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APPLICATION OF POLY(OXYETHYLENE) HOMOPOLYMERS IN SUSTAINED RELEASE SOLID FORMULATIONS

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ABSTRACT

Water soluble poly(oxyethylene) homopolymers, with molecular mass ranging from four hundred thousand to four million, were used as carriers to generate, by direct compression techniques, sustained release matrix tablets of both water-soluble and insoluble bioactive agents. Dissolution studies showed that the release kinetics of the tablets depends upon the solubility and molecular mass of polymer, solubility of drug, and the ratio of the drug to polymer in the tablets. Following drug release, the tablet components dissolved leaving behind no residue, or "ghost", as is commonly observed with wax-based systems.

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INTRODUCTION

Owing to the worldwide decline in the number of pharmacologically active new chemical entities reaching the marketplace, interest in the development of new drug delivery systems, particularly in the area of controlled release, has been on the forefront of pharmaceutical research (1). This is because a well-designed dosage form may not only improve the efficacy and safety of the active ingredient, but also can help to extend the patent life and hence the profitability derived from the marketed products.

Over the years, different types of controlled release dosage forms, including matrix systems have been developed (2, 3). Fabrication of matrix type oral dosage forms generally involves direct compression of tablet excipients, or preparation of aqueous, solvent or wax-based granulations which are subsequently compressed to provide tablets of different sizes and shapes. These systems are capable of sustaining the release of drugs over an extended period of time and are not susceptible to dose dumping. Most of these, however, leave behind, following drug release, tablet residues or "ghosts" which can cast doubt in the patient's mind regarding the performance of the dosage form. Ideally, therefore, the tablets should contain a carrier or binder that dissolves in body fluids once it delivers the active agent as intended. In these systems, the carrier on the surface of the tablet initially hydrates during dissolution, to generate an outer viscous gel layer (4). This phase is then followed sequentially by tablet bulk hydration, swelling and erosion. The overall dissolution rate and, ultimately, drug availability are controlled by the rate of swelling, diffusion through the gel layer (5,6) and/or erosion (7, 8, 9).

Recent work with poly(ethylene oxide) homopolymers (10, 11),(supplied by Union Carbide under the trade name of "Polyox" (12)), indicated that tablets containing these polymers as carriers do not only have sustained release properties, but they also do not leave residues following drug release. These polymers are, therefore, suitable for the development of controlled release tablets. The homopolymers are prepared by anionic polymerization of ethylene oxide and have an average molecular mass ranging from one hundred thousand to eight million. As polyethers, the polymeric chains are capable of forming strong hydrogen bonds with water, a property that is responsible for their high water uptake and eventual dissolution. Because these polymers hydrate, swell and eventually erode during the dissolution course, the mechanism of release is a complex process involving drug diffusion, polymer swelling and/or erosion. The

dominance of one mechanism over the others depends upon tablet excipients and solubility of the active ingredient.

The objective of this study is, therefore, to describe and characterize the release kinetics in aqueous media of tablets containing poly(oxyethylene) as the rate controlling carrier and model drugs that are either highly water-soluble or poorly water soluble.

THEORETICAL CONSIDERATIONS

Four main mechanisms of release are possible from monolithic tablets containing an uniformly distributed load of drug. The first and most often encountered mechanism is drug diffusion through the outside layers of the tablet, also known as "Ficknian" release, or "Case I" mechanism (4). The release rate of monolithic tablets containing a water insoluble carrier and a water soluble drug decreases as a function of time, because the diffusional path length for drug release increases with time, as the solvent front moves toward the center of the tablet. The release kinetics follows the square root of time up to 60 % drug depletion (13, 14), as described in equation (1):

$$(1) \quad M_t/M_\infty = (A[D\ C_s\ (2C_d - C_s)])^{1/2}\ t^{1/2}$$

where A is the tablet surface area, D is the drug diffusivity, C_s is the drug solubility in the dissolution medium and C_d is the drug loading concentration in the matrix. This relation holds true until drug depletion or tablet erosion cause, respectively a negative or positive deviation from the square-root of time dependance (15).

The second case, where drug release is swelling controlled, is known as "zero order" release or "Case II" mechanism (4). In this case, the following equation can successfully describe the fraction of drug released:

$$(2) \quad M_t/M_\infty = 1 - [1 - k_0\ t\ /\ C_0\ r]^n$$

where r is the radius of sphere or cylinder or half thickness of a slab, k_0 is the erosion constant, C_0 the uniform initial drug concentration, and n an exponent depending on the geometry of the release device, and which is 3, 2, or 1 in the case of a sphere, cylinder or infinite slab, respectively (11).

In the case of an infinite slab where the surface does not change with time, n =1 and (2) simplifies as follows:

(3) $M_t/M_\infty = k_0 t / C_0 r$

In this case, the release rate is independent of time and follows the "zero order" kinetics. In practice, this ideal situation has never been observed. A third mechanism of release involves devices made from water soluble or swellable polymers, where drug diffusion and tablet swelling occur concurrently. This mechanism has been described as "non- Ficknian" transport and the release is controlled both by swelling and diffusion (8).

The release rate may be described by a combined $t^{1/2}$ / zero order kinetics, as shown by equation (4):

(4) $M_t/M_\infty = k_1 t^{1/2} + k_2 t$

where k_1 and k_2 are two phenomenological constant describing respectively the square root of time dependent release and the time independent release. The use of two independent constants k_1 and k_2 allows the quantitative evaluation of the contribution of Ficknian or non-Ficknian release to the overall rate of release.

A fourth mechanism of drug release from soluble matrices is erosion. During dissolution, the outer gel layer fully hydrates, swells and erodes. The sequential steps of wetting, hydration, swelling, and erosion continue throughout the dissolution course until the water-soluble components of the tablets dissolve completely.

Mathematical expressions describing the release rates of solely erodible systems are usually quite involved and may be written only if the solubilization kinetics of the polymer are known (7). This mechanism of release is described as "Super Case II" (16) and often follows a super-linear kinetic of release, as described by equation (5):

(5) $M_t/M_\infty = k t^m$

where m may be equal or greater than 1 and depends on the relative rates of tablet erosion and tablet swelling.

In some cases, the release kinetics may approach zero order if the rate of solvent front advancing toward the tablet core and the rate of surface

erosion are comparable and occur at the same time (17, 18). Under such conditions, the drug diffusive path length will approximately remain constant and, assuming no surface area changes, provide zero order release kinetics. Since tablets containing water-soluble polymers also swell and erode, it is possible to assume that the total tablet area will remain constant for most of the dissolution course.

EXPERIMENTAL

Materials

Polyox polymers (Union Carbide, Danbury, CT, M. M. (Average) = 4,000,000, 2,000,000 and 400,000), diphenhydramine hydrochloride (Parke Davis, Holland, MI), CI-936 (diphenylethyl(adenosine), Parke-Davis, Ann Arbor, MI), and magnesium stearate (Witco) were used as received.

Polymer Characterization

Poly(oxyethylene) polymers were characterized by viscosity measurements using a Brookfield viscometer according to the procedure described in the manufacturers technical bulletin (11). Values obtained for each grade were within specifications.

Tablet Compression

The carrier and the active ingredient were first blended in different ratios. After the addition of a lubricant, the final blend was compressed into tablets using a single punch Stokes E tablet machine and standard concave (3/8") tooling.

Dissolution

Dissolution studies were conducted using USP Apparatus II (paddles), at a rotation speed of 75 r.p.m. The dissolution medium for diphenhydramine hydrochloride tablets was water while 0.1 N hydrochloric acid was used for CI-936, an experimental drug with poor water solubility. Samples were withdrawn automatically at preset time intervals and analyzed spectrophotometrically.

RESULTS AND DISCUSSION

Consistent with the properties of water-soluble, high molecular mass polymers, poly(oxyethylene) polymers dissolve slowly to generate highly

viscous solutions (12). It is these characteristics that make them suitable for the development of controlled-release solid dosage forms. During dissolution, tablets containing these polymers produce a gel layer on the surface and swell upon contact with the dissolution media. The thickness of the gel layer controls drug release. The thickness of the gel changes depending on the rate of solvent front progress toward the inside of the tablet, the degree of swelling, and on the erosion rate of the tablet outer layers. The rate of the solvent front advancement is controlled by drug properties, as well as the relative amounts of the drug and polymer in the tablet formulation. The rate of erosion of the outer layers is also controlled by factors such as solubility of drug and polymer, the drug/polymer ratio, and polymer average molecular mass. Therefore, during dissolution, the gel layer thickness may increase, decrease, or remain constant as a function of time, thereby modifying the release rate accordingly.

Water Soluble Drug

The release of diphenhydramine hydrochloride, a highly water soluble drug (solubility >1 g/ml), from tablets containing poly(oxyethylene) homopolymers as carriers appears to be controlled, after a brief induction time, by a contribution of drug diffusion, through the outer hydrated layers of the poly(oxyethylene) matrix, and surface erosion. Following the induction time, the release kinetics approximate the square root of time with a positive deviation from linearity toward the end of the dissolution course (Figs. 1-3). This deviation becomes more pronounced as the average molecular mass of the polymer decreases. A probable cause of the positive deviation may be the disintegration and subsequent dissolution of the release modulating gel layer. While poly(oxyethylene) homopolymer are water soluble, they erode very slowly during the early part of the dissolution course. This is probably because diphenhydramine hydrochloride locally produces a high ionic concentration in the hydrated layer of the tablet and delays polymer dissolution until most of the drug is depleted. Examination of the tablets made from the two higher average molecular mass polymers shows that, during dissolution, they swell but do not appear to erode substantially until most of the drug is released. The overall release rates of the tablets decreased with an increase in polymer fraction irrespective of the polymer molecular masses.

Furthermore, tablets containing a very high drug content (9:1) relative to the polymers of the three different average molecular masses release the drug at fast rates and show marked positive deviations from linearity. The

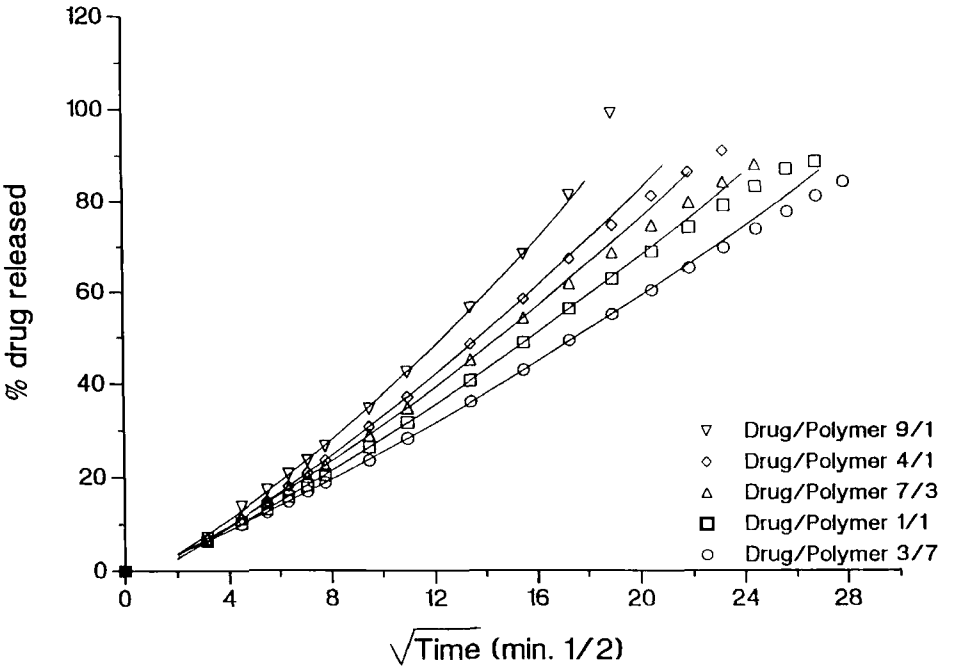

FIGURE 1.
Release Profiles of Diphenhydramine HCl / Poly(oxyethylene) 4 Million Average Molecular Mass Tablets in Water.
USP II (paddles), 75 rpm, 37° C.
Symbols: Experimental Points. Line: Model.

limited amount of polymer in the formulation cannot generate a firm gel, and promote erosion for an extended period of time.

The overall release rate of diphenhydramine hydrochloride was also found to depend upon the molecular mass of the polymer in the tablet formulation. As expected, as the average molecular mass of the polymer is increased, the release rates decreased proportionately.

Since tablets containig the highly water soluble diphenhydramine hydrochloride, hydrate, swell and erode, the release rates are controlled simultaneously by diffusion and erosion. As a result, the release kinetics of diphenhydramine hydrochloride from poly(oxyethylene) based tablets follows a mixed zero/one-half order as described by equation (4) where the zero order release mechanism contributes substantially to the total release,

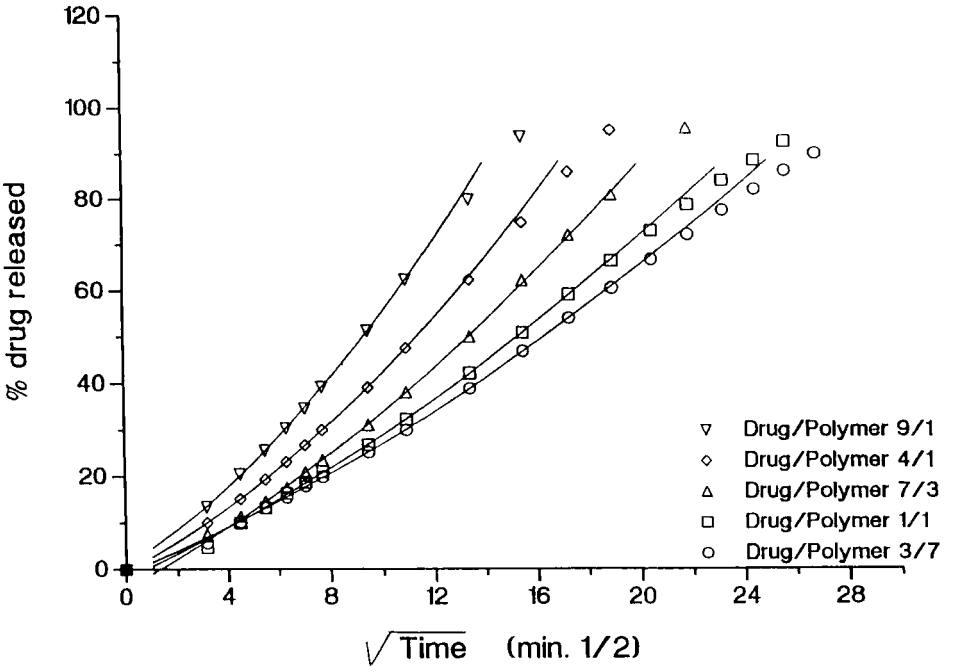

FIGURE 2.
Release Profiles of Diphenhydramine HCl / Poly(oxyethylene) 2 Million Average Molecular Mass Tablets in Water.
USP II (paddles), 75 rpm, 37° C.
Symbols: Experimental Points. Line: Model.

especially at high drug/polymer ratios and using poly(oxyethylene) of low molecular mass, which dissolves faster than the other two grades.

The release constants k_1 (min.$^{-1/2}$, diffusion control) and k_2 (min.$^{-1}$,erosion control) are given in Table 1-3. The values were calculated by fitting the experimental data, between of 10 and 70 % of drug release, for tablets based on poly(oxyethylene) 2 ans 4 million average molecular mass, and between 5 and 70 % for poly(oxyethylene) 400,000, to a non-linear regression based on equation (4).

The results obtained show that diffusion controlled release rate constant k_1 decreases with decrease in drug/polymer ratio to a limiting value which it is independent of the polymer molecular mass (Fig. 4).

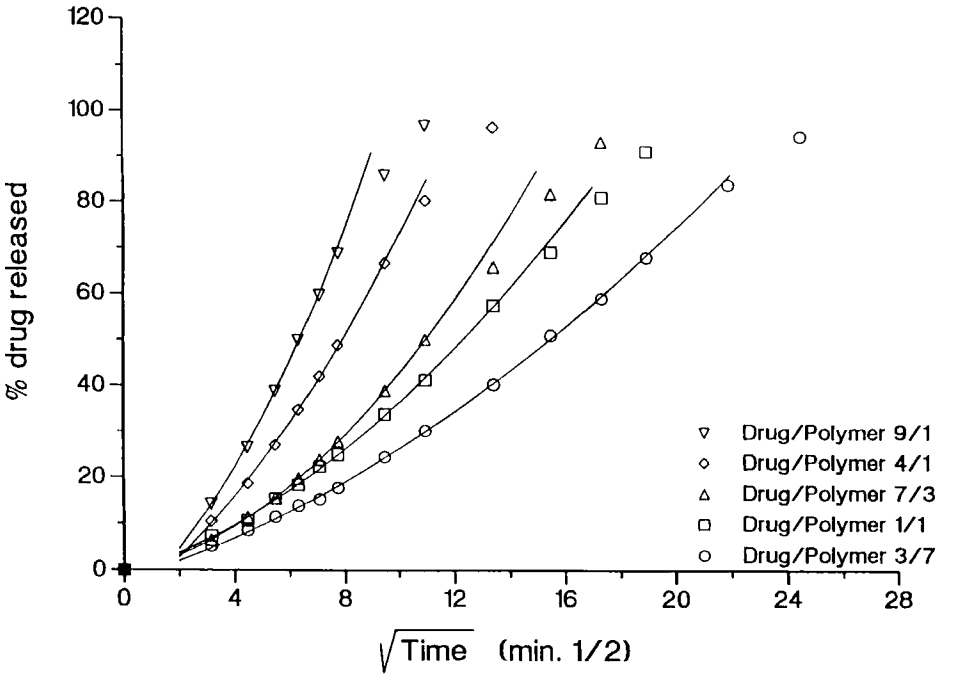

FIGURE 3.
Release Profiles of Diphenhydramine HCl / Poly(oxyethylene) 400,000 Average Molecular Mass Tablets in Water.
USP II (paddles), 75 rpm, 37° C.
Symbols: Experimental Points. Line: Model.

TABLE 1.
Dissolution Rate Constants for Diphenhydramine Hydrochloride/ Poly(oxyethylene) Four Million Tablets.

Drug/Polymer	k_1	k_2	Correlation Coefficient
9/1	.03040	.001002	.9997
4/1	.02915	.000709	.9999
7/3	.02847	.000510	.9999
1/1	.02544	.000379	.9999
3/7	.02462	.000275	.9984

TABLE 2.
Dissolution Rate Constants for Diphenhydramine Hydrochloride/ Poly(oxyethylene) Two Million Tablets.

Drug/Polymer	k_1	k_2	Correlation Coefficient
9/1	.03332	.002063	.9998
4/1	.02970	.001264	.9998
7/3	.02927	.000831	.9999
1/1	.026783	.000508	.9998
3/7	.02511	.000415	.9997

TABLE 3.
Dissolution Rate Constants for Diphenhydramine Hydrochloride/ Poly(oxyethylene) 400,000 Tablets.

Drug/Polymer	k_1	k_2	Correlation Coefficient
9/1	.05765	.00574	.9994
4/1	.04258	.00374	.9997
7/3	.02912	.00196	.9994
1/1	.02744	.00129	.9998
3/7	.02461	.00068	.9998

Polymers with high average molecular masses have a high number of chain entanglement or crystallites per unit volume which reduce the permeation rate of the dissolution medium through the tablets and the subsequent diffusion of the drug molecules through the gel layer. Consequently, the average path length that drug molecules traverse before they are released becomes both longer and more tortuous as polymer average molecular mass increases.

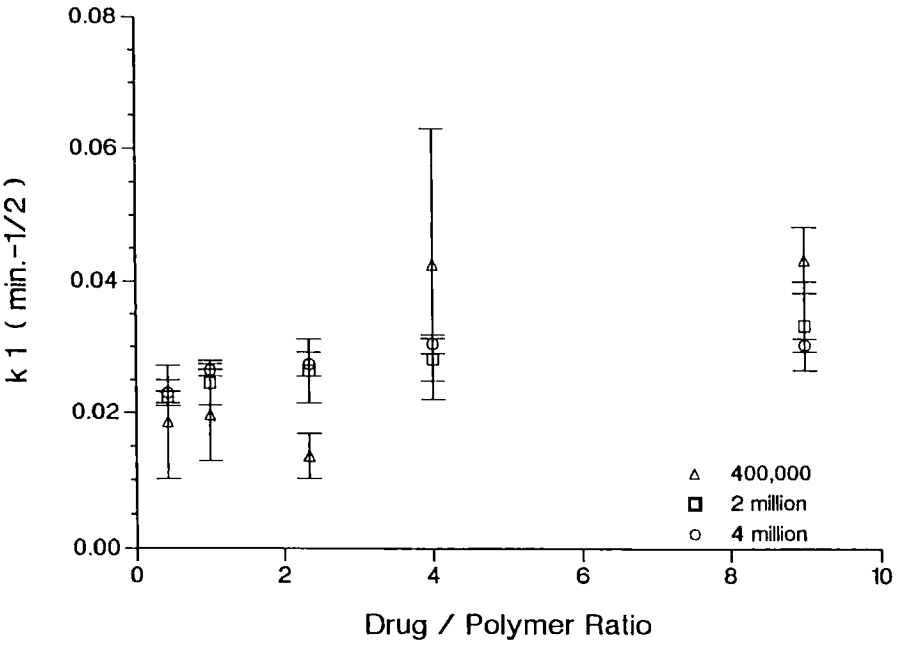

FIGURE 4.
Release Constant k_1 as a Function of Drug to Polymer Ratio and Polymer Average Molecular Mass from Tablets Containing Diphenhydramine HCl and Poly(oxyethylene).
95 % Confidence Interval.

At low drug to polymer ratios, the polymer fraction is so high that it will not allow the formations of preferential channels in the matrix trough which the drug can be relesed. Furthermore, the polymeric chains are completely entangled, regardless of their length, and drug can only be released by diffusion through them, thus explaining the similarities in k_1 values.

On the other hand, at higher drug/polymer ratios, preferential drug release channels can be formed and also the level chains entanglement becomes dependent on average chain lenght, so that diffusional release rates become dependent on polymer molecular mass.

Erosion controlled release rate constant k_2 (Fig. 5) increases with increase in drug/polymer ratio; it also decreases as polymer average molecular mass

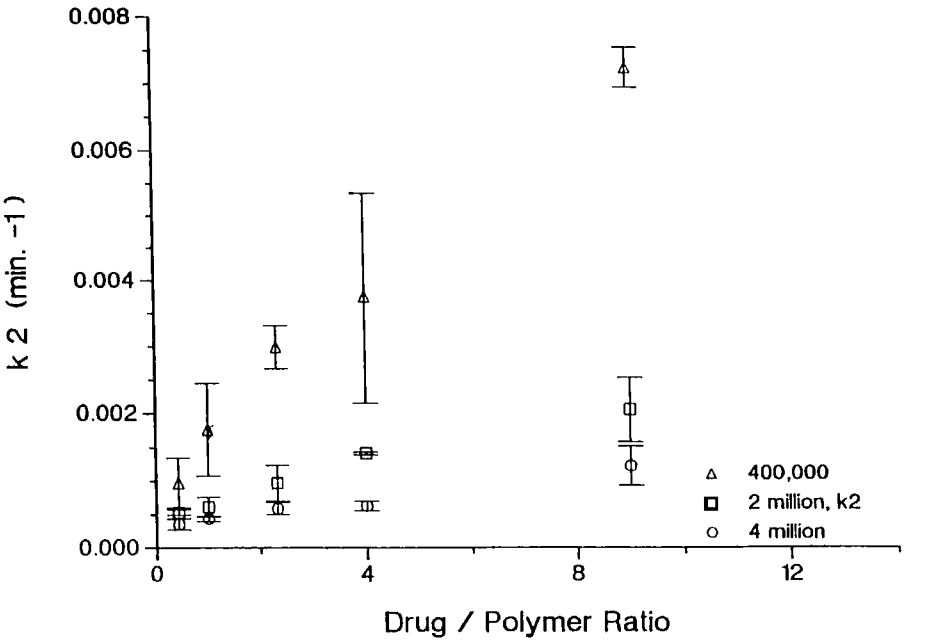

FIGURE 5.
Release Constant k_2 as a Function of Drug to Polymer Ratio and Polymer Average Molecular Mass from Tablets Containing Diphenhydramine HCl and Poly(oxyethylene).
95 % Confidence Interval.

increases, since polymers of high molecular mass dissolve at a slower rate and are more sensitive to "salting out" effects.

Comparison of k_1 and k_2, after dimensional normalization done by squaring k_1,(Fig. 6), shows their relative contribution to the overall release rate from each polymeric system. At all drug/polymer ratios, diffusion release constant k_1 is slightly higher, than k_2 for poly(oxyethylene) 4 million based tablets, while the opposite happens for poly(oxyethylene) 2 million; on the other hand, tablets made from poly(oxyethylene) 400,000 show a k_2 that is substantially higher than k_1, an indication that erosion is the dominant mechanism in the overall release rate.

Poorly Water Soluble Drug.

CI-936, chemically known as diphenylethyl(adenosine), is an experimental drug that has a low water solubility (about 2.5 mg/ml). Tablets containing

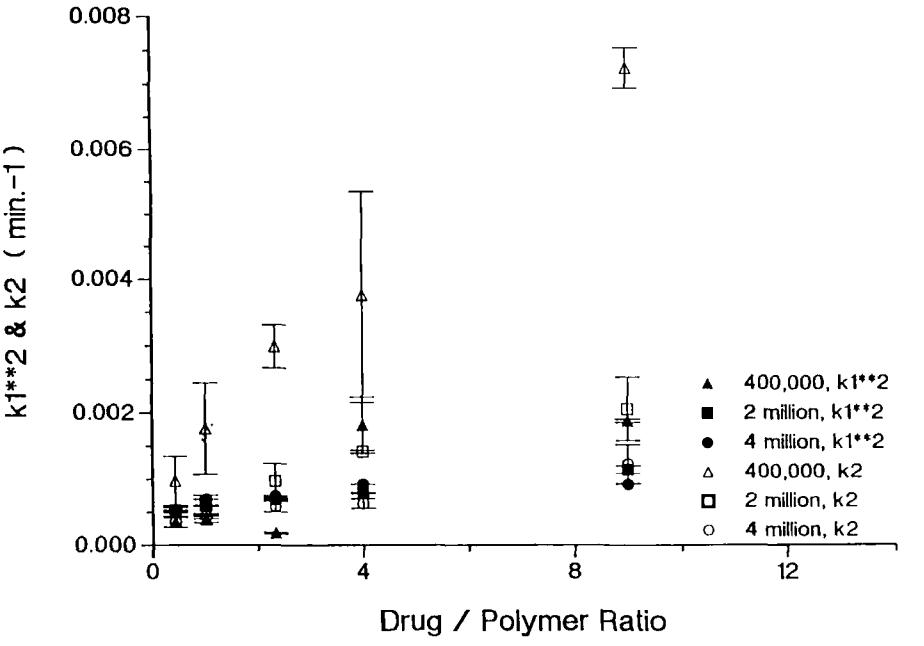

FIGURE 6.
Release Constants k_1^2 and k_2 as a Function of Drug to Polymer Ratio and Polymer Average Molecular Mass from Tablets Containing Diphenhydramine HCl and Poly(oxyethylene).

the drug showed a dissolution behavior that is quite different from that described above. Because of the low solubility of the drug in the medium, dissolution of the drug in the solvent front is limited. Furthermore, the drug does not ionize and consequently does not affect polymer dissolution appreciably. As a result, surface erosion is the dominant release mechanism, although initially the release rate of CI-936 appears to be controlled to a large extent by diffusion of the drug through the gel layer which forms on the surface of the tablet following hydration. The release rate of CI-936 decreases with a decrease in the drug/polymer ratio down to a minimum (5/5 for poly(oxyethylene) 4 and 2 million or 7/3 for the 400,000 grade) then increases again (Fig. 7-9). The release rate appears to be controlled by erosion at both high and low drug to polymer ratio and by diffusion at intermediate ratios.

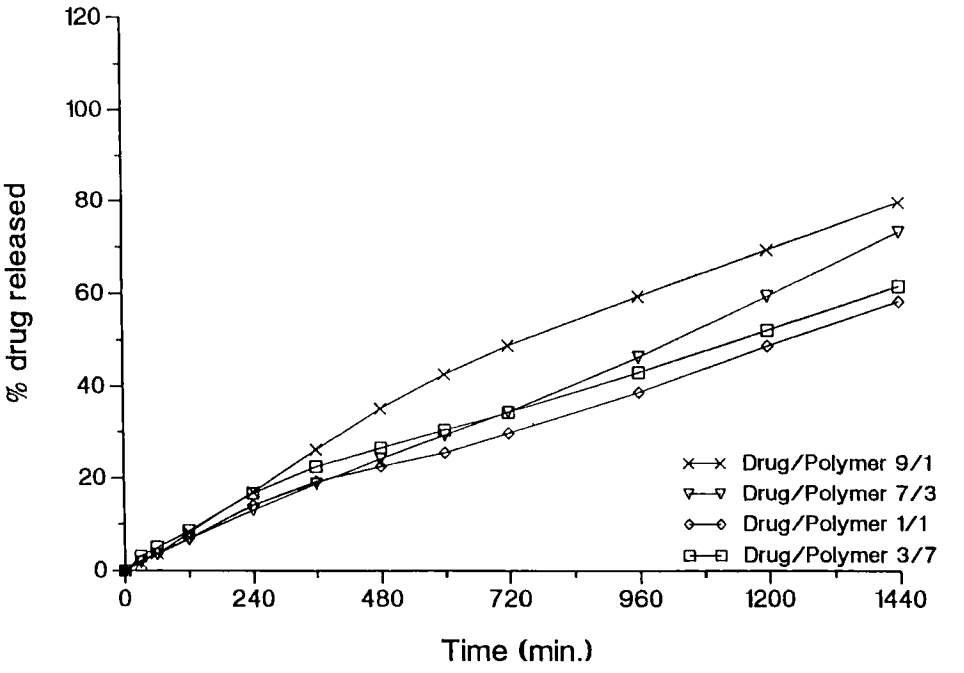

FIGURE 7.
Release Profiles of CI 936 / Poly(oxyethylene) 4 Million Average Molecular Mass Tablets in pH 1.2 HCl.
USP II (paddles), 75 rpm, 37° C.

At high drug/polymer ratio the release rate is fast not only because the quantity of polymer that is used tp bind the tablet components in the matrix is low, but also the gel layer that is formed on the surface is not strong enough to slow drug diffusion toward the outside of the tablet. Visual observation of the tablets during dissolution shows that they erode without significant swelling; this leads to a decrease in surface area which in turn is responsible for the reduction in the dissolution rate.

Tablets with an intermediate drug/polymer ratio contain enough polymer to form a gel layer capable of slowing drug diffusion and release as well as a sufficient quantity of poorly water soluble drug to reduce solvent penetration and delay polymer dissolution. A combination of these two factors, therefore, slows drug release, especially during the early part of dissolution. Release profiles of intermediate formulations approximate the

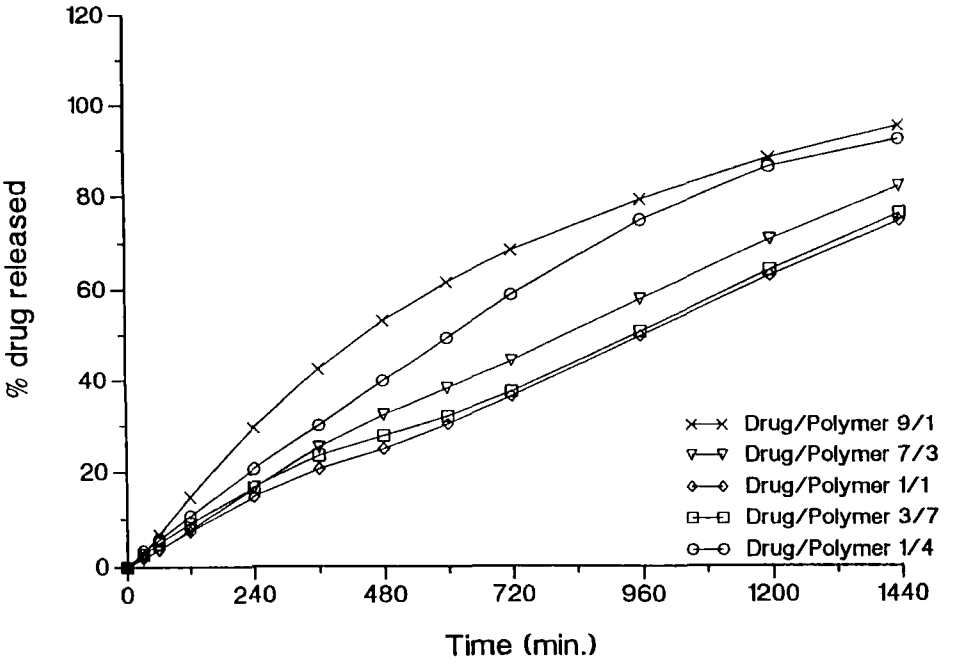

FIGURE 8.
Release Profiles of CI 936 / Poly(oxyethylene) 2 Million Average Molecular Mass Tablets in pH 1.2 HCl.
USP II (paddles), 75 rpm, 37° C.

square root of time during the early part of dissolution and then show a discontinuity, suggesting that release control shifts from diffusion to erosion when the polymer becomes sufficiently hydrated.

At low drug to polymer ratio, the release rates tend to be faster because the solvent penetrates the tablet core unimpeded, depending only on the hydration rate of the polymer. Hydration is followed immediately by surface erosion.

In an attempt to better understand the physical changes occurring during dissolution, tablets with varying drug/polymer ratio were removed from the dissolution medium during the dissolution course, dried, and visually evaluated. It was found out that tablets with intermediate drug/polymer ratio were, at a given time, larger than those with high or low drug to polymer ratio.

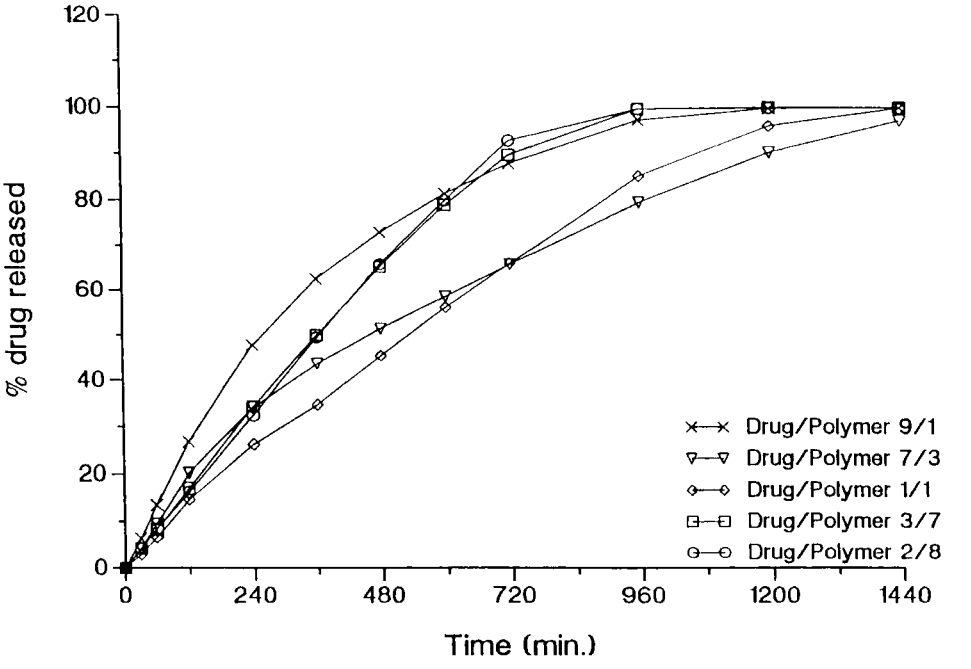

FIGURE 9.
Release Profiles of CI 936 / Poly(oxyethylene) 400,000 Average Molecular Mass Tablets in pH 1.2 HCl.
USP II (paddles), 75 rpm, 37° C.

Tablets with high drug/polymer ratio exhibited overall higher release rates. The dissolution rates were high enough initially but decrease as dissolution proceeds. Tablets with low drug to polymer ratio show a linearly time dependent release profiles which indicate that drug release becomes erosion controlled immediately. Furthermore, in this case, the tablets swell considerably, while eroding, thus keeping the total surface area from changing significantly.

CONCLUSION

Poly(oxyethylene) polymers are hydrophilic materials suitable for the development of monolithic drug delivery formulations. These polymers can be easily loaded up with drugs of different solubility characteristics and tailored to give the desired release profiles.

The rerlease rates of the tablets do not only depend upon the common formulation variables such as drug/polymer ratio, polymer average molecular mass, and the solubility of the drug, but also on the ionization state of the drug molecules.

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