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EFFECT OF TEMPERATURE OF DISSOLUTION ON THE RELEASE KINETICS OF PHENOBARBITONE FROM POLY (DL-LACTIC ACID) MICROCAPSULES: CALCULATION OF ACTIVATION ENERGY.

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ABSTRACT

Poly (DL-lactic acid) [DL-PLA] microcapsules containing phenobarbitone (core:polymer, 1:2) were prepared using three different molecular weight polymers, 20,500, 13,300 and 5,200. Buffer pH 9 were used to study dissolution rate at temperatures of 10^{o}, 15^{o}, 20^{o}, 25^{o}, 30^{o} and 37^{o}C. The release mechanism followed "Higuchi's" square root of time relationship at all these temperatures and allowed calculation of release rate from the straight line portion of release curve. These microcapsules showed an initial burst phase release followed by a lag phase; both of these phases are affected by the temperature of dissolution and polymer molecular weight. The normalized release rate [K_{h2}/SSA] was found to lower linearly with the lowering of temperature with all three polymers. Arrhenius plot of the normalized release rate allowed calculation of the activation energy (Ea) for the polymers. It was found to lower linearly with the increase in DL-PLA polymer molecular weight.

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INTRODUCTION

Poly(lactic acid) [PLA] has been known for its excellent biodegradability and in vivo insertion of microcapsules prepared form this polymer also showed excellent histocompatibility[1-3]. Wide range of synthetic drugs, peptide hormones, enzymes have been encapsulated using this polymer[4-7]. The release mechanism of small molecular weight drugs depends on both diffusion through polymer membrane and erosion of polymer matrix, whilst the release mechanism of larger molecules such as peptides or enzymes are dependent on the rate of erosion of polymer matrix[6,8]. This rate of degradation and erosion of PLA matrix is dependent on polymer molecular weight. The DL-PLA microcapsules containing phenobarbitone has been shown to swell and erode in the aqueous environment which finally fragmented after release of drug[9]. The diffusion of drug and erosion of polymer matrix would be affected by the dissolution condition, such as temperature. When the coating polymer is thermoplastic in nature, such as PLA, this temperature of dissolution would be of prime importance. In this study DL-PLA microcapsules containing phenobarbitone were subjected to different dissolution temperatures to investigate the effect of polymer molecular weight on the release behaviour.

EXPERIMENTAL

Materials: Poly (DL-Lactic acid), mol. wt. 20,500 (Sandoz), 13,300 & 5,200 (synthesized, Jalil); Phenobarbitone, (Sigma), Acetonitrile, HPLC grade (Fisons); Light liquid paraffin (BDH); Span 40, (Atlas); Petroleum ether, b.p. 40-60, analar, (Fisons); other chemicals were of reagent grade purity.

Method of Microencapsulation: Microcapsules were prepared using the emulsification (W/O) and organic solvent evaporation technique previously reported[10]. Microcapsules of nominal C:P ratio of 1:2 were prepared using all three different molecular weight DL-PLA polymers.

Particle size and Specific surface area determination: Microcapsules, suspended in 0.9% NaCl, solution containing 0.0001% Nonidet P40 as dispersant, were measured by the Coulter counter (model TAII/PC Al Accucomp) coupled to a population accessory and interfaced with an Apple IIe computer. Measurements were also made after deaggregation by sonication for 30 seconds (Kerry sonicator). The specific surface area of the microcapsules was calculated from the particle size data of a known sample weight.

Dissolution studies: All dissolution test were carried out using a U.S.P. XXI dissolution apparatus. The whole system was automated using a spectrophotometer (Philips PU 8620 UV/VIS/NIR) and a computer (Opus PCIII) to capture and analyse data. 240 nm wave length was used for analysis. The temperature of dissolution bath was maintained at lower temperatures, 10, 15, 20, 25°C using a chiller unit (Churchill Instrument, England) and 30° & 37°C was maintained by inbuild heating system of the dissolution bath (Coply). Stirring rate was maintained at 100 rpm and the temperature at 37°C. The dissolution medium was buffer pH9. 50 mg of microcapsules were introduced into the flask.

RESULTS AND DISCUSSION

Microcapsules (core:polymer, 1:2) containing phenobarbitone (PB) were prepared using different molecular weight DL-PLA; 20,500 [DL-PLA1], 13,300 [DL-PLA2] and 5,200 [DL-PLA3]. Dissolution temperatures ranging from 10°C to 37°C were used to study the release properties in buffer at pH 9. The DL-PLA microcapsules containing PB microcapsues has been found to follow a square root of time dependent release mechanism (to be published). The "Higuchi" plots of the release data from DL-PLA3 at different temperatures are shown in fig. 1. This shows that variations of dissolution temperature did not change the release mechanism, i.e. all follow a $t^{1/2}$ dependent release pattern after the initial burst effect and subsequent lag phase. Microcapsules

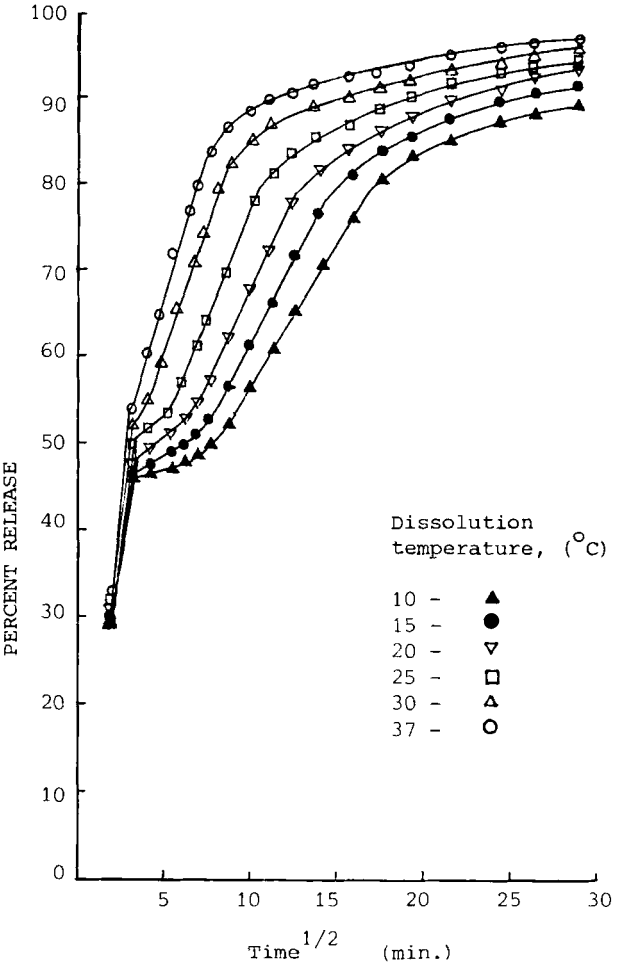

FIGURE. 1.

"Higuchi" plots of phenobarbitone release from DL-PLA3 microcapsules (C:P, 1:2) at different temperatures of dissolution. Temp. of dissolution, °C: 10, ▲; 15, ●; 20, ▽; 25, □; 30, △; 37, ○. Dissolution conditions: Stirring rate, 100 rpm; Buffer, pH 9.

prepared from DL-PLA1 and DL-PLA2 also showed similar release pattern. The quantity of PB released during the "burst" phase was reduced at lower dissolution temperatures with all three polymer which is attributable to the lower extraction of PB from the vicinity of the microcapsule surface as the temperature decreases.

The steady state release rate (K_{h2}) of PB from these microcapsules was also reduced with a decrease in dissolution temperature (Fig.1), which correlates well with the Arrhenius kinetic relationship:

$$k = A\, e^{-Ea/RT} \quad \text{.....(1)}$$

The use of the release rate per unit specific surface area [K_{h2}/SSA] according to this relationship gives an equation 2.

$$\log(K_{h2}/SSA) = \log A - \frac{Ea}{2.303R\,T} \text{.....(2)}$$

where logA would be a temperature independent intercept on the "Y" axis of the Arrhenius plot, log(K_{h2}/SSA) vs. 1/T (Fig.2). The slope of the straight line (Ea/2.303R) will allow the calculation of Ea of a polymer under specified dissolution conditions, such as pH of the buffer, stirring rate, etc.

Arrhenius plots of the normalized release rate (K_{h2}/SSA) from microcapsules prepared from all three DL-PLA polymers showed a straight line relationship (Fig. 2) indicating that variations in the dissolution temperature caused changes in the release rate according to Arrhenius relationship. The decrease in the normalized release rate with the decrease in dissolution temperature is attributable to the lowering of PB solubility in the bulk solution. In addition, decreased temperature will also decrease the intrinsic diffusivity, because of thermoplastic nature of the polymers.

The slopes of the Arrhenius plot is represented by Ea/2.303R, which is a function of activation energy. The calculated values were 2.9, 4.16, and 5.54 Kcal/mole for the polymers DL-PLA1, DL-

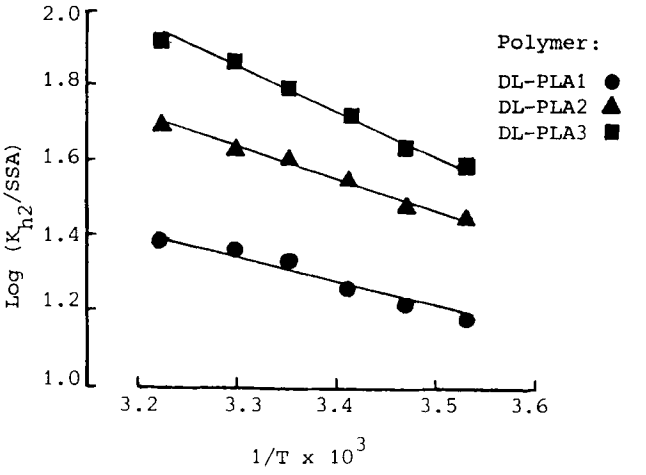

FIGURE. 2.

Arrhenius plot of normalized steady state release rates (K_{h2}/SSA) from microcapsules (C:P, 1:2) of different molecular weight polymer. Microcapsules of polymer: DL-PLA1, ● ;DL-PLA2, ▲ ; DL-PLA3, ■ . Dissolution conditions: Stirring rate, 100 rpm; Buffer, pH 9.

PLA2 & DL-PLA3 respectively. These values will depend on many factors within the microcapsule system, such as, core properties, polymer properties, and dissolution conditions. In this study, all the parameters were kept constant, except the molecular weight of the DL-PLA polymer used to prepare the microcapsules, so that any changes in the "Ea" would be associated with the polymer properties and molecular weight. When the "Ea" values for different DL-PLAs were plotted against their molecular weight a straight line relationship was found (Fig. 3), indicating an increase of activation energy with a corresponding decrease in the polymer molecular weight. This is attributable to variations in intrinsic polymer properties in response to temperature variations. The low molecular DL-PLA polymer showed lower T_g value. When reduction of PB solubility is achieved by reducing dissolution temperature the latter will also affect the glass

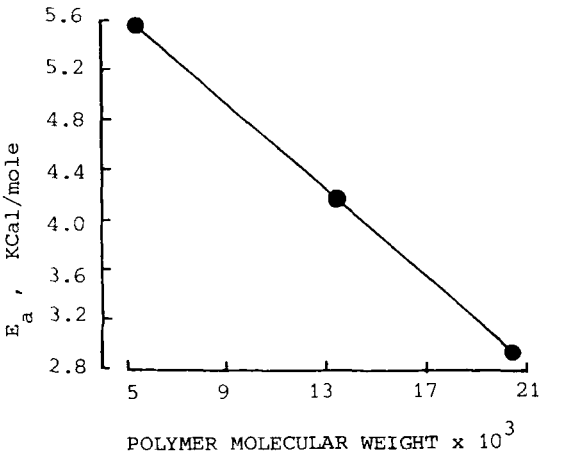

FIGURE. 3.
Effect of DL-PLA polymer molecular weight on the activation energy (E_a, calculated from the slopes of fig 2.).

transition temperature (T_g) of these glassy polymers. In addition, the morphological changes during dissolution were also affected by the temperature. DL-PLA3 microcapsules undergo extensive pore formation and cracking during dissolution at 37°C, but SEM studies, after dissolution at 10°C for 15 hours, showed fewer pores and less fragmentation. By contrast, the microcapsules from the high molecular weight polymer, DL-PLA1, showed little difference in morphology after dissolution under the same conditions. Degradation and erosion of DL-PLA increases with an increase in temperature[11,12] .

This relationship between Ea and DL-PLA polymer molecular weight is possibly only an empirical one, applicable only to these microcapsule system. The calculated "Ea" values were obtained from the dissolution data of pH 9 and may be different at other pHs. It has been found that the release from these microcapsules is proportional to the solubility of PB in the dissolution medium (to be published). Therefore, any change in the "Ea" due to the changes in pH of the dissolution medium will also be proportional, provided other parameters remain constant.

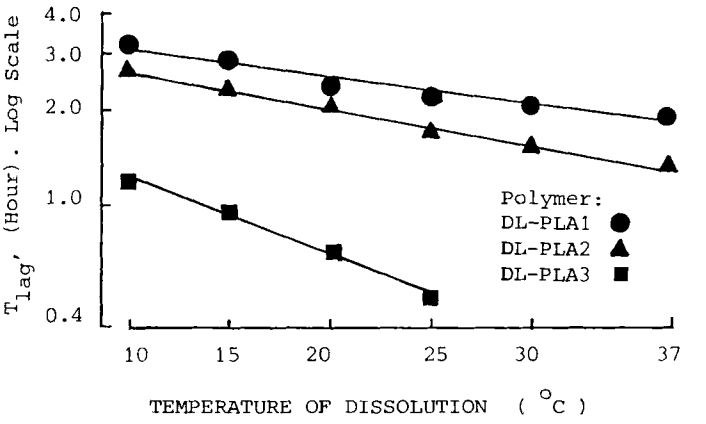

FIGURE. 4.

Effect of dissolution temperature on the dynamic lag time (T_{lag}) of microcapsules (C:P, 1:2). Microcapsules of polymer: DL-PLA1, ●; DL-PLA2, ▲ ; DL-PLA3, ■ . Dissolution conditions: Stirring rate, 100 rpm; Buffer, pH 9.

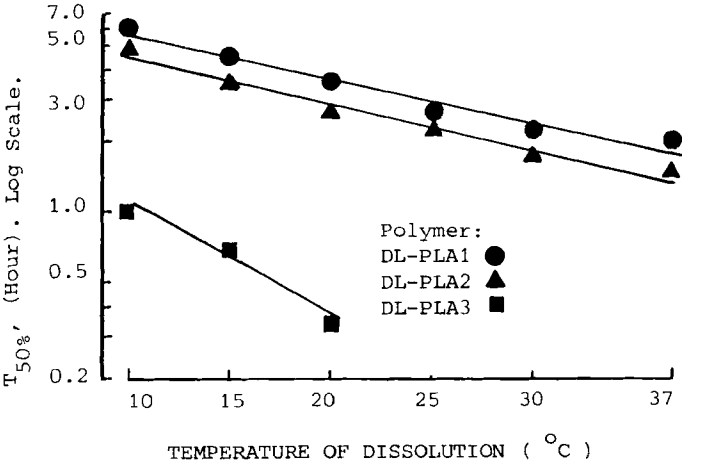

FIGURE. 5.

Effect of dissolution temperature on the time for 50% PB release ($T_{50\%}$) of microcapsules (C:P, 1:2). Microcapsules of polymer: DL-PLA1, ● ; DL-PLA2, ▲ ; DL-PLA3, ■ . Dissolution conditions: Stirring rate, 100 rpm; Buffer, pH 9.

Reduction of the dissolution temperature exponentially increases the "dynamic" lag time (Fig. 4) attributable to the reduced dydrodynamic activity of water at the lower temperature. This causes a longer polymer hydration time for the membrane, thereby exponentially increasing the lag phase. In addition, by lowering the dissolution temperature the polymer chain movement will also be reduced, which will impede water penetration into the membrane more than at higher temperatures. Thus the low molecular weight polymer DL-PLA3 did not show any lag phase at 30 & 37°C, which is close to the T_g of this polymer; and when the temperature was reduced further, a significant lag phase was observed (Fig. 1), which increased exponentially with the reduction of temperature (Fig. 4). DL-PLA1 & DL-PLA2 showed a lag phase at all temperatures and the extent of which follows the same pattern as in DL-PLA3. The time for 50% release ($T_{50\%}$) also increased exponentially with the decrease in temperature (Fig. 5), which was responsible for both an increase in the "dynamic lag time" and a lowering of the release rates.

CONCLUSION

It can be concluded from this study that the release properties of the low molecular weight drugs form poly(DL-lactic acid) is temperature dependent, which may be attributable to both reduction of core solubility in the bulk phase and lowering of diffusivity of the polymer membrane. The latter is also dependent on the polymer molecular weight. A known value of "Ea" of a particular polymer will allow in the prediction of release rates in different temperatures.

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