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A COMPARATIVE STUDY OF RELEASE KINETICS BEHAVIOR MODELS AND SHELF LIFE ASSESSMENT of BACITRACIN ZINC-LOADED PLA COMPOSITES

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Highlights

- Investigation of release kinetic behavior of Bacitracin Zinc in PLA using mathematical models.
- Comparison of PLA composite biomaterials having different Bacitracin Zinc content ratio.
- Assessing shelf life and suitability of PLA/Bacitracin Zinc composites for biomedical usage.

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ABSTRACT: Mathematical modeling aims to simplify the complex process of drug release and to gain knowledge about the release mechanisms specific to a given material system. Consequently, a mathematical model focuses primarily on one or two important factors. Drug release aims to maximize the bioactivity of both naturally derived and synthetically derived macromolecules, thus increasing their clinical applicability and improving the overall quality of life. This study focused on fabricating PLA composites with different weight percentages of Bacitracin Zinc (0.5, 1.0, and 2.0) and evaluating their potential as a drug delivery system. To understand the release mechanism of Bacitracin Zinc from the PLA composites, we developed a Franz diffusion kinetic model and a mathematical model for cumulative release kinetics. The Franz diffusion model was utilized to analyze the release behavior of the PLA/Bacitracin Zinc composite structure. The results indicated a sustained release rate, following a Zero Order release kinetics pattern. Furthermore, the shelf life of the composite structure was determined to be 125 days. Python programming was employed to model the release behavior and estimate the shelf life of Bacitracin Zinc (0.5, 1.0, and 2.0) incorporated into the PLA matrix to compare different weight percentages' behavior and shelf life.

Keywords: *Bacitracin Zinc, Composite, PLA, Drug release kinetic, Franz diffusion kinetic model*

1. INTRODUCTION

The solute transport from drug-loaded polymeric matrices occurs via the diffusion of the active substance, which entails the swelling and erosion of the matrix structure of the polymeric material, whether it is biodegradable [1]. Non-biodegradable and biodegradable polymers are widely used in drug delivery systems because they can be used as a drug carrier [2], [3]. The solute transport system in non-biodegradable polymeric matrices is primarily governed by diffusion. Reservoir-type non-biodegradable polymers encompass systems that employ an inert coating material to serve as a membrane controlling the release rate. In such polymers, the release kinetics remain relatively constant and are unaffected by the concentration gradient, instead primarily governed by the thickness and permeability of the polymeric membrane. In contrast to matrix-type non-biodegradable polymers, the release mechanism in reservoir-type systems is predominantly driven by Fickian diffusion, wherein the release rate correlates with the concentration gradient, diffusion distance, and degree of swelling [4], [5]. On the other hand, biodegradable polymers exhibit a predisposition towards undergoing degradation via hydrolysis or enzymatic reactions. These polymers commonly incorporate chemically unstable bonds, including ester, amide, and anhydride bonds, which are prone to undergoing cleavage during degradation processes [6], [7]. Surface and bulk degradation are two distinct modes of degradation commonly observed in polymers. Surface-degrading polymers exhibit degradation primarily on the outer surface of the material, whereas bulk-degrading polymers experience degradation uniformly throughout the bulk. Water plays a critical role in hydrolysis, making water ingress into the polymer device crucial for investigating both release and dissociation kinetics [8], [9]. The degradation of semicrystalline polymers unfolds in two distinct stages. In the initial stage, water permeates the amorphous regions, initiating random hydrolytic cleavage of

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susceptible bonds, such as ester bonds. The subsequent stage commences as a substantial portion of the amorphous regions becomes disrupted. As degradation progresses, the polymer chains undergo breakage, leading to measurable changes in the average molecular weight of the polymer. Consequently, assessing temporal alterations in the average molecular weight is a quantitative measure for tracking the degradation process [10].

Bacitracin Zinc is a widely utilized antibiotic medication in topical ointments and creams. It exhibits efficacy against specific bacterial strains and is primarily employed for preventing and treating skin infections. The mechanism of action of Bacitracin Zinc involves interference with bacterial cell wall synthesis, leading to the inhibition of bacterial growth and facilitating the process of wound healing [11]. Multiple factors, particularly topical formulations, influence the release kinetics of Bacitracin Zinc. The diffusion-controlled release is a common mechanism whereby the release rate depends on the formulation's concentration gradient and diffusion properties. Matrix-controlled release is another approach employed in certain formulations wherein Bacitracin Zinc is incorporated within a matrix or polymer system [12]. Release occurs through either diffusion or erosion of the matrix, impacting the release kinetics. For solid dosage forms, the dissolution-controlled release may be predominant, where the dissolution rate and solubility of Bacitracin Zinc determine the release profile. Some formulations may exhibit a combination of release mechanisms, such as an initial burst release followed by sustained release. It is crucial to acknowledge that specific release kinetics can vary based on formulation design, manufacturing processes, and the presence of excipients [13]–[15].

PLA (polylactic acid), a biodegradable polyester, is a prominent polymer utilized to develop particulate drug delivery systems [16]. It belongs to a class of polymers distinguished by the presence of ester bonds. The synthesis of PLA involves the ring-opening copolymerization of two monomers [17]. Exploiting its hydrophobic nature, various emulsification processes are employed to fabricate PLA nano/microparticles with core-shell architectures, enabling the encapsulation of hydrophobic drugs within their hydrophilic cores [18]. It is worth noting that hydrophobic drugs tend to disperse preferentially in hydrophobic environments [19]. The release behavior of PLA particle delivery systems typically exhibits an initial burst phase followed by a nearly zero-order release phase [20]. Biodegradable polyesters, such as PLA and PLGA (poly(lactic-co-glycolic acid)), have been extensively utilized to develop controlled delivery systems, including implants and microparticles, for intramuscular or subcutaneous administration [21]. The primary goals of this research endeavor encompass examining the mathematical behavior model concerning the release kinetics of Bacitracin Zinc when incorporated into PLA polymer for drug release applications. Additionally, the study uses mathematical models to compare the PLA composite biomaterial loaded with different weight percentages of Bacitracin Zinc (0.5, 1.0, 2.0) while assessing and comparing the shelf life of PLA/Bacitracin Zinc composites. Consequently, the study intends to deliberate on the applicability and suitability of these composites for biomedical purposes.

2. MATERIAL AND METHODS

2.1. Production of Bacitracin Zinc-Loaded Pla Composites

Poly (lactic acid) (PLA 4060D, pellet form) was procured from Nature Works LLC. The solvents used chloroform (CHL, with a molecular weight of 119.38 g/mol), were obtained from Merck without requiring additional purification. Bacitracin (catalog no. B0125, Poole, UK) was purchased from Merck. Item № 21212; CAS № 1405-89-6; Purity ≥70% (Bacitracin A, B1, B3 mixture; Molecular formula; $C_{66}H_{101}N_{17}O_{16}S \bullet Zn$; Formula weight: 1486). To prepare the PLA solution, PLA was dissolved at a weight ratio of 12% using 100 mL of CHL. The prepared PLA solution added various weight percentages of Bacitracin Zinc (0.5, 1.0, and 2.0 wt. %). The mixture was stirred using a magnetic stirrer for 2 hours at room temperature. The resulting working groups were designated as PLA/Bacitracin Zinc (0.5), PLA/Bacitracin Zinc (1.0), and PLA/Bacitracin Zinc (2.0). Subsequently, 25 mL of each working group was poured into 9 cm glass Petri dishes and dried in an oven at 40°C for 24 hours. The dried composites were then stored in a desiccator for further analysis.

2.2. Characterization of Bacitracin Zinc-Loaded Pla Composites

The structural characteristics of the Bacitracin Zinc-loaded PLA composites were performed using Fourier Transform Infrared Spectroscopy (FT-IR; Thermo Scientific. Ltd., US) to identify the covalent bonds in the structure of composites. The spectra were obtained in transmission mode, with scans ranging from 4000 to 400 cm^{-1} wavenumber, and a resolution of 2 cm^{-1}. A total of 15 readings were collected. Scanning Electron Microscopy (SEM; TESCAN. Ltd., Czech Republic (VEGA 3 LMH)) analysis was employed for examining the surface morphology features of the Bacitracin Zinc-loaded PLA composites. To enhance conductivity, a thin layer of gold was deposited on the samples using a sputter coater device (Emitech K550X, UK) at around 1 kV. Imaging was conducted at an accelerating voltage of 15 kV, with images captured at varying magnification levels.

2.3. Mathematical Modeling of In Vitro Franz Diffusion Release for Bacitracin Zinc-Loaded Pla Composites

To begin the study, linear calibration curves were constructed for five concentrations of Bacitracin Zinc (0.5, 1.0, and 2.0 wt. %). The release characteristics of Bacitracin Zinc from the composites were then investigated at various intervals. The first step involved weighing and placing 10, 20, and 30 mg of Bacitracin Zinc-loaded PLA composites into separate Eppendorf tubes containing 1 ml of phosphate-buffered saline (PBS) with a pH of 7.4. The release of Bacitracin Zinc from the 12% PLA composites was conducted using a thermal shaker (BIOSAN TS-100C) and 1 ml of fresh PBS. At different time intervals, 1 ml of PBS was withdrawn from the Eppendorf tubes and transferred to a quartz bath with a capacity of 1 ml. The initial procedure involved obtaining calibration graphs to identify the primary peak corresponding to fucoidan in all the composites. For this purpose, a Shimadzu UV-1280 UV-VIS spectrophotometer machine was utilized. The process commenced by allowing the PBS solution to remain in the Eppendorf tubes and the samples to shake inside the thermal shaker for 15 minutes. After 15 minutes, the solutions were removed from the Eppendorf tubes and individually analyzed using the spectrophotometer. After analysis, fresh PBS was added again, and the samples were left in the thermal shaker for up to 150 hours.

Determining the drug's dissolution profile can be accomplished by employing diverse mathematical models, where choosing an appropriate mathematical function is crucial in defining the profile. These models, including the zero-order, first-order, and Higuchi models, elucidate the underlying mechanism governing the drug's release process. Specifically, the zero-order equation:

$$Q_t = Q_0 + K_0 t \quad (1)$$

Where the amount of drug (Q_t) dissolved over a given period (t) with the inclusion of the initial amount of drug (Q_0) in the solution, which is usually equal to zero, and the zero-order release constant (K_0) in units of concentration per time. Similarly, the first-order equation:

$$\log C = \log C_0 - K_t/2.303 \quad (2)$$

Where measures the rate of change of the initial concentration of the drug (C_0) over time (t) and the first-order constant (K). Higuchi's equation:

$$Q_t = K_H * t^{1/2} \quad (3)$$

Where the amount of drug (Q_t) is released over a given period (t) using the release rate constant (K_H) for the Higuchi model, the data is fitted according to the Korsmeyer–Peppas model to ascertain the precise mechanism behind the drug release process. This model:

$$Mt/M\infty = K * t^n \quad (4)$$

Where describes the general solute release behavior from a controlled release polymer system and uses the fraction of drug (M_t/M_∞) released over time (t), the release rate constant (K), and the release exponent (n) to characterize different releases for cylindrical-shaped matrices.

2.4. Bacitracin Zinc Stability

The most commonly employed *in vitro* technique for assessing dermal absorption involves the topical application of the active ingredient in a suitable formulation onto the surface of a skin sample [22]. Dissolution tests, predominantly utilizing the Franz Diffusion device, are widely utilized for evaluating composite formulations [23], [24]. In this study, composite samples containing the active substance benzalkonium chloride (Bacitracin) were carefully placed on the membranes within Franz diffusion cells. The composite samples were centrally positioned within the Franz device, ensuring consistent exposure. The lower compartment of the cells was filled with a 2.5 mL volume of media, while the upper compartment accommodated a 1.5 mL sample for examination. The experiment was meticulously conducted under controlled conditions, maintaining a constant ambient temperature of 37ºC with continuous agitation. At pre-determined intervals, specifically at the 15th and 30th minutes, and subsequently at the 1st, 2nd, 4th, 6th, 8th, and 24th hours, 2.5 mL aliquots of the sample were withdrawn from the lower compartment and promptly replaced with fresh medium equilibrated to 37ºC. This process was repeated throughout the experimental period to ensure continuous monitoring. The concentration of the active substance in the collected samples was subsequently quantified using high-performance liquid chromatography (HPLC). The cumulative percentage of the active substance passing through the cells was plotted against time to evaluate the cumulative dermal absorption profile. The cumulative percentage of the active substance passing through the cells at the end of the 24 hours was calculated by analyzing the resulting curve. Statistical analysis of the cumulative mass losses for the composite samples was conducted using a Python program.

3. RESULTS AND DISCUSSION

Figure 1A. shows the FT-IR spectra of PLA, Bacitracin Zinc, and PLA/Bacitracin Zinc (2.0) samples. The shared identifiable peaks within the FT-IR spectrum of both PLA and PLA/Bacitracin Zinc composites were found to be in the regions of 1900–1650 cm^{-1} (corresponding to the stretching vibration of C=O) and 1300–1000 cm^{-1} (indicating the stretching vibration of C–O and the framework vibration of C–C). Notably, two distinct peaks emerged within the range of 3540–3180 cm^{-1} due to the presence of NH2 and NH groups in the PLA structure [25], [26]. In the FT-IR spectrum, the specific absorption peaks (1746 cm^{-1}, 1092 cm^{-1}) characterizing PLA remained unchanged without any noticeable deviation. The key chemical constituents of Bacitracin Zinc encompass C=O, C=N, NH_2, NH, –OH, and C–S groups. An overlapping of peaks from certain functional groups within PLA, and Bacitracin Zinc was evident due to their shared chemical moieties. The intensity of the characteristic absorption peaks (3244 cm^{-1}, 1651 cm^{-1}, and 1539 cm^{-1}) associated with Bacitracin Zinc [27] experienced a significant reduction. This decline pointed out a physical interaction between Bacitracin Zinc and the carrier materials, implying that the incorporation of Bacitracin Zinc into PLA did not result in alterations to their underlying chemical structures. Figure 1B. and Figure 1C. demonstrate the SEM images of PLA and PLA/Bacitracin Zinc(2.0) samples, respectively. Upon analysis of SEM in Figure 1B., it becomes evident that the PLA polymer demonstrated a film structure devoid of any observable deformations. This observation shows the PLA polymer's capability to undergo successful film formation. In contrast, Figure 1C, depicting the surface imagery of the film specimen incorporating Bacitracin Zinc within the PLA polymer, revealed an absence of adverse effects on PLA film formation attributed to Bacitracin Zinc. Notably, no deformations were induced by Bacitracin Zinc. Consequently, a deduction can be drawn that the composite materials comprising Bacitracin Zinc-loaded PLA can indeed be effectively produced without compromising the film formation process. Moreover, the obtained results exhibit concurrence with prior research conducted on polymeric

composites loaded with biomolecules [28]–[30].

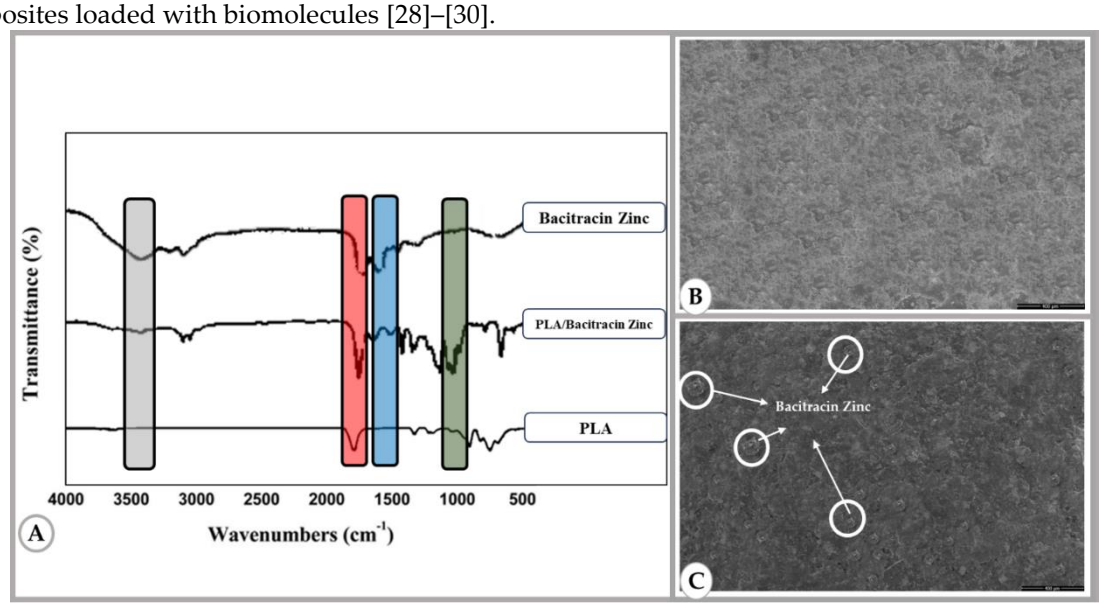

Figure 1. A. FT-IR spectra of Bacitracin Zinc, PLA and Bacitracin Zinc (2.0)-loaded PLA, B. SEM images of PLA and C. of Bacitracin Zinc (2.0)-loaded PLA composite

Table 1. Franz diffusion cumulative release kinetics model (R^2 value after 24 hours)

	Bacitracin Zinc-loaded PLA composite materials		
Model	**PLA/Bacitracin Zinc(0.5)**	**PLA/Bacitracin Zinc(1.0)**	**PLA/Bacitracin Zinc(2.0)**
Korsmeyer-Peppas	0.9023	0.8854	0.9020
Zero-order	0.9965	0.9897	0.9952
Firs-order	0.9423	0.9406	0.9343
Hixson	0.9817	0.9817	0.9817
Higuchi	0.9682	0.9556	0.9670

Understanding release kinetics systems and the intricate interplay between the active ingredient and the biomaterial system is crucial for designing effective delivery systems tailored to specific applications. Furthermore, developing doped polymeric matrices necessitates the utilization of robust mathematical models to uncover the underlying solute transport mechanisms. This study group aims to offer a fresh perspective on the structure-function relationship of biodegradable PLA polymers, specifically focusing on drug release kinetics and employing mathematical modeling techniques. The cumulative release kinetics model for PLA polymer containing 0.5% bacitracin zinc exhibited a zero-order pattern, with a correlation coefficient (R^2) of 0.9968 (Figure 2.A). Similarly, the cumulative release behavior of 1% Bacitracin zinc loaded into PLA polymer adhered to a zero-order kinetics model, displaying a correlation coefficient (R^2) of 0.9897 (Figure 2.B). The release kinetics model for PLA composite loaded with 2% Bacitracin zinc demonstrated a zero-order trend as well, with a correlation coefficient (R^2) of 0.9952 (Figure 2.C). The study employed Fick's law as the basis for modeling the drug release kinetics of Bacitracin zinc. The cumulative logarithmic linear release model of Bacitracin zinc is illustrated in Figure 1.D, representing its relationship with logarithmic time. The release kinetics analysis for Bacitracin zinc-loaded PLA composites consistently yielded zero-order kinetics across all three ratios (0.5, 1.0, and 2.0), as evident in Figures 2A, 2B, and 2C. Comparative analysis of Korsmeyer-Peppas, zero-order, first-order, Hixson, and Higuchi models, each possessing correlation coefficients of 0.90 and above, was performed (Table 1.). This evaluation revealed that the zero-order model exhibited the best fit, with the optimal ratio being "0.5". In a prior investigation, drug delivery kinetics were explored on Poly(lactic acid-co-lysine) (PLL)/poly(L-lactic acid) (PLLA)/Bacitracin (BAC) nanofibers, resulting in a correlation coefficient (R^2) of 0.98. The

relatively high PLLA ratio hindered complete diffusion of BAC from the nanofibers due to BAC encapsulation. Consequently, the researchers concluded that this circumstance contributed to the cumulative release of BAC [25]. According to Gokhale [31], the diffusion biodegradability of the drug system, swelling of the polymeric matrix, and material degradation are the key factors influencing solute transport from drug-containing polymeric matrices. By utilizing various mathematical models, the optimized composites for achieving the desired drug release profile were determined as PLA/Bacitracin Zinc(0.5), PLA/Bacitracin Zinc(1.0), and PLA/Bacitracin Zinc(2.0). Several mathematical models were examined to describe the emission pattern, including Zero Order, First Order, Higuchi, Hixon, and Korsmeyer-Peppas release kinetic models. The Fickian linear curve profile was observed, indicating a Zero Order release kinetic diffusion profile. Statistical analysis in Python was conducted to determine the cumulative amount of the active ingredient at the end of 30 days. In line with Fu et al. [32], the PLA polymer material used in this study is biodegradable, and the implementation of the Franz diffusion mathematical model was deemed appropriate for the release of active drug materials within this structure. Similarly, Bao et al. [33] performed in vitro release kinetic modeling using the Franz diffusion method for an ointment formulation, considering the high viscosity of the ointment and extended contact times. During their Franz diffusion study, Salamanca et al. [27] obtained a working profile following Zero Order diffusion, with an R^2 value of 0.929, in a linear Fickian equation applied in a cellulose membrane environment (pH 7.4). Gokhale [31] determined the release kinetics working model as Korsmeyer-Peppas, yielding an R^2 value of 0.996 based on the Fickian law. Baert et al. [34] employed the Franz diffusion model to create release kinetics in both skin and artificial skin media, yielding an R^2 value of 0.926 after 24 hours of measurement, and identified the release profile according to Korsmeyer.

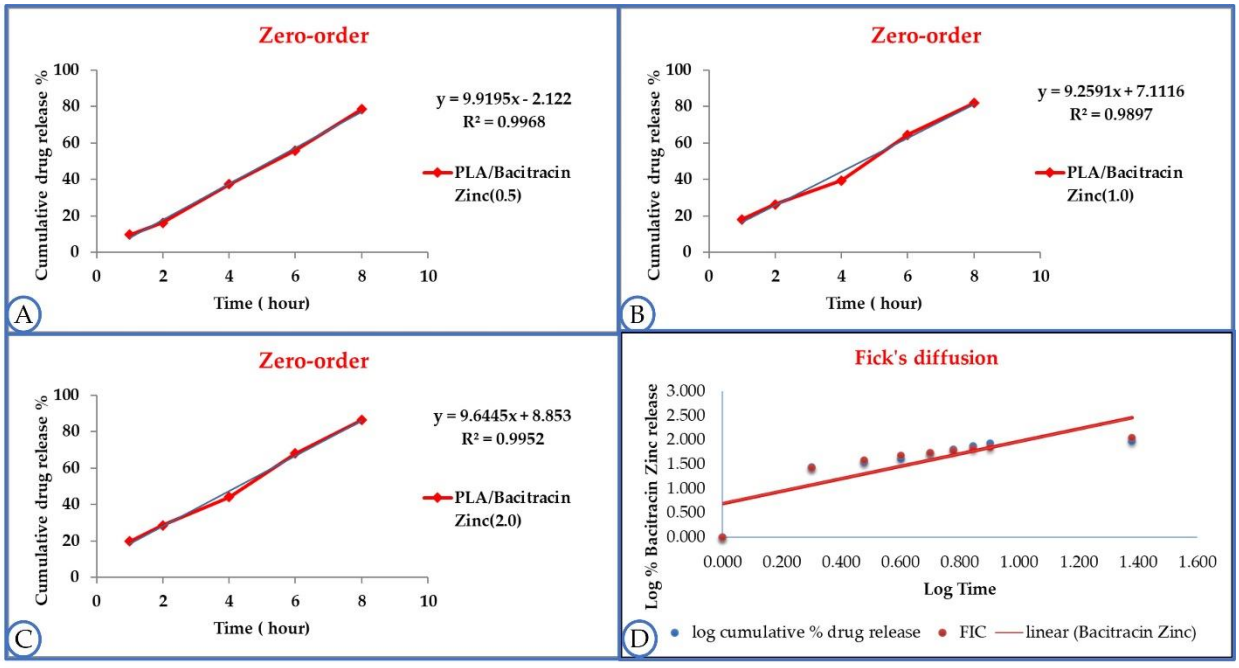

Figure 2. Franz Diffusion mathematical models A. Zero Order modeling of PLA/Bacitracin Zinc(0.5), B. Zero Order modeling of PLA/Bacitracin Zinc(1.0), C. Zero Order modeling of PLA/Bacitracin Zinc(2.0), D. Fick's diffusion of Bacitracin Zinc

The stability specification study revealed significant findings regarding the PLA/Bacitracin Zinc composites. For the PLA/Bacitracin Zinc(0.5) composite, the shelf life was 31.6 days (Figure 3A.), falling within a time range where we can have at least 50-95% confidence in the response. Similarly, the PLA/Bacitracin Zinc(1.0) composite exhibited a shelf life of 35.4 days (Figure 3B.), within a time range where we can have at least 50-95% confidence in the response. In the case of the PLA/Bacitracin Zinc(2.0) composite, the shelf life was 125.2 days (Figure 3C.), within a time range where we can be at least 50-95%

certain of the response. Overall, the release kinetics and shelf-life statistics analysis of the PLA study group indicate that the best working sample within the specified range (90-110%) is the PLA/Bacitracin Zinc(2.0) composite, with a shelf life of 125 days. Enhanced and extended shelf life holds significant prominence for polymers and composites destined for diverse applications across multiple domains, including biophysics, medicine, biomedical, and various other realms within biotechnology [35]–[37]. Based on these results, even if all samples have an acceptable shelf life, PLA/Bacitracin Zinc(2.0) may be the preferred better choice for different biomedical applications. In addition, the results obtained are in agreement with the studies on the shelf life of bacitracin biomolecule [38], [39].

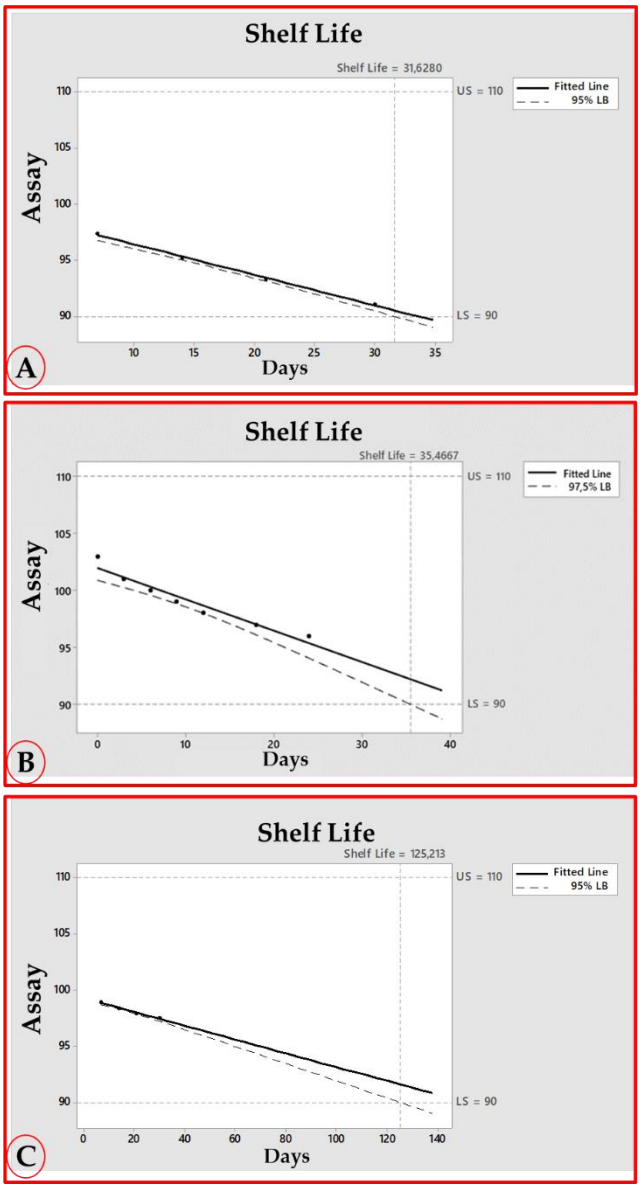

Figure 3. A shelf life of A. PLA/Bacitracin Zinc(0.5), B. PLA/Bacitracin Zinc(1.0), C. PLA/Bacitracin Zinc(2.0)

4. CONCLUSIONS

In this study, Bacitracin Zinc biomolecule with different amounts was loaded into PLA polymer and Bacitracin Zinc-loaded PLA composite materials were successfully prepared with simple casting method. As a result of the loading of Bacitracin Zinc into PLA polymer, PLA/Bacitracin Zinc(2.0) showed the best

shelf life and PLA/Bacitracin Zinc(0.5) showed the best behavior kinetics. Zero-order model of the release behavior obtained by the Franz diffusion study was observed as the most appropriate behavior. In the zero-order mathematical model, R^2 values of PLA/Bacitracin Zinc(2.0) and PLA/Bacitracin Zinc(0.5) were obtained as 0.9952 and 0.9968, respectively. The shelf life of PLA/Bacitracin Zinc(2.0) with Phyton analysis was found as 125 days, and the usability of PLA/Bacitracin Zinc(2.0) composite biomaterial in biomedical applications may be more effective in terms of the shelf life behavior. Nevertheless, the PLA/Bacitracin Zinc(0.5) composite, which displayed favorable and suitable release kinetics, also demonstrated an adequate shelf life. This suggests that these materials could be considered a favorable option for potential utilization in biomedical applications.

Declaration of Ethical Standards

The authors followed all ethical guidelines, including authorship, citation, data reporting, and publishing original research.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Data Availability

Not applicable.

5. REFERENCES

[1] D. Y. Arifin, L. Y. Lee, and C. H. Wang, "Mathematical modeling and simulation of drug release from microspheres: Implications to drug delivery systems," *Advanced Drug Delivery Reviews*, vol. 58, no. 12-13, pp. 1274-1325, 2006, doi: 10.1016/j.addr.2006.09.007.

[2] O. Pillai and R. Panchagnula, "Polymers in drug delivery," *Current Opinion in Chemical Biology*. vol. 5, no. 4, pp. 447-451, 2001, doi: 10.1016/S1367-5931(00)00227-1.

[3] M. Chasin and R. Langer, Eds., *Biodegradable polymers as drug delivery systems*. New York: Marcel Dekker, 1990.

[4] J. Siepmann and F. Siepmann, "Mathematical modeling of drug delivery," *International Journal of Pharmaceutics*, vol. 364, no. 2, pp. 328-343, 2008, doi: 10.1016/j.ijpharm.2008.09.004.

[5] S. B. Lin, K. S. Hwang, S. Y. Tsay, and S. L. Cooper, "Segmental orientation studies of polyether polyurethane block copolymers with different hard segment lengths and distributions," *Colloid Polym. Sci.*, vol. 263, pp. 128-140, 1985, doi: 10.1007/BF01412787.

[6] L. K. Fung and W. M. Saltzman, "Polymeric implants for cancer chemotherapy," *Advanced Drug Delivery Reviews*, vol. 26, no. 2-3, pp. 209-230, 1997, doi: 10.1016/S0169-409X(97)00036-7.

[7] J. Heller, R. W. Baker, R. M. Gale, and J. O. Rodin, "Controlled drug release by polymer dissolution. I. Partial esters of maleic anhydride copolymers—properties and theory," *J. Appl. Polym. Sci.*, vol. 22, no. 7, pp. 1991–2009, 1978.

[8] J. Heller, "Controlled release of biologically active compounds from bioerodible polymers," *Biomaterials*, vol. 1, no. 1, pp. 51-57, 1980, doi: 10.1016/0142-9612(80)90060-5.

[9] K. R. Kamath and K. Park, "Biodegradable hydrogels in drug delivery," *Adv. Drug Deliv. Rev.*, vol. 11, no. 1-2, pp. 59-84, 1993, doi: 10.1016/0169-409X(93)90027-2.

[10] U. Edlund and A. C. Albertsson, "Degradable polymer microspheres for controlled drug

delivery,"*in Degradable Aliphatic Polyesters, Advances in Polymer Science*, Springer, Berlin, Heidelberg, vol. 157, pp. 67-112, 2002, doi: 10.1007/3-540-45734-8_3.

[11] J. Yao, S. Zhang, W. Li, Z. Du, and Y. Li, "In vitro drug controlled-release behavior of an electrospun modified poly (lactic acid)/bacitracin drug delivery system," *RSC Adv.*, vol. 6, no. 1, pp. 515–521, 2016.

[12] M. A. Repka, S. Prodduturi, M. Munjal, and P. Mididoddi, "Matrix-and reservoir-based transmucosal delivery systems: tailoring delivery solutions," *Am. J. Drug Deliv.*, vol. 2, pp. 173–192, 2004.

[13] D. Cai, B. Zhang, J. Zhu, H. Xu, P. Liu, Z. Wang, J. Li, Z. Yang, X. Ma, and S. Chen, "Enhanced bacitracin production by systematically engineering S-adenosylmethionine supply modules in Bacillus licheniformis," *Front. Bioeng. Biotechnol.*, vol. 8, pp. 305, 2020.

[14] M. Goldraich and J. Kost, "Glucose-sensitive polymeric matrices for controlled drug delivery," *Clin. Mater.*, vol. 13, no. 1–4, pp. 135–142, 1993.

[15] I. Lavon and J. Kost, "Mass transport enhancement by ultrasound in non-degradable polymeric controlled release systems," *J. Control. release*, vol. 54, no. 1, pp. 1–7, 1998.

[16] L. Singh, V. Kumar, and B. D. Ratner, "Generation of porous microcellular 85/15 poly (DL-lactide-co-glycolide) foams for biomedical applications," *Biomaterials*, vol. 25, no. 13, pp. 2611-2617, 2004, doi: 10.1016/j.biomaterials.2003.09.040.

[17] C. E. Astete and C. M. Sabliov, "Synthesis and characterization of PLGA nanoparticles," *Journal of Biomaterials Science, Polymer Edition*, vol. 17, no. 3, pp. 247-289, 2006, doi: 10.1163/156856206775997322.

[18] Y. Kakizawa, R. Nishio, T. Hirano, Y. Koshi, M. Nukiwa, M. Koiwa, J. Michizoe, and N. Ida, "Controlled release of protein drugs from newly developed amphiphilic polymer-based microparticles composed of nanoparticles," *J. Control. Release*, vol. 142, no. 1, pp. 8-13, 2010, doi: 10.1016/j.jconrel.2009.09.024.

[19] D. K. Sahana, G. Mittal, V. Bhardwaj, and M. N. V. R. Kumar, "PLGA nanoparticles for oral delivery of hydrophobic drugs: Influence of organic solvent on nanoparticle formation and release behavior in vitro and in vivo using estradiol as a model drug," *J. Pharm. Sci.*, vol. 97, no. 4, pp. 1530-1542, 2008, doi: 10.1002/jps.21158.

[20] Y. P. Li, Y. Y. Pei, X. Y. Zhang, Z. H. Gu, Z. H. Zhou, W. F. Yuan, J. J. Zhou, J. H. Zhu, and X. J. Gao, "PEGylated PLGA nanoparticles as protein carriers: Synthesis, preparation and biodistribution in rats," *J. Control. Release*, vol. 71, no. 2, pp. 203-211, 2001, doi: 10.1016/S0168-3659(01)00218-8.

[21] L. Brannon-Peppas, "Recent advances on the use of biodegradable microparticles and nanoparticles in controlled drug delivery," *International Journal of Pharmaceutics*, vol. 116, no. 1, pp. 1-9, 1995, doi: 10.1016/0378-5173(94)00324-X.

[22] T. J. Franz, "Percutaneous absorption. On the relevance of in vitro data," *J. Invest. Dermatol.*, vol. 64, no. 3, pp. 190-195, 1975, doi: 10.1111/1523-1747.ep12533356.

[23] L. Bartosova and J. Bajgar, "Transdermal Drug Delivery In Vitro Using Diffusion Cells," *Curr. Med. Chem.*, vol. 19, no. 27, pp. 4671-4677, 2012, doi: 10.2174/092986712803306358.

[24] B. Godin and E. Touitou, "Transdermal skin delivery: Predictions for humans from in vivo, ex vivo and animal models," *Advanced Drug Delivery Reviews*, vol. 59, no. 11, pp. 1152-1161, 2007, doi: 10.1016/j.addr.2007.07.004.

[25] J. Yao, S. Zhang, W. Li, Z. Du, and Y. Li, "In vitro drug controlled-release behavior of an electrospun modified poly(lactic acid)/bacitracin drug delivery system," *RSC Adv.*, vol. 6, no. 1, pp. 515–521, 2015, doi: 10.1039/c5ra22467e.

[26] F. Ciftci, N. Duygulu, Y. Yilmazer, Z. Karavelioğlu, R. Çakır Koç, O. Gündüz, and C. B. Ustündag, "Antibacterial and cellular behavior of PLA-based bacitracin and zataria multiflora nanofibers produced by electrospinning method," *Int. J. Polym. Mater. Polym. Biomater.*, vol. 72, no. 4, pp. 319–334, 2023, doi: 10.1080/00914037.2021.2008391.

[27] S. Afzal, K. Barkat, M. U. Ashraf, I. Khalid, Y. Mehmood, N. H. Shah, S. F. Badshah, S. Naeem, S.

A. Khan, and M. Kazi, "Formulation and Characterization of Polymeric Cross-Linked Hydrogel Patches for Topical Delivery of Antibiotic for Healing Wound Infections," *Polymers (Basel).*, vol. 15, no. 7, pp. 1652, 2023.

[28] F. Ciftci, "Release kinetics modelling and in vivo-vitro, shelf-life study of resveratrol added composite transdermal scaffolds," *Int. J. Biol. Macromol.*, vol. 235, pp. 123769, 2023, doi: 10.1016/j.ijbiomac.2023.123769.

[29] Y. Srisuwan and Y. Baimark, "Preparation of biodegradable silk fibroin/alginate blend films for controlled release of antimicrobial drugs," *Adv. Mater. Sci. Eng.*, vol. 2013, Article ID 412458, 2013, https://doi.org/10.1155/2013/412458.

[30] M. Makaremi, H. Yousefi, G. Cavallaro, G. Lazzara, C. B. S. Goh, S. M. Lee, A. Solouk, and P. Pasbakhsh, "Safely dissolvable and healable active packaging films based on alginate and pectin," *Polymers (Basel).*, vol. 11, no. 10, pp. 1594, 2019.

[31] A. Gokhale, "Achieving zero-order release kinetics using multi-step diffusion-based drug delivery," *Pharm. Technol. Eur.*, vol. 38, no. 5, 2014.

[32] Y. Fu, G. Fodorean, P. Navard, and E. Peuvrel-Disdier, "Study of the partial wetting morphology in polylactide/poly[(butylene adipate)-co-terephthalate]/polyamide ternary blends: case of composite droplets," *Polym. Int.*, vol. 67, no. 10, pp. 1378–1385, 2018, doi: 10.1002/pi.5651.

[33] Q. Bao, J. Shen, R. Jog, C. Zhang, B. Newman, Y. Wang, S. Choi, and D. J. Burgess, "In vitro release testing method development for ophthalmic ointments," *Int. J. Pharm.*, vol. 526, no. 1-2, pp. 145-156, 2017, doi: 10.1016/j.ijpharm.2017.04.075.

[34] B. Baert, J. Boonen, C. Burvenich, N. Roche, F. Stillaert, P. Blondeel, J. van Bocxlaer, and B. de Spiegeleer, "A new discriminative criterion for the development of franz diffusion tests for transdermal pharmaceuticals," *J. Pharm. Pharm. Sci.*, vol. 13, no. 2, pp. 218-230, 2010, doi: 10.18433/j3ws33.

[35] J. F. PJ, K. J. Arun, A. A. Navas, and I. Joseph, "Biomedical applications of polymers—An overview," *Macromolecules*, vol. 28, no. 4, pp. 939–944, 2018.

[36] F. Cavalieri, A. El Hamassi, E. Chiessi, and G. Paradossi, "Stable polymeric microballoons as multifunctional device for biomedical uses: synthesis and characterization," *Langmuir*, vol. 21, no. 19, pp. 8758–8764, 2005.

[37] J. C. Middleton and A. J. Tipton, "Synthetic biodegradable polymers as orthopedic devices," *Biomaterials*, vol. 21, no. 23, pp. 2335–2346, 2000.

[38] R. Waterman, J. Lewis, and K. C. Waterman, "Accelerated stability modeling for peptides: a case study with bacitracin," *AAPS PharmSciTech*, vol. 18, no. 5, pp. 1692–1698, 2017.

[39] M. Asghari, A. AlizadehDoghikalaey, R. Safari, and A. Arshadi, "The effect of the Z bacitracin on the shelf–life of the silver carp during refrigeration," *Iran. J. food Nutr.*, vol. 3, pp. 31–38, 2011.