Synthesis of Gelatin Graft Itaconic Drugs

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ABSTRACT *- This work involved preparation new drug adhesive to treatment the wounds and inflammations, as bio adhesive , which have high viscosity and treatment the wounds by the adhesion of the wound when it put as well as the rapidity treatment of external inflammation, because it remains inherent to the position of injury fast time,. A new bio adhesive polymer was prepared by modification of Gelatin structure with Itoconic acid as a insertion by using ceric* ion ,it *was substituted with amino drugs produced amide polymer. This design carries controlled delivery which could release the entrapped drug over an extended period of time due to its biodegradable, nontoxic and slow digesting nature.* The *prepared adhesive drug polymer* was *characterized by FTIR, ^{1}H-NMR spectroscopes, thermo gravimetric analysis TGA and DSC were considered. Physical properties of prepared polymer* was *measured, 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 compared at zero time and after 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 noted to be promising.*

Keywords: *Gelatin , controlled delivery, adhesive drug polymers , Graft Copolymer*

INTRODUCTION

The modification of natural polymers is a promising technique for the making a new drugs . 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. In 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].. Gelatin is a biopolymer[46] that has very

broad applications in the food, pharmaceutical industries[47] and cosmetics for its viscoelastic properties to act as gelling agent, thickener, or stabilizer. Gelatin is soluble in water,[48] translucent, colorless, brittle when dry, flavor less, solid substance, derived from the collagen. It is natural polymer derived protein; it is the partially hydrolyzed form of collagen extracted from tissues such as bones and skins of animals through thermal hydrolysis using either an acid or alkali. The functional group of gelatin, for example, –NH2, CONH, and –COOH explained.

Gelatin has been used for many years in the pharmaceutical industry for the preparation of capsules like albumin. Gelatin presents properties favorable to drug delivery applications, such as being non-toxic, biocompatible and a stabilizer with sustained drug release characteristics[49].

Over the past few decades, gelatin-based adhesives have slowly been replaced by a variety of synthetics. Recently, the natural biodegradability of gelatin adhesives is being realized. Today, gelatin has a wide variety of adhesive and composite applications uses such as food packaging or wood adhesives, automotive, and production industries[50]

Materials

Gelatin . Guaifenesin, and procaeinwere purchased from SiGma Chemicals , All other solvents and reagents were of analytical grade

Instrumentation

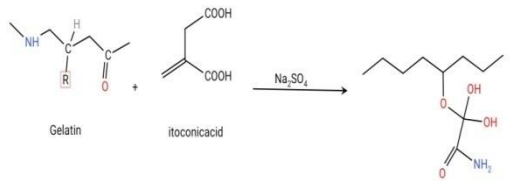
Melting point was measured using Thermal Microscope (Kofler-method), and Reichert thermovar, Stuart SMP 30. Infrared spectrophotometer measurements were performed using Shimadzu FT-IR 8400 series Fourier Transform, ^{1}H-NMR spectra were measured with a bruker spectrophotometer model ultra-shield at 300.13 MHz in DMSO-d6. U.V-Visible double beamscanning spectrophotometer VARIAN (UV-Vis)-100 Conc, at room temperature.

preparation of Gelatin grafted Itaconic acid (G1)

(2 g) Gelatin was mixed with (2 g) of itocon acid in a glass flask and (Na2S2O8) was added with a quantity of (0.5) g

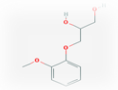
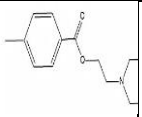
The mixture was heated at 60C for one hour and then the mixture was cooled and placed in an hourglass for 72 hours.
Purify the drug with ethanol before the diagnostic test; Melting Point 160 C°

B-Substitution of (G1) with drugs(G1A-G1B)



(0.56Gm) of Gelatin- g-Itaconic acd was dispersed in (2ml) of dioxin, (0.28 Gm) of Guaifenesin, (0.5 mL) of DMF was added to the mixture, It was refluxed with stirring for 1 hour at (90 0C), the colored solution was filtered, the filtrate was isolated and the solvent was evaporated, the off Wight product Gelatin-g- [N-Guaifenesin Itaconic acd] was washed with two timesdi ethyl ether and dried at (50 0C) in a vacuum, conversion (70 %). Similar procedure was used for preparation with other amino drug such as procaine all physical properties were listed in Table (2-2).

Table (2) Physical properties of prepared polymers (G1A-G1B)

Pol.	-Drugs	Color	Softening point 0C	Conversion ratio %
G1A	 Guaifenesin	Off Wight	115-125	80
G1B	 Procaine	Orange	60 – 75	70

***Controlled drug release* :-**
Release of G1A 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.

Results And Discussion

Grafted copolymerization of unsaturated monomer on gelatin backbone could added new properties and more attention gelatin- g- itoconic was modified with amino drugs which acted as.

Figure (1) FTIR spectrum of (G1A) [Gelatin-guaifensin] copolymer containing hydroxylic group as characteristic absorption bands was appeared at (3250 cm-1) in addition to υ (-NH) at (3155 cm-1), absorption of amide υ (C=O) appeared at (1649 cm-1), and band at (1728) cm-1 due to υ (C=O) stretching vibration of acid.

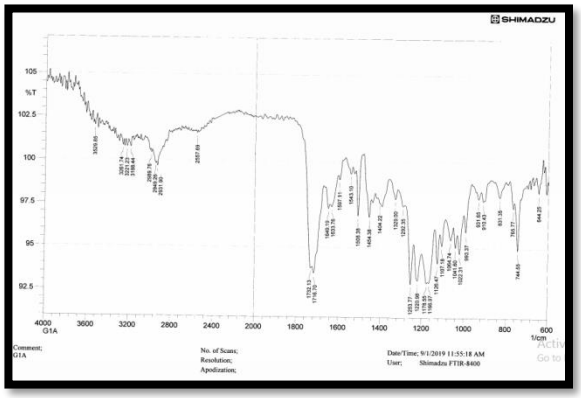


Figure (1) FTIR spectrum of G1A

Figure (2) FTIR spectrum of (G1B) FT-IR spectrum of prepared compound [G1B] showed absorption band at (3261) cm-1 due to υ (OH) stretching vibration, and at (3200) due to the υ (NH) stretching, band at (1660) cm-1 due to (C=O) stretching vibration of amide, and (1714) cm-1 due to (C=O) stretching vibration of acid.

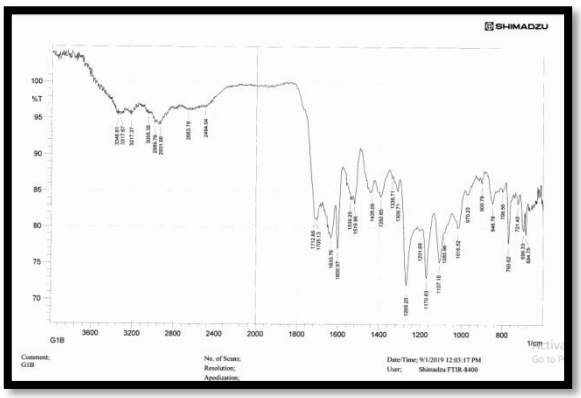


Figure (2) FTIR spectrum of (G1B)

Figure (3) FT-IR spectrum of prepared compound [G1C] showed the absorption band at (3375) cm-1 related to (OH) stretching vibration, and (3171) due to the υ (NH) stretching, band at (1647)

cm-1 correlated to (C=O) stretching vibration of amide, and (1716) cm-1 due to (C=O) stretching vibration of acid

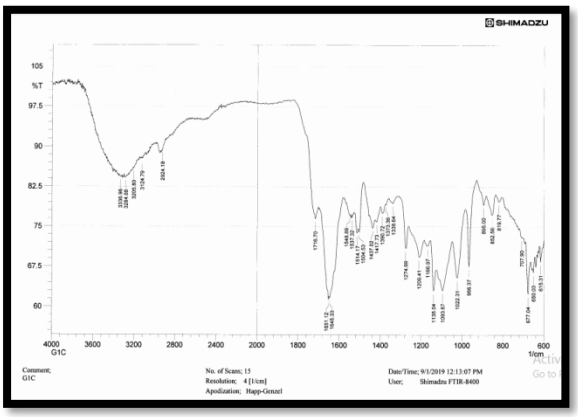


Figure (3) FTIR spectrum of (G1C)

Figure (4) FT-IR spectrum of prepared showed absorption band at (3227) cm-1 due to (NH) stretching, and (1651) cm-1 due to (C=O amide) stretching, and (1602) cm -1 due to (NH) bending, peak at (1705) cm-1 correlated to (C=O) stretching vibration of acid

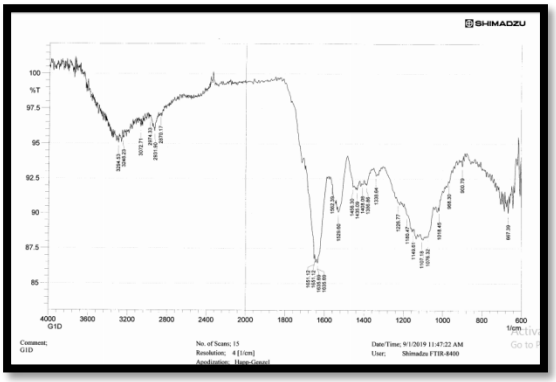


Figure (4) FTIR spectrum of (G1D)

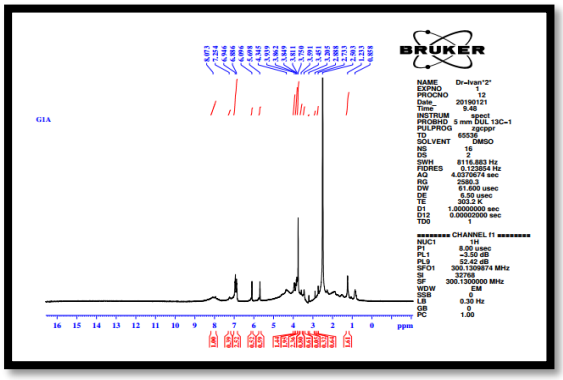
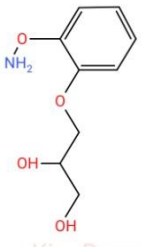


Figure 5 .H-NMR Spectrum of G1A

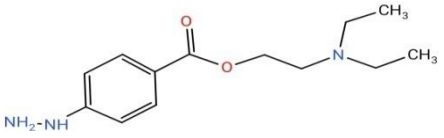
The ^{1}H-NMR spectrum of prepared polymer (G1A)which shown the following signals 1.1 ppm (Singlet, 3H, CH3) for ring methyl nadic, 1.35 ppm, (Triplet, 2H, CH2) for ring methyl nadic, 1.71 ppm (Singlet, 6H, 2CH3), 2.5 ppm (Triplet, 1H, -CH-COOH), 5.7 ppm (Singlet, 1H, OH) for starch, 6.2 ppm (Singlet, Ar-OH), 6.6-7.3 ppm (4H, Aromatic ring), 7.9 ppm (Singlet,1H, CO-NH amide).

The ^{1}H-NMR spectrum of prepared polymer (G1B)which shown the following signals 0.85 ppm (Singlet, 3H, CH3) for ring methyl nadic, 2.2 ppm (Singlet, 6H, Ar-CH3), 3.0 ppm, (doublet, 2H, CH2) for starch, 6.8-7.5 ppm (Multiple, 5H), 8.1 ppm (Singlet,1H, NH-NH amide).

Mechanisms of drug as shown in the Scheme 3



Scheme (4) Mechanism of G1B



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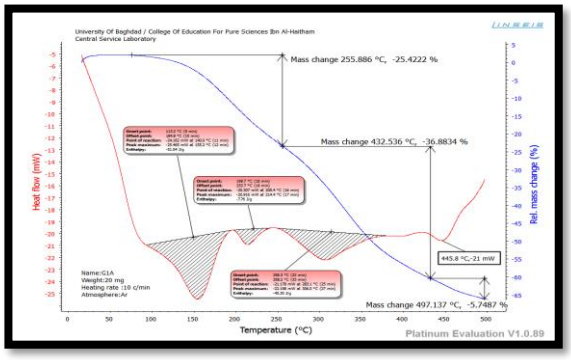

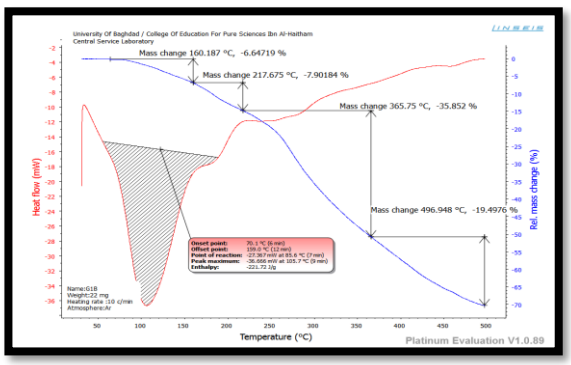

Figure (8) DSC and TGA Analysis

Thermal stability of prepared polymers were investigated by (TGA and DSC) Table (3) TGA showed the results of some prepared drug polymers which indicated the high thermal resistance and showed their steps of weight loss-temperature. This high thermal resistance indicated the high interaction between amide hydrogen bonding through the polymer chains and led to best sustain drug release. Several thermal stability parameters were determined from TGA and DSC curves as shown in Table (3) Thermal stability of some selective compounds were investigated by thermo gravimetric analysis (TGA). The change in weight was measured as a function of temperature which gave valuable information about the thermal stability of the prepared compounds. Several thermal stability parameters were determined from TGA and DSC curves as following :-
Decomposition temperature (DT). Two type of DT were determined 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 at which the sample lost of its total weight In this study (17-22) mg. was taken from the prepared polymers 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. The above parameters which were determined for some of the prepared compounds, were explained and listed in the Table (3).

Table (3a) TGA analysis of some drug polymers

Table (3b) DSC analysis of some drug polymers
Table (3) TGA showed the results of some prepared drug polymers which indicated the high thermal resistance and showed their steps of weight loss-temperature. This high thermal resistance indicated the high molecular weight of the prepared polymers with high interaction between amide hydrogen bonding through the polymer chains and led to best expire date to protect the drug.

Conclusions

In this study new design natural polymers could be prepared, due to their outstanding characteristics, have received more attention in the field of controlled drug delivery. Modification of natural polymers gave them new or improved properties. Modified polymers are large important and improve numerous controlled release systems. The present work with the new methods working for the modification of poly peptide and poly saccharides and the developments in designing novel drug delivery systems. In this thesis, many types of drug polymers were obtained by the different following methods:-

Modified of some natural polymers such as (starch, glycogen, gelatin) by using free radical polymerization.

These new prepared drug polymers have suitable properties and the release of drugs gradually controlled in different pH values.

The substitution of bioactive drugs on the chain of polymers could lead to most accuracy, effectiveness, no toxicity, long life and water soluble

In this research, the prepared drug polymers were higher hydrolysis in basic medium than acidic medium, this lead to using as specific site.

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