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Synthesis of Substituted Gelatine Grafted Maleic Anhydride as Drug Copolymer

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Abstract
In this research the structural modification of gelatin(A_1) was carried out with maleic anhydride as a grafted copolymer(A_2) to enhance and add new function groups such as acid anhydride which can used to be easy substituted with amino drug such as Amoxilline (A_3) ,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 carries copolymer was characterized by FTIR and UV Spectroscopes. Thermal analysis was studied the prepared drug copolymer was analyzed in different pH values.at $37C^0$,as in vitro study and controlled drug release was compared at zero time and after four days .Swelling percentage were calculated in water ,acidic and basic medium .
Keywords: Gelatin, Copolymer, Drug Copolymer

Introduction

Grafted copolymerization of unsaturated monomer on to natural polymers to add new properties and more attention tissue engineering and tissues adhere[1-3].Gelatine can be used for the production of biocompatible materials in the pharmaceutical and medical applications[4] it was reported the synthesis of gelatin- based hydrogel nano composites by grafting acrylic acid and acrylamide on to gelatin [5] Biological systems produce proteins that possess the ability to self-assemble into complex, yet highly ordered structures [6] . These remarkable materials are polypeptide copolymers that derive their properties from precisely controlled sequences and compositions of their constituent amino acid monomers. There has been recent interest in developing synthetic routes for preparation of *significant. Biopolymers have drawn considerable attention in designing hydrogel wit idely applied biopolymer is alginic acFor the past few decades, biodegradable polymers have been applied as carriers for controlled delivery of low molecular weight drugs as well as bioactive proteins [11-12].Biodegradable polymers, either synthetic or natural, are capable of being cleaved into biocompatible by products through chemical or enzyme-catalyzed hydrolysis. This 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 [13-14], physicochemical properties of the polymers and drug [15- 16], thermodynamic compatibility between the polymers and drugs [17], and the shape of the devices [18-19]. Maleic anhydride (MAN) is an excellent monomer which can provide reactive anhydride or carboxylic groups withnucleophilic molecules. [20]. MAN has an extremely low tendency to homopolymerize in a radical polymerization condition; on the contrary, it copolymerizes with a variety of donor monomers[21]. The chemical modification of synthetic polymers allows the control of their mechanical and thermal properties [22] and expands their explicabilities, as introduction of MA on the non-polar backbone of polyolefins and rubbers has overcome the disadvantage of low surface energy of these polymers, improving their surface hydrophilicity for the benefit of printing and coating applications, and adhesion with polar polymers(polyamides), [23-]. One of the most common monomers in the polymer modification is MA and its isostructural analogues such as *N*-substituted maleimides, fumaric, citraconic and itaconic acids and their esters amides, imides, and anhydrides of these dicarboxylic acids[24]. monomers, can be used graft copolymerization reactions blends and composites of biopolymers and synthetic polymers also constitute a wide area of materialscithe properties of pure, synthetic polymers and pure biological polymers are often inadequate for producing materials with good chemical mechanical thermal, and biological charateristics,[25] Amoxicillin, an acid stable, semi - synthetic drug belongs to a class of antibiotics called the Penicillins (- lactam antibiotics). It is shown to be effective against a wide range of infections caused by wide range of Gram - positive and Gram - negative bacteria in both human and animals[26]. It is a congener of ampicillin (a semi - synthetic aminopenicillin) differing from the parent drug only by hydroxylation of the phenyl side chain[27]

Experimental

Gelatin (from Parvar Novin-E Tehran Co.), potassium persulfate (APS, from Fluka), an Acrylic acid (Merck) purification. All other chemicals were also analytical grade. .FTIR Spectra were receded by(4000-400)cm^{-1}on a Shimadzu Spectrophotometer .Melting points were determined on Callencamp MF B-600 melting point

apparatus. Electronic Spectra measurements using CINTRAS-UV visible Spectrophotometers.Thermogravimetric Analysis differential Scanning Calorimetric(DSC) were carried out Shimadzu model 50 WS thermal analysis instruments respectively .An accurately weighted of sample was placed in an aluminum cup and sealed .The experiment consisted of heating the sample from 500C^0 under the continues flow of dry nitrogen gas (50ml-min^{-1}) at a heating rate 10 C^0 min^{-1}

Preparation of Graft Copolymer (A_1):-[28]
A general procedure for chemically graft copolymerization of Maleic anhydride(MA)) onto gelatin backbones was conducted as follows:
(Gelatin (1.0 g) was added to a three-neck reactor equipped with a mechanical stirrer The reactor was immersed in a thermo-stated water bath preset at a desired temperature(70^{o}C). Then 0.10 g of APS as an initiator was added to gelatin solution and was allowed to stirring for 10 min. After adding APS, variable amounts of (MA0.5 g) was added simultaneously to the gelatin solution. After 20 min, the reaction product was allowed to cool to ambient temperature. The graft copolymer poured to excess non solvent diethyl ether20 mL) and remained for 1 h to dried.

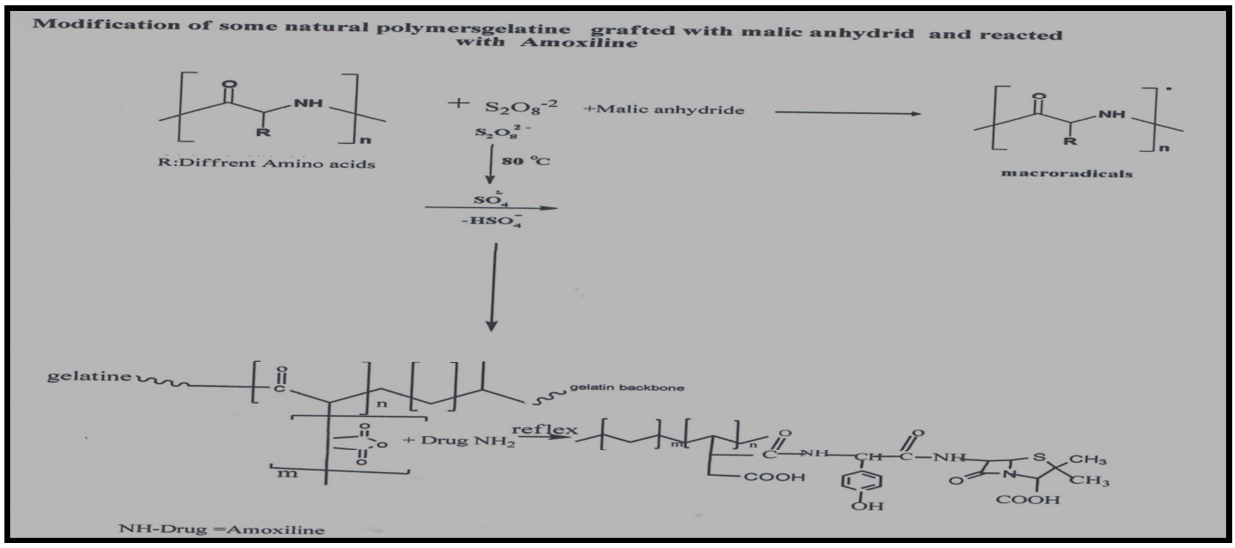
Substitution of Amoxilline on Gelatine
Grafted Maleic anhydride A_2:-[24]
In a 50 ml round bottom flask provided with magnetic stirring ,1gm of Gelatine g- Maleic anhydride Copolymer was dissolved in 1 ml of DMF and 5ml of acetone ,0.5gm of Amoxilline dissolved in 2ml acetone was added .the mixture was reflexed for 1hr .The mixture was cooled .A yellow residue of Gelatine N-Amoxillinyl maleamic acid copolymer was separated ,then washed with diethyl ether ,dried the yield was 65% softening point was higher than 300C^0.

Controlled drug release:-[28].
A 100mg of modifide polymer was kept in cylinder contaning of 100 ml of buffer solution at 37C^0 without stirring .the sample was prriodically withdrown and anlyzed by UV.Spectrophotometer at suitable (ƛmax) for every prepared sample to determined the amount of the release of drug from prodrug ,directly from softwar bailt for many times using different PH values 1.1 and 7.4

Swelling percentage:-[29-30]
Samples of the drug polymer with a mass of (1.50 ±0.053g) were placed into a Petridish; which was filled with water and placed in a hood at room temperature.The swelling percentage % was calculated in water and different PH values.

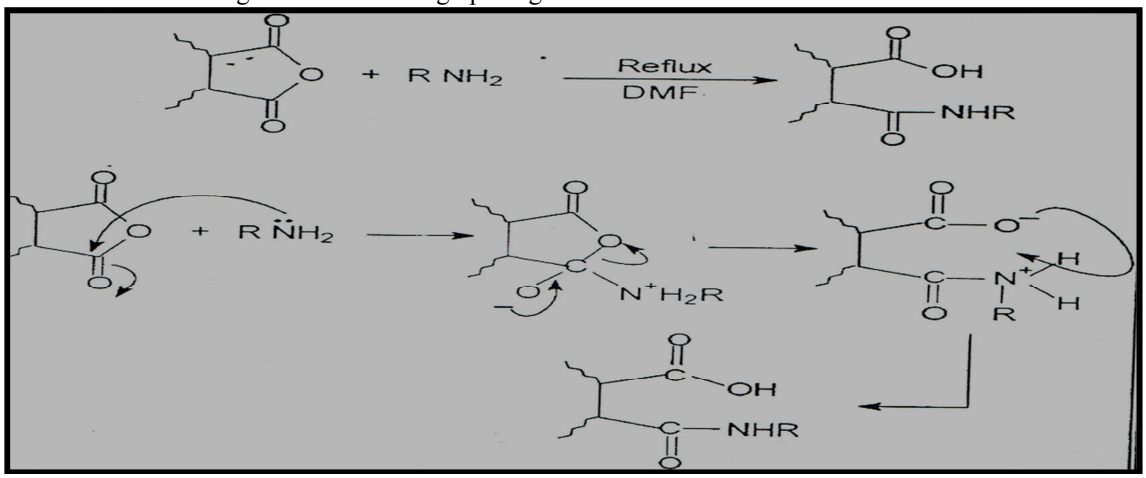
Viscosity measurement:-
Ubbelhode ,capillary viscometer was used to determined of viscosities of prepared polymer at 25C^0 ,and the relative ,specific ,reduced and intrinsic viscosities from the intercept of graph by plotting ηred VS C%

Results and discussion
Maleic anhydride (MA) was grafted onto gelatin backbones in a homogeneous medium using APS as a radical initiator. A general reaction mechanism for poly gelatin-g-maleic anhydride is shown in Scheme 1. At the first step, the thermally dissociating initiator, i.e. APS, is decomposed under heating to produce sulfate anion-radical Then, the anion-radical abstracts hydrogen from one of the functional groups in side chains (i.e. COOH, NH2) of the substrate to form corresponding radical these macroradicals initiated monomers grafting onto gelatin backbones led to a graft copolymer.schem (1) illustrated mechanism of the reaction :



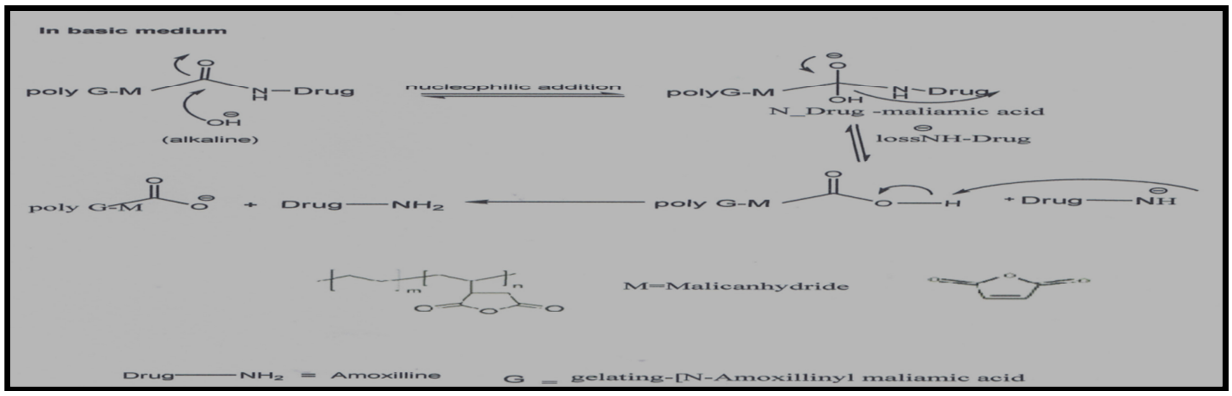
Scheme (1) reaction of gelatin with maleic anhydride and drug NH_2(Amoxilline)

Fig.1 shows the FTIR spectra of the gelatin substrate and the synthesized copolymer The band observed at 1695 cm-1 can be attributed to C=O stretching in carboxamide functional groups of substrate backbone (Fig.2). Th graft copolymer product comprises a gelatin backbone with side chains that carry carboxylate and carboxamide functional groups that are evidenced by peaks at 1541and 1649 cm-1 respectively .The characteristic band at 1541 cm-1 is due to asymmetric stretching in carboxylate anion that is reconfirmed by another peak at1419 cm-1 which is related to the symmetric stretching mode of the carboxylate anion . The stretching band of the grafted carboxamide groups overlapped with that of the gelatin portion of the copolymer gelatin N-drug maliamic acid.Fig(1) FTIR spectrum of gelatin Fig (2)FTIR spectrum of A_1 containing Gelatin grafted Malic anhydride gave the characteristic absorption of carbonyl group of anhydride peak was appeared at 1790 and 1850 cm^{-1},Fig (3) FTIR spectrum of A_2Gelatin g-[N-Amoxillinyl maliamic acid] copolymer containing carboxylic group as characteristic absorption was appeared at 3500-3000 cm^{-1} in addition and ν(-NH)at 3250cm^{-1}in addition to carbonyl group of CONH at 1650cm^{-1} and νC=O carboxylic at 1720cm^{-1} and at 1735cm^{-1} of Lactam.Scheme(2) indicated the following mechanismof ring opening reaction.

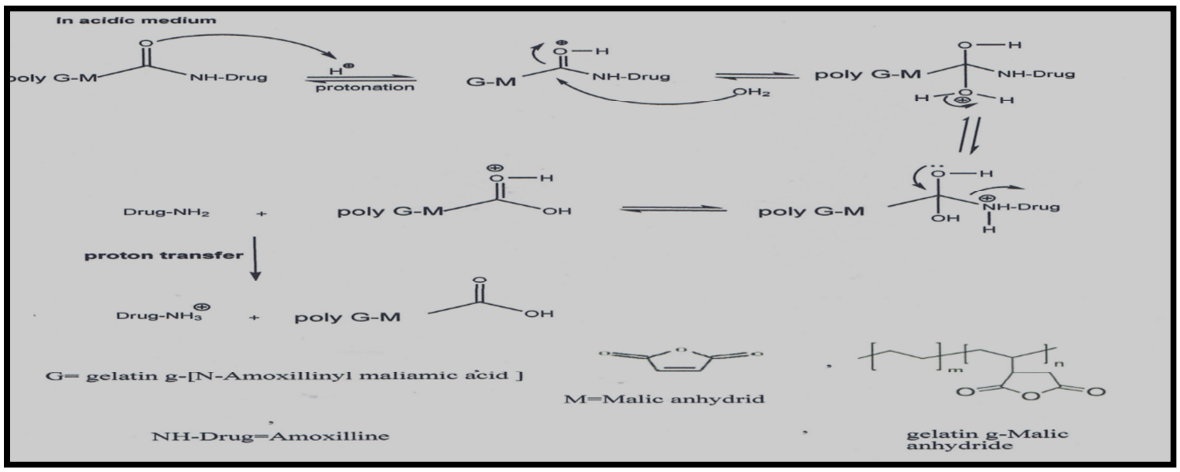


Scheme (2) opening ring of Maleic anhydride by amino group of Amoxilline

Controlled drug release was studied in different pH values indicated the higher rat of hydrolysis in basic medium as shown in Sheme (3) and (4)



Scheme (3) hydrolysis of NH drug in basic medium



Scheme (4) hydrolysis of NH drug in acidic medium

Swelling percentage of A_2 was studied in water and acidic medium ,it was found no swelling ,it was stable but A_3 was found has 20% swelling percentage in water and 25% in acidic medium and 35% in basic medium.

Fig (6)and (7) DSC of prepared grafted copolymer (A_2)and (A_3) respectively ,exhibit thermal stability is as showed below for (A_2) grafted copolymer with T_g=169.1C^0 ,Onset 168.08C^0,Endset 175.5,Heat -10.77J/g.

After ring opening of gelatin grafted maleic anhydride with Amoxilline ,the drug polymer (A_3) was exhibited higher thermal stability due to formation grafted maleamic acid with T_g=212.7C^0,Onset 211C^0,Enset 216C^0,Heat -7.96J/g

Conclusion

It was concluded from this work that the Maleic was used as a spacer between Gelatin and Amoxilline will producing carboxylic groups from ring opening reaction ,which could enhanced the solubility of natural drug copolymer with sustained drug release through hydrolysis of amide groups which could hydrolyzed in PH 7.4 is higher than PH1.1 at 37C^0which intended the period of hydrolysis about four days .

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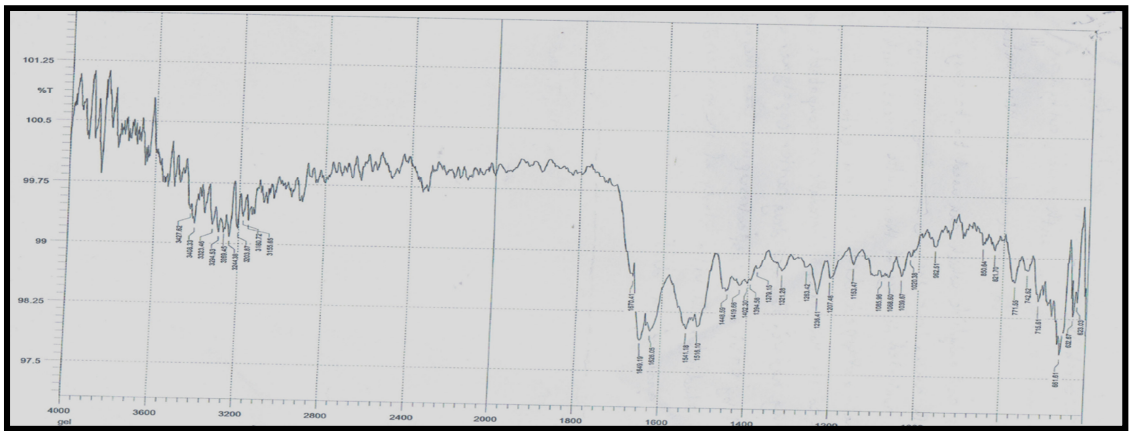

Fig (1) FTIR spectra of Gelatin

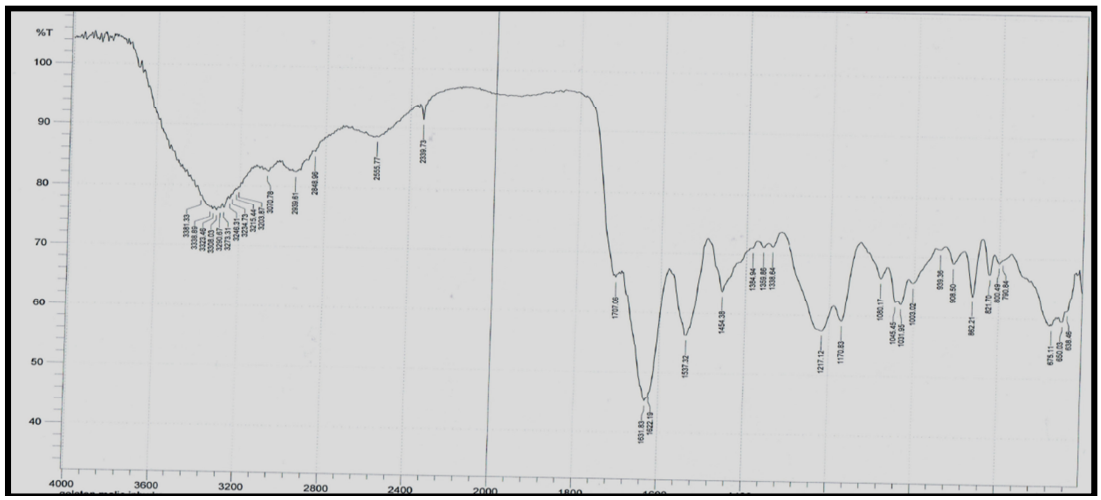

Fig (2)FTIR Spectra of Copolymer Gelatin –G-Maleic anhydride

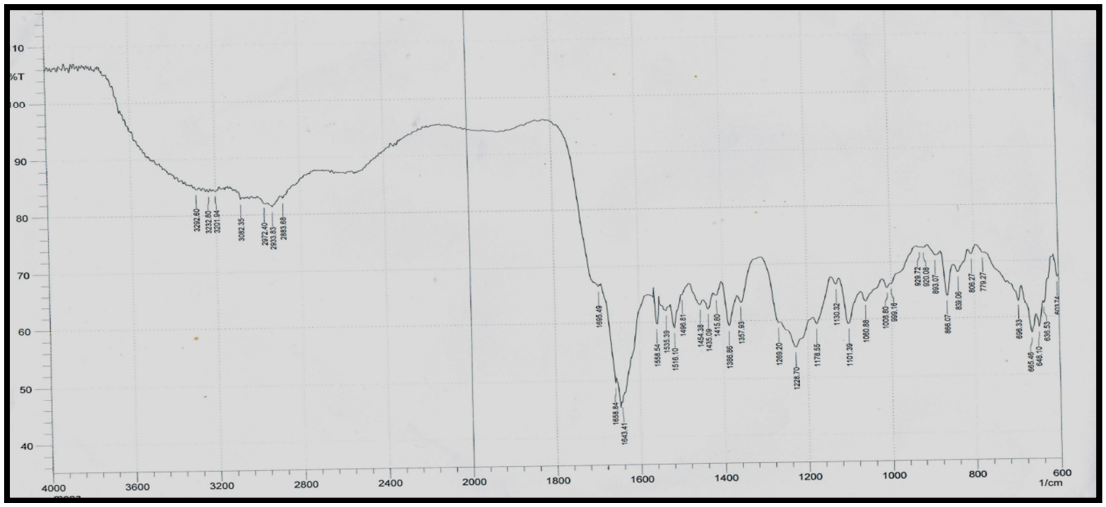

Fig (3)FTIR Spectra of Copolymer Gelatin –G-Maleic anhydride substituted with NH-Drug (Amoxiline)

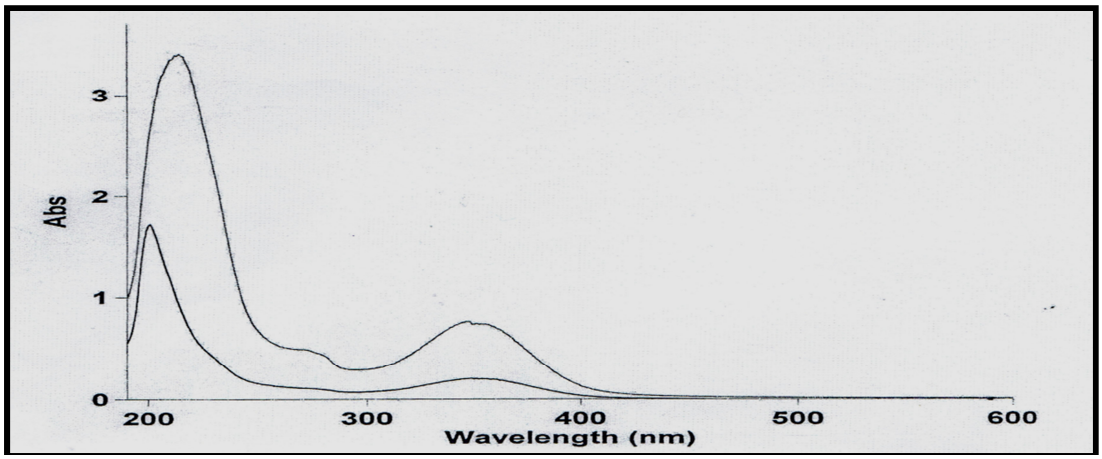

Fig (4)UV spectra hydrolysis of A_2in pH 1.1

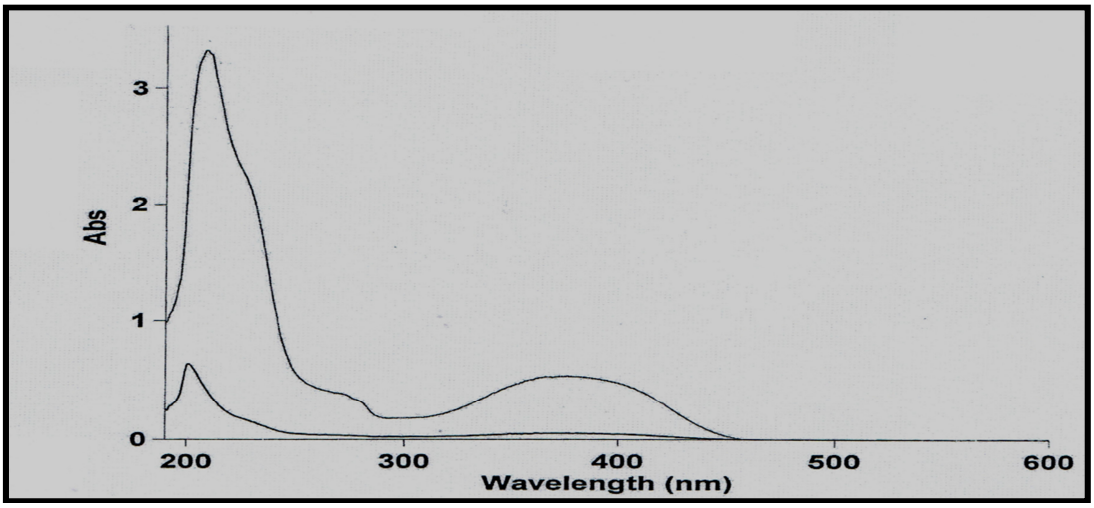

Fig (5)UV spectra hydrolysis of A_2in PH7.4

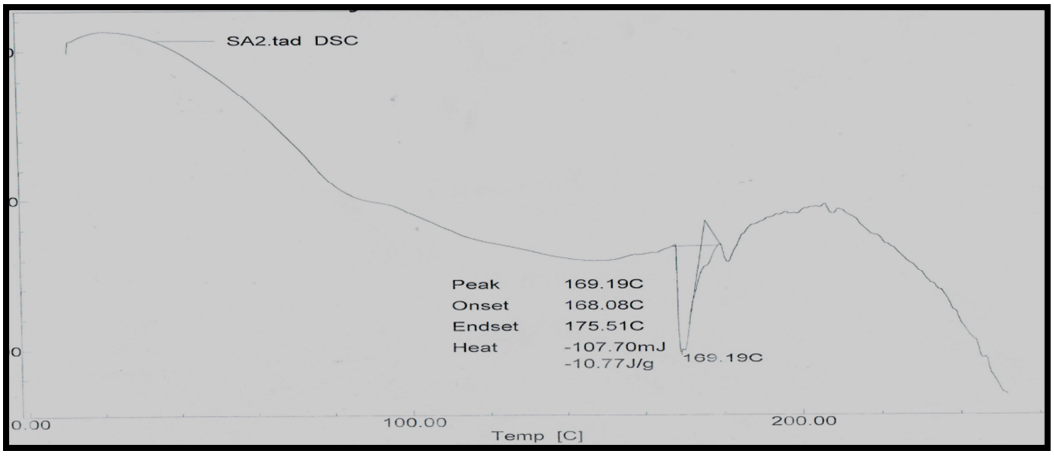

Fig (6) DSC of Gelatin- G- Maleic anhydride

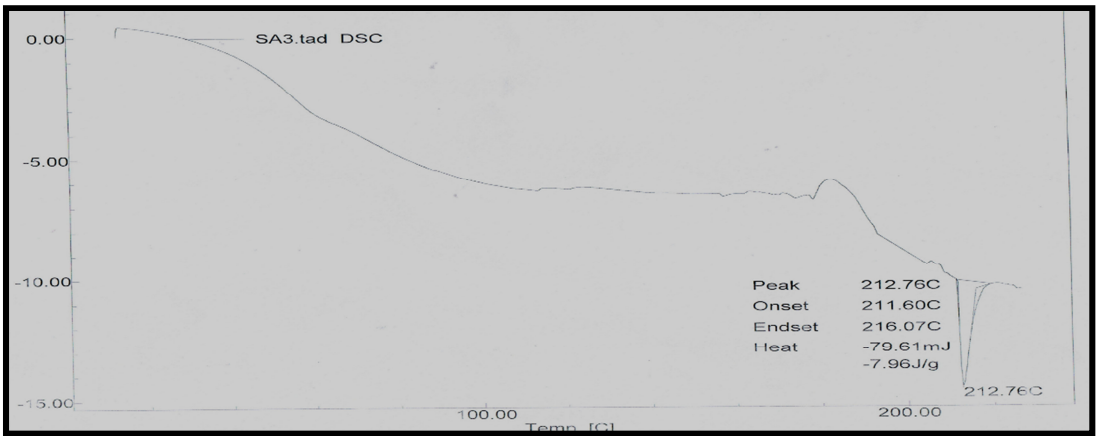

Fig (7) DSC of Gelating- Maleic anhydride[N-Amoxillinyl Maleamic acid

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