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RESEARCH PAPER

Effect of Physicochemical Factors on the Release Kinetics of Hydrophilic Drugs from Poly(L-Lactic Acid) (L-PLA) Pellets

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ABSTRACT

Poly(L-lactic acid) (L-PLA) pellets intended for either parenteral or oral use were successfully prepared by a direct compression technique without the use of heat or organic solvents. Salicylic acid and theophylline were chosen as drug candidates. The drug release from pellets was affected by the compression pressure. The Higuchi plots of the drugs showed a $t^{1/2}$ dependent drug release pattern. The release rates of these drugs from PLA pellets were directly correlated to their solubilities in the dissolution media. At lower pH (<7), the release of salicylic acid was found to be slower than theophylline; however, at higher pH (>7), the release of salicylic acid was faster than that of the theophylline. The release rate of salicylic acid was higher at higher pHs, which was related to the increase in solubilities. Pellets were annealed at 20, 40, and 80°C. A lower release rate was observed with increasing temperatures. Above the glass transition temperature (T_g) of the polymer, the release of drugs was significantly decreased. The drug release was independent of the ionic strength of the media for both salicylic acid and theophylline. We showed earlier that no drug-polymer interactions or polymer degradation were observed when studied by differentials scanning calorimetry (DSC) and infrared spectroscopy (IR) (1). The release mechanism was primarily physical diffusion and leaching during the experimental period. We conclude that the release of low molecular weight (MW) drugs from the high MW L-PLA was independent of the pH and the ionic strength of the dissolution media, but was dependent on the polarity of the drug and formulation factors, such as compression pressure and annealing temperature.

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INTRODUCTION

Poly(lactic acid) (PLA) is a biodegradable polyester that has been used for the preparation of sustained-release (SR) drug delivery systems (1). Current methods to prepare these dosage forms include the use of heat and/or organic solvents, either of which are capable of influencing release kinetics of drugs (2–4). Degradation of PLA is pH dependent and it increased in both strongly acidic and strongly alkaline solutions, indicating general acid/base catalysis of hydrolytic reaction of PLA (5). Few reports have appeared in the literature on pH-independent SR dosage forms containing drugs which have low solubility in a certain pH range (6,7). In these studies, we used two different drugs which have different solubilities in different pHs. Understanding the mechanism of drug release from PLA polymers is crucial (2). The effects of the dissolution medium, such as buffer composition, ionic strength, surface tension, enzyme activity, and addition of food on the release rates of a drug have to be considered, but few investigations have been made concerning these points (8,9). In these studies, a number of physicochemical factors were considered to evaluate the release kinetics of low molecular weight (MW) drugs from PLA pellets.

EXPERIMENTAL

Poly(L-lactic acid) (L-PLA), viscosity average MW = 61,300, was supplied by Boehringer Ingelheim (Germany). All other chemicals were of standard reagent grade from BDH, England. The composition of the buffer solutions has been described (10).

Solubility Determinations

An excess amount of the candidate drug (approximately 2 g) was dispersed in 50 ml buffer solution and stirred for 48 hr at 37°C. After filtration and dilution, the drug content was determined spectrophotometrically at 270 and 298 nm for theophylline and salicylic acid, respectively, using a Pye Unicam (UK) SP8-400 spectrophotometer.

Preparation of Matrix Disks

Appropriate amounts of salicylic acid or theophylline were mixed with 50 mg L-PLA in a mixer for 30 min. One hundred milligrams of this mass was directly compressed on a Perkin-Elmer (Germany) hydraulic presser with 5 ton pressure or as mentioned in the text.

Annealing of Pellets

Initial weights of pellets were measured heated at 25, 40, and 80°C in a hot-air oven for 15 min or as mentioned in the text. The pellets were then cooled and ready for drug release studies.

Incubation and Analysis

Each pellet was placed in an Erlenmeyer flask filled with 100 ml of the dissolution media and incubated at 37°C in an incubator (Memmert, Germany). Five milliliters of each sample was withdrawn at appropriate time intervals and replaced with a freshly prepared buffer medium. After 4 days, the samples were rinsed in distilled water and then dried completely in a vacuum desiccator for 3 days. Each pellet was weighed measured and the weight loss calculated to determine pellet erosion or degradation as described before (1). To detect potential drug degradation during drug release studies, physical mixtures of drug and polymers were run.

Pellet Hydration

The pellets were equilibrated in different pH buffer solutions ($n = 3$). The sample weight was monitored until equilibrium was reached. The pellet hydration was calculated as follows:

% Pellet hydration = (equilibrium hydrated pellet weight − dry pellet weight) × 100% dry pellet weight

Effect of Ionic Strength

The effect of electrolyte concentration on L-PLA release kinetics was performed using a previously described method (11). Different dissolution fluids containing increasing amounts of KCl were prepared to get ionic strengths 0.085, 1.70, 3.40, 5.10, 6.80, and 10.20 $\times 10^{-1}$.

RESULTS AND DISCUSSION

Solubility of Drugs

The solubility of theophylline in the different buffer solutions was not influenced by the composition of the buffers (Table 1). The slightly higher solubilities at pH 2 and 10 were caused by the initiation of salt formation

Table 1

Saturation Solubilities of Salicylic Acid in Different Buffer Media

Buffer, pH	Mean Saturation Solubility ± SD (mg/ml) (n = 3)	
	Salicylic Acid	Theophylline
2.0	2.0 ± 0.06	1.51 ± 0.07
5.0	7.1 ± 0.5	1.12 ± 0.04
7.4	21.9 ± 0.7	1.30 ± 0.05
10	115 ± 1.5	1.35 ± 0.02

of theophylline (pK_a 0.3, pK_a 8.6). The solubilities of salicylic acid were higher with an increase in pH and the highest solubility was observed at pH 10 (Table 1).

Effect of Compression Pressure

Pellets were made at different compression pressures to investigate the effect of the compression pressure on drug release kinetics. The percent release of drugs at 2 and 10 ton compression pressure after 40 hr were 80 and 62% for salicylic acid and 60 and 46% for theophylline, respectively. These results suggest that higher mechanical strength of the pellets hinders leaching of the drug from the lipophile matrices. A 5-ton compression pressure was selected as a standard protocol for favorable release studies.

Effect of Drug Loading

No significant differences in release mechanism can be observed with increasing drug loadings of theophylline in pellets from 10 to 50%. The Higuchi release kinetics remained unchanged (R^2 = 0.95–0.99). An increase in release rates was observed as a result of drug loading, which was correlated with the amount of the drug incorporated into pellets. The release of salicylic acid becomes faster as the drug loading was increased from 10 to 50% (Fig. 1). However, drug release from pellets was found to be indistinguishable when drug loading was increased further. For all subsequent studies, pellets with 50% drug were evaluated. The diffusion of water into the pellets was greatly facilitated by the water uptake of the drugs, not by the water uptake of the lipophilic polymer. This implies that the leaching of the drug and the water diffusion are the controlling variables rather than the degradation of the polymer.

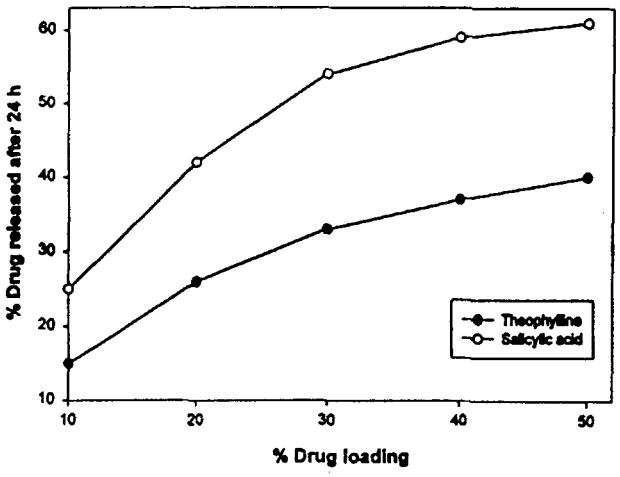

Figure 1. Effect of drug loading on the release of salicylic acid and theophylline from L-PLA pellets prepared under 5 ton pressure. Drug release was studied in distilled water at 37°C in an incubator. All data are the mean of at least three determinations with CV less than 10%.

Effect of pH

Theophylline was released more rapidly in alkaline pH than salicylic acid, and both drugs released to a lesser extent in acidic medium. For theophylline, the percent drug release after 40 hr was 67, 62, 60, and 53% at pH 2, 5, 7.4, and 10, respectively. The solubility of theophylline was eliminated as a variable factor on the release of theophylline. On the contrary, the solubility of salicylic acid was significantly affected by pHs, observed as an increase in the solubility of the drug in alkaline solutions (Fig. 2). The release mechanism of drugs followed the Higuchi release mechanism characteristic of the drug release from the PLA pellet. The Higuchian release rate for salicylic acid was 2-fold higher at pH 7.4 and 4.5-fold higher at pH 10. The release rates of theophylline at higher pHs were not significantly different ($p > 0.05$). Since there was no polymer degradation during the experimental periods (1), the release rates were correlated with the solubilities of the drugs in the media.

The release of drugs into the buffer solutions can be predicted by the pH partition hypothesis. For example, salicylic acid is a weak acid that can exist in solution as either the un-ionized (U) or ionized (I) form. The ratio of ionized to un-ionized drugs (I/U) can be estimated by the Henderson–Hasselbach equation for an acid:

$$pH - pK_a = \text{Log } (I/U)$$

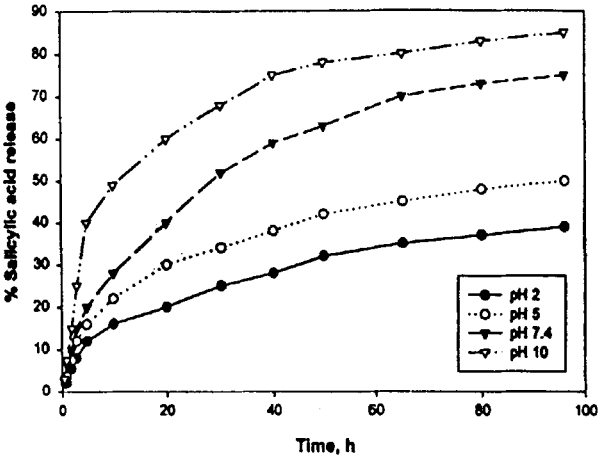

Figure 2. Effect of pH on the release kinetics of salicylic acid from L-PLA pellets. Drug release was studied in different buffers with indicated pHs at 37°C in an incubator. All data are the mean of at least three determinations with CV less than 10%.

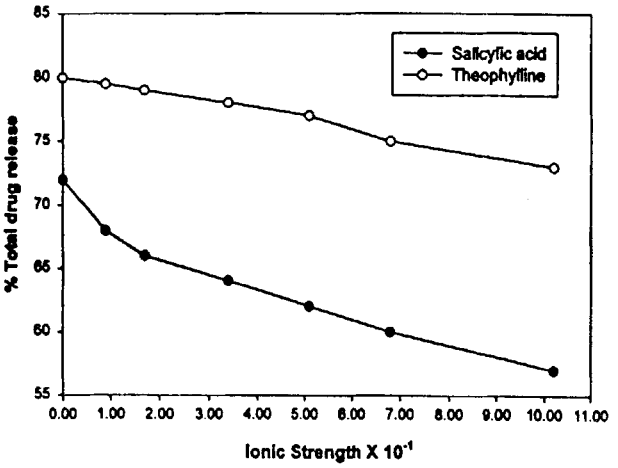

Figure 3. Effect of ionic strength on the release of salicylic acid and theophylline from L-PLA pellets prepared under 5 ton pressure. Different ionic strength solutions were prepared using KCl as described earlier (11). All data are the mean of at least three determinations with CV less than 10%.

The pK_a of salicylic acid is 3.0, so in a pH 7.4 buffer solution the ratio of approximately 25,000/1 (I/U) exists. This ratio is even higher at pH 10, 10^7/1 (I/U). The conversion of un-ionized drugs to the ionized form in the release media provided a strong driving force for the diffusion of salicylic acid into the media. As the pH of the buffer solution decreased, the I/U ratio reduced and the driving force for the salicylic acid was diminished accordingly, resulting in a slow diffusion rate.

Effect of Ionic Strength

Because the pellet was lipophilic and stable during the experimental time limit, any effect of ionic strength on pellet hydration was considered to be negligible. An increase in the ionic strength may lower hydrodynamic activity of the dissolution fluid because of the presence of a higher number of ionic species. This will retard water penetration into the pellet and consequently lower the release rate. We investigated the effect of electrolyte concentration on the rate of erosion of L-PLA. It was found that the electrolyte concentration had no significant effect on the rate of drug release. The rate of drug release at higher electrolyte concentrations, such as at 10.2×10^{-1}, was comparable to that of the 0.85×10^{-1} solution (Fig. 3).

Effect of Annealing

Annealing temperatures 20, 40, and 80°C were used to study the release properties of drugs in distilled water. These pellets containing salicylic acid and theophylline follow a biphasic Higuchian release mechanism (Figs. 4 and 5). In both cases, a three-fold decrease in release rates at 60 and 80°C compared to unannealed pellets was observed because of less extraction of the drug from the vicinity of pellets. Above the T_g of the polymer (57°C), drug release from the pellets was significantly affected because of the effect of T_g on free

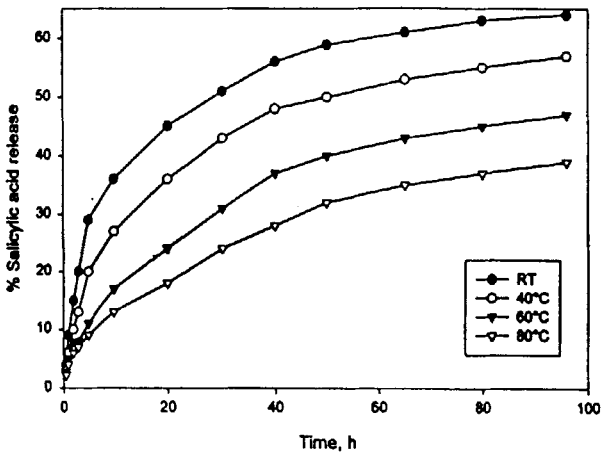

Figure 4. Effect of annealing on the release kinetics of salicylic acid from L-PLA pellets. Pellets were annealed for 15 min in a hot-air oven at different temperatures. Drug release was studied in distilled water in an incubator. All data are the mean of at least three determinations with CV less than 10%.

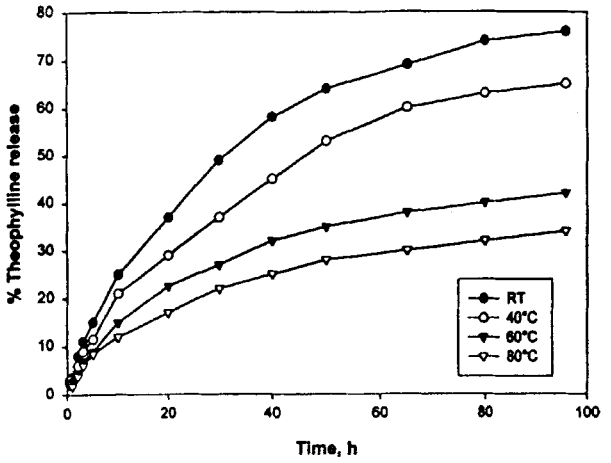

Figure 5. Effect of annealing on the release kinetics of theophylline from L-PLA pellets. Pellets were annealed for 15 min in a hot-air oven at different temperatures. Drug release was studied in distilled water in an incubator. All data are the mean of at least three determinations with CV less than 10%.

volume, permeability, and chain mobility of the polymer as described earlier (12).

Pellet Stability

Pellet hydration was found not to be a contributing factor to drug release (Table 2). The minimum hydration of the pellet is related to the lipophilicity and stability of the polymer. The polymer was found to be intact when analyzed by IR spectroscopy (1). There was no interaction observed between the drug and the polymer when analyzed by DSC (1). Moreover, visual observation of the pellets during release studies revealed that the pellets were not swelled or eroded (data not shown). Also, no drug–polymer interactions or polymer degradations were observed in the UV absorbance profile or in the inspection of the pellet shape.

Table 2

Effect of Media on Hydration of L-PLA Pellets

	% Pellet Hydration	
Medium	Salicylic Acid	Theophylline
pH 2.0	5.90 ± 0.66	6.05 ± 0.53
pH 5.0	7.10 ± 0.88	6.40 ± 0.72
pH 7.4	11.20 ± 0.75	7.95 ± 0.85
pH 10	19.42 ± 0.81	8.10 ± 0.25

CONCLUSIONS

The drug release from high MW PLA can be modulated by using physicochemical parameters such as compression pressures, percent drug loading, and annealing. When the drug solubility was ignored, no differences of the drug release with a change in pH or ionic strength were observed. The release of a drug from L-PLA pellets can be significantly reduced with higher annealing temperatures. The release kinetics of the ionic drug is related to its solubility and the release mechanism is mainly the result of leaching and physical diffusion for 4 days from high MW PLA pellets. These pellets could potentially be used as implantable or oral drug delivery systems. Pellets could be designed to release the drug at a desired rate at any pH; i.e., the drug would be released pH independently in the gastrointestinal tract.

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