# Controlled Release From Triple Layer, Donut-Shaped Tablets With Enteric Polymers

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Cherng-ju Kim[1]

[1]College of Pharmacy, University of Arkansas for Medical Sciences, 4301 W Markham St, Little Rock, AR 72205

## ABSTRACT

The purpose of this research was to evaluate triple layer, donut-shaped tablets (TLDSTs) for extended release dosage forms. TLDSTs were prepared by layering 3 powders sequentially after pressing them with a punch. The core tablet consisted of enteric polymers, mainly hydroxypropyl methylcellulose acetate succinate, and the bottom and top layers were made of a water-insoluble polymer, ethyl cellulose. Drug release kinetics were dependent on the pH of the dissolution medium and the drug properties, such as solubility, salt forms of weak acid and weak base drugs, and drug loading. At a 10% drug loading level, all drugs, regardless of their type or solubility, yielded the same release profiles within an acceptable level of experimental error. As drug loading increased from 10% to 30%, the drug release rate of neutral drugs increased for all except sulfathiazole, which retained the same kinetics as at 10% loading. HCl salts of weak base drugs had much slower release rates than did those of neutral drugs (eg, theophylline) as drug loading increased. The release of labetalol HCl retarded as drug loading increased from 10% to 30%. On the other hand, Na salts of weak acid drugs had much higher release rates than did those of neutral drugs (eg, theophylline). Drug release kinetics were governed by the ionization/erosion process with slight drug diffusion, observing no perfect straight line. A mathematical expression for drug release kinetics (erosion-controlled system) of TLDSTs is presented. In summary, a TLDST is a good design to obtain zero-order or nearly zero-order release kinetics for a wide range of drug solubilities.

**KEYWORDS:** Enteric polymers, donut-shaped tablets, triple layer tablets, erosion, diffusion.

## INTRODUCTION

Orally administering drugs to patients over an extended time and at a controlled release rate, preferably at a constant linear release rate, is advantageous in some medical applications.[1]

**Corresponding Author:** Cherng-ju Kim, College of Pharmacy, University of Arkansas for Medical Sciences, 4301 W Markham St, Little Rock, AR 72205. Tel: (501) 686-5090; Fax: (501) 562-6510. E-mail: ckim@uams.edu

There are many extended release pharmaceutical systems currently known: monolithic matrices, membrane reservoirs, swellable polymers, erodible polymers, ion exchange resins, osmosis, and geometrically modified systems.[2,3] Some of these systems do not exhibit zero-order release kinetics or are not produced in a form that is amenable to large-scale manufacturing processes. For instance, monolithic matrices—fabricated from water-insoluble polymers, a drug, and excipients—exhibited first-order release kinetics or square-root-of-time kinetics because of a longer drug diffusion time and a decrease in releasing surface area with time.[4] Geometrically modified systems (eg, semihemispheric, pie-shaped, and multiholed shaped tablets) that provided an increase in releasing surface area with time and that had surfaces coated with water-insoluble polymers and impermeable polymers could not be practically produced in large-scale manufacturing processes, even though zero-order release kinetics were possibly obtained over an extended time.[5-7]

Perforated, coated tablets (PCTs) that were formed with a central hole and used water-soluble excipients (eg, lactose) exhibited a constant or slightly increased drug release rate over a short time (3-4 hours).[8] On the other hand, a PCT formed with a water-insoluble polymer (eg, ethyl cellulose) showed square-root-of-time release kinetics with a prolonged release time. A donut-shaped tablet formed with a mixture of a hydrophilic polymer (eg, polyethylene oxide), a drug, and excipients was shown to exhibit zero-order release kinetics for poorly water-soluble drugs (eg, theophylline) and anomalous release kinetics for highly water-soluble drugs.[9] Another problem associated with hydrophilic polymer-based tablets is that these tablets can dump dose; that is, when not fully hydrated the hydrophilic polymers become very viscous and adhere to solids and biological surfaces. The surface of the tablets then peels off and the drug dose is dumped into the patient. To avoid dose dumping problems, a coated donut-shaped tablet (CDST) was introduced with parabolic and zero-order release kinetics that made it able to accommodate a wide range of drug solubilities.[10] Disadvantageously, however, drug release from CDSTs is significantly slowed down or may even stop once viscous liquids or foods are placed in the central hole.

In this paper, a triple layer, donut-shaped tablet (TLDST) (Figure 1) is introduced so that zero-order, or substantially

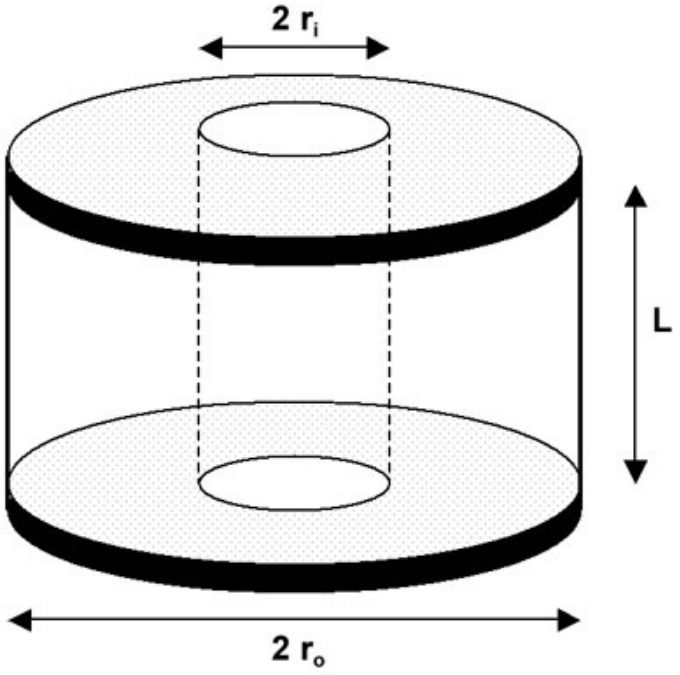


**Figure 1.** Triple layer, donut-shaped tablet.

zero-order, drug release kinetics can be obtained over an extended time; the tablet does not adhere to solids and biological surfaces, thereby leading to dose dumping; and the drug release is not stopped by physical interaction of the tablet with other elements, such as foods. A TLDST consists of a core tablet comprising one or more than one enteric polymer, a drug, and excipients where the enteric polymer is substantially hydrophobic but highly soluble in an aqueous medium above a pH of ~5. The top and bottom layers are composed of a water-insoluble polymer. The effect of drug properties (eg, solubility, salt forms of weak acid/base, drug loading) on the release of drugs from TLDSTs is investigated. Mathematical interpretation of drug release kinetics for TLDSTs is presented.

## Experimental Methods

### *Materials*

Enteric polymers (Eudragit S, Kollicoat MAE, and hydroxypropyl methylcellulose acetate succinate [HPMCAS]) were generously supplied by various manufacturing companies (Rohm America, Piscataway, NJ; BASF, Mount Olive, NJ; and Shin-Etsu, Tokyo, Japan, respectively). Model drugs (diltiazem HCl, verapamil HCl, labetalol HCl, sulfathiazole, theophylline, hydroxypropyl theophylline, caffeine, glipizide, diclofenac Na, and naproxen Na) and Mg stearate were purchased from Sigma Chemical (St Louis, MO). Ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC) E50 were kindly supplied by Dow Chemical (Midland, MI). Na monobasic phosphate, Na dibasic phosphate, and NaCl were purchased from Aldrich Chemical (Milwaukee, WI).

### *Preparation of TLDSTs*

Fifty milligrams of ethyl cellulose (EC) powder (viscosity 100 cP) (bottom layer) was poured into a tablet die (10 mm diameter). The powder was then pressed by a flat surface punch with a hand. Next, 300 mg of a mixture of HPMCAS LF, a model drug, and Mg stearate (1%) was blended using a mortar and pestle and poured on top of the bottom layer, then pressed with a punch. Finally, 50 mg of ethyl cellulose was poured on top of the second layer. Then the 3 layers were compressed under 5000 pounds of force with a Carver Press (Wabash, NJ). The triple layer tablets were then drilled with a high-speed, hand-press drill (7/64″ hole size) to obtain TLDSTs.

### *Testing TLDSTs*

Drug release kinetic studies were performed in a pH 7.4 solution prepared from 0.01M $NaH_2PO_4$ and 0.01M $Na_2HPO_4$ in 0.1M NaCl, and in a pH 1.5 solution prepared from concentrated HCl in 0.1M NaCl at 50 rpm and 37°C. The USP paddle method was employed in this study. The amount of the model drug released from the TLDST was pumped continuously from dissolution media into a diode-array UV/Vis spectrophotometer 8453 (Agilent Technology, Wilmington, DE) with a multicell transport. Absorbance was measured every 30 minutes. The concentrations were measured as follows: diltiazem HCl at 278 nm, verapamil HCl at 278 nm, labetalol HCl at 306 nm, glipizide at 278 nm, sulfathiazole at 306 nm, theophylline at 290 nm, hydroxypropyl-theophylline at 286 nm, caffeine at 296 nm, diclofenac Na at 300 nm, and naproxen Na at 330 nm.

### *Drug Release Kinetic Analysis*

Drug release kinetics were analyzed by the following phenomenological expression[11]:

$$\frac{M_t}{M_\infty} = kt^n \qquad (1)$$

where $M_t$, $M_\infty$, $k$, and $n$ are the amount of drug released at time $t$, the initial amount of drug in a tablet, the constant, and the release exponent, respectively. The exponent n shows the linearity of release kinetics. The first release data point has been excluded in this analysis to eliminate the effect of drug burst from the tablet surface.

If drug release kinetics are controlled solely by a surface erosion process without drug diffusion, the drug release rate may be expressed as follows:

$$\frac{dM_t}{dt} = 2\pi\, Lk_e\, C_o\, (x + y) \qquad (2)$$

where $k_e$, $C_o$, $x$, and $y$ are the erosion rate constant, the initial drug concentration in a tablet, the outer radius of a tablet, and the inner radius of a tablet, respectively. However,

$$x + y = r_o + r_i$$

according to Equation 3:

$$\begin{aligned} \textit{surface area at } t &= 2\pi\, L(\, x + \, y) \\ &= 2\pi\, L(r_o - a) + (r_i + a) \\ &= 2\pi\, L(r_o + r_i\,) \end{aligned} \qquad (3)$$

where a is the radially eroded thickness of the core tablet. Thus, Equation 2 becomes:

$$\frac{dM_t}{dt} = 2\pi\, Lk_e\, C_o\, (r_o + r_i\,) \qquad (4)$$

Integrating Equation 4 yields:

$$\frac{M_t}{M_\infty} = \frac{2k_e}{r_o \; - \; r_i}\; t \qquad (5)$$

where $M_\infty = \pi\, LC_o\, (r_o^2 \; - \; r_i^2\,)$.

## Results and Discussion

The enteric polymers Eudragit S and Kollicoat MAE were not fabricated into a compressed tablet because of a lack of binding ability; cellulose acetate phthalate and hydroxypropyl methylcellulose phthalate were able to form a tablet but bulked up in water. Only HPMCAS made a tablet under pressure without bulking up in water. However, all enteric polymers were able to form tablets with assistance from binders. In this study, HPMCAS was used mostly. Even though this polymer has been employed for extended release dosage forms,[12,13] the effect of drug properties (eg, solubility, drug type, loading) on the release of drugs from tablets made with HPMCAS has not been fully characterized. The polymer surface de-protonates and erodes (ie, surface erosion controlled) when the enteric polymer is placed in pH 7.4. Most hydrophilic polymers (eg, hydroxypropyl methylcellulose and polyethylene oxide) adhere fast to the glass dissolution vessel upon contact with the dissolution medium. When the adhered tablets are detached mechanically from the vessel, the portion held firmly peels off from the tablet. In vivo, dose dumping may result. However, HPMCAS tablets moved around the bottom of the dissolution vessel under paddle agitation, showing there was no adherence to the vessel wall.

As model drug compounds for this study, 4 neutral drugs, HCl salts of 3 weak base drugs, and Na salts of 2 weak acid drugs were chosen, with various solubilities. In general, as drug solubility and drug loading increase, the drug release rate from a simple, nonswellable/nonerodible matrix system increases. It will be found out in this study whether general drug release kinetics are applicable to polymer erosion–controlled matrix systems via the ionization and erosion of polymer chain.

Figure 2 shows the effects of pH and tablet shape on the release of theophylline (solubility 1%) from HPMCAS tablets (10% loading). The release of theophylline from triple layer tablets without a hole (TLT) at pH 7.4 provided the longest release time, while donut-shaped tablets without bottom and top layers (DST) gave the shortest release time. This is in accordance with the availability of the drug releasing surface area (DST>regular tablet>TLDST>TLT). As expected, the release of theophylline from the TLDSTs was minimal at pH 1.5 because HPMCAS was intact at the pH and drug release kinetics were governed by the drug diffusion process alone, as others have reported.[13] Also, the

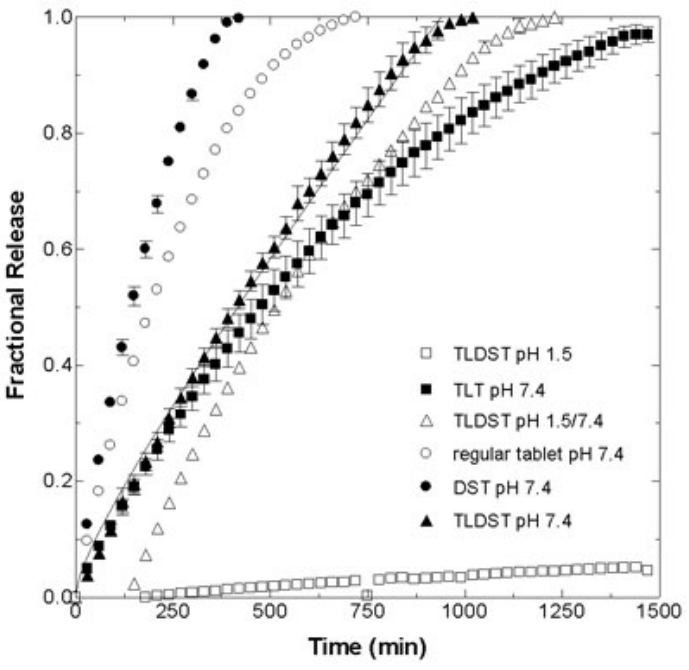


**Figure 2.** The effect of pH and tablet shape on the release of theophylline (10% loading) from HPMCAS tablets (Equation 6). DST indicates donut-shaped tablet; HPMCAS, hydroxypropyl methylcellulose acetate succinate; TLDST, triple layer, donut-shaped tablet; TLT, triple layer tablet.

drug release profile of theophylline from TLDSTs at pH 7.4 for the entire release period was in parallel with that of TLDSTs placed at pH 1.5 for 2 hours followed by pH 7.4. The exponents n for different tablet shapes (TLT, regular tablet, DST, and TLDST) were 0.65, 0.82, 0.84, and 0.92. This finding is very reasonable, given the change in surface area with time. In fact, the TLT is a cylindrical geometry in which the releasing surface area decreases with time more dramatically than it would for a regular tablet, which is a combined geometry of slab and cylinder, or a DST, whereas the TLDST provides a constant surface area with time, as shown in Equation 3. A constant surface area can shield the effect of geometry in the release of drugs from matrices.

The effect of drug loading and solubility of neutral drugs on the release of the drugs at pH 7.4 is presented in Figure 3. At a 10% drug loading level, there was no significant difference in drug release kinetics among the neutral drugs studied, whose solubilities range from 0.05% to 53%. This indicates that at this drug loading level, drug release kinetics were governed by the surface erosion process, with a minute contribution of drug diffusion because release profiles were not perfectly straight, as would be anticipated from Equation 5. For a very water-soluble drug (eg, hydroxypropyl theophylline), the rate of drug diffusion was a little faster than it was for other drugs even at 10% loading, showing a release exponent of 0.93. At 10% drug loading, drug molecules were not connected to one other and thus did not form a continuous network to the releasing surface, so drug diffusion was restricted. However, as drug loading increased, drug release kinetics were governed by both polymer erosion and drug diffusion to a higher degree, and thus the exponent n decreased. For instance, the release exponents for 10% and 30% caffeine loading TLDSTs were 1.03 and 0.88, respectively, and the exponent n for 30% hydroxypropyl theophylline was 0.87. In general, for high drug loading, water diffuses into a tablet at a much faster rate than it does for low drug loading, and at high drug loading the drug molecules form channels or connected pores, through which drugs diffuse out at a faster rate. However, for low-solubility drugs (eg, sulfathiazole) there was no noticeable difference in release kinetics between 10% and 30% loading (n = 1.00 and 1.03, respectively) because even high drug content did not expedite water transport into a tablet because of the low absorption of water by the drug. The reduced sensitivity of drug solubility at 10% loading and drug loading (theophylline and sulfathiazole) to drug release kinetics was also found in the release of water-soluble drugs from hydrophilic tablets (eg, polyethylene oxide), where other mechanisms (ie, swelling and erosion) were involved in drug release kinetics in addition to drug diffusion through a matrix.[15]

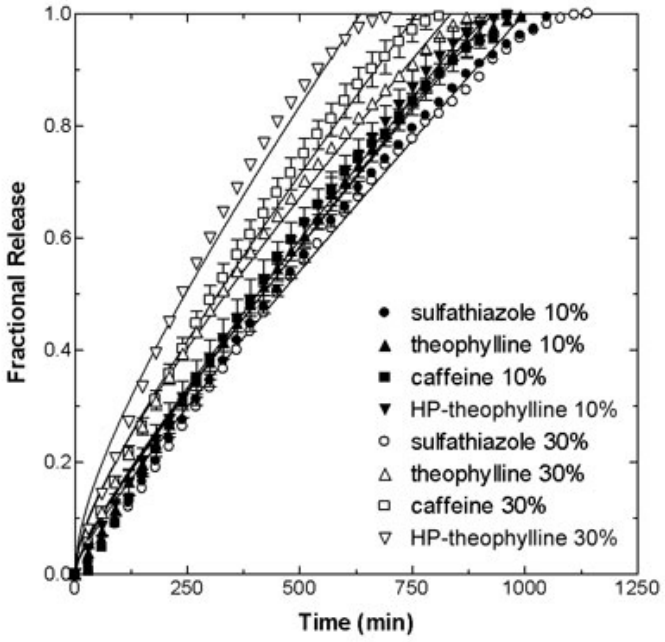


**Figure 3.** The effect of drug solubility and drug loading on the release of neutral drugs from TLDSTs at pH 7.4 (Equation 6). HP indicates hydroxypropyl; TLDSTs, triple layer, donut-shaped tablets.

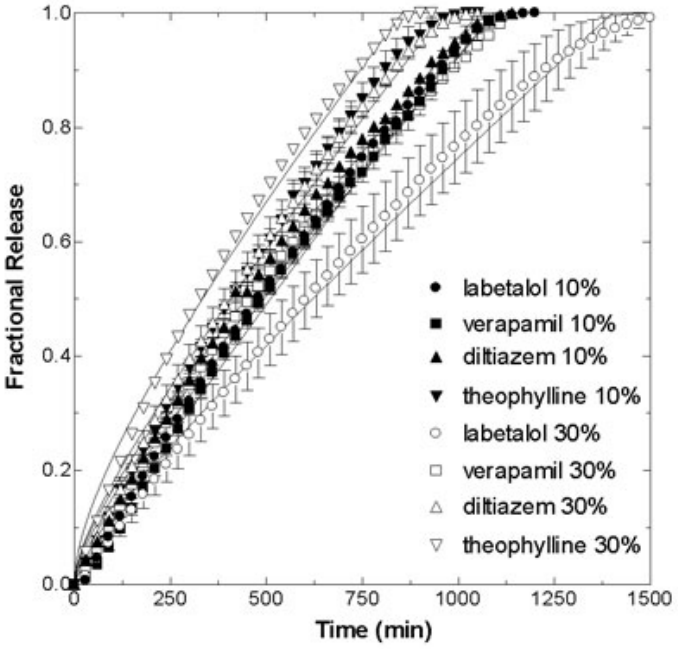


**Figure 4.** The effect of drug type (HCl salt of weak base drug) and drug loading on the drug release from TLDSTs at pH 7.4 (Equation 6). TLDSTs indicates triple layer, donut-shaped tablets.

The effect of drug loading and solubility of HCl salt forms of weak base drugs from TLDSTs on their release is shown in Figure 4. At the 10% drug loading level, drug release profiles were very close to each other, as was found in the release of neutral drugs. The presence of HCl in the TLDST

increased the amount of acid in the tablet that needed to be neutralized by the incoming hydroxyl ions. Thus, it took much longer for HPMCAS to be de-protonated, resulting in a longer release time. In general, HCl salt drugs had more linear release kinetics than did neutral drugs. For example, the release exponents of labetalol HCl (solubility 1.6%) and theophylline at the 10% loading level were 0.98 and 0.92, respectively, whereas at the 30% loading level they were 0.94 and 0.82, respectively. However, at the 10% drug loading level, the contribution of HCl to the retardation of ionization of HPMCAS was minimal. As the drug loading of labetalol HCl increased from 10% to 30%, the drug release rate did not increase (as it had in the release of neutral drugs) but decreased because of the increase in the amount of acid to be neutralized before the polymer eroded and the drug was released. It seems that the drug diffusion process did not play a significant part in the release kinetics even with high drug loading (30%). This trend was not found in the release of water-soluble drugs, regardless of drug type, from non-ionic hydrophilic matrices.[15] Kim and Lee[16] reported, however, a similar observation in the release of labetalol HCl from cross-linked poly(methylmethacrylate-co-methacrylic acid) (P(MMA/MAA)) beads. The release of labetalol HCl from P(MMA/MAA) beads decreased as drug loading increased from 2.7% to 11.0%. For the release of verapamil HCl from TLDSTs, the drug release profiles were superimposed on each other for 10% and 30% loading, as shown in Figure 4. The increase in verapamil HCl content (30%) in TLDSTs was supposed to slow down the drug release rate, as happened in the release of labetalol HCl, but because of the higher water solubility of verapamil HCl (solubility 14%), water-carrying hydroxyl ions came in and de-protonated HPMCAS at a faster rate, leading to a higher drug release rate. As a result, the same drug release kinetics were observed. It was reported that the release rate of propranolol HCl (solubility 6.9%) from P(MMA/MAA) beads decreased as drug loading increased from 6.7% to 12.2% and then increased as drug loading increased from 12.2% to 18.6% and higher.[16] However, the drug release rate of diltiazem HCl (solubility 62%) from TLDSTs increased as drug loading increased from 10% to 30%, but this increase was not as sharp as the release of theophylline (solubility 1%) and hydroxypropyl theophylline (solubility 53%) at 30% loading. This demonstrates that the presence of HCl retarded the ionization of HPMCAS and its erosion, resulting in the slower drug release rate. For HCl salts of weak base drugs, the neutralization of HCl and de-protonation of HPMCAS played a key role in drug release kinetics along with slight drug diffusion. However, the neutralization of the weak acid component (eg, tartaric acid) was not critical for the release of metoprolol tartrate from TLDSTs because fewer hydroxyl ions were required to neutralize tartaric acid than were needed to neutralize HCl (data not shown here).

The effect of drug loading and drug solubility of Na salts of weak acid drugs on their release from TLDSTs is shown in Figure 5. The presence of the Na salts of the weak acid drug compound increased the pH at the eroding surface, and thus HPMCAS dissolved at a faster rate than at the rate. However, the contribution of Na salts to the enhancement of ionization of HPMCAS was minimal at low loading (10%), as observed in the release of HCl salts of weak base drugs. As observed for neutral drugs and HCl salts of weak base drugs, the drug release rates for diclofenac Na and naproxen Na at 10% drug loading were very close to the drug release rate of theophylline at 10% drug loading. This proves once again that drug release kinetics from HPMCAS tablets were controlled by polymer erosion at low drug loading (10%). The release exponents of diclofenac Na and naproxen Na at 10% loading were 0.87 and 1.09, respectively. However, the drug release rate for Na salts of weak acid drugs increased as drug loading increased from 10% to 30%. In addition, the drug release rate of Na salts of weak acid drugs increased, as drug solubility increased more than was the case for neutral drugs. The increase in drug loading of diclofenac Na from 10% to 30% further increased the rate of polymer erosion. This is due to the increased rate of polymer erosion by the larger amount of Na salt of the weak acid presented in TLDSTs. Drug release kinetics were enhanced by the presence of Na salts of weak acid drugs and retarded by the presence of HCl salts of weak base drugs when compared with the release of neutral drugs.

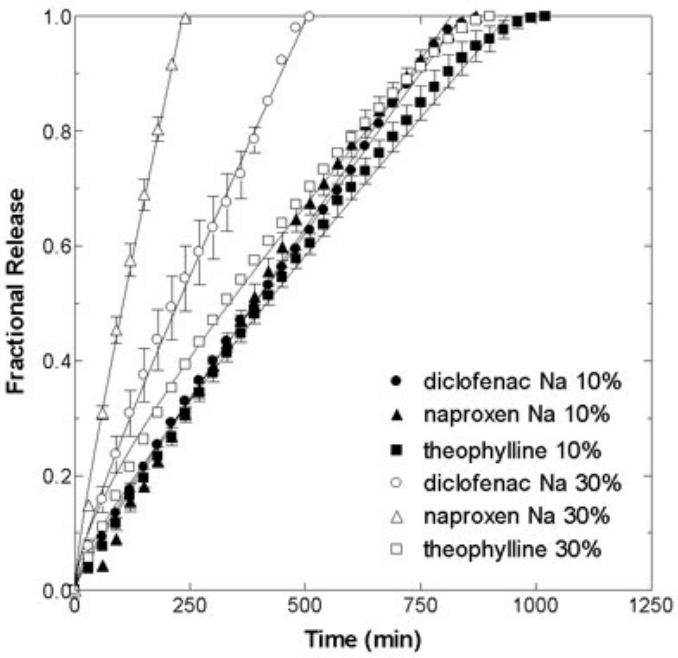


**Figure 5.** The effect of drug type (Na salt of weak acid drug) on the drug release from TLDSTs at pH 7.4 (Equation 6). TLDSTs indicates triple layer, donut-shaped tablets.

When the drug release mechanism is governed by a polymer erosion process, the exponent n is very close to unity. Only sulfathiazole (10% and 30%), hydroxypropyl theophylline (10%), theophylline (10%), and caffeine (10%) from neutral drugs; naproxen Na (10%) from the Na salt form of weak acid drugs; and diltiazem HCl (10%), verapamil HCl (10%), and labetalol HCl (10% and 30%) from the HCl salt forms of weak base drugs appeared to render close to zero-order kinetics (n>0.9). Only up to 80% drug release data were used to determine the effect of drug properties (eg, solubility, drug type) and drug loading on the erosion rate constant, $k_e$, by Equation 5. Table 1 shows the values of $k_e$, ranging from $1.45 \times 10^{-3}$ to $2.36 \times 10^{-3}$ mm/min along with the release exponent n. It is interesting to point out that Equation 5 is the identical equation for slab geometry (erosion-controlled system) from both sides of which tablet drug release takes place. When a drug is more than slightly soluble in water or drug loading is below the drug's solubility (eg, 10%), drug release kinetics for TLDSTs may be inferred analogically from slab geometry by the following equation[17]:

$$\frac{M_t}{M_\infty} = \sqrt{\frac{16Dt}{3(r_o - r_i)}} + \frac{2k_e}{r_o - r_i}\, t \qquad (6)$$

where D is the drug diffusion coefficient in a matrix. Equation 6 describes the effect of drug diffusion of erodible matrix systems. The values of D and $k_e$ are listed in Table 1. In general, there was no clear trend on the erosion rate constant and drug diffusion coefficient with drug solubility and drug loading. The 2 parameters (D and $k_e$) are probably interrelated. However, one may find a trend if the Deborah number ($Deb_{release}$) is used as defined by this equation[18]:

$$Deb_{release} = \frac{D}{k_e\,(r_o - r_i)} \qquad (7)$$

The Deborah number indicates the relative importance of polymer erosion rate and drug diffusion rate. When the Deborah number is large, the drug diffusion in a matrix is important in drug release kinetics. However, a large Deborah number does not mean that the drug release rate always becomes faster. For example, even though the naproxen release rate at 30% loading was much faster than that of hydroxypropyl theophylline, the Deborah numbers for naproxen Na and hydroxypropyl theophylline at 30% loading were 0.0276 and 0.171, respectively. This demonstrates that the drug release kinetics of naproxen Na at 30% loading were governed by polymer erosion because of the additional amount of alkaline substance (eg, Na) in the matrix. In general, the Deborah number increases as drug loading increases, showing that the contribution of drug diffusion to drug release kinetics becomes larger.

**Table 1.** Release Exponent, Erosion Rate Constant, and Diffusion Coefficient*

| Drugs | Solubility† (%) | Drug Loading (%) | n | $k_e$ ($\times 10^3$mm/min)‡ | D ($\times 10^8$cm$^2$/sec) | $k_e$ ($\times 10^3$mm/min)§ | $Deb_{release}$ |
|---|---|---|---|---|---|---|---|
| Sulfathiazole | 0.05 | 10 | 1.00 | 1.99 | 1.58 | 1.46 | 0.018 |
| | | 30 | 1.03 | 1.94 | NC | NC | NC |
| Theophylline | 1.0 | 10 | 0.92 | 2.15 | 2.37 | 1.50 | 0.026 |
| | | 30 | 0.84 | NC | 8.65 | 1.25 | 0.115 |
| Caffeine | 2.0 | 10 | 1.03 | 2.18 | 2.60 | 1.56 | 0.020 |
| | | 30 | 0.88 | NC | 6.95 | 1.52 | 0.076 |
| HP-theophylline | 53 | 10 | 0.93 | 2.20 | 2.25 | 1.56 | 0.024 |
| | | 30 | 0.87 | NC | 15.10 | 1.47 | 0.171 |
| Labetalol HCl | 1.6 | 10 | 0.98 | 1.83 | 1.80 | 1.29 | 0.023 |
| | | 30 | 0.94 | 1.45 | 1.92 | 0.96 | 0.033 |
| Verapamil HCl | 14 | 10 | 1.06 | 1.79 | 0.28 | 1.56 | 0.003 |
| | | 30 | 0.91 | 1.86 | 3.17 | 1.16 | 0.046 |
| Diltiazem HCl | 62 | 10 | 0.92 | 1.99 | 4.33 | 1.14 | 0.063 |
| | | 30 | 0.89 | NC | 4.83 | 1.24 | 0.065 |
| Diclofenac Na | 3.7 | 10 | 0.87 | NC | 0.95 | 1.86 | 0.009 |
| | | 30 | 0.81 | NC | 5.13 | 2.68 | 0.032 |
| Naproxen Na | 15 | 10 | 1.09 | 2.36 | 0.55 | 1.99 | 0.005 |
| | | 30 | 0.88 | NC | 9.77 | 5.89 | 0.028 |

*HP indicates hydroxypropyl; NC, not calculated.

†37°C and Bari[14] for solubility values.

‡Equation 5.

§Equation 6.

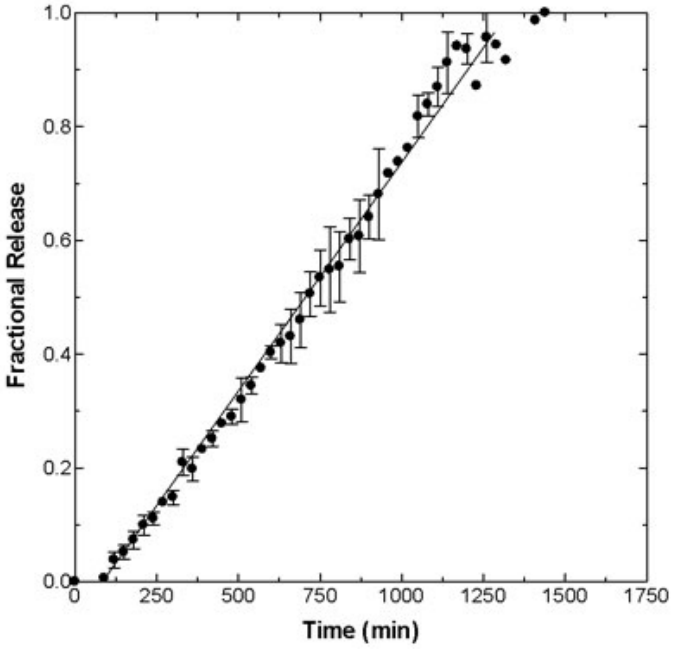


**Figure 6.** The release of glipizide from TLDSTs (300 mg and 9 mm diameter, 7/64″ hole) comprising HPMCAS, Eudragit S, Kollicoat MAE, ethyl cellulose, and HPMC E50 at pH 7.4. HPMC indicates hydroxypropyl methylcellulose; HPMCAS, hydroxypropyl methylcellulose acetate succinate.

To elucidate a more detailed mechanism of drug release kinetics from HPMCAS tablets (erosion/diffusion-controlled system), separating minute diffusion from erosion and evaluating the effects of drug loading and solubility on drug release, one should use a different geometry in which the precise mathematical equation is known.[17] Results of a study in which this approach was used will be presented soon.

Applications of HPMCAS (or any single enteric polymer) for extended release dosage forms as a main drug carrier are limited by the fact that a large quantity of the polymer (300-400 mg) is needed. A combination of various enteric polymers with other polymeric excipients (eg, EC, HPMC) may be employed for pharmaceutical applications. In this way, the quantity of individual enteric polymers in the whole TLDSTs may be much less. Figure 6 shows the release of glipizide from TLDSTs composed of HPMCAS, Eudragit S, Kollicoat MAE, EC, and HPMC E50. Because of the very low solubility of the drug (≈15 mg/L) and a constant surface area provided by TLDST, linear release kinetics with a time lag were obtained with no drug diffusion.

## CONCLUSION

TLDSTs composed of the enteric polymer HPMCAS provided controlled release dosage forms at a substantially linear release rate for a variety of water-soluble drugs (neutral drugs, HCl salts of weak base drugs, and Na salts of weak acid drugs). Because of the nature of HPMCAS, drug release kinetics were governed by the erosion of the polymer with a small degree of drug diffusion because release profiles were not perfect straight lines, even though a constant surface area of TLDST was provided. Drug release kinetics were enhanced by the presence of Na salts of weak acid drugs and retarded by the presence of HCl salts of weak base drugs when compared with the release of neutral drugs.

## ACKNOWLEDGMENTS

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