Synthesis of Prodrug Polymer as Ring opening of PVP

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ABSTRACT

In this work a new drug polymer was prepared from reaction of polyvinylpyrrolidone (PVP) with doxycylin in 10:1 dioxane: dimethelyformad solvent mixture. The prepared drug polymer was formed with 85% conversion percentage. The physical properties were studied and intrinsic viscosity was equal to 0.23 dl/g. The drug polymer was characterized by FT-IR and UV spectroscopy. The swelling % was studied in different non solvents. The elemental analysis and DSC were analyzed. The controlled release rates for drug polymer were studied in different pH values a37^{o}C for 4 days. The softening point of the prepared doxycyclin drug polymer was 143.4^{o}C to 150.3^{o}C with ΔH=-189.89 J/g.

تحضير مقدمات دوائية بوليمرية بفتح حلقة البولي فانيل بايرولدنيون

الخلاصة

في هذا البحث حضر بوليمر دوائي من تفاعل البولي فاينيل بايروليدينون مع عقار الدوكسيسايلين في مذيب الدايوكسان والداي مثيل فورمايد بنسبة 10:1 فكان ناتج التحوير بنسبة 85% درست الصفات الفيزيائية واللزوجة الجوهرية للبوليمر والتي تساوي (0.23dl/g) وشخص البوليمر الدوائي الناتج بواسطة الأشعة تحت الحمراء والأشعة فوق البنفسجية، وقيست نسبة الانتفاخ المئوية في اللامذيبات. وأجري التحليل الدقيق للعناصر وتم إجراء التحليل الحراري DSC . وكذلك درست سرع التحرر الدوائي من البوليمر المحضر في دوال حامضية مختلفة عند37 م لمدة 4 أيام. وكانت درجة سيولة البوليمر تساوي: 143.4^{o}C -150.3^{o}C والتغير في الإنثاليبي(189.89) ميكروجول/غم .

INTRODUCTION

Doxycycline is used in prophylaxis against malaria. It should not be used alone for initial treatment of malaria, even when the parasite is doxycycline-sensitive, because the antimalarial effect of doxycycline is delayed. This delay is related to its mechanism of action, which is to specifically impair the progeny of the apicoplast genes, resulting in their abnormal cell division. The action of polymeric drugs in vivo usually depends on hydrolytic on enzymatic cleavage of drug modify from the polymer [1]. Doxycycline is used in the treatment and prophylaxis of

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Bacillus anthraces, it is also effective against Yersinia pestis (the infectious agent of bubonic plague), and is prescribed for the treatment of Lyme disease [2-5], ehrlichiosis [6, 7] and Rocky Mountain spotted fever. In fact, because doxycycline is one of the few medications shown to be effective in treating Rocky Mountain spotted fever (with the next-best alternative being chloramphenicol), doxycycline is indicated even for use in children for this illness. Otherwise, doxycycline is not indicated for use in children less than eight years. Doxycycline, like other antibiotics, will not work for colds, influenza, or other viral infections. A polymer is a large molecule composed of many smaller units called monomers that are bonded together. In addition to eliminating the necessity of removal, the five key advantages [8] that polymeric drug delivery products can offer are: sustained delivery of drug, stabilization of the drug, release rate that is less dependent on the drug properties and steadier release rate with time. In diffusion controlled systems the release rate typically declines with time.

If an application requires rapid development and commercialization, than the polymer selection will most likely be made of among those polyesters that have already received regularly approval. Another factor to be taken into account is choice, whether to use homo polymers consisting of single monomeric repeating unit or copolymers containing multiple monomer species. A review that describes in detail the relationship between polymer properties and performance in drug delivery applications have been published [9].

In some cases, the term biodegradation is limited to the description of chemical processes (chemical changes that alter either the molecular weight or solubility of the polymer) [10, 11]

Degradation by erosion normally takes place in devices that are prepared from soluble polymers. In such instances, the device erodes as water is absorbed into the system causing the polymer chains to hydrate, swell, disentangle and ultimately dissolved away from the dosage form. Alternatively, degradation can also result from chemical changes to the polymer including cleavage of covalent bonds, ionization and protonation either along the polymer backbone or on pendent side chains [12-14].

The purpose of this research was to synthesize polymer based smart bioactive doxycycline prodrug polymer and one of the main goal of this work is to investigate the efficient drug carrier and the effect of pH values on drug release at 37^{o}C .

Chemicals and Apparatus

Doxycycline was provided from college of Pharmacy and all other chemicals were purchased from Mereck, and polyvinylpyrrolidinone was obtained from Fluka.All available chemical reagents were used without further purification. FT-IR spectra were taken on a Shimadzu spectrophotometer recorder over the range 4000-400cm^{-1}. Ultraviolet spectra were recorded using Shimadzu UV-Vis recorder. Differential Scanning Calormeter (DSC) study was carried out on a Shimadzu-60 instrument (Japan) at a heating rate of 10^{o}C min^{-1}, under air (normal), not vacuum. Temperature range from -140^{o}C up to 600^{o}C. The detector type K for the furnace temperature.

Experimental

Modification of Polyvinylpyrrolidinon PVP with Doxycycline:

A mixture of (5g, 0.045 mole) of PVP and 10:1 ml of Dioxane: DMF were placed in a round bottomed flask equipped with a reflux condenser and magnetic stirrer. Then (1.621g, 0.045 mole) of dissolved Doxycycline was added gradually, refluxed for 1hr. then the mixture left for 10 hours. The colorless viscous polymer was precipitate from 50ml of ethanol; the pure polymer was obtained 85% conversion.

Controlled Release Study:

100 mg of modified drug polymer was placed in a cylinder containing 50ml of buffer solution with (PH: 7.4 or 1.1) and 50ml dioxane in water bath at 37°C without stirring. A sample from the release medium was periodically withdrawn and analyzed by UV. at 300 nm to determine the amount of the released drug. A calibration curve was constructed with software built in the computerized UV. Spectrophotometer, the amount 0.1 mg of the released drug was determined directly from the software for 4 days, using the calibration curve in different pH values at 37°C.

Swelling percentage of prepared polymer was studied and equals to 8% for 26 hours using mixed solvent like acetone and 10% hexane. The Swelling percentage was calculated according to:

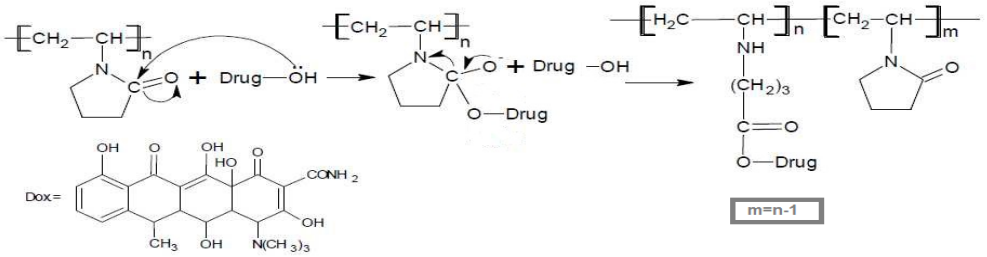
$$\Delta_m = (m_1 - m_o) / m_o * 100$$

When: m_o is the weight of the dry drug polymer at time 0.

m_1 is the weight of swallowed polymer in non-solvent.

Results and Discussion

Poly (N-vinyl-2-pyrrolidinone) is a white hydroscopic powder, forming hard clear films. Physical properties are determined on films or powder. The polymer strongly interacts through dipole-dipole attraction. The ring opening reaction of PVP with OH of the drug is illustrated in the mechanism [4] shown in scheme (1):



Scheme 1

Due to the presence of –OH group, which is strong nucleophile attach, the ring opining of pyrrolidinone produced prodrug polymer. The poly vinyl pyrrolidinon connected with hydroxyl of drug moiety affords both protection and specific transport properties with longer acting release with higher reactivity in suitable site and this type of drug polymer, which hydrolysis in fabrications conditions to delivery of agents, for therapeutic against diseases state, and sustained rate, target delivery of drugs and minimize toxicity and enhanced selectivity.

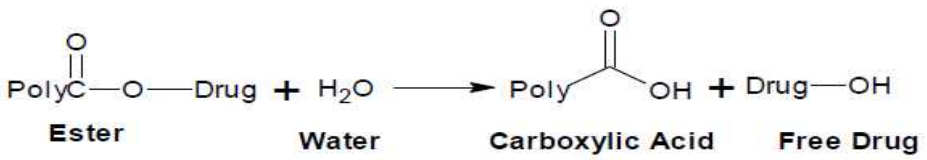
The structural characterization was done by FT-IR spectrum Figure(2) showed peaks at 3275 cm^{-1} assigned to –NH and the absorption appeared at 1633 cm^{-1} and 1681 cm^{-1} assigned to C=O stretching of ester and 3080 cm^{-1} was attributed to C-H stretching of aromatic ring and peak at 2960 cm^{-1} assigned to aliphatic C-H stretching; on the other hand, the FT-IR showed peaks at 1580 cm^{-1} and 1600 cm^{-1} due to C=C stretching of the aromatic ring of doxycycline, the FT-IR of drug polymer Figure(2), which compared with Figure (1) of FT-IR spectra of PVP [15-17].

Figure (3) shows the softening point of the drug polymer and it was 143.4-150.3°C, which measured by using differential scanning calorimeter DSC analysis, obtained high thermal stability and ΔH=-189.89J/g.

The physical properties of prepared doxycycline polymer were studied such as intrinsic viscosity, which was measured at 30°C with Ostwald viscometer by using dioxane as solvent ($[\eta]_{in}$= 0.23dl/g).

Figure (4) explain the effect of pH values on the rate of controlled release and profiles of mole fraction of doxycycline ratio to total moles present in the sample swelling versus time at pH values 7.4 and 1.1 at 37°C. The only nucleophile acyl substitution reaction that amides is hydrolysis, esters are fairly stable in water, but the ester bond is cleaved on the heating in presence of strong acid or bases. Normally, this cleavage produces a free drug carboxylic polymer.

The release of the drug at suitable condition gradually with outside effect, this hydrolysis of ester group, which shown in the following mechanism [14].



The hydrolysis rate of this ester bond acts higher hydrolysis in basic medium, than acidic medium, due to more neuclophilic attack of –OH than H_2O molecule. In acid, however, the hydroxyl is protonated giving free drug unit [18-22].

Figure (5) demonstration the Swelling percentage of prepared drug polymer in 10% hexane and acetone, this equals to 8% for 26 hours.

Conclusion

It was concluded, that the prepared prodrug was analyzed by controlled drug release, it was found that in a basic medium could hydrolysis higher than acidic medium, this due to the presence of OH^- which was a stronger nucleophilic with respect to H_2O or H^+, and the rate of release was prolonged about four days, this indicated the advantage of drug carrier polymer as adoxycycline prodrug delayed and sustained release of drug over long time with corresponding decrease of side effect.

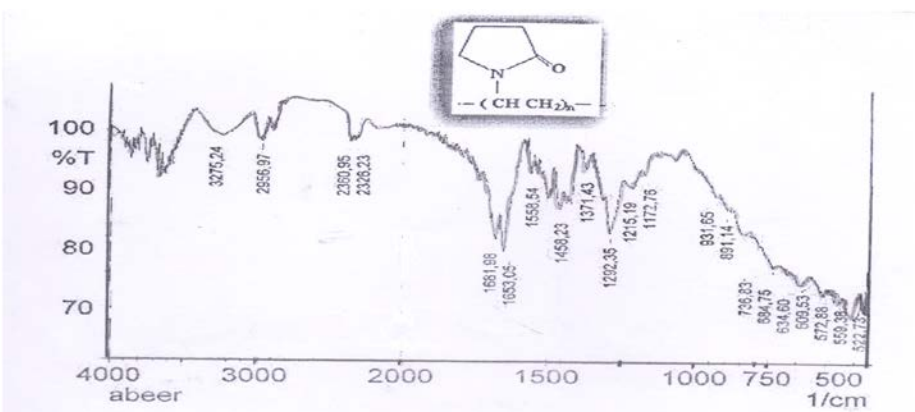


Figure (1) FT-IR Spectrum of Polyvinylpyrrolidone

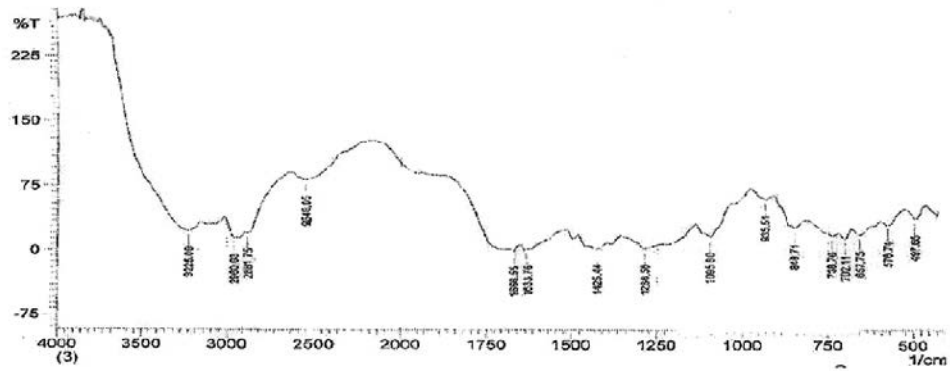


Figure (2) FT- IR Spectrum of Polyvinylpyrrolidone with Doxycycline

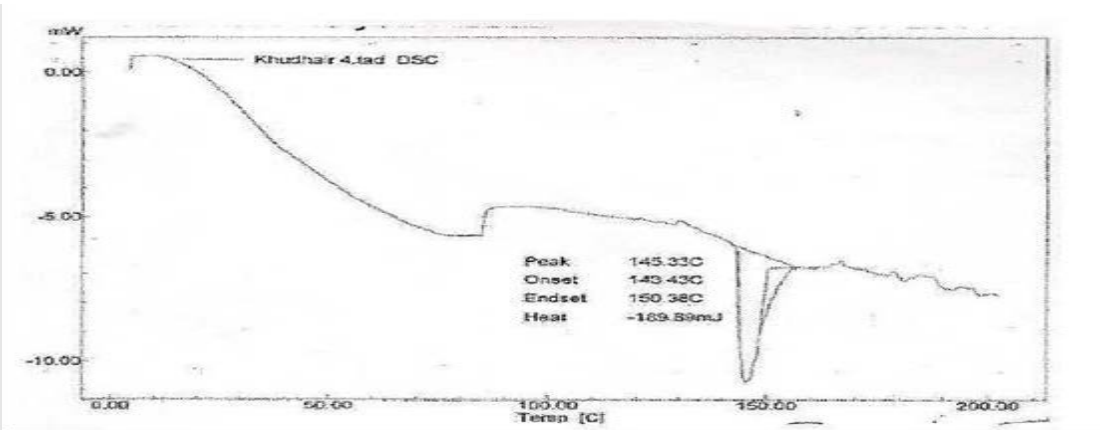


Figure (3) Thermal Analysis (DSC) Result of Polyvinylpyrrolidone with Doxycycline

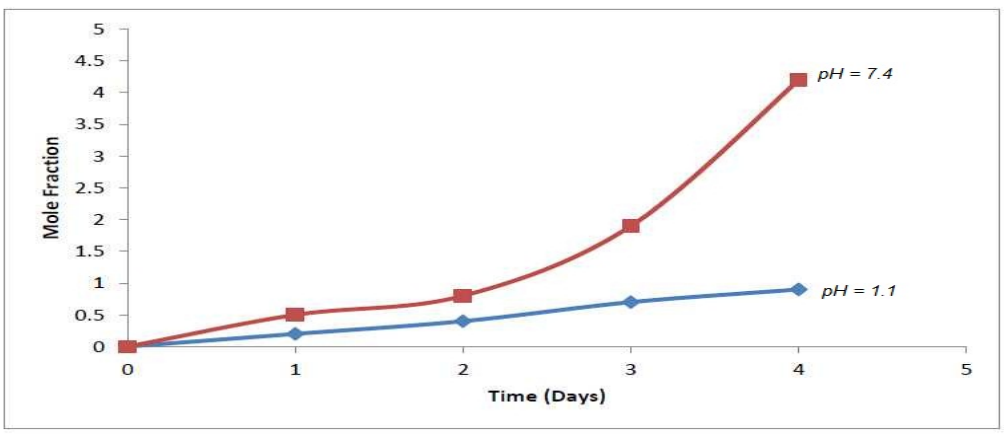


Figure (4) Controlled Release Drug Polymer at 37℃ in Different pH Values

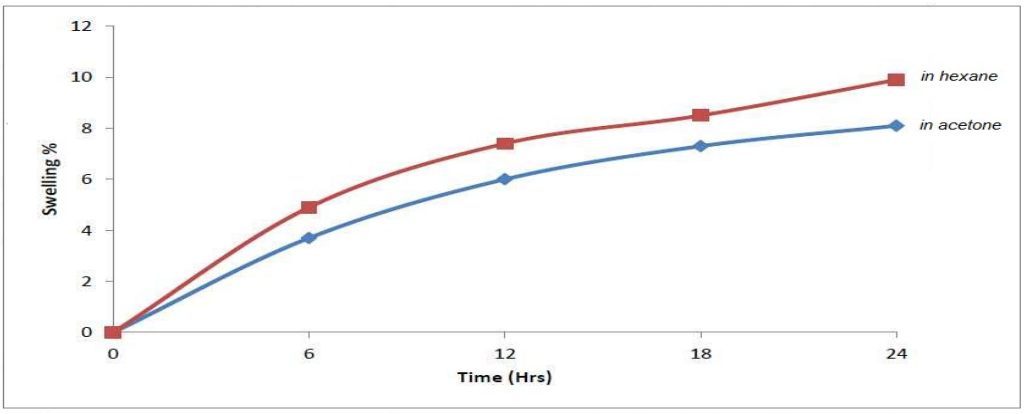


Figure (5) Swelling% of Prepared Drug Polymer

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