DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(10), 1279-1294 (1991)

RELEASE KINETICS OF POLYMERIC PRODRUGS OF PINDOLOL (PDL)

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ABSTRACT

Various type of pendant chain polymeric prodrugs of pindolol were synthesized and their release characteristics were evaluated. Non linear regression analysis of various mathematical models indicated a best fit was obtained in all cases by a concomitant zero and first order release pattern. The effect of load (w/w pindolol) and backbone (polymer type) were studied. An increase on load in the high molecular weight dextran (T - 70) resulted in a proportional increase in fraction of release exhibiting first order kinetics and a proportional decrease in the zero order rate constant. Across the three polymers studied, a polymer with a large first order fraction also had a large zero order rate constant and a faster overall release pattern.

INTRODUCTION

Drug delivery systems are designed to get the drug into the body through the various routes of administration. The delivery system can be designed to be the rate limiting step when evaluating the duration of action of a drug compound. Such a design might take the shape of polymeric prodrug forms of the drug where the either the lysis of the drug from the polymer or the

diffusion of the drug, once free, through the polymer could be rate limiting (1-5). Besides the obvious advantages with regard to patient compliance upon increasing the dosing interval, it is possible to see a reduction in systemic side effects which would be due to the overall stable but lower plasma concentrations in a conventional sustained release delivery system. Additionally, we would certainly see a significant reduction, if not elimination, of systemic side effects in cases where the drug is applied on or in the effector organ in a system which meters out miniscule amounts of drug in sufficient concentrations to effect the organ but those same amounts result in infinitesimally small concentrations when diluted out further in the body. An example of a system which employs this concept, if not the polymeric prodrug design, is the Progestasert^{R}, a T shaped contaceptive reservior system designed to deliver progesterone for more than a year (6). It has been hypothesized that release of drugs from polymeric prodrugs could also be a mechanism whereby this concept might be realized.

The release rate characteristics of polymeric prodrugs made with various polymers and as well as percentage loads (w/w PDL/total) were evaluated using several kinetic models. Several parameters, such as solubility, % load, polymer backbone, cross-linking, formation of a complex, were evaluated in an attempt to catagorize some factors which might influence either the rate or the order of PDL release.

MATERIALS AND METHODS

Materials:

Pindolol free base (M.W. 248.32, purity 99.98%, pKa = 8.8, lot 79001) was donated by Sandoz Pharmaceuticals, Basal, Switzerland. The cellulose semipermeable membrane (No. 132638) used for dialysis studies, with a M.W. permeability limit of 1000, was purchased from Spectrum Medical Industries, Inc., Los Angeles, CA Dextran T10 (10,000 dalton, lot 6930) and T70 (70,000 dalton, lot 8027) were purchased from Pharmacia Fine Chemicals, Inc., Piscataway, NJ.

Amylose (M.W. 150,000, lot KB 081711) was purchased from Aldrich Chemical Company, Inc., MIlwaukee, WI.

All other chemicals used were were analytical or reagent grade.

Methods - Synthesis:

Biodegradable pendant chain polymeric prodrugs of PDL have been designed and synthesized to be used as sustained release forms of the drug (7,8). The synthesis involved the esterification of the drug with succinic acid, used as a leash to hold the drug to the polymer, and the subsequent esterification of the hemisuccinate to the backbone, either dextran or amylose to form a noncrosslinked polymeric prodrug. Esterification in the opposite order yielded cross-linked polymeric prodrugs. Thus:

Process 1:

PDL + Leash --> PDL hemisuccinate

PDL hemisuccinate + Polymer --> Noncrosslinked polymeric prodrug

Process 2:

Polymer + Leash --> Polymer hemisuccinate

Polymer hemisuccinate + PDL --> Crosslinked polymeric prodrug

Both the processes are essentially identical, differing in only the order of mixing. Route 1 is as follows:

PDL was dried by dissolving in dimethyl sulfoxide (DMSO), which had been previously dried over molecular sieves and subsequently the DMSO is vacuum distilled off. The resultant dry PDL was cooled and kept under dry nitrogen positive pressure. Succinic anhydride was dissolved in tetrahydrofuran (THF), which had been previously distilled from calcium hydride. The resultant solution was added to the dry PDL and allowed to react for two days. The THF was vacuum distilled off and the resultant pindolol leash was characterized by IR, NMR and elemental analysis (Galbraith Labs, Knoxville, TN). Under positive dry nitrogen pressure in a glove bag, the dried PDL leash was dissolved in DMSO and placed in a dried flask fitted with a rubber septum through which 1,1'dicarbonyldiimidazole (CDI) disolved in dry DMSO was added and allowed to react for 24 hours at 44°C. The polymer (either one of the dextrans or amylose), previously dried over P_2O_5 under full vacuum, was dissolved in dried DMSO and added to the PDL - CDI and allowed to react for three days at 55°C. Acetone was added for one day and centrifuged. The precipitate was subsequently washed twice with methanol and stored under vacuum. Charaterization, as above, was done in each case.

Methods - Release studies:

Isotonic Sorensen's Phosphate buffer (pH 7.4) was used throughout the study.

PDL concentration was routinely studied by U.V. spectrophotometry at the absorbance peak of 264 nm which appeared to be uneffected by pH over the range studied. PDL was verified to be intact by electron capture gas chromatography.

All glassware was sterilzed by autoclave and solutions were sterilized by filtration thru a 0.22 micron filter.

The release of PDL was studied using a modification of the dynamic dialysis system used by Meyer and Guttman (9) which separates the small free pindolol from the large undiffusible molecules. The system is a small diffusion chamber (5 mL) with a semipermiable membrane emersed in a large (95 mL) water jacketed (37^{o}C) "sink" chamber. Both chambers were stirred with teflon coated magnetic stir bars. The sink chamber had ports sealed with sterile filters. Sampling intervals were flexible and dependent on release characteristics. Five mL samples were replaced with fresh buffer and total amount released was determined by the methods of Wurster and Taylor (10) and Cobby (11). The membrane transport of PDL and PDL hemisuccinate was not rate-limiting in the system as described since approximately 90 % of these compounds passed through the membarane in 50 hours as compared to 500 hours for the fastest releasing prodrug.

RESULTS AND DISCUSSION

Table I lists the various prodrugs of pindolol were prepared using the methods desribed above. In general, the release data was

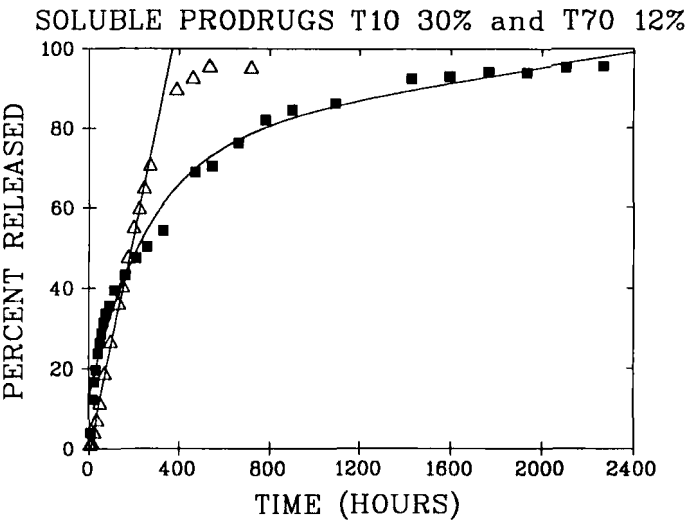

Fig. 2. Release Profiles for Soluble Prodrugs of PDL.
Key: Cpd. - open triangles, Cpd. f - solid squares.

With greater than 80% of the compounds appearing in the medium in 50 hours and these rate constants are orders of magnitude larger than ones observed in the polymeric prodrug, diffusion through the membrane was deemed not rate limiting.

The results of the release studies for the soluble prodrugs (noncross-linked, relatively low load), Dextran T 70 12% load (compound c - open triangles) and Dextran T 10 30% load (compound f - solid squares), are shown in Fig 2. Compound c apparently exhibited zero order release (A=B=E=0) through 80% released with a correlation coefficient of 0.999. The parameters for the equation are C (SD)= 0.273 (.004) %/hr and D (SD) = -1.25 (0.022) %. The negative D is indicative of a lag time. The release rate profile of compound f had a major component which followed the Higuchi model that described the profile to be linear with the

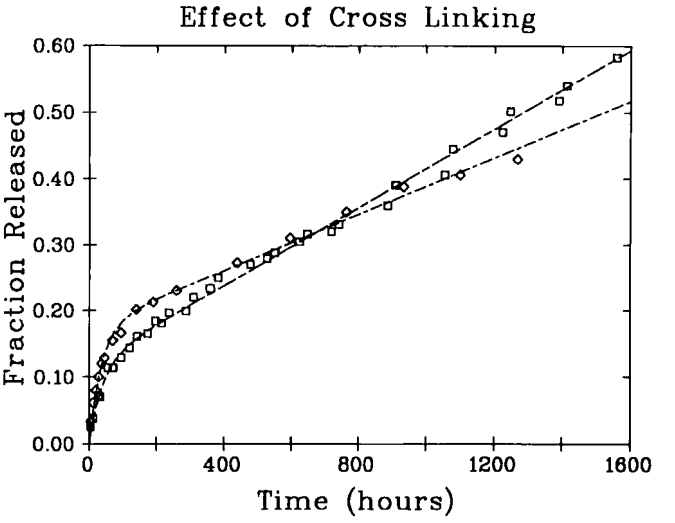

Fig. 3. Influence of crosslinking on the Release Profile of Prodrugs of PDL. Key: Cpd. b - open squares, Cpd. d+ - diamonds

square root of time (A=B=C=0). The parameters for this data set are D (SD) = 0.059 (0.014) and E (SD) = 0.277 (0.00091) with a correlation coeficient of 0.990.

The release rate profiles of the the insoluble prodrugs (cross-linked or relatively high load) appeared to have both a zero and an independant first order component (D=E=0) as shown in Figs. 3-5. In Fig. 3, compound b (Dextran T 70 - 24% load - squares) is compared to compound d+ (Dextran T 70 - 26% load crosslinked - diamonds). Both compounds were relatively insoluable in the buffer. The net effect of crosslinking appeared to be relatively insignificant as the fraction subject to first order release increased from A = 0.119 to 0.175 while the first order release rate constant did not change (B = 0.0248 = 0.026). However, the

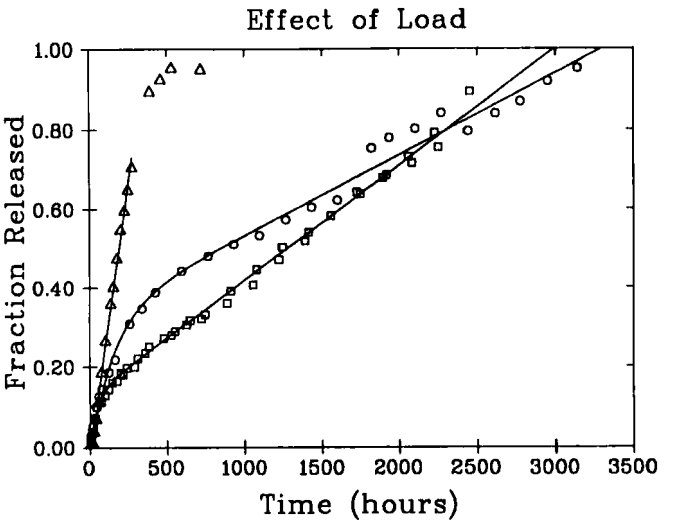

Fig. 4. Effect of PDL Load on the Release Profiles of Prodrugs of PDL. Key: Cpd c 12% PDL - triangles, Cpd. b 24% PDL - squares, Cpd. a 41% PDL - circles.

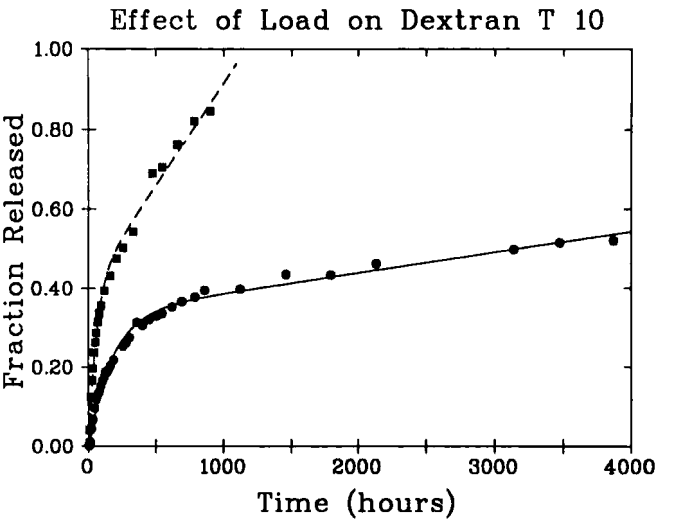

Fig. 5. Influence of Load on the Release Rate Profiles of Prodrugs of PDL with Dextran T10 Backbone. Key: Cpd. f 30% PDL - diamonds, Cpd. e 45% PDL - solid circles.

TABLE III

Computed Parameters for Various Compounds Tested

Cpd	Parameter			
	A (SD)	B (SD)	C (SD)	Corr.
a	0.326 (0.016)	0.006 (0.0032)	0.00021 (7.5E-6)	0.997
b	0.119 (0.0043)	0.0248 (0.0042)	0.000297 (3.3E-6)	0.998
c			0.00273 (3.8E-5)	0.999
d+	0.175 (0.006)	0.026 (0.0026)	0.0002 (8.6E-6)	0.998
e	0.332 (0.0072)	0.006 (0.0029)	0.000053 (3.5E-6)	0.998
e*	0.264 (0.024)	0.0048 (0.00057)	0.000142 (2.2E-5)	0.999
h	0.558 (0.01)	0.032 (0.0018)	0.00029 (1.4E-5)	0.997

release rate constant for the zero order fraction was reduced by a third (from C = 0.000297 to 0.0002) as shown in Table III.

Figure 4 illustrates the effect of PDL load (% w/w PDL) on the release profiles of prodrugs with a Dextran T 70 backbone. Compound c (12% PDL - triangles) was soluble while compound b (24% PDL - squares) and compound a (41% PDL - circles) were not. Compound c as seen earlier exhibited a zero order release while compounds b and a appeared to be best fit in a model combining both a zero and first order components. Comparing compounds a and b, it can be observed that the fraction of the compound which exhibits first order release is almost tripled (A= 0.119 to 0.326) while the first order release constant is reduced by a factor of 4 (B = 0.245 to 0.006) and the zero order release rate constant is reduced by a third (C = 0.000297 to 0.00021) as shown in Table III.

Overall, prodrugs with lower loads of PDL (a hydrophobic molecule) had visibly higher solubility. They exhibited a faster release rates than their high load counterparts.

The effect of load on the release rate profiles of prodrugs with a Dextran T 10 backbone is depicted in Fig. 5. Compound f (30% PDL - diamonds) was soluble in dissoolution medium while compound e (45% PDL - solid circles) was not. The release characteristics of compound f have been previously described. Compound e exhibited both a zero and a first order component as did the insoluble Dextran T 70 compounds shown in Table III.

When compounds a,e and h (aproximately the same load on different polymers) are compared, the first order componant to be virtually unchanged as observed in Fig. 6. However, the zero order rate constant is reduced by a factor of 4 when the insoluble dextran prodrugs were compared. Additionally, the amylose prodrug exhibited a marked increase in fraction released which followed a first order process (0.56 as compared to 0.33) as well as an increase by a factor of five in both the first order rate constant (0.032 as compared to 0.006) and the zero order rate constant (0.00029 as compared to 0.000053).

In Fig. 7, the addition of ethylenediamine to compound e to make compound e*, a soluable form of the same compound, did not apreaciably appear to modify the release characteristics of PDL over the time. Howerver, carrying the study out to 4000 hours confirmed the initial observation that although there was a reduction in both the fraction and release rate of the first order

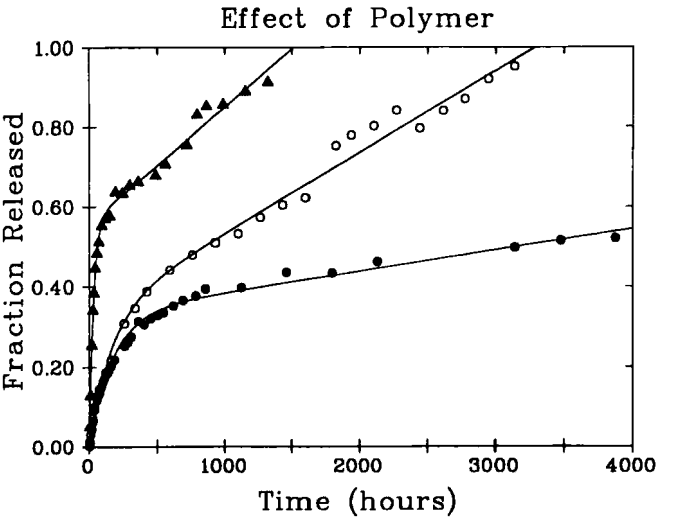

Fig. 6. Effect of Polymer on Fraction PDL Released as a Function of Time. Key: Cpds. a, e, h; solid triangles, open circles, solid circles, respectively.

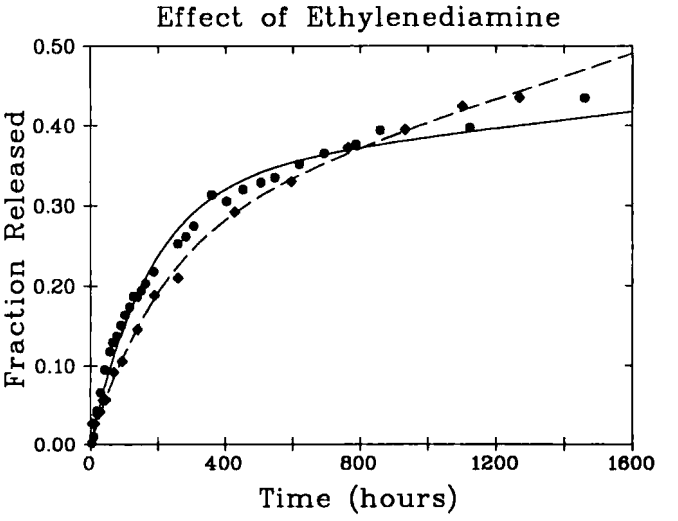

Fig. 7. Effect of Ethylenediamine on Fraction PDL Released as a Function of Time. Key: Cpds. e, e*; solid circles, solid squares, respectively.

component, the zero order component release rate was markedly increased (0.000142 as compared to 0.000053).

Prodrug made with amylose had a faster release profile than its dextran counterparts, possibly as a consequence of the primary hydroxyl groups available in the amylose but not in the dextran. Low molecular weight dextran prodrugs appeared to be more soluble at a given load and thus have a faster release rate than their high molecular weight counterparts. In addition, the importance of the first order component increased with the load while the zero order component in both fraction and rate constant decreased..

CONCLUSIONS

The following conclusions can be drawn:

For the soluble prodrugs (noncross-linked, relatively low load), the release rate profiles followed the Higuchi model that described the profile to be linear with the square root of time. The rate limiting step for these prodrugs appeared to be hydrolysis. The release rate profiles of the the insoluble prodrugs (cross-linked or relatively high load) appeared to have both a zero and an independant first order componant.

The prodrugs having lower loads of PDL (a hydrophobic molecule) had visibly higher solubility. They exhibited a faster release than their high load counterparts.

Prodrug made with amylose had a faster release profile than its dextran counterpart, possibly as a consequence of the primary hydroxyl groups available in the amylose but not in the dextran.

Low molecular weight dextran prodrugs appeared to be more soluble and thus have a faster release rate than their high molecular weight counterparts. In addition, first order rate constants were primary with the low molecular weight polymers and not as important with the high.

Cross-linking did not influence the release rate characteristics, except in solubility. So also with the formation of a soluble, high load, complex. Thus, even though the formation of an ethelamine diamine complex improved the solubility of the higher load, insoluble prodrugs, no increase in release rate was seen.

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