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Biodegradable thermoplastic polyurethane composites as potential plating systems in pediatric facial fractures

BY

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ABSTRACT

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Title: Biodegradable thermoplastic polyurethane composites as potential plating systems in pediatric facial fractures.

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Due to the rapid growth of facial bone in the pediatric age group, the use of metallic plates would require a second surgical intervention to remove it. The alternative is biodegradable plating systems which are safe but not without complications, including learning curve, decreased stability, cost, and infection. The addition of hydroxyapatite to the synthesized thermoplastic polyurethane (TPU) may affect its structural and morphological properties. Hydroxyapatite is the inorganic part of the bone that is used as reinforcement in many applications. Plate systems comprising composites including hydroxyapatite (u-HA) particles have been developed for clinical use due to their osteoconductive capacity. The effects of hydroxyapatite addition on thermoplastic 'polyurethane's degradation, thermal, structural, and morphological characteristics were examined.

This work aims to find an alternative material that can replace the commercial system used nowadays in bone fixation (made either from l-lactide or d-lactide) and overcome its disadvantages such as late degradation tissue response and foreign body reaction. The H12MDI based thermoplastic polyurethane was prepared using 12% HS 50:50 BD-Poly D, L-lactide -co-glycolide, then the composites were prepared by the addition of 3 and 15% of hydroxyapatite, respectively.

The properties of the polymer and its composites have been characterized by Fourier transform spectroscopy (FTIR), carbon nuclear magnetic resonance (C^{13} NMR), scanning electron microscopy (SEM), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray diffraction (XRD), and In vitro degradation analysis. It was found that the TPU is semi-crystalline and porous. The melting point and the decomposition temperature of the composites increased with the addition of HA compared to the pure TPU. with incubation in the buffer for 45 and 90 days. The melting point was found to be increased for the polymer as well as for the composites. SEM analysis showed that the polymer is porous, and the filler fills these pores in the composites, increasing its melting point and making the surface smoother. X-ray test showed that the crystallinity of the polymer raised with the addition of the filler. Regarding the degradation, the TPU showed a better degradation rate than the composites as it lost around 30%of its mass after two months only, while the composites lost about 10%. It was confirmed that the synthesized TPU-HA composite could be a promising candidate for bone repair systems.

DEDICATION

First and foremost, praises and thanks to God, the Almighty, for His showers of blessings throughout my research journey to complete the work effectively.

My completion of this work could not have been achieved without the support and love of my parents, My little brother and sister, my family in-law, and my friends.

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Chapter 1: Introduction

The need for biodegradable materials, especially biodegradable polymers, is increasing with time in almost all applications and, most notably in the biomedical applications as these materials are in direct contact with the patients and due to their potential merits compared to the non-degradable materials, especially in pediatric surgery.

Aliphatic polyesters are the most used kind of degradable polymers due to their advantages such as hydrolysis, mineralization [1] susceptibility, oxidation [2, 3], and the rate of degradation, which can easily be controlled through modifying the polymer structure involving the molecular weight, end groups, hydrophobic-hydrophilic balance, the degree of crystallinity and the glass transition temperature. Polyglycolic acid (PGA) and Polylactic acid (PLA) is considered the first materials used in the biomedical field, such as in sutures, and increasingly developed into other biomedical applications such as tissue regeneration and implants. PLA is widely used in polymer research due to its physical properties and degradation characteristics, making it preferable for many applications such as medical devices, packaging applications, clothing fibers, blow-molded bottles, etc.

PLA has two stereoisomers: D and L (PLDA and PLLA, respectively), prepared from the racemic mixture of L-lactide and D-lactide. PLLA is the most favorable semi-crystalline polylactide. In addition to the individual polymers, an interesting alternative made by the reaction between the monomers or the cyclic dimers of the glycolic and lactic acid in different ratios depending on the application needed is poly lactide-co-glycolide (PLGA). PLGA copolymers have desirable features, including a constant degradation rate, mechanical resistance, and regular individual chain geometry [4-6].

Furthermore, another area of increasing research activity is that of degradable polyurethanes. [7-11] Thermoplastic polyurethanes (TPUs) are versatile polymers made by reacting diisocyanate and a mixture of a chain extending diol and/or diamine and a polymeric polyol.

This research aims to synthesize bio-degradable materials with improved degradation properties than those used nowadays and with potential applications such as facial bone fixation in trauma surgeries.

Chapter 2: Literature review

Facial fractures are considered a challenging case, especially in the pediatric population, in terms of approach treatment techniques and their effect on growth. Before choosing the appropriate treatment modality, many factors must be considered, such as the ’patient’s age, the cause of the injury, the medical history, etc. Plenty of devices have been used to fix the facial bone after trauma. Specific characteristics should be available in these devices to preserve the mechanical characteristics of the bone during healing, such as high strength, wear, and fatigue resistance. It must be secure and easy to use also. After removing the implanted device, it is a feature that there is no bonding between the implants and the tissues around. The implant material must support and enhance the formation of the bone, this kind of material is called osteoinductive material [1]. Since 1858, implanted materials made of metals have been used in the fixation of facial bones. In the 20th century, metal alloys were used and showed an advantage over individual metals due to their corrosion and infection resistance. Chromium, nickel, and molybdenum are examples of the materials used in different stainless steel and alloys used in bone fixation. In the 1960s, implanted devices made of titanium have been used and still considered as a gold standard and

required in the majority of the fixation treatments, especially in adults due to their ultimate characteristics such as high strength, ease to handle, minimal scattering with the computed (CT) scanning and compatibility with the radiography and MRI. [2-4]. However, there are many disadvantages to the titanium plating system, such as its temperature sensitivity and the possible need for a second surgery to eliminate it. Also, it can cause palpability in areas of thin, soft tissue, metal allergy and secondary infection. Other rare disadvantages include bone resorption, pain, wound dehiscence, and interference of bone growth in children. [5, 6]. Because of all these drawbacks, titanium implants need to be replaced by resorbable materials that are considered the best choice, especially in pediatrics, due to their properties that overcome the titanium drawback. The properties of these bioresorbable and biodegradable fixation devices are rigid, biocompatible, provide stability to the bone without affecting healing, do not interfere with imaging techniques, and there is no need for a second surgery. Decreased pain, no corrosion, or accumulated metals in the tissues are other advantages of these plating systems. reduced stress-shielding of biodegradable plates because these implants can bear less load initially, and then it will transfer gradually. [2, 4, 7]. However, biodegradable fixation devices are not free of disadvantages that are mostly related to their mechanical properties compared to titanium plating systems yet, are still very common in use and preferred as they are secure, effective, and flexible [8, 9].

These implants are made of biodegradable polymers, either of natural or artificial origin. Polyesters have been the most used biodegradable synthetic polymers in orthopedics since the 1960s. These devices were first used in facial fracture surgeries in 1971. PGA, PLA and PLLA are the most commonly used polyesters.

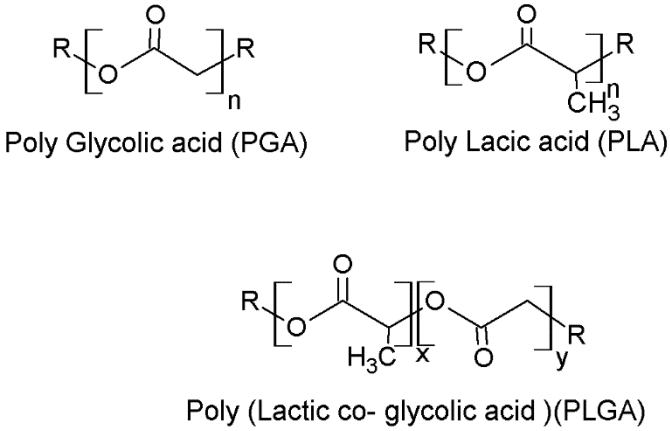

Figure 1: The chemical structure of PGA,PLA and PLGA[1]

PGA (polyglycolic acid) is the first biodegradable polymer used clinically; this high molecular weight polymer has a rapid degradation rate that is noted in 4-7 weeks after implantation. This period is not sufficient for the bone to heal. Also, there is difficulty in removing the accumulated acid-degradation products. These factors reduce pure PGA utilization in maxillofacial surgeries [11].

Polylactic acid (PLA) is another biodegradable polymer with a molecular weight higher than PGA. This polymer has a slow degradation rate that can reach 3.5 years until total degradation occurs. This can result in foreign body reactions, insufficient intensity, and late-degradation tissue response. PLA have two stereoisomers: L-and d lactide (PLLA and PLDA, respectively) [9]. Poly -l- lactide PLLA has been utilized as a maxillofacial material since the 1990s. It is considered as (the first generation). PLLA is hydrolysis-resistant because of its crystallinity and hydrophobicity.

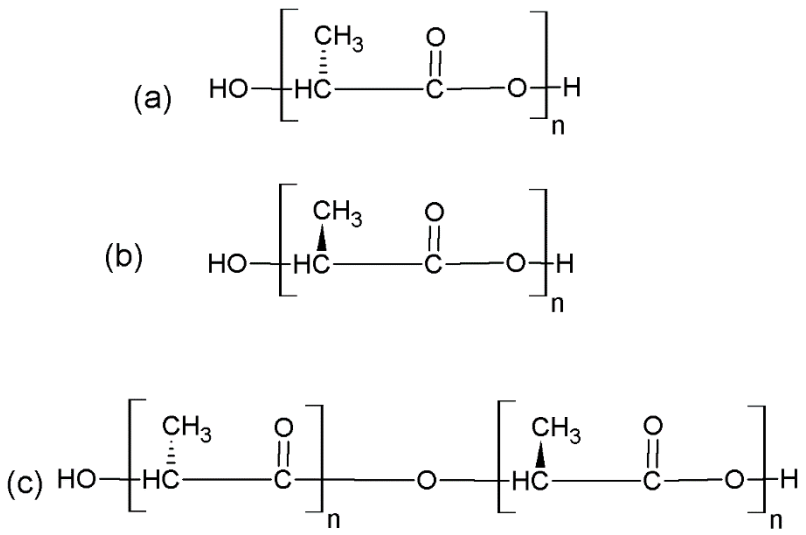

Figure 2:The chemical structures of (a)(PLLA), (b) (PDLA), (c) (PDLLA).[2]

Recently, a group of scientists used two devices made of PLLA, FixsorbMX, and Grand Fix had overcome several problems such as materials' insufficient intensity, foreign-body type reactions, and the late response of degradation tissue. They made shape modifications on Grandfix-flate type from its actual shape to create an innovative system available on the market as a flat, thin, bioresorbable plate system. This system was typical for mid-facial osteosynthesis applications because it does not require much strength as it is not load-bearing or load-sharing area of facial bone. The plate is stiff and has a mechanical strength like traditional poly-L-lactic acid plates due to its width. It is more suitable for minimizing the palpability of the face, particularly at the easily facial palpated areas, such as the orbital rim zygomaticofrontal sutures [13].

Different polymers were then mixed to form a copolymer, which is considered a second-generation device. These devices are preferred over pure polyglycolic and poly-lactic acid due to their enhanced mechanical characteristics and degradation rate. By controlling the composition and the ratio of the monomers used, the copolymers can provide sufficient strength for 6-8 weeks for a complete resorption period of a year to18 months. Generally, more content of glycolide causes a more rapid degradation rate. Commercial devices made of different monomers such as glycolic and trimethyl

carbonate have also been shown to be more flexible and have lower rates of degradation when compared to pure Polyglycolic acid (about seven months) and are appropriate as interference screws for bone-tendon graft fixation [14].

One promising polymer is biodegradable amorphous terpolymers made of glycolide, lactides and caprolactones repeating units randomly distributed. These polymers were synthesized, and their degradation profile was characterized. The composition of these synthesized polymers allows the control of the polymers' degradation stages. The first stage (where the mechanical properties are constant) can be assorted from less than a week to 20 weeks followed up with a steady decrease of mechanical characteristics (bending stress decreases in 8 - 20 weeks) without dramatic mechanical failure and bulk degradation in comparison to the Poly-L-lactic acid [15]. The polymers made of lactic and glycolic acids have much attention in research compared to the alternative ones. One of these polymers or copolymers is polylactide co glycolide PLGA. This polymer has been used and is still in many applications because of its desirable properties and the ability to modify according to the application in need. PLGA copolymers with more lactide content are less hydrophilic and absorb waterless, which leads to a slower degradation of the polymer chains [16]. While polyglycolic acid is highly crystalline, the crystallinity disappears rapidly in copolymers of lactide and glycolide. This morphological change leads to a rise in the rate of hydration and hydrolysis [17].

Another significant material that has been used in biomedical applications is hydroxyapatite HA. Hydroxyapatite is the main inorganic solid component of the hard tissues in bones. It could also be utilized as a vital implant component due to its excellent biocompatibility, bioactivity, no immunogenicity and osteoconductive nature [1]. Hydroxyapatite could not be utilized instantly as an implant due to its free powder-

like nature or needle-like particles, which hinders its densification, resulting in brittle films, making it hard to process [5]. Therefore, it has been mixed with other materials, especially the polymers, in different ratios to form the composite that can meet the worldwide requirements in implants synthesis.

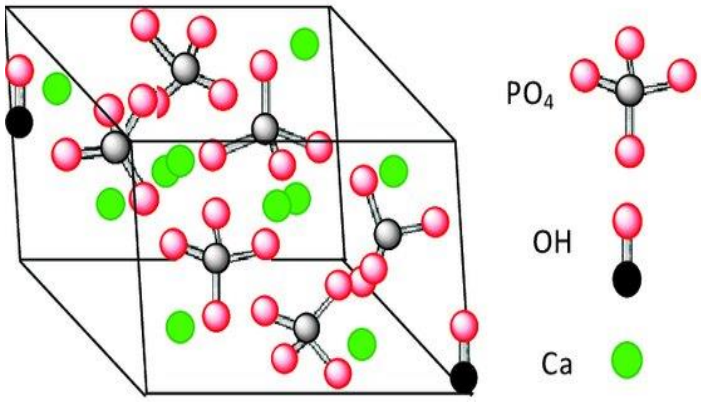

Figure 3: The structure of hydroxyapatite crystals[3].

Hydroxyapatite/Poly-l-lactic acid bioactive/resorbable material in which hydroxyapatite has been linked in Poly-l-lactic acid because of its osteoconductive capacity. These materials can be used for complete replacement by the tissues of the bone. Furthermore, by comparing the previous bioresorbable polymers and this composite, this composite provides further stable boney segment retention due to its high strength involving bending strength and modulus, shear, and impact strength in comparison with poly-l-lactic acid devices. It has significantly impacted the clinical advantages and can be the following generation materials in maxillofacial surgery.

The previous study is an example that has shown that using hydroxyapatite/poly l-lactic acid plating system for mid-facial fractures fixation gave satisfactory results in terms of their stability when compared to titanium plating system [4, 13]. Another kind of material which have a great deal of attention in the biomedical field is thermoplastic polyurethane TPU. This polymer has been widely utilized in recent years. It is a class of polymers created from 3 main components: a diisocyanate, a polyol, and a chain

extender. It has two segments: hard and soft segments. The soft segments are made of polyols like polyester.

On the other hand, the hard segments are made from diisocyanate and a chain extender component. The chain extender is typically a small molecule with hydroxyl or amine groups. In comparison, the hard segments contribute to hardness, tensile strength, impact resistance, stiffness, and modulus. On the other hand, soft segments contribute to elongation, water absorption, softness, elasticity, and degradability. Therefore, from the ’application’s perspective, it is possible to synthesize various polyurethanes whose characteristics can easily be changed by changing the structures of soft and hard segments.

The isocyanate can be aliphatic or aromatic isocyanate, particularly important for getting biocompatible material utilized for their synthesis substrates that are non-toxic and degraded into non-toxic compounds. In medical applications, 4,4'-methylene Di cyclohexyl diisocyanate (H12MDI) successfully replaced 4,4'-diphenylmethane diisocyanate (MDI), especially in the synthesis of biodegradable materials, which led to a decrease in the risk of the creation of carcinogenic aromatic diamine as a degradation product of polyurethane-based on MDI [19]. Polyurethanes were never utilized for load-bearing fixation, but they have been demonstrated to be promising

membranes for guided tissue regeneration and porous structures for filling bone defects [15].

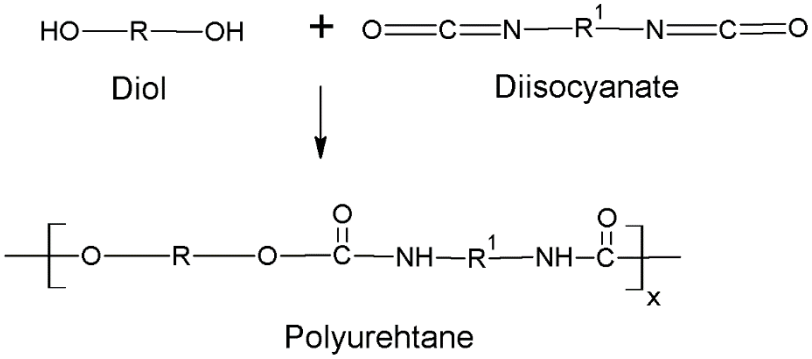

Figure 4: The genereal reaction of polyurethane synthesis .

Chapter 3: Experimental

3.1. MATERIALS

1,4-butanediol (99%, ITS/intertrade technical supplies) was used as received.

Dibutyltin dilaurate (95%, ITS/intertrade technical supplies) was used as received.

N, N-dimethylformamide (anhydrous,99.8%, ITS/intertrade technical supplies) was used as received.

Phosphate buffer solution (ITS/intertrade technical supplies) was used as received.

Poly butylene adipate (song won industrial group) was used as received.

Dicyclohexylmethane-4,40-diisocyanate (99.5%, H12MDI, Covestro Desmodur W) was used as received.

Hydroxyapatite HA (ITS/intertrade technical supplies) was used as received.

BD based Poly D, L-lactide -co-glycolide (2000g/mol, HAI HANG INDUSTRY CO., LTD), a 50:50 mixture of D, L-lactide and glycolide, was used as received.

3.2. INSTRUMENTATION

3.2.1. Structural characterization

3.2.1.1. Nuclear magnetic resonance (C_{13} and H_1 NMR)

Nuclear magnetic resonance is a physical technique that includes the ’nuclei’

absorption and remission of electromagnetic radiation in the magnetic field. The NMR spectra help to identify the composition of the sample and the distribution of the monomer units. The polymer is dissolved in the appropriate solvent then subjected to the analysis.

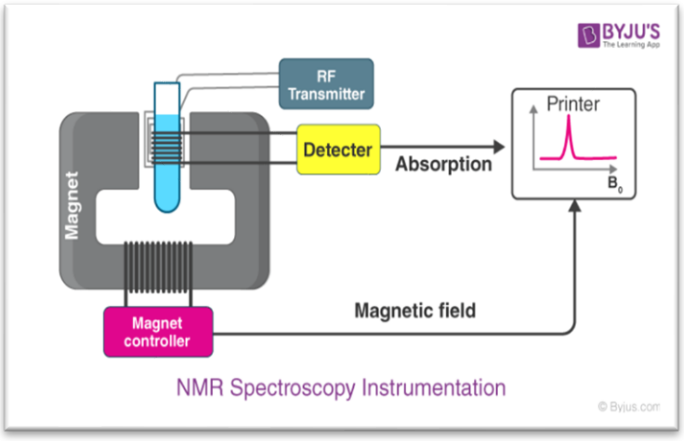

Figure 5:NMR spectroscopy instrumentation

3.2.1.2. Fourier transform infrared (FTIR) spectroscopy.

FTIR spectroscopy is an analysis method utilized to get the infrared spectrum of emission, absorption, and photoconductivity of all material phases (solid, liquid or gas). By this technique, different functional groups can be detected in a spectrum range between 4000 cm^{-1} and 400 cm^{-1}. The sample is being dissolved in an appropriate solvent and layered on NaCl crystal, and after the evaporation of the solvent, the analysis is done.

FTIR was used to identify the disappearance and existence of the peaks of interest, which prove the formation of our product, such as the disappearance of the isocyanate peak and the creation of the urethane peak. The instrument used spectrum 400 FTIR from PerkinElmer using UATR with 4 cm^{-1} and eight scan rates.

Figure 6:Fourior transform infrared spectroscopic device

3.2.1.3 X-ray diffraction XRD

This test is a non-destructive method utilized to analyze the structure of the materials and study the degree of crystallinity. It is also used to determine the crystalline phases found in the material. XRD test (Empyrean, PANalytical, UK) for the polymer and the composites were carried out. The scan range (2θ) was specified from 4° to 80° where the phase analysis was performed in the θ–2θ scanning. Copper (Cu) is used as the anode material. With generator voltage equal to 45 kV and tube current equal to 40 mA. Cu Kα radiation is typically composed of two spectral lines Kα1 and Kα2 with the wavelengths 1.5405 Å and 1.5444 Å respectively, so the Kα ratio (Kα2Kα1⁄) equals 0.500.

Figure 7:Empyrean X-ray diffraction (XRD) device.

3.2.2 Invitro Degradation analysis.

A degradation procedure has been done on the synthesized TPU, synthesized commercial PU resin, and their composites .six discs are made out of each material, weighted, and then immersed in a container filled with phosphate buffer solution pH (7.4) and left for three months. After every two weeks, one disc discharged from the solution, weighted then analysis was performed. The remaining mass percentage (mr) was computed for each disc with the following equation:

$$m_r = \left(\frac{m_{dry}}{m_0}\right) \times 100$$

Where m_{dry} refers to the mass after drying, and m_0 refers to the initial mass before incubation in the buffer.

3.2.3 Morphological characterization

3.2.3.1 Scanning electron (SEM) microscopy

This is an analysis technique widely utilized in examining the surface morphology of the samples. This technique includes the interaction between the electrons in the focused beam and the atoms of the sample under examination, which

generates the SEM images. Much information concerning the surface topography and the composition of the sample can be obtained from SEM.

This test is done on the polymer and its composites before and after the incubation in the buffer to examine the distribution of the hydroxyapatite filler into the composite and follow the formation of holes or the cracks associated with the degradation of the polymer and its composites.

Figure 8: Quanta 200 scanning electron microscopy

3.2.4. Thermal characterization

3.2.4.1 Differential scanning calorimetry (DSC)

It is defined as a thermo analytical method that is utilized to identify the characteristics of the materials, especially the thermal properties, by using a differential scanning calorimeter where the difference between the heat amount needed to raise the temperature of the sample and the reference is calculated as a function of temperature.

The sample and the reference are kept at the same temperature during the whole procedure. The analysis curves were drawn depending upon the heat flux versus temperature or time. The Thermal transition and the decomposition behavior of the

polymers and the produced product were conducted by this technique with a temperature range from -50ºC to 300ºC at a rate of 10 degrees/min under a nitrogen atmosphere.

Table 1 DSC experimental conditions.

Cycle No.	Cycle name	Temperature (ºC)	Time (min)
1	Heating	-50~300	1
2	Hold 1	300	370
3	Cooling	300 ~-50	370
4	Heating 2	300	370
5	Hold 2	300	1

Figure 9:Diffrential scanning calorimeter device.

3.2.4.2 Thermogravimetry (TG) analysis

Thermogravimetric analysis (TGA) is an analytic method utilized to determine the thermal stability of a specific material and its fraction of volatile components by tracking weight change occurring as a sample is heated at a steady rate. The measurements are usually conducted in air or an inert atmosphere, for example, in helium or argon, and the weight is documented as a function of rising temperature. This test is used to identify the thermal degradation of the polymer and its composites. The samples are conducted at a heating rate of 10deg/min from 25 ºC to 400 ºC with a

20ml/min flow rate.

Figure 10:Thermogramimetric analysis device.

3.3. Procedure

3.3.1 Synthesis of thermoplastic polyurethane TPU

The following procedure produces an H12MDI based TPU performed in a reaction flask under an inert N2 atmosphere. A 250 ml beaker was used and charged with 6.23 g (3.12 mmol) of PBA, 6.23g (3.12mmol) of 2000g/mol BD-PLGA and 100 ml of dimethylformamide DMF solvent. The beaker is put aside to permit the polyols to dissolve. A 500ml two neck reaction flask was charged with 100 ml dimethylformamide DMF ,6.161 g (23.4 mmol) of H12MDI ,1.493 g (16.5 mmol) of 1,4-butanediol BD and 0.032g (0.051 mmol) of Di butylene tin dilaurate DBTDL. The reaction flask was sunk into a 40 ºC silicon oil bath, fitted with a mechanical stirrer, and linked to a hose immersed in water to check if there were bubbles to ensure that the flask was sealed. The solution was permitted to react with stirring for a half-hour, after which the previously weighed polyol solution was charged, and the reaction was carried on for an extra 22 h. Following completion of the reaction, DMF solvent has been removed by rotatory evaporation. The product was washed with chloroform and

poured into a 300 ml PTFE dish and placed in a vacuum oven at around 50 ºC overnight to remove the chloroform. Six discs (1 mm thick) were made from the produced polymer and weighted, then stored in a phosphorus buffer solution for three months. Every two weeks, one disc was dried and weighed then analysis was performed[4].

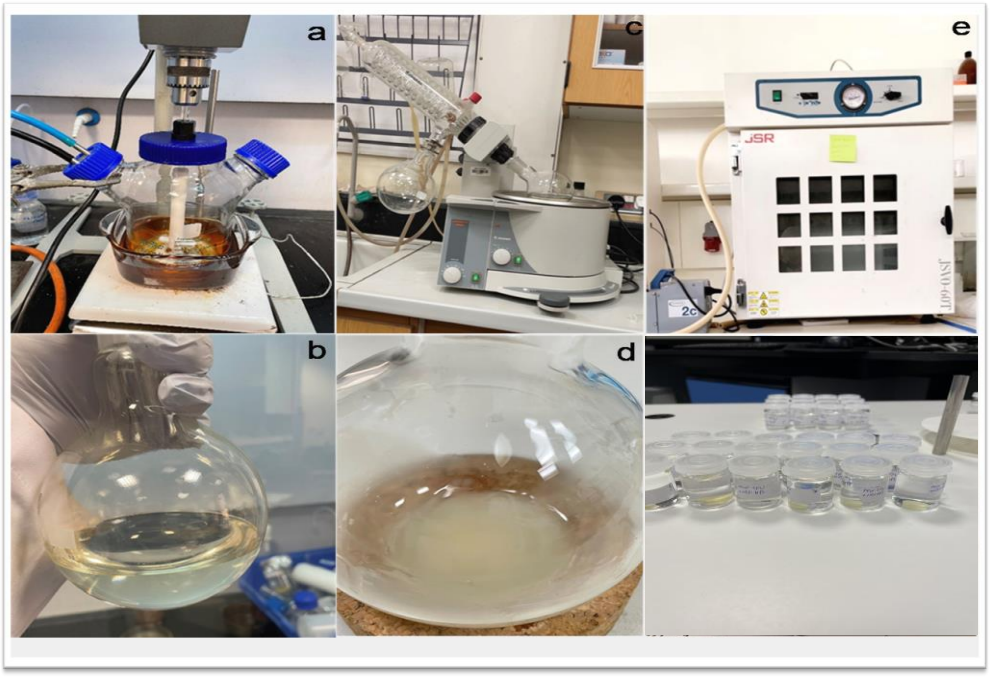

Figure 11:The polymer synthesis procedure (a)Reaction set up (b) Produced polymer (c) Rotatory evaporation to evaporate the solvent (d) Polymer after the solvent evaporation(e) Vacuum oven to get rid of the chloroform (f) Discs in buffer solution.

The synthesis reaction is shown in (Figure 13) where Di cyclohexyl methyl 4,4-diisocyanate was used as the aliphatic diisocyanate part. The aliphatic diisocyanate produces a non-toxic aliphatic diamine opposite to the aromatic one, which is toxic. The H12MDI reacts with 1,4-butanediol as the chain extender part. Then a mixed polyester is used to reach a good balance of physical and thermal characteristics and enhance the degradation rate.

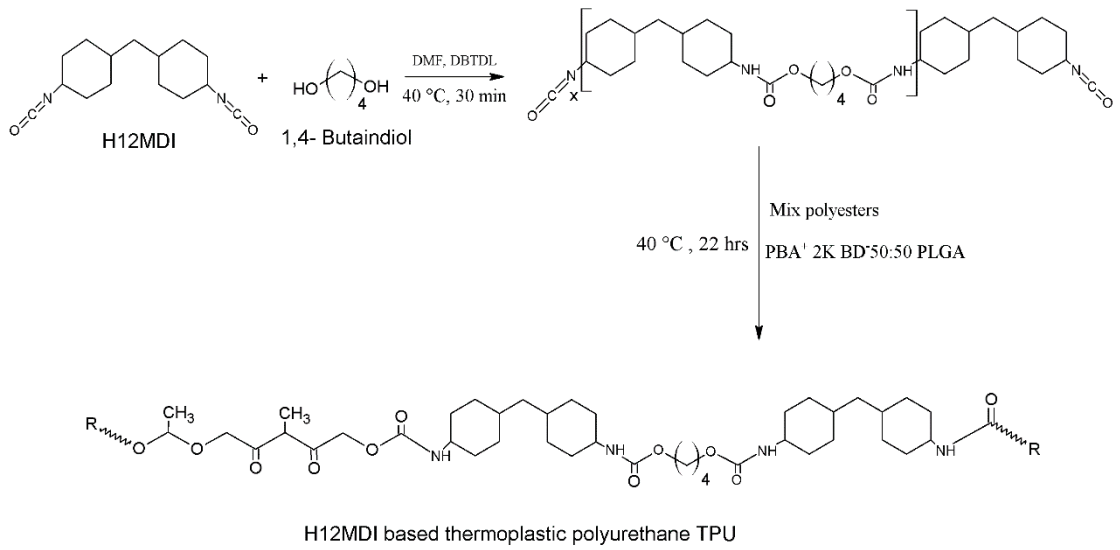

Figure 12:Synthesis of H12MDI based thermoplastic polyurethane TPU.

The mechanism of the urethane bond formation (figure 14) is a nucleophilic substitution reaction (a kind of chemical reaction that includes the substitution or the replacement of a nucleophile with another or a less active element with the more active one). The nucleophile of oxygen attacked the carbonyl of the diisocyanate and led to the formation of two intermediate resonance complex structures (A and B). It was found that the intermediate complex B is more stable than the intermediate complex A. As the carbonyl group is much stronger than the C=N group.

Also, the N- atom is more electropositive than the O- atom. 'That's why the intermediate complex B is the one that tends (more) to react with the added polyol. The N- atom will attack the cation (H+) and lead to the urethane bond formation and the chain extender release [4], replaced by the polyol made of DL-lactide -co-glycolide.

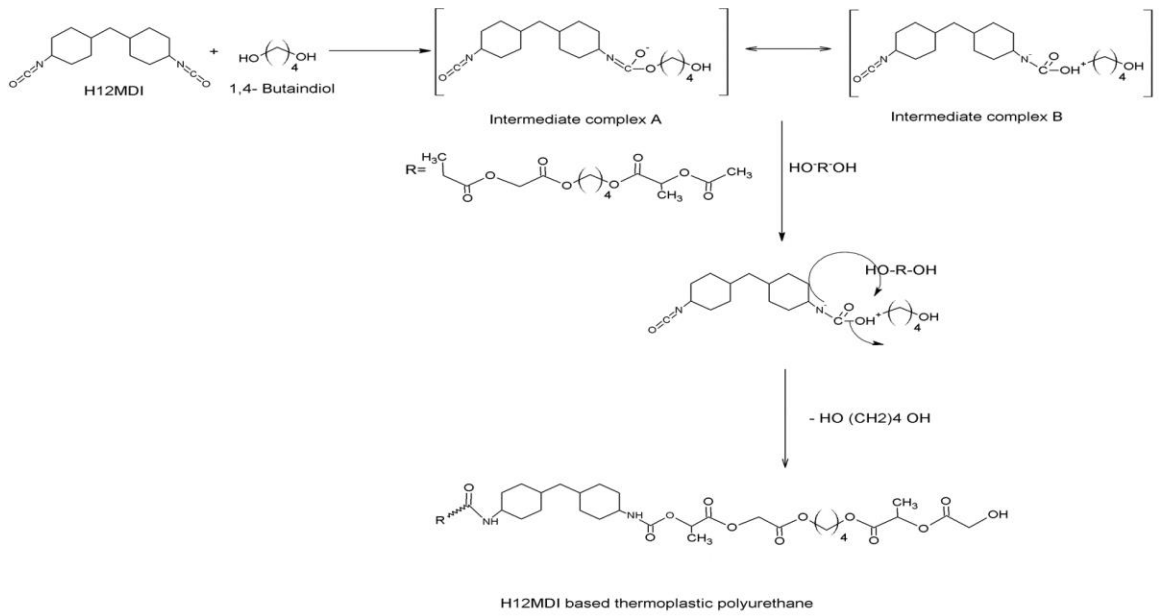

Figure 13: The mechanism of the synthesis of H12MDI based thermoplastic polyurethane TPU.

3.3.2 Synthesis of the TPU composites

TPU and 3%hydroxyapatite composite: A 2.27 g of polyurethane and a 0.4 g (15%) of hydroxyapatite were dissolved separately in DMF then mixed and placed in a vacuum oven overnight at around 50 ºC to get dry, and after six discs were made and stored in buffer solution for three months, after every two weeks, one disc discharged from the buffer solution, dried, and weighted and sent to analysis.

TPU and 15%hydroxyapatite composite: A 3.03 g of polyurethane and a 0.09 g (15%) of hydroxyapatite were dissolved separately in DMF then mixed and placed in a vacuum oven overnight at around 50 ºC to get dry, and after six discs were made and stored in buffer solution for three months, after every two weeks, one disc discharged from the buffer solution, dried, and weighted and sent to analysis.

Chapter 4: Results and Discussion

In this project, we used a mixture of two essential materials: thermoplastic polyurethane TPU and hydroxyapatite HA. Thermoplastic polyurethane is made by the reaction between the dicyclohexylmethane-4,4- diisocyanate (H12MDI) and a mixed polyol system consisting of 12% hard segment HS (refers to the amount of chain extender) and 2000g/mol 50PBA/50BD-PLGA (refers to the mol% and type of polyols) where the PLGA consists of 50:50 poly D, L-lactide co-glycolide PLGA.

Different properties and degradation characterization techniques took place on the synthesized TPU and its composites to detect the change in the properties and the degradation rate of the polymer and the composites in a buffer solution medium.

4.1 Fourier transform infrared FTIR spectroscopy

This test has been done on the produced thermoplastic polyurethane and its composites to ensure of the presence of a urethane bond that informs the formation of the polymer by confirming the chemical groups or linkages within a polymeric structure, along with the extent of hydrogen bonding, conformation, accessibility, and interaction between polyurethane's hard and soft segments. And comparing it with the spectra of H_{12}MDI for more confirmation.

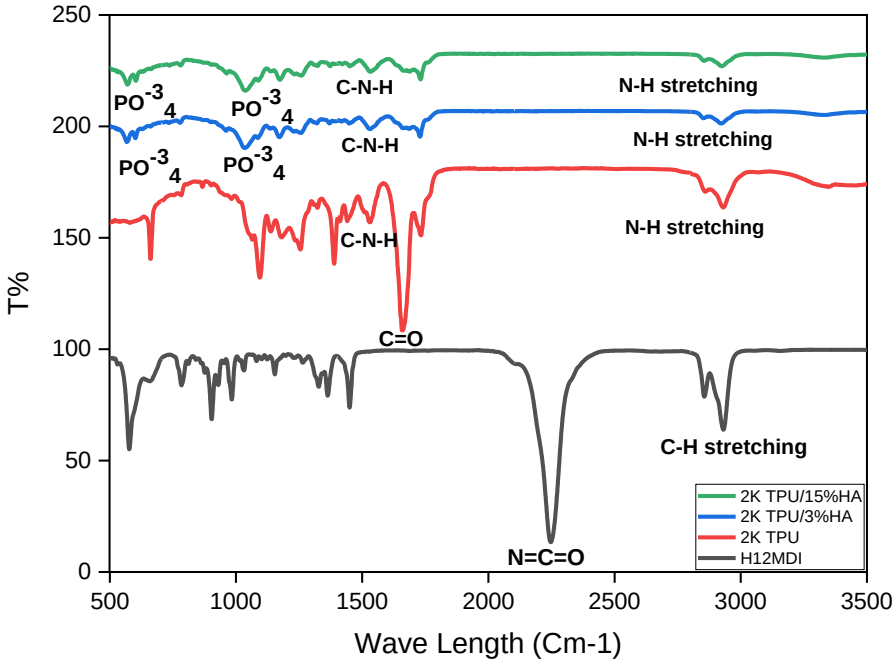

Figure 14: FTIR of the synthesized polymer and its composites in comparison with H12MDI.

The FTIR spectra confirm the creation of urethane linkages by observing the respective peak positions. The spectra of H12MDI exhibited a peak at 2245 cm^{-1}, a unique relation to the unreacted isocyanate group O=C=N. Additionally, C-H peaks showed around 2998 cm^{-1} related to the cyclohexyl rings. The isocyanate peak disappears with the formation of the polymer as a result of the reaction between the isocyanate group and the polyol and the formation of the urethane linkage(C-N-H).The urethane linkage peaks showed at the wavenumber ranged (1500-1531 cm^{-1}) in the TPU spectrum according to the study of Gabriel et al.[5].

2k TPU spectrum showed a peak around (1700- 1760 cm^{-1}) associated ester carbonyl (C=O) stretching of urethane carbonyl. Still, it is not clear in composites spectra, demonstrating that a chemical bond was formed between carboxyl groups (from polyurethane PU) and Ca2+ (from hydroxyapatite structure), so the C=O group is overwhelmed in the composite's spectrums. This peak indicates the formation of more hydrogen bonding, which could lead to strong interference and intermolecular

interactions[6].

Additionally, vibration peaks found at 3200- 3332 cm^{-1} related to the amide N-H stretching in urethane, indicating the formation of polyurethane polymer by the reaction between the isocyanate and the polyester. These last peaks are not present in the IR spectra of H_{12}MDI.

Additional PU peaks have been observed in 1448, 1385 and 1252 cm^{-1} belonging to the bending vibration of CH_3 or CH_2 groups. The peaks at 2920 and 2850 cm^{-1} are the asymmetric and symmetric vibrations of the CH_2 groups and mainly represent the hard and soft segments, respectively. The peaks found in the TPU and H12MDI spectra were compatible with the peaks found in the literature[4].

Bands at 961, 865, 601 and 561 cm^{-1} are allocated to the vibration of the phosphate group (PO_4), In addition to the carbonate ($CO3^{-2}$) group that forms weak peaks between 870 and 880 cm^{-1} and more intensive peaks between 1460 and 1530 cm^{-1} (in hydroxyapatite) that proved the presence of the filler in the composites according to the studies [7].

4.2 Nuclear magnetic C13 NMR resonance

This test was utilized to track isocyanate-to urethane conversion and to confirm the inclusion of polyol components.

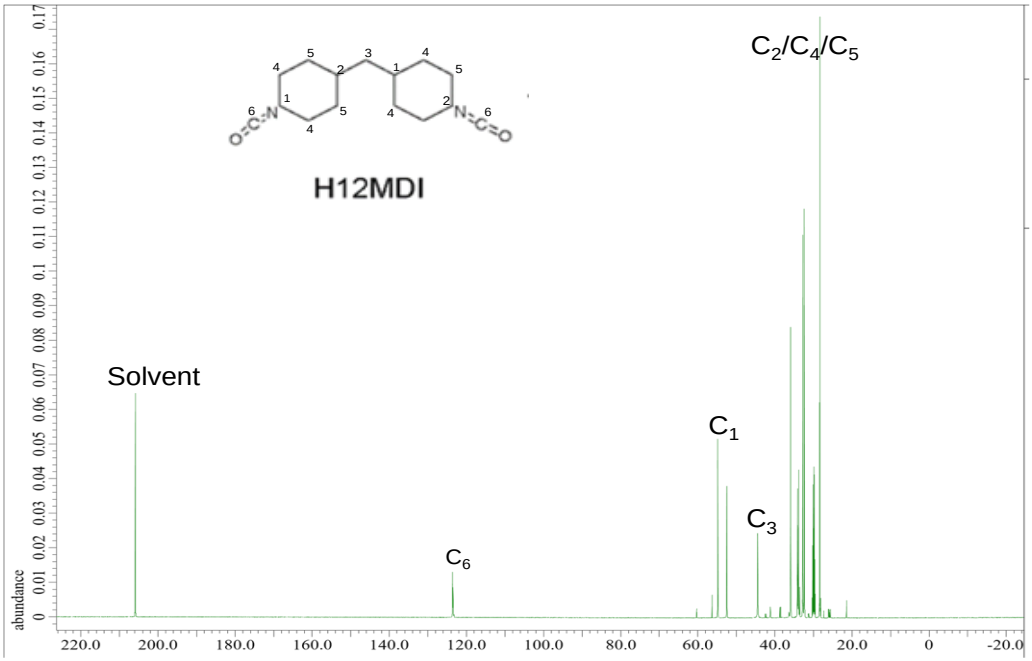

Figure 15: C13NMR of H12MDI

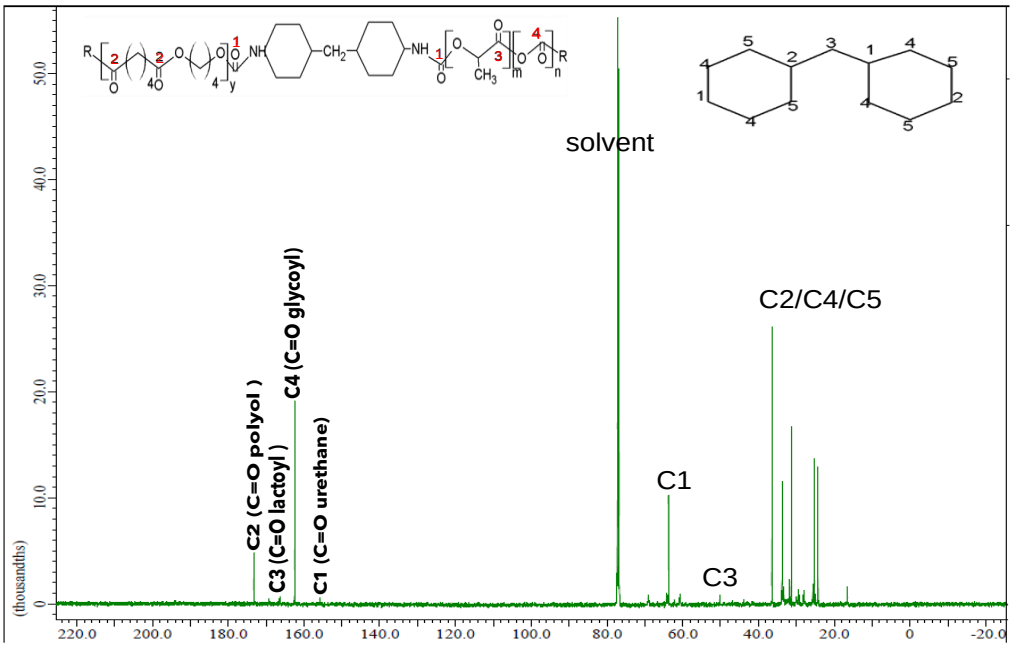

Figure 16: C^{13}NMR of H_{12}MDI based thermoplastic polyurethane.

The isocyanate carbon peak of H_{12}MDI is noticeable at 122.3 ppm (C6) as in Figure (16) and the other peaks represent each of the aliphatic cyclohexyl rings. Also, the solvent used in the NMR sample preparation is shown at a peak after 200 ppm.

The TPU spectrum (Figure 17) showed the extinction of the isocyanate peak

in addition to the creation of a urethane carbon peak at 157 ppm due to the chemical reaction between the isocyanate part and the OH group from 1,4 butanediol (as catalyst) and later with the polyol (as the chain extender) that proved the formation of the synthesized polymer. The carbonyl carbons of the two polyols, butylene adipate at 173.1 ppm (C2), and the PLGA lactoyl units at 169.1 ppm (C3) and the glycoyl units at 166.3 ppm(C4). A significant peak at around 78 ppm represents the solvent used in the test sample preparation. All the peaks of interest for the polymer and the composites are in agreement with the literature mentioning polyester polyurethane. The change in other works will be depending upon the isocyanate and polyol type.[8, 9]

4.3 Microscopic images

A morphological investigation of the pure polyurethane and the composites was carried out using an optical microscope for the qualitative evaluation of the samples tested to assess the adhesion between the polymer and the filler. Pure TPU gave a clear surface under an optical microscope, while after the inclusion of the hydroxyapatite on its surface, a uniform distribution was observed according to the study of Mutua et al. [10].Spherical and oval-shaped hydroxyapatite particles well adhere to the surface with different sizes. Increasing the concentration of the filler with 15% is quite clear and uniform.

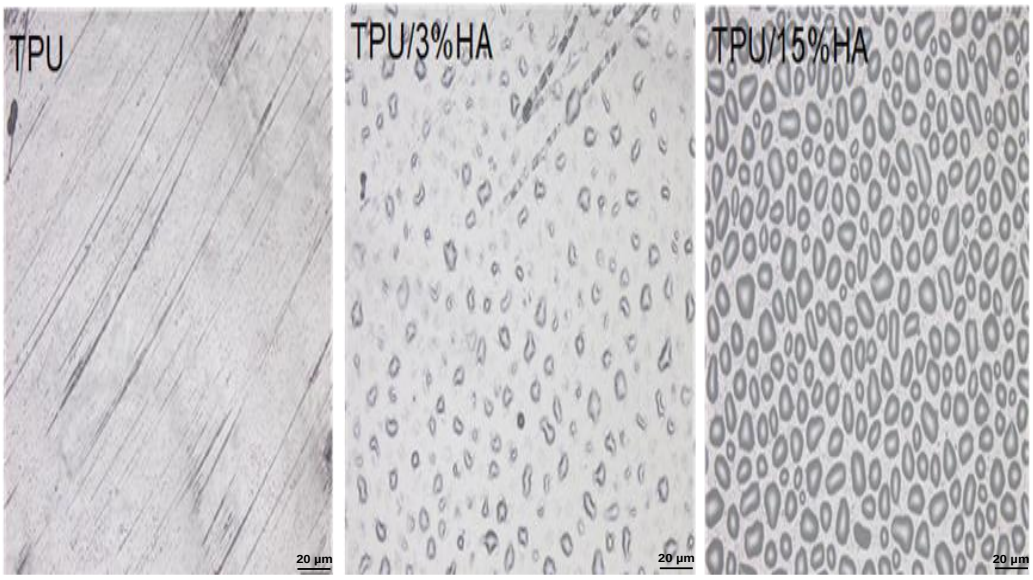

Figure 17: Optical microscopic images of the synthesized TPU and its composites.

4.4 In vitro degradation

In vitro degradation analyses of the samples have been carried out. Discs (1.5 mm thickness) were submerged in 5 mL phosphate buffer saline (PBS, 0.05 M, pH 7.0). At every two weeks, one disc was removed and dried. The weight of the samples before and after incubation was measured with digital balance. And mass remaining calculated. The weight loss of the film samples versus degradation time for the polymer and its composites showed in figure 18.

The 2K-TPU showed a significant decrease in mass during the first two months, around 30% of its weight (this is in agreement to the literature)[4] compared to its composites which showed an only minor decrease. Weight loss can be caused by hydrolysis of ester linkages, followed by the subsequent reduction of molecular weight, to result in water-soluble oligomeric and/or monomeric products. As found from the SEM and XRD tests, the polymer is semi-crystalline with less crystallinity index than the composites, and its more porous, which will make the permeation of buffer into the polymer easier than in the composites. And as we saw how the filler increases the crystallinity degree (crystallinity index from XRD), which reflects on

the strength and materials resistance and adds some obstacles that decrease the flexibility of the polymer main chain, reducing the probability of chemical bonds cleavage, and thus slowed the degradation rate.

Both composites showed an increase at the beginning before the degradation started to decrease. This is because of the solvent residues found in the material from preparation which disappears with incubation.

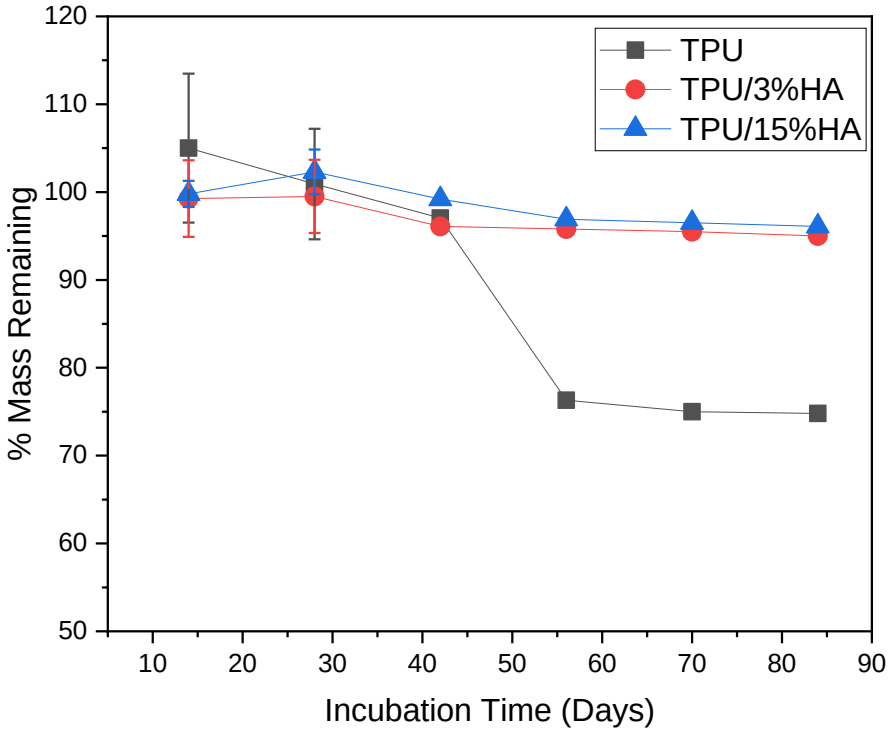

Figure 18: Remaining mass % of the synthesized thermoplastic polyurethane and its composites vs. the incubation time in the buffer.

4.5 Scanning electron microscopy SEM

EDS and SEM were utilized on each disc after every two weeks of incubation in the buffer to investigate the morphological characteristics of the polyurethane and its composites.

The SEM images below (Figure 23) presented the synthesized pure polymer and its composites after reinforcing the polymer with 3 and 15 % hydroxyapatite, respectively. The images have shown that the polyurethane consists of a distribution of high and interconnected pores. The pores range in size from µm to nm. In comparison, the images of the composites showed heterogeneous porous structures with polyangular pores. Our findings were similar to other studies that noted that hydroxyapatite particles were adhered to pores walls because without a completely homogenous distribution. In addition, the surface of these porous bio-composites is rough, and this can help promote cellular adhesion and induce new bone formation[11-13].

EDS results gave the element mapping for the pure polymer and the composites. The EDS of the pure polymer (Figure 24) presented the exitance of C and O, the main components of the polymer. While the EDS results of the composites (Figures 25 and 26) indicated hydroxyapatite formation and incorporation by showing the existence of P, Ca and K peaks which became more intense with increasing the filler concentration, and which confirms that the composites contained hydroxyapatite in the form of calcium and phosphorus atoms in the TPU matrix[5]. Figure (27) showed the change in the surface texture with increasing the content of the filler, the porosity and pore average size decreased. This change in the size of the pores with the addition of the filler can be because of the chemical bond that formed between carboxyl groups (from polyurethane PU) and Ca^{2+} (from HA structure).

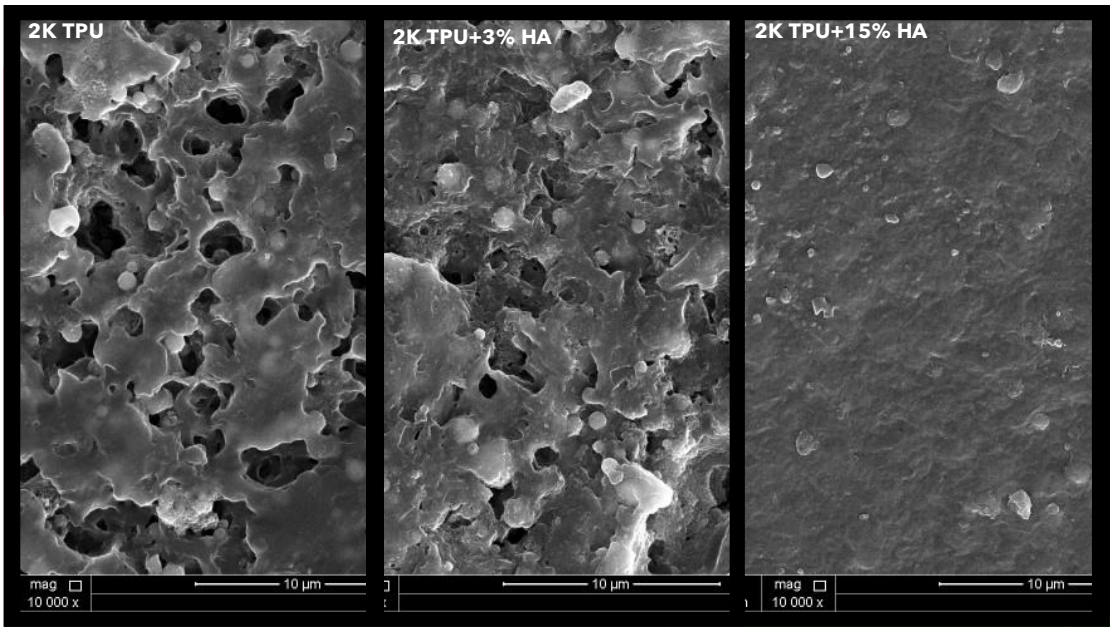

Figure 19: SEM images of synthesized TPU reinforced with three and 15%hydroxyapatite before incubation.

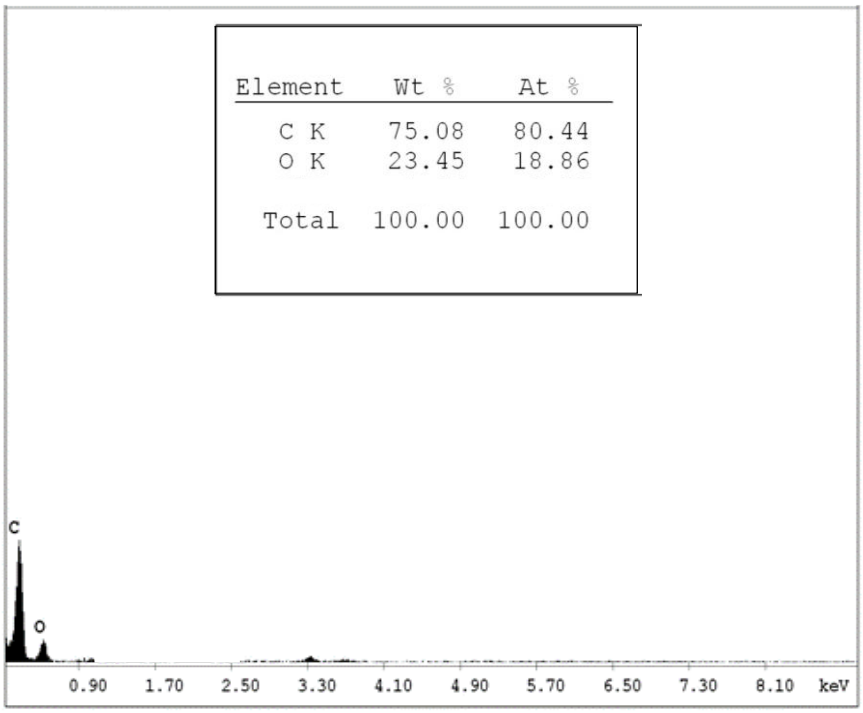

Figure 20: EDS of the thermoplastic polyurethane.

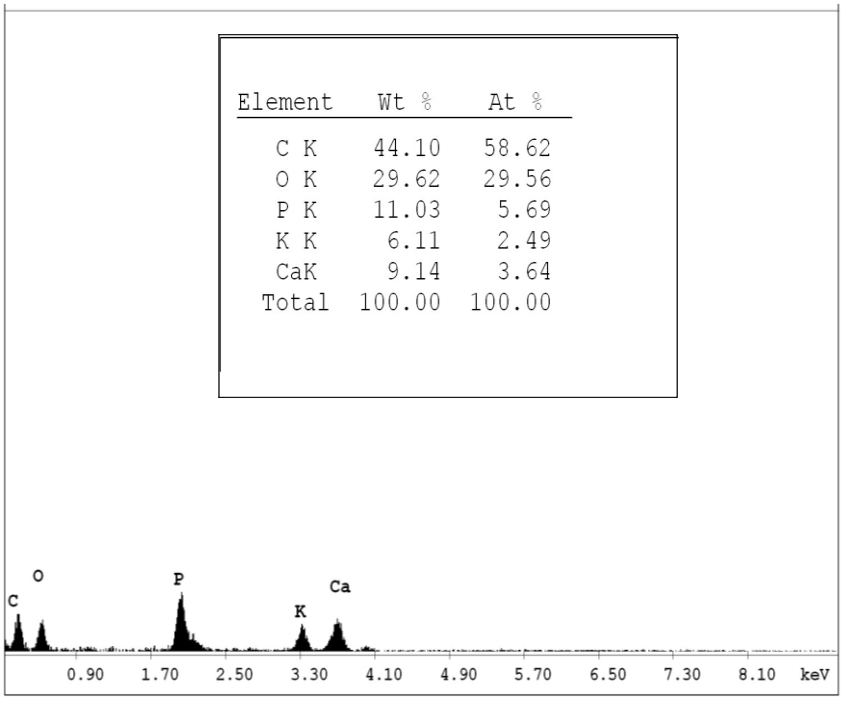

Figure 21:EDS of thermoplastic polyurethane/3%hydroxyapatite composite.

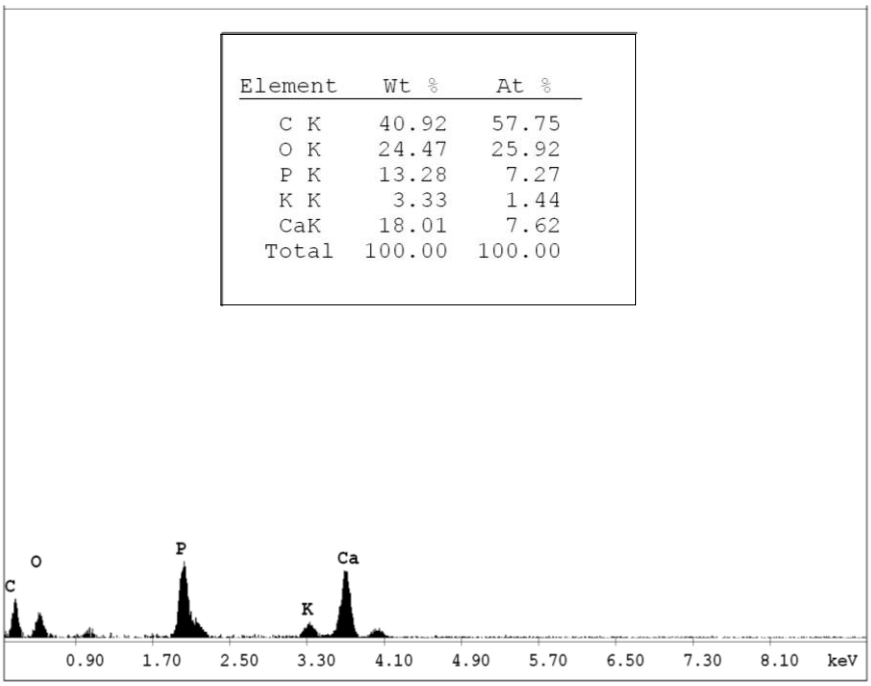

Figure 22:EDS of thermoplastic polyurethane/15% hydroxyapatite composite.

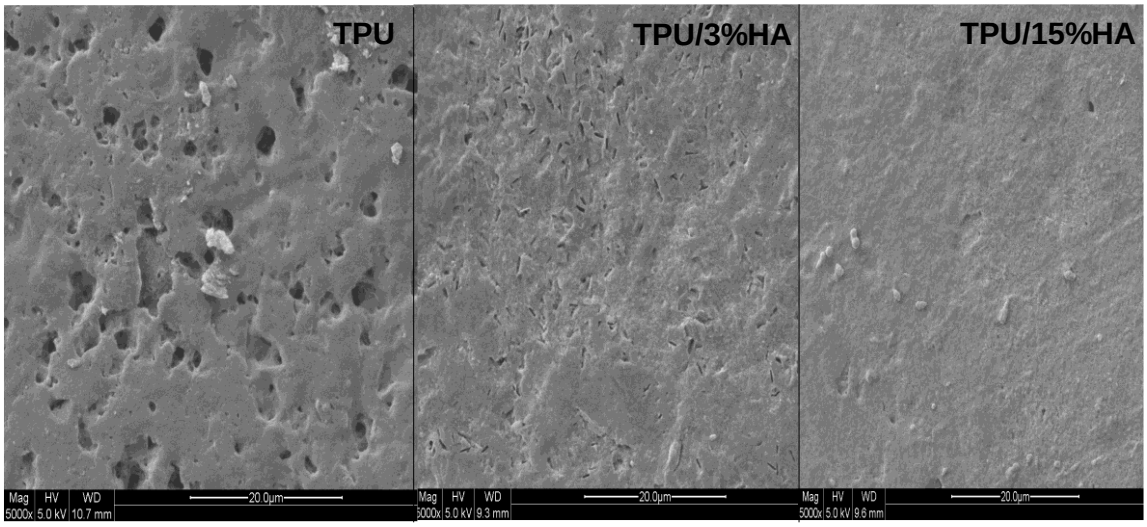

Figure 23: SEM of thermoplastic polyurethane and its composites showed changes in pores size and surface texture with incubation.

4.6 DSC (differential scanning calorimetry)

DSC analysis has been done on the discs of synthesized TPU and its

composites before incubation in buffer, after 45 days and after 90 days. In order to follow the change in the thermal characteristics of the materials and to know the extent of degradation.

The DSC curves of the synthesized TPU and its composites showed a peak in the first heating run, which is the melting peak and no peak during the cooling run. We might think that the polymer is amorphous, but A small step is found in the curves that represent the glass transition temperature. This indicates that the polymer has some degree of crystallinity (supported by the XRD diagram and the crystallization index %), so it takes too much time for recrystallization to happen. Also, we can find that the melting points of the composites are higher compared to the pure polymer. This can be an indication of increasing the strength or the material resistance to heat in the presence of the filler, and it makes sense as the filler increased the degree of crystallinity of the pure polymer as found from XRD. Figure (28) showed that the melting point of the pure polymer increased after 45 days of incubation as well as the melting point for the composite Figures (29 and 30). This is because the pure polymer is semi-crystalline and porous as we got from the SEM and DSC which will help the permeation of the buffer easily inside the polymer while the melting point for the composite increases with incubation because hydroxyapatite has higher melting point than the polymer so with incubation, the polymer start to degrade first and that filler left , so the melting point increases to reach the melting point of the filler or maybe because this is the time needed to the polymer and the composites to be fully penetrated by the buffer .After 90 days of incubation, the melting point for the composites started to decrease as the materials were now saturated with buffer , and the degradation started to take place in a higher manner. As for the pure polymer, it was increased a little bit because the polymer has more pores than the composites and

needs more time before the buffer fully penetrates it.

Regarding the broad peaks showed for the pure polymer and its composites with incubation time, this is related to the hard segment (C=ONH) that indicates the polyurethane formation. These two parts (the carbonyl CO and the NH) were mixed by a hydrogen bond and formed an interaction (reinforcement). This interaction is found before incubation as it's a significant part that represents the polyurethane. Still, it but it became stronger and more significant with incubation time and that is why the melting point increased as well with incubation time.

We might notice that this broad peak is clear more in the pure polymer diagram as the hard segment part in the composites will be in a chemical bonding with the hydroxyapatite, and this might overwhelm the effect of the hard segment and make the broad peak not that much obvious for the composite compared to the polymer, but the effect is still there.

The Tg found to be increased with the addition of the filler, which makes sense as the filler increases the crystallinity of the pure polymer (Tg=34.1ºC for TPU ,37.7ºC for 3%HA composite and 36.7ºC for 15%HA composite). The introduction of crystallinity into a polymer system not only increases the breadth and measured position of the glass transition temperature but has also been shown to reduce the enthalpy. It was found in the literature that the enthalpy of the semi-crystalline polymer was found to be considerably lower than that of its fully amorphous counterpart. Although a reduction in enthalpy may be expected due to a reduced amorphous content and the segmental mobility by increasing the crystallinity. [14, 15].

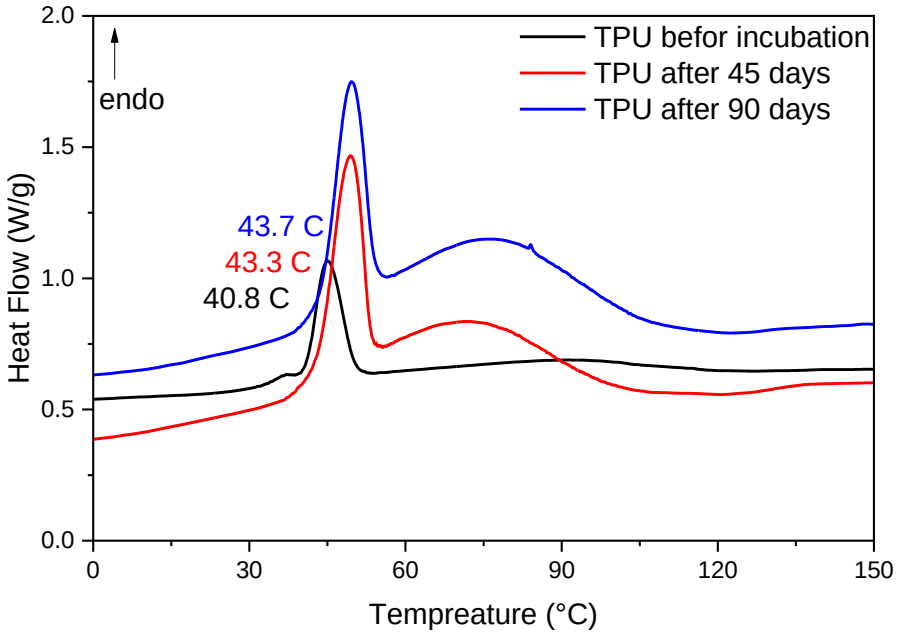

Figure 24:DSC of thermoplastic polyurethane.

Table 2:DSC charactrization of thermoplastic polyurethane.

sample	Onset Temperature (°C)	Peak Temperature (°C)	Enthalpy (J/g)
TPU before incubation	40.8	45.1	17.57
TPU after 45 days	43.3	49.4	23.31
TPU after 90 days	43.7	49.3	31.2

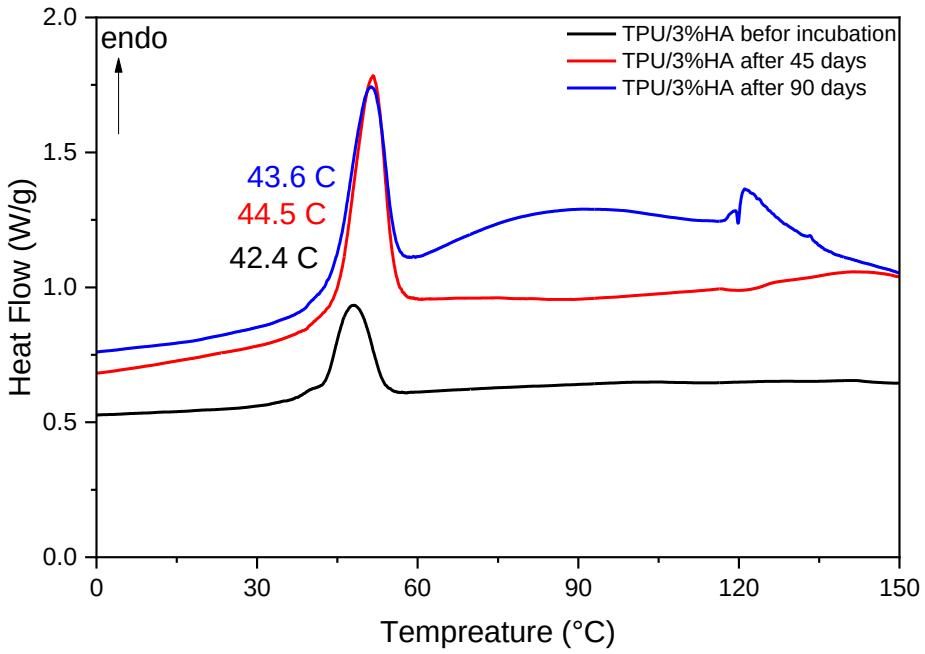

Figure 25: DSC of thermoplastic TPU /3% hydroxyapatite composite .

Table 3: DSC charactrization of thermoplastic polyurethane/ 3%hydroxyapatite composite.

sample	Onset Temperature (°C)	Peak Temperature (°C)	Enthalpy (J/g)
TPU/3%HA before incubation	42.4	48.1	16.69
TPU/3%HA after 45 days	44.5	50.9	22.48
TPU/3%HA after 90 days	43.6	50.6	23.62

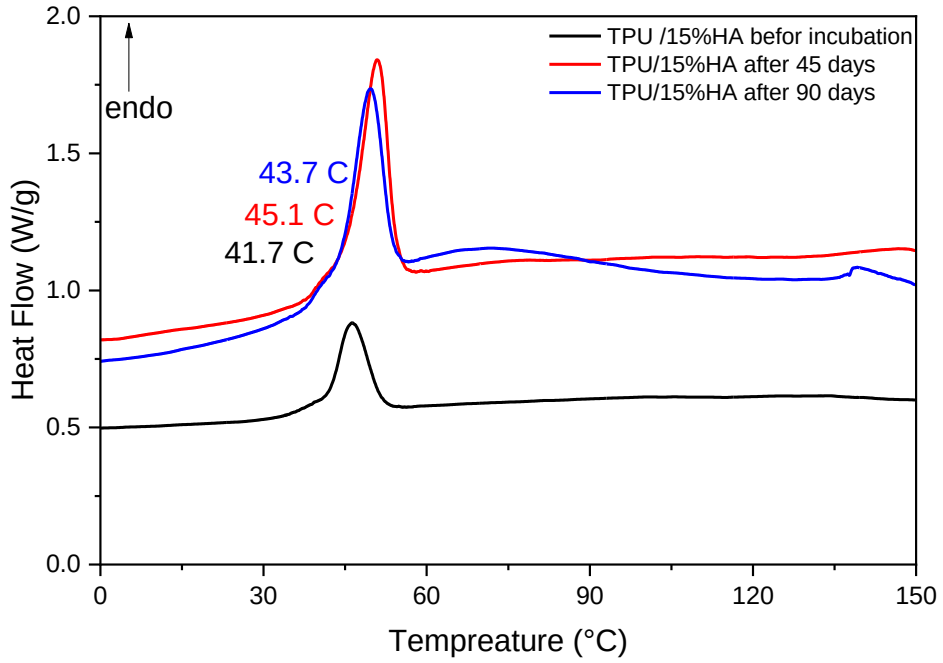

Figure 26:DSC of thermoplastic polyurethane/15% hydroxyapatite composite.

Table 4: DSC charactrization of thermoplastic polyurethane/ 3%hydroxyapatite composite.

Sample	Onset Temperature (°C)	Peak Temperature (°C)	Enthalpy (J/g)
TPU/15%HA befor incubation	41.7	46.4	14.51
TPU/15%HA after 45 days	45.1	50.7	17.31
TPU/15%HA after 90 days	43.7	49.4	23.63

4.7 Thermogravimetric analysis TGA

The thermal behavior of the synthesized TPU and its composites can be detected through the TGA analysis. TGA thermograms of the nanocomposites have been seen to move toward higher starting decomposition temperatures compared to neat polymer[16], indicating the enhanced thermal stability of the system by the presence of

the filler. This might have been because the hydroxyapatite nanoparticles had better thermal stability when compared with the thermoplastic polyurethane TPU matrix. Therefore, effectively prevent the heat transfer into the TPU matrix. Such behavior can be related hydrogen bonding interactions between amide groups of TPU and the hydroxyl groups of the filler.

The first drop that happened in the curves of the pure polymer and its composites before incubation is because of the solvent utilized in the synthesis of the discs, this solvent is removed in buffer. This is why we noticed a more stable curve with incubation time, and which was also reflected in the starting decomposition temperature for the pure polymer and its composites and made it increase, which demonstrated more stability.

Figure (31) showed that the pure polymer has two stages of weight loss, the first one within range of (200- 370) ºC which is assigned to the scission and depolymerization of soft segments (polyols)[17]. The maximum decomposition temperature in this step is 354 ºC for neat polymer.

The second step ranges from (380 to 450) ºC, where TPU degradation is associated to the breakage of urethane bonds (soft segments) that dissociate into primary amines, or olefins and carbon dioxide[18]. The maximum decomposition temperature in this step is 453.78 ºC for pure polymer.

This behavior matched the trend found in the literature that mentioned that the polymer has two- stages of weight loss. In comparison, the composite has one stage at a temperatures higher than that where polymer decomposition or melting starts could be because of PU and HAP interactions and formation of composites[19].

The remaining weight % for the pure polymer ,3%, and 15% hydroxyapatite composites before incubation are 0%, 3% and 15%, respectively, as the filler used is

an inorganic material that needs very high temperature to decompose, and it will not be dangerous inside the human body as hydroxyapatite is a major component of the bone.

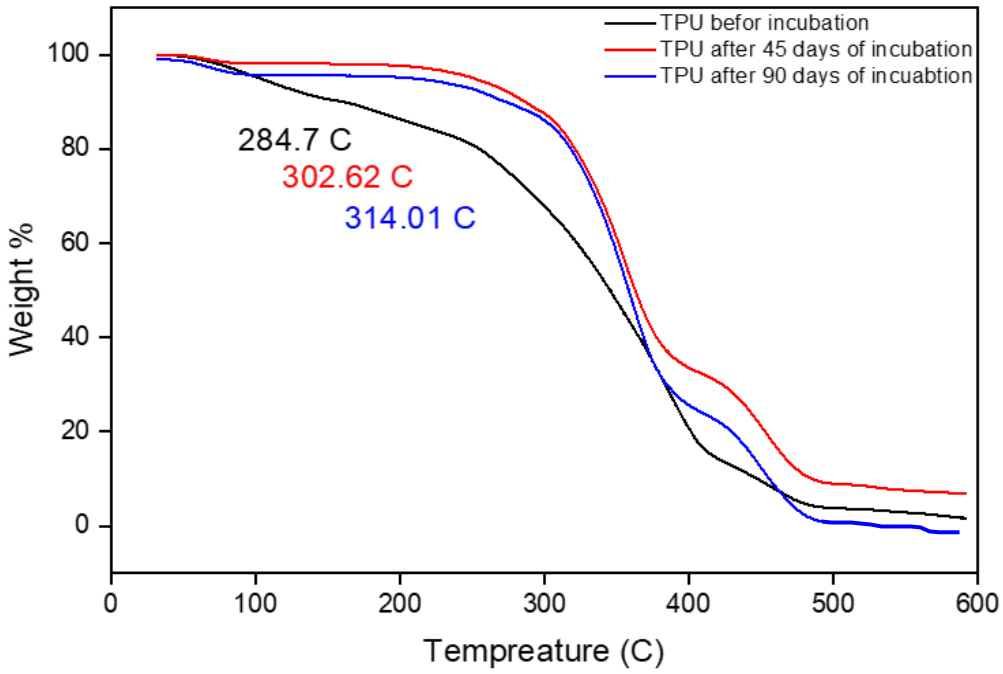

Figure 27:TGA of pure thermoplastic polyurethane.

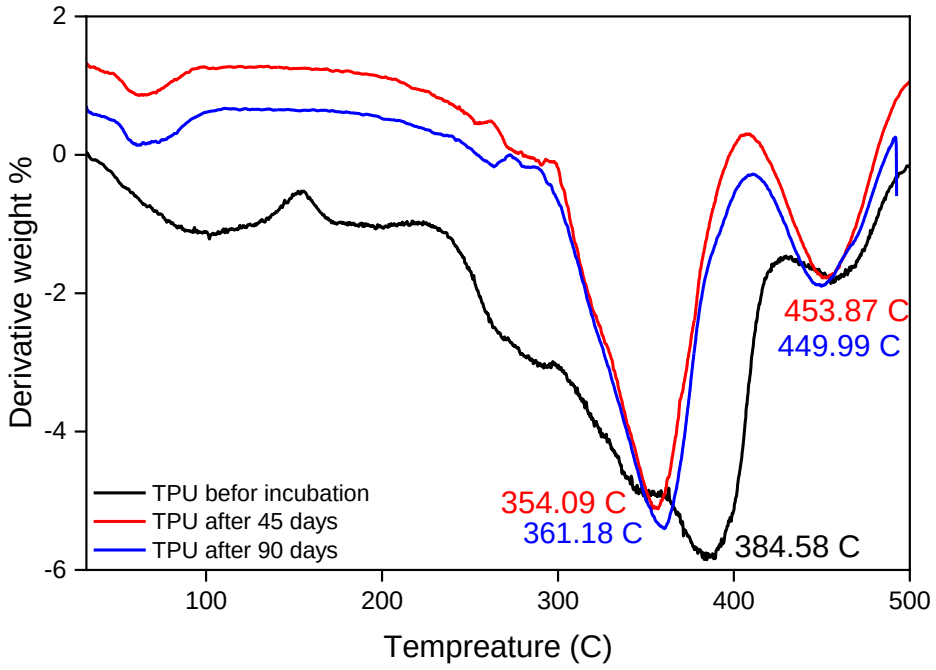

Figure 28: TGA of the derivative weight % of pure thermoplastic polyurethane .

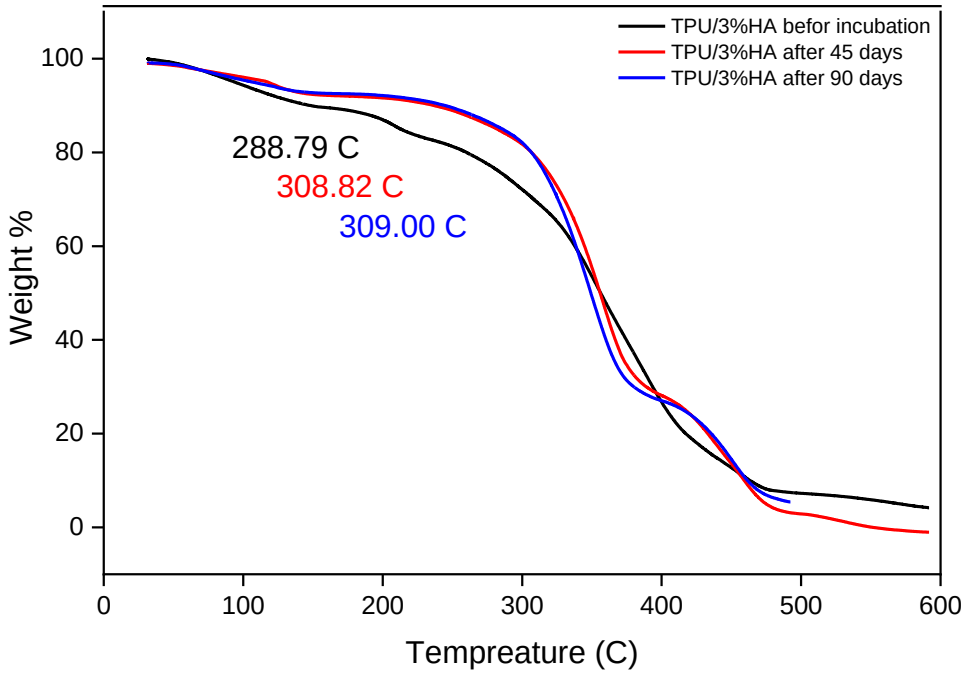

Figure 29: TGA of thermoplastic polyurehtane/3%hydroxyapatite composite.

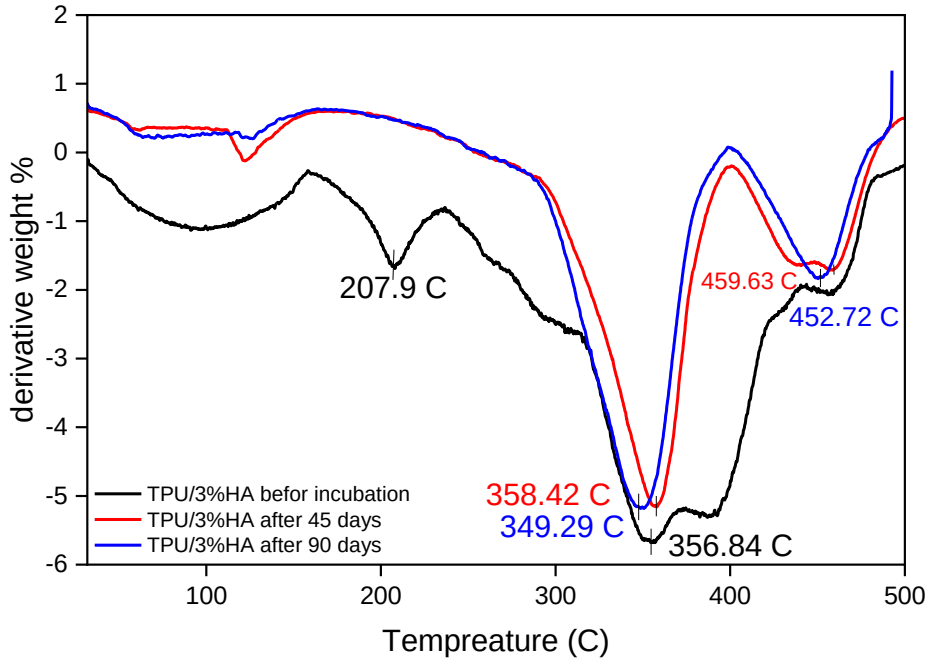

Figure 30: TGA of the derivative weight % of thermoplastic polyurethane/3%hydroxyapatite composite.

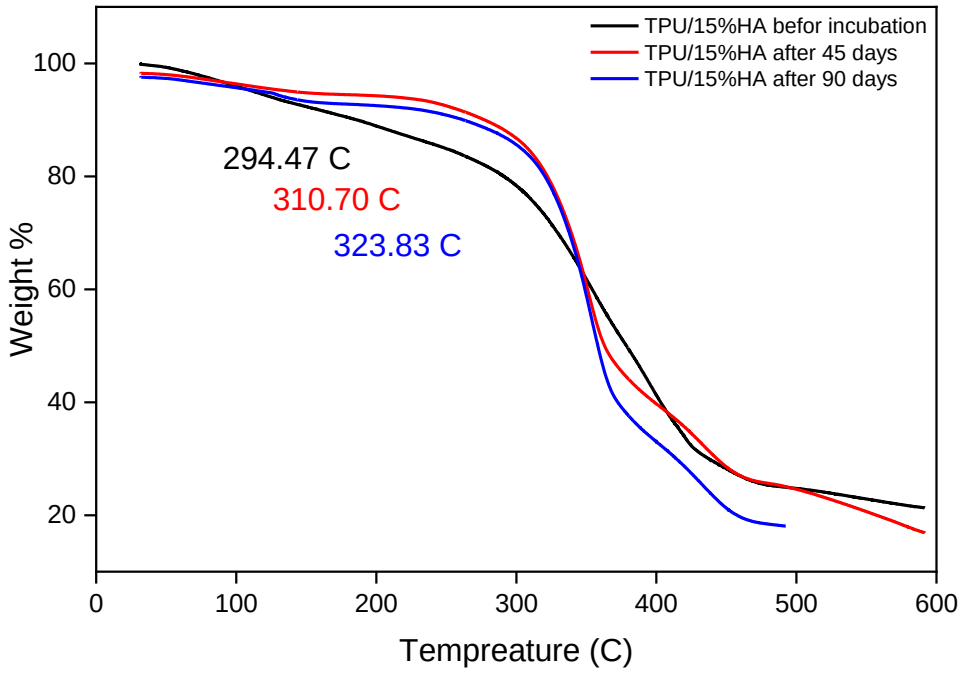

Figure 31: TGA of thermoplastic polyurethane /15% hydroxyapatite composite.

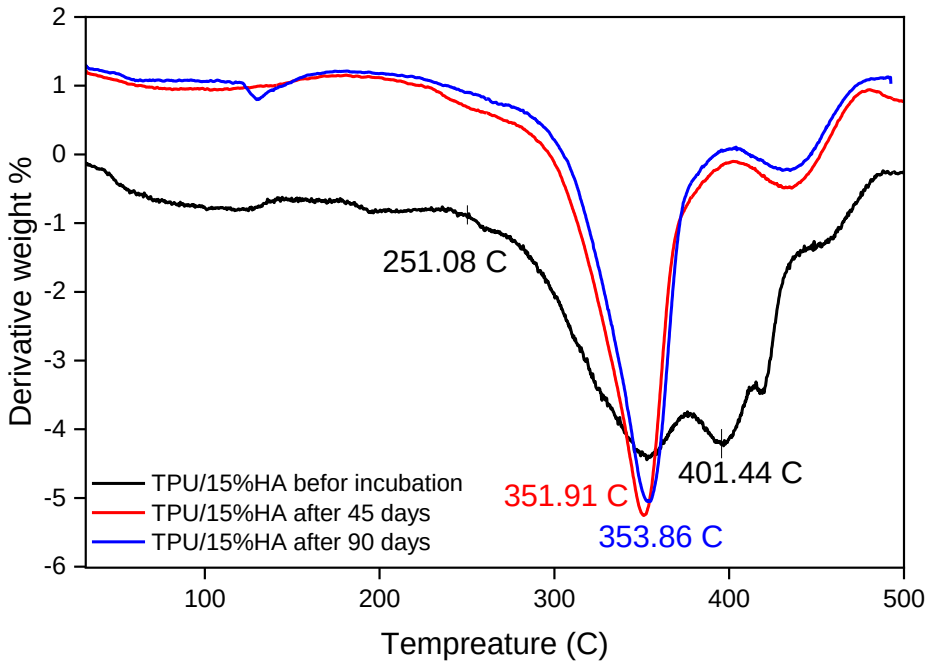

Figure 32:TGA of deivative thermoplastic polyurethane/15%hydroxyapatite composite.

Table 5:Thermal properties of the synthesized polymer and its composites before incubation, after 45 days, and after 90 days.

Sample Decomposition temperature	2K-TPU	2K TPU/3% HA	2K TPU/15% HA
Before incubation	284.7	288.79	294.47
After 45 days	302.62	308.82	310.70
After 90 days	314.01	309.00	323.83

4.8 X-ray diffraction (XRD)

The X-ray diffraction (XRD) tests have been done on the pure polymer and its composites to check the crystallinity of the materials and support the results from the other tests.

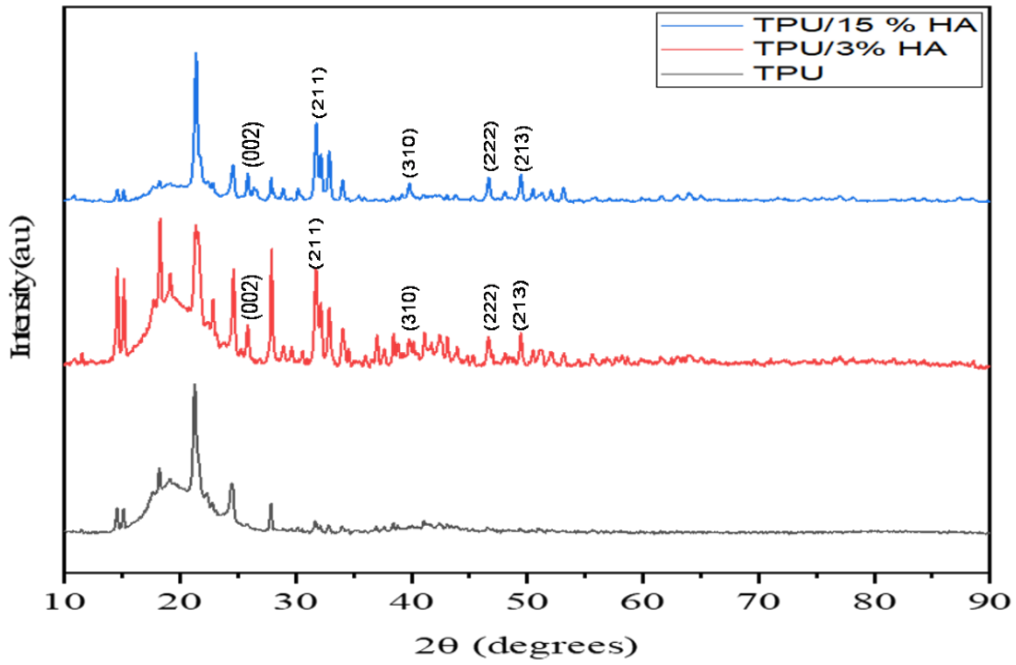

Figure 33: XRD diffractogram of the thermoplastic polyurethane and its composites.

For the TPU, a broad diffraction peak ranging from 15 to 25 was seen. This shows that the TPU matrix contained not just the disordered structure of the amorphous phase but also the short-range regularly ordered structures of the soft and hard segments. This is in agreement with the literature[20]. Also, the Tg observed from the DSC figures indicate the presence of some degree of crystallinity in the materials; however, it's not very strong as the polymer has very low crystallinity compared to the amorphous parts, so it can be called a semicrystalline polymer.

From the calculations of the crystallinity index, it was found to be around 56% (for the pure polymer), 75%(TPU/3%HA), and 84% (TPU/15%HA). This is an indication of increasing the crystallinity of the polymer with the addition of the filler, which will make the material stronger and will reflect on the degradation rate as we mentioned earlier from the in-vitro degradation analysis where the polymer has the highest degradation rate compared to the composited as it has the lowest degree of crystallinity. The additional crystalline peaks showed in the diagram of the composites with 2θ values of 25.80, 31.63, 39.41, 46.68 and 49.28 degrees, respectively, related

to the (002), (211), (310), (222), and (213) planes of HA. This is an additional confirmation that the nano hydroxyapatite particles were successfully introduced into the TPU matrix[21, 22].

Conclusion

We designed and manufactured a porous system based on elastomer polyurethane, for potential use in pediatric facial fractures. The effect of the hydroxyapatite addition on the thermal, morphological and degradation characteristics of the thermoplastic polyurethane has been investigated. The proposed biodegradable polymer and the composites have showed improvement of thermal properties and were able to undergo hydrolytic degradation in buffer solution. The use of completely aliphatic reagents minimized the potential for toxic degradation byproducts making it a prospective replacement for the commercially available brands.

Further studies are needed for the proposed system, including animals and biological studies. Also, utilizing different polyester types with different molecular weights to prepare thermoplastic polyurethane to follow the change in the degradation rate and the thermal properties. Furthermore, the proposed system can be prepared in different forms like fibers and used in other important applications such as bone graft tendon application.

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