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Gelatin grafted with drug

Firyal Mohammed Ali Alsalami 

Al-Mustansiriyah University, College of Science, Department of Chemistry, Baghdad

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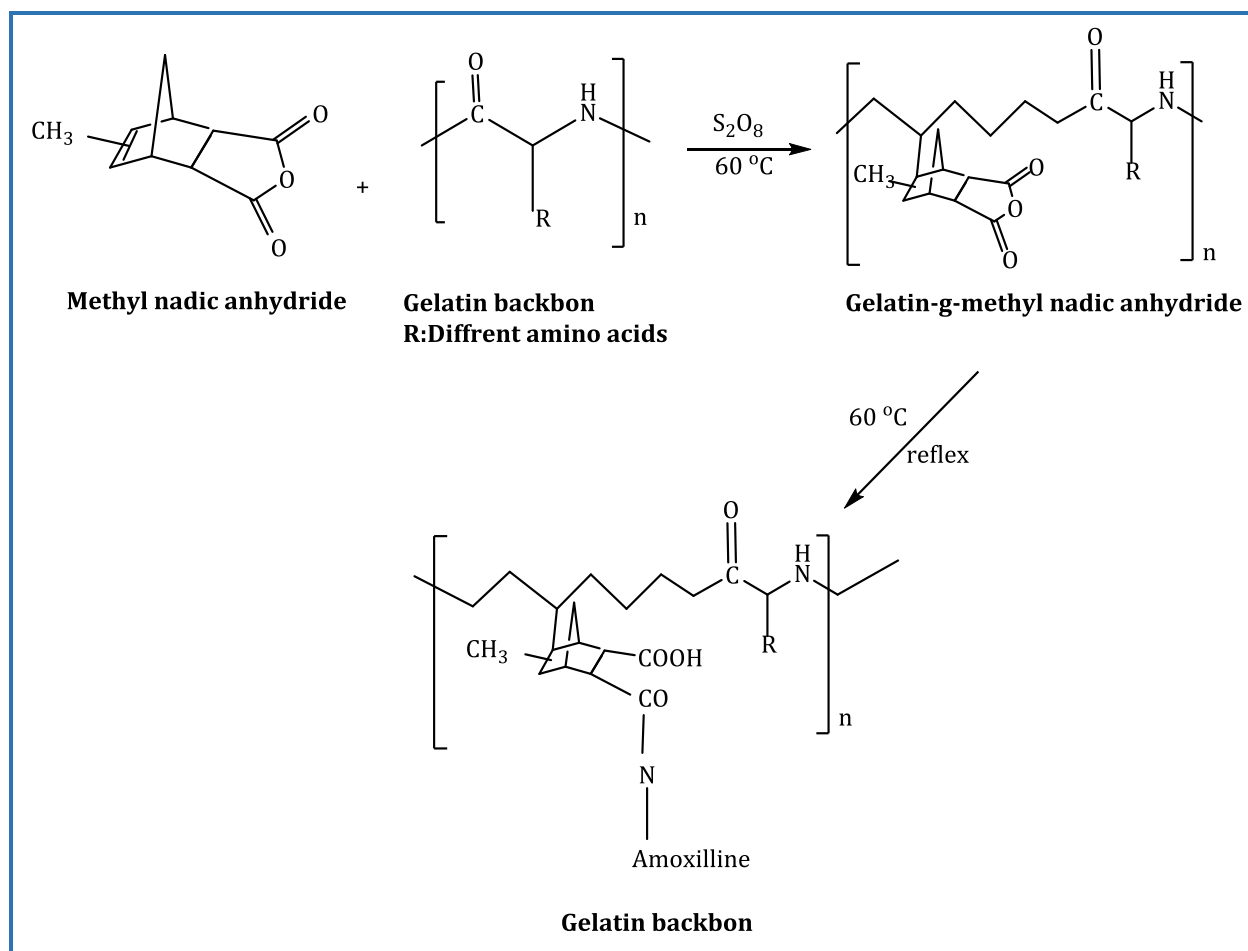
KEYWORDS

Gelatin
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Methyl-5-norbornene-2,3-dicarboxylic anhydride

ABSTRACT

In this research a novel drug polymer was prepared. The gelatin as a natural polymer has been used in the pharmaceutical and biomedical for the controlled release through grafted copolymerization with un saturated acid anhydride such as methyl nadic anhydride (Methyl-5-norbornene-2,3-dicarboxylic anhydride), formatted gelatin-g-methyl nadic anhydride copolymer A₁, then modified to its corresponding polymer A₂ by substituted amoxilline as useful derivative as biomaterial. The prepared drug biopolymer was characterization by FT-IR spectroscopy and controlled drug release was considered in different buffer solution at 37 °C as in vitro study and controlled drug release was compared at zero time and after many days, the methyl nadic anhydride which was used as a spacer between gelatin and amoxilline. It can provide functional groups which are pendant through backbone of polymer substituted with drug through amide groups lead to good sustain release rate for hydrolysis through amide attachment gradually for many days. This design of carries for controlled delivery of the therapeutic agent which could release the entrapped drug over an extended period and control the drug release was compared at zero time and after few days, indicated the rate of hydrolysis in basic medium is higher than acidic medium through hydrolysis of amide groups. It was observed that modified drug release with extended drug action via slow release, also this study gave a new drug polymer and in vivo performance was indicated that it will be talented for some bio active applications.

Graphical Abstract



Introduction

Methyl nadic anhydride is an important chemical raw material of electronic information, synthetic resins and plastics, pesticide and pharmacy, and so on; and can be prepared with low material costs [1]. It is also used as a raw material has better air-drying property, higher thermal resistance, better surface finish, and improved electricity property, erosion resistance and mechanical intensity than resins synthesized by hexahydrophthalic anhydride and tetrahydrophthalic anhydride.

The hexahydro-3,6-methanophthalic anhydride is a product after hydrogenation of a nadic anhydride [2, 3]. Compared with the nadic anhydride, the hexahydro-3,6-methanophthalic anhydride has a higher chemical stability and superior physical/chemical property and lower viscosity. The product there of has a lighter solid color and is more weather resistant [4, 5].

Gelatin is a natural polymer which is produced by the partial hydrolysis of the collagen derived from the skin or bones, white connective tissues. Gelatin derivative of protein is used in food, cosmetics, pharmaceuticals and photographic industries for its gel forming abilities, non-toxicity and

cheap [6, 7]. In pharmaceuticals, gelatin is used as the capsule shell for the controlled drug release. Due to the various potential uses of the gelatin, it has been used to modify the gelatin to enable improved or alternative applications [8, 9], the modification of gelatin through graft copolymerization has grown significantly. Biomaterials had founded applications such as artificial organs, tissue engineering, components of medical devices, and dentistry. The functional polymers as delivery were used as the agents for therapeutics against the variety of disease [10]. It was included that delivery of drugs at a sustained rate, targeted delivery of drugs at specific sites (To minimize toxicity and enhance selectivity for certain antitumor agents), as well as prodrugs with polymers acting as carrier molecules [11, 12]. The main reason for the development of these polymeric-drug carriers is to obtain the desirable properties such as sustained therapy, slow drug release, prolonged activity, as well as decreased drug metabolism [13, 14].

The drug molecule is chemically bonded to a polymer backbone and the drug is released by hydrolytic or enzymatic cleavage. The rate of drug release is controlled by the rate of hydrolysis. This approach provides an opportunity to target the drug to a particular cell type or tissue [15, 16]. The usual mechanism for degradation is by hydrolysis or enzymatic cleavage of the labile heteroatom bonds, resulting in a scission of the polymer backbone. Macro organisms can eat and digest polymers, and also initiate a mechanical, chemical, or enzymatic aging [17–20].

Biodegradable polymers with hydrolysable chemical bonds are researched extensively for biomedical, pharmaceutical, agricultural, and packaging applications [20]. In order to be used in medical devices and controlled-drug-release applications, the biodegradable polymer must be biocompatible and meet other criteria to be qualified as the biomaterial-process able, sterilizable, and capable of controlled stability or degradation in response to biological conditions [21–24]. Gelatin based polyester urethane scaffolds of different compositions were prepared from lactic acid [25, 26]. Degradation and swelling studies of the gelatin based polyester urethane scaffolds in phosphate buffer saline (PBS) were achieved keratinocyte cells were learnt within scaffolds, which showed good cell adherence [27]. The inevitable foreign body reaction towards implanted materials challenges the stability and an active intervention strategy would be desirable to treat inflammation locally [28, 29]. The controlled release of the anti-inflammatory drug Dexamethasone from the neural microelectrodes in the rat hippocampus had an impact on probe-tissue over 12 weeks of implantation rationale, and clinical applications, existing and potential, physicochemical characterization was study as in vitro permeation assessment across porcine buccal mucosa [30–32].

Experimental

Materials and methods

The gelatin (Merck) was used as received. Methyl nadic anhydride was purchased from Fluka. Ammonium persulfate (APS, Merck) was used without purification. All other chemicals were of analytical grade. Amoxilline was obtained from BDH company.

Synthesis of gelatin-G-methyl nadic anhydride(A₁)

Granules of gelatin (3 g) were dissolved in few drops of acetone. The APS (0.1 g, 0.0034 mole) dissolved in 1 mL of water, the mixture was added and stirred at 60 °C for 10 min until it reaches a viscous state (4 g, 0.0022 mole), of methyl nadic anhydride was added, the mixture was heated and stirred about 20 min. The grafted co polymer was collected by filtration and re-dispersed in the diethyl ether several times to remove the excessive methyl nadic. The precipitate was then filtered, and dried under the vacuum. Gelatin-g-methyl nadic anhydride was obtained as white polymer with 90%. [Table 1](#) shows the physical properties of the new product (A₁) gelatin-g-methyl anhydride.

Substitution of Amoxilline on (A₁) gelatin-g-methyl anhydride

0.50 g of gelatin-g-methyl anhydride was dispersed in 3 mL of dimethyl formamide (DMF), then (0.01 g, 0.3 mol) of amoxilline dissolved in acetone was added to the (Gelatin-g-methyl nadic anhydride) and stirred by manetic at 60 °C about 30 min, the yellow precipitate was collected and filtrated and then washed with ethanol and dried at room temperature. [Table 2](#) demonstrates the physical properties of A₂.

The controlled released study

A 100 mg of drug polymer was kept in a cylinder containing 100 mL buffer solution with different pH values at 37 °C. A released sample periodically withdrawn and analyzed by UV. Spectroscopy at specific λ_{\max} 270 nm was used to determine the amount of the released drug unite. A calibration curve was constructed with a software built in the computerized UV. Spectrophotometer, the amount of the released drug was determined directly from the software for many days, using the calibration curve in different pH values at 37 °C. [Figure 1a](#) and **b** showed UV spectrum of many days of controlled release. In pH=7.4 and drug release in pH=1.1 [[21](#), [22](#)].

Table 1. physical properties of A₁

Pol. No.	Grafted polymer	Color	Softening point (°C)	Conversion (%)
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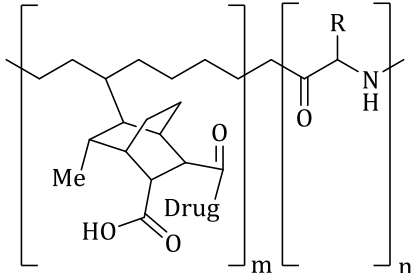
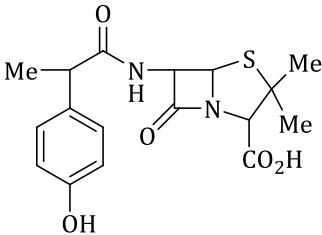
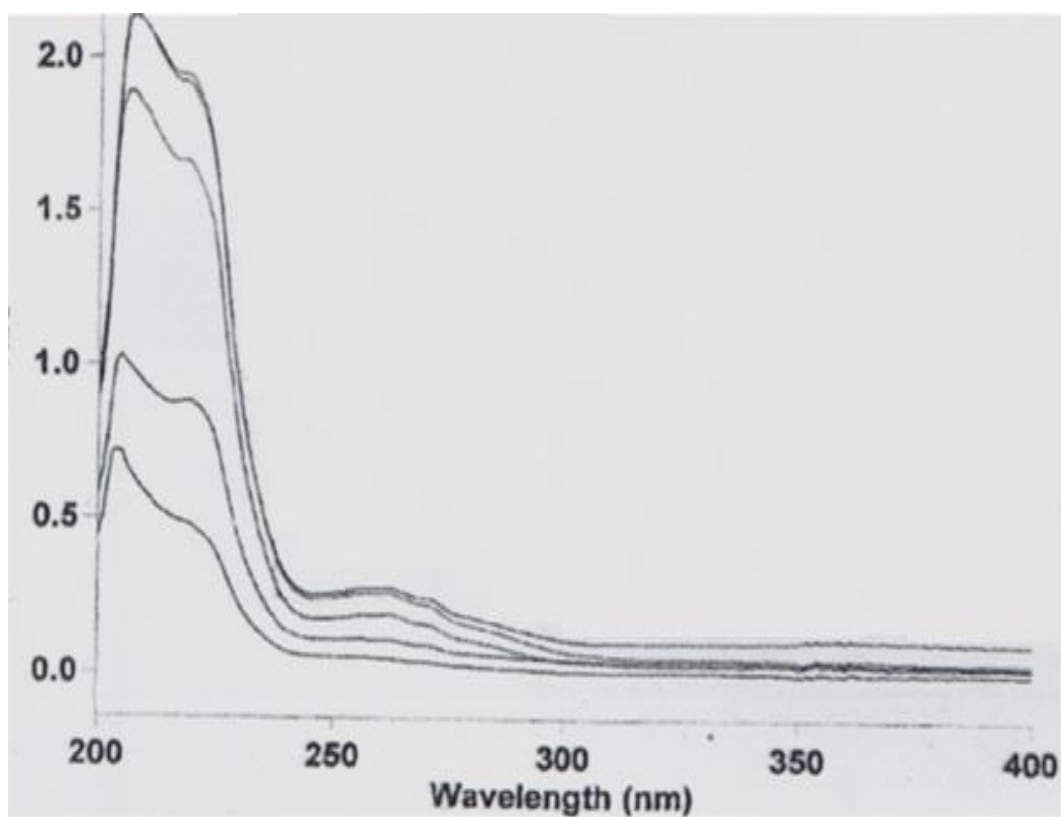
A ₁		White	175-188	90
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Table 2. Physical properties of prepared Polymers A₂

Pol. No.	Grafted polymer	Color	Softening point (°C)	Conversion (%)
A ₂		Brown	171-189	66



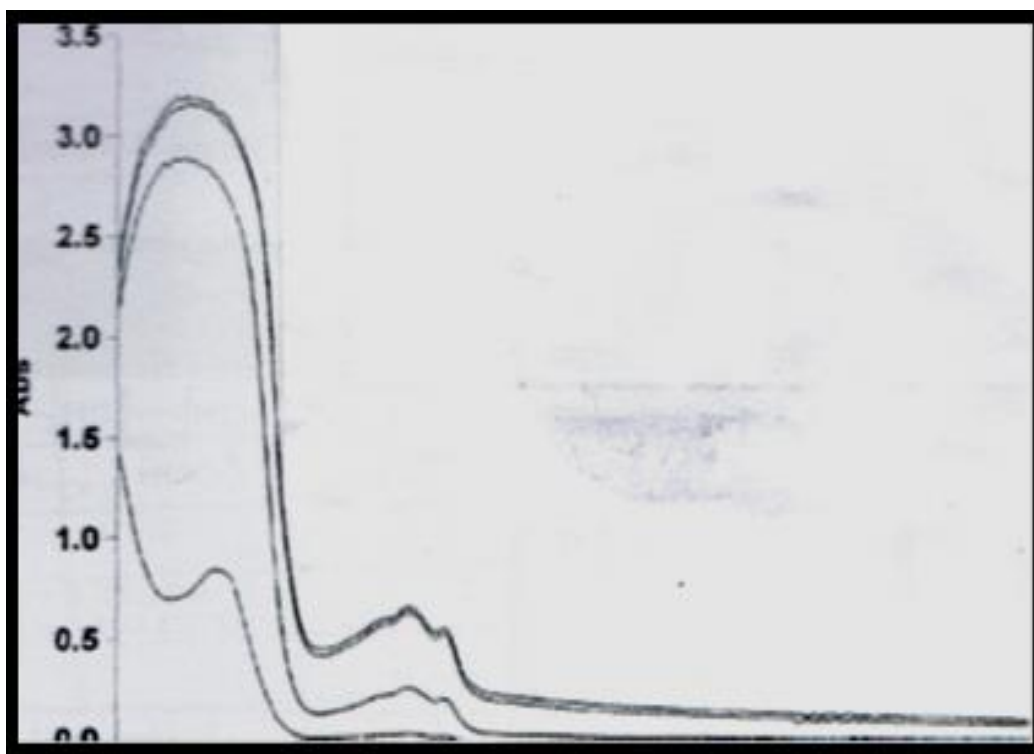


Figure 1. a) UV Spectrum of drug in pH=7.4, b) UV Spectrum of drug release in pH=1.1

Swelling Percentage of Prepared Polymer A₂

(0.15 g) of prepared polymer was immersed in three different swelling solutions: water, acidic, basic medium. The samples were placed in the swelling solution and the weight of the swollen samples was measured as a function of time. The excess surface water was removed with a dry piece of filter paper. The degree of swelling for each disk sample after 24 h was calculated they ranged between 200 to 300 swelling percentage [23, 26].

Results and discussion

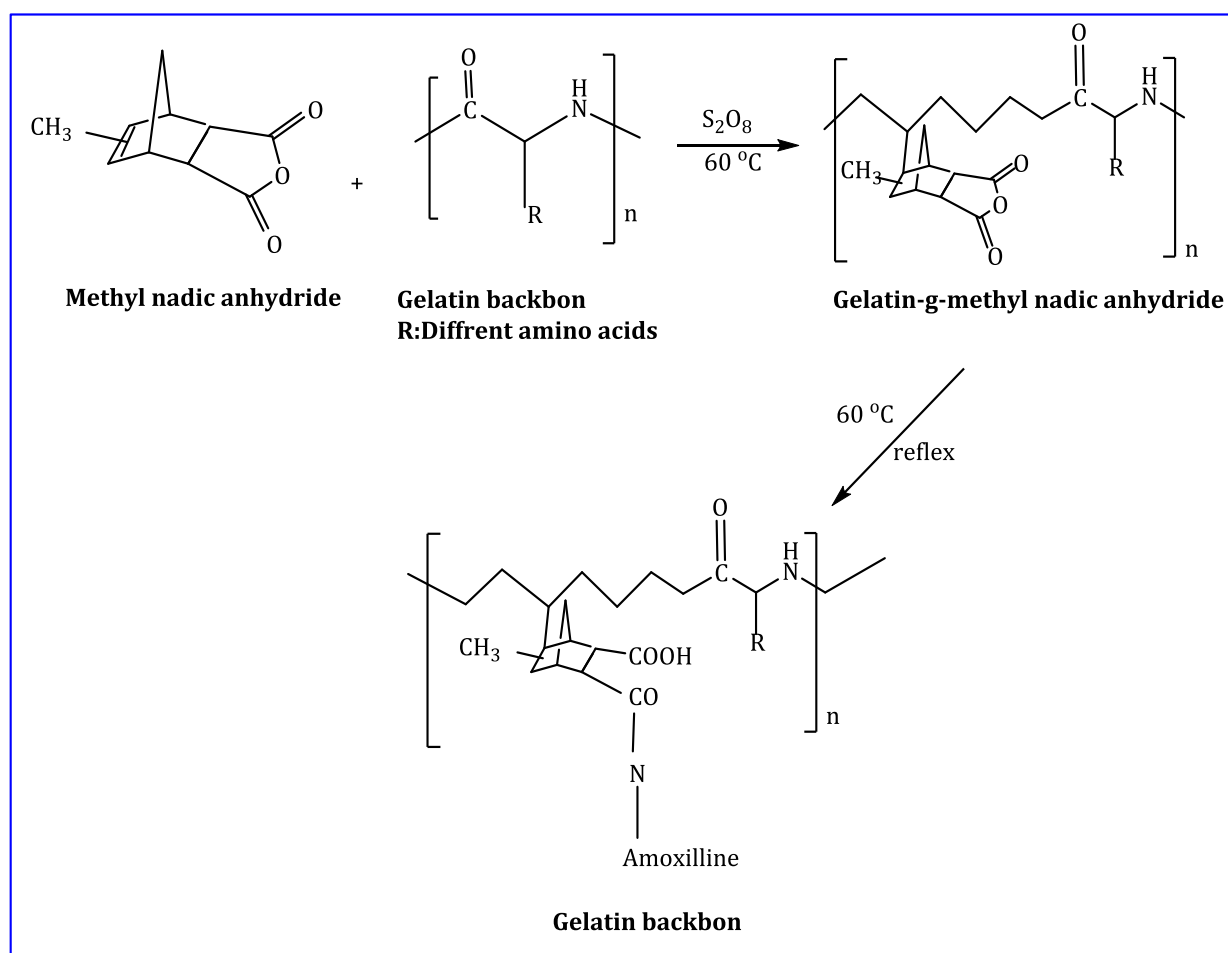
A natural, polymers are bio and environmentally degradable. A polymer based on a C–C backbone tends to resist degradation, whereas heteroatom-containing polymer backbones confer biodegradability. Graft copolymerization of gelatin backbone carried out with monomer, it added new properties and more attention production (A₁) as grafted copolymer which was modified with Amoxiline which acted as neocluphile attack as illustrated in [Scheme 1](#).

The FT-IR spectrum of the gelatin ([Figure 2](#)) was compared with the FT-IR spectrum of gelatin grafted methyl nadic anhydride (A₁) ([Figure 3](#)) it appeared the characteristic absorption of carbonyl group hydride anhydride absorption at 1780 cm⁻¹ and 1840 cm⁻¹, and 1640 cm⁻¹ for carboxamied functional group be attributed to C=O stretching of functional due to a symmetric stretching

carboxylate. The ring opening of the substituted methyl nadic anhydride by nucleophile attack to carbonyl group of anhydride.

FT-IR spectrum of the drug polymer (A_2) (Figure 4) showed that the characteristic absorption was appeared at $3450\text{--}2900\text{ cm}^{-1}$ and at 1650 cm^{-1} of carbonyl of carboxylic also the main OH carboxylic acid groups of Amoxilline appeared at 3380 cm^{-1} .

Gelatin is a natural polymer which is available, sustainable, renewable, possessing a better biocompatibility and non-toxicity, when it grafted with the methyl nadic anhydride become more capability to substituted with salbutamol through NH group which acted higher nucleophile than other hydroxyl groups of salbutamol. The C=O amide was formed which successful for hydrolysis through pH=7.4 and pH=1.1 the UV. spectra of A_2 at λ_{max} 270 nm indicated the sustain release of drug through 4-5 days respectively in acidic and basic medium (Figure 5).



Scheme 1. Ring opening of methyl nadic anhydride

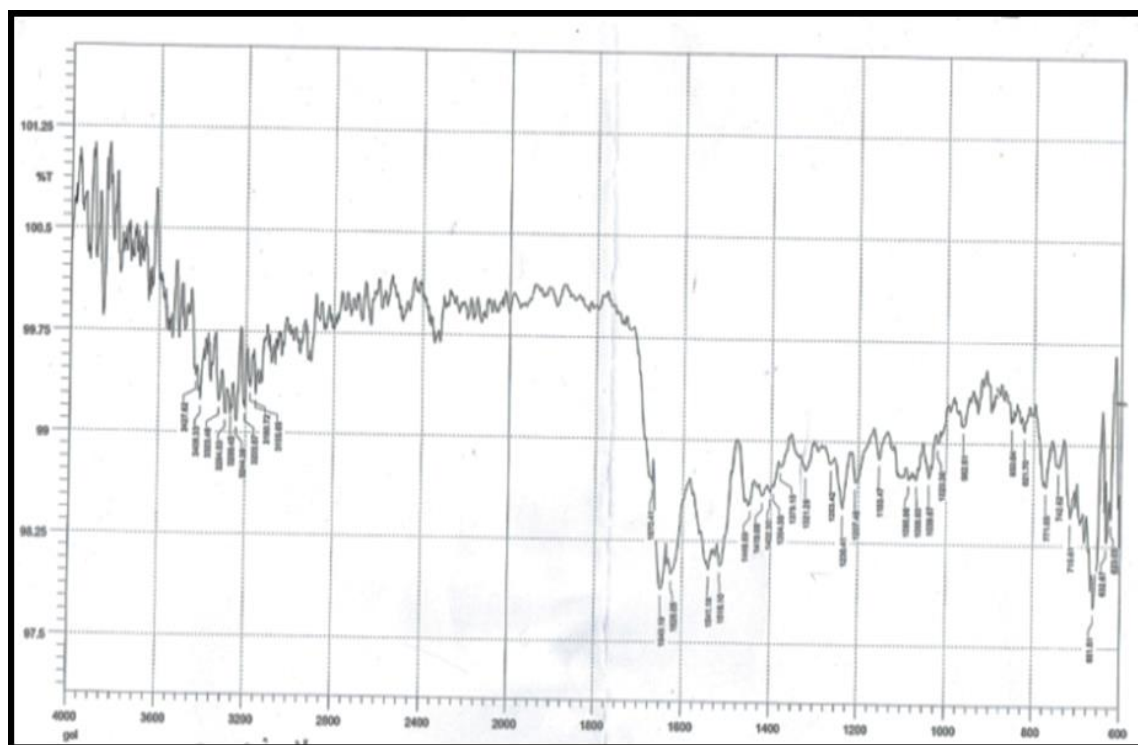


Figure 2. FT-IR Spectrum of gelatine

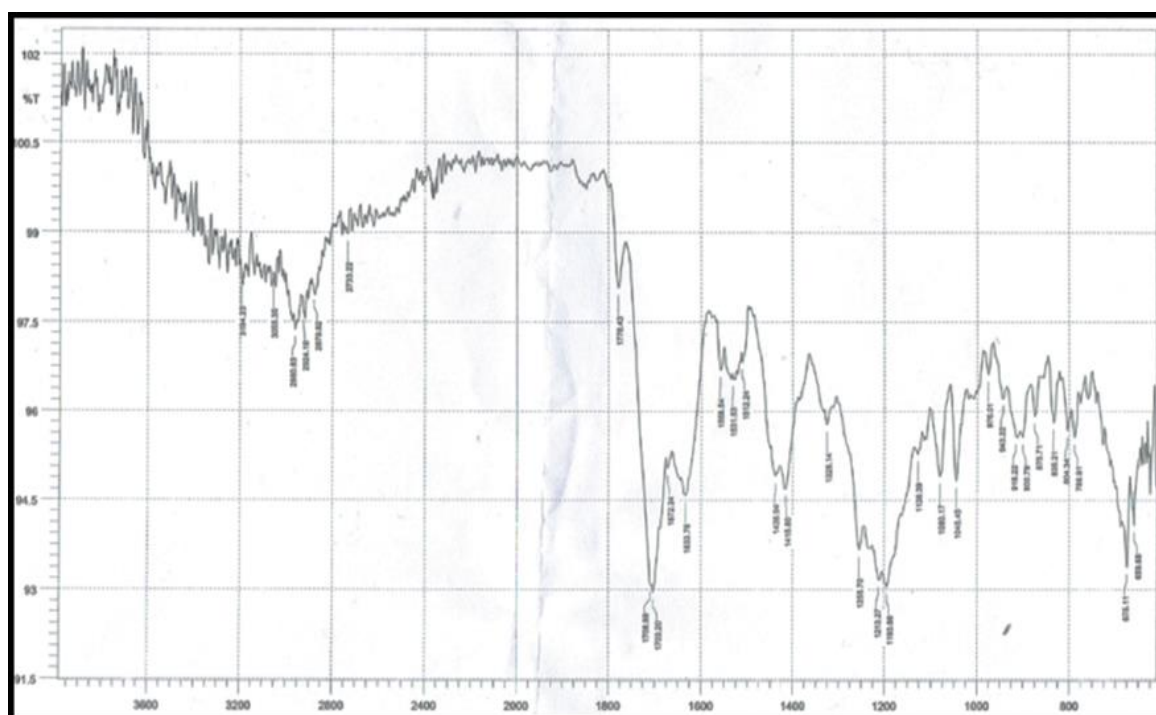


Figure 3. FT-IR Spectrum of gelatine-g-methyl nadic anhydride(A₁)

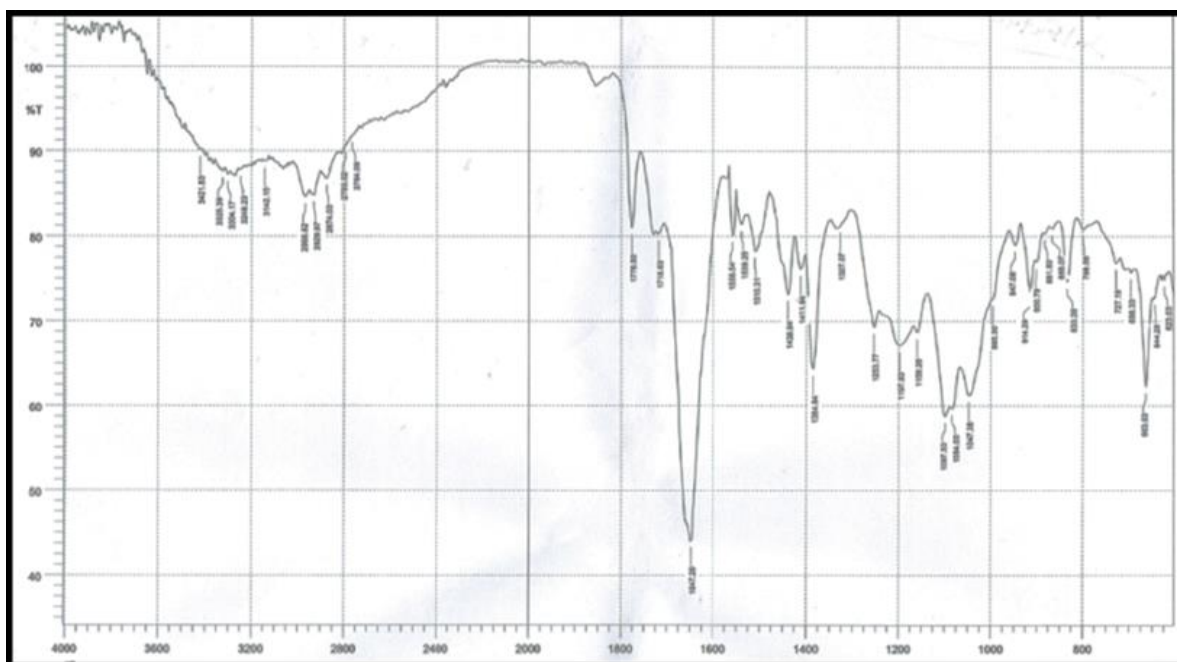


Figure 4. FT-IR Spectrum of gelatin-g-methylnadic anhydride substitution with amoxilline

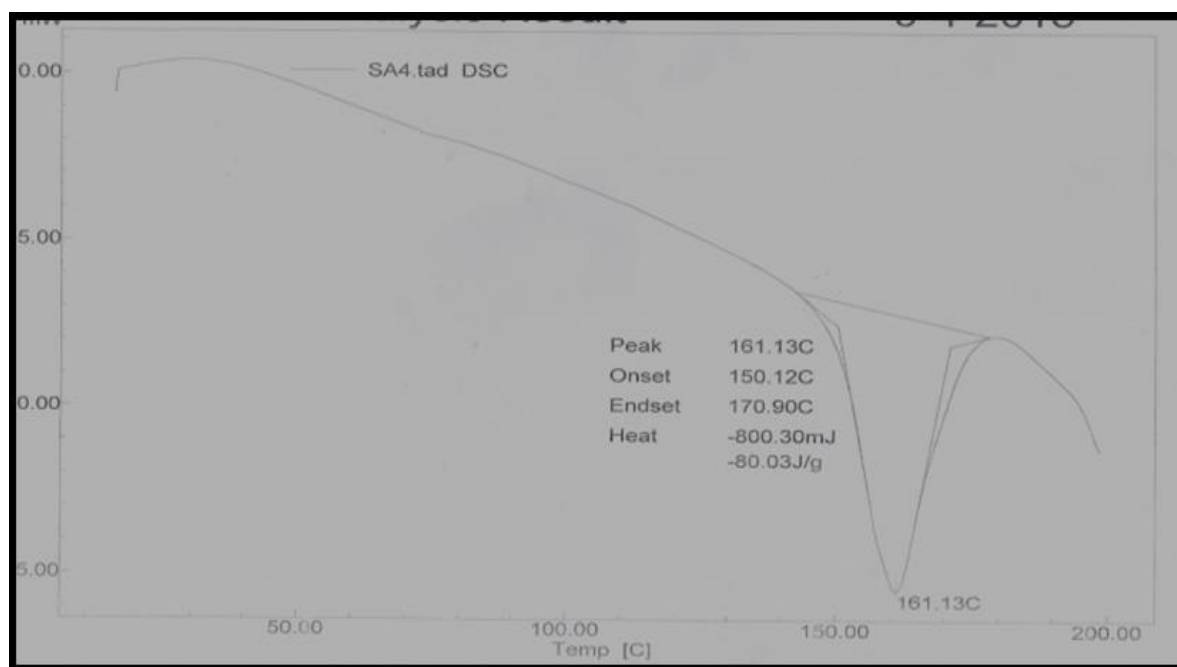


Figure 5. DSC of gelatin-g-methyl nadic anhydride Substitution with amoxilline(A₂)

Conclusion

It was concluded that the methyl nadic anhydride which was used as a spacer between gelatin and Amoxilline. It gave good functional groups which are pendant through the backbone of drug polymer

with good sustain release rate through the hydrolysis of the amide attachment through 4-5 days in days in pH=7.4. It also influenced the thermal stabilities were shifted to 161.1 °C for A2, it has an efficient product with good stability.

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Orcid

Firyal Mohammed Ali  0000-0002-9309-9737

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