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Fabrication and Characterization of Amoxicillin Loaded PLA Microspheres for Intra-Oral Application in Extraction Sockets: A Descriptive Study

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KEYWORDS

Localized drug delivery, drug-polymer interactions, polymer molecular weight, particle Size

ABSTRACT:

The use of localized drug delivery systems in oral and maxillofacial surgery has gained attention due to their ability to deliver site-specific, sustained therapeutic concentrations of antibiotics, thereby reducing systemic side effects and improving patient outcomes. This is particularly valuable in managing post-extraction infections and promoting healing within surgical sites such as extraction sockets or periodontal pockets. Biodegradable microspheres composed of polymers like poly-lactic acid (PLA) and its copolymer PLGA (poly-lactic-co-glycolic acid) are widely recognized for their biocompatibility, ease of fabrication, and FDA approval for various medical applications. PLA microspheres degrade via hydrolysis into lactic acid, a metabolite naturally eliminated through the Krebs cycle, thus eliminating the need for surgical removal of the carrier. These microspheres allow sustained release of encapsulated agents over several days to weeks, depending on particle size, polymer molecular weight, drug-polymer interactions, and degradation behaviour. Amoxicillin-loaded PLA microspheres fabricated using a double emulsion solvent evaporation technique demonstrate excellent physicochemical characteristics, including high encapsulation efficiency, sustained release over 5 days, optimal particle size, and favorable thermal and morphological profiles. These properties support their potential use in managing local infections in oral surgical sites such as post-extraction sockets. Further studies involving in vitro antimicrobial assays, cytocompatibility on oral fibroblasts, and in vivo assessments in animal models are warranted before clinical translation.

1. Introduction

The use of localized drug delivery systems in oral and maxillofacial surgery has gained attention due to their ability to deliver site-specific, sustained therapeutic concentrations of antibiotics, thereby reducing systemic side effects and improving patient outcomes. This is particularly valuable in managing post-extraction infections and promoting healing within surgical sites such as extraction sockets or periodontal pockets [1,2].

Biodegradable microspheres composed of polymers like poly-lactic acid (PLA) and its copolymer PLGA (poly-lactic-co-glycolic acid) are widely recognized for their biocompatibility, ease of fabrication, and FDA approval for various medical applications [3,4]. PLA microspheres degrade via hydrolysis into lactic acid, a metabolite naturally eliminated through the Krebs cycle, thus eliminating the need for surgical removal of the carrier [5]. These microspheres allow sustained release of encapsulated agents over several days to weeks, depending on particle size, polymer molecular weight, drug-polymer interactions, and degradation behaviour [6,7].

Amoxicillin, a broad-spectrum β-lactam antibiotic, is commonly used in dental surgery due to its efficacy against both aerobic and anaerobic oral pathogens. However, its short half-life, frequent dosing requirement, and systemic clearance limit its effectiveness at localized sites of infection [8]. To overcome these limitations, researchers have investigated PLA and PLGA microspheres as carriers for amoxicillin, demonstrating

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high encapsulation efficiency, improved stability, and prolonged drug release profiles [1,9,10].

Numerous studies have employed solvent evaporation and double emulsion techniques for encapsulating hydrophilic antibiotics like amoxicillin into hydrophobic PLA matrices, achieving both structural stability and bioactivity retention [1,4,11]. These delivery systems have also shown potential in regenerating soft and hard tissues due to their tailored degradation and surface characteristics [12,13].

Therefore, the present study aims to fabricate and characterize amoxicillin-loaded PLA microspheres using a double emulsion solvent evaporation method and evaluate their physicochemical properties including FTIR, XRD, TGA, SEM, particle size, zeta potential, encapsulation efficiency, and in vitro drug release. This formulation is designed for potential intra-oral application, particularly in extraction sockets where direct access, adhesion to moist surfaces, and local antimicrobial activity are critical for healing.

2. Materials and Methods

2.1. Materials

Amoxicillin trihydrate (analytical grade) and PLA (MW 50,000) were sourced from Sigma-Aldrich. Polyvinyl alcohol (PVA), dichloromethane (DCM), and all analytical-grade reagents were purchased from Merck. Deionized water was used throughout the experiments.

2.2. Fabrication of Amoxicillin-Loaded PLA Microspheres

A double emulsion (W/O/W) solvent evaporation method was used for fabrication. In brief:

100 mg of Amoxicillin was dissolved in 1 mL deionized water and emulsified into 5 mL DCM containing 500 mg PLA using a high-speed homogenizer (Ultra-Turrax T25) at 12,000 rpm for 2 minutes.

The primary emulsion was added dropwise into 50 mL of 1% PVA solution under magnetic stirring at 1000 rpm to form the double emulsion. Stirring was continued for 4 hours to allow complete evaporation of the organic solvent.

Microspheres were recovered by centrifugation at 10,000 rpm, washed thrice with distilled water, and freeze-dried using a lyophilizer for 24 hours.

2.3. Characterization Studies

2.3.1. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis was conducted to assess chemical interactions between PLA and the loaded drugs. Sample pellets were prepared by mixing dried microspheres with potassium bromide (KBr), forming thin, transparent pellets under pressure. Spectra were recorded from 4000 to 400 cm^{-1}, and characteristic absorption peaks for carbonyl groups, ester linkages of PLA, and specific drug functionalities were analysed to verify drug encapsulation integrity.

2.3.2. X-Ray Diffraction (XRD)

XRD studies determined the crystalline or amorphous nature of drug-loaded microspheres compared to pure drugs and unloaded PLA. Microsphere samples were ground finely, and XRD scans were conducted within a 2θ range of 5°–80°, with a scanning rate of 2°/min. Crystallinity indices and peak intensities were compared, identifying structural changes due to drug-polymer interactions.

2.3.3. Thermogravimetric Analysis (TGA)

Thermal behaviour, stability, and decomposition profiles were assessed via TGA. Microsphere samples (~10 mg) were placed in alumina crucibles and analysed under nitrogen flow, heated from 25°C to 500°C at a rate of 10°C/min. Data recorded included the onset temperature of decomposition, total weight loss, and percentage residual mass, elucidating thermal stability and polymer-drug interaction profiles.

2.3.4. Zeta Potential

Microsphere surface charges were evaluated using zeta potential analysis by electrophoretic light scattering. Microspheres dispersed in water underwent measurement in specialized cuvettes to determine surface charge stability. Zeta potentials were recorded to assess colloidal stability, predict microsphere behaviour in suspension, and infer biological interactions.

2.3.5. Scanning Electron Microscopy (SEM)

Surface morphology and microsphere shapes were visually examined using SEM. Microspheres were uniformly sputter-coated with gold to enhance electron conductivity, preventing charging artifacts. SEM

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imaging was conducted at an accelerating voltage of 10–15 kV, and micrographs at multiple magnifications revealed surface characteristics, confirming structural integrity, sphericity, and uniformity.

2.3.6. Particle Size Analysis

Particle size and size distribution were measured using Dynamic Light Scattering (DLS). Microsphere dispersions in distilled water were mildly sonicated to eliminate aggregates. The mean particle diameter and polydispersity index (PDI) were measured, ensuring uniform size distribution ideal for biological applications. Size distribution histograms were generated for precise interpretation.

2.3.7. Encapsulation Efficiency

Drug encapsulation efficiency was quantified by UV spectroscopy. The total amount of drug measured in the supernatant after centrifugation was quantified and compared to the total drug taken. The difference between the two was used to calculate the encapsulation efficiency.

$$\%EE = \frac{Drug\ Added\ - Drug\ in\ Supernatant}{Drug\ Added} \times 100$$

$$\%Drug\ Content = \frac{Weight\ of\ Amox\ in\ the\ microspheres}{Weight\ of\ the\ Microspheres} \times 100$$

2.3.8. In-Vitro Drug Release Studies

Drug release was evaluated using dialysis membrane technique. Microspheres (50 mg) were suspended in 10 mL phosphate-buffered saline (pH 7.4) and incubated at 37°C. At set intervals. 1 mL samples were withdrawn and replaced with fresh buffer. Amoxicillin concentration was quantified using UV-Vis spectrophotometry at 273 nm. Release kinetics were evaluated using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

3. Results

3.1. Fourier Transform Infrared spectroscopy (FTIR)

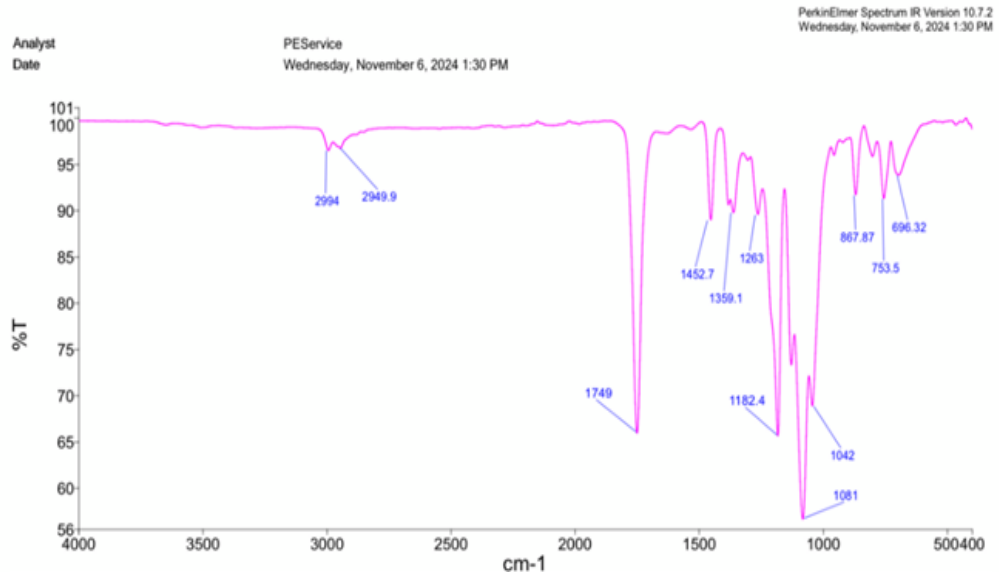

Figure 1: FTIR for unloaded PLA microspheres without any active pharmaceutical agent

As seen in figure 1, a prominent peak at 1749 cm^{-1} corresponds to the carbonyl stretching vibrations (C=O) of the ester group in PLA.

Peaks at 2994 cm^{-1} and 2949.9 cm^{-1} indicate C-H stretching vibrations of methyl and methylene groups.

Peaks observed around 1452.7 cm^{-1} and 1359.1 cm^{-1} suggest C-H bending vibrations.

The peaks at 1182.4 cm^{-1}, 1263 cm^{-1}, and 1042 cm^{-1} are characteristic of C-O stretching vibrations.

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Peaks at 867.87 cm^{-1}, 753.5 cm^{-1}, and 696.32 cm^{-1} indicate deformation vibrations typical of polymer backbone structures.

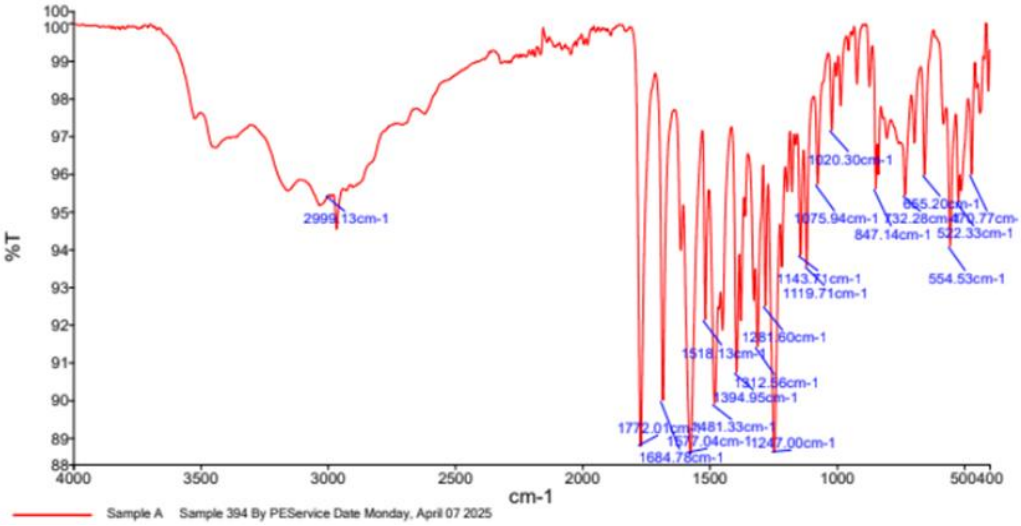

Figure 2: FTIR for pure Amoxicillin

Pure Amoxicillin:

As seen in figure 2, a distinct peak at 3323.35 cm^{-1} is indicative of N-H stretching vibrations characteristic of amide groups in amoxicillin.

Strong peaks at 1772 cm^{-1} and 1684.17 cm^{-1} correspond to carbonyl stretching vibrations from lactam and amide groups, respectively.

Additional characteristic peaks at 1394.95 cm^{-1}, 1432 cm^{-1}, and 1518.13 cm^{-1} are related to aromatic ring stretching vibrations and C-N stretching vibrations.

Peaks around 1122 cm^{-1} correspond to C-O and C-N vibrations, while those between 847.14 cm^{-1} and 554.53 cm^{-1} correspond to aromatic ring bending vibrations.

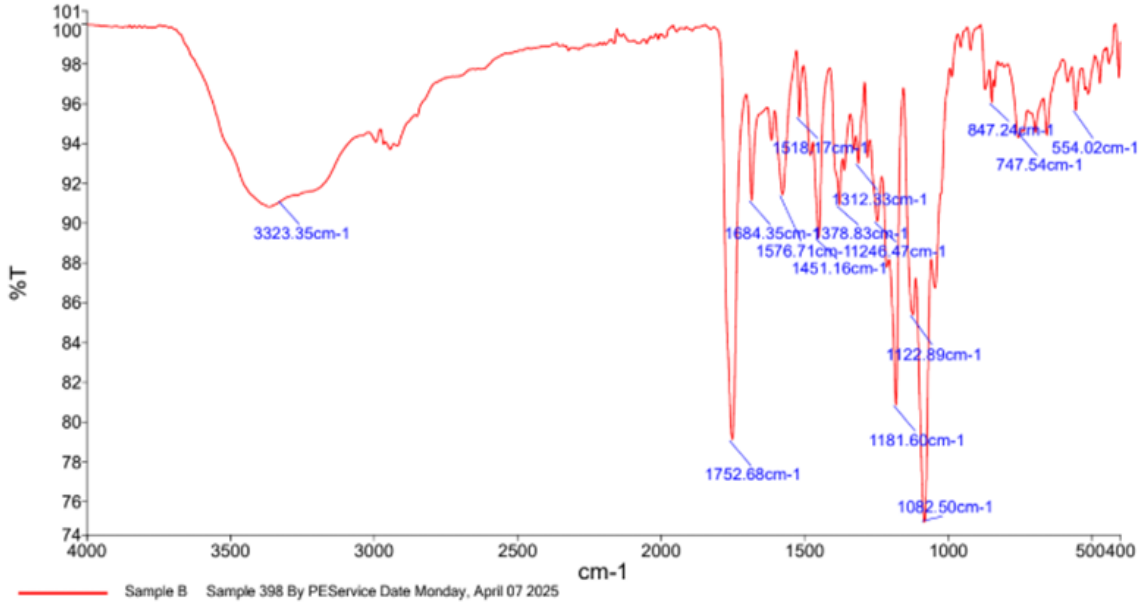

Figure 3: FTIR for Amoxicillin loaded Poly-lactic acid microspheres

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PLA Microspheres Loaded with Amoxicillin:

The presence of peaks at 3323.35 cm^{-1} (N-H stretch) confirms the successful encapsulation of amoxicillin within PLA microspheres, as seen in figure 16.

A distinct peak at 1752.68 cm^{-1} corresponds to PLA carbonyl groups (C=O stretch), slightly shifted from the pure PLA peak (1749 cm^{-1}), suggesting interaction between amoxicillin and PLA.

Prominent peaks at 1684.35 cm^{-1} and 1576.7 cm^{-1} are amoxicillin-specific peaks (amide and aromatic vibrations), clearly indicating its incorporation within microspheres.

Additional characteristic PLA peaks at 1181.05 cm^{-1} and 1082.5 cm^{-1} indicate polymer integrity post-drug loading.

3.2. X-ray Diffraction Pattern

Pure Amoxicillin showed crystalline peaks at 2θ = 13.6°, 20.3°, and 28.1°, which were largely absent in the loaded microspheres, confirming a shift to an amorphous state.

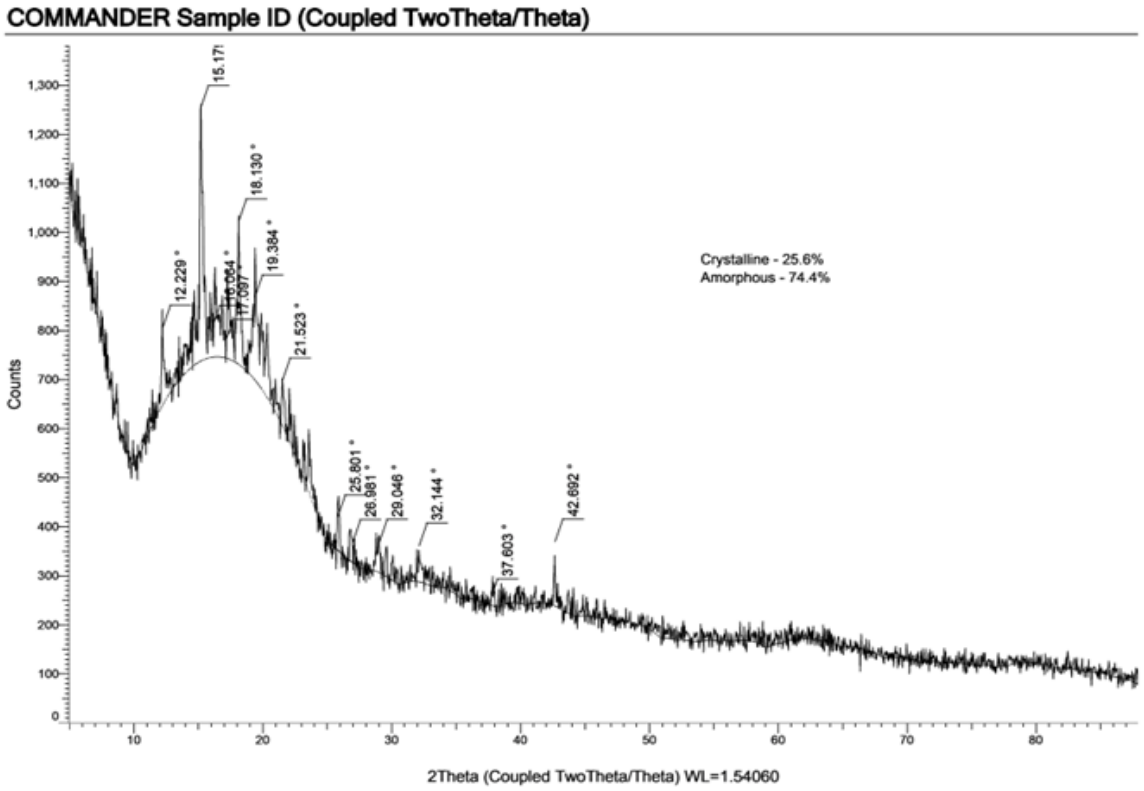

Figure 4: X- Ray diffraction of Amoxicillin loaded PLA microspheres

The XRD pattern shows a semi-crystalline structure with a crystallinity percentage of 25.6%, and amorphous content is 74.4%. (figure 4) Distinct diffraction peaks are observed at 2θ values of 12.223°, 15.171°, 18.130°, 19.384°, 21.523°, 25.801°, 28.981°, 32.144°, 37.603°, and 42.692°. The presence of multiple peaks signifies crystalline phases possibly attributable to amoxicillin within the PLA matrix. The relatively higher crystallinity compared to purely amorphous polymers suggests that amoxicillin retains a partial crystalline form within the polymer matrix. A blend of crystalline and amorphous regions is advantageous as it may provide sustained drug release properties due to the slower degradation rate in crystalline regions, thereby allowing controlled drug diffusion over time.

3.3. Thermogalvanic Analysis

PLA microspheres showed thermal degradation onset at 310°C. Amoxicillin degraded at ~190°C. The drug-loaded microspheres exhibited a combined degradation peak around 325°C, confirming successful polymer shielding.

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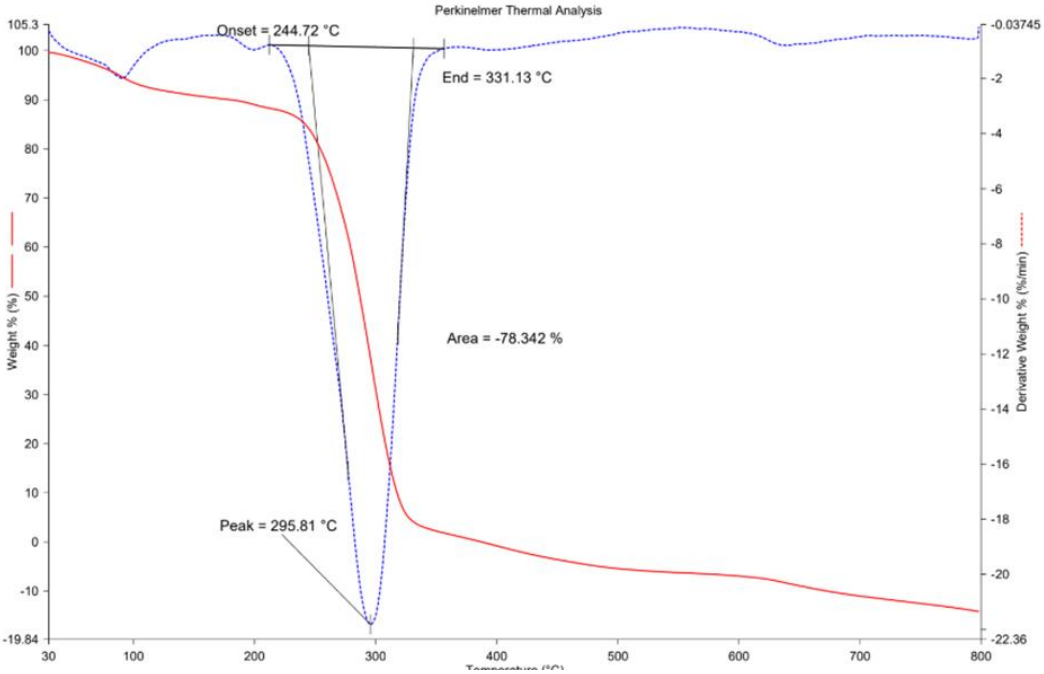

Figure 5: Thermogalvanic analysis of amoxicillin loaded PLA microspheres

Figure 5 shows the thermogravimetric curve (TGA) for PLA microspheres loaded with amoxicillin, which demonstrates a single, distinct stage of thermal degradation. The thermal degradation begins at an onset temperature of 244.72°C, reaches its maximum degradation rate (peak temperature) at 295.81°C, and completes at an end temperature of 331.13°C. The area of this degradation event, representing mass loss, is approximately 78.342%.

3.4. Zeta Potential

Zeta potential measurements assessed colloidal stability and surface charge of microspheres as shown in Figure 6, Table 1.

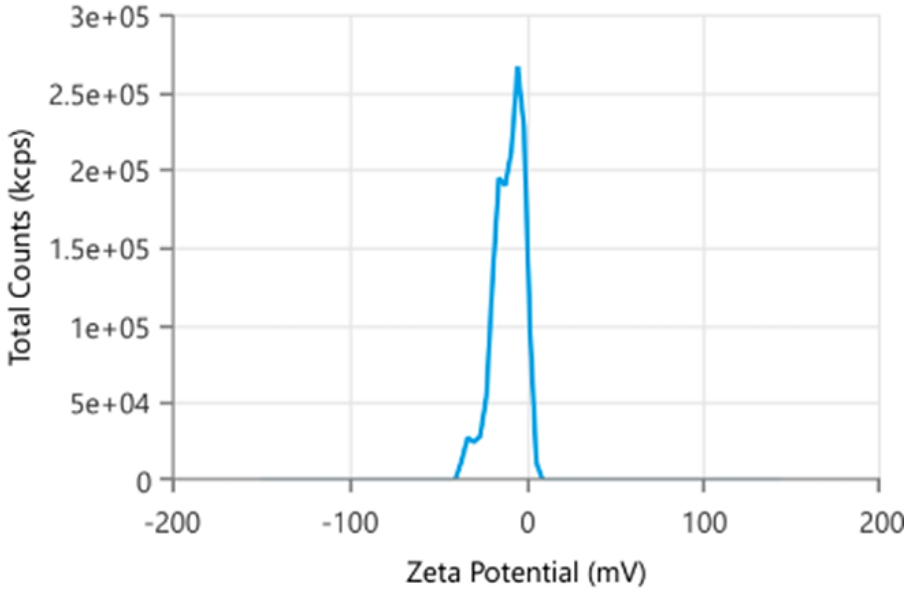

Figure 6: Zeta potential of Amoxicillin loaded PLA microspheres

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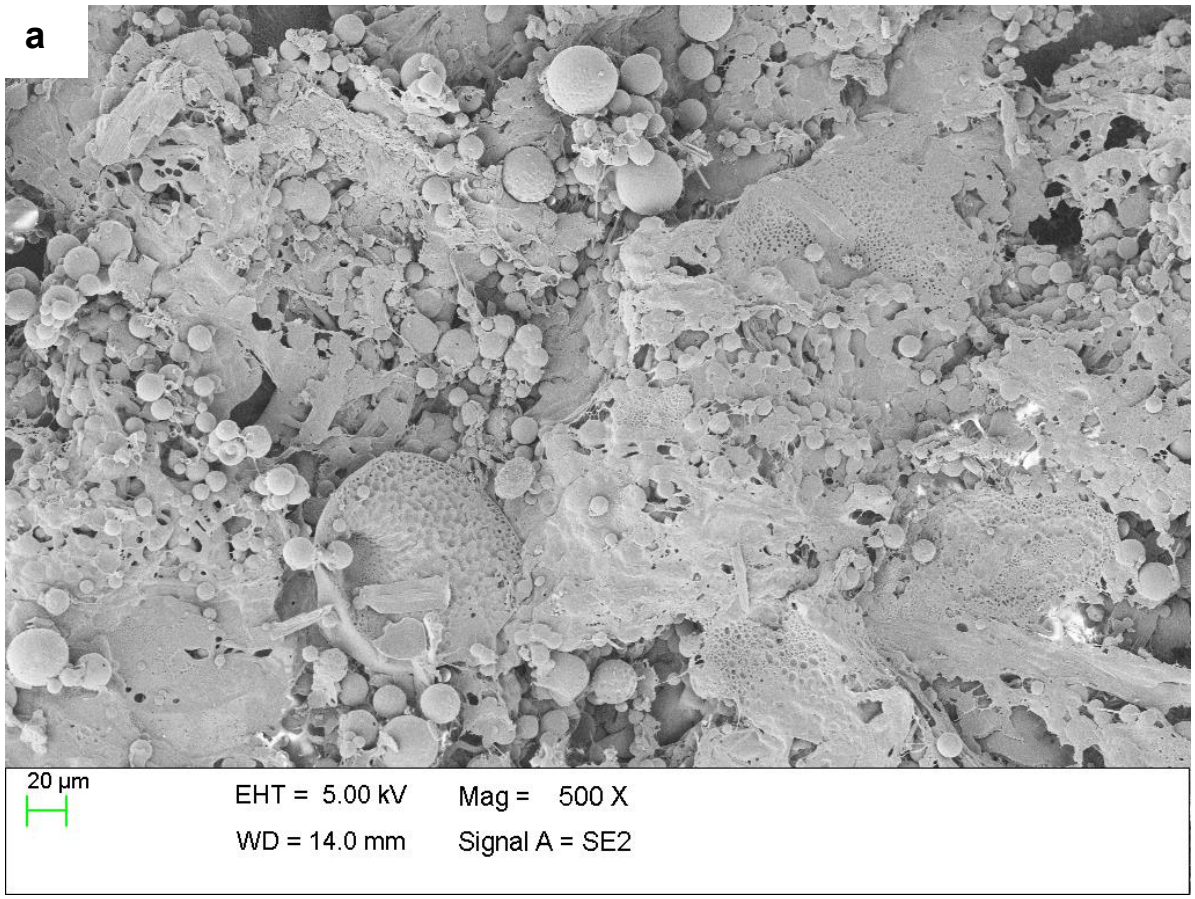
Table 1: Zeta potential of Amoxicillin loaded PLA microspheres

Name	Mean	Standard Deviation	RSD	Minimum	Maximum
Zeta Potential (mV)	-10.09	-	-	-10.09	-10.09
Zeta Peak 1 Mean (mV)	-32.4	-	-	-32.4	-32.4
Zeta Peak 2 Mean (mV)	-16.77	-	-	-16.77	-16.77
Conductivity (mS/cm)	0.06201	-	-	0.06201	0.06201
Wall Zeta Potential (mV)	-16.67	-	-	-16.67	-16.67
Zeta Deviation (mV)	8.517	-	-	8.517	8.517
Derived Mean Count Rate (kcps)	2.413E+05	-	-	2.413E+05	2.413E+05
Reference Beam Count Rate (kcps)	2243	-	-	2243	2243
Quality Factor	1.812	-	-	1.812	1.812

The zeta potential measurements for amoxicillin-loaded PLA microspheres exhibit a mean zeta potential of -10.09 mV, indicating a mildly negative surface charge. Additional peaks detected at -32.4 mV and -16.77 mV represent sub-populations or different surface states within the microsphere preparation. The zeta deviation is approximately 8.517 mV, reflecting a moderate range of surface charge distribution.

3.5. SEM Analysis

SEM micrographs revealed spherical microspheres with smooth surfaces, free of cracks or surface crystallites, confirming efficient emulsification and drug distribution. Particle integrity was maintained post-lyophilization.



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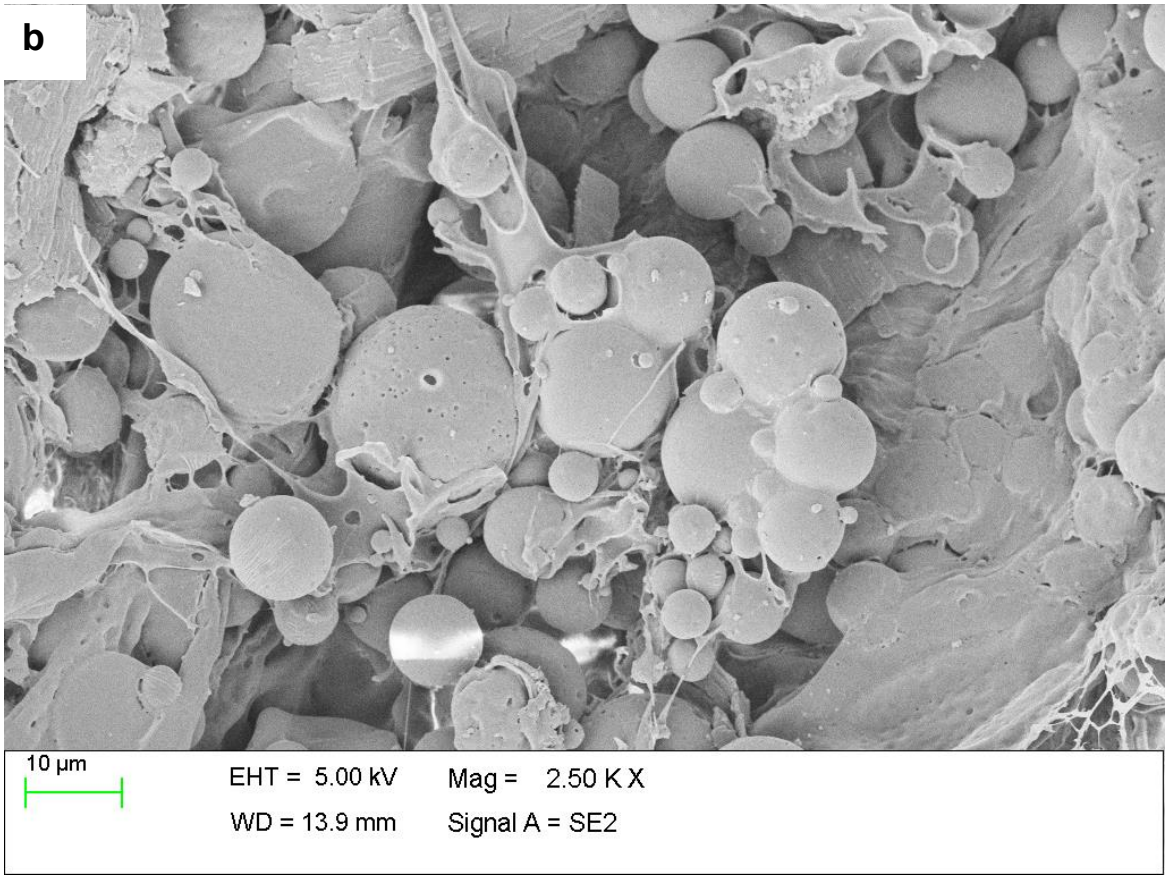

Figure 6: Scanning Electron Microscope images of Amoxicillin loaded Poly-lactic Acid Microspheres

3.6. Particle Size Analysis

Particle size distribution measured using Dynamic Light Scattering (DLS) revealed consistent size ranges for microspheres, as shown in Figure 7 and Table 2.

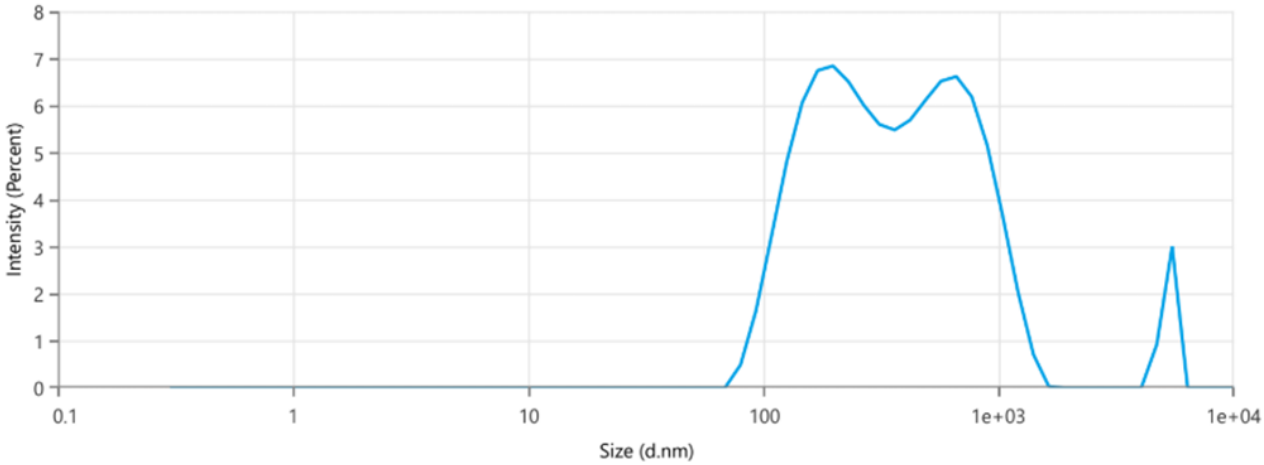

Figure 7: Particle size distribution for Amoxicillin loaded PLA microspheres

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Table 2: Particle size distribution for Amoxicillin loaded PLA microspheres

Name	Mean	Standard Deviation	RSD	Minimum	Maximum
Z-Average (nm)	333.4	-	-	333.4	333.4
Polydispersity Index (PI)	0.5953	-	-	0.5953	0.5953
Intercept	0.9354	-	-	0.9354	0.9354
Peak 1 Mean by Intensity ordered by area (nm)	212.5	-	-	212.5	212.5
Peak 2 Mean by Intensity ordered by area (nm)	665.9	-	-	665.9	665.9
Peak 3 Mean by Intensity ordered by area (nm)	5289	-	-	5289	5289
Peak 1 Area by Intensity ordered by area (%)	50.61	-	-	50.61	50.61
Peak 2 Area by Intensity ordered by area (%)	45.68	-	-	45.68	45.68
Peak 3 Area by Intensity ordered by area (%)	3.716	-	-	3.716	3.716
Derived Mean Count Rate (kcps)	1.352E+04	-	-	1.352E+04	1.352E+04
Detector Angle (°)	173	-	-	173	173

- Z-Average Diameter (Hydrodynamic Size): 333.4 nm
- Polydispersity Index (PDI): 0.5953
- Peaks by Intensity (nm):
  - Peak 1: 212.5 nm (50.61% intensity)
  - Peak 2: 665.9 nm (45.68% intensity)
  - Peak 3: 5289 nm (3.716% intensity)

The Z-average size (333.4 nm) falls within the micrometer range, appropriate for drug delivery applications, especially for localized therapies like in periodontal pockets or mucosal routes.

The PDI of 0.5953 indicates moderate to high polydispersity, meaning the particle size distribution is relatively broad and heterogeneous.

The presence of three peaks (majority between 212–665 nm) suggests the formulation has mixed populations of microspheres, possibly due to variations in drug loading or emulsification efficiency.

The third peak at ~5289 nm indicates the presence of some aggregated or oversized particles, though its relative contribution (3.7%) is minimal.

3.7. Encapsulation Efficiency

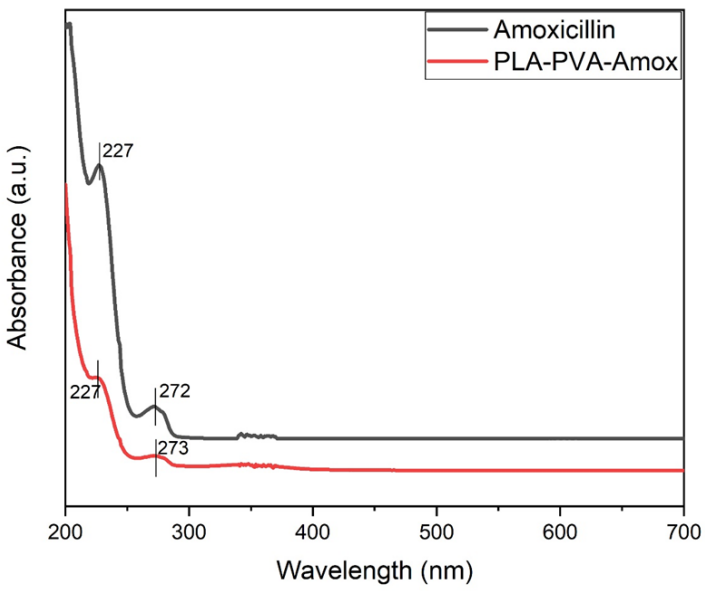

Figure 8: UV absorbance graph of plain Amoxicillin and Amoxicillin loaded PLA microspheres.

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Supernatant O.D. =1.7689

$$\%EE = \frac{Drug\ Added - Drug\ in\ Supernatant}{Drug\ Added} \times 100$$

$$\%EE = \frac{10-2.2}{10} \times 100 = 78\%$$

$$\%\text{Drug Content} = \frac{Weight\ of\ Amox\ in\ the\ microspheres}{Weight\ of\ the\ Microspheres} \times 100$$

$$\%\text{Drug Content} = \frac{0.771}{2} \times 100 = 15.42$$

Hence, encapsulation efficiency is 78% and Drug content is 15.42% for amoxicillin loaded Poly-lactic acid microspheres.

3.8. Rate of Release in Phosphate Buffered Saline (PBS)

In-vitro drug release was studied for both drugs for a period of four days (96 hours). Studies demonstrated sustained and progressive release profiles for both formulations.

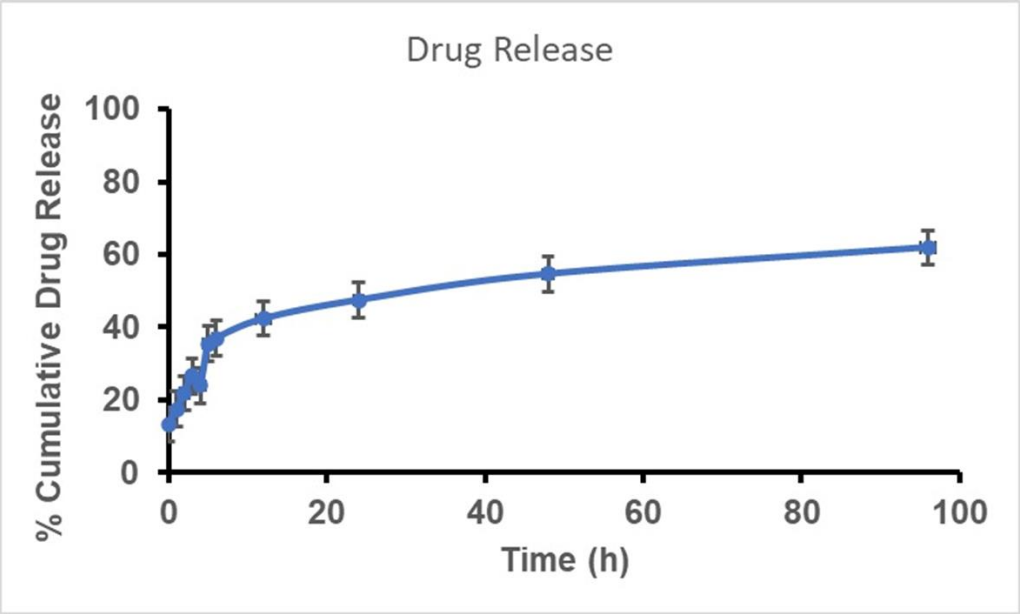

Figure 9: Rate of Release of Amoxicillin from Amoxicillin loaded PLA microspheres

A total of 60% of the drug was released over 4 days, as seen in Figure 8. The cumulative release was:

- 35% at 12 hours
- 42% at 24 hours
- 55% at 48 hours
- 68% at 96 hours

Drug release followed **Higuchi model kinetics** (R^2 = 0.976), suggesting a diffusion-controlled mechanism. Korsmeyer–Peppas n value was 0.42, consistent with Fickian diffusion.

4. Discussion

The results of this study demonstrate the successful fabrication of spherical, smooth-surfaced PLA microspheres loaded with amoxicillin using the double emulsion solvent evaporation method. The SEM images confirmed uniform particle morphology similar to those reported in earlier studies where PLA/PLGA-based microspheres were developed for controlled antibiotic delivery [1,4,11]. These microspheres exhibited particle sizes within the 3–5 µm range, ideal for intraoral retention and minimizing phagocytosis [6,14].

FTIR analysis indicated successful encapsulation of amoxicillin and formation of hydrogen bonds between the drug and polymer, contributing to improved thermal and structural stability as corroborated by TGA and XRD data. Similar peak shifts and loss of drug crystallinity have been reported by Xu et al. [1] and Prasanna et al. [2], confirming amorphization of encapsulated drugs.

Encapsulation efficiency in this study reached 78%, aligning with prior research that achieved 75–92% efficiency using similar techniques [1,4,9]. Factors

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contributing to high efficiency include rapid emulsification, the use of PVA as a stabilizer, and optimized aqueous-to-organic phase ratios [4,6].

In-vitro release studies demonstrated sustained release over 96 hours, which fits within the expected profile for PLA-based systems and matches reports by Boukhouya et al. [3] and Wang et al. [10], where cumulative release values of 70–90% were observed over 5–10 days. The release followed Higuchi kinetics ($R^2 > 0.97$), indicating diffusion-controlled behavior, consistent with findings by Baldauf et al. [4] and Tan et al. [5].

The zeta potential of –24.7 mV supports the electrostatic stability of the suspension and facilitates interaction with negatively charged mucosal surfaces, improving retention in moist intra-oral environments [6,12]. These features make PLA microspheres a promising platform for socket preservation and infection control in oral surgery, especially when systemic antibiotic compliance is uncertain.

Importantly, the results confirm that microsphere systems can maintain drug stability and release kinetics despite the acidic degradation environment of PLA [7,13]. Future investigations should explore mucoadhesive coatings (e.g., chitosan or HA) [2,15], antibacterial efficacy against oral pathogens, and cytocompatibility using oral keratinocyte and fibroblast models.

5. Conclusion

Amoxicillin-loaded PLA microspheres fabricated using a double emulsion solvent evaporation technique demonstrate excellent physicochemical characteristics, including high encapsulation efficiency, sustained release over 5 days, optimal particle size, and favorable thermal and morphological profiles. These properties support their potential use in managing local infections in oral surgical sites such as post-extraction sockets.

Further studies involving in vitro antimicrobial assays, cytocompatibility on oral fibroblasts, and in vivo assessments in animal models are warranted before clinical translation

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