

## Modification of Polyvinyl Pyrrolidinone, Chitosan with Paracetamol As a Drug Carrier Polymer

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### Abstract:

The drug polymer was prepared by modification of polyvinylpyrrolidinone (PVP) with paracetamol through ester group formation, and partially ring opening of PVP with paracetamol, could let the chitosan to graft on other rings of PVP.

Also the NH<sub>2</sub> group of chitosan was reacted with PVP produced a new copolymer biopolymer; the prepared polymers were characterized by UV, FT-IR, <sup>1</sup>H-NMR Spectroscopies, DSC thermal analysis was carried out.

Controlled drug release was studied in different PH values. The physical properties and intrinsic viscosity were measured. The work aimed to prolong the sustainable drug delivery system.

**Key word:** Polyvinylpyrrolidinone, Drug polymer, Chitosan

### الخلاصة :

حضر البوليمر الدوائي من تحويل بولي فاينيل بايروليدينيون مع الباراسيتامول بفتح حلقة PVP وتكوين مجاميع استيرية، ثم تفاعل المجاميع الامينية للكييتوسان بفتح حلقات PVP المتبقية مكوناً بوليمر مطعم. كذلك حضر بوليمر مشترك جديد من تفاعل الكيتوسان مع PVP. شخّصت البوليمرات المحضرة بطرائق طيفية مثل الاشعة فوق البنفسجية والاشعة تحت الحمراء، وطيف الرنين النووي المغناطيسي. اجري التحليل الحراري التفاضلي المسعري. درست سرعة التحلل الدوائي للباراسيتامول، كما درست الصفات الفيزيائية وعينت اللزوجة الجوهرية للبوليمر المحضر.

### Introduction:

Chitosan as one of the most abundant natural polymer, it is a copolymer of glucosamine and N- acetylglucosamin derived from the natural polymer, chitin is a poly (N- acetyl glucosamine) and can be obtained in an impure form mostly from crab and shrimp shells. For the preparation of chitosan, chitin is de acetylated under basic conditions to yield a copolymeric chain with variable glucosamine to N-acetylglucosamine ratios. Most commonly used chitosans have 70 to 90% of their repeat units' deacetylated<sup>[1]</sup>.

A major challenge in the production of chitosan is its purification to achieve a sufficiently low endotoxin level, which is suitable for biomedical and pharmaceutical applications.

High purity chitosan has been described to have good compatibility and

low toxicity<sup>[2]</sup>, a non-immunogenic and non-carcinogenic<sup>[3,4]</sup>.

The growing interest in chitosan as a biomaterial and source for a suitable carrier for bioactive agent's over the past 15 years led to a substantial increase in research activities relevant to chitosan modification<sup>[5]</sup>. Co-administration of therapeutic polypeptides such as insulin with protease inhibitor increases their bioavailability<sup>[6-10]</sup>.

However, introduction of protease inhibitors leads to disruption of natural intestinal processes including digestion of nutritive proteins<sup>[10]</sup>. Chitosan-EDTA (ethylene-diamine-tetra acetic acid) is a bio adhesive copolymer, can be covalently linked to the Bowman-Birk inhibitor, which inhibits the proteases trypsin, chymotrypsin, and elastase. Providing a new adhesive drug carrier matrix with local prevention of enzymatic degradation<sup>[11]</sup>.

A further advantage is the easy manipulation of chitosan via modification with different reactive group as side chains allowing adaptation of physicochemical properties, like transfection, efficiency, stability, or solubility<sup>[12]</sup>.

Chitosan metal complexes with bivalent metal ions, including Cu II, Zn II, and Fe II<sup>[13]</sup>.

Using microorganism especially organic compounds to control wood. By fungi has been exploited in recent years<sup>[14]</sup>.

Synthesis and characterization of a new derivative of chitosan<sup>[15]</sup>.

Antimicrobial just packaging using chitosan and its metal complex<sup>[16]</sup>. The aim of this study includes the synthesis of drug polymer which has been prolonged delivery system in pH=7.4 are higher than acidic media.

## **Material and methods:**

### **Chemicals and Apparatus:**

Chitosan was purchased from BDH; all available chemical reagents were used without further purification, such as dioxin, DMF and Ether. FTIR spectra were taken on Shimadzu spectra photometers recorder over therang 500-4000cm<sup>-1</sup>. Ultra Violet spectra was recorded using Shimadzu UV-VIS, differential scanning calorimeter (DSC) was carried out on a Shimadzu-66 instrument (Japan) at a heating rate of 10°C min<sup>-1</sup> under air (normal), thermal analyzes (DTG) were determined by analyzer type 1106 Cario Irba.

Intrinsic viscosity was measured by capillary viscometer type Ostwald viscometer at 30°C. Polymer swelling % was determined using the relationship as shown below:

$$S \% = (M_1 - M_0) / M_0 \times 100$$

Where M<sub>0</sub>: is the mass of dry polymer.

M<sub>1</sub>: is the mass of swelled polymer.

### **Experimental:**

#### **Ring opining of polyvinyl pyrrolidinone (PVP) with Chitosan (1)<sup>[18]</sup>:**

A 100 ml round-bottomed flask equipped with a reflux condenser was charged with 20ml DMF, 3g (0.02mole) poly vinyl pyrrolidinone and 2.5g (0.02mole) chitosan. The mixture was stirred for about 3hours at 80°C. The stirring was continued for another hour, and then the mixture was cooled at room temperature. The solvent was evaporated under vacuum, washed the yellow product by ethanol and dried at 50°C. mp. = 235°C, the yield was 90%.

#### **Reaction of paracetamol with PVP (2):**

(1g, 0.01mole)PVP was suspended in 5 ml DMF, (1.5g, 0.01mole) of dissolved paracetamol in 10 ml of acetone was added to the mixture, refluxed for 2hours, the solvent was evaporated, the product was washed by ethanol for several times and dried at 50°C, yield was 80%, mp. = 247°C.

#### **Modified Chitosan with prepared polymer (2) to new amide-ester polymer (3):**

(1g, 0.01mole) of PVP paracetamol polymer (2) was dissolved in 10 ml of DMF, the suspended chitosan (1g, 0.01mole) in 10 ml DMF was added gradually to the mixture, refluxed for 3hr. then cooled and evaporated under vacuum pressure. The product was washed by ether and dried at room temperature, and the yield % was 75% as pale yellow product.

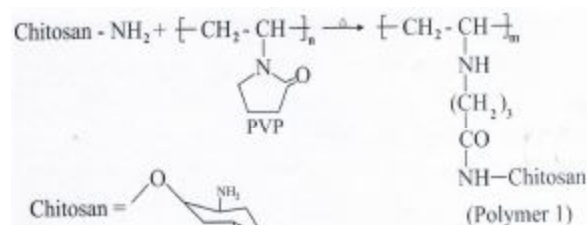
#### **Controlled drug release study:**

(100 mg) of polymer (3) was placed in (100ml) of buffer solution with PH 1.1 or 7.4 at 37°C, 3ml of solution was tested using UV.Spectrophotometry at 340nm, the UV.Spectra was recorded continuously for every day. Fig (3) shows the UV-Spectra of hydrolysis of drug polymer (3).

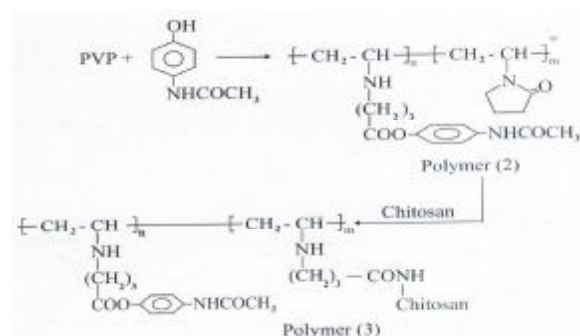
The control drug release included the weight% of drug release respect to time as shown in Fig (4).

**Result and Discussion:**

In this study, the poly vinyl pyrrolidinone, was grafted by chitosan which has -NH<sub>2</sub> group acted as nucleophile attack to produced ring opening of pyrrolidinone ring as shown in scheme (1 and 2).



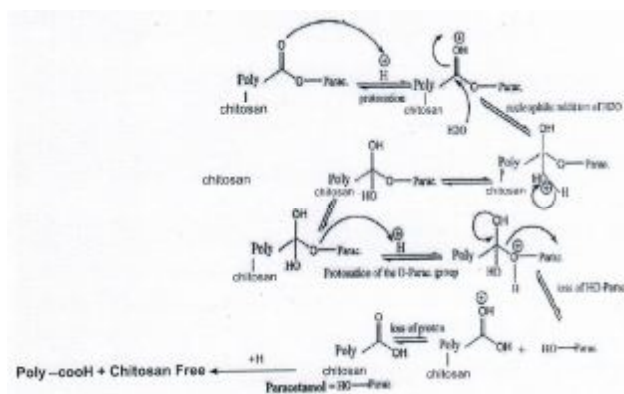
**Scheme-1**



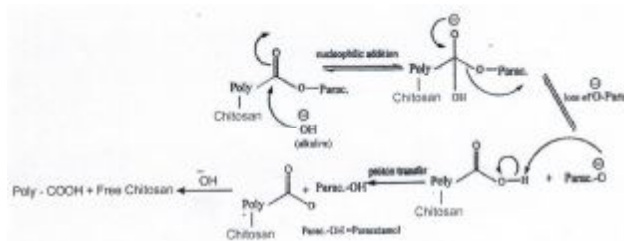
**Scheme-2**

Paracetamol is used for relief of headaches and other minor aches, it could react with PVP and specific transport with longer acting due to hydrolysis of ester bond as a pendant units through main chain of polymer, and to increase the hydrolysis of paracetamol units and to prolong analysis, the other pyrrolidnone rings grafted with chitosan as a natural polymer to convert the prodrug polymer (3) to a good biocompatibility and to converted polymer to be used in pharmaceutical application as sustained drug release system, and become it is totally biodegradable in wide variety of environment. The following mechanism illustrated the release of paracetamol molecules by hydrolysis in acidic medium [17-22], shows in scheme-3.

The other mechanism of hydrolysis of prodrug polymer in basic medium which illustrated as in scheme-4 [18].



**Scheme-3**



**Scheme-4**

Figure-1, FT-IR spectrum of polymer (1), shows the absorption of (-OH) carboxylic acid at 3440 cm<sup>-1</sup> as broad band and the absorption at 3200 cm<sup>-1</sup> due to the amide (-NH), the (C-H) aromatic of paracetamol ring was observed at 3030 cm<sup>-1</sup> and (C-H) aliphatic at 2942 cm<sup>-1</sup>. The(C=O) amid observed at 1645 cm<sup>-1</sup>, and at 1155cm<sup>-1</sup> is due to(C-O) stretching.

Figure-2: <sup>1</sup>H-NMR spectrum of polymer (2) showed (δ 7-7.1) ppm, d. of (4H aromatic) of paracetamol, was observed in low field δ 3.5ppm,s. of 3H (CO-CH<sub>3</sub>), δ2.5ppm,d. of (2CH),δ 0.8 ppm and δ1.7ppm,t. of (2H,CH<sub>2</sub>).

Figure-3 shows the UV-spectra of hydrolysis of drug polymer.

Figure-4 shows the effect of PH effect on the rate of release and profiles of mole fraction of paracetamol (ratio of the moles of paracetamol to total moles present in the sample) versus time at pH values 1.1 and 7.4 at 37°C. Rate of hydrolysis of this ester bond acts as base is higher than acid. The result shows higher hydrolysis at higher PH value. In acidic media, H<sup>+</sup> is bonded to oxygen atom of C=O group and increase the positive charge of carbon atom, consequently, it promotes the nucleophile attack of

water, due to the presence of OH in alkaline media which is a strong nucleophile in respect to water, the rate of hydrolysis of ester takes place faster than acidic. Intrinsic viscosity was determined for the prepared

polymer (3) by using Ostwald viscometer and DMF as a solvent at 30°C ( $\eta_{in} = 1.4$  dl/g). DSC analysis of polymer [3] revealed high thermal stability with softening point at (273-283) °C and  $\Delta H = 190.9$ J/g as shown in figure-5.

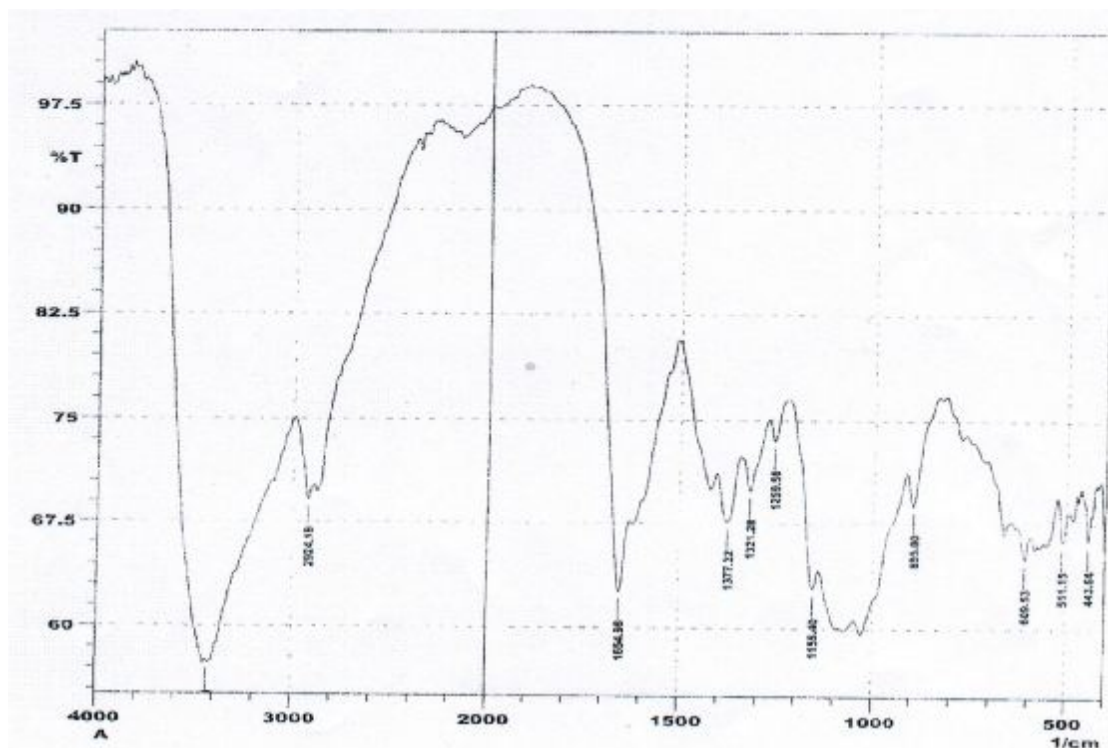


Figure-1: FT-IR spectra of chitosan-PVP polymer (1).

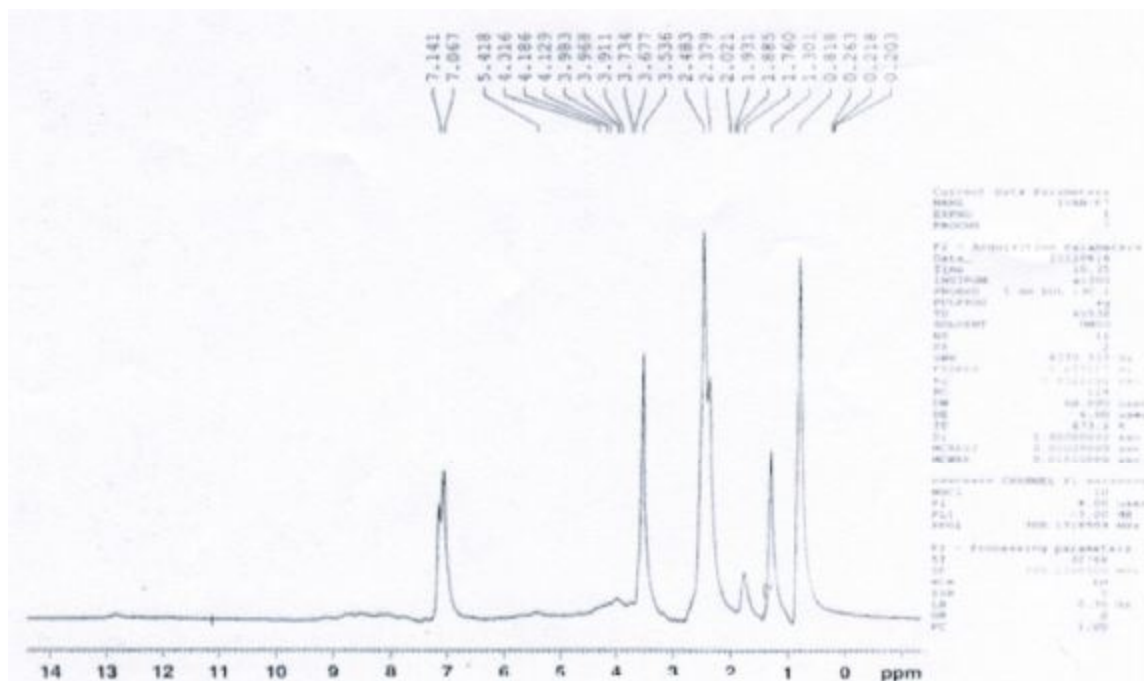


Figure-2: <sup>1</sup>H-NMR spectra of PVP drug polymer (2).

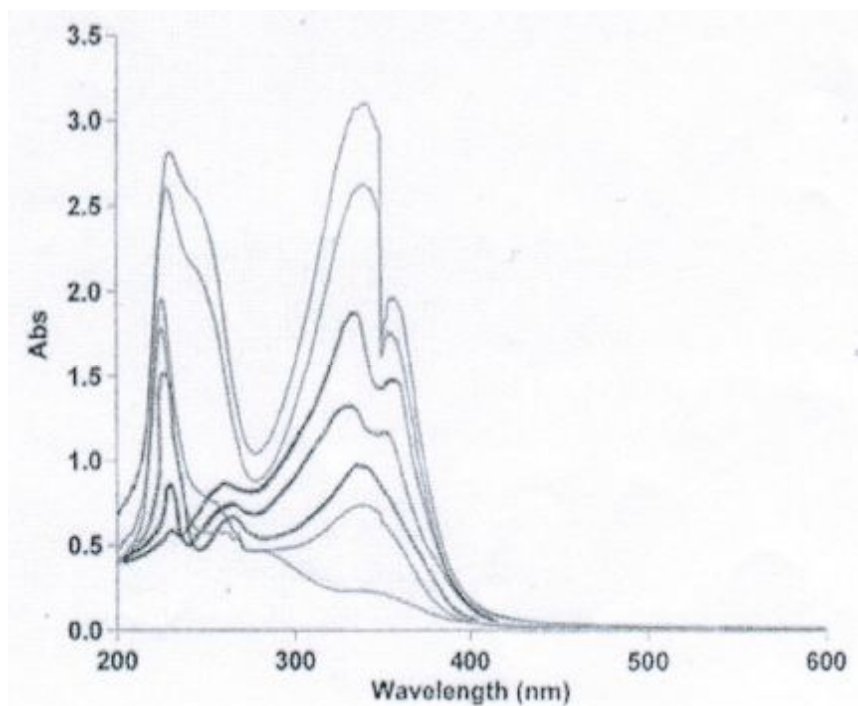


Figure-3: UV-spectra of drug polymer (3) hydrolysis.

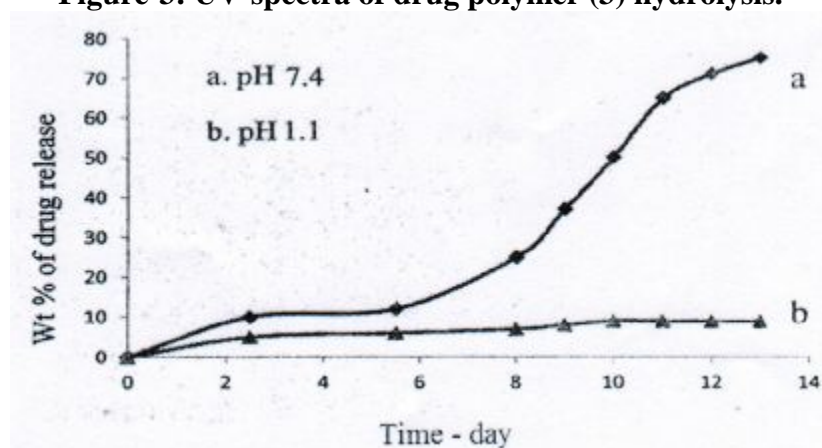


Figure-4: Controlled drug release at 37°C of polymer (3).

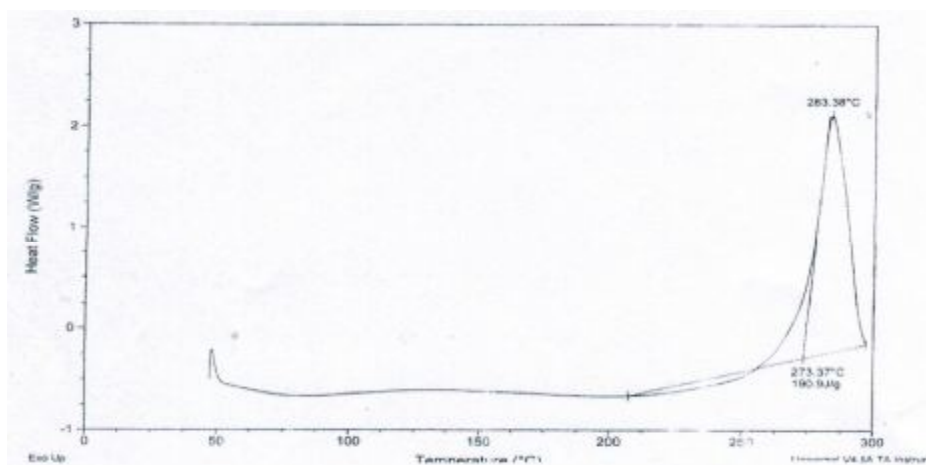


Figure-5: DSC analysis of drug polymer (3).

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