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Research Article

Synthesis, characterization and Antifibrinolytic activity of Carboxylated Polyvinylpyrrolidone conjugation with Tranexamic acid

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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 aimed to prepare and formulate a topical polymer conjugate with a biologically active component for the treatment of bleeding using tranexamic acid as a drug model. this polymer conjugate leads to the release of the drug in a sustained manner in order to prolong the contact time of the drug with broken skin for the best antifibrinolytic activity. The polymeric matrix involved carboxylated Polyvinylpyrrolidone. Therefore, carboxylated polyvinylpyrrolidone was modified by amide bonding with tranexamic acid (P1), complexing of the resultant product with iodine (P2), synthesis of ether tranexamic acid (P3), synthesis of methylol tranexamic acid (P4), and esterification of methylol tranexamic acid (P5). These polymers were modified to improve their properties and to control the drug release. The FTIR and DSC spectroscopies and 1HNMR spectroscopies were used to determine the drug content of these derivatives. Thus, we aimed to study the antifibrinolytic activity of all compounds (P1–P5) evaluated at various concentrations using in vitro clot lysis assays in human plasma. When employed in high doses, the antifibrinolytic activity of compound P5 exhibits a higher level of antifibrinolytic activity compared to that of pure tranexamic acid.

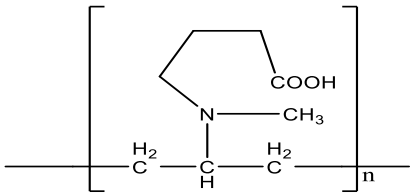
Keywords: Biologically Active Components, Polymer Conjugation, Vitro Clot Lysis

Introduction

Polymers are the most versatile class of biomaterials and are widely used in biomedical applications including contact lenses, pharmaceutical vehicles, implantation, artificial organs, tissue engineering, medical devices, and dental materials (Jagur-Grodzinski, 2006; Middleton & Tipton, 2000) . All of this is due to the unique properties of polymers, which created a completely novel concept when they were first proposed as biomaterials (Al-uobody et al., 2020). A new material developed for structural applications is totally resorbable and weakens over time. Catgut sutures were the first to use this principle successfully, and later bone fixation, ligament augmentation, plates, and pins had mixed outcomes (Gomes & Reis, 2013, Drselen et al., 2001). polymers make possible the localization of pharmaceuticals to sites of inflammation or tumours(Gharibjanian et al., 2009).

Polyvinylpyrrolidone (PVP)

Povidone is a synthetic polymer derived from the radical polymerization of the monomer N-vinylpyrrolidone. German chemist Walter J. Reppe patented this method in 1939 based on his acetylene research (Haaf et al., 1985). Polyvinylpyrrolidone (PVP) has several desirable properties that make it suitable for various applications. It is characterized by its non-toxic nature, lack of ionic charge, inertness, ability to withstand high temperatures, pH stability, biocompatibility, and a versatile affinity for both hydrophilic and hydrophobic medicines (Koczkur et al., 2015)(Kurakula & Koteswara Rao, 2020) . PVP is a water-soluble polymer with fluctuating molecular weight and viscosity. Initially, PVP was used as a plasma volume expander in the 1940s (Kurakula & Koteswara Rao, 2020) PVP entered the hair aerosol market in the 1950s, replacing shellac resin as a hair fixative agent (Teodorescu et al., 2019). In the pharmaceutical, biomedical, cosmetics, and food industries, PVP has acquired a valuable function in recent years(Teodorescu et al., 2019), (Kurakula & Koteswara Rao, 2020),(Bampidis et al., 2022). Advances in PVP synthesis have produced photopolymers of diverse molecular weights, copolymers, and crosslinked PVP due to its unique characteristics and chemistry (Awasthi et al., 2018) .



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(Kurakula & Rao, 2020). Specific molecular weight PVP that is suitable for the desired application has to be selected. Researchers have used PVP ranging from conventional dosage forms to controlled release systems (Jenkins et al., 1956) .

Topical/transdermal preparations

Preparations for topical or transdermal administration in transdermal products such as ointments, lotions, and gels, PVP is used to create hydrogels (which function as diffusion matrices) and as a crystal growth inhibitor in certain drug-adhesive matrix systems. PVP is utilized as an adhesive in a number of mucoadhesive drug delivery systems due to its superior adhesion properties, as well as its physiological safety and inertness(Chun et al., 2013)(Sizílio et al., 2018) and transdermal systems due to its properties such as adhesion, crystal inhibition, and Solubilization, etc. (Suksaeree et al., 2017). Transdermal products include lubricants, patches, and buccal tablets intended for skin or mucous membrane adhesion (Giuliano et al., 2018)(Rac et al., 2019).

Bleeding in the wounds

Bleeding is the passage of blood from the circulatory system to the tissues, the external environment, or a cavity. Excessive blood loss can be fatal in cases of severe trauma. The most life-threatening conditions in patients are primarily the result of excessive blood loss, i.e., an abrupt decrease in total blood volume in the circulatory system and disruption of oxygen supply to the tissues. The size and rate of hemorrhage also depend on the size of the damaged blood vessel,

whether the laceration is superficial or deep, and whether the vessel was crushed. This is because cut wounds are more likely to hemorrhage than compressed wounds. Patients with blood diseases (hemophilia, leukemia, thrombocytopenia) frequently suffer from life-threatening bleeding. Some drugs (anticoagulants, aspirin) also contribute to the incidence of hemorrhage (Asatullayev & Jabborova, 2022). In external hemorrhage, blood is expelled into the external environment. In such cases, when examining the patient, the condition, direction, and extent of the bleeding laceration should be taken into consideration (Asatullayev & Jabborova, 2022).

Anti-fibrinolytic

Antifibrinolytic are a class of medications that promote blood clotting by retarding the disintegration of clots that have already formed. TPA contains the amino acid lysine, which is an essential amino acid. Thru lysine-binding sites, plasminogen is activated into clot-dissolving plasmin, which dissolves thrombus Included in the class of antifibrinolytic are tranexamic acid, apportioning, and epsilon-aminocaproic acid(Huang et al., 2014).

Tranexamic acid

Trans-4-(amino methyl) cyclohexane carboxylic acid (C8H15NO2).It is a structural counterpart of crucial amino acid lysine. It inhibits plasminogen activation by locking lysine-binding sites. It is usually given intravenously in cardiac procedures to reduce bleeding and transfusions(Myles et al., 2017).It is a cost-effective hemostatic agent. Due to the possibility of thromboembolic complications, its use is restricted to operative contexts. Several patients reportedly suffered seizures after receiving higher quantities (Huang et al., 2014).Tranexamic Acid (TXA) and other anti-fibrinolytic agents can reduce blood loss through a reversible interaction with plasminogen and the active protease, plasmin. TXA can be administered intravenously or topically / by infiltration, and the preponderance of published research indicates that both methods are efficacious(Kim et al., 2015) . Fibrin is continuously deposited and eliminated by fibrinolytic mechanisms at the cellular level. Tranexamic acid inhibits fibrin proteolysis by preventing the attachment of plasminogen and plasmin(Plawinski et al., 2023) .By preserving the fibrin matrix, antifibrinolytic agents increase collagen synthesis and tensile strength within granulation tissue in cutaneous lesions (Ali et al., 2022) . Figure (2) illustrates the chemical structure of tranexamic acid.

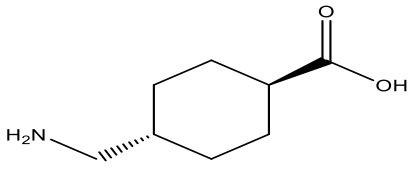


Figure 2 . Structure of tranexamic acid.

The aim of this work:

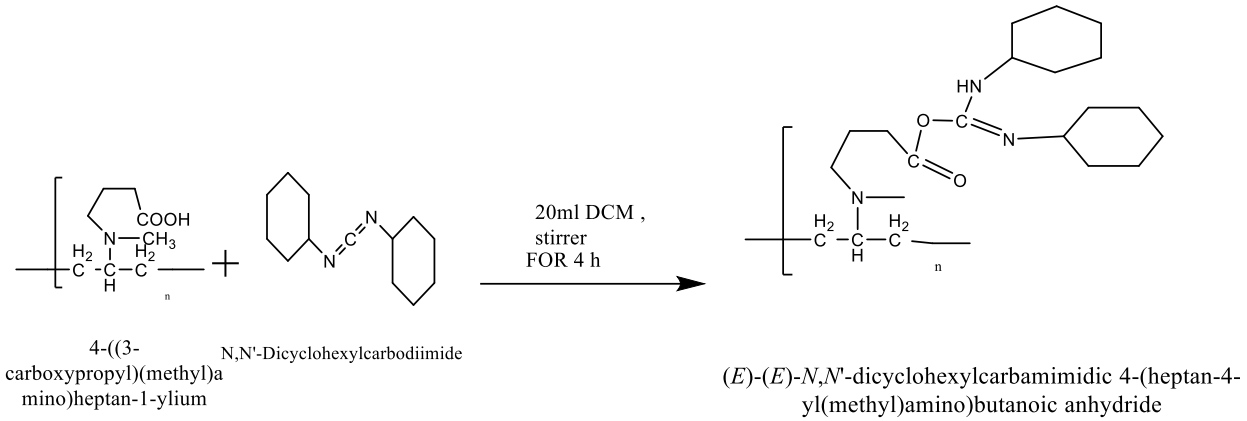
Synthesis of carboxylated PVP terminate tranexamic acid derivatives (P1), Synthesis of carboxylated PVP terminate tranexamic acid and complex with iodine (P2), Synthesis of ether derivatives tranexamic acid (P3),Synthesis of methylol terminate of tranexamic acid (P4) , Synthesis of ester of methylol terminate of tranexamic acid (P5) and study of antifibrinolytic activity .

Material and methods

Acetone, Deionized water, Formaldehyde 37%, Hydrochloric acid, Tranexamic acid, Sodiun 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 progress. On a Perkin-Elmer spectrometer, IR spectra were captured. On a Bruker 400 Avance II, the 1H and NMR spectra were acquired with Chloroform/d/DMSO-d6 as the solvent and TMS as the internal standard. DSC was used to establish the 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 placed in a round bottom flask (250mL), then (20 ml) of dichloromethane (DCM) was added, and the mixture was heated and refluxed for four hours. The mixture was then allowed to settle before being transferred to a beaker (150 ml) to exhaust the solvent. The resulting granules were ground in a mortar and pestle for later characterization. The equation of this reaction are below:

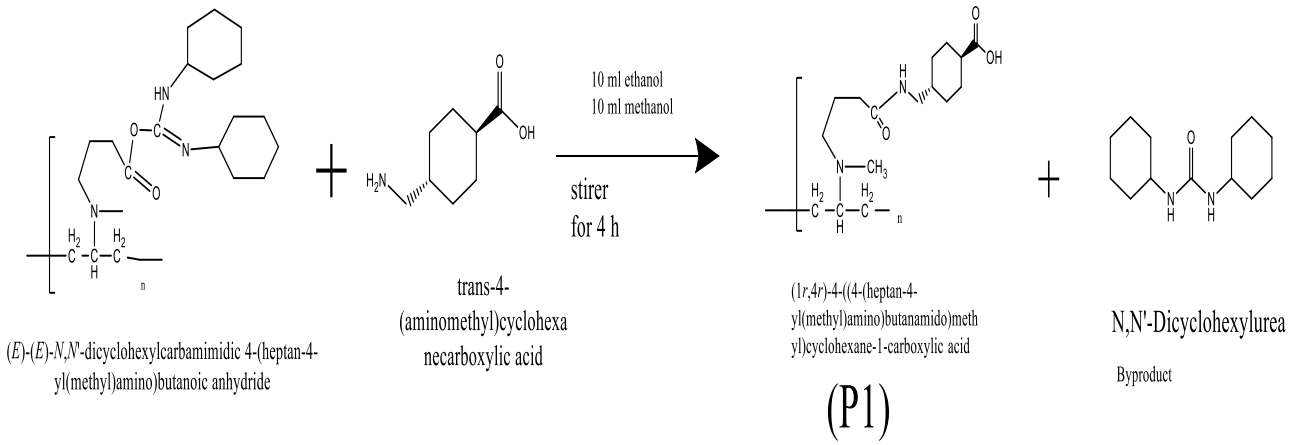


Scheme 1 . method of Activation of carboxylated Polyvinylpyrrolidone.

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

Dissolve (3.5 gm, 8.9 mmol) of activated carboxylated Polyvinylpyrrolidone (PVP) in (10 ml) of methanol and (1.5 gm, 9.5 mmol) of tranexamic acid (TXA) in (10 ml) of ethanol, respectively. Then, these components were combined in a 250mL round-bottomed flask, heated with a hot-plate magnetic stirrer, and allowed to reflux for four hours. the solvent is then evaporated. The product was rinsed three times with acetone to produce white solid granules (purity amide). These granules were then milled with a mortar and pestle for later characterization. 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} ; ^1H 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).

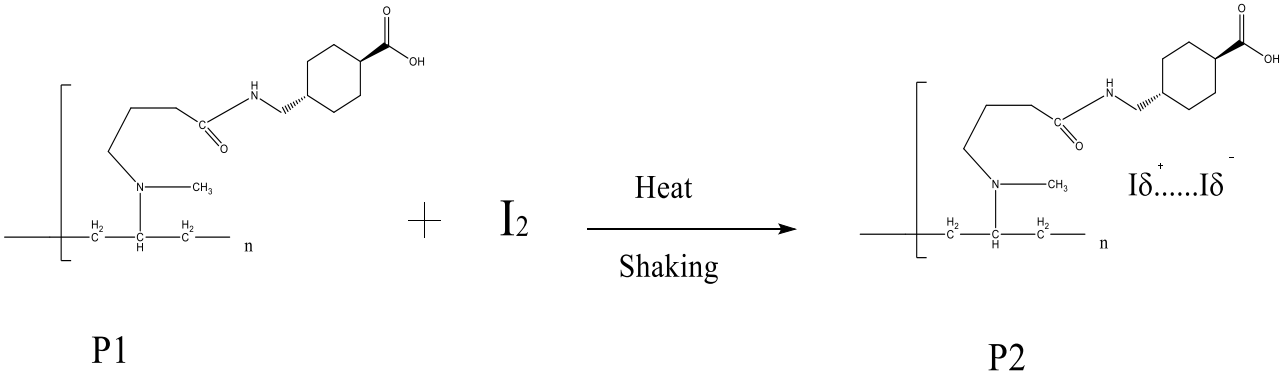
Formation of (P1) are shown in equation bellow :



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 in a 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.

Synthesis ether versions of tranexamic acid (P3):

The following steps were taken to make a yellow lubricant: In a round-bottom flask (250 mL), we put in 1 gramme (6.36 mmol) of tranexamic acid (TXA) and 20 ml (37% formaldehyde). These were mixed together to make a solution. We then added 3 drops of diluted HCL (10%) and heated the solution with a hot plate magnetic stirrer at 60 to 70 degrees Celsius for four hours. After adding 20 ml of absolute ethanol to dissolve the oily substance, the mixture was neutralized to a PH of 7 with 10% NaOH, filtered, and desiccated. Using TLC technique, the reaction process was observed. Yield (55%), Rf (0.7), IR: 3475-3410 (OH), 2953 (CH), 1654.9 (C=O), 1408 (CH) cm^{-1}; 1H NMR (400 MHz, DMSO) δ 4.66 (s, 6H), 2.20 – 1.96 (m, 9H), 1.91 – 1.79 (m, 3H), 1.79 – 1.68 (m, 2H), 1.67 – 1.58 (m, 1H), 1.24 (qt, *J* = 13.5, 6.0 Hz, 3H), 0.83 (ddt, *J* = 21.7, 13.0, 7.3 Hz, 3H). Synthesis of (P3) are showen in equation bellow:

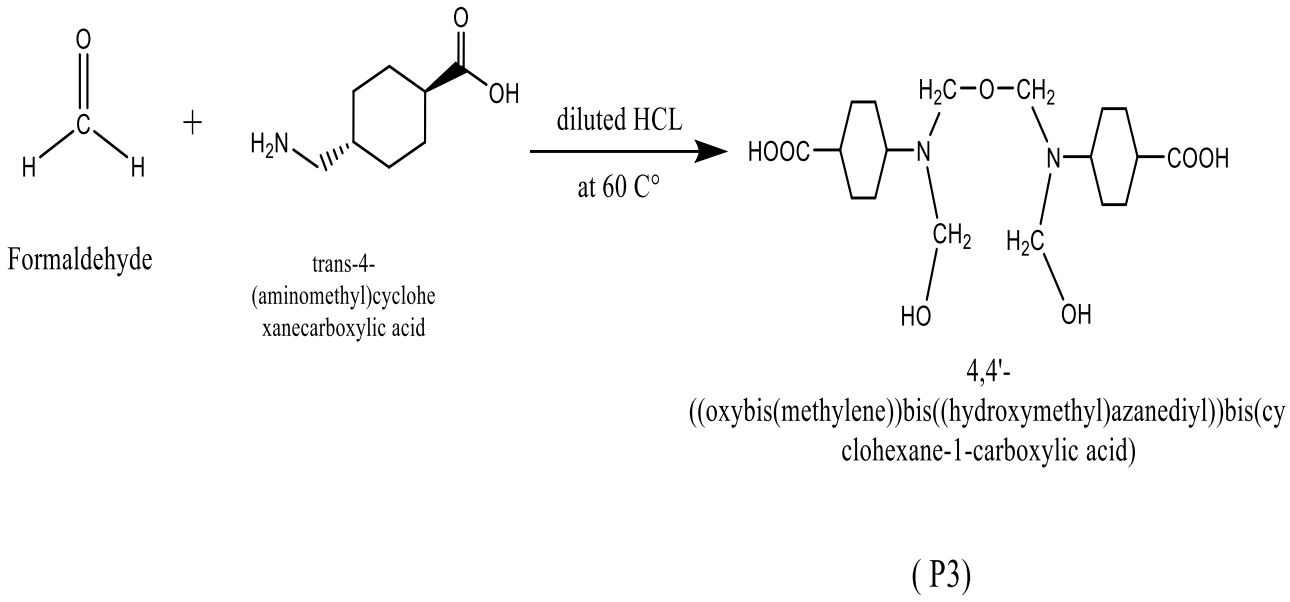


Figure 4 . Synthesis of ether tranexamic acid(TXA) (P3).

Methylol tranexamic acid (TXA) (P4) is synthesized as follows:

In a 250mL round-bottom flask, 1 gm (6.36 mmol) of tranexamic acid (TXA) and 20 mL of Formaldehyde 37% were added and mixed to produce a yellow-colored solution, then droplets of diluted NaOH lead were added to form white granules in solution, and the PH of the solution was determined to be 10. The mixture was then heated for four hours at (60-70 C°) using a sensitive hot-plate magnetic stirrer. And continue the reaction until the product is concentrated.

Then we added 20 ml of absolute ethanol to dissolve the product, neutralized the mixture to PH 7 with 10% HCL, filtered and desiccated the product using filter paper. TLC was utilized to monitor the reaction process. Yield (80%), Rf (0.6), IR: 3441-3423 (OH), 2937.5(CH), 1593.2 (C=O), 1409 (CH) cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 8.42 (s, 1H), 4.59 (s, 1H), 3.82 (s, 8H), 3.53 – 3.36 (m, 2H), 2.50 (d, J = 2.0 Hz, 1H), 2.08 (s, 2H), 2.05 – 1.94 (m, 1H), 1.90 – 1.69 (m, 2H), 1.22 (ddd, J = 16.4, 10.0, 3.3 Hz, 1H), 0.90 – 0.75 (m, 1H). Synthesis of (P4) are showen in equation bellow:

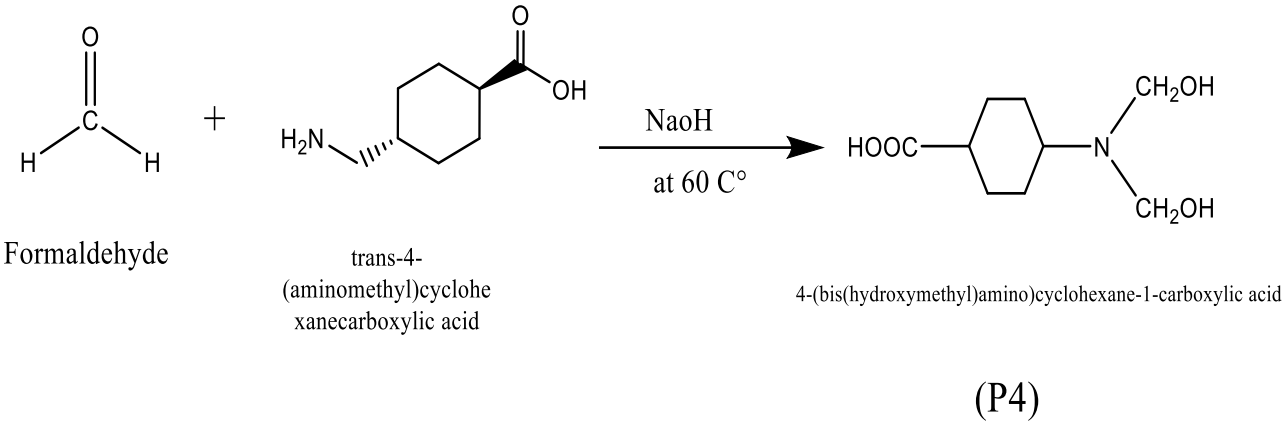


Figure 5 . Synthesis of methylol tranexamic acid(TXA) (P4).

Synthesis of acyl chloride of methylol tranexamic acid(TXA):

In round bottom flask (250mL) we added (3 gm) of methylol TXA and dissolved into (10 ml) of DCM, then we added (2 ml) of thionyl chloride and dropwise for (2-3) hours lead to form yellow product.

This reaction are showen below :

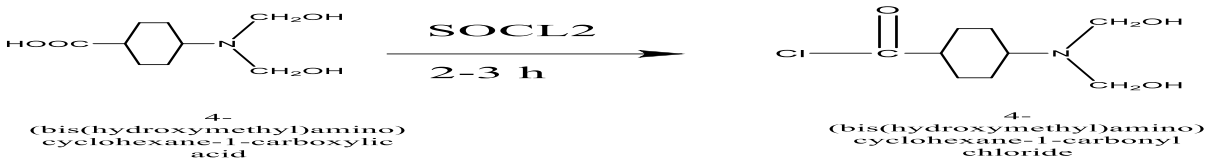


Figure 6. Synthesis of acyl chloride of methylol tranexamic acid(TXA).

Ester of methylol-terminated tranexamic acid (TXA) (P5) synthesis

In round bottom flask (250mL), which contain (3 gm, 13.53 mmol) of acyl chloride of methylol tranexamic acid(TXA), Add (20 ml) of dry ethanol, then mixed together by hot plat magnetic stirrer at (25 C°) lead to form white product. then evaporate the solvent and form ester TLC technology was used to monitor the reaction process. Yield (70%), Rf (0.7), IR: 3446.7 (OH), 3937.5(CH), 1701.2-1656 (C=O), 1454 (CH) cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 4.70 (s, 1H), 4.62 (d, *J* = 4.3 Hz, 1H), 3.27 (s, 1H), 3.09 (d, *J* = 7.2 Hz, 2H), 2.81 (d, *J* = 6.9 Hz, 3H), 2.65 (s, 9H), 2.12 (ddd, *J* = 14.1, 10.6, 6.6, 3.2 Hz, 3H), 1.93 – 1.83 (m, 9H), 1.74 – 1.59 (m, 5H), 1.31 (qd, *J* = 12.6, 3.0 Hz, 5H), 1.22 (dt, *J* = 11.2, 3.6 Hz, 2H), 1.01 – 0.87 (m, 5H).

Formation of (P5) are showen in equation bellow:

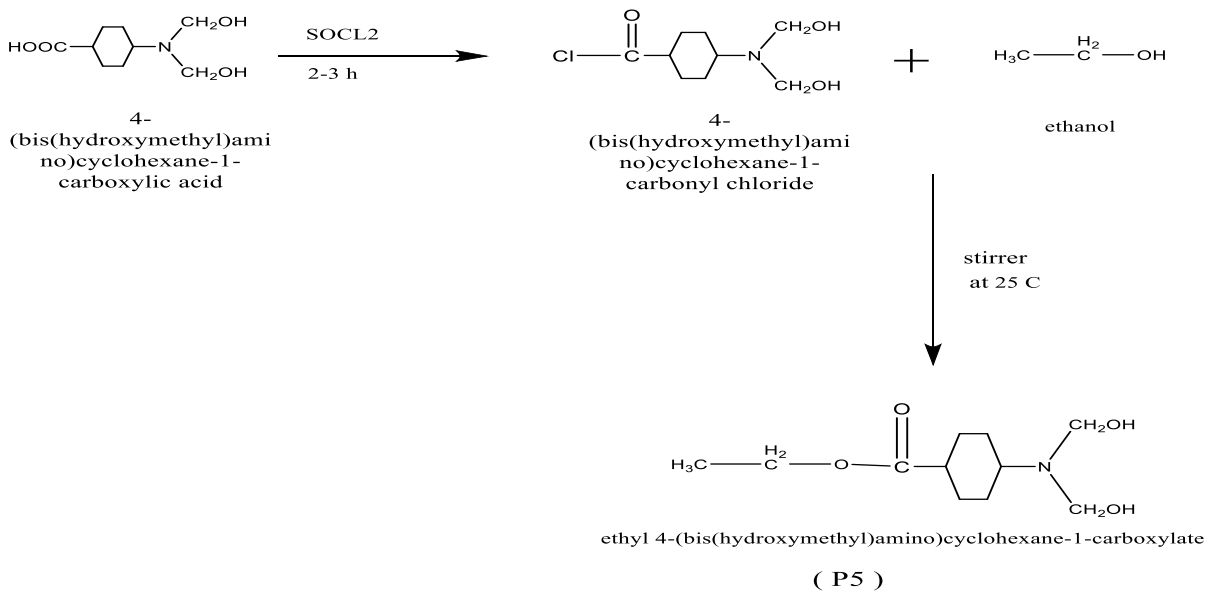


Figure 7. Synthesis of ester of methylol tranexamic acid(TXA) (P5).

Antifibrinolytic effect

Using in vitro clot lysis assays with human plasma, the antifibrinolytic activity of each compound was determined. 96-well flat-bottom plates were utilized for the tests. Pre-formed plasma emboli were produced by combining 140 µL of plasma, 20 µL of tissue factor, and 20 µL of a 100 mMCaCl2 solution. The mix was kept at 37 °C for 30 minutes so that it could fully coagulate. This HCl buffer was used to make a solution of TPA and the substance being studied, and 20 µL was put on top of each plasma clot. The end tPA concentration for all tests was 10.0 µg/mL, which is based on a 200 µL amount. Then, the absorption at a range of 405 nm was measured every minute at a temperature of 37 °C to figure out how dense the clot was The test was done for up to six hours, or until the clot was completely broken up. To find the lysis rate, the absorbance slope for each test was used. This slope was found by adding up the first and last values of absorbance at different times. The last number was the one at 6 hours, which is when the clot was completely broken up. Absorbance slope = A bsfinal – A bsinitial t final – t initial (1). Divide this number by the same slope for the test where there was no substance (tPA present) to get the rate of

fibrinolysis.).(Bosch-Sanz et al., 2022) : Rate of fibrinolysis (%) = Slope Compound/Slope PA*100

Results

The IR spectra are showen in figures bellow

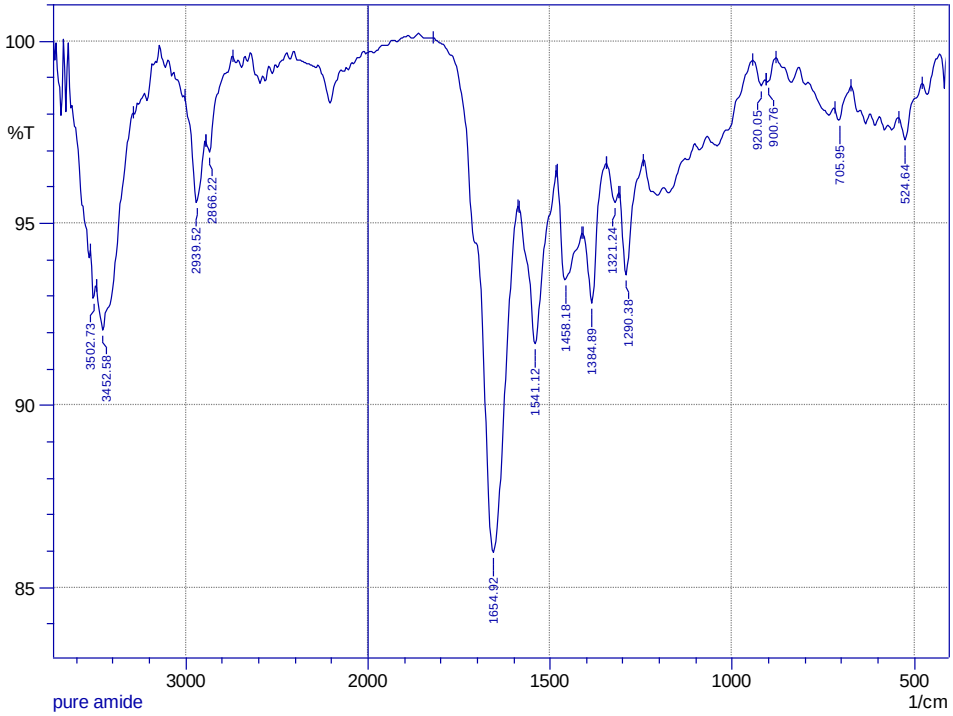


Figure 3. The FTIR spectrum of P1

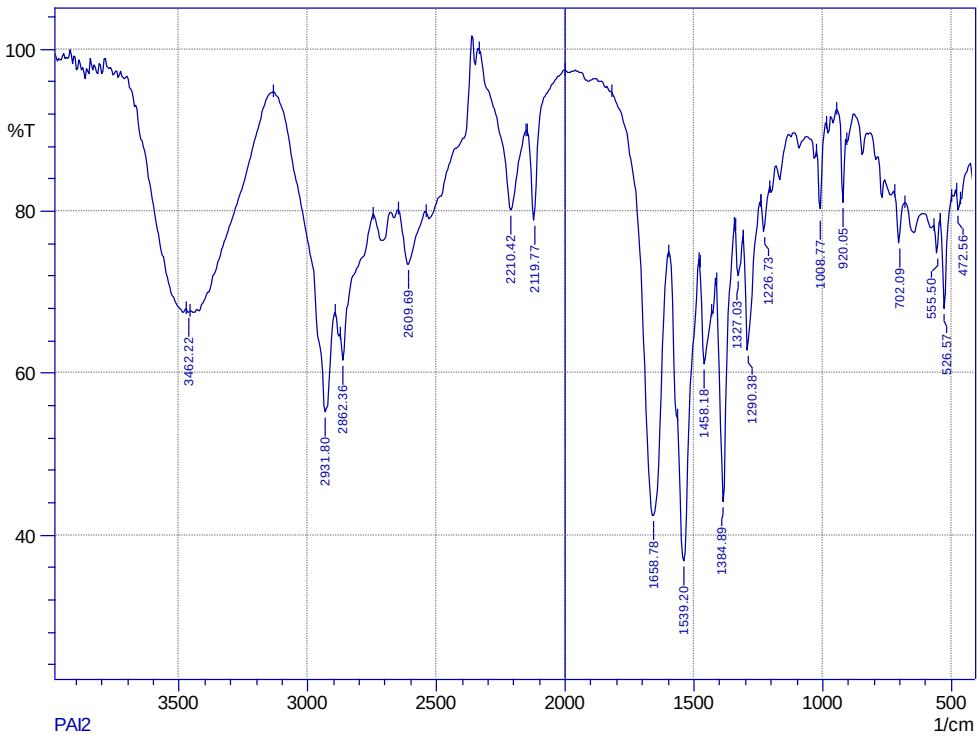


Figure 4. The FTIR spectrum of P2

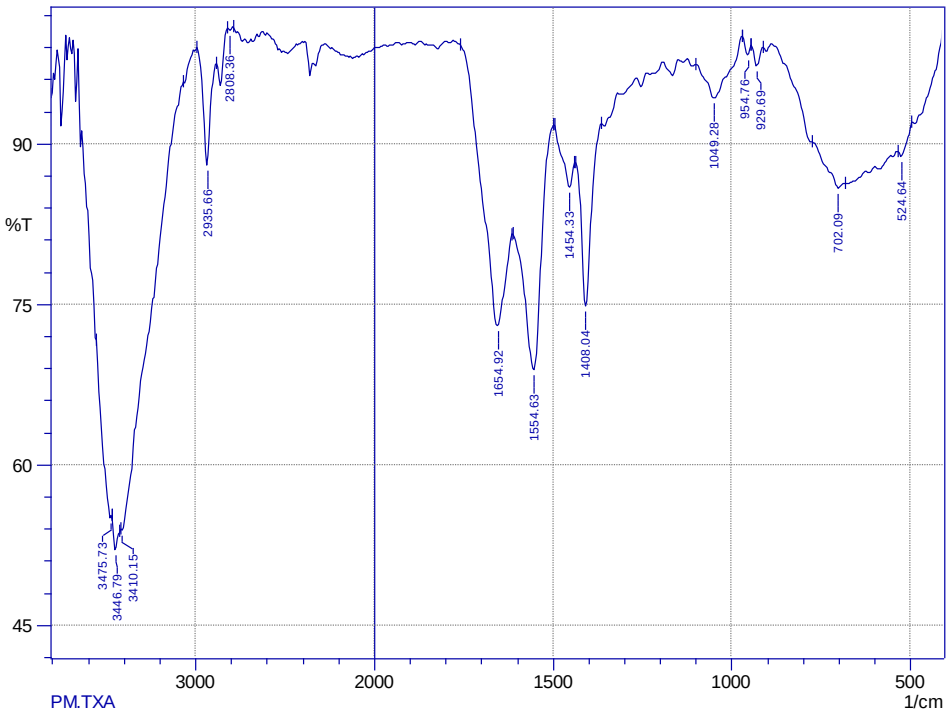


Figure 5. The FTIR spectrum of P3

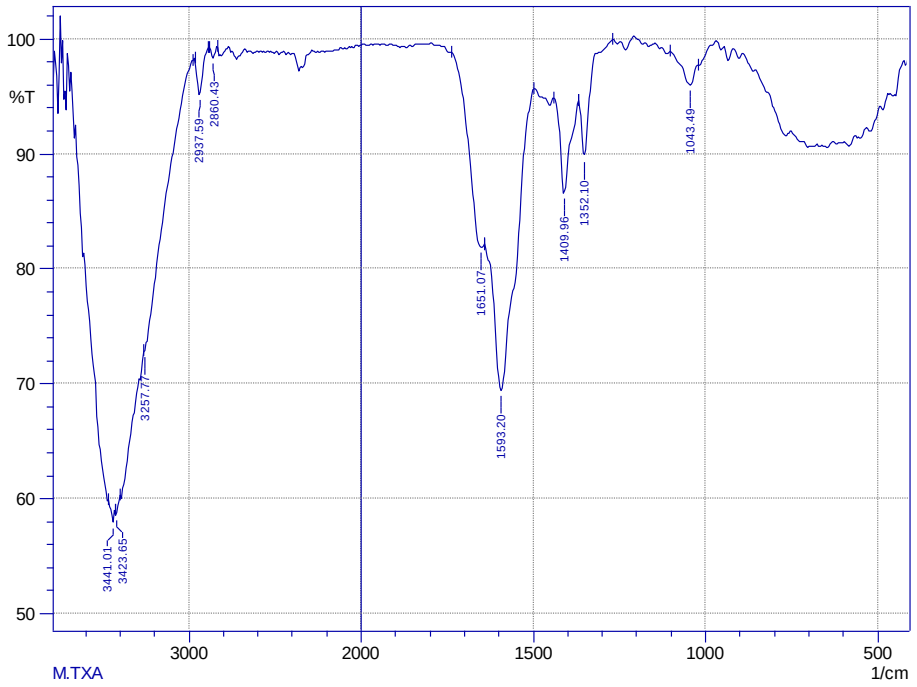


Figure 6 . The FTIR spectrum of P4

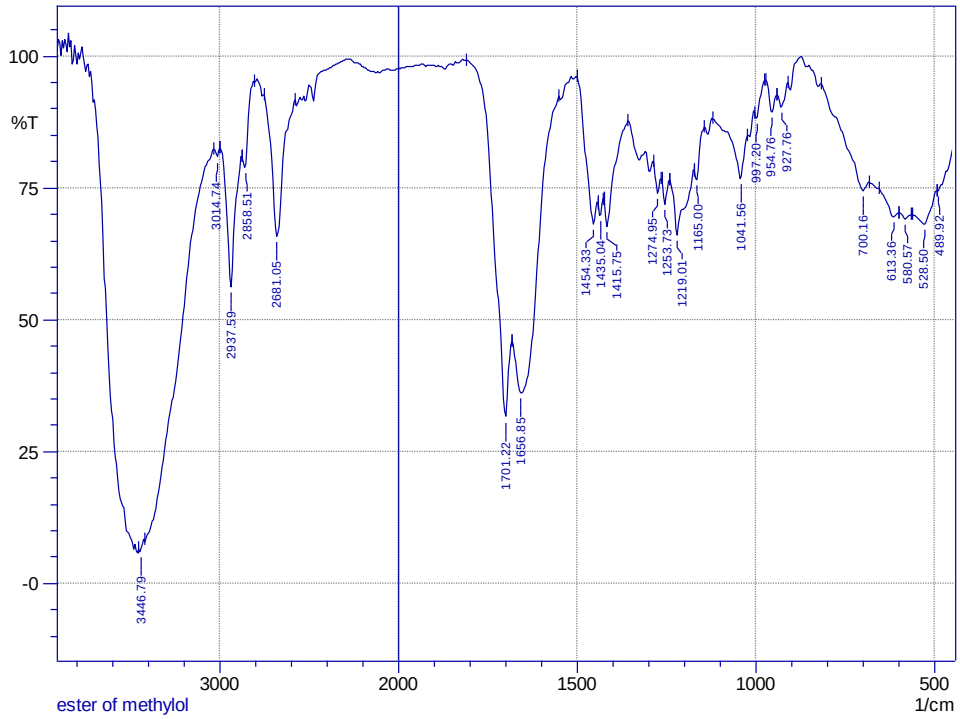


Figure 7. The FTIR spectrum of P5

The HNMR spectra are showen in figures bellow :

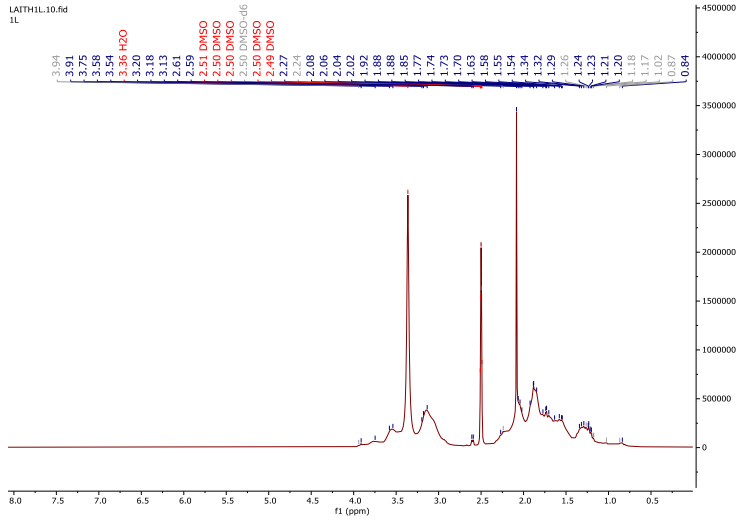


Figure 8 . The HNMR spectra of compound P1.

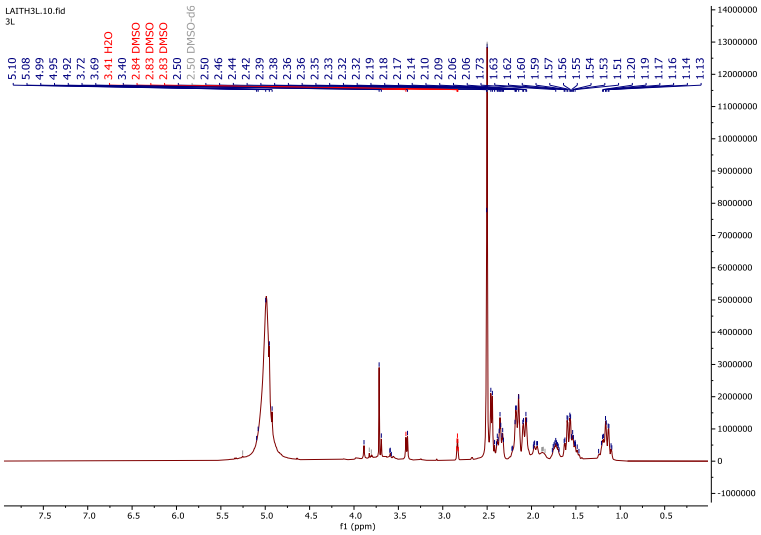


Figure 9. The HNMR spectra of compound P3.

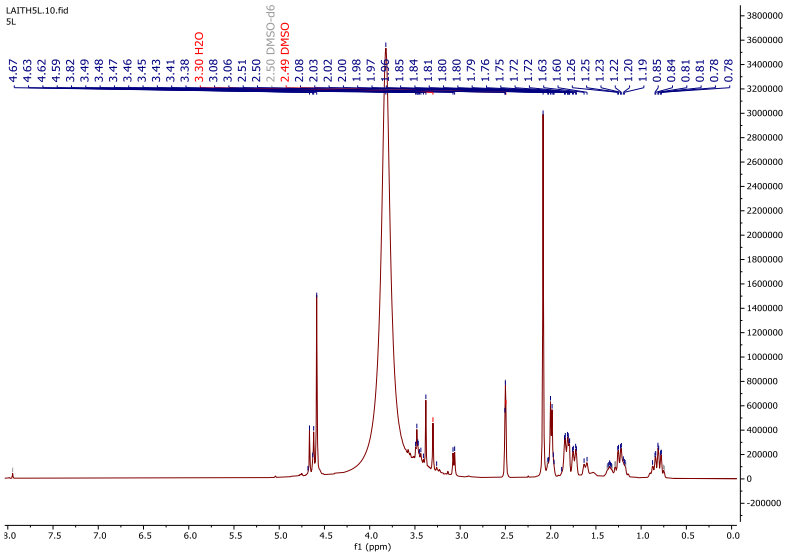


Figure 10. The HNMR spectra of compound P4.

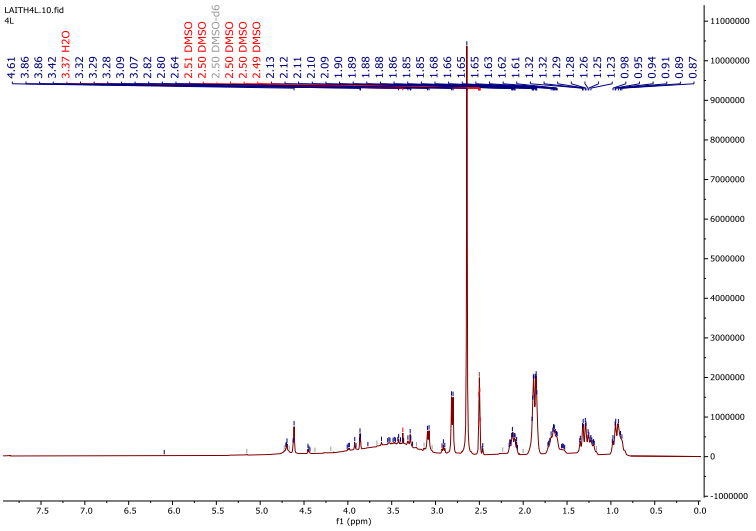
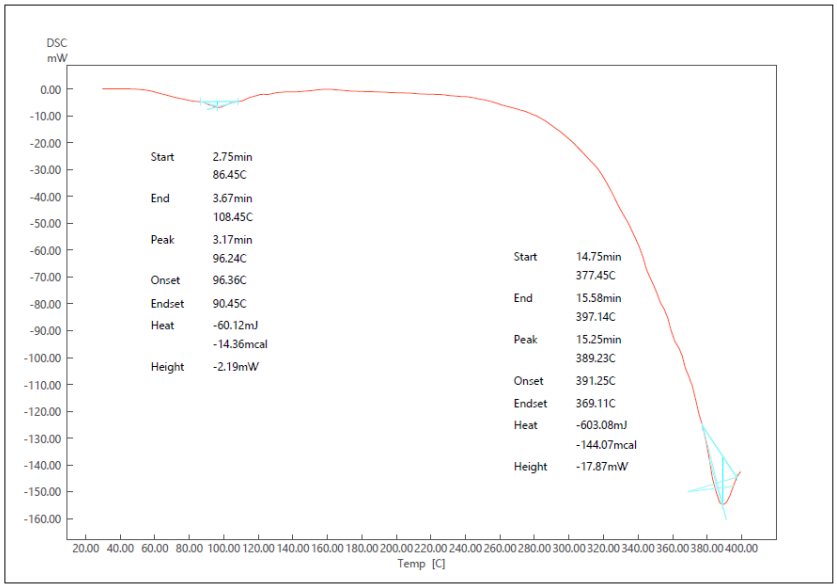
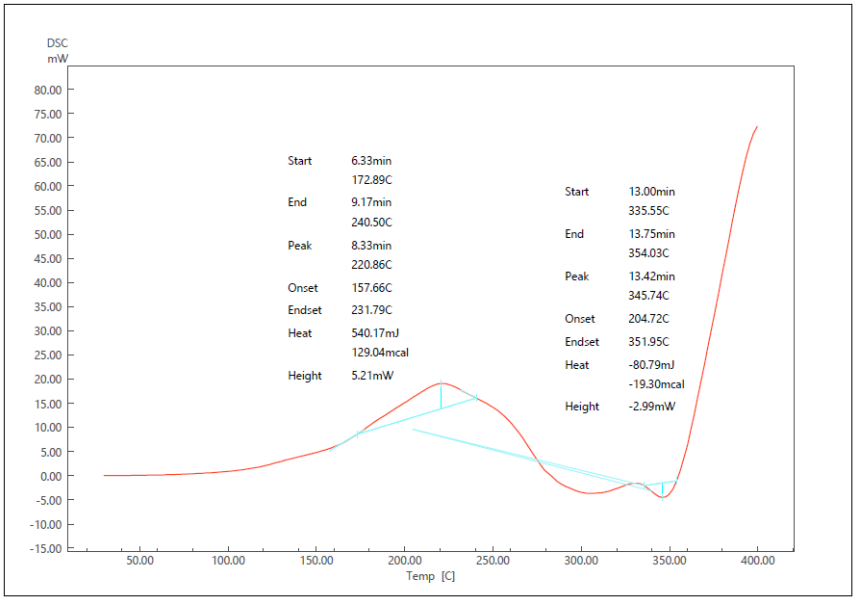


Figure 11 . The HNMR spectra of compound P5.

The DSC are showen in figures bellow:



Figures 12 . DSC thermogram of P1



Figures 13 . DSC thermogram of P2

The antifibrinolytic activity are showen in figures bellow:

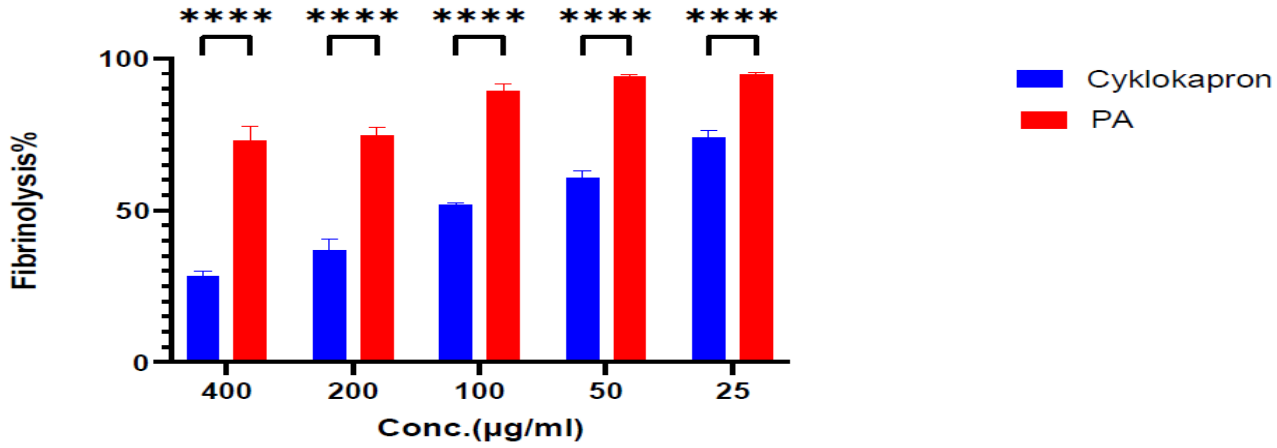


Figure 14 . Antifibrinolytic of P1

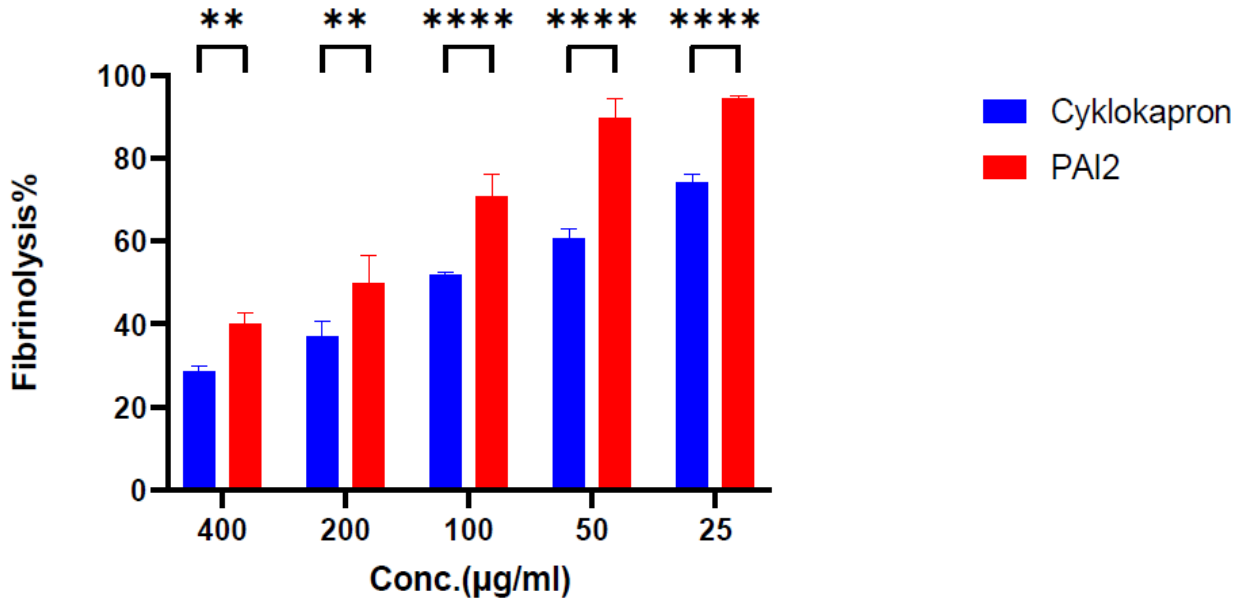


Figure 15 . Antifibrinolytic of P2

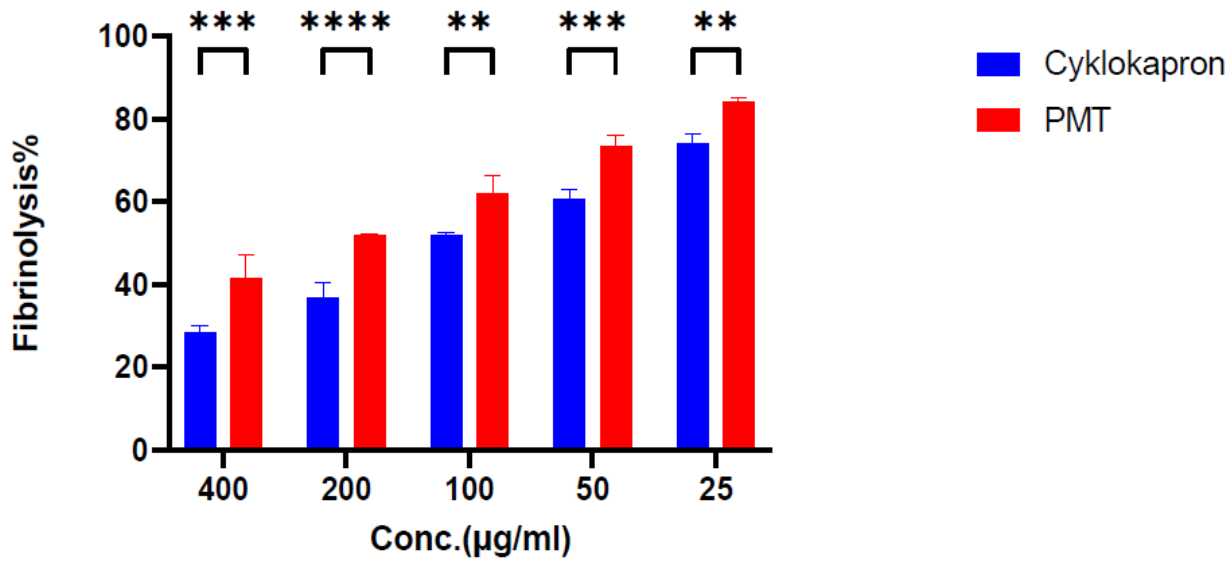


Figure 16 . Antifibrinolytic of P3

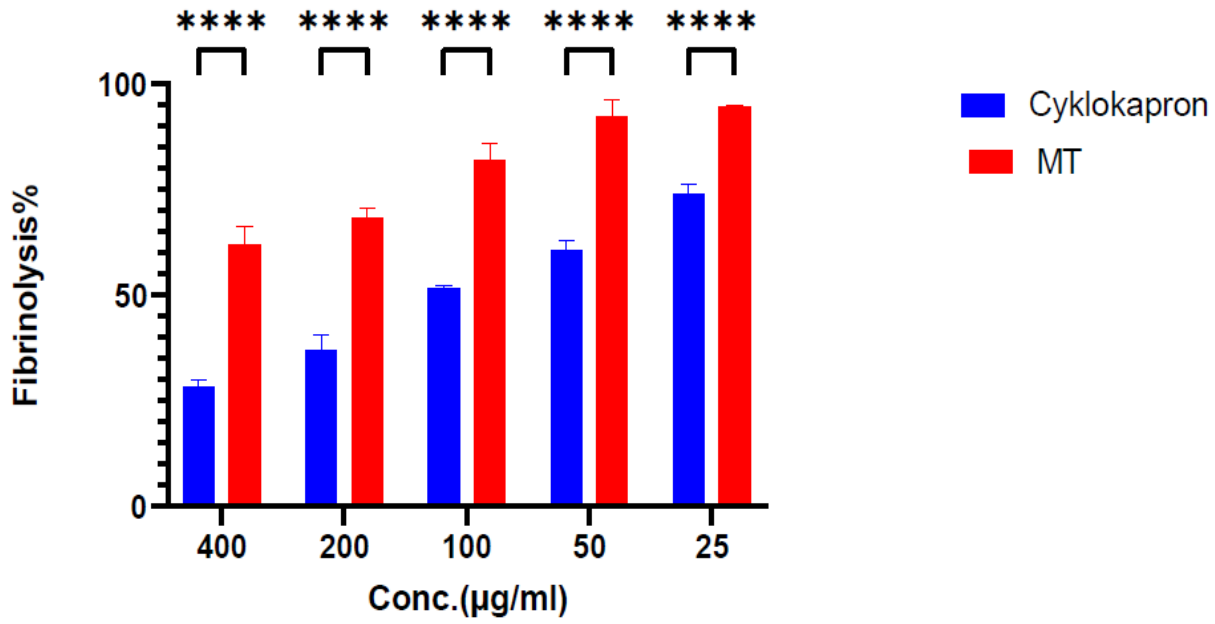


Figure 17 . Antifibrinolytic of P4

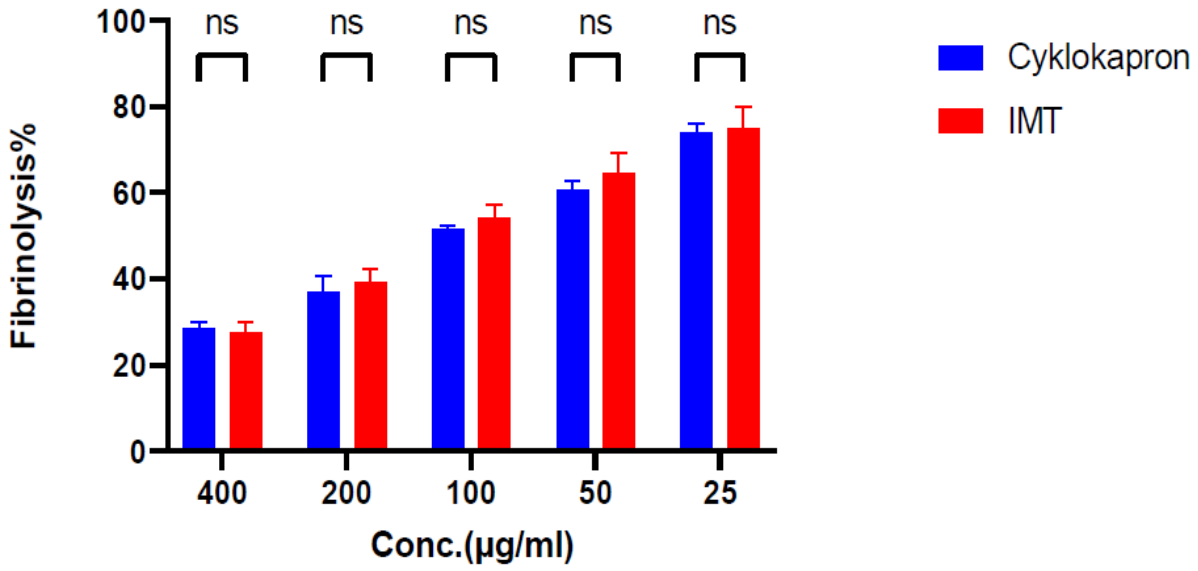


Figure 18 . Antifibrinolytic of P5

Discussion

An amide bond forms between carboxylated polyvinylpyrrolidone (PVP) and tranexamic acid. This was proven by the rise of a clear band at 3452.5 cm-1, which is due to the N-H stretching of the amide. Also, the disappearance of COOH stretch at 3282.8 cm^{-1} of polyvinylpyrrolidone (PVP) confirm amide bond formation between carboxylated polyvinylpyrrolidone (PVP) and tranexamic acid. The band at 1541.1 cm^{-1} assigned for N-H bending of amide. In the FTIR spectrum of P2, a band at 3462.2 cm-1 is linked to the N-H stretching of amide, and a band at 1539.2 cm-1 is linked to the N-H bending of amide. The band at 2931.8 cm^{-1} assigned for C-H stretch vibration. The band at 11384.8 cm^{-1} assigned for C-H bending of compound. The band at 1658.7 cm^{-1} assigned for C=O stretch of carbonyl group of amide. new band occur in 526.57 cm^{-1} which refer to iodine (C^{-I}) .

The FTIR spectra of P3 show the presence of the band at the range 3475.7-3410.1 cm^{-1} indicates O-H stretch of carboxyl group. Also, appearance a band at 2953.6 cm^{-1} attributed stretch vibration of C-H aliphatic. . The band at 1654.9 cm^{-1} assigned for C=O stretch carbonyl group. The FTIR spectra of P4 show the presence of the broad band at the range 3441-3423.6 cm^{-1} indicates O-H stretch of carboxyl group. Also, appearance a band at 2937.5 cm^{-1} attributed stretch vibration of

C-H aliphatic. The band at 1593.2 cm^{-1} assigned for C=O stretch carbonyl group. The FTIR spectra of P5 show the presence of the broad band at 3446.7 cm^{-1} indicates O-H stretch of methylol group. Also, appearance a band at 2937.5 cm^{-1} attributed stretch vibration of C-H aliphatic. The band at 1701.2 – 1656.8 cm^{-1} assigned for C=O stretch carbonyl group of ester. The band at 1253.7 – 1219 cm^{-1} assigned for C-O stretch of ester.

The appearance of the 1H-NMR spectrum for compound (P1) show of 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. The appearance of the 1H-NMR spectrum for compound (P3) show of quartet -signal at 1.50 – 1.65 for CH2 of two ring, single-signal at 4.95 for CH2 of (2HC-O) , single-signal at 4.92 for (O-H) of alcoholic group , single-signal at 9.78 for (O-H) of carboxylic acid. The appearance of the 1H-NMR spectrum for compound (P4) show of multiple -signal at 1.63 for CH2 of ring, doublet-signal at 5.02 for CH2 of (2HC-N), single-signal at 4.24 for (O-H) of alcoholic group, single-signal at 8.84 for (O-H) of carboxylic acid. The appearance of the 1H-NMR spectrum for compound (P5) show of multiple -signal at 1.65 for CH2 of ring, single-signal at 4.70 for CH2 of (2HC-N) , single-signal at 4.62 for (O-H) of alcoholic group , appearance signal at 1.21 for (CH3). The DSC thermograms showed that all products have different results from that of polyvinylpyrrolidone (PVP)and tranexamic acid. For P1 exhibited two phases endothermic peak, One endothermic peak at about 86.45 °C, other endothermic peak at about 377.45 °C, due to dehydration of polymer by heating. the disappearance of an endothermic fusion peak at 92.34ºC has indicated that the polyvinylpyrrolidone (PVP)has reacted with tranexamic acid successfully. It can be observed that the endothermic values of P1 were higher than those in PVP pure tranexamic acid. This may be contributed to the water evaporation which elucidated the molecular and physical changes resulted from chemical modification. These findings indicated that, the P1 had more thermal stability than the original polymer, because of strong chemical bonds resulted from the interaction between polyvinylpyrrolidone (PVP)and tranexamic acid. As shown in Figures (12). The P2 undergo an exothermic phase at 240.5 °C due to the dissociation of the amide bond between polyvinylpyrrolidone (PVP) and tranexamic acid (which leads to the decomposition of PVP and the production of heat). The P1 does not have this exothermic peak, which means the P1 is more thermally stable than the P2. This might be attributed to formation of hydrogen bonding throughout amino groups that responsible for the stabilizing effect. and one endothermic peak at 335.55 °C .

It can be observed that the endothermic values of P2 were higher than those in polyvinylpyrrolidone (PVP) and pure tranexamic acid. This may be contributed to the water evaporation which elucidated the molecular and physical changes resulted from chemical modification. As shown in Figures (13).

Antifibrinolytic

Tranexamic acid's ability to inhibit fibrinolysis and products are studies in different concentration (25 µg/ml, 50 µg/ml, 100 µg/ml, 200 µg/ml, 400 µg/ml). For P5 in concentrations (25 µg/ml, 50 µg/ml, 100 µg/ml, 200 µg/ml) it is show higher antifibrinolytic activity than P1, P2 , P3 and P4 , but in higher concentration (400 µg/ml) the P5 show higher antifibrinolytic activity than pure tranexamic acid. As shown in figure (18). P1 exhibits antifibrinolytic activity at varying concentrations, but at levels below those of purified tranexamic acid. As illustrated in figure (14). The addition of iodine to P2 increased the antifibrinolytic activity of P1 at various concentrations, but it remained inferior to that of purified tranexamic acid. As depicted in figure (15). From this information we find that the bind of tranexamic acid with polyvinylpyrrolidone lead to decrease the antifibrinolytic activity of tranexamic acid. For P3 it is show higher the antifibrinolytic activity than P1 and P2, but in concentration (200 µg/ml, 400 µg/ml) the antifibrinolytic activity of P2 is higher than P3, all these effect still below the pure tranexamic acid. As shown in figure (16).

For P4 it is lower antifibrinolytic activity than P1, P2 and P3, as shown in figure (17). In low dose (25 µg/ml) the P4 and P1 has same antifibrinolytic activity, but in high dose (400 µg/ml) the P4 has higher antifibrinolytic activity than P1.

Conclusion

It could be seen that PVP extensive use in medical and pharmaceutical fields is dictated by its highly interesting properties (*e.g.* biocompatibility, biodegradability, easy preparation, excellent film forming capacity, very good adhesive and emulsifying properties, good mechanical stability, excellent chemical resistance, odorless and high barrier properties, etc.) .Synthesis of new carboxylated polyvinylpyrrolidone terminate the tranexamic acid and the result product was complex with iodine, also prepare of new derivative of tranexamic acid (ether derivatives tranexamic acid , Synthesis of methylol terminate of tranexamic acid , Synthesis of ester of methylol terminate of tranexamic acid) . Esterification of methylol tranexamic acid (P5) it give antifibrinolytic effect more than of standard tranexamic acid in high concentration (400 mcg/ml) .

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