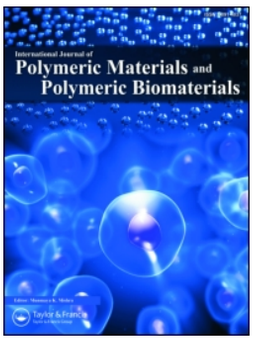

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Preparation and characterization of carvedilol-loaded poly(D,L) lactide nanoparticles/microparticles as a sustained-release system

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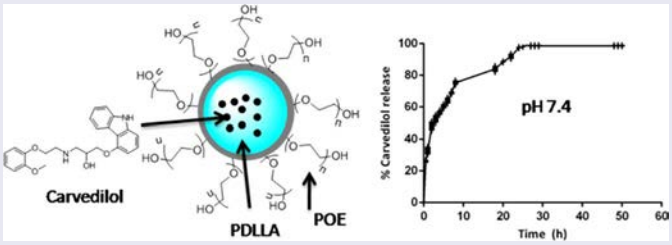
ABSTRACT

Carvedilol poly(D,L)-lactide nanoparticles/microparticles were prepared. The size and morphology of the developed particles were optimized to study the carvedilol release profile by studying the effect of organic solvents and polymer amount through atomic force microscopy analysis. Spherical particles were obtained with a minimum size of 125 nm in the case of acetone and a maximum size of 970 nm in the case of dichloromethane affording microparticles formation. The interaction was confirmed by differential scanning calorimeter and Fourier transform infrared. The *in vitro* release profile of the multicompartment system (pure carvedilol, loaded nanoparticles and microparticles) has shown a sustained release with Korsmeyer–Peppas with T lag model.

GRAPHICAL ABSTRACT



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Atomic force microscopy; hydrophobic drug; poly(D,L)-lactide nanoparticle/microparticles; sustained-release system

1. Introduction

Biodegradable polymeric particles have attracted huge interest in the last decades in several pharmaceutical fields especially in the development of effective drug delivery systems of hydrophobic drugs [1–5]. These particles can be utilized to improve the bioavailability of drugs by increasing water solubility of the loaded drug, improving stability of sensitive drugs, and achieving extended drug effect by offering a sustained delivery, which consequently improve the therapeutic efficacy and safety of the administrated drug [6–9]. Poly(D,L)-lactide (PDLLA), the amorphous polymeric form of polylactide, is one of the most commonly used polymers. It has been approved by the Food and Drug Administration for medical and drug delivery applications. It can be hydrolyzed totally in the physiological fluids by the cleavage of the ester bond and metabolized to water and carbon dioxide through Krebs cycle [10,11]. Several techniques were used in order to develop polymeric particles by using PDLLA. Nanoprecipitation method developed by Fessi et al. [12] is considered the most commonly used one. This technique has the advantages to produce particles in a simple and an easy manner and the avoidance of the usage of highly toxic organic solvents [13,14]. Although this technique is widely used, various limitations exist such as the difficulties to obtain a narrow size distribution, and the effects of the solvent used and the amount of the polymer on the size and the size distribution of the obtained particles.

Carvedilol, as a model of a hydrophobic drug, is an antihypertensive drug that acts as a nonselective $\beta/\alpha 1$ blocking agent and it is commonly used to treat congestive heart failure and to reduce the mortality of cardiovascular problems in patients with post-myocardial infarction [15]. The systematic bioavailability of carvedilol is about 25–35% with half-life of 6 h and consequently provoke poor patient compliance because of the multiple daily dosing [16,17]. Various attempts have been developed in order to improve patient compliance such as the controlled-release technologies [18,19]. However, polymeric particles have the advantage over the conventional controlled-release pharmaceutical dosage forms in protecting the drug from the chemical and enzymatic degradation and the hepatic metabolism of the drug [20,21]. As an example

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in 2014, Varshosaz et al. [22] designed and developed lectin-modified poly(ethylene-*co*-vinyl acetate) mucoadhesive NPs of carvedilol by an O/W solvent evaporation method with low drug concentration of 37.5 wt% of polymer. To our knowledge, no one has reported previously the development of multiparticulate system for controlled release of carvedilol based on PDLLA polymer.

Herein, we aim to study the effect of the organic solvent used and the amount of the polymer on the size of the obtained particles and to develop novel carvedilol-loaded PDLLA nanoparticles/microparticles decorated with polyoxyethylene polymer, a masking agent of phagocytoses, with a concise size and high loading capacity in order to obtain a multiparticulate drug delivery system of carvedilol with sustained-release behavior. Atomic force microscopy (AFM) has been used to determine the size, size distribution, and morphology of the obtained particles as AFM is considered a powerful tool of analysis since it is used in ambient condition of the sample [23–27].

2. Experimental

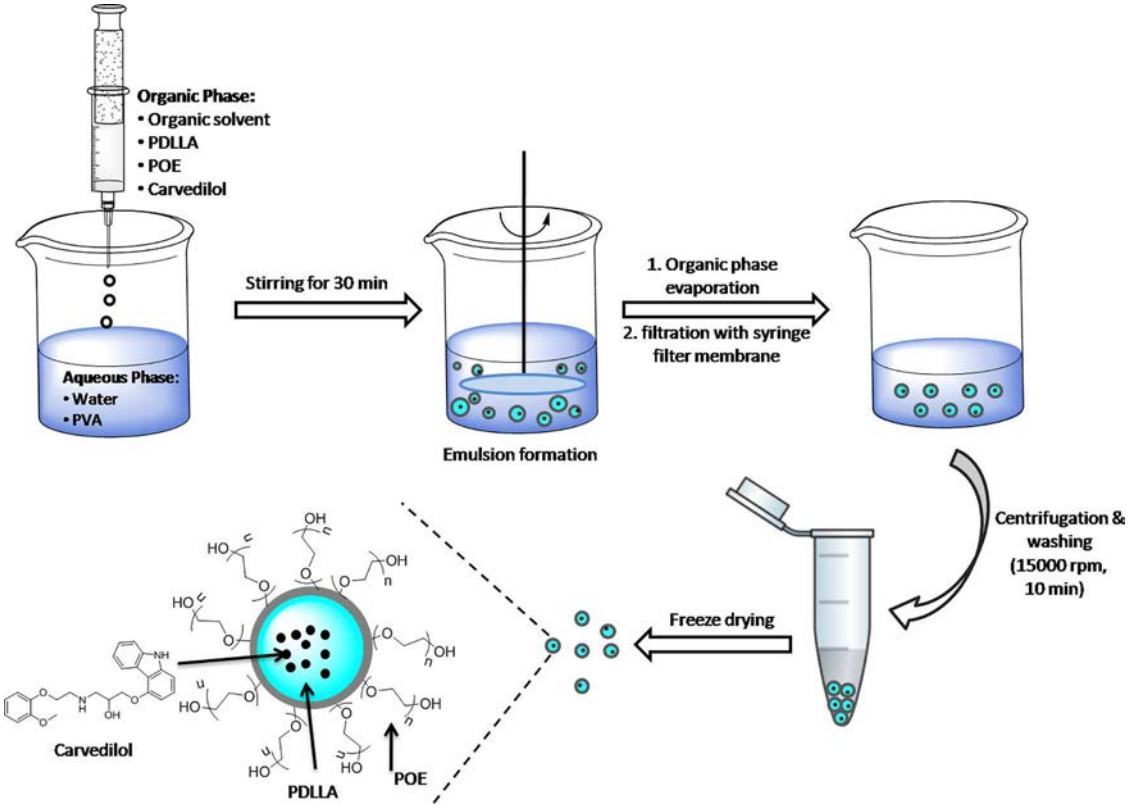
2.1. Materials, reagents, and instrumentation

Poly(D,L) lactide polymer (intrinsic viscosity of 0.25–0.35 dL g^{-1} and molecular weight of 18,000–28,000), poly oxyethylene cetyl ether (POE), and polyvinyl alcohol (PVA) surfactants were purchased from Sigma-Aldrich (Germany). Carvedilol (a micronized powder with particle size 90% less than 80 µm) was donated from Bait Jala Pharmaceutical Company in Palestine. HPLC grade organic solvents were used (ethanol, methanol, acetone, tetrahydrofuran, acetonitrile, and dichloromethane). Acrodisc GF syringe filters of 200 and 1,000 nm size were purchased from Sigma-Aldrich, and Spectra/Por 4 dialysis membrane (12–14 kD MWCO, 25 mm flat width, 100 foot length) was purchased from Spectrum Laboratories, Inc. (USA).

For the quantification of the loaded carvedilol, a calibration curve was constructed using a Jenway 7315 UV/Visible Spectrophotometer with quartz cuvettes. An FTIR Spectrometer (Nicolet iS5, Thermo Fisher Scientific Company, USA) was also used. AFM using a tapping mode-AFM system with WSxM software designed by Nanotec Electronica (Madrid, Spain) was used for image analysis. Differential scanning calorimeter (DSC) of TA instruments with a closed aluminum pan under nitrogen gas was used at a heating rate of 10°C min^{-1} over the temperature range between 25 and 400°C.

2.2. Preparation of PDLLA particles

Poly(D,L) lactide particles were prepared using nanoprecipitation technique as shown in Scheme 1. In this procedure the organic phase was prepared using various quantities of PDLLA polymer (12.5, 25, or 50 mg) and POE (5 mg). These components were dissolved in various quantities of organic solvents (acetone, tetrahydrofuran, acetonitrile, ethanol, and dichloromethane) according to Table 1. The organic phase was added drop by drop to the aqueous phase that contained 3 g of 1% PVA and 7 mL of Milli Q water under mild stirring. The formed milky emulsion was left 30 min under mild stirring. After that, the organic solvent was evaporated using a rotary



Scheme 1. Schematic representation of nanoprecipitation method and its relevant chemistry.

Table 1. Formulas of PDLLA nanoparticles preparation.

	Formulas and quantities									
Materials	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
PDLLA (mg)	50	50	50	50	50	50	50	50	25	12.5
PVA 1% (g)	3	3	3	3	3	3	3	3	3	3
Polyoxyethylene cetyl ether (mg)	5	5	5	5	5	5	5	5	5	5
Acetone (mL)	5	0	0	0	2.5	2.5	0	0	5	5
Tetrahydrofuran (mL)	0	5	0	0	2.5	0	2.5	0	0	0
Acetonitrile (mL)	0	0	5	0	0	2.5	2.5	0	0	0
Ethanol (mL)	0	0	0	5	0	0	0	0	0	0
Dichloromethane (mL)	0	0	0	0	0	0	0	5	0	0
Milli Q water (mL)	7	7	7	7	7	7	7	7	7	7

PDLLA, poly(D,L) lactide; PVA, polyvinyl alcohol.

evaporator. The obtained system was filtered using a 200-nm pore size membrane syringe filter; in the case of dichloromethane as solvent the particles were filtered by a 1-μm pore size syringe filter. Centrifugation was done at 15,000 rpm for 10 min to precipitate the particles and wash with Milli Q water three times to remove residual PVA. The particles were collected and solubilized in 2 mL water and left in a refrigerator to be lyophilized the next day.

To optimize the conditions of the prepared PDLLA particles various formulas were prepared. The organic solvent and the amount of PDLLA were modified. The size, morphology, and size distribution of the PDLLA particles were assessed using AFM technique.

Once the conditions had been optimized, 2 mg of carvedilol was added to the organic phase and the same procedure was followed.

2.3. Preparation of AFM samples

The samples were deposited on a substrate ($5 \times 5\ mm^2$) of mica and were allowed to dry at room temperature. The AFM images were treated with WSxM 5.0 Develop 6.5 software [28]. The size and size distribution were determined by taking the average of 100 counted particles.

2.4. Encapsulation efficiency of carvedilol

The total amount of carvedilol that had been loaded was determined by dissolving a known amount of the obtained particle powder in a volume of Milli Q water and measuring the absorbance by spectrophotometer at $\lambda_{max} = 240$ nm using the blank PDLLA particles as a reference in order to eliminate their interference. Unloaded carvedilol was also determined after centrifugation of the particles at 15,000 rpm for 10 min and encapsulation efficiency calculated according to Eq. 1:

$$\text{Encapsulation efficiency} = \frac{\text{total drug content (mg)} - \text{free dissolved drug (mg)}}{\text{drug amount used(mg)}} \quad (1)$$

2.5. Differential scanning calorimetry

Five milligram samples were accurately weighed and heated on a closed aluminum pan at a heating rate of $10°C\ min^{-1}$ over the temperature range between 25 and 400°C and cooled to room temperature in two-cycle form.

2.6. In vitro drug release profile

In vitro release profile for carvedilol was carried out using a bag dialysis membrane (cutoff 14 kDa) as described here. Five milligrams of carvedilol-loaded PDLLA nanoparticles (NPs) or microparticles (MPs) were dissolved in 5 mL of phosphate buffer (pH 7.4 or 6.8) and injected inside the membrane bag by a syringe. After that, the dialysis bag was immersed in a 900-mL phosphate buffer (with pH of 7.4 or 6.8) at room or body temperature ($25 \pm 1°C$; $37 \pm 1°C$) under mild stirring at a rate of 50 rpm as recommended by the FDA dissolution procedure for carvedilol tablet [29]. At scheduled time intervals, 5 mL of the release medium was removed and replaced with the same volume of fresh buffer and then analyzed by a UV spectrophotometer to calculate the amount of drug released at $\lambda_{max} = 240$ nm as:

$$\%\ \text{drug release} = \frac{\text{amount of drug released at time } t\ \text{(min)}}{\text{total amount of nanocapsulated drug (mg)}} \times 100\% \quad (2)$$

In addition, *in vitro* release profile of a mixture of pure carvedilol, carvedilol-loaded NPs, and carvedilol-loaded MPs (1:1:1) was constructed at body temperature and at two pH values (6.8 and 7.4).

2.7. Drug release kinetics

Seven kinetic models were used to analyze the data of carvedilol release from the obtained carvedilol-loaded PDLLA particles and were computed using DDsolver, which is an Excel-plugin module [30]. The used models were zero order, zero order with T lag, first order, first order with T lag, Korsemeyer–Peppas, Korsemeyer–Peppas with T lag, and Higuchi model. The linear regression (R^2) and Akaike information criterion (AIC) were calculated [31–37].

3. Results and discussion

The particles were prepared using a nanoprecipitation technique, and different parameters were controlled and varied in order to find the optimum conditions to obtain the best particles. Moreover, the particles were covered by a layer of polyethylene oxide, which acts as a protective mask against opsonization of the drug transporter and subsequently prevents phagocytosis by the mononuclear phagocyte system [38,39].

In this study two formulation parameters were optimized and studied because they had a major impact on the size, shape, and size distribution of the particles using the PDLLA ($M_{wt} = 18{,}000–28{,}000$) as the targeted polymer in the whole study. These two parameters were the quantity of the polymer and the type of organic solvent. Accordingly, the temperature and the stirring speed were kept constant (room temperature and mild stirring at 300 rpm).

3.1. Effect of the organic solvent

Four different water-miscible organic solvents (acetone, ethanol, tetrahydrofuran, and acetonitrile) were used in order to optimize the conditions to give the desired particle size, shape, and size distribution. Mixtures of these solvents in a 1:1 ratio (acetone:tetrahydrofuran, acetone:acetonitrile, and tetrahydrofuran:acetonitrile) were also tested for the same purpose. To evaluate the effect of water immiscibility on the particles, dichloromethane was selected as the organic solvent according to Sawalha et al. [40]. Eight formulas were prepared and analyzed by AFM in order to determine the size, morphology, and size distribution of the obtained particles (Table 1). An excess amount (50 mg) of PDLLA was selected in order to minimize the effects of polymer concentrations on the particles.

All solvents provided the same spherical shape. However, a difference in particle size was observed (Table 2). In fact, all miscible organic solvents produce particles in the nano size and acetone alone produced the smallest polymeric nanoparticles (NPs) with the narrowest size distribution, as can be observed in Figure 1 and Table 2.

Table 2. Average size and size distribution of the different formulas.

Formula	Average size (nm)	Size distribution (nm)
F1	160	150–170
F2	260	200–300
F3	400	340–440
F4	480	400–500
F5	190	180–210
F6	230	210–270
F7	240	200–250
F8	970	950–1,100
F9	100	90–120
F10	125	120–140

Ethanol gave the largest nanoparticles when compared with the other miscible solvents (tetrahydrofuran, acetonitrile, and mixtures) (Figures S1–S6, Table 2). Mixtures of the miscible organic solvents made a difference in terms of the particle size and size distribution. The acetonitrile and tetrahydrofuran mixture gave a larger nanoparticle size compared with the other two mixtures (Figures S2–S6, Table 2). This indicates that a mixture of solvents decreases the surface tension with the aqueous phase. The addition of acetone to another organic solvent positively affected the interfacial tension of the system, because it gave smaller PDLLA nanoparticles when compared to the other solvent mixtures (Table 2). This is in accordance with the published studies showing that the addition of a water-miscible solvent decreases the interfacial tension, and so the removal rate from the particle increases, which solidifies the particles much more quickly and, therefore, decreases the particle size [40,41]. Indeed, organic–aqueous phase interactions play a major role during the diffusion process in the formation of particles. On the other hand, the water-immiscible solvent dichloromethane produced PDLLA microparticles (MPs) instead of nanoparticles (Figure 2, Table 2). This can be explained because the removal of dichloromethane from the aqueous phase was slow because of the low water miscibility, which affected the coacervation of the polymer. In fact, this process took much more time, which allowed the liquid to aggregate and form larger particles. This can be explained as dichloromethane is a water-immiscible solvent, so its removal and evaporation rate would be slow and so the solidification and precipitation processes would take longer time. This allows the remained liquid droplets to aggregate and coalesce, leading to larger and wider distributed droplets. However, in the case of water-miscible solvents, especially acetone, the evaporation rate is quicker because of the decrease of the interfacial tension of the droplets. This may lead to a faster precipitation and solidification of the polymer, which may result in a smaller size and better size distribution of the obtained particles as has been previously shown by Sawalha et al. [40] who prepared microparticles using dichloromethane in the organic phase. The size of these particles decreased upon the addition of a miscible solvent like ethanol.

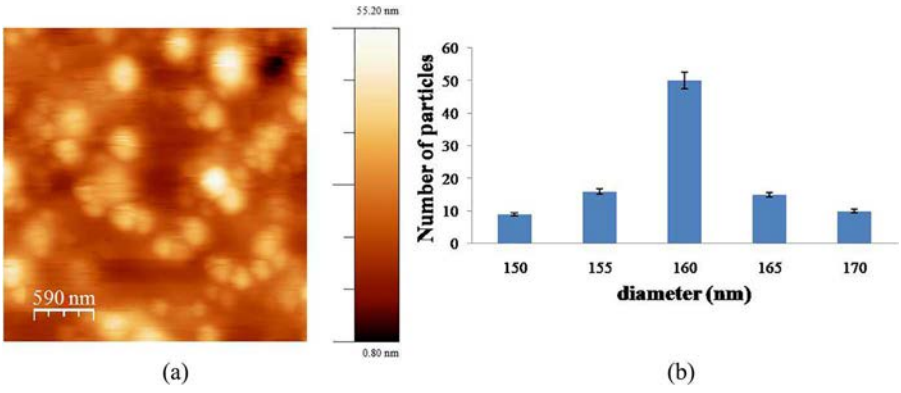


Figure 1. (a) AFM image of PDLLA nanoparticles (acetone as the solvent); (b) histogram obtained from AFM analysis.

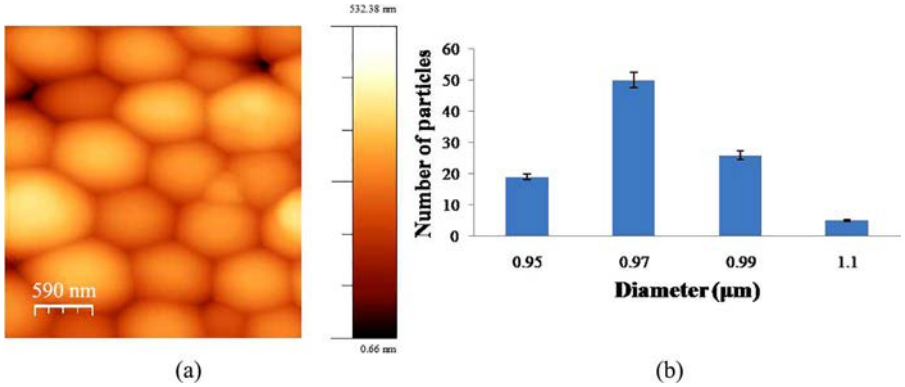


Figure 2. (a) AFM image of PDLLA microparticles (dichloromethane as the solvent); (b) histogram obtained from AFM analysis.

3.2. Effect of the amount of the polymer

Once the most suitable solvent was determined, the effect of the amount of the polymer on particle size, shape, and size distribution was assessed. All other parameters were fixed and acetone was used. For this purpose, three different factorial amounts of PDLLA were studied (12.5, 25, and 50 mg). The use of 50 mg of PDLLA gave the largest particle size (Figure 1, Table 2). When 12.5 mg of PDLLA was used, the smallest and narrowest particle size was obtained; an average size of 100 nm and a size distribution between 90 and 120 nm was observed (Figure 3, Table 2), while 25 mg of PDLLA gave an average size of 125 nm and a size distribution of 120–140 nm (Figure S7, Table 2). At all PDLLA levels, a spherical shape was obtained. However, using less than 12.5 mg of the polymer was insufficient to form nanoparticles with proper shape. Therefore, the optimum amount of the polymer was 12.5 mg.

It was observed that any increase in the polymer amount increased the average particle size. This effect can occur for two reasons: (1) an increase in the polymer chain per volume ratio, i.e., more polymer chain interactions and therefore more polymer aggregates will diffuse into the aqueous phase and thus form larger particles. On the other hand, (2) an increase in polymer concentration will affect the viscosity of the organic phase; a higher viscosity will in turn hold back the shear forces of the emulsion, as has been discussed by other researchers [42,43].

Therefore, the optimum conditions in the preparation of PDLLA nanoparticles are 12.5 mg of the PDLLA amount and using acetone as an organic solvent. However, PDLLA microparticles have been obtained in the case of using dichloromethane as an organic solvent.

3.3. Carvedilol-loaded PDLLA nanoparticles and microparticles

Once the method of preparation had been optimized, both PDLLA nanoparticles and microparticles were loaded with carvedilol. The morphology, size, and size distribution were evaluated using AFM. According to AFM analysis, maintenance of the spherical shape was observed, while the average size of both drug-loaded nanoparticles and microparticles increased. In fact, the average size of nanoparticles and microparticles was increased up to 30 and 23%, respectively. This increase may indicate the successful encapsulation of carvedilol inside the particles (Figures S8 and S9). The loading capacity of PDLLA nanoparticles and microparticles was estimated using a UV spectrophotometer. A calibration curve of carvedilol at $\lambda_{max} = 240$ nm was established in order to measure the carvedilol concentration that had been loaded inside the particles.

The absorbance of PDLLA nanoparticles and microparticles was measured at 240 nm, and the encapsulation efficacy was calculated according to Eq. 1. Both nanoparticles and

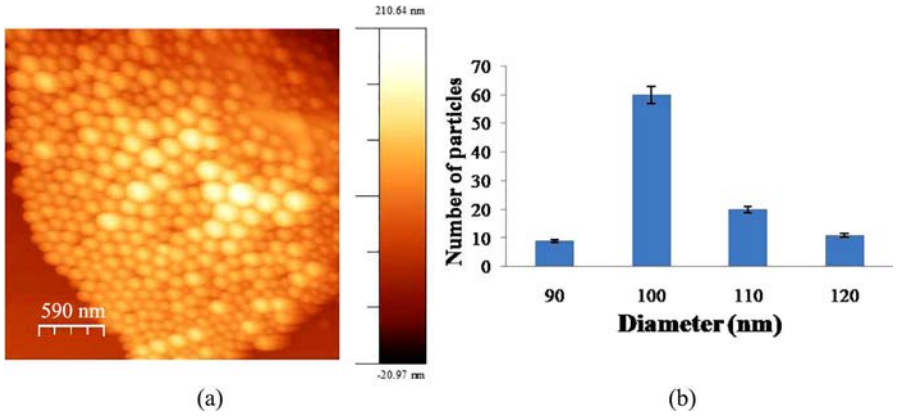


Figure 3. (a) AFM image of PDLLA nanoparticles (with 12.5 mg quantity of PDLLA); (b) histogram obtained from AFM analysis.

microparticles showed comparable loading efficiency with 57 and 55% loading capacity, respectively.

3.4. Differential scanning calorimetry analysis

Differential scanning calorimetry was conducted to confirm the interaction between the carvedilol and PDLLA polymer in both the microparticle and nanoparticle formulations and to study the thermal stability of the interaction. As can be observed in Figure 4, the DSC spectrum of the pure carvedilol displayed a sharp melting peak at 120°C (Figure 4a). Meanwhile, an endothermic peak at 55°C was observed in Figure 4b, which corresponds to the T_g of the amorphous PDLLA polymer. Interestingly, these two endothermic peaks were observed in the DSC spectra of both the carvedilol-loaded nanoparticles and those at 57 and 119°C in the case of the microparticles (Figure 4c) and at 56.5 and 117°C in the case of the nanoparticles (Figure 4d). This confirms the interaction between the carvedilol and PDLLA as the two characteristic peaks were observed with a slight shifting from the pure drug or PDLLA because of the interaction. A decrease in the temperature of the loaded carvedilol in both formulations is due to its encapsulation, and the observed peak corresponds to the carvedilol adsorbed in the surface of the particles, which is related to the immediate release of the drug as seen in the *in vitro* release section.

3.5. Fourier transform infrared analysis

In the spectrum of pure carvedilol, the observed peak at 3,340 cm^{-1} is assigned to the O–H or N–H stretching vibration of carvedilol (Figure 5a). In the spectra of carvedilol-loaded PDLLA nanoparticles various peaks appeared (Figure 5b). The peak at 2,904 cm^{-1} confirms the stretching C–H of the CH_3 and CH_2 of PDLLA polymer and the peak at 1,741 cm^{-1} corresponds to the stretching vibration of the carbonyl group on ester. More interestingly, intermolecular hydrogen bonding causes the broadness of FTIR peaks, as can be perfectly observed in the spectrum of the carvedilol-loaded nanoparticles at 3,341 and 1,741 cm^{-1}, which confirms the hydrogen bond formation between carvedilol and PDLLA polymer.

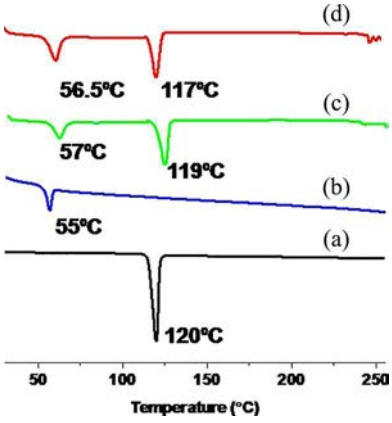


Figure 4. DSC spectra of carvedilol-loaded nanoparticles and microparticles. (a) Pure carvedilol, (b) PDLLA, (c) carvedilol-loaded microparticles, (d) carvedilol-loaded nanoparticles.

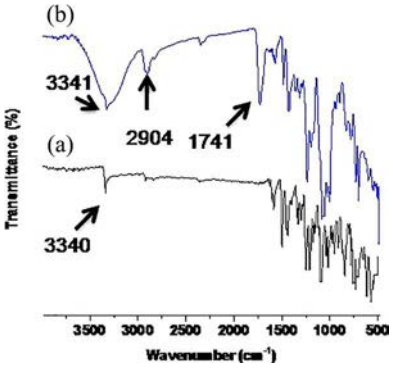


Figure 5. FTIR spectra of carvedilol-loaded PDLLA nanoparticles. (a) Pure carvedilol, (b) carvedilol-loaded PDLLA nanoparticles.

3.6. In vitro *release study*

In vitro study was conducted at two different temperatures (25 and at 37°C) and using two different release media, pH 6.8 and 7.4, and using dialysis membrane bags.

Despite the temperature and pH changes, both carvedilol-loaded PDLLA nanoparticles and microparticles showed sustained-release behavior when compared to the carvedilol pure drug (Figure 6). In all cases, almost all the loaded quantity of carvedilol was released and normalized to the release profile of the pure carvedilol. However, carvedilol release from microparticles was slower than that from nanoparticles. Loaded microparticles showed complete release (97%) within 48 h while nanoparticles released carvedilol (98%) within 24 h (Figure 6).

This difference in drug release between loaded nanoparticles and microparticles was expected because nanoparticles have a higher total specific surface area than microparticles.

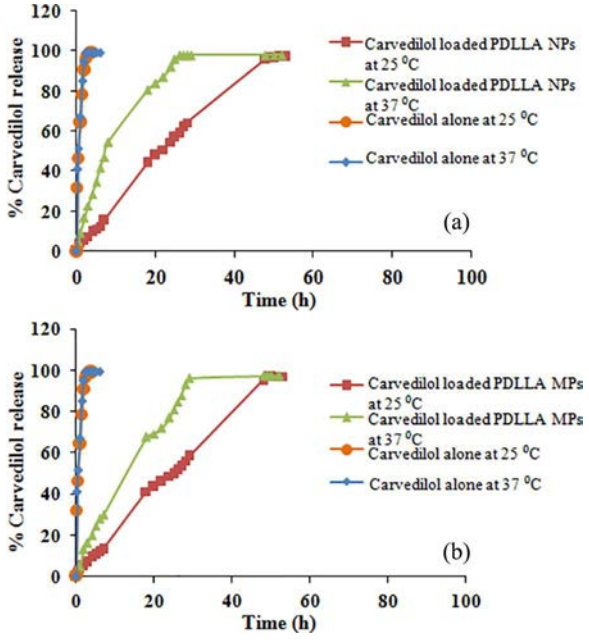


Figure 6. Percentage release of carvedilol at two different temperatures using phosphate buffer (pH 6.8) from (a) carvedilol-loaded PDLLA NPs (average size 130 nm) and (b) carvedilol-loaded PDLLA MPs (average size 1.2 µm). All experiments were conducted in triplicate.

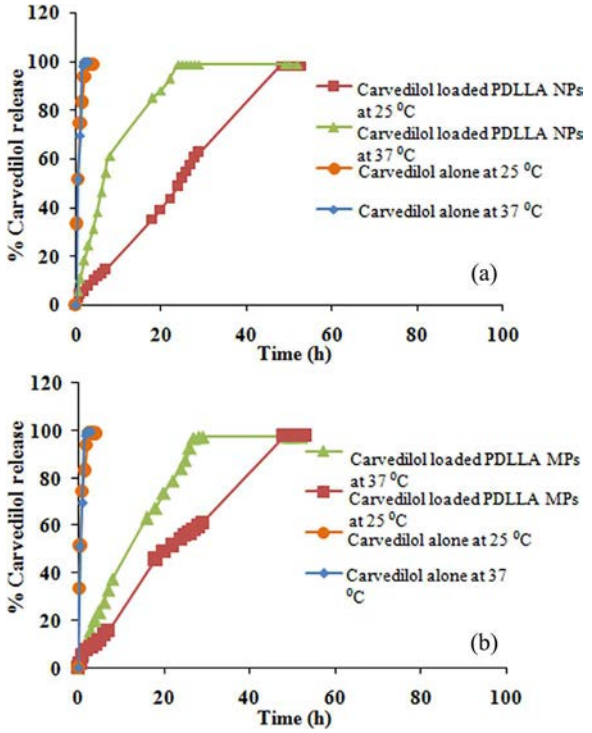


Figure 7. Percentage release of carvedilol at two different temperatures using phosphate buffer (pH 7.4) from (a) carvedilol-loaded PDLLA NPs (average size 130 nm) and (b) carvedilol-loaded PDLLA MPs (average size 1.2 µm). All experiments were conducted in triplicate.

In fact, the larger surface area-to-volume ratio consequently increases the degradation of the polymer, which results in release of the loaded drug [44,45].

Regarding the effect of temperature on the release of carvedilol, greater drug release was observed at body temperature than at room temperature. The effect of temperature on drug release was also maintained despite the pH of the buffer (Figures 6 and 7). This is due to higher permeability of the polymer membrane at body temperature than at room temperature, as was reported by Zhang and Wu [46].

Regarding the effect of pH on the release pattern of carvedilol, a decrease in the rate of drug release was observed when the pH was changed from pH 6.8 to 7.4 (Figures 6 and 7). This pH-dependent release is due to the kinetic of hydrolysis of PDLLA that has been reported to be pH dependent [47].

These findings suggest that a mixture of these products could result in a sustained-release formulation with an immediate release of the pure carvedilol. Accordingly, the release pattern of carvedilol from a mixture of the pure drug, and loaded nanoparticles and microparticles with a composition ratio of 1:1:1 was evaluated at body temperature using the above phosphate buffers (Figure 8).

Analysis of release profile can provide important information regarding the mechanisms involved in the release of carvedilol from nanoparticles and microparticles. In fact, several release mechanisms were suggested. These include desorption of the drug from the surface of the polymeric matrix, diffusion through the pores or wall of the matrix, disintegration of the particles with subsequent release, and dissolution and erosion of the matrix or the polymeric wall [48,49]. The release profiles were assessed using different kinetic models in order to find the best sustained-release model to fit the data. Model selection was based on the measure of fit of linear regression (R^2) and the value of AIC, a measure of goodness of fit based on maximum plausibility. For a given data set, the most suitable model should show the lowest AIC and R^2 close to 1. As can be seen in Table 3, the best-fit linear regression line (0.972) and the lowest AIC (143.4211) for carvedilol release at body temperature and pH 6.8 was observed using Korsemeyer–Peppas with T lag model. Same results were observed at body temperature and pH 7.4 with R^2 and AIC equal to 0.971 and 142.76, respectively.

These findings are in accordance with the literature, because the selected model should demonstrate similarity between observed and predicted release [50]. In fact, Korsemeyer–Peppas with T lag model is often used to describe the drug release behavior from polymeric systems when the mechanism of drug release is not well known or when more than one kind of release mechanism is involved [51,52].

In fact, the mechanism involved is diffusion when the release exponent (n) is equal to 0.43. When the value of n is in the range $0.43 < n < 0.85$, the suggested release is an anomalous transport that does not obey Fick's Law. Values of n less than 0.43 indicates a porous system in which transport occurs by a combination of diffusion through the polymeric matrix and diffusion through the pores. In our study the calculated n value was less than 0.43. This indicates a transport mechanism of carvedilol by a combination of diffusion through the polymeric matrix and diffusion through the pores.

These results open the door toward a novel carvedilol sustained-release formulation for both oral and parenteral routes. In fact, the release profile at pH 6.8 simulates a sustained-

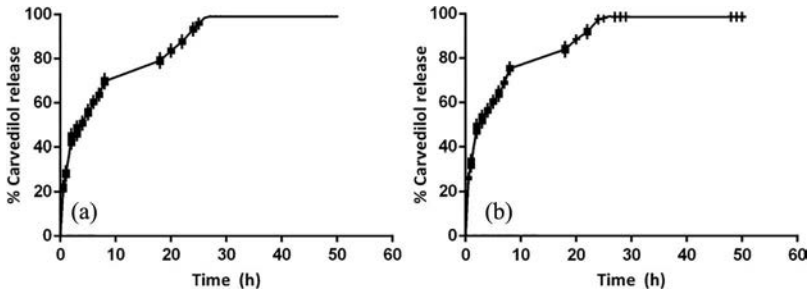


Figure 8. (a) Percentage release of carvedilol from a mixture of carvedilol powder, PDLLA loaded nanoparticles, and microparticles at pH 6.8 and at body temperature. (b) Percentage release of carvedilol from a mixture of carvedilol powder, PDLLA loaded nanoparticles, and microparticles at pH 7.4 and at body temperature. All experiments were conducted in triplicate.

Table 3. Dissolution data modeling for a mixture of carvedilol powder, PDLLA-loaded nanoparticles and microparticles at ph 6.8 and 7.4 and body temperature.

	pH 6.8 at 37°C		pH 7.4 at 37°C	
Dissolution model	R^2	AIC	R^2	AIC
Zero order	−0.2549	223.1151	−0.6237	227.325
Zero-order with T lag	0.7027	193.4302	0.64932	195.608
First-order	0.9286	160.0641	0.92738	158.965
First-order with T lag	0.9622	148.0503	0.96134	147.095
Korsmeyer–Peppas	0.9639	147.0444	0.96105	147.262
Korsmeyer–Peppas with T lag	0.972	143.4211	0.97101	142.761
Higuchi model	0.7606	186.6694	0.63273	194.625

PDLLA, poly(D,L) lactide; AIC, Akaike information criterion.

release pattern for the production of capsules or tablets that contain multiunit systems composed of pure carvedilol powder, and loaded nanoparticles and microparticles. This would release the drug at defined time intervals where carvedilol powder gives the initial dose while loaded nanoparticles and microparticles give the maintenance doses. This type of multiple unit system has received increasing interest because it has great advantages over single-unit systems. In fact, carvedilol sustained-release capsules are available as a single-unit system; these units show some disadvantages including regarding the safety and efficacy of the dosage form [53]. These disadvantages could be overcome by the use of the above-described multiple unit system.

Regarding parenteral sustained-release systems, the release pattern of carvedilol and loaded nanoparticles and microparticles at pH 7.4 and at 37°C showed an ideal controlled-release profile that was fit to the Korsmeyer–Peppas with T lag model because R^2 was also close to 1 and the AIC was the lowest among all models, as can be seen in Table 3.

According to these findings, our mixture could be produced as a powder for injection. This formulation will have a pH close to that of the blood. In fact, this would be of great interest in this field, especially for carvedilol, because it is not available as an injection because of its insolubility. Moreover, this system could be used to develop and formulate sustained-release systems as injectable preparations and oral solid dosage forms such as tablets and capsules.

4. Conclusion

The production of PDLLA particles with high encapsulation efficiency for carvedilol is possible using the nanoprecipitation technique. The smallest and narrowest size distribution of PDLLA nanoparticles was obtained when acetone was used as the organic solvent and 12.5 mg of PDLLA polymer was used and PDLLA microparticles was obtained with dichloromethane when used as solvent. PDLLA nanoparticles and microparticles improved carvedilol solubility and dissolution with a loading capacity of 57 and 55%, respectively. DSC and FTIR experiments confirm the encapsulation and the interaction between the carvedilol and the developed PDLLA nanoparticles and microparticles. *In vitro* release showed sustained-release behavior for many hours at room and body temperature at two different pH levels (6.8 and 7.4). Carvedilol release was slower at room temperature and at pH 6.8. The Korsmeyer–Peppas with T lag model was the best one to explain the sustained-release behaviour. This work could drive further attempts to prepare a novel injected nanosuspension of carvedilol and to solve many associated problems.

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