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RESEARCH ARTICLE

Effects of Drug Solubility, Drug Loading, and Polymer Molecular Weight on Drug Release from Polyox® Tablets

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ABSTRACT

This study investigated the effects of polymer molecular weight, drug solubility, addition of a water-soluble excipient, and drug loading on zero-order release kinetics and elucidated the release mechanism of a drug from directly compressed tablets. Directly compressed tablets consisting of polyethylene oxides (PEO) (MW = 0.9, 2.0 and 4.0 × 10^6) and drugs (solubility ranging from 290 to 25,000 mg/l) were formulated with or without a water-soluble excipient (lactose). For PEO tablets (MW = 0.9 × 10^6), drug release is primarily swelling/erosion controlled for drugs for which solubility is below 1%, resulting in zero-order release kinetics. For PEO tablets (MW = 4.0 × 10^6), drug release is controlled at a zero-order rate by the dissolution rate of the drug at high loading (39%). At low loading (20%), drug diffusion through the swollen gel layer becomes the governing release mechanism. For a highly water-soluble drug (e.g., diclofenac Na), drug diffusion is the controlling mechanism regardless of the molecular weight of the PEOs. Zero-order release kinetics can be achieved with PEO tablets (MW = 0.9 × 10^6) for drugs for which solubility is below 1%. PEO tablets (MW = 2.0 × 10^6) provided zero-order release for poorly water-soluble drugs (below 0.2%) at 39% drug loading. It is possible to attain zero-order release kinetics with PEO tablets (MW = 4.0 × 10^6) using a drug which has a solubility of less than 0.1%.

INTRODUCTION

Extended release of biologically active drugs is highly desirable for drugs that have characteristically short half-lives. There are a number of approaches for preparation of extended-release dosage forms (1,2). Although monolithic systems, composed of hydrophobic polymers and excipients, are commonly used for extended-release dosage forms because they are not costly or difficult to produce, they provide a square-root of time (sqrt) kinetics. There are several ways to improve the release kinetics of these extended-release dosage forms ranging from non-Fickian to zero-order release. Incorporation of hydrophilic polymers into monolithic matrices modifies sqrt kinetics to anomalous kinetics attributable to the swelling and erosion of the hydrophilic polymers. In particular, monolithic matrix systems governed by the swelling and erosion processes of the polymers provide a zero-order rate resulting from the synchronization of the swelling and erosion which causes boundaries to move (3,4). However, it is rare to find hydrophilic and pharmaceutically applicable polymers that furnish the synchronization of the two processes (swelling and erosion).

Recently, Apicella et al. (5) and Kim (6) have demonstrated that a polyethylene oxide (PEO) matrix can generate balanced rates of swelling and erosion. In PEOs of 0.6, 0.9, and 2.0×10^6, synchronization of the swelling and erosion processes was observed. In contrast, PEOs possessing a molecular weight of 4.0×10^6 did not furnish the balanced processes of swelling and erosion; rather it was observed that the swollen gel layer kept increasing until the entire polymer was hydrated, followed by a decrease in size because of the erosion of the swollen gel (5,6). Because of the synchronization of the swelling and erosion of the polymers having a molecular weight of less than 2.0×10^6, zero-order release profiles have been observed from theophylline and acetophylline, whereas anomalous release kinetics were reported for the polymers of MW = 4.0×10^6 (5,6). Apicella et al. (5) and Kim (6) used laminated film tablets and smaller compressed tablets, respectively. Furthermore, Kim (7) developed donut-shaped tablets to achieve zero-order release kinetics from the polymers of MW = 4.0×10^6.

In this study, we investigated the effect of polymer molecular weight, drug solubility, addition of a water-soluble excipient, and drug loading on the zero-order release kinetics of PEO tablets, and elucidated the release mechanisms of drugs from directly compressed tablets.

MATERIALS AND METHODS

Materials

Polyox®-WSR NF (PEO) of average molecular weights 0.9, 2.0, and 4.0×10^6 was supplied by Union Carbide (Danbury, CT). Theophylline anhydrous USP, salicylic acid USP, sulfapyridine, and lactose USP were purchased from Amend Co. (Irving, NJ), and magnesium stearate USP was obtained from Mallinckrodt Chemical (Jersey City, NJ). Diclofenac Na and sulfathiazole were purchased from Sigma Chemical Co. (St. Louis, MO). Ethanol (200% proof) was obtained from Pharmaco Co. (Bayonne, NJ). All materials were used as received.

Preparation of Tablets

The ingredients (PEO, drug, and magnesium stearate) were blended and then compressed using a Carver press machine (model C, Wabash, IN). All tablets contained 1 wt% magnesium stearate as a lubricant. Tablet punches with flat surfaces were used to prepare all of the tablets with an 11.1 mm diameter and a weight of 550 mg, except for the sulfathiazole tablets (400 mg and 9.5 mm diameter), in order to finish the experiments within a reasonable time frame. All tablets were charged with formulation, and a compression of 4000 lb was exerted by hand.

Testing of Tablets

In vitro release of drugs from the PEO tablets was carried out in distilled/deionized water by using the USP basket procedure at a stirring rate of 100 rpm at 37°C. Theophylline, diclofenac Na, salicylic acid, sulfapyridine, and sulfathiazole were chosen as model drugs. The release of diclofenac Na, theophylline, salicylic acid, sulfathiazole, and sulfapyridine was assayed by an HP8252A diode-array spectrophotometer (Hewlett Packard) at 250, 244, 298, 268, 288, and 296 nm, respectively. Because of the low solubility of the drugs (sulfathiazole and sulfapyridine), the dissolution medium was replaced a few times to maintain sink conditions during the in vitro dissolution test.

The release kinetic data (up to 60% release) were treated by the following phenomenological equation (8):

$$\ln \frac{M_t}{M_\infty} = \ln k + n \ln t \qquad (1)$$

where M_t, M_∞, k, and n are the amounts of drug released at time t, the total amount of drug in the tablet, the constant, and the exponent for the release kinetics, respectively. Zero-order and anomalous release kinetics are represented by $0.89 < n < 1.0$ and $0.45 < n < 0.89$, respectively, for a swellable cylindrical matrix (8). A linear regression analysis was performed and a correlation coefficient (r^2) ≥ 0.99 was obtained. Duplicate or triplicate experiments were carried out for each formulation, but only a representative experiment is shown in this study for the clarity of figures because data were found to be very close (or superimposed) to each other.

RESULTS AND DISCUSSION

Preliminary reports show that high molecular weight PEOs are good candidates for oral extended-release dosage forms (6). PEOs of MW = 0.9 and 2.0×10^6 provide a constant release of drugs from compressed tablets. However, those tablets were of smaller size (≈ 180 mg), resulting in difficulties in identifying the fundamental release mechanisms of drugs from the PEO tablet matrices. In this study, PEO tablets of 550 mg and dimensions of 3.5 × 11.1 mm were used. The release profiles of drugs from PEO tablets of MW = 4.0×10^6 (PEO4) are shown in Fig. 1. Apicella et al. (5) and Kim (6) reported that the synchronization of the swelling and erosion of the polymer (PEO4) was not observed under a stereomicroscope. Drug release from PEO4 tablets is controlled by the swelling of the polymer at the early stage of release followed by the erosion of the polymer at the later stage of release. Drug release takes place through the swollen gel layer for almost half of the release time so that the release kinetics are anomalous because of the high swelling of PEO4. It was shown (9,10) that the high swelling of the polymer furnishes an increase in drug diffusivity, resulting in the deviation from the Fickian release kinetics toward zero-order kinetics. While PEO4 is fully swollen, drug release is carried out by diffusion through the gel and erosion of the swollen gel. The surface area of the swollen gel that accommodates drug release diminishes with time. Figure 1 illustrates the effect of drug solubility on the drug release from PEO4 tablets (39% loading). As drug solubility decreases, the duration of drug release increases. The release of diclofenac Na (2.5% solubility in water) is characterized as non-Fickian kinetics where $n = 0.72$ up to 70% release followed by a long tailing at the later stage of release. In this case, drug diffusion through the swollen gel matrix

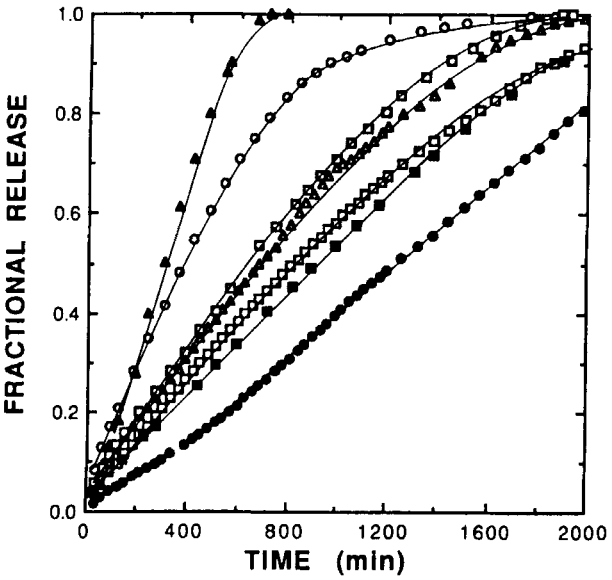

Figure 1. Effect of drug solubility on the release of drugs from PEO4 tablets (39% loading): (○) diclofenac Na; (□, △) theophylline; (□, ■) salicylic acid; (●) sulfathiazole; (▲) sulfapyridine.

is the governing step for the drug release, and the swelling of the polymer causes the release kinetics to shift to anomalous transport. As drug solubility decreases below 1% (theophylline and salicylic acid), drug release slows because of the longer dissolution time of the drug in the matrix. Because of this slow dissolution of the drug, the contribution of drug diffusion on the drug release from the PEO4 tablets with 39% loading becomes smaller, and the swelling of the polymer and the dissolution of the drug are comparable to control the release kinetics of theophylline and salycilic acid. Drug release takes place by the dissolution of the drug followed by drug diffusion. This results in further linear non-Fickian kinetics in which $n = 0.79$ and $n = 0.81$ for theophylline and salicylic acid, respectively. Linear release kinetics of theophylline can also be obtained from highly swellable/nonerodible tablets (11).

As drug solubility decreases further below 1000 mg/l, the dissolution of the drug becomes a dominant process in controlling the drug release from PEO4 tablets. This accounts for a constant release with $n = 0.96$ and $n = 1.10$ for sulfathiazole and sulfapyridine up to 85–90% release, respectively. Upon contact with water, the PEO4 polymer goes through a transition, and swollen polymer is formed. The swelling front penetrates inwardly to the core of the matrix, leaving the suspended drug behind.

It takes about 10–12 hr to complete the hydration process (swelling) of the entire PEO tablet. The solid/dissolved drug is suspended in the swollen gel and is released through the erosion of the hydrated polymer during the hydration process. This erosion is then followed by the dissolution of the drug in large volumes of the dissolution medium along with the diffusion of the dissolved drug, which is a smaller portion. Because of the low solubility of sulfathiazole (590 mg/l, the drug release shows a slightly sigmoidal profile, and for much lower solubility drugs a time lag was observed (not shown in Fig. 1) (12). Smaller tablets (9.5 mm diameter) were used for the release of sulfathiazole in order to finish the release test within a reasonable time frame. However, it is justifiable to draw a conclusion from release data based on the smaller tablets and extend it to the regular size tablets (11.0 mm diameter) because the ratio of diameter to thickness of the smaller tablets is less than that of the larger tablets. Unexpectedly, a much shorter release time was observed for sulfapyridine. We postulate that PEOs may form an associate complex with sulfapyridine, evidenced by the lower swelling of the polymer.

A constant release of drug from an inert matrix was reportedly obtained for these systems controlled by the dissolution of the drug (13,14). A mathematical model describing dissolution controlled systems can be expressed by

$$\frac{\partial c}{\partial t} = \frac{1}{x^n}\left(\frac{\partial}{\partial x} Dx^n \frac{\partial c}{\partial x}\right) - k_d\,(c_s - c) \tag{2}$$

where c is the dissolved drug concentration in the matrix, t is the time, D is the diffusion coefficient, c_s is the drug solubility, k_d is the dissolution rate constant, x is the diffusional distance, and n = 0, 1, and 2 for a slab, cylinder, and sphere, respectively. If the dissolution rate constant is very small, the second term on the right side of Eq. (2) is the rate-limiting process for overall release behavior.

When the drug diffusion coefficient is time dependent and/or position dependent, drug release is zero-order along with a drug dissolution contribution (14). Even if the dissolution front advances further toward the core of the matrix, the increasing time of drug diffusion from the drug dissolution front to the dissolution medium is faster than the rate of drug dissolution. The increase in the drug diffusion coefficient can be accounted for by the swelling of the polymer in this study. Also, the erosion of swollen polymer shortens the travel distance of the dissolved drug from the dissolution front to the surrounding medium. It has been reported that the higher the polymer swells, the more linear the release kinetics (10,11). In the extreme case, zero-order release kinetics can be obtained purely by the polymer swelling (9). However, in this study the drug in the polymer matrix is suspended until the swollen polymer erodes at the gel/dissolution medium interface. As the molecular weight of the PEO decreases, however, the release mechanism shifts to the swelling/erosion-controlling processes of polymer. The synchronization gel layer of PEO of MW = 0.9×10^6 (PEO0.9) and PEO of MW = 2.0×10^6 (PEO2) was reportedly established between the rate of swelling and the rate of erosion of the swollen polymer (6). A mathematical expression for this process is given by (3,15)

$$\frac{M_t}{M_\infty} = \alpha\sqrt{t} + \beta t \tag{3}$$

where α and β are constants. Eq. (3) describes that drug release takes place by a combination of drug diffusion (the first term on the right side) and polymer erosion (the second term on the right side). However, polymer relaxation does not take place at the swelling front because PEOs are not glassy polymers (glass transition temperature, T_g, below zero) in the dry state. When synchronization of the two fronts is obtained, the second term on the right side dominates, resulting in linear release kinetics via polymer erosion. Except for diclofenac Na, the release profiles of theophylline, salicylic acid, and sulfathiazole from PEO0.9 and PEO2 tablets yield zero-order kinetics (75–85% release), as illustrated in Figs. 2 and 3. The influx of water into the polymer matrix is enhanced by the presence of highly water-soluble drugs, such as diclofenac Na. Water penetration becomes much faster than the rate of swelling, leading to the rapid diffusion of the drug even through the unswollen polymer matrix. As a result, anomalous kinetics prevail over zero-order kinetics. However, the release kinetics of diclofenac Na from PEO0.9 and PEO2 tend to favor a linear release changing from n = 0.72 for PEO4 tablets to n = 0.85 and 0.91 for PEO2 and PEO0.9 tablets, respectively. The values of the release exponent n for PEO2 tablets are 0.83, 0.86, and 1.12 for theophylline, salicylic acid, and sulfathiazole, respectively, whereas those for PEO0.9 tablets are 1.01, 0.97, and 1.17 for theophylline, salicylic acid, and sulfathiazole, respectively. This results from the greater contribution of the swelling/erosion (synchronization) processes of the polymer in comparison to drug diffusion in the swollen gel.

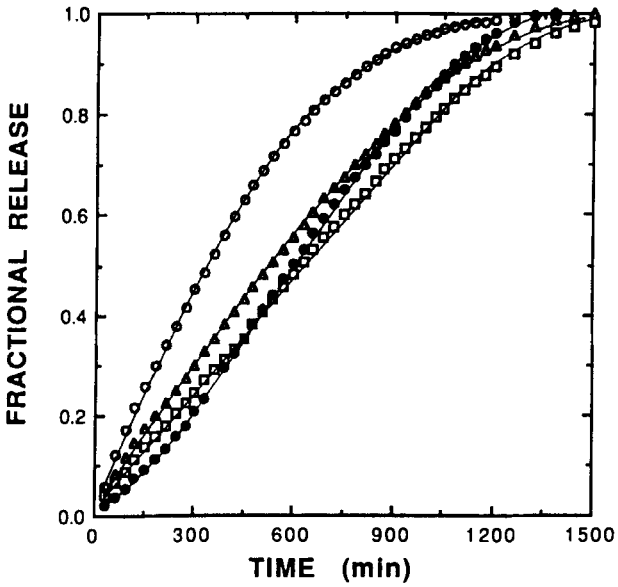

Figure 2. Effect of drug solubility on the release of drugs from PEO2 tablets (39% loading): (○) diclofenac Na; (Δ) theophylline; (□) slicylic acid; (●) sulfathiazole.

The effect of drug loading on the kinetics from the PEO4 tablets is illustrated in Fig. 4, which shows that the effect of drug loading is dependent upon drug solubility. As drug loading increases from 20 to 39%, the release of diclofenac Na from the PEO4 tablets becomes

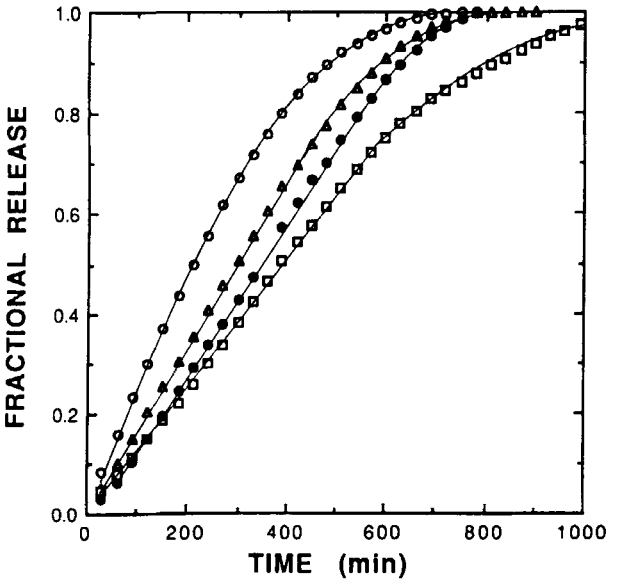

Figure 3. Effect of drug solubility on the release of drugs from PEO0.9 tablets (39% loading): (○) diclofenac Na; (Δ) theophylline; (□) salicylic acid; (●) sulfathiazole.

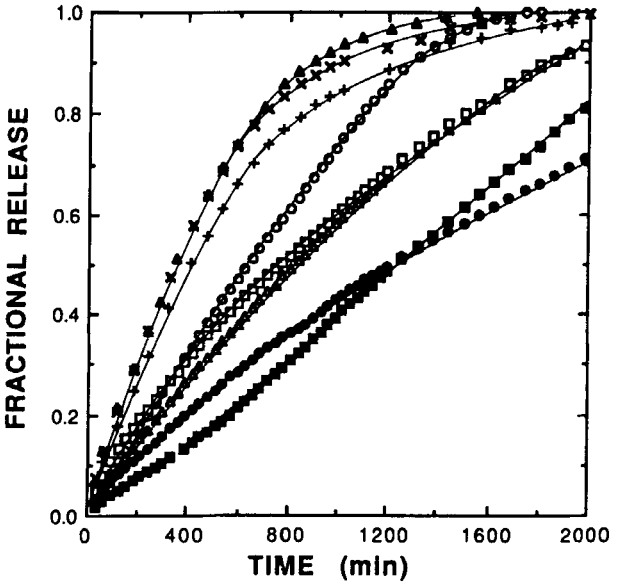

Figure 4. Effects of drug loading and a water-soluble additive on the release of drugs from PEO4 tablets: (▲) diclofenac Na (39% drug, 0% lactose); (x) diclofenac Na (20% drug, 19% lactose); (+) diclofenac Na (20% drug, 0% lactose); (○) salicylic acid (39% drug, 19% lactose); (□) salicylic acid (20% drug); (Δ) salicylic acid (39% drug); (●) sulfathiazole (20% drug); (■) salfathiazole (39% drug).

faster because when the loading becomes higher, drug diffusion controls the release kinetics. In other words, the properties of the polymer, such as swelling and erosion, become lesser contributing factors in the release kinetics. However, as drug loading increases for salicylic acid and sulfathiazole, drug release slows, resulting in more favorable release kinetics, exhibiting $n = 0.81$ and $n = 0.94$ for salicylic acid and sulfathiazole, respectively. For the 20% drug-loading PEO4 tablets, the release kinetics exponent n is 0.72 and 0.78 for salicylic acid and sulfathiazole, respectively. This observation was also found for PEO2 and PEO0.9 tablets. This indicates that drug diffusion plays a more important role in the release kinetics at the 20% loading level where the majority of drug in the matrix is in the dissolved state, whereas at the 39% loading level a smaller portion of drug is suspended in the matrix. Therefore, as long as a high drug loading is maintained for poorly water-soluble drugs (i.e., salicylic acid), the addition of a water-soluble excipient to the matrix does not influence the release kinetics other than to cause shortened release time as shown in Fig. 4. Figure 5 summarizes the effects of drug loading, drug solubility, and polymer molecular weight on release kinetics. For sulfathiazole, the release profiles

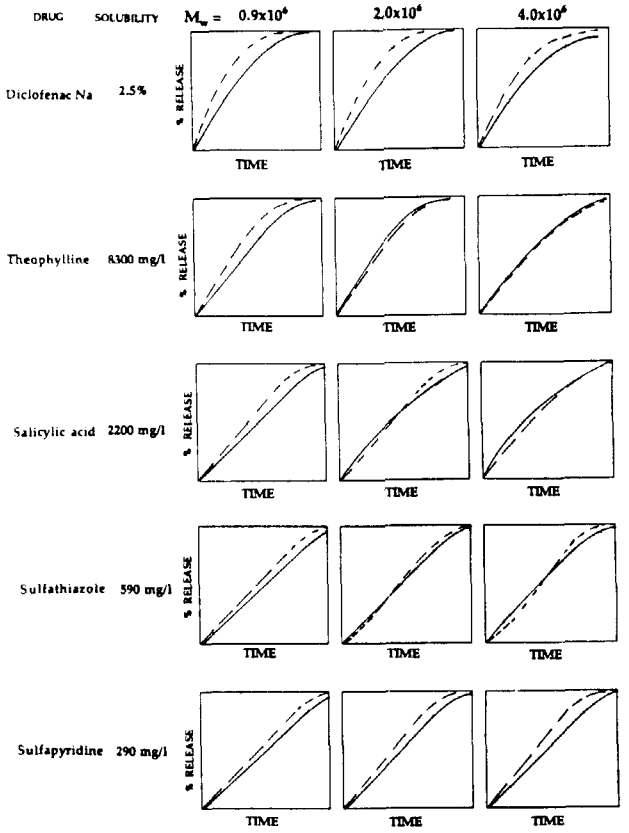

Figure 5. Summary of effects of drug solubility, PEO molecular weight, and drug loading on the release of drugs from PEO tablets: (—) 20% loading; (---) 39% loading.

from the 20 and 39% loaded PEO4 tablets cross over each other at the middle of the release profile. It seems that the rate of drug diffusion is faster than the rate of drug dissolution. In this case, the diffusion of the dissolved drug (a large portion) in the 20% loaded PEO4 tablets is more rapid at the early stage of release than that (a small portion) of the 39% loaded PEO4 tablets. The crossover of two release profiles from PEO2 tablets occurs at a slightly higher drug solubility (salicylic acid).

However, when drug solubility is about 290 mg/l, drug release kinetics become zero-order regardless of the drug loading (20 and 39%), and the drug release rate becomes faster at the higher loading. This is attributable to the release mechanism for a drug with very low water solubility, for which the drug release occurs by the erosion of the polymer followed by the dissolution of the drug in the dissolution medium. As a result, the higher loading in the matrix and the smaller fractions of polymers in the matrix give rise to the faster erosion rate of the polymer. For PEO0.9 tablets, drug release is governed by the swelling/erosion processes of the polymer, giving rise to the faster dissolution of the polymer with zero-order kinetics as the drug loading increases. For the release of diclofenac Na from the PEO0.9 tablets, drug diffusion is a controlling factor for the release kinetics, so that at the lower drug loading a linear release (n = 0.93) results.

Like capsules that produce dosage forms that can release different doses with the same release kinetics, tablets should be designed with a different formulation to achieve the same release profiles. This can be achieved by adding a water-soluble excipient in a tablet (low dose). Figure 4 also presents the effect of a water-soluble component on the drug release kinetics. An additional water-soluble component in the matrix reduces the polymer content and enhances the hydration of the polymer matrix by osmotic pressure. The release of diclofenac Na from PEO4 tablets, displaying that drug release is enhanced by the higher drug loading, is increased by the addition of a water-soluble excipient (lactose). As a result, the release of diclofenac Na from a PEO4 tablet containing 39% loading is superimposable, except in the final stage of release, with that from a PEO4 tablet containing 20% drug/19% lactose, provided each tablet has the same total weight.

In conclusion, the controlling mechanism of drug release from PEO tablets is dependent upon the drug solubility, drug loading, the addition of a water-soluble excipient, and the molecular weight of PEOs. For a highly water-soluble drug (e.g., diclofenac Na), drug diffusion is the rate-controlling step for the PEOs investigated in this study. This leads to anomalous transport behavior with aid from the swelling of the polymer, whereas for poorly water-soluble drugs the swelling/erosion process of the polymers is the dominating mechanism for PEOs of MW = 0.9 and 2.0 × 10^6, resulting in zero-order kinetics. For a PEO of MW = 4 × 10^6, drug release is governed by drug dissolution for poorly water-soluble drugs (salicylic acid and sulfathiazole) with aid from the swelling of the polymer for which the diffusion coefficient is enhanced by the swelling of polymers. For low loading levels (20%) of poorly water-soluble drugs, the effect of dissolution of the drug on the linear release kinetics diminishes, resulting in anomalous transport behavior.

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