TẠP CHÍ HÓA HỌC & ỨNG DỤNG

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Tòa soạn:

164 đường Tựu Liệt
xã Tam Hiệp, huyện Thanh Trì, Hà Nội
ĐT: (024) 62885957 - 0983 602 553
Email: tapchihoahocvaungdung@gmail.com
Tài khoản: 002704060000831
Ngân hàng Quốc tế-VIB, số 5, Lê Thánh Tông, Hà Nội.

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RELEASE OF LOVASTATIN DRUG FROM POLY(LACTIC ACID) BIOMATERIAL

NGUYEN THI BICH VIET[1], VU QUOC MANH[2], TRAN THI KIEU GIANG[1], DOAN THI YEN[1],
VU THI THUONG[1], HA MANH HUNG[3], NGUYEN DANG DAT[1], VU QUOC TRUNG[1], NGUYEN NGOC LINH[2,*]
1. Faculty of Chemistry, Hanoi National University of Education, 136 Xuan Thuy, Cau Giay, Hanoi, Viet Nam
2. Faculty of Pharmacy, Thanh Do University, Kim Chung, Hoai Duc, Hanoi, Viet Nam
3. Faculty of General Education, Hanoi University of Mining and Geology,
Duc Thang, Co Nhue, Bac Tu Liem, Hanoi, Viet Nam
*Email: nnlinh@thanhdouni.edu.vn

SUMMARY:

Poly(lactic acid)/Lovastatin (PLA/Lov) biocomposites were successfully synthesized via the solution mixing method. The chemical structure, morphology, and thermal properties of lovastatin-carried biocomposites were characterized by Fourier Transform Infrared (FTIR) spectroscopy, Field emission scanning electron microscope (FESEM), and Differential Scanning Calorimetry (DSC), respectively. The results indicated that among 5 synthesized PLA/Lov biocomposites, PL10 with 10% wt. of Lov exhibited the most effective dispersion of lovastatin into the polymer matrix with a particle size in the range of 500–650nm. PL10 also exhibited the most uniform morphology and the smallest melting point (148.5°C). The release of lovastatin from PLA/Lov biocomposites in pH 2.0 and pH 7.4 buffer solutions was investigated using UV-Vis spectroscopy. The results indicated that the released lovastatin content was 27.26–40.58% and 32.73–54.25% after 30 hours of testing, respectively. Of the five biocomposites, PL10 showed the most reasonable results of drug release, with a lower release at pH 2.0 and a better release at pH 7.4, with a percentage of 27.26% and 54.25%, respectively.

Keywords: *Poly(lactic acid)/lovastatin biocomposites, lovastatin release.*

I. INTRODUCTION

According to the Biopharmaceutics Classification System (BCS), drugs are categorized into four types based on their solubility and permeability[1]. Among them, BCS class II drugs are characterized by high permeability but low aqueous solubility, which tends to limit drug absorption[2-4]. Research on drug formulations to improve the bioavailability of poorly soluble drugs by increasing their solubility and dissolution rate is one of the major challenges in the pharmaceutical preparation field. Poorly soluble drugs usually have a crystalline structure. Therefore, by developing new drug formulations, it is possible to change the crystalline structure to an amorphous form, improve the permeability by using hydrophilic carriers, and decrease the particle size[5-6]. There are several methods to enhance the drug solubility, such as (i) particle size reduction, (ii) nanosuspension, (iii) use of surfactants, (iv) salt formation, (v) use of prodrugs, (vi) pH adjustment, (vii) use of hydrotrope, (viii) solid dispersion, (ix) bio-based nanocomposite fabrication, etc. [7-9]. Among them, bio-based nanocomposite fabrication is one of the most promising techniques to ameliorate drug solubility and bioavailability, and being environmentally friendly[10-14].

Lovastatin (Lov) is a well-known prescription drug in the statin class. It lowers blood fat by competitively inhibiting 3-hydroxy-3-methyl-glutaryl Co-enzym A (HMG-CoA) reductase, reducing cholesterol synthesis in livers and decreasing cholesterol concentration in cells[15]. Lowering "bad" cholesterol and triglycerides and increasing "good" cholesterol helps reduce cardiovascular risks, preventing strokes and heart attacks. Lov exhibits poor bioavailability (<5%) due to its poor water solubility (0.4×10^{-3} mg/ml), low dissolution rate (53.9%), and short half-life (1-2 hours)[16-18]; therefore, regular medication is needed to maintain therapeutic levels in the blood[19]. There have been several studies on materials to improve the water solubility and bioavailability of Lov with a high degree

of oral absorption and extended delivery potential, such as Lov-containing phospholipid bilayers [20], Lov-carrying nanoparticles[21], or poly(lactic acid) microspheres[22]. Researchers also focused on the effects of the combined compositions and the ratios on the ability to control the Lov drug release in solutions simulating fluids and the human body, such as carrageenan/gellan gum[23], chitosan/alginate[24], chitosan/fish collagen [25],...

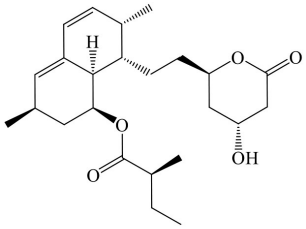
Poly(lactic acid) (PLA) is a versatile and environmentally friendly biopolymer that is widely applied in industrial fields such as packaging, textiles, disposable plastic tableware, etc., thanks to its thermoplastic behavior as well as its biodegradable, compostable, and recyclable properties. Especially, PLA is also known as a biocompatible material that emerged in various medical applications, from tissue generation[26], orthopedic[27], and cardiac[26] uses to drug delivery systems[28].

In this study, the solution mixing method was employed to prepare PLA/Lov biomaterial using PLA as a polymer matrix to disperse Lov while investigating the optimal ratio of Lov: PLA content by analyzing the structure, morphology, thermal properties, and drug release ability of the synthesized biocomposites. This work aimed to improve the solubility and release of Lov in two simulated solutions of gastric juice in the lower stomach and duodenum.

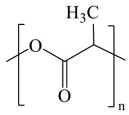
II. EXPERIMENTAL

2.1. Materials

Lov (white powder ≥ 98%) from Rhawn, China; PLA (solid, M_w = 65,000g/mol, melting point 264-269°C) from Sigma-Aldrich; and other chemicals including dichloromethane, ethanol, HCl, NaOH, KOH, and KH_2PO_4 supplied by Xilong Chemical Co. (China) were used without further purification. The structural formulas of Lov and PLA are shown below.



Lovastatin



Polylactic acid

2.2. Preparation of PLA/Lov biomaterial

PLA/Lov biomaterial samples were prepared by the solution mixing method according to the procedure as follows: A Lov solution in 5 ml of ethanol was added slowly to a PLA solution in 12ml of dichloromethane while stirring at a speed of 2.10^4rpm. High speed supports increasing the capacity of the solution of Lov in the solution of PLA[29]. Next, the mixture continued to be stirred at a speed of 400rpm for 1.5 hours. The obtained solution was poured into a petri dish and allowed to evaporate naturally for 24 hours. By varying the Lov: PLA content ratio, different PLA/Lov biomaterial samples were obtained, as shown in Table 1.

Table 1: Symbols and the composition of the PLA/Lov samples

No.	Sample symbol	PLA content (g)	Lov content (g)
1	PL5	0.5	0.025
2	PL7	0.5	0.035
3	PL10	0.5	0.050
4	PL15	0.5	0.075
5	PL20	0.5	0.100

2.3. Characterization

A Thermo Nicolet Nexus 670 FTIR spectrometer was used to analyze the chemical structure and functional groups of the PLA/Lov biocomposites. The morphology of the biomaterial was recorded using an SEM Hitachi S-4800 scanning electron microscope. Thermal properties were characterized by a DSC-60 Plus Shimadzu.

The drug release of Lov from the PLA/Lov biomaterial was investigated by a YOKE UV1900 Double Beam UV-Vis absorption spectrophotometer with a calibration curve.

2.4. Establishing a calibration curve of Lov in two buffer solutions

Two buffer solutions were prepared: a pH 2.0 buffer simulating gastric juice in the lower stomach and a pH 7.4 buffer simulating small intestinal fluid in the duodenum area.

Dissolve 19.0mg and 26.3mg of Lov in 200ml of pH 2.0 and pH 7.4 buffer solutions, respectively. Dilute these two solutions to different concentrations of Lov and measure the absorbance of the diluted solutions at the maximum wavelength (λ_{max}). The results obtained are presented in Table 2.

Table 2: Absorbance of Lov solutions of different concentrations at pH 2.0 and pH 7.4

Dilution	pH 2.0		pH 7.4	
	C_{Lov}, mol/l	Absorbance, A	C_{Lov}, mol/l	Absorbance, A
x4	7.838×10^{-5}	0.161	10.85×10^{-5}	2.380
x6	5.266×10^{-5}	0.132	7.233×10^{-5}	1.708
x8	3.919×10^{-5}	0.114	5.425×10^{-5}	1.216
x10	3.135×10^{-5}	0.103	4.340×10^{-5}	0.996
x12	2.613×10^{-5}	0.096	3.617×10^{-5}	0.890
x16	1.960×10^{-5}	0.085	3.100×10^{-5}	0.679
x18	1.724×10^{-5}	0.079	2.712×10^{-5}	0.618

The data in Table 2 was subjected to a linear regression to obtain two calibration equations that express the dependence of the absorbance on the concentration of Lov released in solution, and the results are shown in Table 3. It can be seen that the linearities of the two calibration curves are satisfied ($R^2 > 0.991$). Therefore, these equations can be used to determine the Lov content released from the biocomposite in the studied buffer solutions.

Table 3: Standard equations of absorbance *vs.* Lov concentration in pH 2.0 and pH 7.4 buffers

Buffer	λ_{max} (nm)	Standard equation	R^2 coefficient
pH 2.0	238.8	$A = 1325.7\ C_{Lov} + 0.06$	0.9916
pH 7.4	239.6	$A = 21956.0\ C_{Lov} + 0.04$	0.9951

2.5. Study on the effect of Lov content on the release of Lov drug from the PLA/Lov biomaterial

The release of Lov medicine from the PLA/Lov biomaterial was investigated in pH 2.0 and pH 7.4 buffers with a certain amount of PLA/Lov samples fixed in 0.2l of buffer solution and maintained at 37°C. Then the mixture was stirred at 400rpm. The absorbance of the solution was recorded every hour by taking out 5ml of solution, filtering, and measuring A at λ_{max}. Each time, 5ml of the corresponding buffer was added to keep the mixture volume constant during the experiment. The experiment lasted from 1 hour to 30 hours and was repeated three times to obtain the average value of absorbance.

The Lov content present in the solution was determined using the corresponding standard equation above. The percentage of Lov drug released in time *t* (hours) is calculated according to the formula:

$$C_{Lov}\ (\%) = \frac{m}{m_o} \times 100\%$$

where C_{Lov}: the percentage of Lov drug released (%)
m: the amount of Lov released (g)
m_o: the initial amount of Lov (g)

III. RESULTS AND DISCUSSION

3.1. Structure, morphology, and thermal properties of PLA/Lov biocomposites

3.1.1. FT-IR spectra of PLA/Lov biocomposites

The results of FTIR analysis for Lov, PLA, and biocomposite are presented in Figure 1 and Table 4. Both FTIR spectra of Lov and PLA show characteristic bands of -CH sp^3 at 2,994-2,865cm^{-1} for stretching vibrations and 1,459-1,355cm^{-1} for bending vibrations. Besides, the stretching vibrations of the C-O group appear at 1,082-1,072cm^{-1} and 1,262-2,158cm^{-1}. For Lov, the C=O stretching vibrations are found at 1,747cm^{-1}. Meanwhile, for PLA, the band attributed to the stretching vibrations of C=O is shifted to a lower wavelength number range (1,722-1,696cm^{-1}), and a valence vibration of -OH appears at 3,537cm^{-1} along with characteristic bands of valence and deformation vibrations of =CH at 3,015cm^{-1} and 966cm^{-1}, respectively.

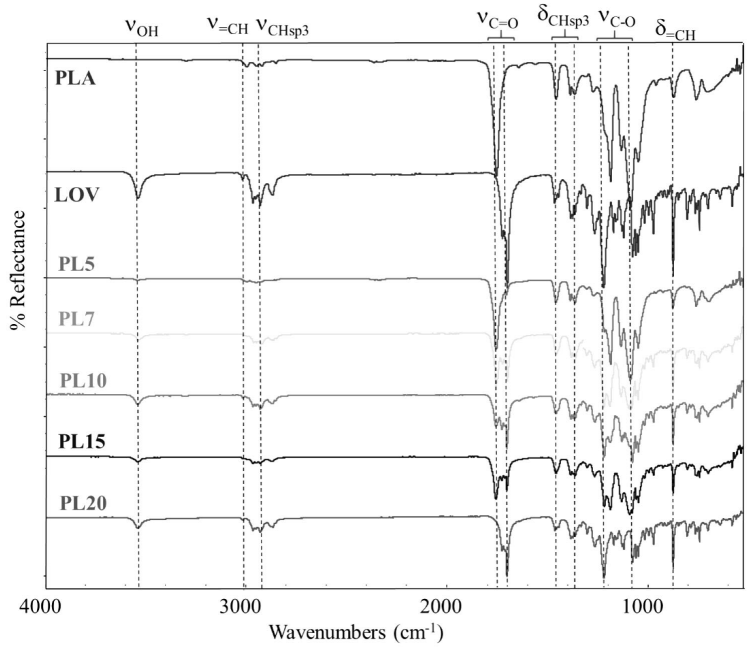


Figure 1. FT-IR spectra of PLA, Lov, and PLA/Lov biocomposites

Table 4: Characteristic FTIR spectral signals (cm^{-1}) of PLA/Lov biocomposites

Sample	ν_{OH}	$\nu_{CH\ sp3}$	$\delta_{CH\ sp3}$	$\nu_{=CH}$	$\delta_{=CH}$	$\nu_{C=O}$	ν_{C-O}
PLA	-	2994-2950	1452-1382	-	-	1747	1082; 1262
Lov	3537	2964-2865	1459-1355	3015	966	1722-1696	1072; 1258
PL5	3542	2994-2947	1455-1382	-	970	1754-1695	1083; 1265
PL7	3539	2963-2927	1456-1381	3015	968	1755-1697	1074; 1259
PL10	3538	2960-2927	1456-1369	3015	968	1754-1697	1074; 1260
PL15	3537	2961-2927	1455-1381	3018	968	1755-1697	1075; 1260
PL20	3537	2964-2927	1459-1380	3015	968	1722-1697	1072; 1260

In the FTIR spectra of the studied PLA/Lov materials, all characteristic bands of PLA and Lov are found, as shown in Figure 1 and Table 4. Notably, the valence vibration of the C=O group appears in two ranges, one at 1,955-1,954cm^{-1} (corresponding to PLA) and the other at 1,722-1,695cm^{-1} (corresponding to Lov). However, there are minor changes in the PLA/Lov biocomposites compared to the initial PLA and Lov, caused by the variation of the Lov ratio loaded in PLA. In these PLA/Lov biocomposites, there are Van der Waals interactions between molecules or hydrogen bonds between -OH and C=O groups. Therefore, physical interactions have formed between Lov and PLA molecules.

3.1.2. Morphology of PLA/Lov biocomposites

It can be seen from FESEM images of Lov and the PLA/Lov biocomposite samples in Figure 2 that Lov exists in rod-shaped crystals with a size of 15-20 nm. However, when Lov was dispersed into the PLA polymer matrix, Lov particle size decreased to 200-650nm with a tendency to aggregate into clusters. Particles in PL samples have different sizes and tend to aggregate or return to their original rod shape depending on the dispersion ability and Lov ratio in the PLA matrix[30]. It was caused the formation of hydrogen bonds and weak interactions between molecules that form a spatial structure in the materials[31-32], as follows: When the low contents of Lov reduced the porosity of the structure; therefore, Lov particles were difficult to disperse into the polymer matrix. However, when too high contents of Lov were introduced into the material, it can cause steric hindrance, which limited the number of hydrogen bonds between Lov molecules and the PLA matrix, thereby decreasing the ability to disperse Lov particles into the PLA matrix, causing cluster aggregation of Lov particles[28, 31].

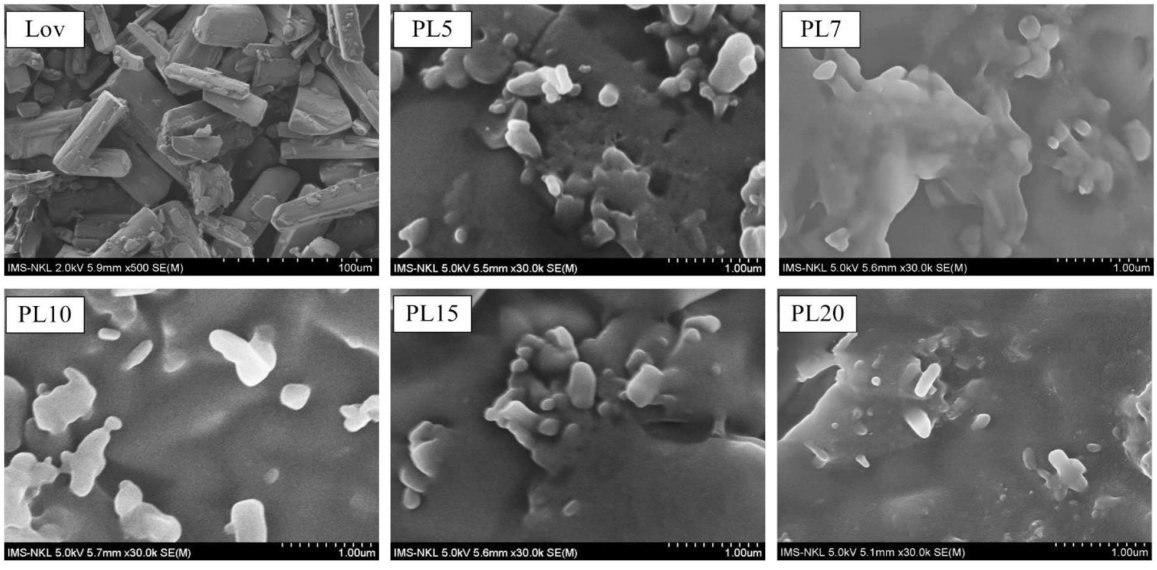


Figure 2. FESEM of Lov and PLA/Lov biocomposites

3.1.3. Thermal properties of PLA/Lov biocomposites

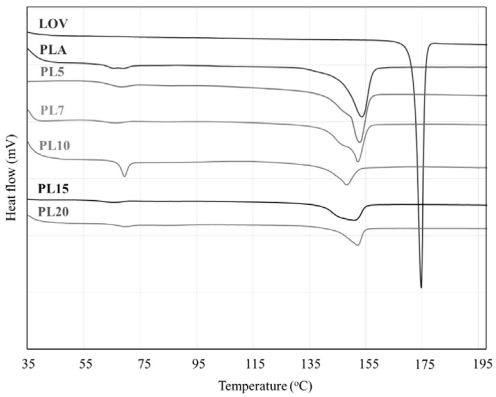


Figure 3. DSC diagrams of Lov, PLA, and PLA/Lov biocomposites

Table 5: DSC parameters obtained with Lov, LPA, and PLA/Lov biocomposites

Sample	First endothermic peak (°C)	Second endothermic peak (°C)
Lov	-	174.6
PLA	66.8 - 67.9	153.8
PL5	68.3	153.0
PL7	66.2	152.5
PL10	69.0	148.5
PL15	65.6	151.7
PL20	68.3	151.4

The DSC results presented in Figure 3 and Table 5 revealed that the single Lov sample has an endothermic peak corresponding to its melting point at 174.6°C and the melting process occurs in the range of 172-177°C. This result is consistent with previous works and demonstrates the high purity of Lov[32-33]. Meanwhile, the DSC diagram of a single PLA shows two endothermic peaks, in which the second one corresponds to the melting at 153.8°C, consistent with the literature[34].

All PL samples exhibited two endothermic peaks in the ranges of 65.6-69.0°C and 148.5-153.0°C. However, the first endothermic peak can be attributed to the dehydration process of PLA and is too minor, only clearly observable in the sample PL10. This may be due to the uniform dispersion of Lov particles in the PLA matrix for the sample PL10, increasing its durability and reducing its dehydration ability.

When combining Lov and PLA in the composites, the melting point of the PLA/Lov materials is in the range of 148.5-153.0°C. This might be because when Lov was dispersed into the structure of the PLA polymer matrix, the size of Lov particles decreased, reducing the crystallinity, and thereby reducing the melting point of the composite compared to Lov[35]. Moreover, it can also be due to the formation of hydrogen bonds between Lov particles and the PLA matrix, leading to a lower particle size[34]. The sample PL10 has the lowest melting point (148.5°C), showing the uniform dispersion of Lov into the polymer matrix. This result is also consistent with the SEM result of the sample.

3.2. Lovastatin release from PLA/Lov biocomposites

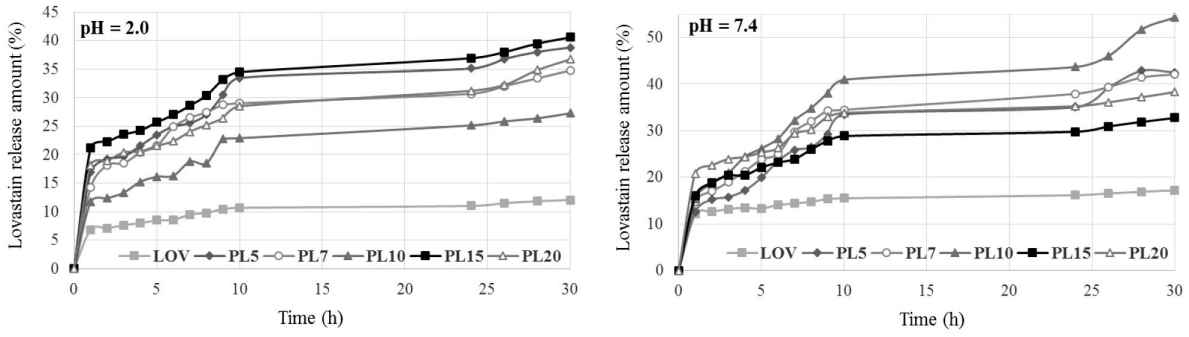


Figure 4. Time-dependent plots of Lov amounts released from PLA/Lov biocomposites in pH 2.0 *(left)* and pH 7.4 *(right)* buffers

The drug release testing results over time during 30 hours in the two buffer solutions are presented in Figure 4: in the simulated environment of lower gastric juice at pH 2.0 (on the left) and in the simulated environment of small intestinal fluid in the duodenal area at pH 7.4 (on the right). The release mechanism of Lov drug from PLA/Lov biocomposites consists of the penetration of water into the PLA polymer matrix and diffusion of the drug dispersed in the matrix due to swelling of the polymer.

It can be seen from Figure 4 that in pH 2.0 buffer, the Lov percentage released is in the range of 27.26-40.58%. Notably, the samples PL15 and PL5 exhibit the highest Lov release levels, of 21.19% and 18.18%, respectively, after 1 hour; 40.58%, and 38.80% after 30 hours. In contrast, sample PL10 had the lowest drug release level of 27.26% after 30 hours. Based on the results, the sample PL10 was found to have optimal drug release behavior because, with this sample, Lov could be better protected in gastric juice since its introduction.

In the pH 7.4 environment, Lov release preferentially occurs at a faster rate to ensure absorption of Lov into the bloodstream. This may be due to the swelling and the decomposition of-PLA were faster in a pH 7.4 environment than in a pH 2.0 environment[28], thereby releasing Lov better. It can be seen that after 30 hours, the sample PL10 showed the most effective Lov release of 54.25% with the fastest rate, while the other samples only gave drug release levels in the range of 32.73-42.28%.

The investigation was also conducted with a control sample of a single Lov, and the results show that the Lov release level was 12.06% at pH 2.0 and 17.21% at pH 7.4. Based on the Lov drug release level, the optimal Lov: PLA ratio (1:10) was found in the sample PL10 because the Lov release was lower in pH 2.0 (gastric juice) and better in pH 7.4 (small intestinal fluid) with drug release levels of 27.26% và 54.25%, respectively, facilitating the absorption of Lov drug into the blood.

IV. CONCLUSION

The poly(lactic acid)/lovastatin biocomposites were fabricated with different mass ratios of Lov:PLA. The investigations of chemical structure, morphology, and thermal properties revealed that the Lov:PLA ratio of 1:10 (in the sample PL10) gave the optimal results with Lov particle size of 500-650nm and the best dispersion of Lov into the PLA matrix, which is consistent with DSC result showing a melting point of 148.5^{o}C. In addition, the biocomposite with this Lov:PLA ratio also exhibited the most reasonable drug release properties in the environments simulating gastric juice (pH 2.0) and small intestinal fluid (pH 7.4). The obtained results are the basis for further research on the combination of lovastatin/poly(lactic acid) with other carrier materials to optimize the release ability and control the Lov drug release.

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