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Conception and Evaluation of Biodegradable Implant Rod for Drug Delivery

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Abstract

Polymer implants are an exciting new development in the field of drug delivery systems. Because of their surface and bulk qualities, biodegradable polymers are often used. In the current investigation, a biodegradable implant in the form of a rod was manufactured by the use of a hot melt extrusion process, with PLGA and ethyl acetate serving as the plasticizer. Research was studied on the PLGA/EA rods' deterioration in vitro. At various time intervals, the rods' weight reductions were measured and studied. The techniques of DSC, TGA, and FTIR were used in order to characterize the rods. In order to determine the rod's capability for encapsulating drugs, a drug was first integrated into the rod. The amount of drug in rodents was determined by the use of the UV spectrophotometer method.

Keywords: Drug Delivery, Biodegradable Implant Rod, PLGA, Ethyl Acetate.

Introduction

When biodegradable materials are broken down, they create compounds that are biocompatible [1]. These materials might have a natural or synthetic origin. Because the carbon backbones of biodegradable polymers are so robust and difficult to fracture, the breakdown process often begins with the end group [2]. Using the hot melt extrusion process, drug-incorporated biocompatible implant rods may be produced using the biodegradable polymer PLGA [poly (DL-lactide-co-glycolide)]. [3] Hot melt extrusion (HME) is a procedure that is used to create polymer products that have a consistent density and shape. This process utilizes pressure and heat to melt a polymer and other material in a continuous process [4]. The instrument is comprised of a barrel that can maintain a certain temperature and has one to two moving screws. The material will be conveyed through the barrel as the screws move, which will result in the melting and mixing of the ingredients that are put into the extruder [5].

It has been suggested that biodegradable implants might be implanted within the body with the purpose of delivering a steady dose of drug over an extended period of time. Because the drug is incorporated into biodegradable polymers, the dosage form will continue to release the drug over a prolonged period of time. Additionally, the dosage form may be manufactured in a wide range of sizes and forms [6].

Poly Glycolic Acid (PGA) and poly Lactic Acid (PLA) as well as their copolymers, such as PLGA, are examples of the synthetic biodegradable polymers that find the most widespread use and are members of the polyester family. As a kind of polymer, PLGA was used here. Poly (lactide-co-glycolide), often known as PLGA, is an aliphatic polyester that is biodegradable. It has garnered a lot of attention due to the fact that it has good biodegradability, biocompatibility, nontoxicity, and mechanical strength [7].

Materials and Methods

Poly (D, L-lactide-co-glycolide), ethyl acetate, and a drug(X), which is confidential, are all substances that are utilized as selective estrogen receptor modulators.

Preparation of PLGA Rod

Extruding PLGA with varying concentrations of an additive ethyl acetate (table.1) results in PLGA polymer being given a plasticizing effect, which is necessary for the production of PLGA rods via the Hot- Melt film extrusion process.

Table 1.Different concentrations of ethyl acetate

Additive	Concentration (%)						
Ethyl acetate(EA)	3.5	4.0	4.5	5.0	5.5	6.0	6.5

Incorporation of Drug into the Rods

The biocompatible PLGA/Ethyl acetate rods that were manufactured were intended for use in an advanced model of an ideal controlled drug delivery system. The drug (X) was injected into the PLGA rod using the hot melt extrusion method with varying concentrations of the drug (table 2) as outlined in the following paragraphs.

Table 2.Different composition of drug in percentage

Trial No	Percentage of drug (%)	Amount of drug (g)	Amount of PLGA (g)
T01	10	1.0	4.5
T02	15	0.75	4.25
T03	20	0.5	4
T04	25	1.25	3.75
PLGA/ EA rod	-	-	4.75

Characterization of PLGA Rod

The IR spectra of PLGA/EA rod are compared with the IR spectra of PLGA polymer, and the IR spectra of drug-incorporated rods are investigated using a Thermo scientific instrument with the model number Thermo Nicolet 5700, 32 in the region of 400-4000 cm^{-1}. Using a ramp rate of 10 degrees Celsius per minute, differential scanning calorimetric thermograms were obtained for PLGA rod at temperatures ranging from -20 degrees Celsius to 100 degrees Celsius. The

instruments used were made by TA Instruments. TGA was performed on PLGA polymer and PLGA rods using a Perkin Elmer, Model: TGA 4000, in order to determine the thermal stability of the samples, the maximum temperature at which the materials degraded, and the change in mass with increasing temperature.

Determination of % Drug Content in PLGA Rods

Using methanol as a solvent, the Shimadzu UV-1700 UV Spectrophotometer has been used for the purpose of determining the amount of drug present in both its pure and dose forms.

In Vitro Degradation Study of PLGA/EA Rod

For in vitro degradation experiments, phosphate buffer saline (PBS) solution with a pH of 7.5 and a temperature of 37 degrees Celsius is utilized.

Preparation of Phosphate Buffer Saline (PBS)

Mix together 500 milliliters of distilled water, 1.44 grams of sodium phosphate dibasic, 8 grams of sodium phosphate, 0.25 grams of potassium chloride, and once the mixture is well combined, 0.24 grams of potassium dihydrogen orthophosphate. To a total amount of 1 liter, add water that has been distilled. Two PLGA/Ethyl Acetate rods each measuring one centimeter in length were submerged in two milliliters of phosphate buffer saline. The sample was stored for up to 15 days in a water bath shaker that was maintained at 37 degrees Celsius. The sample was weighed in order to determine the original mass of the rod before it was placed in the degradation medium (W0). For each time period, we evaluated two comparable samples taken from this material in parallel.

After wiping the surface of the chosen samples lightly, their wet weight (Wwet) was measured after they were taken from the buffer solution at each time point.

After that, the samples that were surface dried should undergo a second drying process by being baked in an oven at 60 degrees Celsius for two hours. After that, the weight of the samples after they had been dried out was weighed (Wt). Every single analysis was performed using a pair of eyes. The following equation may be used to determine water consumption as well as weight loss.

Water Absorption

The equation that was used to determine the amount of water calculated in at each time is as follows:

The formula for calculating water absorption is as follows:

(%) Water uptake = [(Wwet -Wt) /Wt] × 100

W wet and Wt are the weight of the polymer sample recovered from PBS and the final constant weight after drying.

Mass Loss

The loss of mass lost was calculated by applying the following equation to the data:

(%) The formula for calculating mass loss is as follows:

(%) Mass loss = [(W0 - Wt) /W0] × 100

W0 and Wt are the initial mass is the final dry mass, respectively.

Result and Discussions

Preparation of Plga /Ea Rod

Hot Melt Extrusion

The results of the various tests that were carried out to determine whether or not the PLGA/EA rod could be produced via hot melt extrusion are presented in Table: Using the hot melt extrusion rod, three PLGA rods with EA concentrations of 3.5% and 4% were produced. The nature of these rods was brittle, and those with EA concentrations exceeding 6% were observed to be drooping or falling. It was discovered that PLGA rod made with an EA concentration of 5% results in a material that is flexible, has high folding endurance, and is stable.

Table 3.Experiments performed to produce PLGA rod using the hot melt extrusion preparation

Sample code	Concentration of EA (%)	Mass of PLGA(g)	Volume of EA (ml)	Rod stability	Diameter(mm)
PLGA-E-3.5	3.5	4.825	0.195	Brittle	0.50-0.61
PLGA-E-4	4.0	4.778	0.222	Brittle	0.50-0.60
PLGA-E-4.5	4.5	4.775	0.250	Flexible	0.72-0.80
PLGA-E-5	5.0	4.750	0.278	Flexible	0.80-1.5
PLGA-E-5.5	5.5	4.720	0.306	Flexible	0.85-0.93
PLGA-E-6	6.0	4.700	0.334	Sagging	0.87-0.96
PLGA-E-6.5	6.5	4.670	0.362	Sagging	0.87-0.96

Because of its ideal flexible nature and thickness, PLGA E-5 was incorporated for drug incorporation studies and subsequent drug incorporation studies. This was due to the fact that PLGA E-5.

Incorporation of Drug into the Rods

Table 4.Appearance and diameter of selected rods

Sample code	Appearance	Diameter (mm)
T01	Rod that is flexible and the colour of a yellowish white.	0.92-1.30
T02	Rod that is flexible and the colour of a yellowish white.	1.05-1.40
T03	Rod that is flexible and the colour of a yellowish white.	1.15-1.35
T04	Rod that is flexible and the colour of a yellowish white.	0.95-1.05
PLGA/ EA rod	Flexible with transparent rod	0.85-1.40

Characterisation of PLGA Rod

Fourier Transform Infrared Spectrometry (FTIR)

The infrared spectra of individual functional groups of PLGA polymer and PLGA rod both reveal molecular vibrations of functional groups, as described in Table 5 and Figure 1. Both spectra show carbonyl stretching at a frequency of around 1,745 cm^{-1}. This is a representation of the carbonyl groups that are included inside the monomer units. The existence of an ester group may be deduced from the observation of C-O stretching bands in the area that spans 1,079-1,451 cm^{-1}. The fact that the PLGA polymer and PLGA rod both had comparable absorption peaks was further evidence that the production process did not affect the polymer's properties.

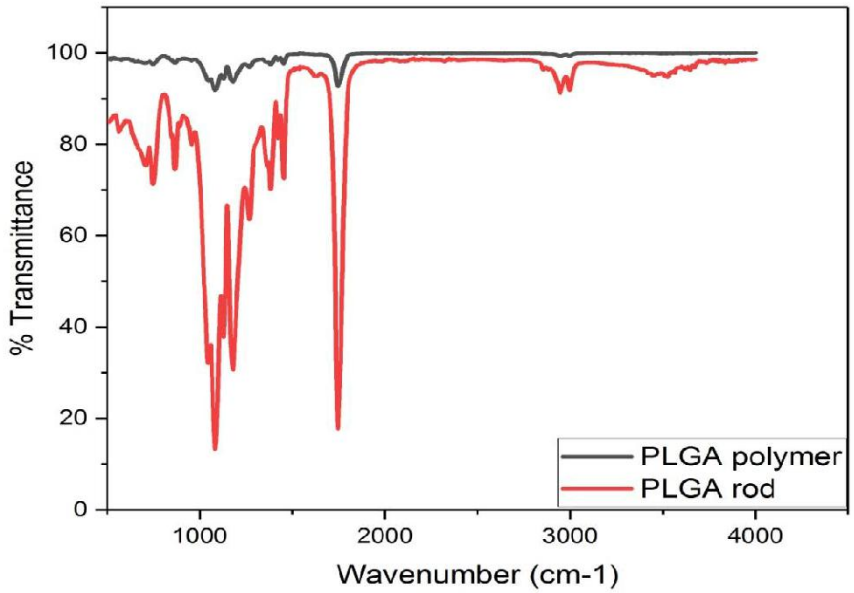

Figure 1.FTIR spectra of PLGA rod as well as PLGA polymer

Table 5.FTIR peaks of functional groups of PLGA polymer and PLGA rod

	Corresponding bands (cm-1)	
Functional groups		
	PLGA polymer	**PLGA rod**
C-H stretches	2900-3000	2900-3000
C=O stretch	1746.78	1747.00
C-O stretch	1079-1451	1079-1451
C-H bend	1400-900	1400-900

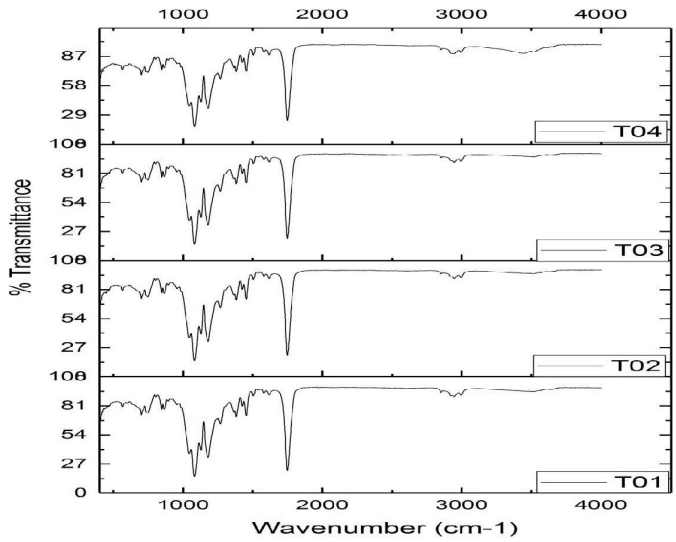

Figure 2.FTIR spectra of drug-incorporated rods consisting of a variety of various components T01, T02, T03, T04

Differential Scanning Calorimetry (DSC)

The DSC thermogram provides further evidence that PLGA polymer and PLGA rod both have an amorphous nature. The glass transition temperature (Tg) for PLGA polymer is shown in Figure 3 to be 34.53 degrees Celsius, whereas the temperature for PLGA rod is 28.82 degrees Celsius. When it is implanted, a polymer that has a glass transition temperature (Tg) close to that of the body may be far more ductile than it seems to be at ambient temperature [8]. The rod transition temperature (Tg) of PLGA rods is lower than that of PLGA polymer, indicating more flexibility. This may be the result of the processing of PLGA rods, which involves the addition of ethyl acetate, a substance that functions as a plasticizer [9]. When a plasticizer is incorporated to a polymeric polymer, the intermolecular distances between the polymer molecules grow, which in turn leads to an increase in the material's flexibility. As a consequence, Tg[10] dropped as a consequence. The use of ethyl acetate as a plasticizer in PLGA rod has the potential to reduce the Tg value by lowering the intermolecular forces that hold the polymer chains together.

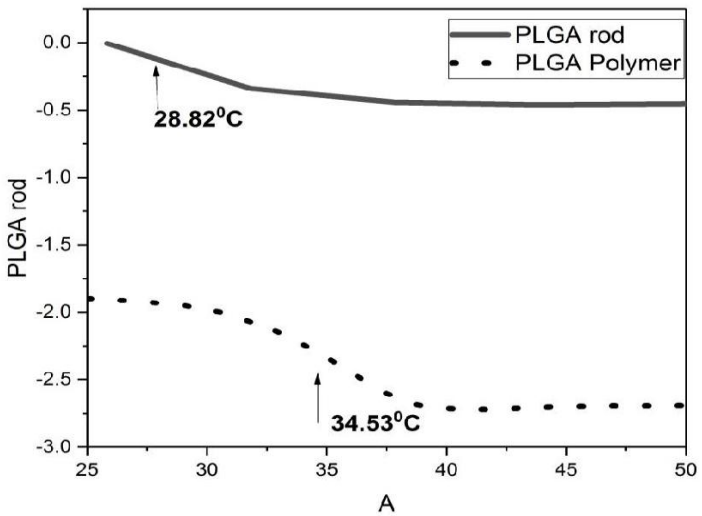

Figure 3.DSC themograms of PLGA rod and PLGA polymer

The DSC thermograms make it clear that the glass transition temperature (Tg) occurs at a temperature that is less than 20 degrees Celsius, which is a lower temperature than the one that occurs in the case of pure polymer (34.5 degrees Celsius). The melting point (Tm) of each of the rods falls somewhere within the given range between 120˚C - 127˚C.

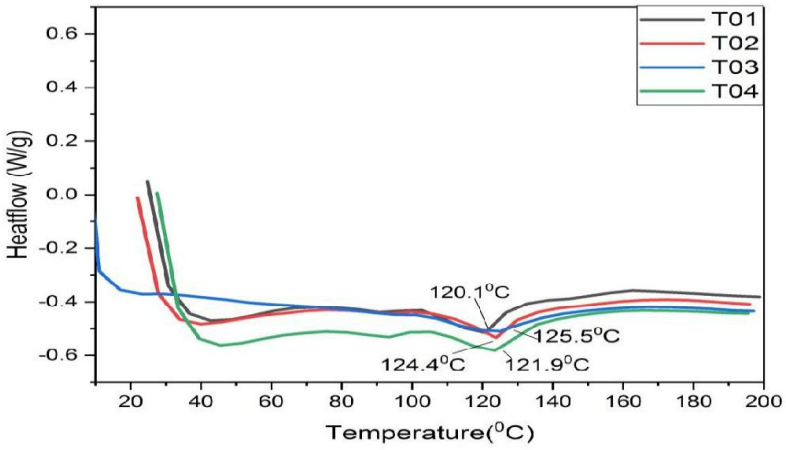

Figure 4.DSC thermograms of drug-incorporated rods of varying compositions and compositional variations

Thermogravimetry (TGA)

The thermo gravimetric analysis of PLGA polymer and PLGA rod, respectively, is shown graphically in figure 5. Thermogravimetric analysis (TGA) performed on PLGA polymer and PLGA rod reveals that the weight of these materials does not change until the temperature of analysis exceeds 270 degrees Celsius.

According to these findings, the temperature range of 400 to 300 degrees Celsius is where the weight loss happens for PLGA polymer and PLGA rod, respectively. The temperature at which PLGA polymer breaks down is greater than the temperature at which PLGA rod breaks down, and this difference may be because PLGA rod contains perhaps trace amounts of residual solvents.

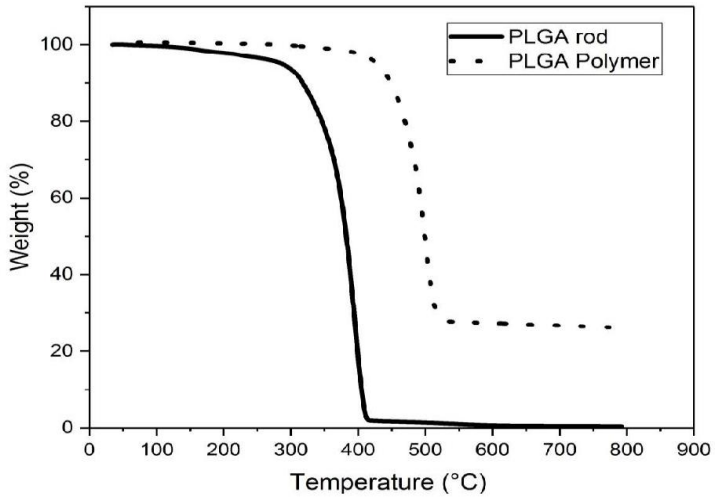

Figure 5.The thermo-gravimetric analysis of PLGA polymer and PLGA rod are shown graphically

Figure 6 shows the thermograms of drug-incorporated rods, which show that the rods are stable up to 270°C. Then, the rods start to break down due to heat, and this process is finished at 350°C. But in the case of PLGA rod, the rod is stable until it reaches a temperature of 300 °C. After that, it starts to break down thermally, and this degradation is finished at a temperature of 380 °C. It may be because the temperature at which PLGA rods break down is higher than that of other drug-incorporated rods.

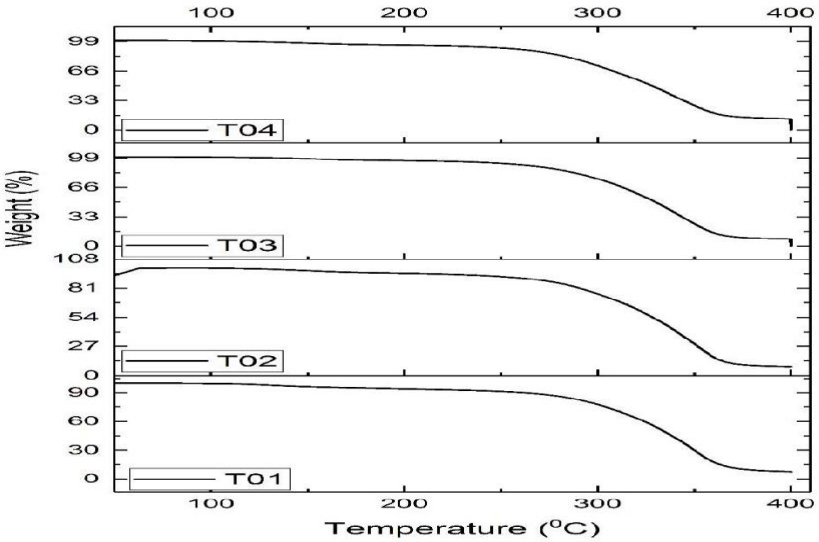

Figure 6.The drug's TGA thermogram had rods with different chemical make-ups

Determination of % Drug Content in PLGA Rods

When the drug was dissolved in methanol and scanned throughout a wavelength range of 200-400 nm, the solution of highest absorbance was found to be at 283 nm.

Table 6.The drug's absorbency along with the corresponding concentrations

Concentration (µg/ml)	Absorbance
12	0.108
25	0.226
50	0.424
75	0.592
100	0.82

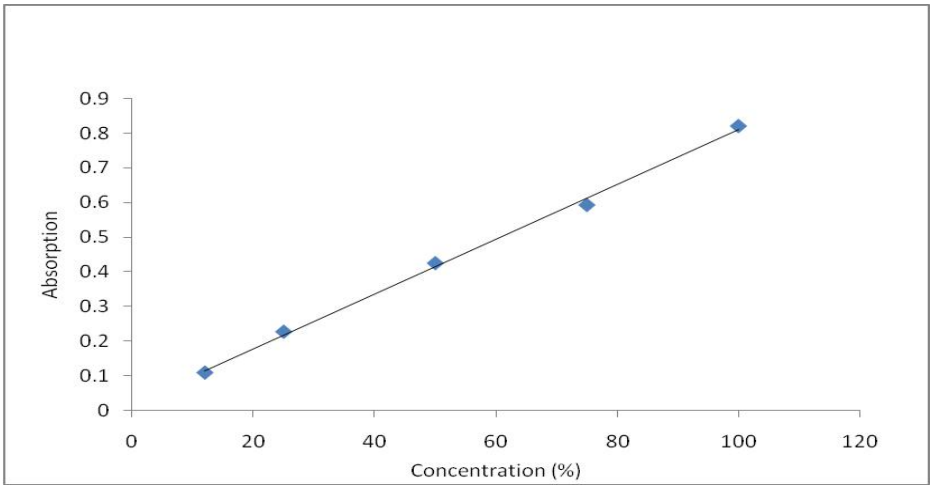

Figure 7.Calibration curve of drug by UV

The method has a correlation coefficient of 0.9978, which suggests that it obeys with Beer's law. Additionally, the method has high linearity.

Table 7.Validation parameters of drug by UV method

Parameter	Result
Absorption Maxima (nm)	283
Standard regression equation	y=0.0079x+0.0197
Correlation coefficient	0.9978

The amount of drug recovered from rod can be calculated from the graph.

Table 8.Concentration of the drug in the rod in percentage

Sample	Absorbance	Amount of drug recovered (mg)	Drug loaded (mg)	Concentration of drug in rod (%)
T01	0.110	11.495	16.66	69%
T02	0.075	7	12.5	56%
T03	0.051	4.081	8.33	49%
T04	0.145	15.86	20.83	76%

In Vitro Degradation Study of PLGA Rods

Degradation of PLGA rods took place in a medium containing 10 mL of phosphate buffer saline (PBS). All of the extruded PLGA rods exhibited behaviors of degradation that were remarkably comparable to one another.

Initially, all of the hydrolytically deteriorated rods, with the exception of the PLGA/EA rod, were opaque white.

In the beginning, PLGA/ EA rod had a translucent appearance, which was consistent with its low crystalline polymer structure.

After one to two weeks, each of the rods became an opaque white color.

Since PLGA is a hygroscopic polymer [11-15], the rods were instantly retained in the medium, and water became diffused inside the rods, which resulted in an increase in the amount of water content. Because of the increasing water content in the rods, regions of micrometer size that scatter light have been formed as a consequence of the increased water content [16-18]. This is the cause of the rod's change in appearance, which was described as becoming foggy and white [19,20]. Figure 8 depicts the temporal profile of water uptake, and Table 9 provides an explanation of how water uptake was calculated.

Table 9.Water uptake values of PLGA/EA rod and drug incorporated rods

Time period	PLGA/EA rod	Drug incorporated PLGA rods			
		T01	T02	T03	T04
1Day	0.59	0.32	0.44	0.54	0.33
1Week	1.17	0.69	0.82	0.91	0.87
2Week	15.60	8.28	9.73	10.2	5.42
3Week	95.50	31.53	45.64	50.78	25.55
4Week	128.82	90.17	98.75	100.21	58.64
5Week	43.09	91.14	55.47	59.64	25.67
6Week	24.45	43.67	32.51	40.52	37.48
7Week	12.53	31.82	27.82	35.24	30.25
8Week	10.80	19.51	15.86	20.28	15.87

After being submerged in PBS, it was seen that the cells' rate of water absorption was modest throughout the first time period up to one week, during which it was noted that the cells' water content reached up to 6%. After that, the period of water swiftly grew from 20% to 100% during the second and third periods respectively. PLGA rods had a discernible increase in size before becoming brittle and splitting apart into two opaque pieces. It suggests that there have been significant structural alterations to the rods throughout this time period. In the subsequent stages of the experiment, the rates of water uptake eventually slowed down after reaching their highest possible values.

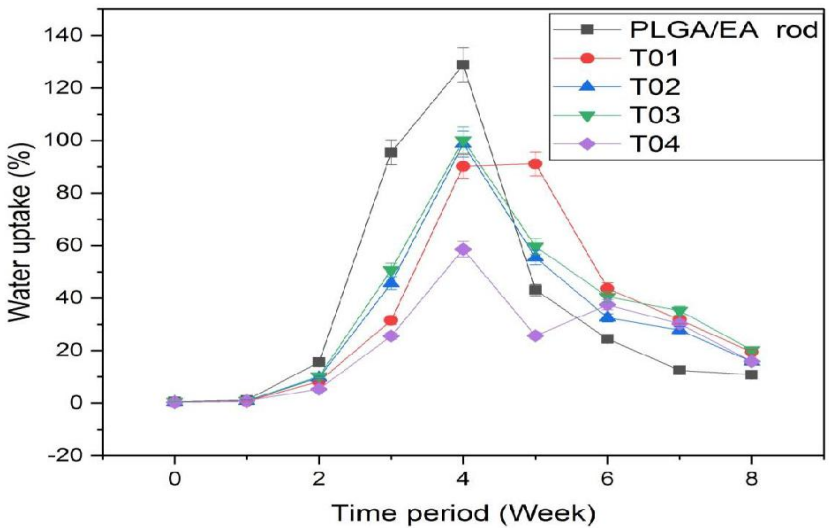

Figure 8.The above graph shows the time profile of water absorption by PLGA/EA rods and drug-incorporated rods

The PLGA rods' weight loss was the defining characteristic of their loss-of-weight. When the samples are stretched, they eventually become brittle and break easily. Table 10 provides a concise summary of the time evolutions of the normalized weight of various PLGA rods, and Figure 9 presents these data in graphical form.

Table 10.Comparison of the mass loss values of PLGA/EA rods with drug-incorporated rods

Time period	PLGA/ EA rod	T01	Drug incorporated PLGA rods (%)		
			T02	T03	T04
1Day	2.65	0	0.04	0.04	0
1Week	5.27	0.1	0.22	0.24	0
2Week	7.94	1.05	1.25	1.38	0.04
3Week	63.76	15.85	25.45	30.61	10.25
4Week	65.53	24.65	38.56	48	15.86
5Week	71.7	30.22	54.36	62.32	20.54
6Week	73.89	45.98	58.54	62.65	30.28
7Week	80.14	50.02	65.64	75.85	38.47
8Week	84.53	63.57	79.65	83.38	40.63

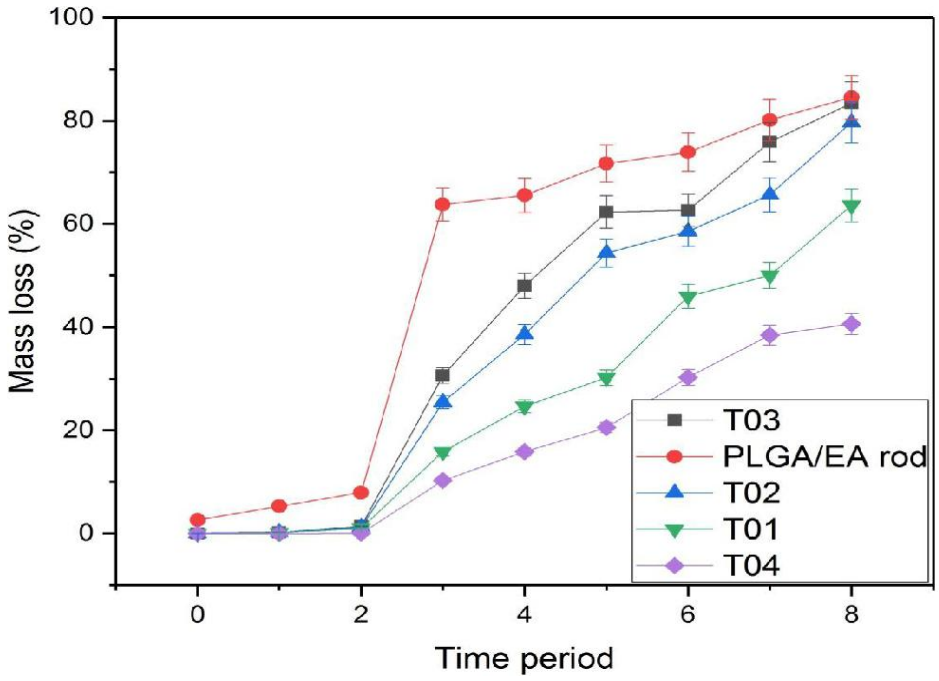

Figure 9.Time profile of mass loss of PLGA/EA rod and drug incorporated rods

Conclusion

When looking for biocompatible and biodegradable polymers that may be employed in a medical device, PLGA is without a doubt an excellent alternative. The extrusion method was prepared in the preparation of drug-incorporated PLGA rods. FTIR, DSC, and TGA were used in order to characterize the structural and thermal morphology of the PLGA rods that had been prepared using Hot Melt Extrusion. The research that was done on the in vitro degradation of PLGA rods in PBS showed that the degradation became much more evident for PLGA/EA rods after they were immersed in the solution for a period of 14 days (without drug). In comparison to after, the

rate of degradation is much higher before the inclusion of the drug (approximately 50 percent). This behavior was seen because there was a decrease in the total mass both before and after the addition of the drug. The recovery of the drug, as assessed by UV, was determined to be 76% for the rod that had 1.25 g of drug incorporated into it. These extruded rods have the potential to serve as an efficient platform for drug delivery.

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