Gelatin Grafted Methyl Nadic Anhydride and Substitution With Salbutamol

Fīryal M. Ali* Sana H. Awad**

*Department of Chemistry, College of Science, Al-Mustansiriya University, Baghdad, Iraq.
**Department of Chemistry, College Science for Women, University of Baghdad, Baghdad, Iraq.

E-mail: dr.frial10@yahoo.com

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 (A₁), then modified to its corresponding polymer (A₂) by substituted salbutamol as useful derivative as biomaterial. the prepared drug biopolymer was characterized by FTIR spectroscopy and thermal analysis was studied controlled drug release was measured in different buffer solution at 37°C.

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 resistance 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- methanophthalic anhydride has a more stabilize chemical toxicity and enhance selectivity for certain antitumor agents ), as well as pro drugs with polymers.
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 asthma which 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 alternative 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](image-url)
Materials and Methods:
The gelatin (Merck) was used as received. Methyl nadic anhydride from Fluka, Ammonium persulfate (APS, Merck) was used without purification. All other chemicals were of analytical grade. The drug, Salbutamol was obtained from BHD.

Synthesis of Gelatine-G-Methyl Nadic Anhydride (A1):
Granules of gelatin (3 gm) were dissolved in few drops of acetone. The APS (0.1 gm, 0.00034 mol) dissolved in 1 ml of water was added and stirred at 60°C for 10 min until it reaches a viscous state. (4. Gm, 0.0022 mol), 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- methyl nadic anhydride was obtained as white (90% g). Table (1) physical properties of compound.

Substitution of Salbutamol on (A1)
Gelatin- g-methyl anhydride (0.50 g) was dispersed in 3 mL of DMF, then (0.3 g) of salbutamole dissolved in acetone was added to the (gelatin-g- methyl nadic anhydride) and stirred by magnetic at 60°C about ½ hr, the Yellow 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 °C | Conversion % |
|----------|----------------------|-------|--------------------|--------------|
| A1       | ![Chemical Structure](image1.png) | White | 175-188            | 90           |
| A2       | ![Chemical Structure](image2.png) | Yellow | 199-210°C⁰      | 64           |

The controlled released study [21-22]
A 1.00 mg of drug polymer was kept in a cylinder containing 100 ml of buffer solution in different pH values at 37 °C without stirring. A released sample periodically withdrawn and analyzed by UV. Spectroscopy at specific $\lambda_{\text{max}}$ 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 0.15 g) were 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 against time after the excess surface water was removed by gently tapping the
surface with a dry piece of filter paper. The (A₁) 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](image)

Fig.(1) FTIR spectrum of gelatin was compared with Fig.(2) of gelatin grafted methyl nadic anhydride (A₁) appeared the characteristic absorption of carbonyl group of anhydride at 1780 cm⁻¹ and 1840 cm⁻¹ can be attributed to C=O stretching in carboamide of functional is due to a symmetric stretching carboxylate and 1640 cm⁻¹ for carboxamied functional group. The ring opening of substituted methyl nadic anhydride by nucleophile attack to carbonyl group of anhydride was illustrated in scheme (4).

![Scheme 4](image)

Fig.(3) FTIR spectrum of drug polymer (A₂) showed characteristic absorption was appeared at 3450-2900 cm⁻¹ and at 1650 cm⁻¹ of carbonyl of carboxylic also the main OH groups of salbutamol were appeared at 3380 cm⁻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 nucleophilic 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 A2at $\lambda_{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 (A1) and (A2) with $T_g$200°C and 161.1°C respectively .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(A1)**
Fig.(3) FTIR Spectrum of Gelatin-g-methylnadic anhydride substitution with Salbutamol(A$_2$)

Fig.(4a) UV Spectrum of Drug in PH 1.4

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

[1] Drexler, H.; Weber; A.; Letzel, S.; Kraus. G.and Schaller, K. H. 1999. Detection and clinical relevance of a type I allergy with occupational exposure to hexahydrophthalic anhydride and methyltetrahydrophthalic anhydride. Int Arch Occup Environ Health 65 (5):279-83.

[2] Grammer, L. C;Shaughnessy, M. A.; Hogan, M. B.; Berggruen, S. M.; Watkins, D. M., and Yarnold P. R. 1995. Value of antibody level in diagnosing anhydride-induced immunologic respiratory disease. J Lab Clin Med 125 (5):650-3.

[3] Welinder, H.; Ottosson., H.; Bensryd, I.; Venge, P. and Skerfving, S. 1994. Nasal challenge shows pathogenetic relevance of specific IgE serum antibodies for nasal symptoms caused by hexahydrophthalic anhydride. Clin Ex Allerg 24(5):440-9

[4] Ritu, V. C.; Parveen K., Veena, C. and Narula, K. 2006. Studies on the curing kinetics and thermal stability of epoxy resins using mixture of amines and anhydrides. J. Appl. Polym. Sci.,(100): 3919.

[5] Ritu, V. C. and Narula, K. 2010. Curing and thermal behavior of DGEBA in presence of dianhydrides and aromatic diamine, J. Appl. Polym. Sci(6): 36-637

[6] Lim-L, T.; Mine, Y. and Tung,A.; 2000. Barrier and Tensile Properties of Transglutaminase Cross-linked Gelatin Films as Affected by Relative Humidity, Temperature, and Glycerol Content, Journal of Food Science,) 64(4):. 616-622.

[7] Sobral-P, J.; Menegalli,A. F. C.; Hubinger, M. D. and Roques, M. A.
2001. Mechanical, Water Vapor Barrier and Thermal Properties of Gelatin Based Edible Films, 15(4): 423-432.

[8] Carvalho, R. A. and Grosso, C. R. F. 2004. Characterization of Gelatin Based Films Modified with Transglutaminase, Glyoxal and Formaldehyde, 18(5): 717-726.

[9] Bergo, P.; Carvalho, R.; Vadala, A.; Guevara, V. and Sobral, P. 2010. Physical Properties of Gelatin Films Plasticized with Glycerol, Studied by Spectroscopic Methods, Materials Science Forum, 6(37): 753-758.

[10] Vanin, F. M.; Sobral, P. J. A.; Menegalli, F. C.; Carvalho, R. A. and Habitante, M. Q. 2005. “Effects of Plasticizers and Their Concentrations on Thermal and Functional Properties of Gelatin-Based Films, Food Hydrocolloids, 19(5): 899-907.

[11] Bergo, P. V.; Carvalho, R. A.; Sobral, P. J.; Bevilacqua, F. R.; Pinto, J. K. and Souza, M. P. 2006. Microwave Transmittance in Gelatin-Based Films, Measurement Science and Technology, 17(12): 3261-3264.

[12] Arvanitoyannis, A.; Nakayama, S.; Aiba, S. and Yamamoto, N. 2008. Edible Films Made from Hydroxypropyl Starch and Gelatin and Plasticized by Polyols and Water, Carbohydrate Polymers, 36(2): 105-119.

[13] C. KangJo, H.; Lee, N. Y.; Kwon, J. H. and Byun, M. W. 2005. Pectin and Gelatin-Based Film: Effect of Gamma Irradiation on the Mechanical Properties and Biodegradation, Radiation Physics and Chemistry, 72(6): 745-750.

[14] Haque, P.; Mustafa, A. I. and Khan, M. A. 2007. Effect of Cross-Linking Monomers on the Physico-Mechanical and Degradation Properties of Photografted Chitosan Film, Carbohydrate Polymers, 68, 1: 109-115.

[15] Ghosh, Pranab, Tapan, D.; and Moumita, D. 2011. Evaluation of Poly (acrylates) and their copolymer as viscosity modifiers, Res. J. Chem. Sci., 1(3): 18.

[16] shikha, D. and Basu, T. 2011. The Role of Structure Directing Agents on Chemical Switching Properties of nanostructured conducting polyaniline (NSPANI), Res. J. Chem. Sci. 1(6): 20-29.

[17] Manimaran, N.; Rajendran, S. Manivannan, M. and John Mary, S. 2012. Corrosion inhibition of carbon steel by polyacrylamide, Res. J. Chem. Sci., 2(3): 52-57.

[18] Johnson, M.; Koman, L. and Neuse, E. 2005. Polymeric drug carriers functionalized with pairwise arranged” J. of Appl. Poly. Sci., 96(1): 10-19.

[19] Lindon, J. C.; Tranter, G. E.; Holmes, J. L. 2000. Encyclopedia of Spectroscopy and spectrometry . Part 1, Canada.

[20] Ali, M.; F.; Abbas, N. M. 2010. Synthesis of poly paracetamol Acrylate and Study of drug Release). fifth Scientific Conference –College of Science-University of Babylon: pp. 236-236, Iraq.

[21] Awad, H.; S.; Hamid, M. M. 2015. (Substitution of gelatin grafted maleic anhydride as drug copolymer, J. of chemistry Material Research.

[22] Ali, M.; F.; H. T.; and Mohsun, A.; S. 2015. (Synthesis and characterization of gelatin –g-acryiyl amide proflavin and controlled release J. Chemical and process ,Engineering Research.
تطعيم الجيلاتين بحامض المثيل نادك اللامائي وتعويضه بالسالبيوتامول

فريال محمد علي
سناء هتورعوا
قسم الكيمياء، كلية العلوم، الجامعة المستنصرية، بغداد، العراق
قسم الكيمياء، كلية العلوم للبنات، جامعة بغداد، بغداد، العراق

الخلاصة:
الجيلاتين من المواد البيولوجية الواعدة والمرغوبة الاستعمال كبوليمر طبيعي والذي بالإمكان تحويله كيميائيا من خلال التطعيم بالبلمرة المشتركة مع الحوامض اللامائية غير المشبعة مثل حامض المثيل نادك اللامائي مكونا جيلاتين مطعم بالبولي مثيل نادك اللامائي(A1) ثم تحويله إلى البوليمر المقابل (A2) بواسطة تعويض السليبتيمول كمشتق مفيد وكمادة بيولوجية دوائية، والتي شنت بواسطة طيف الاشعة تحت الحمراء FTIR ودرس التحليل الحراري ودرس التحرر الدوائي المحكم بدوال حامضية مختلفة بدرجة حرارة 37C.

الكلمات المفتاحية: جيلاتين، مثيل نادك اللامائي، السالبيوتامول