Investigation of the Effectiveness of Polyurethane Composites Containing Gelatin at Different Rates on the Release of Ciprofloxacin

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Summary: Recently, polyurethane materials are widely used for many application areas such as drug delivery systems, biomaterial production, etc. In this study, polyurethane structures containing different amounts of gelatin (5%, 10%) were prepared. A release system was designed with ciprofloxacin adsorption to the prepared polyurethane structures. The structural characterization, thermal properties, surface morphologies of the designed system were determined using appropriate techniques. Monitoring of ciprofloxacin release was carried out by UV-spectrophotometer. It was determined that polyurethane structures containing different proportions of gelatin supported the adsorption of ciprofloxacin and the release slowed down with the increasing gelatin ratio. With this study, many drug delivery systems that can release at different rates and durations depending on the amount of gelatin additive can be designed.

Keywords: Polyurethane, Gelatin, Drug delivery system.

Introduction

Polyurethanes are a group of condensation polymers that contain the chemical urethane (—NHCOO—) group. [1]. For the first time, PU was produced in 1937 by the reaction between diisocyanate and polyester diol. The urethane group is the main repeating unit in PUs. Urethanes are produced from the reaction between alcohol (-OH) and isocyanate (NCO) [2-4]. PUs are generally synthesized from the reaction between isocyanate and polyol molecule in the presence of catalyst or ultraviolet light activation [5]. The isocyanate and polyol molecule must contain two or more isocyanate groups (R− (N = C = O) n ≥ 2) and hydroxyl groups (R '- (OH) n ≥ 2) respectively [6]. The properties exhibited generally depend on the type of polyol and isocyanate from which they are made [7]. Diisocyanates can be divided into aliphatic and aromatic diisocyanates. In general, aromatic diisocyanates are more reactive than aliphatic diisocyanates [8, 9]. Polyurethanes based on aromatic diisocyanates are less biocompatible with toxic degradation products than those synthesized from aliphatic diisocyanates [10]. For this reason, aliphatic isocyanates are preferred in biocompatible PU structure synthesis. Hexamethylenediisocyanate (HMDI) is the most widely used isocyanate in the preparation of biodegradable polyurethanes due to its linear structure [11-13]. Glycerol and polyethylene glycol (PEG) are biocompatible and biodegradable structures used as polyol source in the synthesis of polyurethanes [14-16]. Polyurethanes are considered excellent biomaterials due to their favorable mechanical properties and good biocompatibility [17-21]. Polyurethanes have been used as long-term implant materials, including catheters [22], artificial heart valve [23] wound dressings, angioplasty balloons, ventricular assist devices [24]. Recently, researchers have designed biodegradable polyurethanes for applications such as artificial skin [25] bone graft substitutes [26], drug delivery systems [27], and porous scaffolds [28] to regenerate damaged tissues. Since antibiotics constitute the widely used drug class, release studies are very important. Ciprofloxacin is a broad-spectrum bactericidal antibiotic that acts by binding two of the bacteria's four topoisomerase [29, 30]. Ciprofloxacin is the most potent fluoroquinolone active against a wide range of bacteria. More than 250 million patients have been successfully treated worldwide, and its safety profile has been well documented in a number of commendable scientific publications [31-32]. In this study, PU composites containing different proportions of gelatin were prepared. Ciprofloxacin was loaded with the prepared composites. The characterization, thermal stability, surface morphologies, drug release-kinetic properties of the composite structures obtained within the scope of the study were determined.

Experimental

Materials

Chemicals and solvents used in the synthesis and drug release steps were obtained from Sigma-Aldrich. In the drug release step, a cellulose membrane of 43mm x 27mm, which is also a sigma aldrich brand, was used.

Instrumentation

The infrared spectrum of the structural characterization of the prepared PU composite structures

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was recorded with a Perkin Elmer Spectrum Two model Fourier Transform Infrared Spectrometer. Surface morphologies of composite samples were determined with Leo EV40 brand SEM device at different magnifications at high resolution. Thermogravimetric analysis (TGA) was used to measure the change in physical properties of composite structures as a function of temperature by heating them in a controlled manner. In the analyzes, Shimadzu system 50 model thermogravimetric analysis (TGA) device was used. Drug release studies were followed by Shimadzu model 1601 UV-Spectrophotometer.

Synthesis of Polyurethane Composites Containing Different Proportions of Gelatin

Hexamethylene diisocyanate monomer was used as the isocyanate source in the synthesis. PEG 400, glycerol were used as the diol source. Gelatin is biodegradable, biocompatible and commercially available at relatively low cost, widely used in various pharmaceutical applications such as medical field, tissue engineering, drug delivery systems [33-35]. Gelatin has also a number of OH groups in its molecular structure and should work as multifunctional crosslinker [36]. In this study, PUs containing gelatin at different rates (5%, 10%) were synthesized. PEG 400-glycerol-gelatin source ratios were determined as 94/1/5 and 89/1/10. First of all, PEG-400, glycerol and gelatin in the determined proportions were mixed rapidly at 30 ˚C for 10 minutes in THF. After the mixture medium was made inert, 0.001 mol of hexamethylene diisocyanate monomer was added to the system. Reflux continued for 4 hours at 90 ˚C in an inert environment [37]. The presence of isocyanate as monomer residue in the post-reflux structure was checked with FTIR spectra. After the PU synthesis was carried out successfully, different proportions of gelatin were added and the reaction continued for 1 hour at 40 ˚C. After that, ciprofloxacin was added and reflux continued for 4 hours at 40 ˚C. Drug molecules are attached to this polymer structure by adsorption. The synthesis stages of the PU composite structure obtained are given in Fig.1 (a, b). Solvent in PU composite structures was removed. The solvent removed PU composite structures were left to dry under 40 ˚C in a vacuum oven.

Structural Characterization

The change in the chemical bond structures of the polyurethane composites containing different gelatin ratios and ciprofloxacin structures were investigated by FTIR analysis using the attenuated total reflection (ATR) technique in the 4000-400 cm^{-1} wavelength range.

Thermogravimetric analysis (TGA)

TGA results provide quantitative information about functionalization of synthesized ciprofloxacin / gelatin / PU composite structures. Thermogravimetry curves of composite structures were recorded using Shimadzu TGA-50 analyzers. Curves were obtained at a warming rate of 10 $Kmin^{-1}$ (30mL min^{-1}) in an air atmosphere. The sample weight was taken as 10 mg. Thermal decomposition temperature (Td of these structures) is defined as the temperature at the intersection of the tangents drawn from a point before the main decomposition step and the inflection point of the main step [37].

Surface Morphology

Surface morphologies of synthesized PU composite structures were determined using SEM (Leo EV40). In order to visualize the surface in SEM, it must be covered with a material that reflects the electrons. This substance is gold palladium. The thickness of the coating is adjusted according to the sample. Usually 100 Angstroms. The samples are adhered to the metal stab with two-sided adhesive tape. If necessary, silver paint is applied around the sample and placed in the coating device. The air is displaced by argon gas to prevent the surface from glowing. Coating takes place thanks to gold palladium that passes into the plasma phase [38].

Drug Release Studies

Determining Maximum Absorption Wavelength for Ciprofloxacin

Before monitoring ciprofloxacin release with UV spectrophotometer, the maximum absorption wavelength of ciprofloxacin was determined. For this, ciprofloxacin samples prepared in different concentrations were subjected to scanning in the 200-800 nm range.

Ciprofloxacin Release from Composite Structures

In order to monitor ciprofloxacin release in composite structures with UV spectrophotometer, ciprofloxacin calibration graph was drawn first. The composite structures prepared were left in dialysis bags that were previously activated and made ready. The dialysis bag was monitored for 72 hours with continuous stirring at 50 rpm in a medium containing phosphate buffer at 37 ˚C pH 7.4. Equal volume of fresh buffer was left in the system at each sampling. Measurements were made with UV spectrophotometer in the solution taken from the environment at certain time intervals [39].

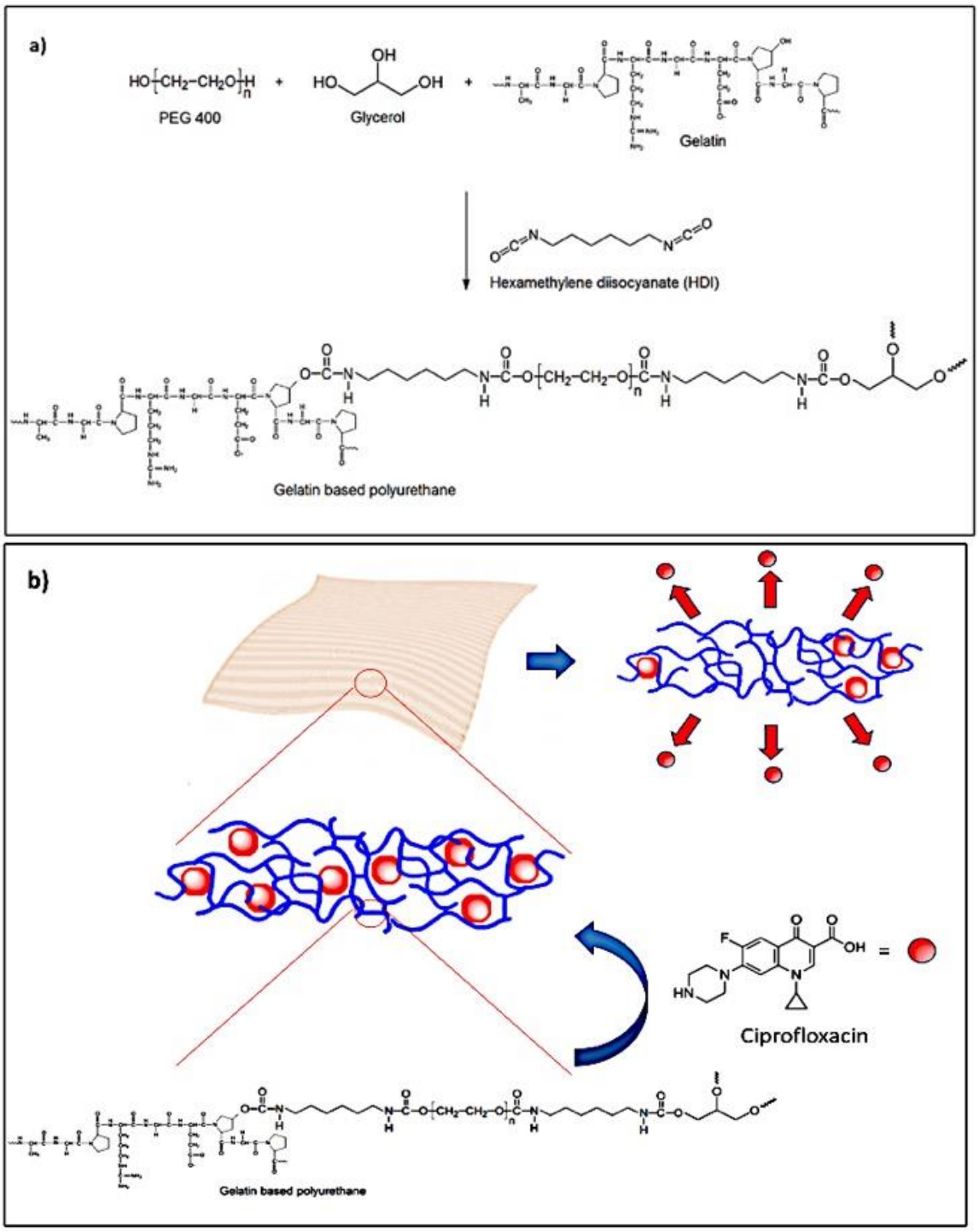

Fig. 1: Synthesis of polyurethane composites containing different gelatin ratios and ciprofloxacin (a, b).

Kinetic Studies

Kinetic models have been developed in which the amount of drug released (Q) is plotted against time (t) or as a function of time Q = f (t). Some kinetic explanations for the amount of dissolved drug as a function of time are zero order, first order, Hixson-Crowell, Higuchi, Korsmeyer-Peppas models [40]. Within the scope of the study, first order and Korsmeyer-Peppas kinetic models were used.

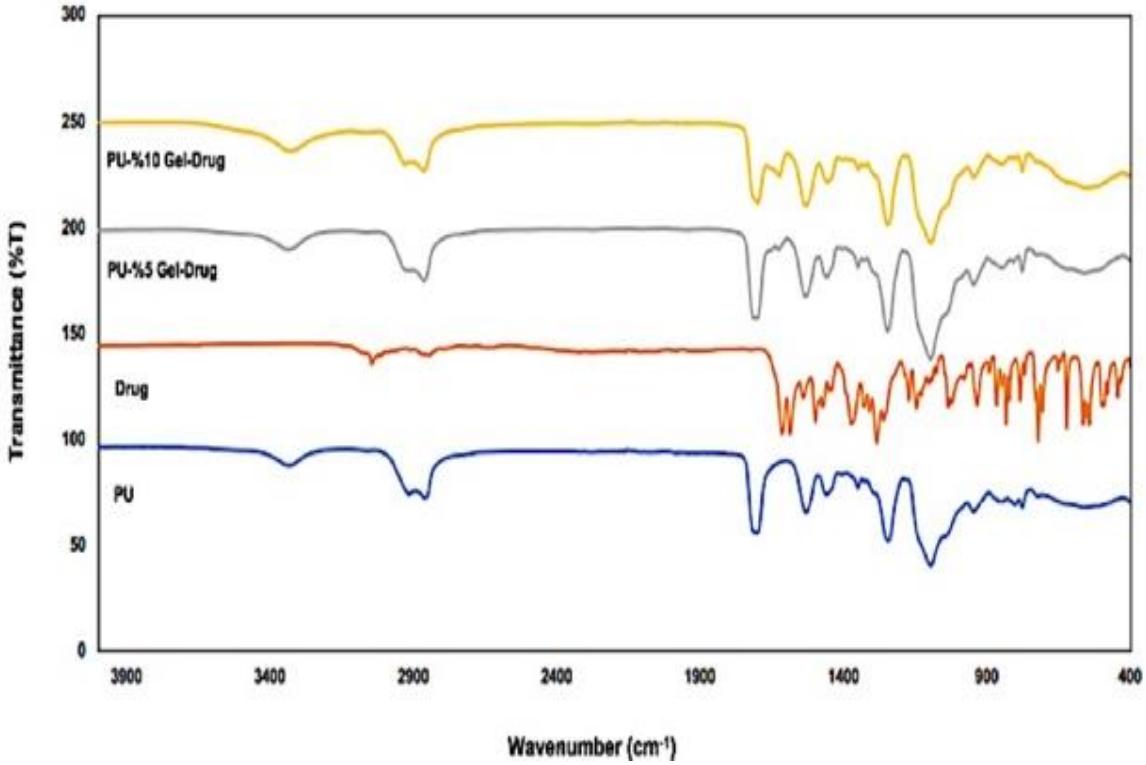

Fig. 2: FTIR spectra for PU, ciprofloxacin and PU-gel-ciprofloxacin composites.

Results and Discussion

Structural Characterization

Synthesised ciprofloxacin/gelatin PU composites were characterized by FTIR spectroscopy techniques. In addition, the thermal and surface morphology properties of these composites were examined with TGA and SEM techniques. Fig.2. shows FTIR spectra of ciprofloxacin/gelatin PU composites. When we look at the spectrum of PU-gelatin and drug loaded composite structures given in Fig.2, the -NH stress peak of the absorption band of 3324 cm^{-1}, the -CH stress peak of 2927-2856 cm^{-1}, the -C = O in urethane structure at 1700 cm^{-1} wavelength. At a wavelength of 1532- 1248 cm^{-1}, peaks are seen due to -NH and -C-C bending. We see characteristic PU absorption bands of 1090 cm^{-1} C-O and 778 cm^{-1} C-H. Characteristic PU absorption bands are in accordance with the literature [41, 42]. When we look at the structure of ciprofloxacin, we see the C = O stretching vibration of 1615 cm^{-1} carboxylic acid and the band originating from quinolone at 1588 cm^{-1} wavelength. It is the O-H group stress vibration, which indicates the presence of C-O stress vibrations at 1498 cm^{-1} and peak carboxylic acid at 1373 cm^{-1}. We see O-H deformation vibration binding at 1284 cm^{-1}, absorption peak of 1035-1022 cm^{-1} strong C-F group. The 1373 cm^{-1} absorption band is due to the protonation of the amine group of the piperazine part [43]. Ciprofloxacin spectrum interpretations are in agreement with the literature [44, 45]. When we look at the spectra given in Fig.2, most of the PU and ciprofloxacin peaks overlap in gelatin based polyurethane composite structures containing ciprofloxacin due to relative similarity and drift. In addition, there are some shifts in composite structures. The 1457 cm^{-1} shift of the protonated amine group band suggests the presence of electrostatic attraction between the protonated amine group and the polymer. Interhydrogen bonds tend to form in composite structures. Thus, it was confirmed by FTIR that ciprofloxacin was loaded into the gelatin based PU structure.

Thermal Results

Thermal stability was evaluated with TGA for polyurethane composite structures containing different proportions of gelatin containing ciprofloxacin. TGA curves of the synthesized composite structures are given in Fig.3. Generally, there are three different mass losses. The polymer has a hard segment originating from isocyanate groups, a soft segment originating from the PEG structure, and glycerol segments that act as a crosslinking agent . Travati et al. mentioned three mass losses in their interpretation of TGA curves for PU structures in their

study. From the decomposition of urethane bonds of the first mass loss, the second and third mass losses are considered to be related to the degradation of the ester groups [46]. Sadeek et al. show that ciprofloxacin is thermally stable in the temperature range of 25–50 ˚C. They also emphasized that ciprofloxacin degradation starts at 50 ˚C and is completed in two stages up to 750 ˚C [47]. As seen in Fig.3, there are three different mass losses in the temperature range of 175-350 ˚C 350-450 ˚C and 450-650 ˚C in polyurethane composite structures loaded with ciprofloxacin prepared using different proportions of gelatin. The introduction of gelatin groups into the structure decreases the thermal resistance of the polymeric structure by approximately 50 ˚C. Since proteins such as gelatin act as a crosslinking agent for the polyurethane structure, as the amount of gelatin increases, the flexibility of the polymer loses. In this way, it becomes difficult for polyurethane chains to get closer to each other and therefore secondary interactions are reduced. Another reason for the decrease in thermal stability is the decrease in these secondary interactions. These three basic mass losses seen in TGA thermograms of polyurethanes are due to degradation of the crosslinker gelatin, degradation of PEG groups and thermoxidative degradation of polyurethanes, respectively. There was an increase in the thermal stability of the polymer when the ciprofloxacin groups entered the structure. This change caused the degradation peak of the soft segments to reach higher temperatures. This change proves us that ciprofloxacin is integrated into the structure.

Surface Morphology of PU Composite Structures with SEM Technique

Surface properties of the synthesized PU structures containing 5% and 10% gelatin and ciprofloxacin were determined by SEM method. In the SEM analysis given in Fig.4, it was seen that the surfaces were smooth, homogeneous and monolithic. Fig.5 and Fig.6 show SEM images of gelatin-based polyurethane structure containing ciprofloxacin. The smoothness of the surface changes with the inclusion of different proportions of gelatin and ciprofloxacin in these images. Some peaks originating from cypro groups occur on the surface. The cipro phases on the surface become more pronounced as the gelatin doping rate increases.

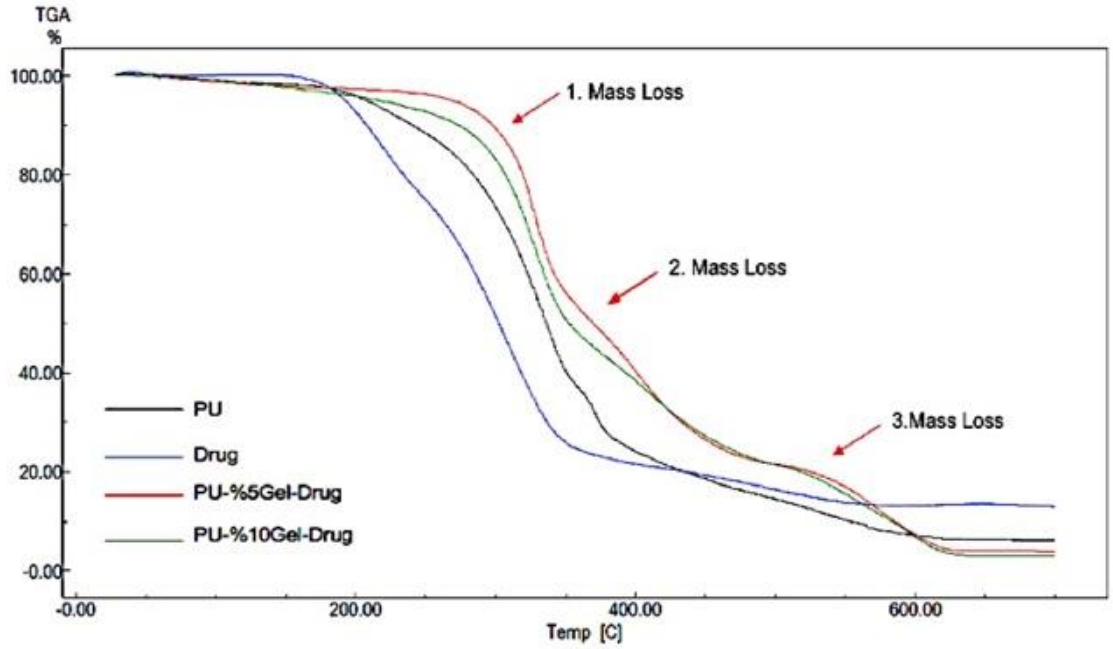

Fig. 3: Thermal analysis of PU, ciprofloxacin and PU-gel-ciprofloxacin composites.

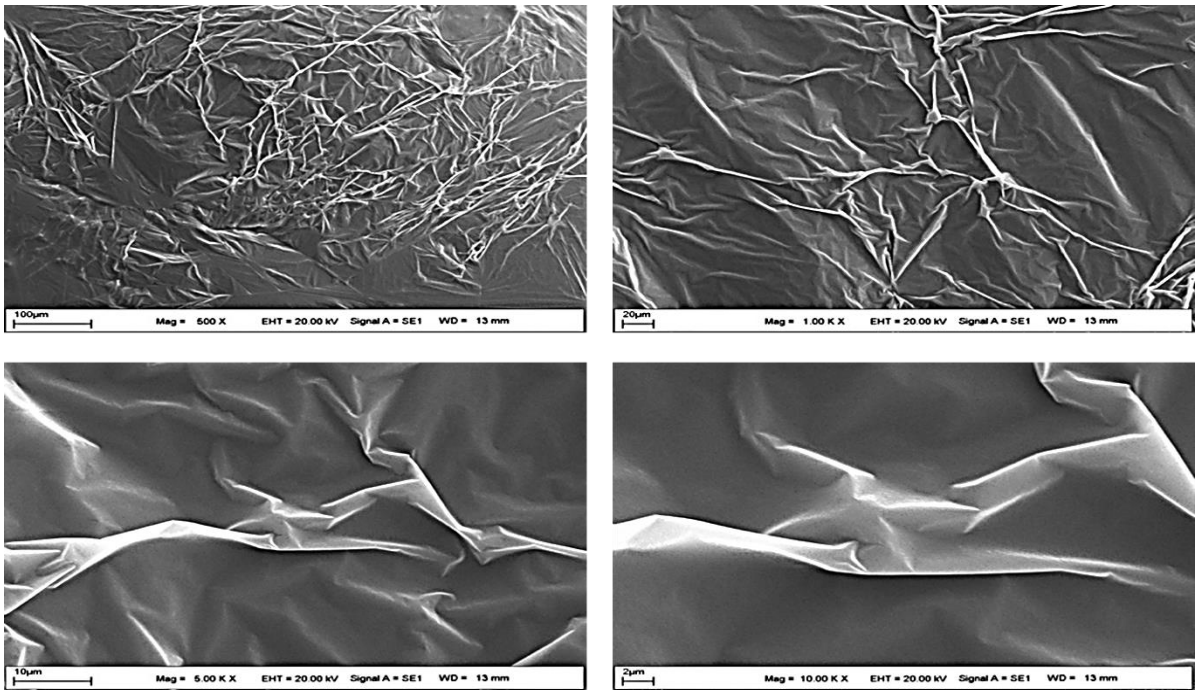

Fig. 4: SEM images of PU structure.

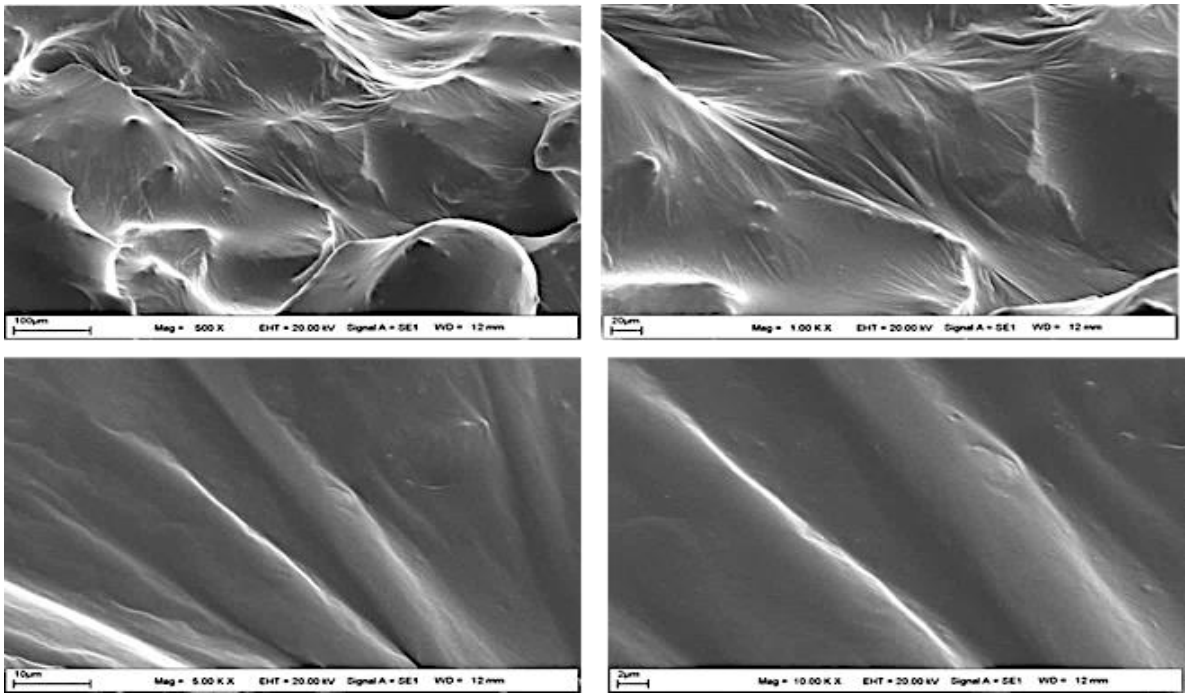

Fig. 5: SEM images of composites containing.

PU-5 % gelatin-ciprofloxacin.

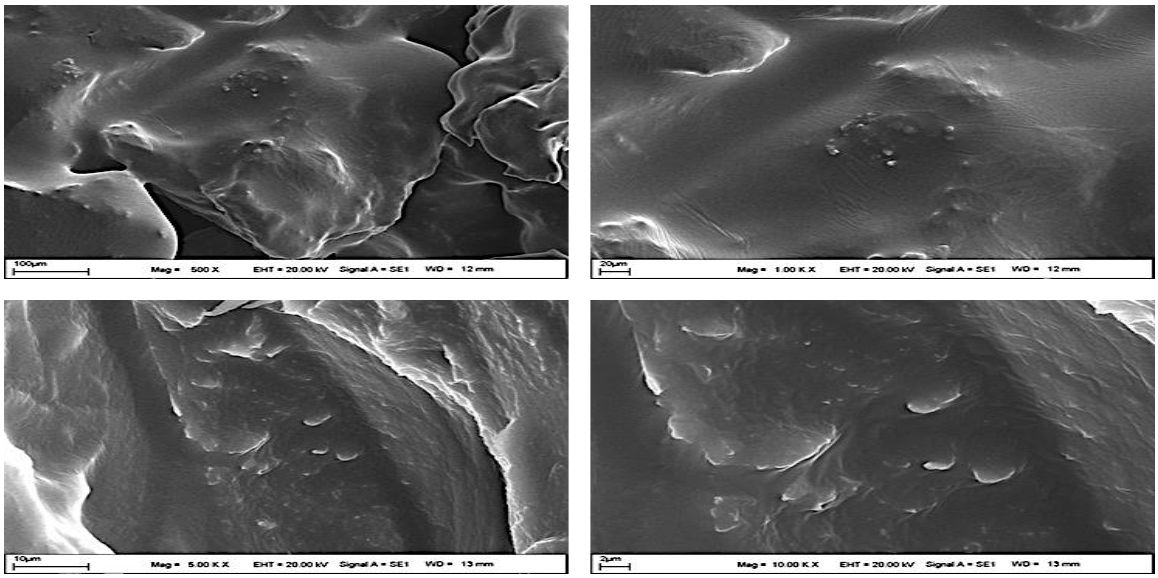

Fig. 6: SEM images of composites containing. PU-10% gelatin-ciprofloxacin.

Determining Maximum Absorption Wavelength for Ciprofloxacin

Ciprofloxacin samples at different concentrations prepared in PBS buffer were scanned in the wavelength range of 200-800 nm. Fig. 7 shows the wavelength range scan for ciprofloxacin. The best UV absorption spectrum was determined as the 270 nm wavelength given in Fig. 7. After this determination, the drug release study was carried out at 270 nm.

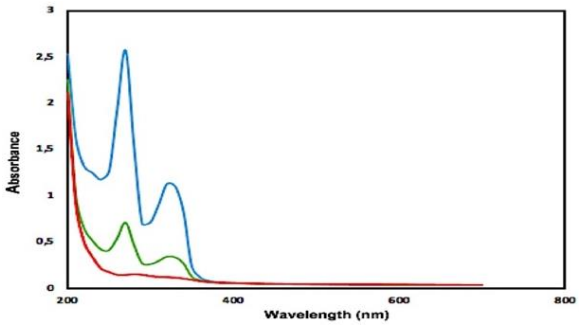

Fig. 7: Wavelength range screening for ciprofloxacin.

Ciprofloxacin Release from Composite Structures

A calibration graph was drawn for ciprofloxacin covering different concentration ranges (0.98-62.5µg / mL) before proceeding with the drug release study. Calibration graph is given in Fig.8. Ciprofloxacin release from PU composite structures containing different amounts of gelatin and ciprofloxacin was studied at 270 nm wavelength. Fig.9 shows ciprofloxacin release studies of polyurethane composite structures containing 5% gelatin and 10% gelatin added ciprofloxacin obtained by measuring at 270 nm. In the study, it was observed that the composite structure containing 5% gelatin showed the maximum release interval within 4.5 hours, but this period extended up to 8 hours in the composite structure containing 10% gelatin. This result shows us that a controlled time adjustment can be made by adjusting the amount of gelatin. In addition, we can see once again that the increasing gelatin rate slows down the release process by drawing attention to the emission difference in the first 5 hours in the release graph. When we look at the literature, there is no study that mentions that ciprofloxacin release from PU structures is related to the amount of gelatin added. Wright et al. made polycarbonate urethane nanofiber scaffolds for ciprofloxacin release. The release from the scaffold was correlated with the concentration of the antimicrobial oligomer (structure consisting of two molecules of ciprofloxacin) [48]. Macocinschi et al. prepared polyurethane-ß cyclodextrin-ciprofloxacin composite films. They associated the release behavior with antimicrobial activity measurement [49]. In another study, Mococinschi et al. obtained electrospun coated and uncoated polyurethane membranes containing ciprofloxacin. They saw drug release behavior similar in the first 500 minutes, and then saw an increase in the release rate in electrosprayed membranes. They observed a lower release percentage and a slower drug release rate in polyurethane membrane structures with high ciprofloxacin content [50]. When we look at the release

systems given for ciprofloxacin, it is mostly related to the drug concentration loaded into the system. The association of ciprofloxacin release with the gelatin doping rate in the composite structures synthesized within the scope of the study contributes to the literature.

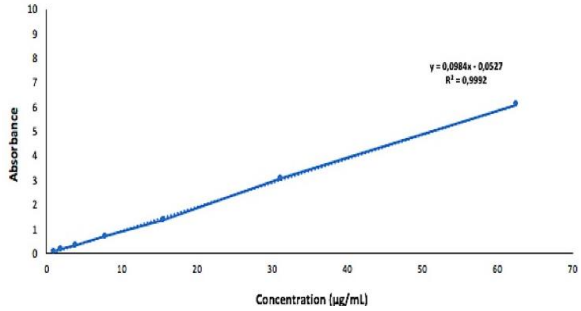

Fig. 8: Ciprofloxacin calibration graph.

Kinetic Studies

In this study, in order to determine the model with the closest drug release profile, a release profile was created with different kinetic models, first order and Korsmeyer-Peppas. Graphics of kinetic models are given in Fig.10 and Fig.11. The highest degree of correlation coefficient determines the appropriate mathematical model that tracks drug release kinetics. Correlation coefficients are given in Table-1. According to the correlation coefficients, it was observed that composite structures containing 5% gelatin and ciprofloxacin fit the first order kinetic model, and composite structures containing 10% gelatin and ciprofloxacin fit the Korsmeyer-Peppas kinetic model. Accordingly, the first order kinetic equation describes the dissolution of the drug in polymeric composite structures that is not effectively enclosed and ready to dissolve from the carrier surface. This rapid process that occurs immediately after immersing the sample in the release medium is called the "burst effect" [51]. It can be concluded that ciprofloxacin release is much faster in a composite structure containing 5% gelatin. In the Korsmeyer-Peppas equation, which indicates the diffusion type the release exponent n was found to be 1.191. This is > 0.89, indicating super case type II. With this in mind, it can be understood that drug release in composite structures is controlled by erosion mechanism [39]. For both release systems analyzed the increase in the gelatin ratio in the composite structures and the increase in the carrier thickness had a positive effect on the elongation of the release.

Table-1: Correlation coefficient (R^2) values of kinetic models.

Composite Structure	Kinetic Model	
	First Order	Korsmeyer-Peppas Plot
PU-5%Gel-Drug	0.9845	0.9611
PU-10%Gel-Drug	0.9578	0.9744

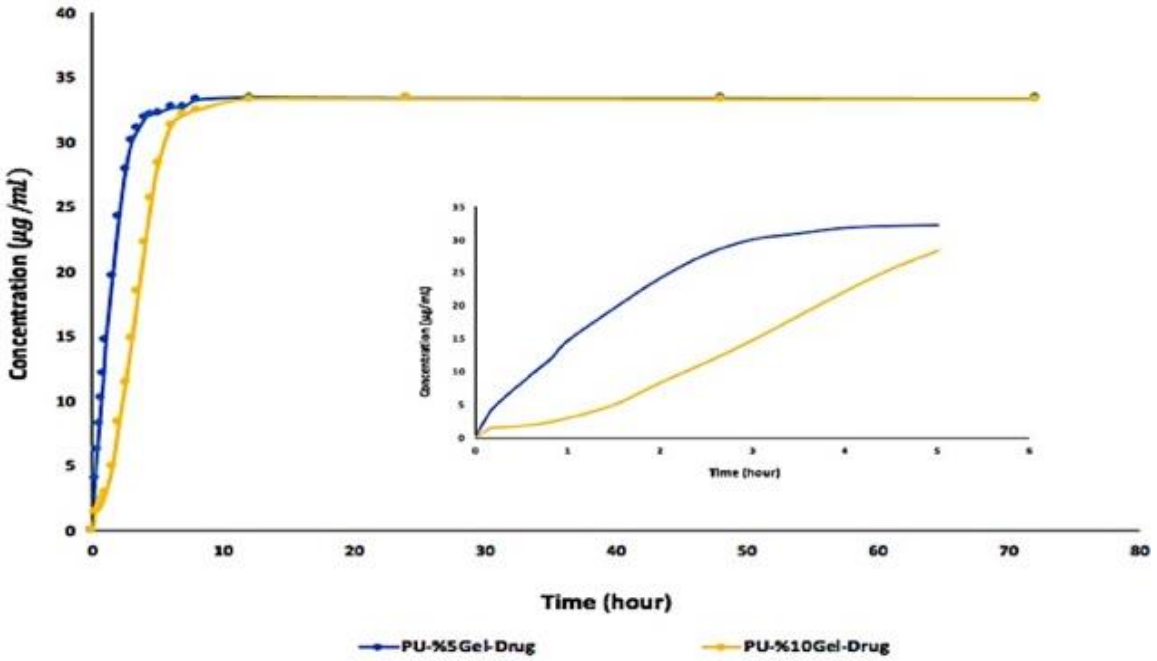

Fig. 9: Ciprofloxacin drug release graph.

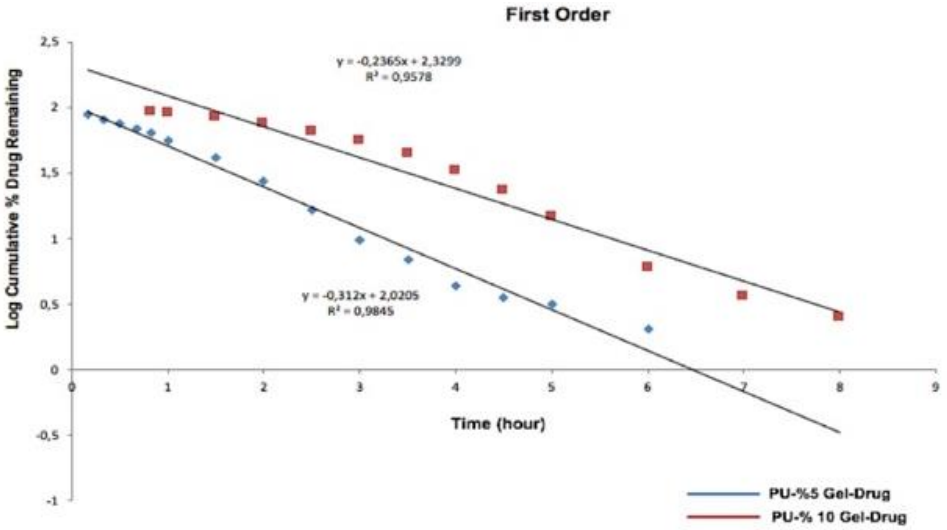

Fig. 10: First order kinetic model.

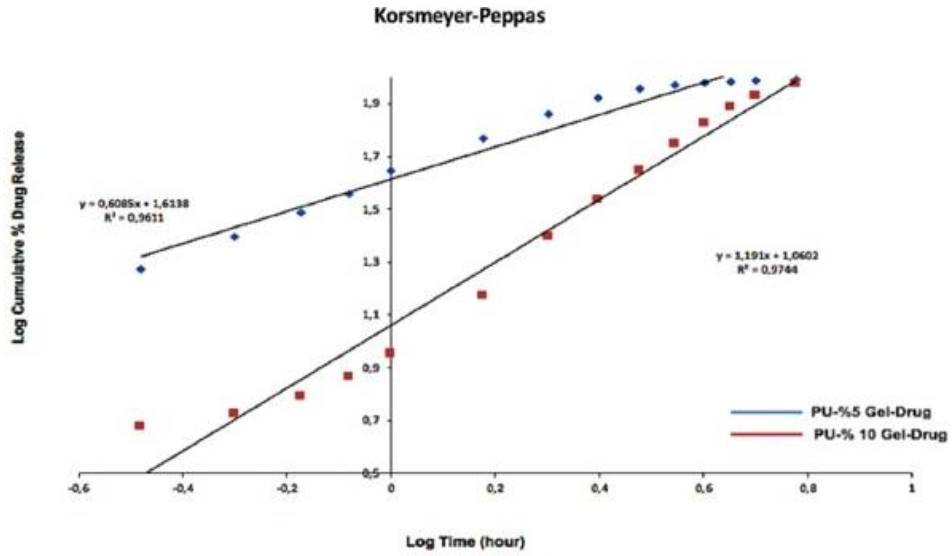

Fig. 11: Korsmeyer-Peppas kinetic model.

Conclusion

Recently, there has been a high interest in drug delivery systems. When we look at the drug release systems, we see that the release time is usually long, the drug administration interval is extended and the patient is not affected by negative and harmful effects.

1. With this work, we see that the hydrophilic microstructure and cavities formed depending on the gelatin, PEG and glycerol content support the adsorption of ciprofloxacin.
2. It was determined that the release of ciprofloxacin was slowed down as a result of the increase in gelatin ratio with the addition of different amounts of gelatin.
3. Based on all these findings, gelatin-based polyurethane composite structures containing ciprofloxacin can be used for many drug releases other than ciprofloxacin.
4. In addition, the study has the potential to contribute to the studies in the field of wound dressing where long releases can occur.

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