



Research Article

A Comparative Study of Progesterone and Lidocaine Hydrochloride Release from Poly(L-lactide) Films

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DMTA**ABSTRACT**

Background: Polyesters have been attractive for development of drug delivery applications because of their biocompatible, biodegradable and non-toxic properties. The objective of work is a comparative study on the release characteristics of two drugs loaded poly (L-lactide) (PLLA) film. Progesterone (Pro) and lidocaine hydrochloride (LidH) were chosen as the hydrophobic and hydrophilic model drugs, respectively. **Methods:** The PLLA films containing drugs (10% w/w) were prepared using the solvent casting method after dissolution in dichloromethane. The PLLA matrices were evaluated by scanning electron microscopy (SEM) and dynamic mechanical thermal analysis (DMTA). *In vitro* drug release studies were carried out at 37°C in ethanol/water for progesterone and phosphate buffer (pH 7.4) for LidH. The release kinetics were explained using Higuchi, Korsmeyer-Peppas and Gallagher-Corrigan equations. **Results:** *In vitro* drug release was found to be controlled by a triphasic profile for LidH and biphasic profile for progesterone. The results revealed that drug release was higher for the LidH-PLLA film than the progesterone- PLLA film. SEM images confirmed that LidH-PLLA film degraded more than did progesterone- PLLA film. **Conclusion:** The results of DMTA demonstrated a slight drug-polymer interaction. The experimental results of drug release approximated three commonly-used semi-empirical models: Higuchi, Korsmeyer-Peppas and Gallagher-Corrigan equations. The R² values show that these mathematic models are suitable for describing progesterone and LidH release from PLLA film.

Introduction

In the recent decades, polylactide has been utilized in medicine and pharmaceutical products because it is biocompatible, biodegradable and non-toxic.¹ Polylactide as polyester contains an asymmetric α -carbon in the D or L form and is a good candidate for the design and performance of a biodegradable controlled delivery system. Polymeric controlled drug delivery systems improve the efficiency of treatment and patient compliance with reducing dosing frequency, and reduce side effects of a drug by optimizing drug concentration for a long time. There are some polyester-based drug delivery products that are commercially available such as Atridox which delivers doxycycline hyclate from PLA, Eligard which delivers leuprolide acetate from polylactide-co-glycolide (PLGA). A number of studies have carried out to optimize of hydrolysis of polyesters and their drug delivery profiles.²⁻⁶

Large number implantable drug delivery devices have been developed over the years. The implants can be introduced by different shapes: films, rods, discs, pellets, and plugs. Several factors such as the thickness, area and implant form, moreover the drug solubility

are affected on the drug release rate.⁷ Potentially, thin film implants have developed to delivery of sensitive drugs that designed for oral, intravaginal and dermal administrations. Currently, there are some implants that have been approved by the FDA. Vaginal Contraceptive Film, VCF, is a vaginal thin film device for release of N-9, a potent spermicide. The advantage of this films are accurate dose administration and easy in use without an applicator, as well as good portability, easy storage, discreet use, and low production cost.⁸

Solvent casting and hot-melt extrusion are two methods have been used to manufacture film dosage forms. Solvent casting method is widely used due to its easiness of processing, low cost, and convenient setup. Speed of film casting and drying time can affect the physicochemical characteristics of films such as content uniformity and mechanical properties.⁸

It is important to understand the mechanism of drug release to develop new polymeric drug delivery devices. Three mechanisms have been identified thus far for controlled drug release from polyesters: Fickian diffusion through the polymer matrix; diffusion through pores in the matrix; and drug release by

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polymer erosion.⁹⁻¹⁰ Predicting precise drug release profiles is difficult because they are managed by the properties of the polymer, drug, and carrier system.⁵ Several factors have influence on the drug release profiles, such as molecular weight and crystallinity of polymer, solubility of the drug in biological fluid, possible polymer–drug interaction, drug loading, physical state of the drug in the polymer matrix, porosity and internal structure of the matrix, polymer composite and device geometry.^{6, 11-12}

However, studies have examined ways to optimize drug release rates and the profiles of biodegradable polymers such as PLGA- and PLLA-based film. Loo *et al.*³ fabricated PLGA and PLLA films for release study of lidocaine base and lidocaine hydrochloride. The electron beam irradiated films were applied to control of hydrolytic degradation of polymer and thereby the drug delivery. They found that an irradiated multi-layer film system has the potential for attaining controlled drug release.

Multi-layer PLGA/PLLA polymeric systems have been developed using a sandwich configuration to achieve controlled release of Sirolimus.¹³ Blending of diblock copolymers with PLGA film was employed to optimize drug delivery. Jackson *et al.*¹⁴ blended PDLLA–PEG into PLGA film to increase the initial drug release rate as required in perivascular applications. In this blended system, a slow sustained release was observed from the 30% (w/w) blended films of which 20% of the loaded drugs were released. Release of sirolimus from PLGA film was studied by Ro *et al.*¹⁵ They evaluated the level of polymer and effect of drug crystallinity on the drug release. They found that film with higher polymer crystallinity eluted less drug than film with amorphous polymer matrices.¹⁵ Cui *et al.*¹⁶ studied paracetamol release from PLLA-based films and electrospun fibers. The effects of fiber diameter and polymeric fiber degradation were evaluated. Fiber characteristics were varied to form an electrospun nonwoven mat as a potential drug delivery system rather than polymer film or particles.¹⁶ Their specific degradation profiles and adjustable drug release behaviors were then studied. Bodmeier¹⁷ studied the release of salicylic acid, caffeine, and quinidine from PLA films and microspheres. They evaluated the effects of the molecular weight of PLA on the drug release profiles. The results showed that the addition of low molecular weight poly (DL-lactide) accelerated the release of the drug from both film and microspheres.¹⁷

It is well known that the mathematical modeling of drug delivery can help design a better particular device. The advantage of mathematical modeling of controlled drug delivery systems is reduction of experiments number and timesaving. In the literature several theoretical or empirical release models are described. In order to design a new drug delivery device, the device composition *i.e.* polymer, drug and additives, and also geometric shape and size should be predicted theoretically to attain preferred drug release profile.¹⁸⁻²⁰

In the present paper the experimental results of drug release approximated with three commonly used semi-empirical models: Higuchi, Korsmeyer-Peppas and Gallagher-Corrigan equation were evaluated. Polylactide films were produced by film casting technique. The lidocaine hydrochloride (lidH, as hydrophilic drug) and progesterone (Pro, as hydrophobic drug) loaded PLLA films were prepared and characterized.

Materials and Methods

Materials

Poly (L-lactide) (RESOMER L210) was purchased from Evonik Röhm GmbH, (Germany) and dichloromethane were obtained from Merck (Darmstadt, Germany). All chemicals were used as received without further purification. LidH and progesterone were purchased from Sigma- Aldrich (USA).

Samples preparation

Drug loaded PLLA matrices were obtained by casting method. PLLA and drugs (10 % w/w) were dissolved in dichloromethane; then cast onto a flat glass plate. Samples were dried at room temperature for one day, and then placed under vacuum for one week. The thickness ranges of the dried films were approximately 150- 200 μm . The PLLA matrices without drugs, containing 10% (w/w) progesterone and LidH were labeled neat PLLA, Pro- PLLA film and LidH- PLLA film.

In order to establish uniformity in the distribution of drug in polymeric films, the drug content uniformity test was carried out for progesterone and lidH. Six rectangular strips of films ($2 \times 1.5 \text{ cm}^2$) were cut and dissolved separately in N-methylpyrrolidone. Then, progesterone and lidH concentrations were determined using a UV-Vis spectrophotometer (Shimadzu UV-1650 PC) at the adsorption maximum of 243 and 462 nm, respectively. Content uniformity values were 98.7 % for progesterone and 101.6 % for lidH with small standard deviation that indicate clearly uniformly distributed of drugs throughout the film.

Measurements

Film's morphological studies

The morphology of polymeric films were directly observed with scanning electron microscopy (SEM) using a Vega Tscan scanning electron microscope (Czech Republic) operating at an accelerating voltage of 10 KV. Prior to SEM analysis, films were gold-coated for 140 s (sputter coater E5200, BioRad, UK).

FTIR spectroscopy

FTIR Spectroscopy was also used in order to evaluate drug loaded PLLA films. The FTIR spectra were recorded using an Equinox 55 (Bruker, Wissemburg, France) in the range of 3500 to 500 cm^{-1} .

Dynamic mechanical thermal analysis

Dynamic mechanical thermal analysis (DMTA) was performed using DMTA- PL (Model: Polymer Laboratory, UK) at a constant frequency of 1 Hz and a heating rate of 5 °C/min. Tan δ and modulus of the samples were determined as a function of temperature.

Released drug analysis

In vitro progesterone and LidH release studies from PLLA films were carried out at 37°C in ethanol/water (60% v/v) and phosphate buffer (pH 7.4), respectively, as release mediums. Since progesterone is a water insoluble drug, ethanol was used as a cosolvent. Solubility of progesterone in ethanol/water (60% v/v) was 25 mg/ml²¹, and for lidH in water was 50 mg/ml.²² To determine the progesterone and LidH release profiles, three samples of drug-loaded film (2*1 cm²) were placed separately in 20 ml release solution. The average weight values of progesterone and lidH loaded films were 25 ± 1.2128 and 28 ± 1.3024 mg, respectively. The samples were allowed to stand in an incubator shaker (with 100 rpm) for predetermined periods of time. It is provided sink condition since the drug concentrations are at least 10 times smaller than the experimental drug solubility. At time intervals of 1

to 250 h, the release medium was withdrawn and immediately replaced with fresh solution. The progesterone and LidH concentrations in the release medium were measured using a double beam UV-Vis spectrophotometer (Shimadzu UV-1650 PC) at the adsorption maximum of 243 and 462 nm, respectively.

Results and Discussion

In vitro drug release study

The amount of drug released from the PLLA films were determined using the drug calibration curve plotted for five concentrations of each drug at λ_{max} . The percentage of cumulative drug release was calculated and plotted versus time. Figure 1 shows the drug release profiles from the PLLA films. The profiles of progesterone and LidH release were biphasic and triphasic, respectively. The drug release stages were: (1) initial fast release phase of drug incorporated at or near the surface of the polymer film; (2) a slower release phase from the diffusion of the drug through the polymer film and; (3) a faster release phase from diffusion through the film and degradation of the film. This observed phasic release is typical for PLA based polymers.

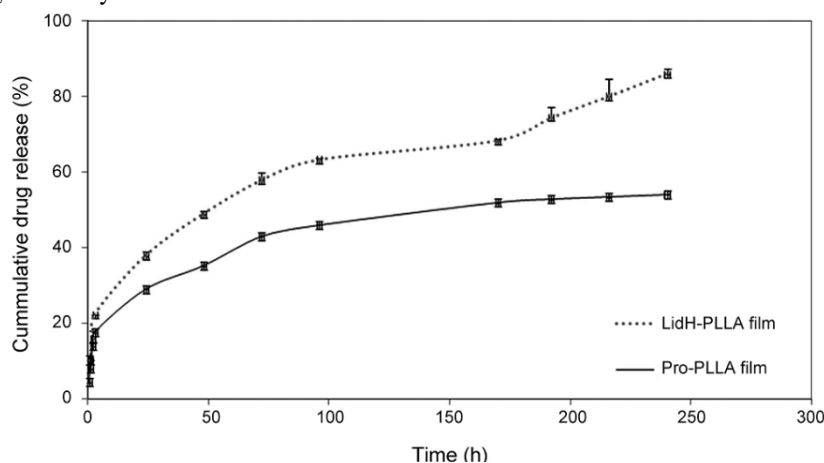


Figure 1. The profiles of percent cumulative drug release from PLLA films containing progesterone: Pro- PLLA film; and lidocaine HCl: LidH- PLLA film. (each point and error bar represents the mean ± SD and n= 3).

It can be found that the films showed sustained release of the drug with a total cumulative release of 55% and 85% for progesterone and LidH, respectively (Figure 1). The rate of LidH release was faster than for progesterone. An increase in amount of LidH released was recorded at about day 7. This could be in response to the onset of degradation and its effect on release. The triphasic pattern and rapid release behavior of LidH can be explained by its hydrophilic nature, which increases water diffusion onto polymeric film, thereby increasing PLLA film degradation and drug release.

Morphology

Figure 2 shows the SEM images of PLLA films after 10 d of immersion in release media. The

biodegradation of PLA in an aqueous medium takes place through hydrolytic scission of the ester groups. The carboxylic acid groups, which are the products of hydrolytic scission, auto-catalyze the process further, thus the hydrolysis rate increases exponentially as the degradation time increases.²³⁻²⁴

As seen in the Figure, the neat PLLA film has a smooth surface (Figure 2b). A cross-section of neat PLLA film indicates that the film undergoes degradation (Figure 2a). The images show pores in the surface and cross-section of LidH film (Figures 2e and f). The formation of pores on the surface of PLLA arises from both the release of LidH and dissolution of the degrading polymer chain. These pores were not significant in the films containing progesterone (Figures 2c and d).

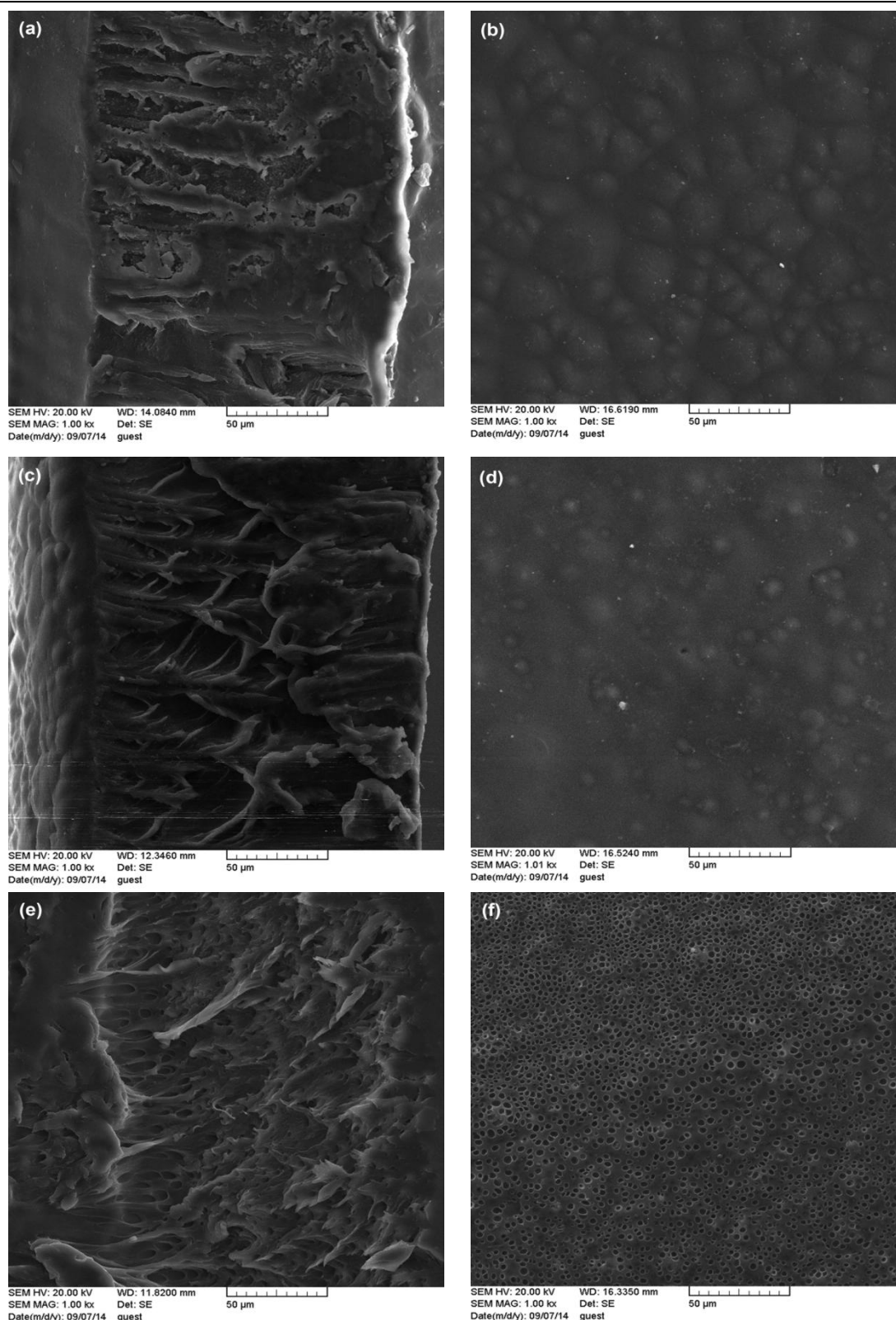


Figure 2. SEM photographs of cross section and surface of PLLA films: neat (a, b), containing progesterone: Pro- PLLA film (c, d); and lidocaine HCl: LidH- PLLA film (e, f) after 10 d of immersion in release media.

This confirms the drug release from LidH-PLLA films is higher than for the pro-PLLA film. The characteristic of loaded drug into the polymeric matrix could be

affected by the biodegradation rate of the polyesters. The release profiles were significantly affected by the tendency of LidH film to absorb water, which increased

film degradation in response to hydrophilic LidH. The results confirm previous *in vitro* drug release studies.

FTIR study

Drugs, interacting physically or chemically with the polymer, may change polymer characteristics compromising the release performances.²⁵ The interaction of polymer and drugs can take place with functional groups in their chemical structures. In this study, it assumes the carbonyl groups of PLLA chain can have important role in H-bonding with amide group of Lid H.

The FTIR spectra of neat PLLA, Pro- and LidH- PLLA films are presented in Figure 3. From the spectrum of neat PLLA, it can be seen that there is a strong absorption band at 1746 cm^{-1} corresponding to the

carbonyl group (C=O), the bands at 2938 and 2973 cm^{-1} are assigned to the C-H stretching vibrations of CH_3 groups in the side chains. As seen in the Figure (Figure 3), the lidH- PLLA film spectrum shows two peaks at region $1790\text{--}1650\text{ cm}^{-1}$, one weak peak near the original (C=O) stretching vibration of C=O was appeared. The sharp peak is related to free carbonyl groups of PLLA chain and one is not bonding with drugs to formation of H-bonding. The weak peak may be ascribed to C=O groups of PLLA that takes red shift due to the interaction of functional groups of drug and PLLA chains. The pro- PLLA film spectrum shows absorption peak of PLLA but it is difficult to detect the all of absorption peak for drug due to the low drug concentration in the PLLA films. A similar study was published by Blasi et al. previously.²⁵

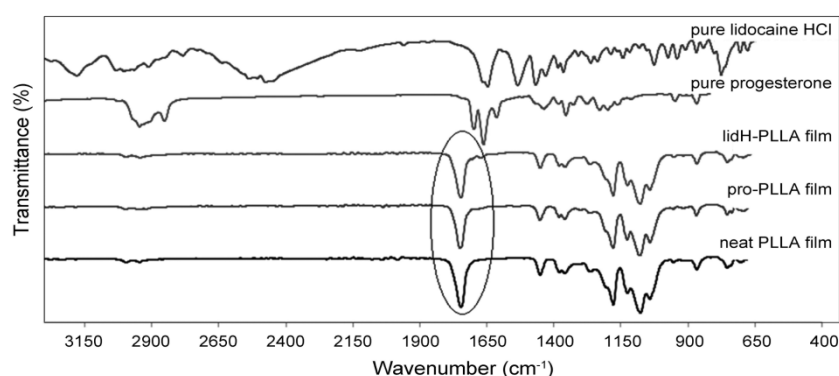


Figure 3. The FTIR spectra of drugs and PLLA films.

Dynamic mechanical thermal analysis

If the embedded drug interacts with the polymer, it can plasticize or anti-plasticize polymers, increasing or decreasing the rate of polymer hydration and its degradation rate. Plasticization may produce major changes in drug release kinetics from the increase in the diffusion coefficient. In fact, the diffusion

coefficient of small molecules through a polymer matrix increases by several orders of magnitude upon transition from a glassy to a rubbery state. This means that the drug molecules have a plasticizing effect with decreases polymer T_g and increases the elastic modulus, resulting in higher polymer flexibility or mobility.²⁵⁻²⁶

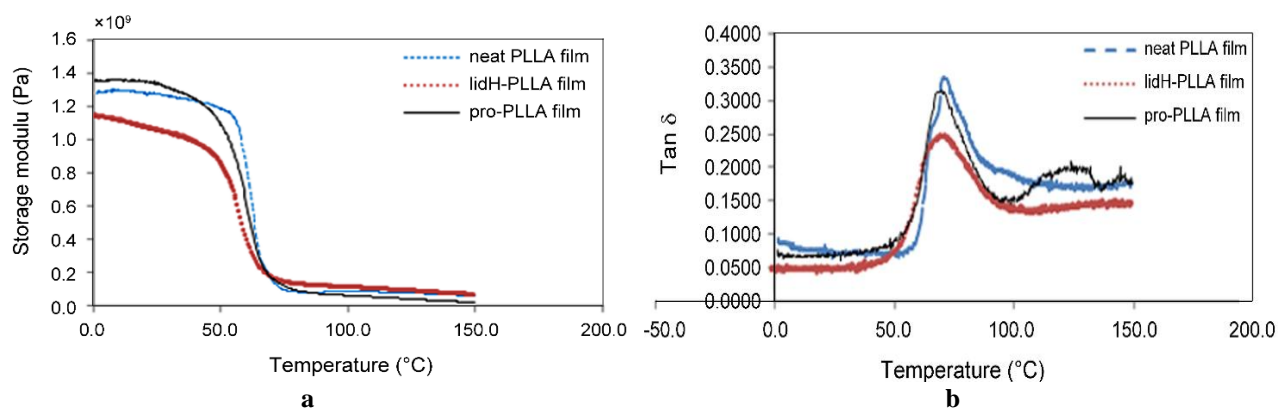


Figure 4. The storage modulus (a) and $\tan \delta$ (b) versus temperature curves for PLLA films (PLLA film containing progesterone: Pro-PLLA film; and lidocaine HCl: LidH- PLLA film).

It was expected that drug release behavior from PLLA delivery system would be influenced by physical or chemical interaction of the drug with the polymer, which can change the T_g of the polymer. Dynamic

mechanical thermal analysis (DMTA) was employed to further investigate the probable interaction between the drug and polymer. Figure 4 shows the storage modulus

and $\tan \delta$ of PLLA matrices as determined by DMTA at 1 Hz plotted versus temperature.

T_g of the PLLA films is the temperature indicated by the $\tan \delta$ peak.²⁷ Figure 4 shows that the $\tan \delta$ peaks shifted slightly toward lower values for LidH-PLLA and Pro-PLLA film rather than for neat PLLA film. This effect was more intensive on LidH-PLLA. This phenomenon is related to the increase in the elastic modulus resulting in higher polymer chain mobility by dispersion of the drug molecules throughout the polymer chains. Figure 4 shows that the storage modulus of the samples containing LidH decreased slightly.

At temperatures below T_g , the Pro-PLLA film showed a higher storage modulus than the neat sample (Figure 4a). This can be explained by the decreased interaction of progesterone molecules with the PLLA chains. Since the progesterone molecules organized themselves into crystal form, the interaction of progesterone molecules with polymer chains decreased. The storage modulus of the LidH-PLLA film decreased in response to the hydrophilic LidH, which shows polar characteristic that can act as a plasticizer to decrease intermolecular interaction of PLLA chains and decrease the storage modulus. At temperatures above T_g , the molten progesterone (melting point 125°C; Figure 4(a)) acted as a plasticizer and decreased the storage modulus. The obtained results confirm the FT IR analysis.

In vitro drug release kinetic study

The drug release kinetic is directed by one or more mechanisms that depend on the composition of the matrix, geometry, preparation method and dissolution

media of drug release. This can be explained by mathematical models in accordance with the desired or required predictive ability and accuracy of the model.²⁸⁻²⁹

Release models having major applications and that best describe drug release are the zero order ($Q = Q_0 - K_0t$), first order ($\ln Q = \ln Q_0 - K_1t$), Higuchi ($Q = K_2t^{1/2}$) and Korsmeyer-Peppas ($Q/Q_0 = Kt^n$) models. K_0 to K_2 are release rate constants, Q/Q_0 is the fraction of drug released at time t and n is the release exponent. The coefficient of correlation (R^2) values are calculated for a linear curve obtained using regression analysis of the plots from these models.²⁹

The Higuchi and zero order models are used to describe the limits for transport and drug release. The decision parameters between these two models are determined by Korsmeyer-Peppas model. Parameter n from the Korsmeyer-Peppas model is used to understand the details of the release mechanisms. The interpretation of n was done as suggested by Peppas:³⁰⁻³¹ with $n < 0.5$ (0.45) for the quasi-Fickian diffusion; $n = 0.5$ (0.45) for the diffusion mechanism; $0.5 < n < 1$ for the anomalous (non-Fickian) diffusion for both diffusion and relaxation (erosion); $n = 1$ (0.89) for case 2 transport (zero order release); and $n > 1$ (0.89) for super case 2 transport (relaxation).

The drug release behavior of the PLLA matrices was described using the best-fitted model. The experimental data were first approximated using the Higuchi and Korsmeyer-Peppas models (Figure 5). The drug release data were fitted to the equation of the Higuchi model to give R^2 values of 0.945 for progesterone and 0.975 for LidH (Table 1).

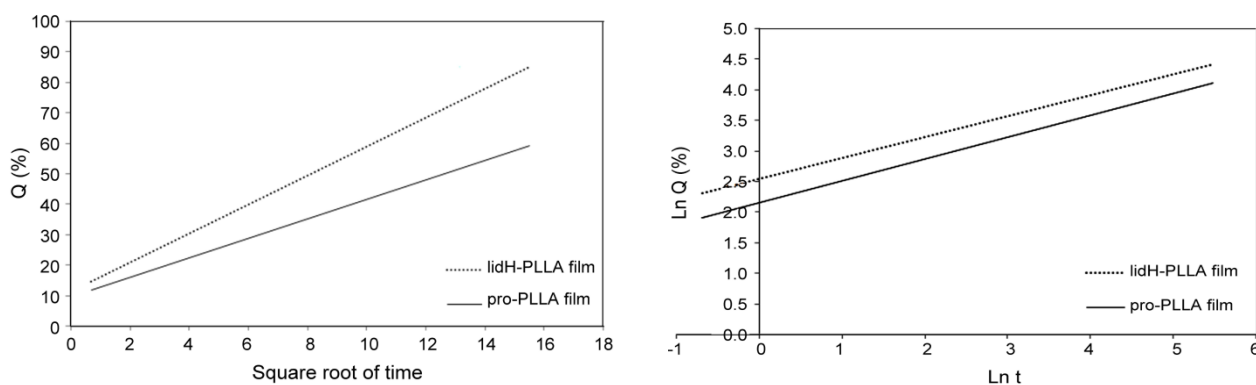


Figure 5. Drug release data from PLLA films approximated with: Higuchi (a) and Korsmeyer-Peppas (b) model (PLLA film containing progesterone: Pro- PLLA film; and lidocaine HCl: LidH- PLLA film).

Table 1. Result of approximation of Higuchi and Korsmeyer-Peppas models to drug release data obtained for PLLA films.

Samples	Higuchi		Korsmeyer Peppas	
	Slop	Regression	Slop(n)	Regression
Pro- PLLA film	3.213	0.945	0.356	0.951
LidH- PLLA film	4.753	0.975	0.343	0.986

The R^2 values of the Korsmeyer-Peppas model for the release data were 0.951 for progesterone and 0.986 for LidH. Table 1 indicates that n equals 0.343 for the

lidH-PLLA and 0.356 for the Pro-PLLA matrices. Since release exponent n of the Korsmeyer-Peppas kinetic model indicates that the drug release

mechanism can be driven by quasi-Fickian diffusion. The common mechanisms applied to evaluate drug release from biodegradable polymeric drug delivery systems are combinations of diffusion and degradation. Drug release occurs concurrently to polymer degradation. In such systems, drug release profiles usually have a sigmoidal shape.³² The Gallagher and Corrigan model is a mathematical model that describes the fraction of drug released from the biodegradable polymeric system. The total fraction of drug released (f_t) at time t is:

$$f_t = f_{t\max} \left(1 - e^{-K_1 t}\right) + (f_{t\max} - f_B) \left(\frac{e^{K_2 t - K_2 t_{2\max}}}{1 + e^{K_2 t - K_2 t_{2\max}}}\right) \quad \text{Eq.(1)}$$

Where $f_{t\max}$ is the maximum fraction of drug released; f_B is the fraction of drug released during the burst effect; K_1 is the first order kinetic constant; K_2 is the rate constant in the polymer degradation phase and $t_{2\max}$ is the time for maximum drug release.^{18,28} Several studies have explained the mechanism of drug release from biodegradable polymeric drug delivery systems.^{19,30,33-34}

The release profile of LidH from PLLA film was found to occur in a triphasic manner. This means that the degradation of the polymeric matrix is significant, as shown by SEM. The kinetic parameters and the mechanism of drug release from the PLLA film were

Table 2. Gallagher-Corrigan model parameters values for PLLA films.

Sample	f_B	k_1, h^{-1}	$f_{t\max}$	K_2, h^{-1}	$t_{2\max}, h$
LidH - PLLA film	0.45	0.04239	0.7442	0.07759	188

The drug release profile was successfully described by the Gallagher-Corrigan models as indicated by an R^2 of 0.946. The lidH release kinetic suggests that the process was determined by diffusion during the initial release and that polymer degradation is the controlling factor. These two mechanisms may appear to play different roles; however, in the release process, the major process is polymer degradation ($K_1 < K_2$).

Conclusion

This study examined the release of progesterone and lidocaine hydrochloride from PLLA film. It was found that LidH was delivered faster than progesterone because of the increase in polymer chain degradation, which was confirmed by SEM. LidH was released in a triphasic profile and progesterone was released in a biphasic profile. These results indicate that PLLA film has the potential for achieving controlled drug release. A study of the physical interactions between neat PLLA and LidH and progesterone were performed using DMTA. The LidH acted as a plasticizer because of its polar and hydrophilic characteristics, thereby decreasing the storage modulus. T_g decreased over that for neat films, which is generally ascribed to polymer/drug interaction, such as hydrogen bonding.

further investigated using the Gallagher-Corrigan equation. MATLAB software was used to fit the Gallagher-Corrigan models to the data.

Figure 6 and Table 2 give the results of approximation of the Gallagher-Corrigan model to the lidH release data obtained for PLLA film. The kinetic profile includes the initial burst release of LidH from the surface of the matrix followed by slow release from drug diffusion and matrix degradation.

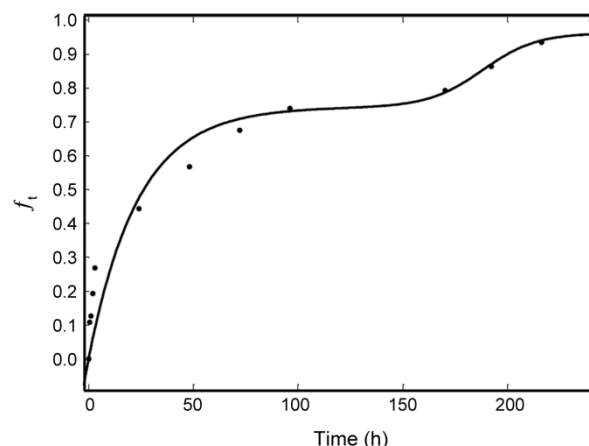


Figure 6. Lidocaine HCl release data from PLLA films approximated with Gallagher-Corrigan model (fraction of drug released, f_t - time).

LidH/PLLA chain hydrogen bonding could be responsible for the observed plasticizing effect.

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Conflict of Interest

The authors report no conflicts of interest.

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