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Baghdad Science Journal **Vol. 13(2s(Supplement))2016**

The 2nd National Conference of Chemistry

DOI: http://dx.doi.org/10.21123/bsj.2016.13.2.2NCC.0163

Gelatin Grafted Methyl Nadic Anhydride and Substitution With Salbutamol

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Received 21/9/2015

Accepted 20/12/2015

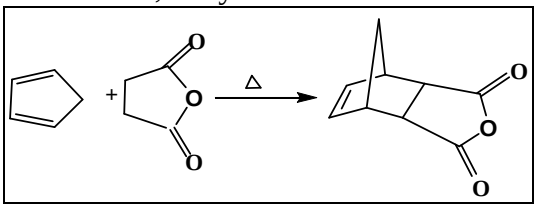
Abstract:

Gelatin a promising biomaterial which is useful and interesting natural polymer which offer possibilities of chemical modification through grafted copolymerization with an saturated acid anhydride such as methyl nadic anhydride formatted gelatin – g- methyl nadic anhydride copolymer (A_1), then modified to its corresponding polymer (A_2) by substituted salbutamol as useful derivative as biomaterial .the prepared drug biopolymer was characterization by FTIR spectroscopy and thermal analysis was studied controlled drug release was measured in different buffer solution at $37C^0$.

Keywords:-Gelatin ,Methyl Nadic Anhydride ,Salbutamol

Introduction:-

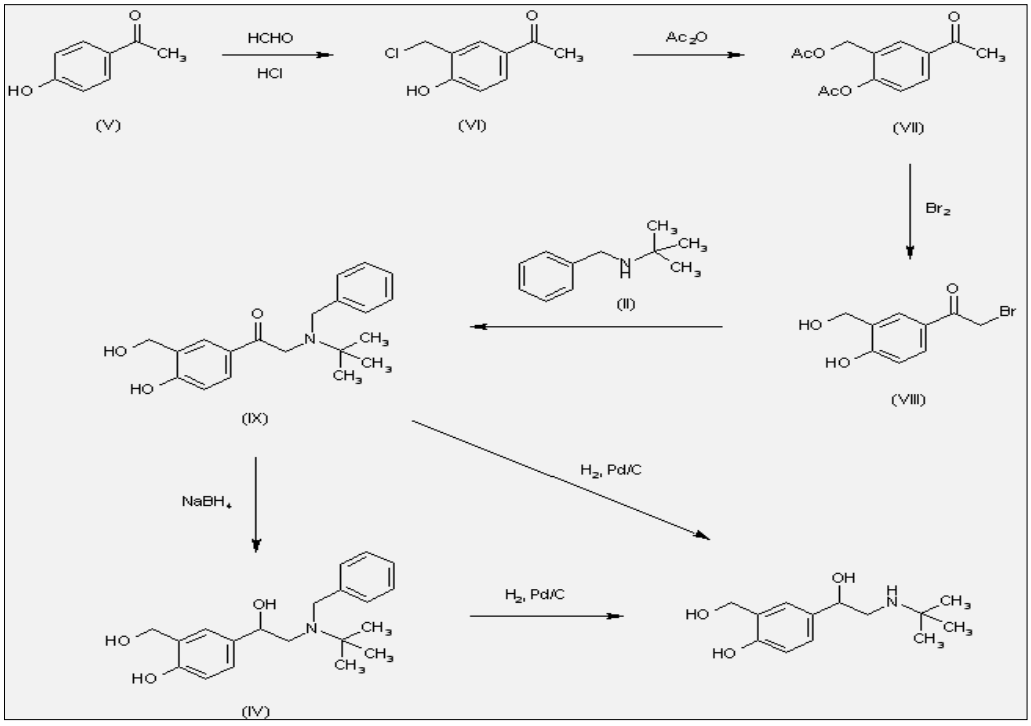
Nadic anhydride is an important chemical raw materials of electronic information, synthetic resins and plastics, pesticide and pharmacy, and so on; and can be prepared with low material costs.[1] such as scheme (1) improved electricity property, erosion re sistance and mechanical intensity than resins synthesized hexahydro phthalic anhydride and tetrahydro phthalic anhydride. The hexahydro-3,6-methanophthalic anhydrid is a product after hydrogenation of a Nadic anhydride[2-3]. Comparing with Nadic anhydride, hexahydra-3,6- metha nophthalic anhydride has a more stabilize chemical toxicity and enhance selectivity for certain antitumor agents), as well as pro drugs with polymers



Scheme (1) preparation of Nadic anhydride

In addition, resins synthesized by using thereof as a raw material have better air-drying property, higher thermal resistance, better surface finish ,and

acting as carrier molecules [11-12]. The main reason for the development of these "polymeric-drug carriers" is to obtain 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]. Salbutamol is one of the β-agonist bronchodilators, the largest group among the various classes of inhaled asthma drugs[17-18]. The recent evolution of β-agonists can be traced back to adrenal extracts that were used to treat asthmawhich is a chronic respiratory disease characterized by inflammation and narrowing of airways in the lungs, the bronchi.synthesis of salbutamol is illustrated in schem(2) [19-20]. been considered to modify gelatin to enable improved or alter-native applications [8-9] the modification of gelatin through graft copolymerization has grown significantly. biomaterials have found applications in such areas as artificial organs, tissue engineering, components of medical devices, and dentistry. The functional polymers as delivery were used agents for therapeutics against a variety of disease states.[10]They include delivery of drugs at a sustained rate, targeted delivery of drugs at specific sites (to minimize structure and physical/chemical property and lower viscosity, and the product thereof has a lighter solid color and is more weather resistance[4-5]. Gelatin is a natural polymer, a produced by the partial hydrolysis of collagen derived from the skin or bones, white connective tissues,. Being derivative of protein, it 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 capsule shell for controlled drug release. Because of various potential uses of gelatin, it has



Scheme(2) Synthesis of Salbutamol

Materials and Methods:

The gelatin (Merck) was usedas received .methyl nadic anhydride from Fluka,. Ammonium persulfate (APS, Merck) was used without purificationAll other chemicals were of analytical grade. Thedrug, Salbutamol was obtained from BHD.

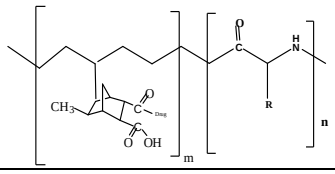
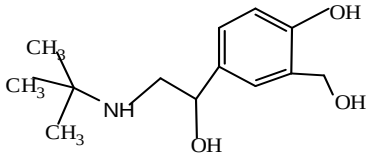
Synthesis of Gelatine-G-Methyl Nadic Anhydride(A_1):-

Granules of gelatin (3 gm) were dissolved in few drops of acetone theAPS (0.1gm,0.00034mol) dissolved in 1ml of water was added and stirred at $60C^0$for 10min until it reaches a viscous state.(4. Gm, 0.0022mol),of methyl nadic anhydride was added ,the mixture was heated and stirred about 20 min. The grafted was collected by filtration and re-dispersed in diethyl ether several times to remove excess of methyl nadic, precipitate was then filtered, and dried under vacuum. Gelatin- g- methy nadic anhydride was obtained as white (90%g). Table (1)physical properties of compound

Substitution of Salbutamol on (A_1)

gelatin- g-methyl anhydride (0.50 g) was dispersed in 3 mL of DMF ,then(0.3g) of salbutamole dissolved in aceton was added to the (gelatin-g- methyl nadicanhydride) and stirred by magnetic at 60°C about ½hr,theYellow precipitate collection and filtrated and then washed with ethanol and dried at room temperature.

Table (1) Physical properties of Compound

Pol. No.	Grafted polymer+Drug	Color	Softening point ^{0}C	Conversion %
A_1		White	175-188	90
A_2	 Salbtamol	Yellow	199-210C^0	64

The controlled released study [21-22]

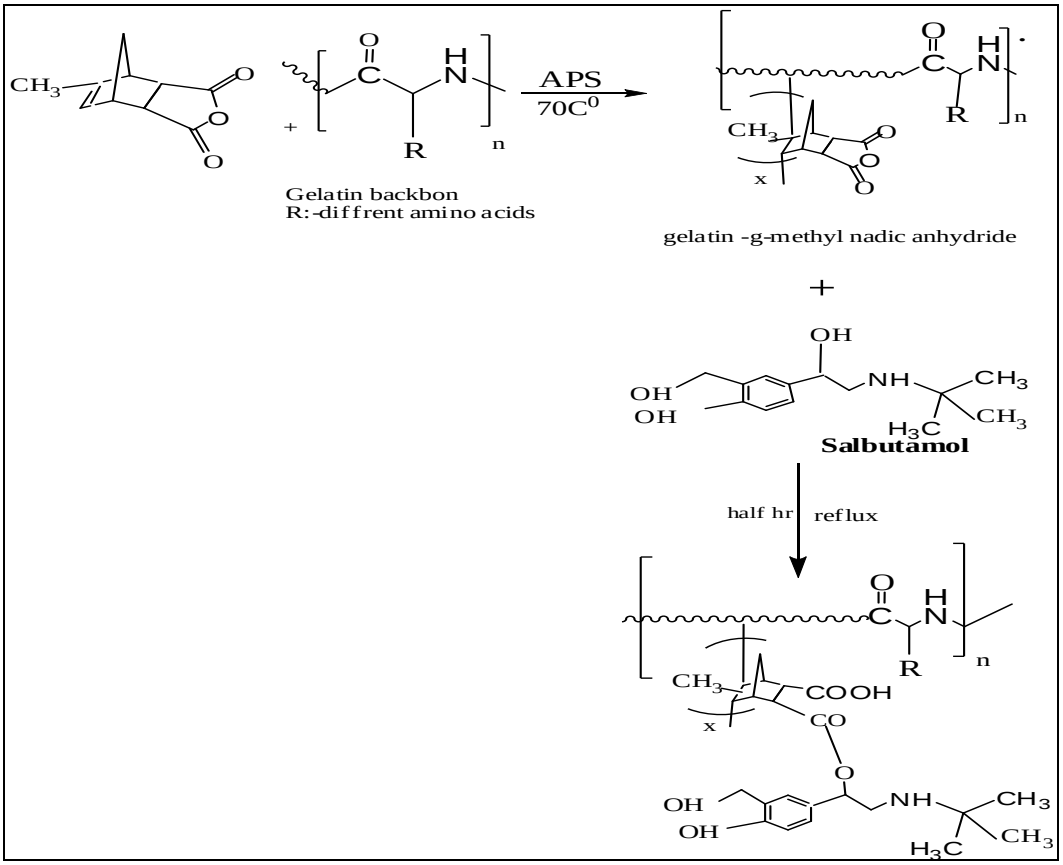
A 1.00mg of drug polymer was kept in a cylinder containing 100 ml of buffer solution in different pH values at 37 ^{0}C without stirring. A released sample periodically withdrawn and analyzed by UV. Spectroscopy at specific λ_{max} 270nm was used to determine the amount of the released drug unite. A calibration curve was constructed with a software built in the computerized. 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.Fig(4a,4b)showed UV. spectrum of many days of controlled release.

Swelling Percentage of Prepared Polymers [23]

In order to study the swelling behavior, the disksamples (approximately 0.15g) were immersed inthree different swelling solutions: water, acidic, basic medium. Thesamples were placed in the swelling solution andthe weight of the swollen samples was measuredagainst time after the excess surface water wasremoved by gently tapping the

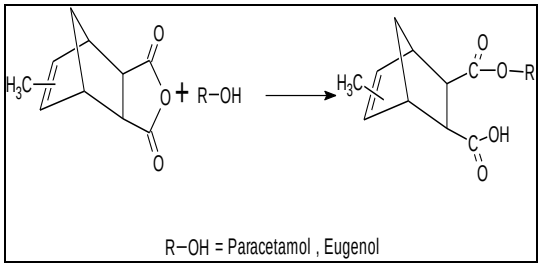
surface with a dry piece of filter paper. The (A_1)grafted copolymer was modified with salbutamol which acted as ring opening of nadic anhydride as illustrated in the scheme(3). could added new properties and more attention production with high stiffness Grafted copolymerization of un saturated monomer on gelatin back bone carries out

Results and Discussion:



Scheme (3) Mechanism of substitution of Nadic Anhydride with Salbutamol

Fig.(1) FTIR spectrum of gelatin was compared with Fig.(2) of gelatin grafted methyl nadic anhydride (A_1) appeared the characteristic absorption of carbonyl group of anhydride at 1780cm^{-1} and 1840cm-1can be attributed to C=O stretching in carboamide of functional is due to a symmetric stretching carboxylate and 1640cm^{-1}for carboxamied functional group.The ring opening of substituted methyl nadic anhydride by nucleophlic attack to carbonyl group of anhydride was illustrated in scheme (4).



Scheme(4) Mechanism of Ring Opening of Nadic anhydride by hydroxyl Drug

Fig.(3) FTIR spectrum of drug polymer (A_2)showed characteristic absorption was appeared at 3450-2900cm^{-1} and at 1650cm^{-1} of carbonyl of carboxylic also the main OH groups of salbutamol were appeared at 3380cm^{-1}.Gelatin is natural polymer which is available ,sustainable

renewable and posses better biocompatibility, non toxic, when it grafted with methyl nadic anhydride become more capability to substituted with salbutamol through OH group which acted ahigher nucleophlic group . The C=O ester e was formed which successful for hydrolysis through pH 7.4 and 1:1 Fig.(4a,4b)showed the UV. spectra of A_2at λ_{max}270nm indicated the sustain release of drug through 4-5 days respectively in acidic and basic medium (24-26). Fig.(5) and Fig.(6) DSC showed the thermal stability of (A_1) and (A_2) with T_g200°C and 161.1C^0respectively .It was concluded that the methyl nadic anhydride which was used as aspacer between gelatin and salbutamol gave good functional groups which are pendant through backbone of drug polymer with good sustain release rate through hydrolysis of ester attachment through 4-5 days ,thy also influenced the thermal stabilities were shifted to 161.1°C has an efficient product.

Acknowledgment:
The authors are grateful for the functional support obtained from Al-Mustansirya University College of Science, Department of chemistry and Women College of Science.

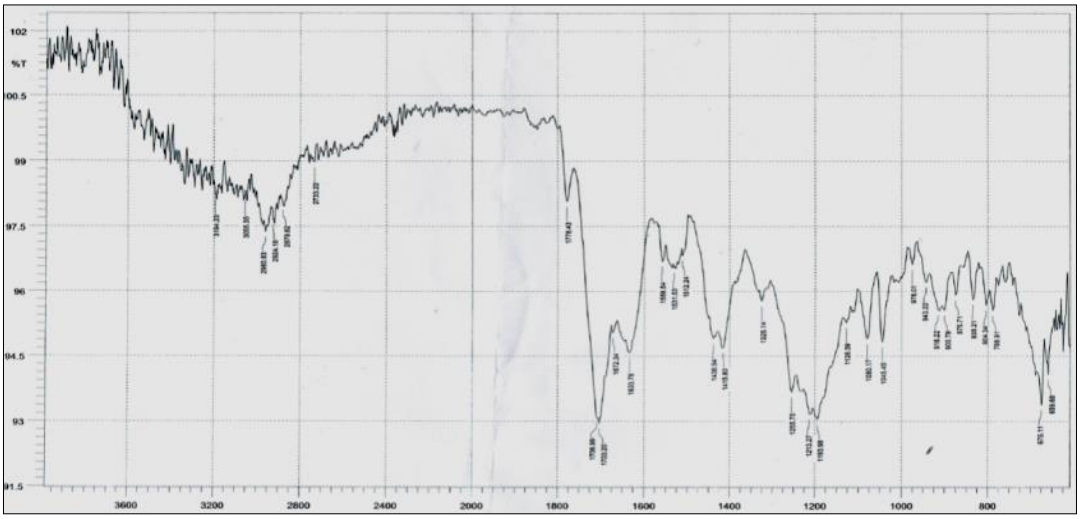


Fig.(1) FTIR Spectrum of Gelatin

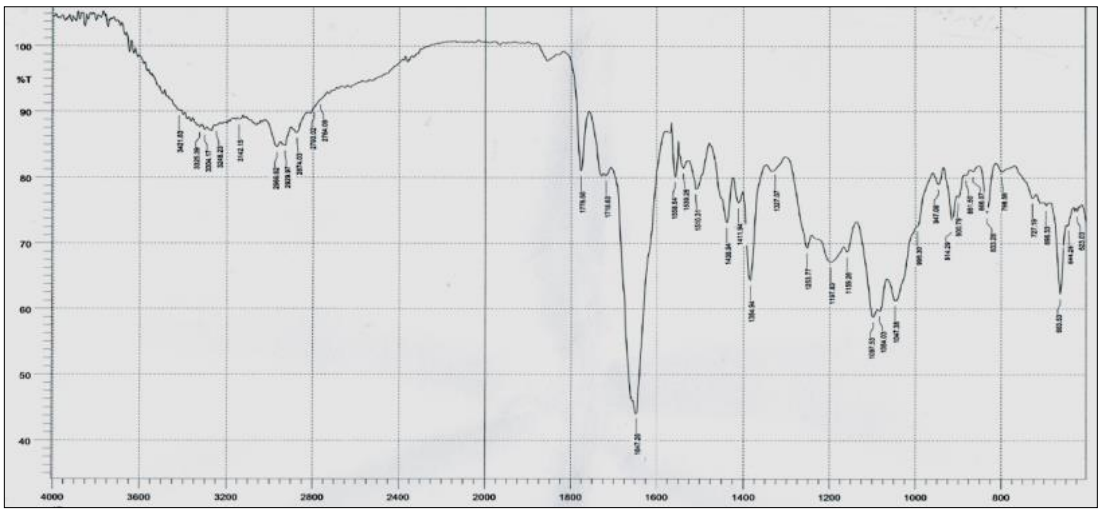


Fig.(2)FTIR Spectrum of Gelatine –g-methyl nadic anhydride(A_1)

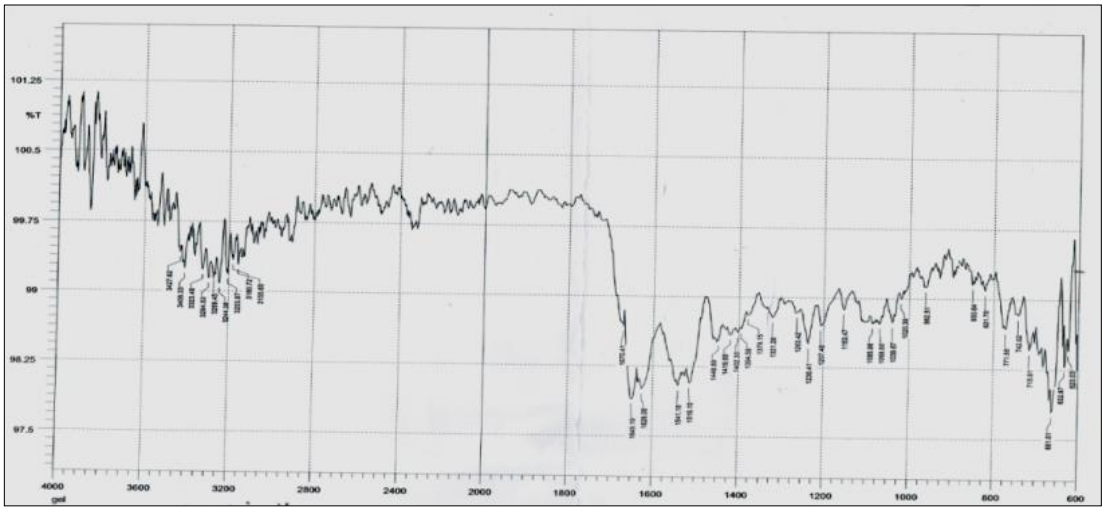


Fig.(3)FTIR Spectrum of Gelatin-g-methylnadic anhydride substitution with Salbutamol(A_2)

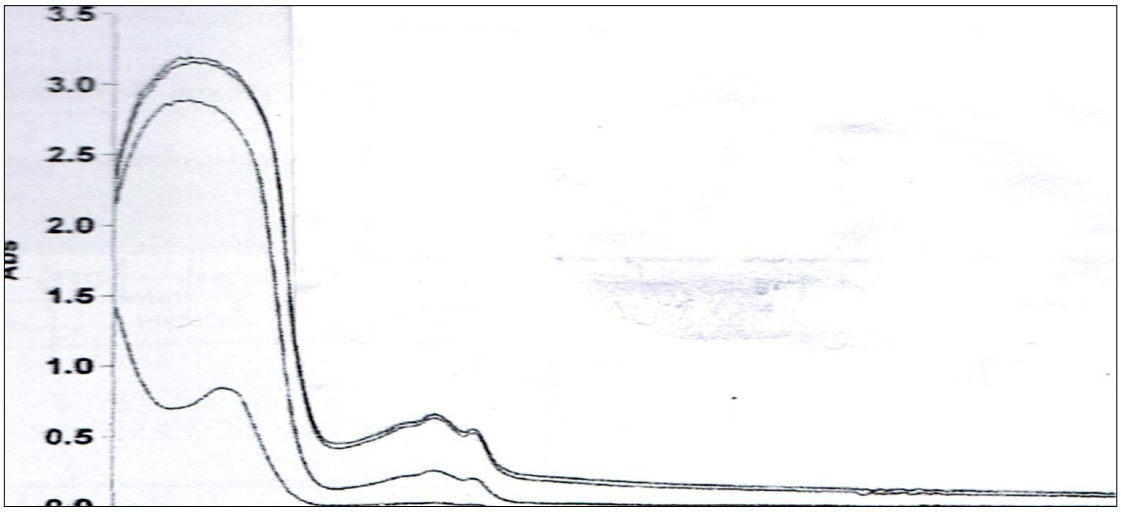


Fig.(4a)UV Spectrum of Drug in PH1.4

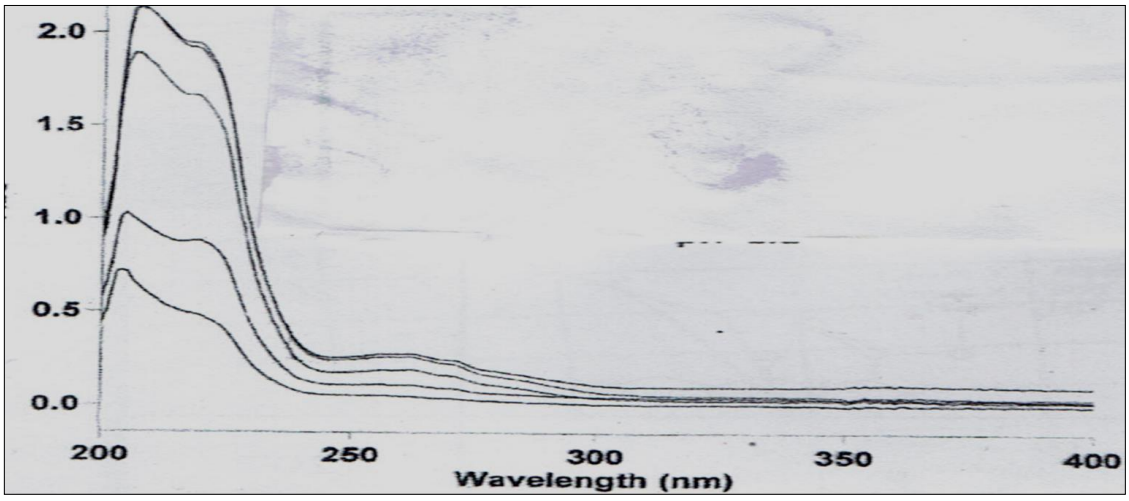


Fig.(4b) UV Spectrum of Drug release in PH 7.1

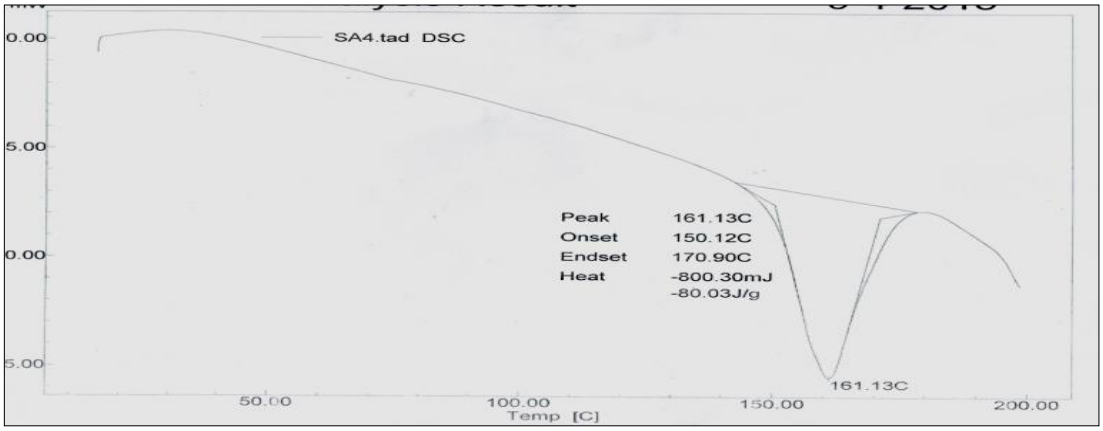


Fig.(6)DSC of Gelatin-g-methyl nadic anhydride Substitution with Salbutamol(A_2)

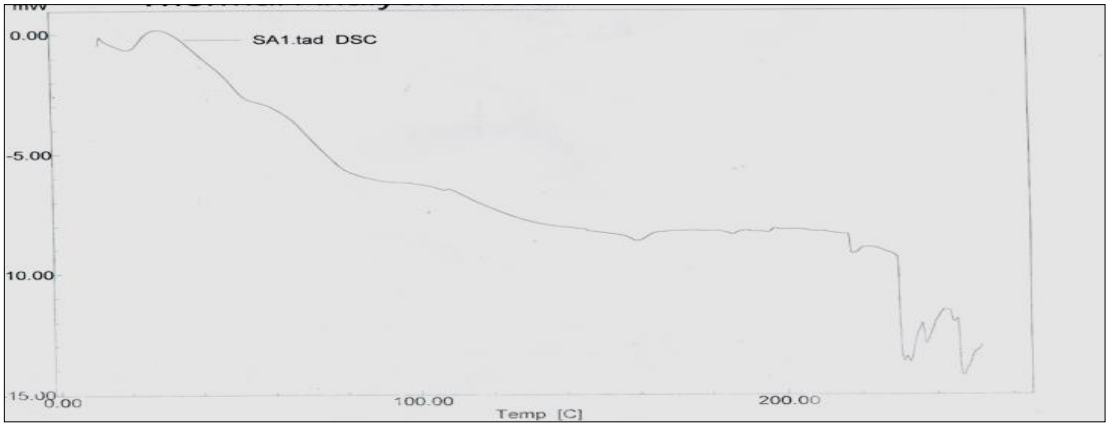


Fig.(5)DSC of Gelatin-g-methyl Nadic anhydride(A_2)

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تطعيم الجيلاتين بحامض المثيل نادك اللامائي وتعويضه بالسالبيوتامول

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الخلاصة:-
الجيلاتين من المواد البايولوجية الواعدة والمرغوبة الاستعمال كبوليمر طبيعي والذي بالامكان تحويره كيميائيا من خلال التطعيم بالبلمرة المشتركة مع الحوامض اللامائية غير المشبعة مثل حامض المثيل نادك اللامائي مكونا جيلاتين مطعم بالبولي مثيل نادك اللامائي(A_1)0 ثم تحويره الى البوليمر المقابل (A_2)بواسطة تعويض السلبتيمول كمشتق مفيد و كمادة بايولوجية دوائية .والتي شخصت بواسطة طيف الاشعة تحت الحمراءFTIR. ودرس التحليل الحراري .ودرس التحرر الدوائي المحكم بدوال حامضية مختلفة بدرجة حرارة^{0}37C.

الكلمات المفتاحية: جيلاتين ،مثيل نادك انهدريد،السالبيوتامول