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Development of Biodegradable Poly (Lactic-Co-Glycolic Acid) (PLGA) Nanoparticles for Sustained Release of Insulin

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Abstract

This research outlines the creation of biodegradable composite nanoparticles made from poly (lactic-co-glycolic acid) (PLGA) designed for the sustained release of insulin. The emphasis is on the interactions between the polymer and the drug at the interface, along with the dynamics of the release matrix. The in vitro release kinetics, surface morphology, encapsulation efficiency, particle size, and polydispersity of insulin-loaded PLGA nanoparticles were analyzed following their production via a double emulsion solvent evaporation method. The nanoparticles composed of the enhanced polymer composite exhibited remarkable colloidal stability, characterized by a narrow polydispersity index of 0.168 ± 0.021 and an average particle size of 185.4 ± 12.6 nm. The encapsulation efficiency was determined to be 78.6 ± 3.2%, while the drug loading was found to be 9.4 ± 0.7%. The establishment of a stable polymer composite system was evidenced by scanning electron microscopy, which revealed smooth, spherical nanoparticles. Insulin was uniformly distributed inside the PLGA polymer matrix without chemical incompatibility, as verified by Fourier transform infrared spectroscopy and differential scanning calorimetry. The first burst release of 12.3 ± 1.8% transpired within the first 6 hours of in vitro release studies, followed by a sustained insulin release of 72.5 ± 3.6% over 120 hours, primarily attributed to diffusion and gradual degradation of the polymer matrix. The produced polymer composite nanoparticles maintained the structural integrity of insulin, exhibiting remarkable storage stability for three months at 4 °C. In conclusion, the results underscore the significance of polymer composite engineering in sophisticated controlled-release drug delivery systems, indicating that PLGA-based polymer composite nanoparticles provide a biodegradable medium for prolonged protein delivery.

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Keywords: Biodegradable polymer matrix, controlled drug delivery, insulin delivery, PLGA nanoparticles, polymer composites, sustained release.

INTRODUCTION

There has been a lot of interest in a new generation of controlled drug delivery systems that

use biodegradable polymeric materials to release therapeutic peptides and proteins over an extended period of time. With their exceptional biocompatibility, adjustable degradation kinetics, and proven regulatory approval for parenteral administration, aliphatic polyesters like poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and especially poly(lactic-co-glycolic acid) (PLGA) have become the biomaterials of choice among numerous synthetic biodegradable polymers. The hydrolytic breakdown of PLGA into lactic acid and glycolic acid, which are then metabolized through the Krebs cycle, reduces systemic toxicity and long-term accumulation, and the polymer has been authorized by both the FDA and the EMA [1, 2].

The physicochemical behavior of PLGA, a copolymer comprising monomeric units of lactic acid and glycolic acid, can be fine-tuned by adjusting its molecular weight, crystallinity, end-group chemistry, and lactide:glycolide ratio. For prolonged drug delivery, a 50:50 lactide-to-glycolide ratio is ideal because of its amorphous shape, which typically shows the quickest degradation rate. Hydrophobicity and degradation are both affected by the amount of lactides present; on the one hand, a higher glycolide content speeds up hydrolysis. The adaptability of polymer compositions allows for the rational development of matrix-controlled release systems that may be customized to meet individual therapeutic needs. Furthermore, PLGA has remarkable processability when working with emulsion solvent evaporation, nanoprecipitation, spray drying, and microfluidic processes. This paves the way for the creation of nano- and microparticulate systems that possess regulated size distribution and effective encapsulation [3, 4].

A continuous biodegradable polymer matrix encases a dispersed drug phase in polymer composite nanoparticles. Encapsulation effectiveness, stability, burst release, and long-term release kinetics are all affected by the interactions between the polymer and protein at the interface of protein delivery systems. The interior architecture of the nanoparticles is impacted by insulin and PLGA's hydrogen bonds, electrostatic forces, and hydrophobic interactions. All of the factors that contribute to the release profile—water penetration, matrix swelling, pore creation, and polymer erosion—are controlled by the composite design. To prevent enzymatic degradation, aggregation, and structural denaturation, polymeric nanoparticles create a protective microenvironment, in contrast to traditional aqueous formulations [5].

Because of its chemical instability, enzymatic breakdown, and short biological half-life, insulin—a peptide hormone crucial for glucose homeostasis—presents considerable formulation issues. Glycemic management requires frequent subcutaneous injections, which can cause patients to not take their insulin as prescribed and cause plasma insulin levels to fluctuate. To lessen the injection frequency and increase the efficacy of treatments, sustained-release biodegradable systems have been thoroughly studied. Low loading efficiency, large initial burst release, and protein instability during manufacture are important constraints of PLGA-based micro- and nanoparticles for insulin encapsulation, while previous investigations have established their practicality [6].

Improving encapsulation efficiency and minimizing burst release have been recent focuses in polymer composite engineering, with an emphasis on optimizing emulsification parameters, solvent systems, stabilizers, and molecular properties of the polymer. For protein-loaded PLGA nanoparticles, the double emulsion ($W_1/O/W_2$) solvent evaporation approach is still a popular choice because it can trap hydrophilic biomolecules in the internal aqueous phase. Additionally, release kinetics are greatly affected by the ability to manage the distribution of nanoparticle sizes, the interfacial surface area, and the porosity of the matrix. To rationally construct sustained protein delivery systems, it is crucial to understand the link between polymer composition, composite microstructure, and matrix-controlled release processes [7].

There is a lack of in-depth research that correlates polymer microstructure, drug-polymer compatibility, temperature behavior, and release kinetics, even though there is a lot of literature on insulin carriers based on PLGA. The development of stable biodegradable nanoparticulate systems with

controllable release profiles necessitates a more thorough comprehension of composite formation and matrix-controlled transport processes [8, 9].

The current research intends to use a double emulsion solvent evaporation technique to create and characterize biodegradable PLGA polymer composite nanoparticles for long-term insulin delivery. Composite microstructure, thermal behavior, encapsulation efficiency, matrix-governed in vitro release kinetics, and polymer-drug interfacial compatibility are given particular attention. This work aims to shed light on the rational design of improved PLGA-based controlled-release systems for sustained protein therapy by integrating polymer engineering concepts with extensive physicochemical evaluation.

MATERIAL AND METHODS

This section describes the experimental procedures, materials, and techniques employed to fabricate, characterize, and evaluate insulin-loaded PLGA polymer composite nanoparticles in vitro.

Materials

We procured poly(lactic-co-glycolic acid) (PLGA) from Evonik Industries in Germany. The usual molecular weight ranges from 30,000 to 50,000 Da, with a lactide to glycolide ratio of 50:50. The Danish pharmaceutical firm Novo Nordisk provided human recombinant insulin. A poly(vinyl alcohol) (PVA; 87–89% hydrolyzed, Mw 30,000–70,000 Da) emulsifying stabilizer was obtained from Sigma-Aldrich in the USA. We procured analytical-grade dichloromethane (DCM) and ethyl acetate from Merck (India). The reagents utilized were of analytical grade and were delivered in phosphate-buffered saline (PBS, pH 7.4). Ultrapure water was prepared using Milli-Q filtration equipment (Millipore, USA).

Preparation of Insulin-Loaded PLGA Polymer Composite Nanoparticles

The water-oil-water ($W_1/O/W_2$) double emulsion solvent evaporation method was employed to fabricate insulin-loaded PLGA polymer composite nanoparticles. A probe sonicator (Vibra-Cell, Sonics, USA) was employed at 40 W for 60 seconds to amalgamate 10 mg mL^{-1} of insulin in 0.01 N HCl with 5 mL of PLGA solution in dichloromethane, thereby producing the primary W_1/O emulsion. To formulate the secondary $W_1/O/W_2$ emulsion, the primary emulsion was combined with 50 mL of an external aqueous phase containing 1.0% (w/v) PVA and agitated at 12,000 rpm for three minutes [10]. The organic solvent was permitted to evaporate entirely to facilitate the formation of hardened polymer composite nanoparticles by agitating the resultant emulsion at ambient temperature with a magnetic stirrer for four hours. To acquire free-flowing nanoparticle powder, the particles were initially gathered using centrifugation at 15,000 rpm for 20 minutes. Subsequently, they were rinsed thrice with distilled water to remove any residual PVA and unencapsulated insulin. Ultimately, they underwent lyophilization for 48 hours at Labconco, USA. Insulin-free PLGA nanoparticles were similarly produced [11].

Particle Size, Polydispersity, and Zeta Potential Analysis

Dynamic light scattering (DLS) and electrophoretic light scattering (Zetasizer Nano ZS, Malvern Instruments, UK) were employed to ascertain the zeta potential, mean particle size, and polydispersity index (PDI) of the polymer composite nanoparticles. A solution of lyophilized nanoparticles (1 mg mL^{-1}) was produced by dispersing them in distilled water and briefly applying ultrasound prior to analysis. Each measurement was conducted thrice at a temperature of 25 °C [12].

Surface Morphology and Composite Microstructure

Scanning electron microscopy (SEM; JSM-7600F, JEOL, Japan) was employed to examine the surface morphology and structural integrity of the polymer composite nanoparticles. Dried nanoparticle samples were affixed to aluminum stubs using double-sided adhesive tape. The samples were subsequently sputter-coated with a thin coating of gold in a vacuum environment. To evaluate the uniformity of size, surface roughness, and particle morphology, micrographs were obtained at different magnifications [13].

Encapsulation Efficiency and Drug Loading

The amount of insulin contained within the polymer composite matrix was measured to assess encapsulation efficiency (EE) and drug loading (DL). Insulin was accurately extracted by dissolving 10 mg of nanoparticles in 2 mL of dichloromethane, followed by the addition of 5 mL of phosphate-buffered saline (pH 7.4) while aggressively vortexing. A UV-visible spectrophotometer (Shimadzu, Japan) was employed for spectrophotometric measurement at 276 nm following the centrifugation that isolated the liquid phase [14]. The subsequent formulas were employed to calculate the encapsulation efficiency and drug loading.

$$EE\ (\%) = \frac{Amount\ of\ insulin\ encapsulated}{Initial\ amount\ of\ insulin} \times 100$$

$$DL\ (\%) = \frac{Amount\ of\ insulin\ encapsulated}{Weight\ of\ nanoparticles} \times 100$$

Fourier Transform Infrared Spectroscopy (FTIR)

The compatibility of the polymer-drug system and its interfacial interactions were evaluated by Fourier transform infrared (FTIR) research. An FTIR spectrometer (PerkinElmer Spectrum Two, USA) was employed to record the spectra of insulin, pure PLGA, physical mixtures, and insulin-loaded nanoparticles using the KBr pellet method, across the range of 4000–400 cm^{-1} [15].

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC 60, Shimadzu, Japan) was employed to analyze the thermal properties and physical state of insulin within the PLGA composite matrix. Approximately 5 milligrams of sample was encapsulated in aluminum pans and subjected to heating under a nitrogen purge, ranging from 30 to 300 degrees Celsius at a rate of 10 degrees Celsius per minute. We examined the thermograms of insulin, PLGA, and insulin-loaded nanoparticles to assess the molecular dispersion and the formation of the composite [16].

In Vitro Release Studies

The dialysis bag diffusion technique was employed to evaluate the insulin release from the polymer composite nanoparticles in vitro. Introduce 2 milligrams of insulin-equivalent nanoparticles into 5 milliliters of pH 7.4 phosphate-buffered saline and subject them to dialysis via a membrane with a molecular weight cutoff of 12,000 Da. The 100 mL of release medium was maintained at 37 ± 0.5 °C and agitated at 100 rpm while the dialysis bag was immersed in it. Two milliliters of the releasing medium were extracted and substituted with fresh buffer at consistent intervals. Spectrophotometry was employed at 276 nm to quantify the released insulin concentration. The release process governed by the diffusion and degradation of the polymer matrix was elucidated by fitting the data to kinetic models (zero-order, first-order, Higuchi, and Korsmeyer-Peppas), subsequently reported as cumulative percentage release [17].

Stability Studies

The lyophilized samples were stored at 4 ± 2 °C and 25 ± 2 °C for three months to assess the physical stability of the polymer composite nanoparticles. We monitored the particle size, zeta potential, and encapsulation efficiency at regular intervals to assess any alterations in the composite's integrity or drug retention [18].

Statistical Analysis

The data were expressed as the mean ± standard deviation, and all experiments were conducted in triplicate. Statistical comparisons were conducted using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test, with a significance threshold of $p < 0.05$.

RESULTS AND DISCUSSION

This section provides a comprehensive description of the insulin-loaded PLGA polymer composite nanoparticles, including their physicochemical properties, composite microstructure, compatibility between polymers and drugs, behavior of release in vitro, stability assessment, and performance during

sustained release.

Table 1. Physicochemical properties of insulin-loaded PLGA polymer composite nanoparticles.

Parameter	Value (mean ± SD, n = 3)
Particle size (nm)	185.4 ± 12.6
Polydispersity index (PDI)	0.168 ± 0.021
Zeta potential (mV)	−21.3 ± 2.4
Encapsulation efficiency (%)	78.6 ± 3.2
Drug loading (%)	9.4 ± 0.7

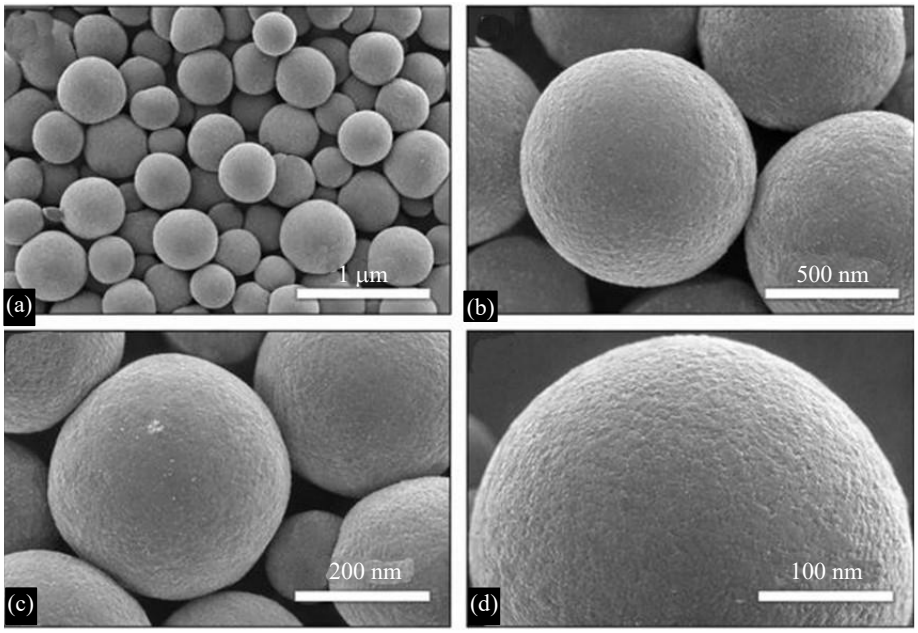

Figure 1. SEM micrographs of insulin-loaded PLGA polymer composite nanoparticles showing spherical morphology and smooth surface architecture at different magnifications.

Physicochemical Characterization of Polymer Composite Nanoparticles

Insulin-loaded PLGA polymer composite nanoparticles were successfully prepared using the double emulsion solvent evaporation technique, producing uniformly dispersed and free-flowing nanostructures. The narrow particle size distribution and consistent surface charge confirm the formation of a stable and homogeneous polymer–drug composite matrix. Key formulation parameters, including particle size, polydispersity index (PDI), zeta potential, encapsulation efficiency (EE), and drug loading (DL), are presented in Table 1. The optimized formulation exhibited an average particle size of 185.4 ± 12.6 nm with a low PDI of 0.168 ± 0.021, indicating a monodisperse nanoparticle population. Such nanoscale dimensions are favorable for controlled drug release and potential systemic application. The zeta potential of −21.3 ± 2.4 mV suggests adequate electrostatic repulsion, contributing to colloidal stability and preventing aggregation. A high encapsulation efficiency (78.6 ± 3.2%) and satisfactory drug loading (9.4 ± 0.7%) were achieved, reflecting effective entrapment of insulin within the PLGA matrix. The efficient encapsulation can be attributed to strong interfacial interactions and proper stabilization of the internal aqueous phase during emulsification, confirming the robustness of the composite formulation process. (Table 1).

Morphological Analysis and Composite Microstructure

Scanning electron microscopy (SEM) images (Figure 1) revealed that the insulin-loaded PLGA polymer composite nanoparticles possessed a uniform spherical morphology with smooth and nonporous surfaces. The particles appeared discrete and well separated, with no visible cracks, surface

irregularities, or aggregation. This indicates controlled solidification of the polymer matrix during the solvent evaporation process. The smooth surface architecture suggests efficient encapsulation of insulin within the polymeric core, with minimal drug deposition on the particle surface. Such morphology is beneficial for reducing the initial burst release and promoting sustained diffusion-controlled drug release. The homogeneous microstructure further confirms the formation of a stable polymer–protein composite system with uniform drug distribution throughout the matrix.

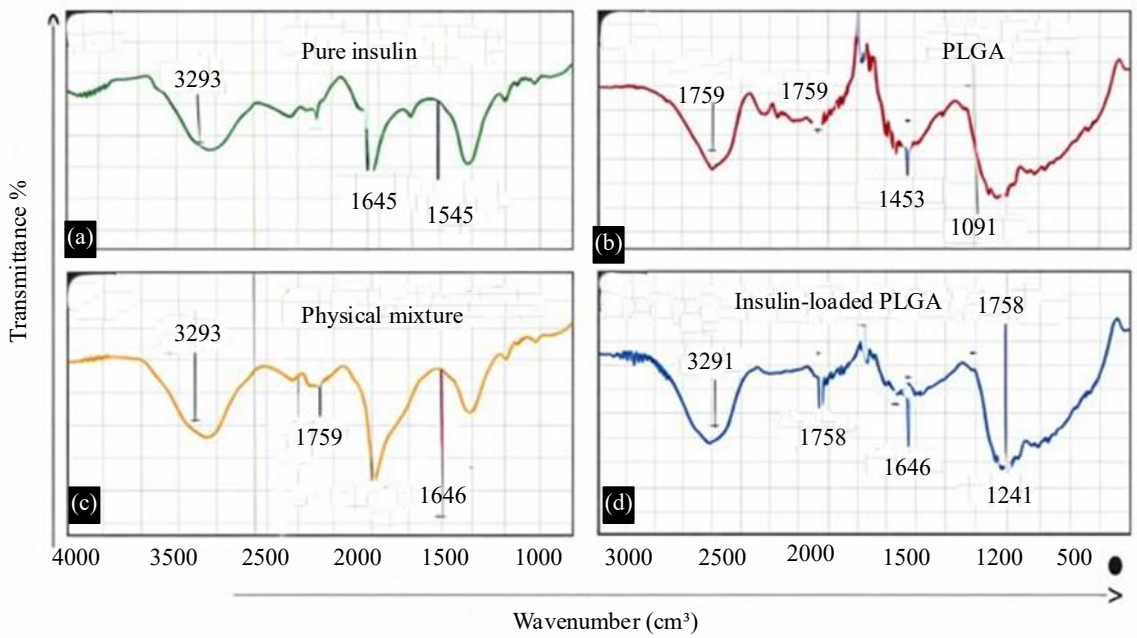

Figure 2. FTIR spectra of (A) pure insulin, (B) PLGA, (C) physical mixture, and (D) insulin-loaded PLGA polymer composite nanoparticles.

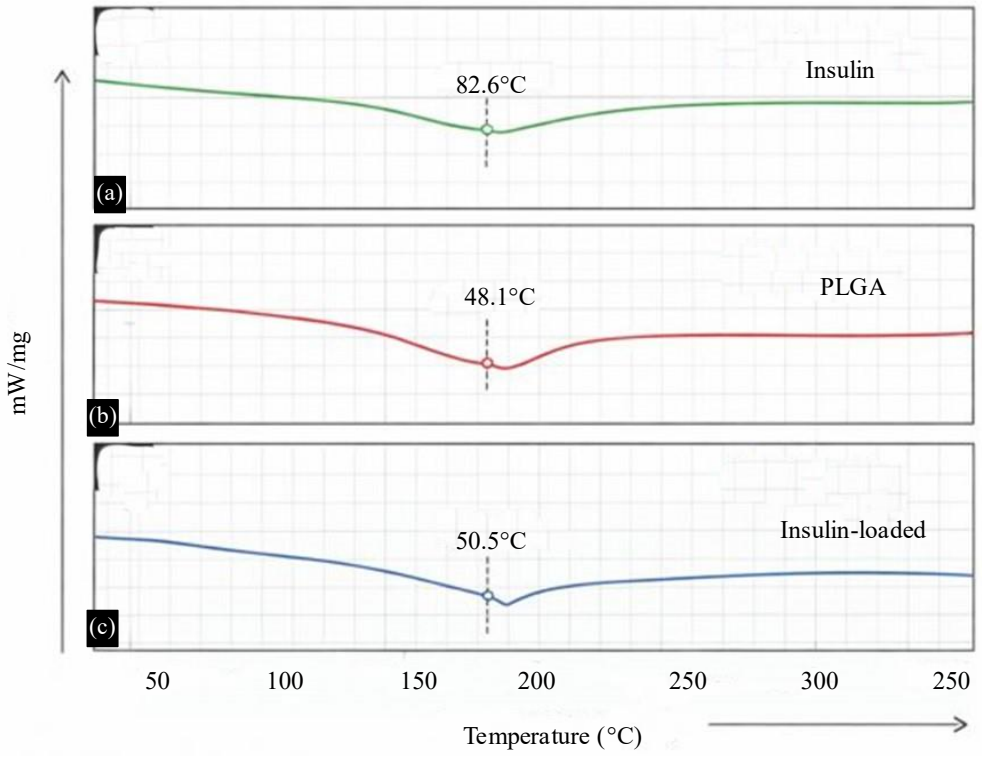

Figure 3. DSC thermograms of (A) insulin, (B) PLGA, and (C) insulin-loaded PLGA polymer composite nanoparticles.

Polymer–Drug Compatibility and Composite Formation

Figure 2 presents the FTIR spectra of pure insulin, PLGA, their physical mixture, and insulin-loaded PLGA nanoparticles. Characteristic amide I and amide II bands of insulin were observed at 1655 cm^{-1} and 1542 cm^{-1}, respectively, corresponding to C=O stretching and N–H bending vibrations. The prominent ester carbonyl (C=O) stretching peak of PLGA appeared at 1758 cm^{-1}, confirming the polymer's structural integrity. In the spectrum of the composite nanoparticles, the characteristic peaks of both insulin and PLGA were retained, with slight broadening and reduced intensity. No new peaks or major shifts were detected, indicating the absence of chemical interactions or degradation during formulation. The minor spectral changes may be attributed to hydrogen bonding or physical entrapment of insulin within the PLGA matrix, confirming successful composite formation without chemical incompatibility.

The findings confirm the physical entrapment of insulin within the PLGA matrix via noncovalent interactions, such as electrostatic forces and hydrogen bonding, indicating the absence of chemical incompatibility. DSC thermal analysis results confirmed the existence of composites (Figure 3). Unlike PLGA, which exhibited a broad glass transition range of 48 to 52 °C, pure insulin demonstrated a sharp endothermic melting peak at approximately 83 °C. The absence of insulin's characteristic melting peak in the composite nanoparticles indicates the molecular dispersion of insulin inside the polymer matrix and its subsequent transition from a crystalline to an amorphous state. To enhance encapsulation stability and regulate release behavior, it is beneficial to amorphize insulin within the polymer composite.

Table 2. In vitro cumulative insulin release from PLGA polymer composite nanoparticles.

Time (h)	Cumulative release (%)
2	6.8 ± 1.2
6	12.3 ± 1.8
12	22.7 ± 2.4
24	34.9 ± 2.9
48	51.6 ± 3.1
72	63.8 ± 3.4
120	72.5 ± 3.6

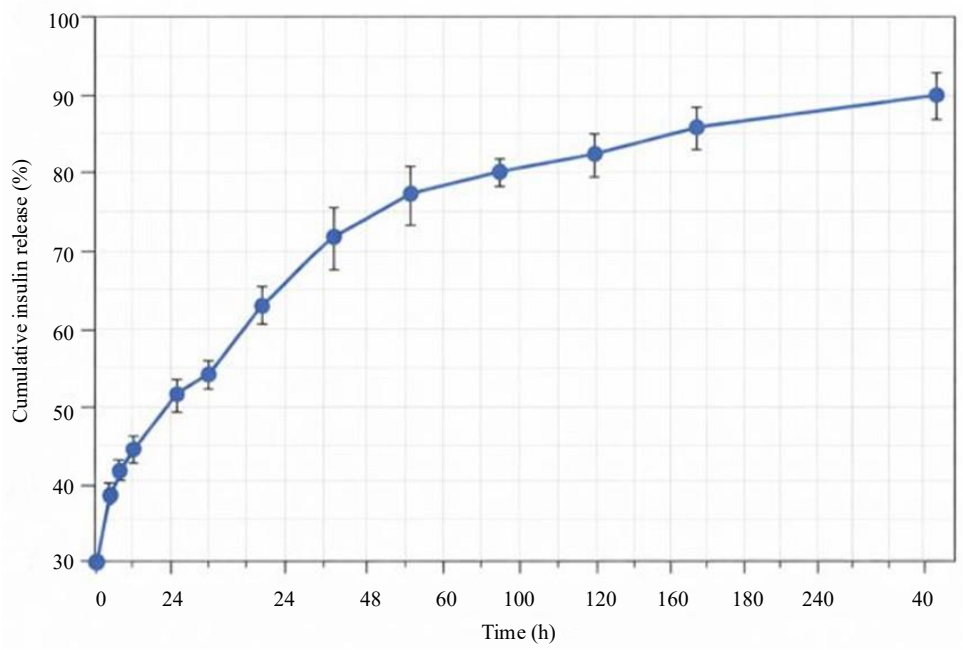

Figure 4. In vitro cumulative release profile of insulin from PLGA polymer composite nanoparticles in phosphate-buffered saline (pH 7.4) at 37 °C.

Table 3. Stability evaluation of insulin-loaded PLGA polymer composite nanoparticles.

Storage condition	Particle size (nm)	Encapsulation efficiency (%)
Initial	185.4 ± 12.6	78.6 ± 3.2
4 °C (3 months)	192.1 ± 14.3	75.9 ± 2.8
25 °C (3 months)	198.6 ± 16.7	73.4 ± 3.1

In Vitro Release Behavior and Matrix-Controlled Release Mechanism

Table 2 presents the release statistics for insulin from PLGA polymer composite nanoparticles, whereas Figure 4 illustrates the cumulative in vitro release curve of the drug. A transient peak of approximately 12% occurred within the initial 6 hours of the biphasic release profile, followed by a consistent and gradual release throughout the subsequent 120 hours. The limited insulin affixed to the surface and the compact polymer composite structure account for the reduced burst effect. Insulin permeates the hydrated polymer matrix while PLGA undergoes progressive hydrolysis throughout the extended release duration. Kinetic modeling indicated that the release data most closely aligned with the Higuchi model ($R^2 = 0.987$) and the Korsmeyer-Peppas model ($n = 0.46$). This indicates that the mechanism is governed by diffusion and that the erosion of the polymer matrix is involved. This research demonstrates that the degradation of polymers and the microstructure of composites significantly influence the rate of insulin release.

Stability of Polymer Composite Nanoparticles

Table 3 summarizes the stability of the optimized insulin-loaded PLGA nanoparticles after three months of storage at 4 °C and 25 °C. Only slight increases in particle size were observed, from 185.4 ± 12.6 nm initially to 192.1 ± 14.3 nm (4 °C) and 198.6 ± 16.7 nm (25 °C), indicating minimal aggregation or polymer relaxation during storage. Encapsulation efficiency showed a small reduction from 78.6 ± 3.2% to 75.9 ± 2.8% at 4 °C and 73.4 ± 3.1% at 25 °C, suggesting minor insulin diffusion over time. However, the overall retention of drug content remained high, confirming that the PLGA matrix effectively preserved insulin stability. The formulation exhibited better stability under refrigerated conditions, likely due to reduced polymer degradation at lower temperatures. Overall, the results demonstrate satisfactory physical stability and drug retention of the polymer composite nanoparticles over the three-month storage period.

The current study demonstrates that PLGA-based polymer composite nanoparticles serve as a robust and adaptable platform for continuous insulin delivery. Due to effective emulsification and polymer matrix design, the composite microstructure exhibits uniformity, regulated particle size distribution, and high encapsulation efficiency [19, 20]. The diminished burst release and prolonged diffusion-controlled dispersion were facilitated by the superior interfacial compatibility of insulin and PLGA. The five-day sustained release property of insulin indicates that diffusion pathways and the degradation of the composite matrix are likely the primary mechanisms governing insulin transport. The polymer matrix prevents the rapid crystallization or aggregation of insulin, while the amorphous dispersion of insulin within it enhances stability. Collectively, these findings indicate that PLGA composite nanoparticles are effective biodegradable carriers for prolonged insulin therapy and underscore the significance of polymer composite design in regulating protein release kinetics [21, 22].

CONCLUSION

The successful development of biodegradable PLGA-based polymer composite nanoparticles for prolonged insulin administration exemplifies the significance of polymer matrix engineering in modulating protein release kinetics. The improved composite system had some amazing features, such as consistent nanoscale dimensions, great stability, high encapsulation efficiency, and great compatibility between polymers and drugs. The structure of the thick composite may have slowed down the release of insulin by allowing it to diffuse and break down polymers. The study shows that polymer composite design can be used in advanced controlled-release drug delivery systems. It also shows that

PLGA polymer composite nanoparticles are a viable biodegradable platform for long-term insulin delivery.

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None

Conflict of Interest

None

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