ceric ammonium nitrate (CAN) as an initiator (Simar, 2011), and grafted copolymer was substituted with amino drug such as ampicillin (M2E).

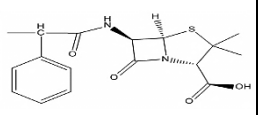
## 2. EXPERIMENTAL METHODS

**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. Differential scanning calorimetry (DSC) and Thermo gravimetric analysis (TGA) were recorded using Shimadzu, Japan. All chemicals were purchased from Fluka and BDH; all the available chemical reagents were used without further purification.

**A-Preparation of starch graft maleic anhydride (M2):** (3.0 gm, 0.018 mole) of starch dissolved in (25ml) of acetone, (0.1gm) (1ml) of ceric ammonium nitrate (CAN), (3gm, 0.03 mole) of maleic anhydride (MA) was added, the mixture was introduced in polymerization bottle, heated about (30) minutes at (60$^0$C), using water bath, the green color product was produced (90%). S.P (122-126$^0$C).

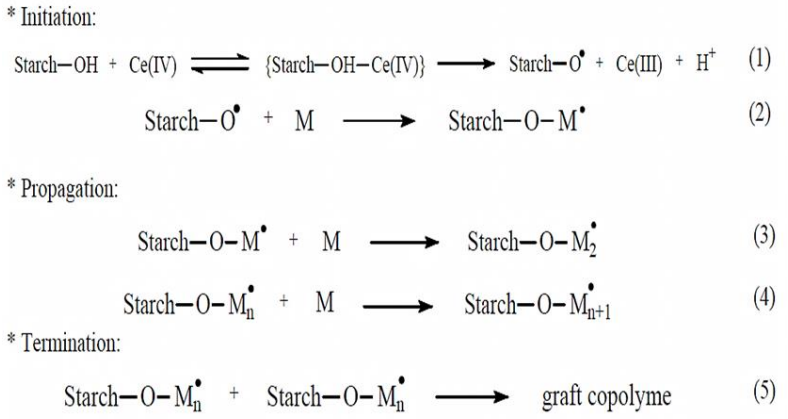
**B-Substituted of (M2) with amino drugs (M2E):** (0.30 gm, 0.0011mole) of starch- g-maleic anhydride (M2) was dispersed in (5ml) of Acetone, (0.50 gm, 0.0013 mole) of ampicillin dissolved in (5ml) of dioxane, (0.5 ml) of DMF was added to the mixture, the mixture was refluxed with stirring about 1 hour at ($90^0$c), the colored solution was filtered, the filtrate was isolated and the solvent was evaporated, the Yellow-green product (M2E) starch-g-[N-Ampicillinyl male amic acid] was washed with di ethyl ether two times and dried at ($50^0$C) in a vacuum, conversion (80%), S.p. (70-$78^0$C). all physical properties were listed in table.1.

**Table.1. Physical properties of prepared Polymer (M2E)**

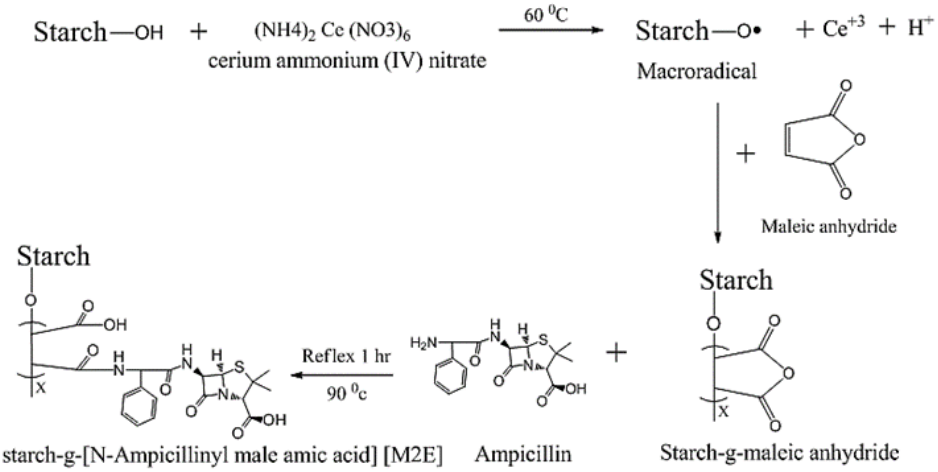
| Pol. No | -Drugs | Color | Softening point $^0$C | Conversion % |
|---|---|---|---|---|
| M2E |  Ampicillin | Yellow-green | 70-78 | 80 |

## 3. RESULT AND DISCUSSION

Chemical modification of starch by grafting with maleic anhydride. Starch can be grafted as main chain of backbone of polymer, it was polymerized and initiated by various initiators (Simar, 2011). Between the different types of initiators, ceric ion give 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 (Denise, 2014) and glucose radicals created by hydrogen abstraction from glucose .Thus, The radical formation on the glucose backbone occur on the oxygen atom (Nguyen, 2010). 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)

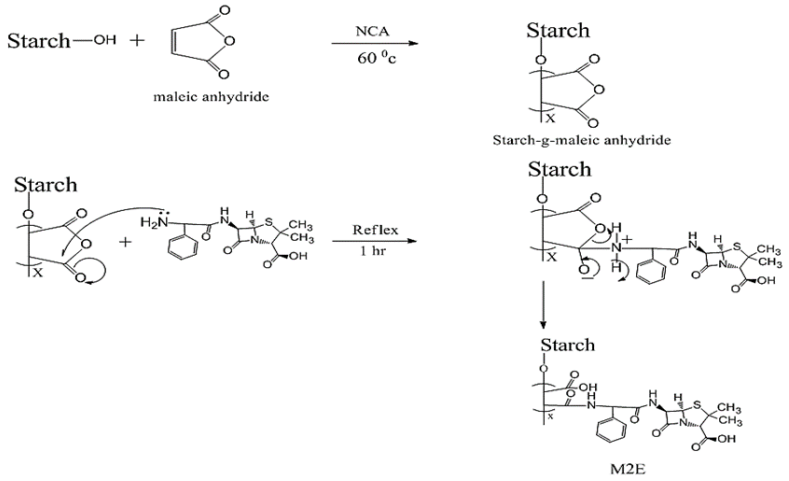



**Scheme.1. The mechanism of grafting reaction of monomer onto starch by CAN:** Graft co polymer was prepared by the reaction of starch with maleic anhydride via ceric ammonium nitrate as a radical initiator. New drug polymer was prepared by the reaction of starch with maleic anhydride and substituted with amoxicillin in reaction below.




**Scheme.2. Starch-g- maleic anhydride and Substituted it with Ampicillin**

The presence of $–NH_2$ group in the drug, which acts as strong nucleophile attack on the C=O group of maleic anhydride produced N-drug substituted, the mechanism of reaction was described as shown below (Isam, 2004).




**Scheme.3. Mechanism of Ring opening reaction of Starch -g- Maleic 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 (M2) starch grafted Maleic 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, FTIR spectrum of (M2E) starch-g-[N-Ampicillinyl male amic acid] copolymer containing hydroxyl group as characteristic absorption which was appeared at (3290 $cm^{-1}$) in addition (-NH)which was observed at (3146 $cm^{-1}$), absorption of amide (CONH) appeared at (1651 $cm^{-1}$), absorption peak at (1716) $cm^{-1}$ due to (C=O) stretching vibration of acid. Other bands of the compounds are listed in table.2.

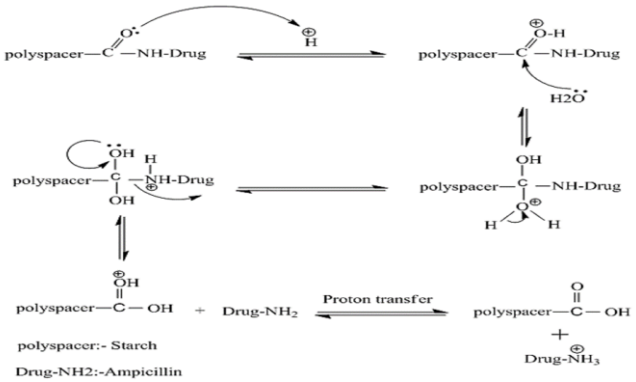
**Table.2. FT-IR absorptions of grafted natural polymers (Starch) with maleic anhydrides and substituted with drug Compound (ampicillin) [M2E]**

| Comp No. | υ(O-H) $cm^{-1}$ alcohol | υ(N-H) $cm^{-1}$ mide | υ(C=O) $cm^{-1}$ amide | υ(C=C) $cm^{-1}$ aromatic | υ(C-H) $cm^{-1}$ aromatic | υ(C-O) $cm^{-1}$ acid |
|---|---|---|---|---|---|---|
| **starch** | 3290 broad | - | - | - | - | - |
| **M2** | 3209 | - | - | - | - | 1327 strong |
| **M2E** | 3290 broad | 3146 | 1651 strong | 1531 | 3063 | 1253 |

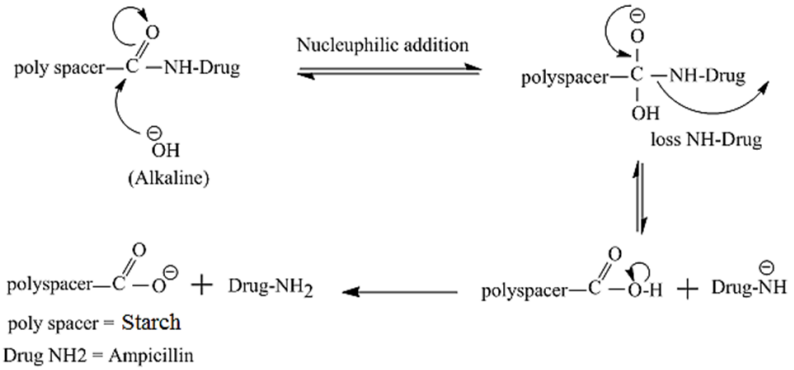
| Comp No. | υ(C=O) $cm^{-1}$ carboxylic | υ(O-H) $cm^{-1}$ carboxylic | υ(C=O) $cm^{-1}$ | υ(C-O-C) $cm^{-1}$ Ether | υ(C-H) $cm^{-1}$ aliphatic | υ other band $cm^{-1}$ |
|---|---|---|---|---|---|---|
| **starch** | - | - | - | 1012-1149 strong | 2928 | - |
| **M2** | 1703 | 2400-3500 Very broad | - | 1080-1213 | 2874-2968 | Anhydride1 776-1855 strong |
| **M2E** | 1716 | 2400-3500 Very broad | 1354 | 1003-1209 | 2850-2916 | - |

The $^1$H-NMR spectrum of prepared polymer (M2E) was showed in figure.4, which showed the following signals 1.2 ppm (Singlet, 3H, $CH_3$), 6.0 ppm (Singlet, 1H, CO-NH amide), 7.3-7.5 ppm (5H, Aromatic ring), 2.0 ppm, (doublet, 1H, -CH).

**Controlled release of drug polymer (M2E):** Hydrolysis of (M2E) was studied, by addition (100 mg) continuously in (100 ml) buffer solution at ($37^0$C). The wave length of $\lambda_{max}$ = (205-260 nm) was measured for 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 observed the sustained release by measuring the mole fraction were constructed from UV. Designated the rate of hydrolysis in basic medium is higher than acidic medium. Mechanism of the hydrolysis of drug polymer was illustrated as shown in the schemes.4 and 5.




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




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

**Thermal Properties of drug polymer** (Ahlam, 2016): 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 prepared drug polymer**

| No. drug polymer | Temperature | Losses weight% |
|---|---|---|
| M2 | 167, 305, 380 | 21, 38, 39 |
| M2E | 496 | 71 |

**Table (4) DSC Analysis of prepared drug polymer**

| No. drug Polymer | Onset Temp. $^0$C | End set Temp. $^0$C | Peak Temp. $^0$C | ΔH J/g |
|---|---|---|---|---|
| M2 | 107 | 154 | 115.6 | 82.74 |
| M2E | 107 | 141.6 | 113.2 | 19.6 |

It was concluded that the thermal stability of drug polymer was more than the room temperature for stored it, this cause more expire date and more protection of the drug satiability.

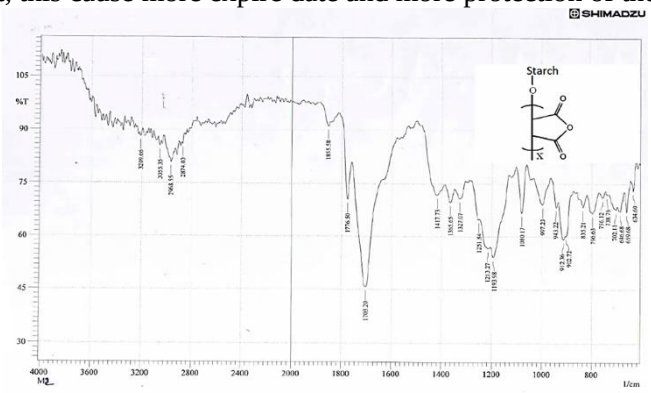



**Figure.1. FTIR spectrum of starch**

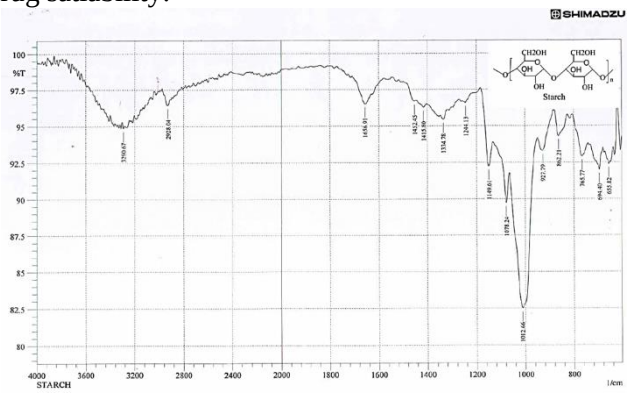



**Figure.2. FTIR spectrum of starch-g-maleic anhydride (M2)**

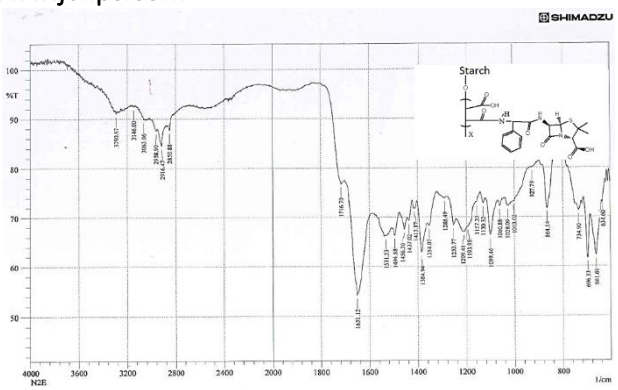



**Figure.3. FTIR spectrum of starch-g-[N-Ampicillinyl male amic acid] (M2E)**

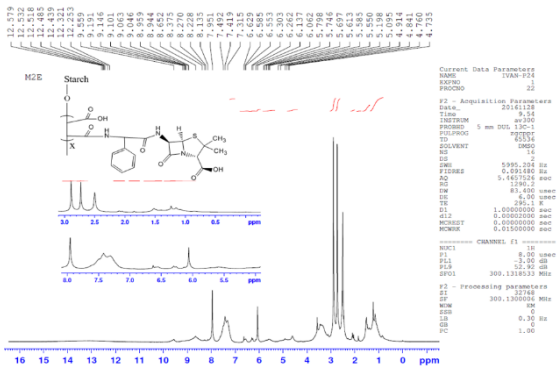



**Figure.4. $^{1}$H-NMR Spectrum of M2E**

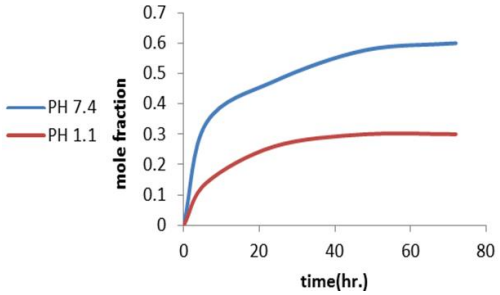



**Figure.5. Rate of hydrolysis of drug polymer M2E**

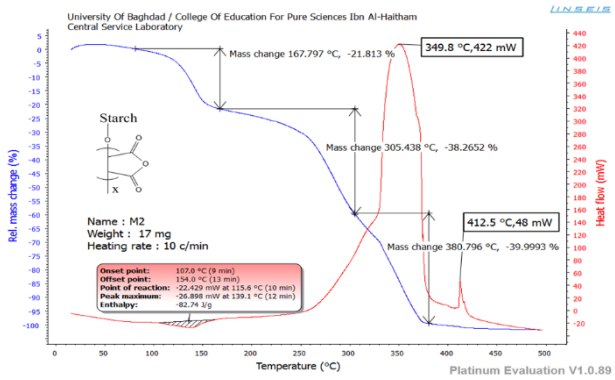



**Figure.6. DSC and TGA Analysis of M2**

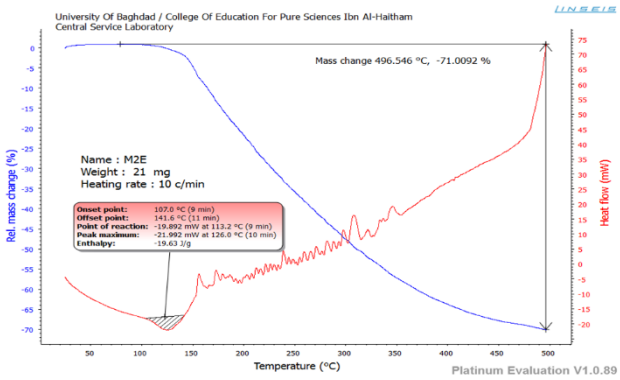



**Figure.7. DSC and TGA Analysis of M2E**

## 4. CONCLUSION

In this research new design natural polymer is prepared, due to their outstanding characteristics has received more attention in the field of controlled drug delivery. The present work with the new method working for the modification of poly saccharides and the developments in designing novel drug delivery systems. This new prepared drug polymer has suitable properties and the release of drug gradually controlled in different pH values. The substitution of bioactive drug on the chain of polymer could lead to most accuracy, effectiveness, no toxicity, long life and water soluble drug polymer. In this research, the prepared drug polymer was higher hydrolysis in basic medium than acidic medium, this lead to using as specific site, and the TGA result of prepared drug polymer indicated the high thermal resistance and showed its steps of weight loss-temperature. This high thermal resistance indicated the high molecular weight of the prepared polymer with high interaction between amide hydrogen bonding through the polymer chains and led to best expire date to protect the drug.

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