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Synthesis, Characterization and Antibacterial Activity of Carboxylated Polyvinylpyrrolidone Conjugation with Tranexamic Acid (TXA)

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Abstract: Polymer conjugation with biologically active components has become a very attractive system as it could improve the efficacy of some drugs. This study aims to prepare and formulate a topical polymer conjugate with biologically active components for a therapy of bleeding using tranexamic acid as a drug model and study the antibacterial activity of the resultant products.

The polymeric matrix involved carboxylated polyvinylpyrrolidone. Hence, carboxylated polyvinylpyrrolidone was bonding with tranexamic acid by an amide bond (P1), resulting in a product complex with iodine (P2).

In order to determine the amount of medication present in these derivatives, FTIR, DSC, and 1HNMR characterization techniques were utilized. The antibacterial potential of the prepared samples (P1, P2) with the use of PVP iodine as a control was studied against different amounts of Grammeme's negative and Grammeme's positive bacteria, including Pseudomonas aeruginosa, E. coli, S. aureus, and K. pneumoniae. There were four different strains of bacteria tested. When bacteria like E. coli and S. aureus were used, the results showed that P1 and P2 were more effective at killing bacteria than PVP iodine.

Keywords: tranexamic acid (TXA); PVP; antfibrinolytic.

Introduction

Polymer

Polymers are the most diverse biomaterials, employed in contact lenses, medicinal carriers, implantation, artificial organs, tissue engineering, medical devices, and dentistry materials [1][2][3]. All of this is because polymers have unique features that made a whole new idea possible when they were first suggested as biomaterials. It was the first time that a material used for structure was made to fully break down and become weaker over time. This idea was first used successfully with catgut stitches. It was then tried, with mixed results, on bone fixation, tendon enhancement, plates, and pins [4][5].

Polyvinylpyrrolidone (PVP)

Povidone is a man-made polymer that is made by a process known as radical polymerization of N-vinylpyrrolidone, which is the monomer. German scientist Walter J. Reppe invented this method in 1939 based on his work on acetylene chemistry [6]. Polyvinylpyrrolidone (PVP) exhibits several

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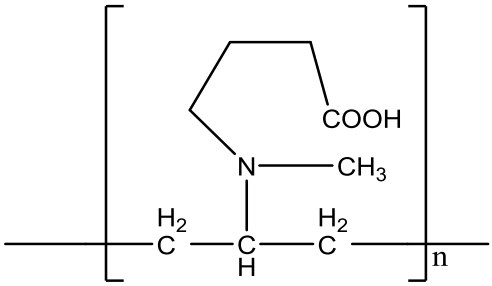
desirable properties, including non-toxicity, non-ionic nature, inertness, resistance to temperature, stability over a range of pH levels, biocompatibility, and a multifaceted attraction towards both hydrophilic and hydrophobic pharmaceutical compounds [7][8] . Some types of PVP have different molecular weights and viscosities, but all of them dissolve in water. People first used PVP as a plasma volume booster in the 1940s [8] . In the 1950s, PVP entered the market for hair treatments and supplanted shellac resin as a hair fixative [9]. However, PVP has since found use in pharmaceuticals [9], biomedical [8], cosmetics ,and food industry [10]. Because PVP has its own unique chemistry and traits, scientists have made progress in synthesizing it to get different types, such as homopolymers with different molecular weights, copolymers, and crosslinked PVP [11] .



4-(heptan-4-yl(methyl)amino)butanoic acid

Figure (1): Structure carboxylated Polyvinylpyrrolidone (PVP)

Applications of PVP

PVP was initially utilized as a blood plasma volume expander or replacement. Later, PVP was used in medical, pharmacy, cosmetics, food, and industry. PVP's unique features and ability to interact with low molecular weight molecules explain its vast variety of uses [12].

PVP is utilized in the formulation of transdermal goods, including as ointments, creams, and gels, for two primary purposes. Firstly, it is employed to create hydrogels, which function as diffusion matrices. Secondly, PVP serves as a crystal formation inhibitor inside certain drug-adhesive matrix systems [13].

PVP is utilized as an adhesive in many mucoadhesive drug delivery systems due to its remarkable adhesive characteristics, as well as its physiological safety and inert nature [14][15]

and transdermal systems due to its properties such as adhesion, crystal inhibition, and Solubilization, etc. [16].

Povidone iodine

Povidone iodine is a chemical compound commonly used in medical and healthcare settings for its antiseptic properties. Polyvinylpyrrolidone-iodine (PVP-I), often known as PVI, is a solution containing iodine that is utilized for the purposes of scrubbing, antisepsis of intact skin, and preoperative showering. It is recommended to employ PVP-I in its most concentrated and uncontaminated state for optimal efficacy. It is advisable to dilute one-third of the solution with water for the purpose of washing polluted wounds [17] . The efficacy of PVI preparations against various bacteria, fungi, and protozoa is widely recognized. Moreover, they exhibit efficacy against both enveloped and non-enveloped viruses. Povidone-iodine (PVI) is believed to possess a diverse range of activities against infections, exhibiting a multimodal mechanism of action. This mechanism involves the oxidation of crucial structures, such as amino acids, nucleotides, and components of the cell membrane [18][19].

Almost all cuts are infected with microorganisms, which usually doesn't hurt the person and may even help the wound heal [20] .

Iodine is mostly used to treat wounds because it kills small germs. Povidone iodine has been used and studied for many years to help wounds heal [21] .

Povidone iodine is characterized by the formation of a combination between iodine and the synthetic carrier polymer known as povidone. It is worth noting that povidone itself lacks any inherent microbicidal action [21].

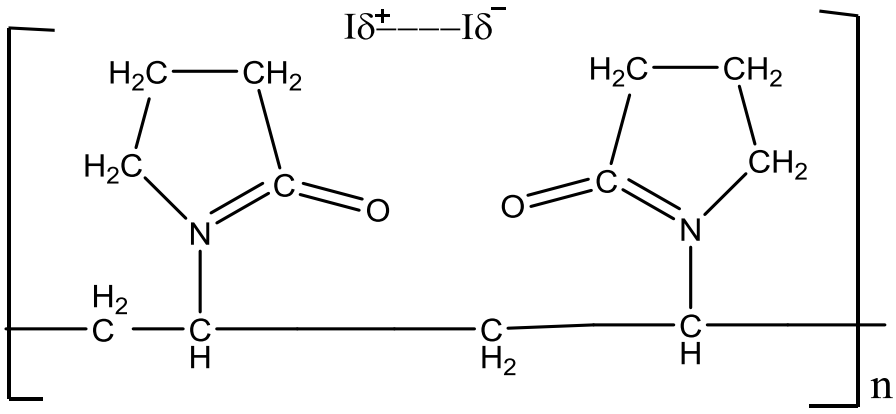


Figure (2) : structure of povidone iodine[22] **.**

Iodine kills microbes by blocking important bacterial cell structures and mechanisms. It also oxidizes nucleotides, fatty acids, and amino acids in bacterial cell membranes, as well as cytosolic enzymes that work in the respiratory chain, denatures and deactivates them [23], [24]. There is proof from experiments done in the lab that iodine not only kills a wide range of germs, but it also reduces inflammation caused by both viruses and the human reaction. There are several possible reasons for these anti-inflammatory benefits, and they have been shown to be useful in clinical settings [25] .

There isn't a lot of information on how antiseptics get into the body. It looks like iodine can be taken in through the skin, but mostly through the mucous. Transdermal iodine uptake, on the other hand, will depend on how well the skin barrier is working. It will be absorbed more if the skin layer is broken, like in cuts, and it will also depend on how old the skin is and how much of it is being applied [26] .

Povidone iodine product labels include general warnings not to use in people who are allergic to povidone iodine or its ingredients, who have thyroid problems, who were born with very low birth weight babies, or who are getting radio-iodine treatment [26] .

Tranexamic acid

Tranexamic acid, also known as trans-4-(amino methyl) cyclohexane carboxylic acid, is a chemical compound with the empirical formula C8H15NO2.The compound in question is a structural counterpart of lysine, which is classified as an essential amino acid. The mechanism of action involves the inhibition of lysine-binding sites on plasminogen, leading to a reduction in its ability to undergo activation. In cardiac procedures, it is a frequent practice to provide the substance intravenously in order to mitigate intraoperative bleeding and reduce the need for transfusion [27]. The affordability of this product makes it a very suitable hemostatic agent. Nevertheless, its use is limited to surgical environments as a result of the potential for thromboembolic consequences. According to reports, higher dosages have been associated with the occurrence of seizures in some individuals [28].

Antifibrinolytic drugs improve collagen production and tensile strength in granulation tissue in wounds, most likely by keeping the fibrin structure intact [29] .

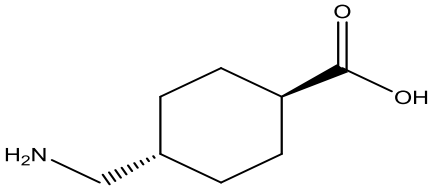


Figure (3): Structure of tranexamic acid

Aim of the work

The aim of this work:

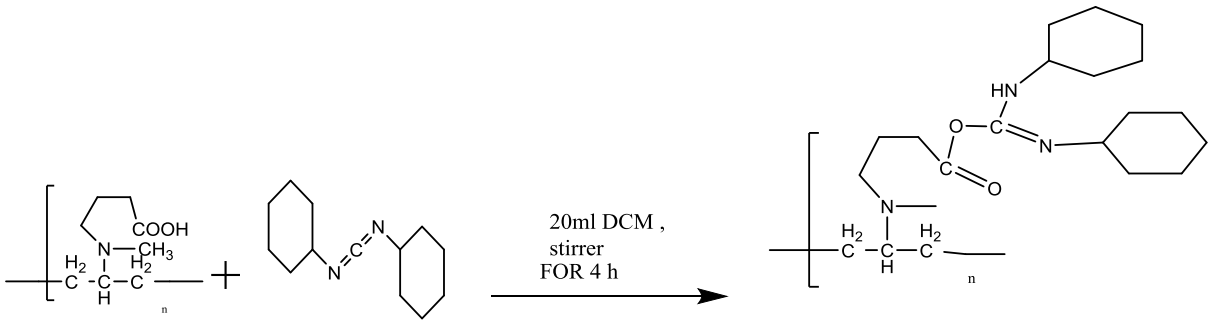
Synthesis of carboxylated PVP terminate tranexamic acid derivatives (P1), Synthesis of carboxylated PVP terminate tranexamic acid and complex with iodine (P2) and study of antibacterial activity.

Material and methods

Acetone, Deionized water, Formaldehyde 37%, Hydrochloric acid , Tranexamic acid , Sodium bicarbonate NAHCO3 ,Molecular sieve , Ethanol absolute , Methanol absolute , Sodium hydroxide NaOH ,Dicyclohexyl carbodiimide DCC ,Dichloromethane DCM . TLC (Silica gel 60 F254) was used to monitor the reaction's development. The IR spectra were captured using a Perkin-Elmer spectrometer. The 1H and NMR spectra were obtained using a Bruker 400 Avance II with Chloroform/d/DMSO-d6 as the solvent and TMS as the internal standard. DSC was used to determine melting points.

Activation of carboxylated Polyvinylpyrrolidone (PVP) :

About (2.1 gm, 12.2 mmol) of carboxylated Polyvinylpyrrolidone and (3 gm, 14.5 mmol) N,N′-Dicyclohexyl carbodiimide (DCC) were poured in a round bottom flask (250mL), then (20 ml) of dichloromethane (DCM) was added as well, and the mixture was heated and refluxed for 4 hours. After allowing the mixture to settle, it was transferred to a beaker (150 ml) to exhaust the solvent, and the granules obtained were ground with a mortar and pestle for later characterization. The following equation represents this reaction:



4-((3-carboxypropyl)(methyl)amino)heptan-1-ylium

N,N'-Dicyclohexylcarbodiimide

(*E*)-(*E*)-*N*,*N*'-dicyclohexylcarbamimidic 4-(heptan-4-yl(methyl)amino)butanoic anhydride

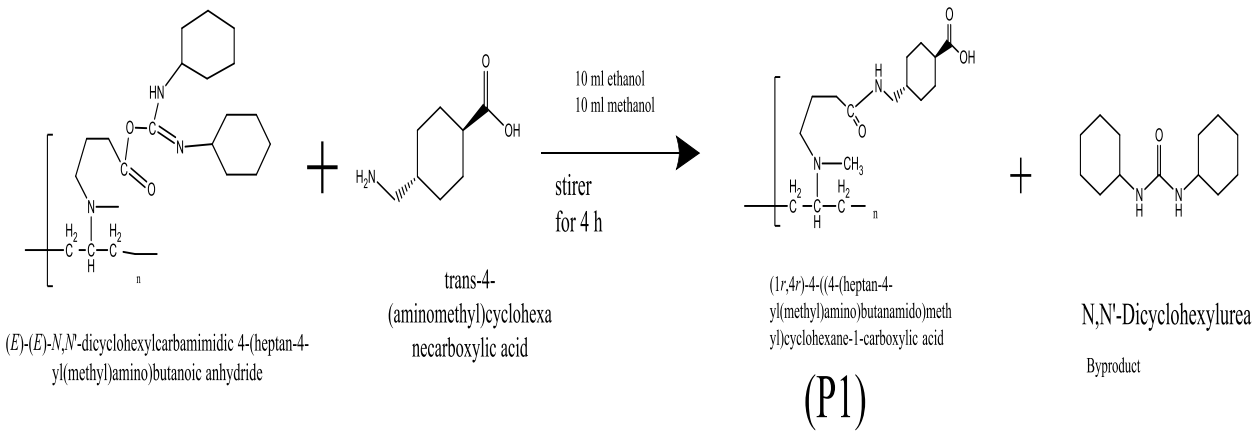
Scheme (1): method of Activation of carboxylated Polyvinylpyrrolidone.

Synthesis of carboxylated PVP terminate tranexamic acid derivatives (P1):

Dissolve (3.5 g, 8.9 mmol) of activated carboxylated Polyvinylpyrrolidone (PVP) in (10 ml) of methanol and (1.5 g, 9.5 mmol) of tranexamic acid (TXA) in (10 ml) of ethanol, respectively. Following this, these components were mixed in a 250mL round-bottom flask, heated with a hot-plate magnetic stirrer, and set aside to reflux for four hours. subsequently, exhaust the solvent. The product was rinsed three times with acetone to generate white solid particles (pure amide), which will be characterized later using a mortar and pestle.

Yield (60%) , Melting Point (377.5 C°) , IR : 3502.7 (OH) , 3452.5(NH) ,3939.5(CH), 1654.9(C=O), 1458.82 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 3.53 (s, 1H), 3.13 (s, 1H), 2.08 (s, 4H), 1.86 (d, *J* = 14.0 Hz, 4H), 1.63 (s, 1H), 1.31 (d, *J* = 20.8 Hz, 1H). milled

Formation of (P1) are showen in equation bellow:

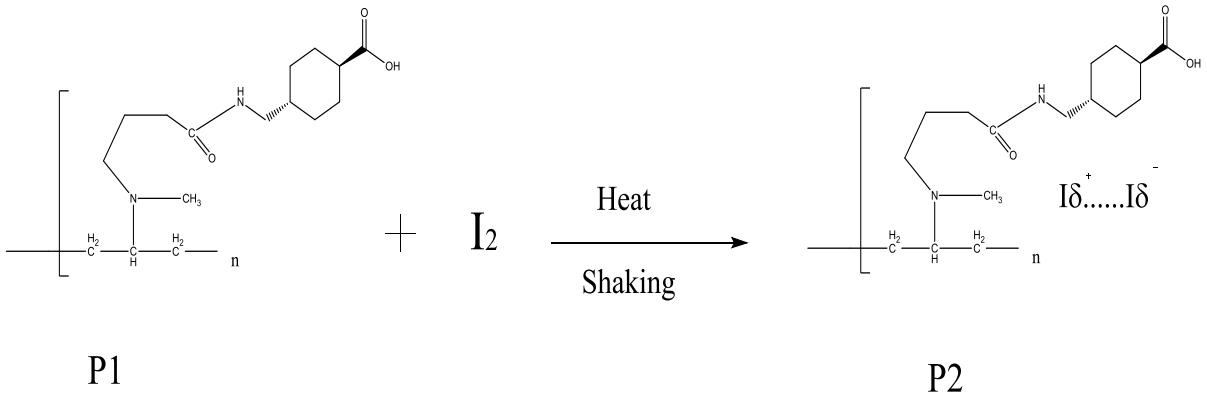


Scheme (2): synthesis of amide (amid bond for tranexamic acid (TXA) and activated Polyvinylpyrrolidone (PVP)) (P1) .

Synthesis of carboxylated PVP terminate tranexamic acid and complex with iodine (P2):

Adding (2 gm, 5.9 mmol) of (P1) and (0.008 gm, 0.06 mmol) of iodine into sealed glass container, Then tightly closed, and uniformly mixing the above-mentioned materials; slowly heating to 70 C° and continuously shaking the mixture on hot plate. The end product was golden brown color(P2 .

Yield (90%), Melting Point (335.55 C°), IR : 3500(OH), 3462(NH), 2931(CH), 1658(C=O), 1386.82 cm^{-1};



Scheme (3): Complex of iodine with p1 to give the P2 .

Antibacterial activity

An agar well diffusion experiment was used to test the antibiotic activity of the Products (P1, P2, and PVP IODINE) against Gram-negative and Gram-positive strains of bacteria [30][31]. The Muller–Hinton (MH) agar, which is about 20mL, was carefully put into clean Petri plates. Using a clean wire loop, the different types of bacteria were taken from their store cultures. Using a clean tip, 6 mm-diameter holes were made in the agar plates after the organisms were grown in a culture. Different amounts of Products (P1, P2, and PVP IODINE) were put into the wells that had been bored: 100 Mcg/ml, 200 Mcg/ml, and 400 Mcg/ml. The plates with the Products (P1, P2, and PVP IODINE) and the test organisms were kept at 37°C overnight before the average width of the inhibition zones was measured and written down [32][33].

Results and discussion

The FTIR tests on P1 showed the presence of a clear band at 3452.5 cm¹ This is because the N-H stretching of the amide acts as a shoulder to ensure the formation of an amide bond between tranexamic acid and carboxylated polyvinylpyrrolidone (PVP). Additionally, the disappearance of the COOH stretch at 3282.8 cm1 of polyvinylpyrrolidone (PVP) confirms the formation of an amide bond between carboxylated polyvinylpyrrolidone (PVP) and tranexamic acid. The FTIR spectrum of P2 reveals a band at 3462.2 cm1 that corresponds to the N-H stretching of amide, and a band at

1539.2 cm1 that corresponds to the N-H bending of amide. The band designated for C-H stretch vibration at 2931.8 cm1. The band at 11384.8 cm1 designated for C-H compound bending. The carbonyl group of an amide's C=O stretch is given to the band at 1658.7 cm1. In 526.57 cm1, a new band appears that is related to iodine (C-I).

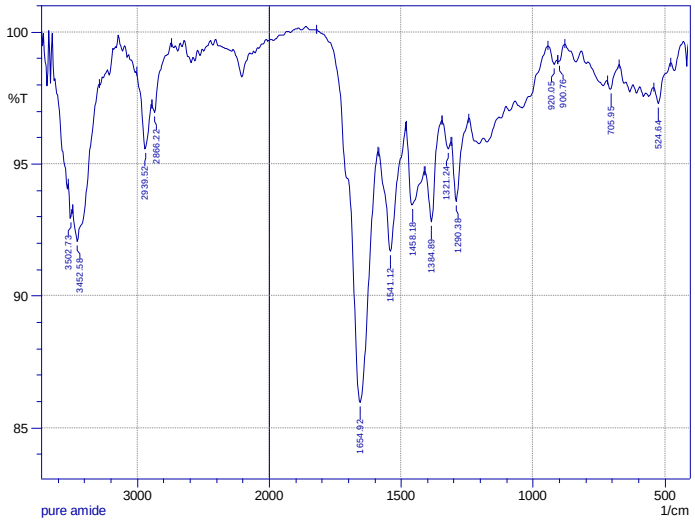


Figure (4): The FTIR spectrum of P1.

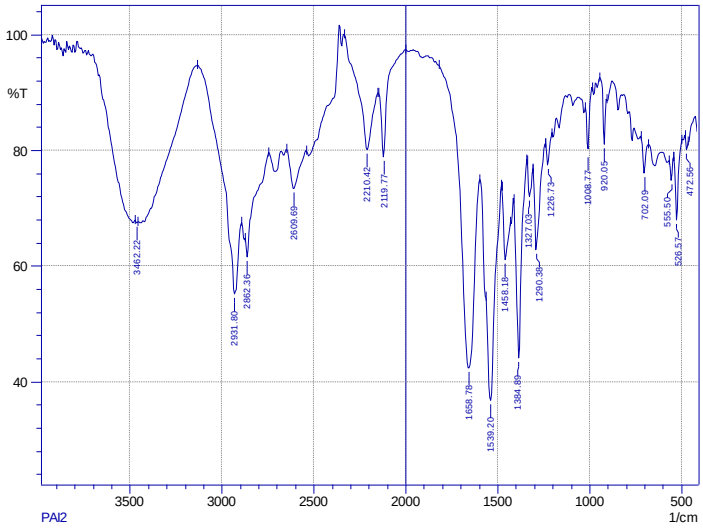
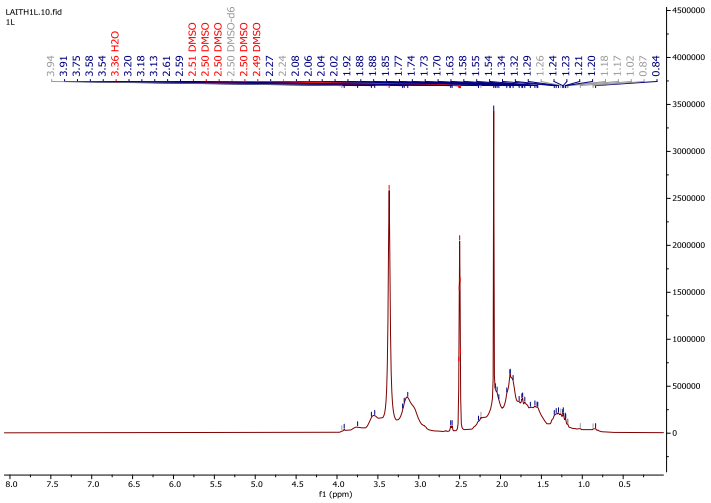


Figure (5): The FTIR spectrum of P2.

The 1H-NMR spectral appearance of the product (P1) show doublet -signal at 1.71 – 1.79 for CH2 of ring , single-signal at 3.78 for CH2 of (2HC-N) , doublet-signal at 8.65 - 8.69 for (N-H) amide , doublet-signal at 3.59 – 3.61 for (O-H) of carboxylic acid.

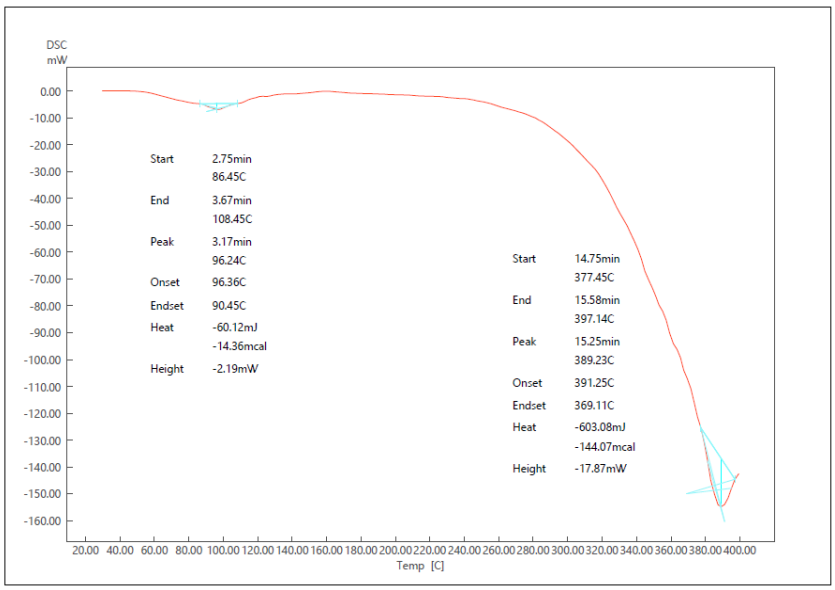


Figure(6) : The HNMR spectra of compound P1.

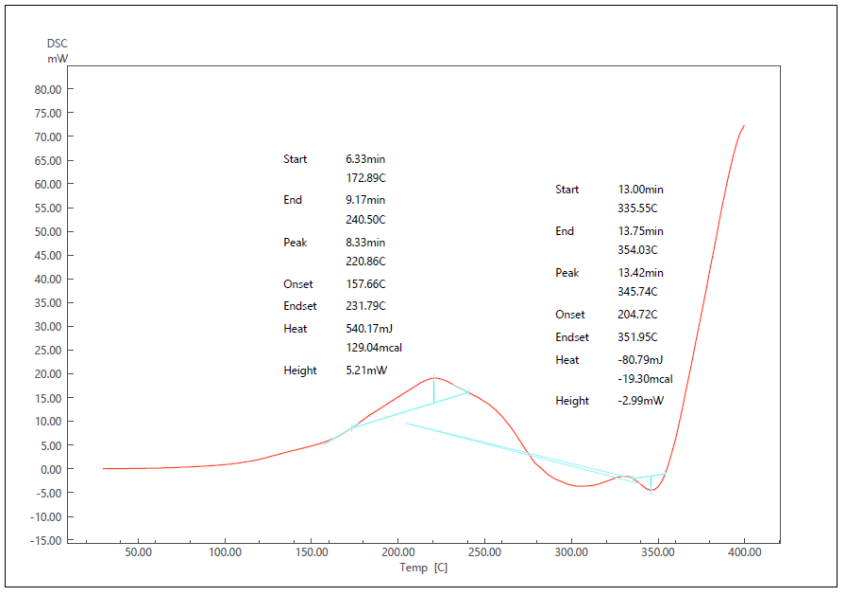
The DSC thermograms demonstrated that outcomes of all products were different from those of polyvinylpyrrolidone (PVP) and tranexamic acid.

Due to polymer dehydration by heating, P1 has two endothermic peaks at 86.45 and 377.45 °C. The absence of an endothermic fusion peak at 92.34^{0}C suggests effective reaction between polyvinylpyrrolidone (PVP) and tranexamic acid. P1 has greater endothermic values than PVP pure tranexamic acid. The molecular and physical changes caused by chemical alteration may have been revealed by water evaporation. Due to strong chemical connections between polyvinylpyrrolidone (PVP) and tranexamic acid, P1 was more thermally stable than the original polymer. See Figures (7).

P2 has an exothermic phase at 240.5 °C for the decomposition of the amide bond between polyvinylpyrrolidone (PVP) and tranexamic acid, which generates heat. P1 does not have this exothermic peak, indicating that P1 is more thermally stable. Hydrogen bonding between amino groups may stabilise this. and one 335.55 °C endothermic peak. P2 had greater endothermic values than PVP and pure tranexamic acid. The molecular and physical changes caused by chemical alteration may have been revealed by water evaporation. As in Figures (8).



Figures (7) : DSC thermogram of P1.



Figures (8) : DSC thermogram of P2.

Antibacterial activity

The pictures (3.27) to (3.38) show the antibiotic effects of different amounts of P1, P2, and PVP iodine, and the table (3.4) gives more information.

The Graph pad prism programme was used to do a statistical study of the data. Average (± SD) of three tests are used to show the data. Show that there is a statistically significant change when $p<0.05$.

For S. **aureus** the antibacterial activity of P1and P2 become greater than PVP Iodine and P2 greater than P1, but in conc. (200 mcg/ml) the antibacterial activity of P1 become same to PVP Iodine

For **P. aeruginosa** the antibacterial activity of P1 become less than PVP Iodine, but in case of P2 the antibacterial activity become more than P1 and PVP Iodine in all concentration use , but in conc. (200 mcg/ml) the antibacterial activity of P2 become same to PVP Iodine .

For **E. coli** the antibacterial activity of P1and P2 become less than PVP Iodine, when use conc. (200 mcg/ml) (400 mcg/ml) the antibacterial activity of P2 become same to P1 .

For **K. pneumoniae** the antibacterial activity of P1and P2 become less than PVP Iodine and P1 greater than P2, but in conc. (100 mcg/ml) the antibacterial activity of P1 , P2 become same to PVP Iodine.

Table (1) Explain the antibacterial activity of nanoparticles

Antibacterial analysis(Zone of inhibition)					
Sample		A	B	C	D
P. aeruginosa	PVP Iodin	6	21	27	28
E.coli	PVP Iodin	6	20	25	26
S. aureus	PVP Iodin	6	13	17	18
K. Pneumoniae	PVP Iodin	6	6	9	10
P. aeruginosa	P1	6	6	6	6
E.coli	P1	6	13	16	17
S. aureus	P1	6	14	17	19
K. Pneumoniae	P1	6	6	7	7.5
P. aeruginosa	P2	6	23	27	29
E.coli	P2	6	15	16	17
S. aureus	P2	6	16	18	20
K. Pneumoniae	P2	6	6	6.5	7

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