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CONTROLLED DRUG RELEASE OF GRAFTED PECTIN

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ABSTRACT

Modification of Pectin as natural polymer was accepted as new bio adhesive polymer, which was grafted with Maleic anhydride as vinylic monomore and insertion by using ceric ion it, was substituted with amino drugs produced amide polymer which do not lose their biological properties. This design carries controlled delivery which could release the entrapped drug over an extended period of time due to its slow digesting nature. The prepared adhesive drug polymer was characterized by FTIR, ^{1}H-NMR spectroscopes, thermo gravimetric analysis TGA and DSC were careful. Physical properties of prepared polymer was quiet, Biological activity was studied for adhesive drug polymer, this new adhesive drug biological polymers were applied on different infected mice and wounds, It gave outstanding results and compliance mice infected with a full recovery by a short period of time. The prepared drug copolymer was analyzed in different pH values at 37 ^{0}C *in vitro* study and controlled drug release was messured through three days . The rate of hydrolysis in basic medium was found higher than acidic medium. It was concluded that modified drug release with extended drug action via slow release and *in vivo* performance was renowned to be talented.

Keywords: Pectin, controlled delivery, adhesive drug polymers, Graft Copolymer

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INTRODUCTION

The modification of natural polymers is a promising technique for the making a new materials. The productive method can change common polymers so as to synthesize natural-based greatest absorbent polymers[1]. Natural polymers are modified as a means to overcome their setbacks such as drop in viscosity, microbial degradation, and partial or low solubility. The most important source of commercial Pectin today is waste from the juice industry in the form of citrus peel, mainly from lemon and lime. Other commercial Pectin are sourced from orange peel and apple pomace, and an emerging new source is from sugar beet from the sugar industryIn addition, modification of natural polymers enhances their drug delivery characteristics and versatility[2]. Modification of polymers should be undertaken such that the natural polymers do not lose their biological properties. The methods of modification include grafting, crosslinking, derivative formation and polymer-polymer blending [3]. Pectin is important structural components of cell walls of the soft non woody parts of fruit, vegetables and terrestrial plants. Within a living plant it is an important structural polysaccharide with functions in plant [6-8]. Pectin and generally refers to Pectin with 50% or more methyl ester groups on the HG backbone, and low DE Pectin (LM Pectin) with fewer than 50%. The methyl-ester content is particularly important in Pectin research as it strongly determines the physical properties of Pectin. The GalA residues at O-2 and O-3 may also be partially esterified with acetic acid in certain plant species such as sugar beet [5]Again, the ratio between acetylated and non-acetylated GalA is referred to as the degree of acetylation (DAc) [9-11]. Well-characterised component constitutes the. [12] They are highly branched structures with neutral sugar side chains of varying degrees of polymerisation attached to O-4 or O-3 position on the α-L- rhamnose residues. [13-16].

Spectin extraction in the laboratory[19-22], tends to be under milder conditions and to have more complex steps

[23]. Extraction may be optimised to preserve or isolate parts of the pectin depending on what is being researched. An alternative method of pectin extraction is microwave-assisted. To create pectins for different functions, the pectin has to be modified [24-28]. This is easily achieved as pectins are unstable and susceptible to changes in pH and temperature. Pectin has good stability in aqueous solution at around pH 3-4. At acidic conditions lower than pH 3 glycosidic bonds and methyl-ester linkages may undergo hydrolysis. The rate of hydrolysis increases with higher temperature and lower pH. [29-32], that mild acid hydrolysis causes the progressive release of sugars accompanied by their rapid degradation [29-32]. The research purpose included modification of Pectin as natural polymer can grafted with Maleic anhydride as vinyl monomer and insertion by using ceric ion, it was substituted with amino drugs produced amide polymer which do not lose their biological properties. This design carries controlled delivery which could release the entrapped drug over an extended period of time due to its slow digesting nature.

Experimental

MATERIALS

Pectin was purchased from Fluka and dried at 110°C for about 2 h. to remove absorbed moisture. Cerium ammonium nitrate (CAN), Maleic anhydridem, Amoxicil procaein and were purchased from Sigma Chemicals, All other solvents and reagents were of analytical grade

Instrumentation

Melting point was 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 beamscanning spectrophotometer VARIAN (UV-Vis)-100 Conc, at room temperature.

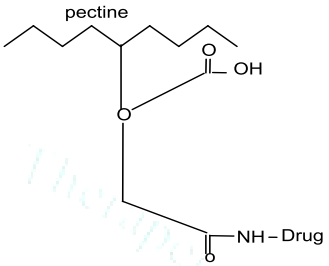
Industrial Pectin have particular specifications, confirmed by the Food and Agriculture Organisation that includes no less than 65% GalA, as well as various other stipulations to fulfil the specification of E440 as a food additive. However**,**

A-preparation of pectine grafted malic anhydride (H1)

(1Gm) of pectin was dissolved in (10ml) of acetone, (o.5ml) of ceric ammonium nitrate solution (CAN), (1Gm) of malic anhydride was added, the mixture was introduced in polymerization bottle, the mixture was heated about (40) minutes at (60 °C), using water bath, the yellow nutty color product was produced (90%), S.P (120-125 °C).

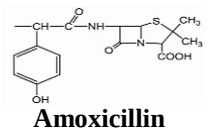
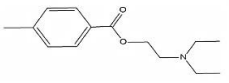
(CAN was prepared by adding 1 Gm from it in 10 ml from 5% HNO3)

B-Substitution of (H1) with amino drugs (H1A-H1B)



(0.30 Gm) of pectine- g-malic anhydride was dispersed in (5ml) of acetone, (0.30 Gm) of amoxicillin dissolved in (5mL) of dioxin, (0.5 mL) of DMF was added to the mixture, was heated with stirring and the best time was 1 hour at (90 °C), the colored solution was filtered, the filtrate was isolated and the solvent was evaporated, the brown product picten-g-[N-amoxicllinyl malic anhydride] was washed with di ethyl ether two times and dried at (50 °C) in a vacuum, conversion (80 %). S. p. (115-125 °C). Similar procedure was used for preparation with other amino drug such as procaine all physical properties were listed in table (2)

Table 1: Physical properties of prepared polymers (H1A-H1B)

Pol.	-Drugs	Color	Softeningpoin°C	Conversion ratio %
H1A	 Amoxicillin	yellow	115-125	80
H1B	 Procaine	Black	60 – 75	70

Controlled drug release

Release of H1A was studied. 100 mg was added continuously in (100 ml) buffer solution at (37 ^{0}C). The wavelength of λ_{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 the sustained

release was measured by the mole fraction constructed from UV spectra.

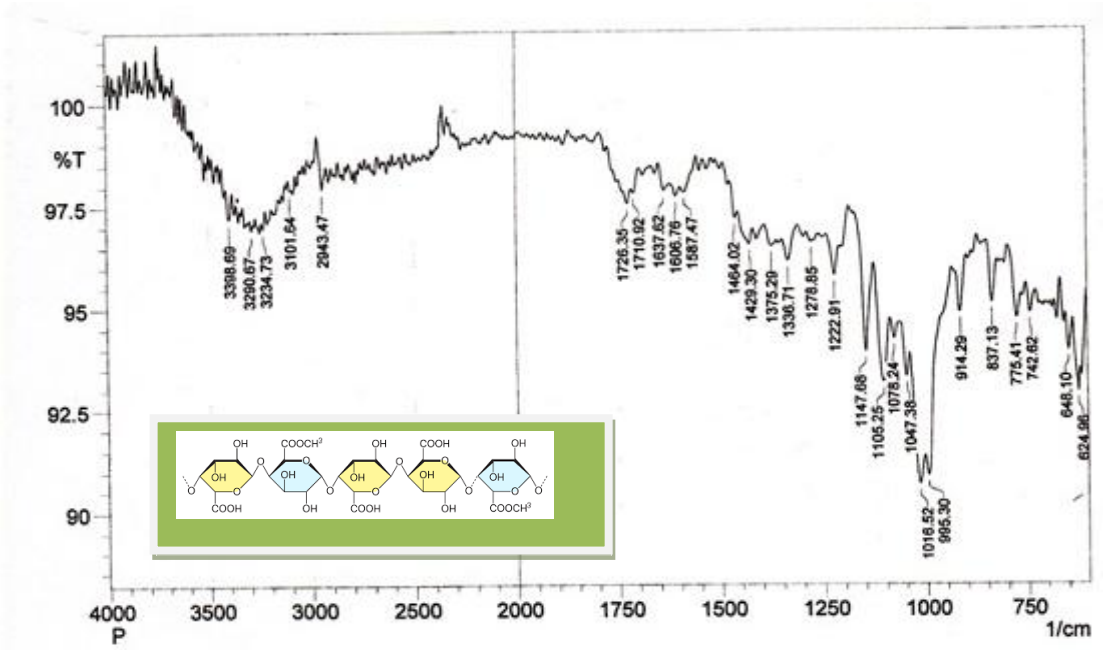
Determination of median lethal (LD_{50}) [33]

In this experiment 6 mice (three male, 3 female) were administered with 3 % H1A. The mice were watched for 72 hours, the LD_{50} value revealed that H1A. has no toxic effect on mice.

RESULTS AND DISCUSSION

Pectin was grafted with Maleic anhydride. Pectin can initiated by ceric (Ce^{+4}) salts ion , because of its high When such as cerium ammonium grafting efficiency. nitrate (CAN) is in the grafting of vinyl monomers onto Pectin, at first a ceric ion–Pectin complex occurs, and then it decomposes to (Ce^{+3}) ion and Pectin radicals created by hydrogen abstraction from Pectin. Thus, the radical formation on the Pectin backbone occurs on the backbone of Pectin polymer acts as the active sites for the graft copolymerization. The mechanism of grafting monomer on to Pectin.

Figure (1) FTIR spectrum of (pectin) showed the main absorption band at (3230) $cm^{-1}$of (O-H) group and (C-O-C) ether absorption bands at (1012-1360)cm^{-1},othr band appeared at (2961) cm^{-1} due to (C-H aliphatic) stretching.



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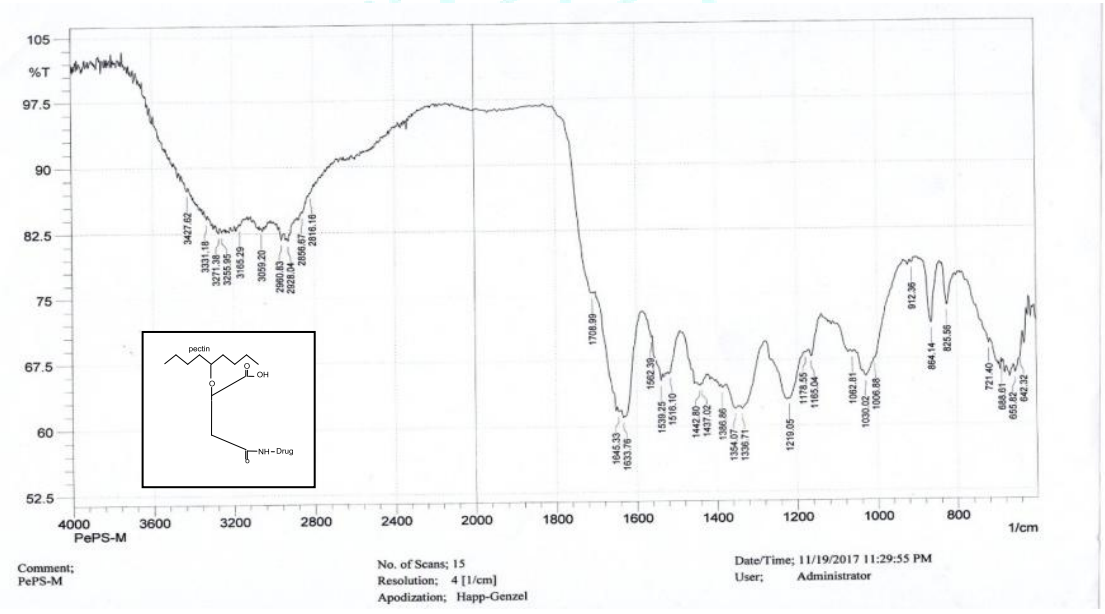


Figure 2: FTIR spectrum of (H1) pectin grafted Maleic anhydride gave the characteristic absorption of carbonyl group of anhydride band was appeared at (1776 and 1855 cm^{-1}) in addition to the pectin backbone absorptions.

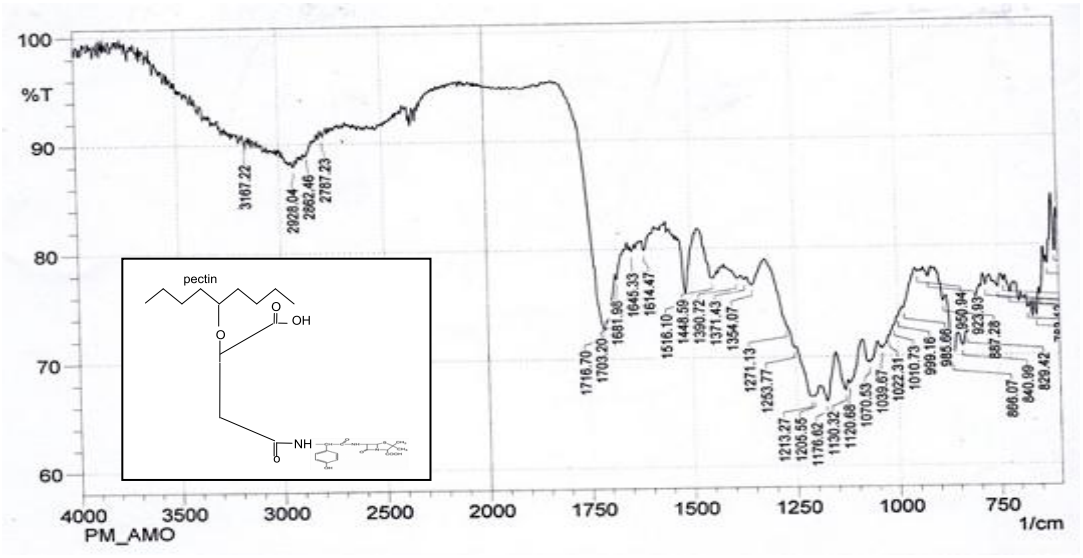


Figure 3: FTIR spectrum of (H1**A**) pectin-g-[N-amoxillin maleamic acid]

Copolymer containing hydroxyl group as characteristic absorption was appeared at (3340 cm^{-1}) in addition (-NH) at (3220 cm^{-1}), absorption of amide (CONH) appeared at (1640 cm^{-1}), band at (1706) cm^{-1} due to (C=O) stretching vibration of acid.

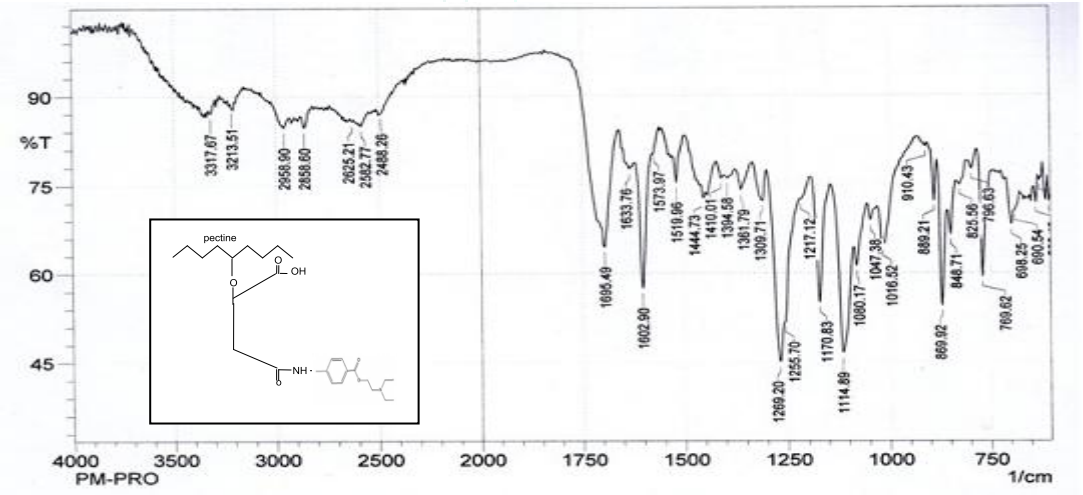


Figure 4: FTIR spectrum of (H1**B**) pectin-g-[N-procain maleamide]

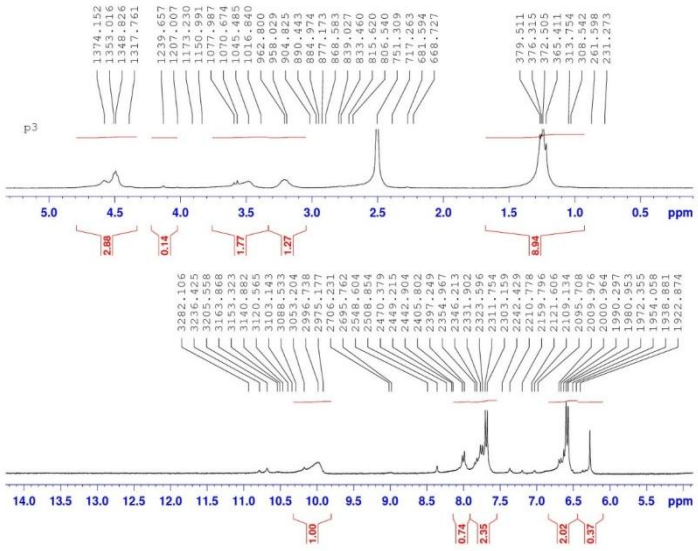


Figure 5: H-NMR Spectrum of pectin maleic procain

^{1}H-NMR spectrum of prepared polymer (H1) was showed in Figure (5), which showed the following signals

1.25 ppm (Triplet, 3H, CH_3), 2.34 ppm (Triplet, 2H, CH_2), 3.6 ppm (Triplet, 2H, CH_2), 6.7 ppm (Singlet,1H, CO-NH amide), 6.8 ppm (Singlet,1H, CO-NH amide), 7.1-7.7 ppm (4H, Aromatic ring).

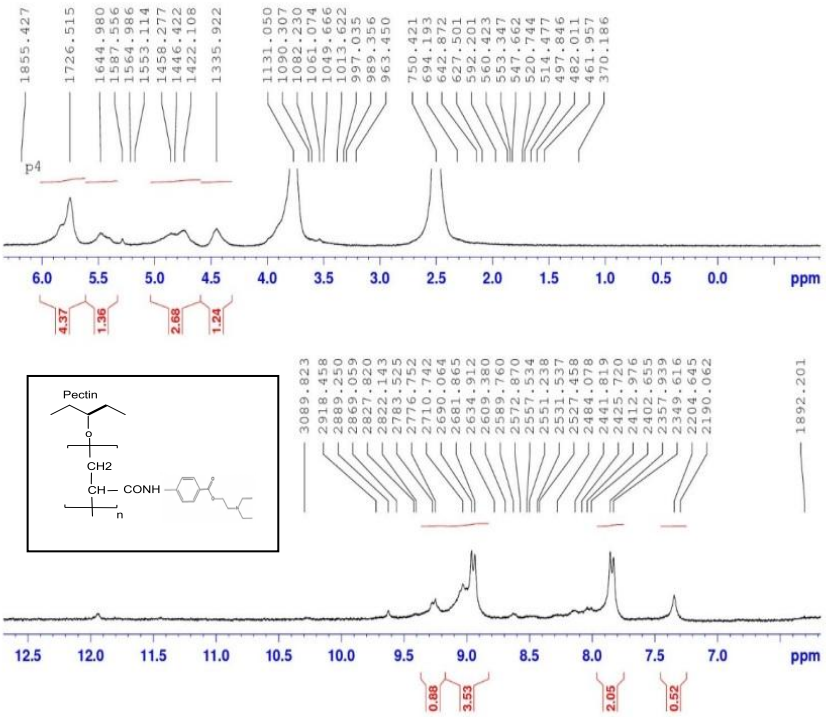


Figure 6: ^{1}H-NMR Spectrum of prepared polymer pectin-g-[N-procaine acrylic acid] was which showed the following signals

1.2 ppm (Triplet, 3H, CH3), 6.2 ppm (Singlet,1H, CO-NH amide), 7.8–7.9 ppm (4H, Aromatic ring), 4.5 ppm (Singlet, OH for pectin), 12.0 ppm (Singlet, 1H, COOH).

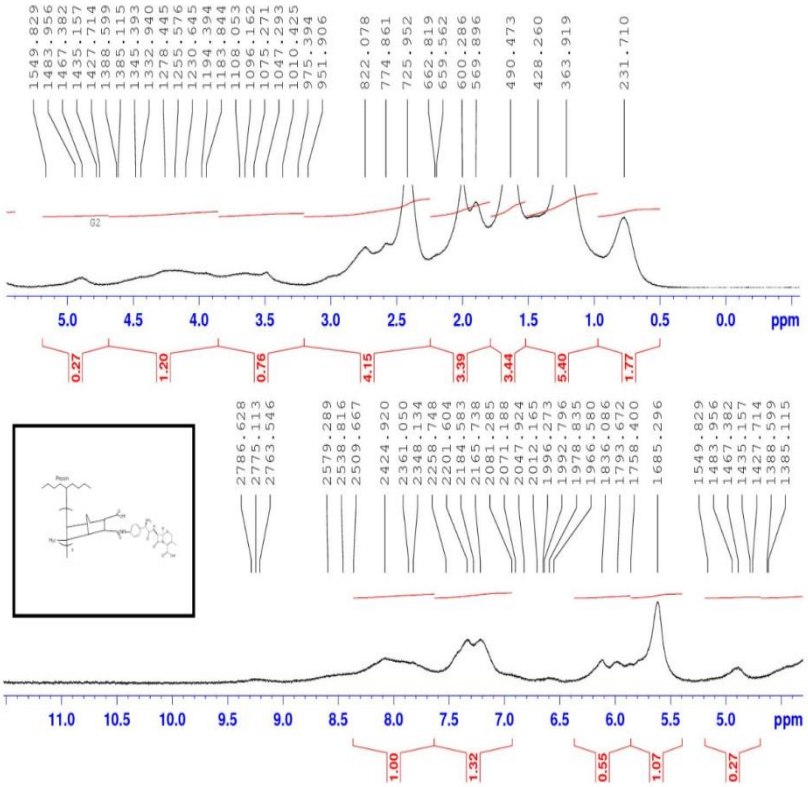
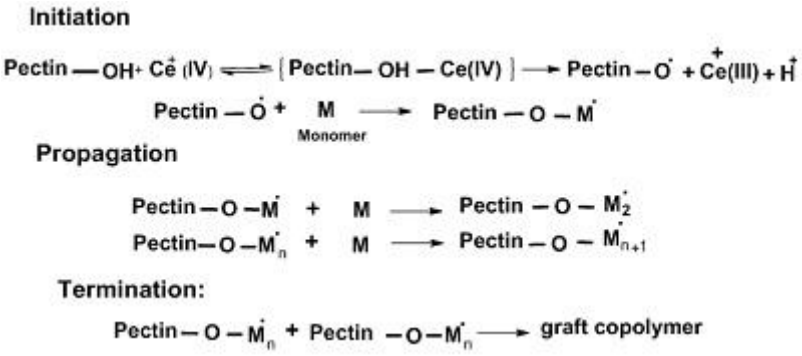


Figure 7: ^{1}H-NMR Spectrum of prepared polymer pectin-g-[N-amoxillin methyl nadic anhydride

^{1}H-NMR Spectrum of prepared polymer pectin-g-[N-amoxillin methyl nadic anhydride was obtained using DMSO-d^{6} as a solvent with TMS as internal standard. The ^{1}H-NMR spectrum of drug polymer indicated the signal assignments in the corresponding formula, which showed the following signals

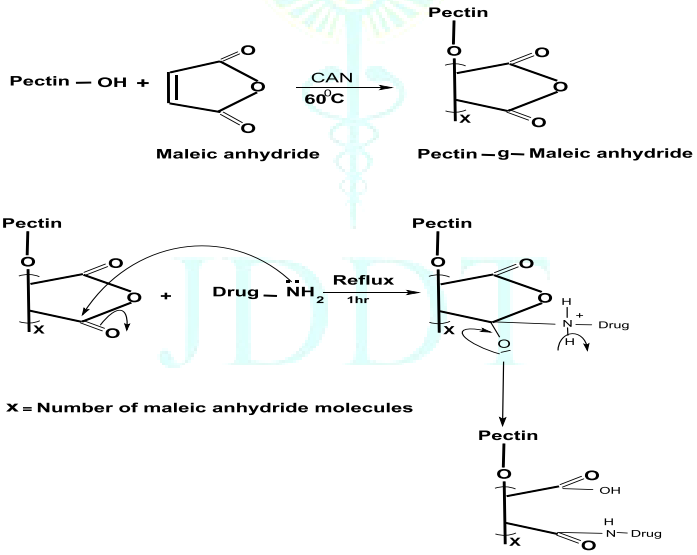
0.85 ppm (Singlet, 3H,) CH_3) formaleic,, 2.2 ppm (Singlet3.0 ppm, (doublet, 2H, CH_2) for pectin, 6.8-7.5 ppm (Multiple, 4H, Ar-H), 8.1 ppm (Singlet,1H, CO-NH amide).

The initiation sites for grafting are created on the glucose backbone. The radical formation on the glucose backbone occur on the oxygen atom. The mechanism of grafting reaction of monomer onto pectin initiated by CAN, as shown in scheme (1)



Scheme (1) Mechanism of grafting reaction of monomer onto pectin initiated by CAN

Graft copolymerization of unsaturated monomer on pectin backbone could added new properties and more attention production, pectin- g- maleic anhydride was modified with amino drugs which acted as ring opening of maleic anhydride by using (CAN) as initiator



Scheme (2) Mechanism of ring opening reaction of pectin -g- maleic anhydride by nucleophilic reaction

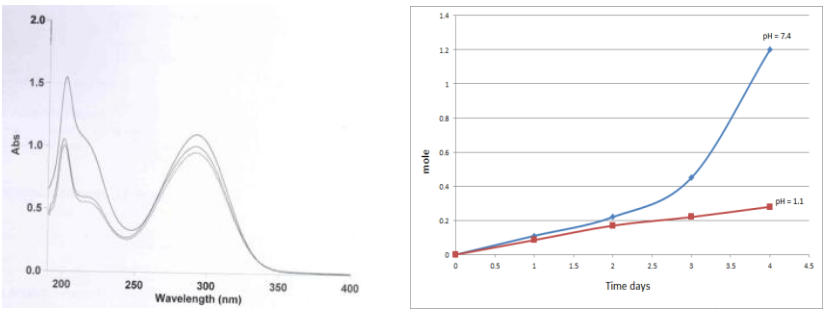


Figure 8: UV Spectrum of hydrolysis of H1A in pH7.4

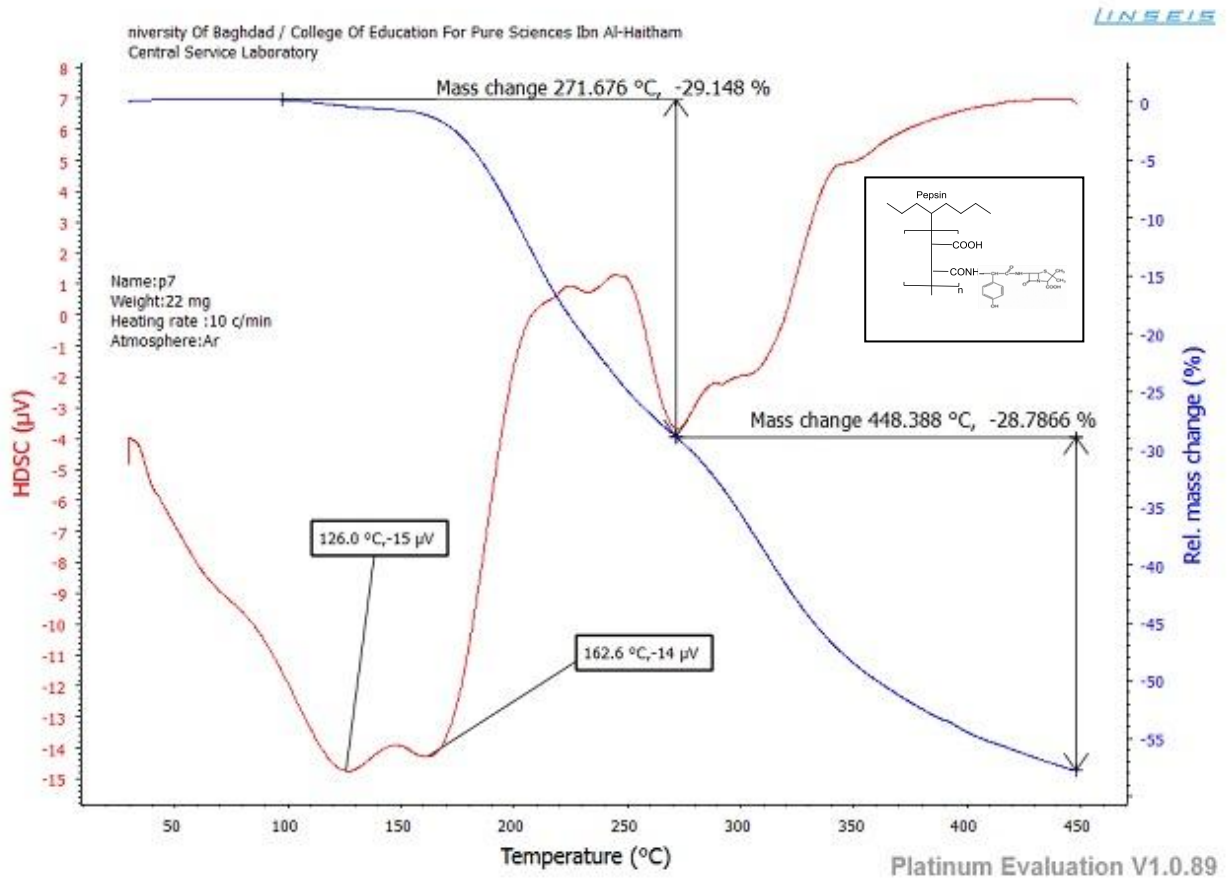


Figure (9) DSC and TGA of polymer H1A

Several thermal stability parameters were determined from TGA and DSC curves. The change in weight was measured as a function of temperature which gave valuable information about the thermal stability of the prepared pectin derivative initial decomposition temperature (T_{endo}) and the optimum decomposition temperature (T_{exo}). Weight loss temperature (Ts), which was determined from the TG curve, which represents the temperature under a programmed heating rate of 10 ^{0}C /mint. under inert atmosphere , (N_2 gas 50 ml/mint). Thus the weight-loss vs. temperature thermo grams were recorded and analyzed. This high thermal resistance indicated the high interaction between amide hydrogen bonding through the polymer chains and led to best protect the drug.

CONCLUSION

A new bio adhesive polymer was prepared by modification of Pectin structure with maleic anhydride as a spacer and grafted copolymer was substituted with amino drugs such as amoxicillin or procaein produced amide polymer. This design carries controlled which could release drug over an extended period of time, Increased water solubility, enhancement of drug bioavailability,T his new adhesive was applied on different infected mice and wounds, It gave good results at a short period of time.

The great advantage of ability to release a drug at specific tissue sites or at preselected intra cellular site., consequently, The bond between the polymer and the drug if stable in gastric juice and is slowly hydrolyzed in alkaline medium, the drug might not be released until it reaches the small intestine, the resulting amide could hydrolyzed specifically in the presence of alkaline pH . Primary polymeric drugs formed by drug coupling with a polymer So by selecting a specific spacer molecule, prolonged released of a drug can also be achieved. And in the same time it is sensitive to stimuli (pH and temperature).

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