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Linearization of Drug Delivery from Sustained-Release Dosage Forms, Synthetic Gel Systems

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ABSTRACT

A linear, apparent zero-order, in vitro release profile may be approximated from triple-pressed tablets using synthetic gum systems in the first and second press coats. This is coupled with varying concentrations of the actives (Melperone HCl, Diethylpropion HCl, and Dyphylline) in the core and press coats. The approximately linear release function obtained from these tablet systems is in stark contrast to a supposedly prolonged release tablet (comparative formulation) from the literature, which actually releases by the square root of time function characteristic of diffusion control. Addition of a placebo press coat to the outside of the synthetic gum systems simply increases the lag times for release (while the placebo coat is undergoing hydration, etc.). The linearity following the lag is reminiscent of saturation kinetics. Results suggest that the almost linear release profile is a function of the concentration of the various layers (core first and second press coats) coupled with the gelation characteristics of the synthetic gums. This zero-order release does not hold for the systems of the comparative formulation taken from the patent literature.

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INTRODUCTION

Traditionally, pharmaceutical dosage forms contain an active component distributed uniformly throughout. For sustained-release dosage forms where release is primarily by diffusion, uniform concentration leads to a nonlinear (non-zero-order) release profile (1–3). In systems where diffusion is the primary release mechanism, the rate of release is dependent on the gradient of the drug concentration between the dosage form and the dissolution environment. Depletion of the drug from the system causes a reduction in the gradient, which slows the release rate. In a previous publication (4) it was shown that a nonuniform concentration can be used to linearize release from delivery systems which release drugs primarily by erosion. A similar approach is presented which linearizes the release of drug from systems where the primary mechanism of release is diffusion. The concentration function is given by:

$$c = \alpha/r^2 \quad (1)$$

where c = concentration, α is a constant, and r is the radius of the cylinder or sphere which is releasing the drug.

THEORETICAL

An approach to sustained release would be to consider a tablet with drug that has a concentration C (gram/gram solid) which is position dependent; e.g., the concentration could be high in the center and low at the surface (periphery) of the tablet. C becomes the function of the radius:

$$C = c(r) \quad (2)$$

For erosion systems, release from cylindrical or spherical dosage forms can be linearized by the use of the function $c = \alpha/r^2$, Eq. (1) (4).

If one assumes that Eq. (1) can apply to diffusion-controlled systems and, in particular, to synthetic gum systems, a theoretically detailed explanation is complex. However, in purely erosion the function $c = \alpha/r^2$, Eq. (1), can be derived with relative ease (4). One only need be concerned with the phenomena of the eroding system surface. Synthetic gum systems which are described herein are multivariable systems. During dissolution, synthetic gum systems expand (increase in volume), hydrate rapidly, and become gelatinous. The viscosity of the gelatinous form has been utilized frequently in pharmaceutical dosage forms to sustain or delay drug release (5–9).

It is not the object of this study to arrive at a mathematical model which is consistent with the experimental results. Some of the factors which may ultimately lead to a mathematical model are presented in the Results and Discussion section.

EXPERIMENTAL

Tablet formulations contain 18% hydroxypropyl methylcellulose (HPMC) 4000 cps, 1.5% zinc stearate, and varying amounts of the active:

1. Melperone HCl or 1-(4-fluorophenyl)-4-(4-methyl-1-piperidinyl)-1-butanone hydrochloride
2. Diethylpropion hydrochloride or 2-diethylaminopropiophenone HCl.
3. Dyphylline or 7-(2,3-dihydroxypropyl)-theophylline and mannitol qs to final tablet weight.

The formulation for a triple-pressed tablet (standard formulation) is given with amounts, in milligrams of each per tablet.

Standard Formulation

A = core (1/4 in.)
B = first press coat (11/32 in.)
C = second press coat (7/16 in.)

	A	B	C
1, 2, or 3	28.6	10.7	10.7
Mannitol	51.9	134.2	190.55
HPMC 4000 cps	18.0	32.4	45.0
Zn stearate	1.5	2.7	3.75
Total	100.0	180.0	250.0

The active, mannitol, and HPMC are mixed for each tablet segment. They are first slugged, then forced through a No. 12 screen and subsequently through a No. 20 screen. The lubricant is then mixed into the screened material. The tableting (Stokes Model F Press) begins with the 1/4 in. core (A). One-half the weight of B is put into the 11/32-in. die. A (compressed) is placed in next, and the remaining amount of B is placed over A. This powder–tablet mix is then compressed. Segment C is incorporated in the same manner to complete the three-phase tablet system.

Dissolution studies were performed using the USP II Method (basket) at 50 rpm in water. Samples were analyzed by UV spectrophotometry.

Amounts of drug for each phase, M_i, in the double or triple tablets are calculated using Eq. (3).

$$M_i = \Delta r/r_o \times C_o \quad (3)$$

Δr is the increment of radius included in a segment; r_o is the total radius of the multiphase system, and C_o is the total amount of drug for the complete system.

Comparative Formulation (example 3) (8)

A. Nucleus, or Innermost Tablet

Active (Dyphylline)	28.6 mg
Talc	61.4 mg
Gylceryl monostearate	20.0 mg
Total	110.0 mg

The glyceryl monostearate is dissolved in alcohol and the mixture is granulated. The active and talc are mixed with the solution, dried, screened, and dried again. The mixture is pressed into a 1/4-in. diameter tablet.

B. First Compressed Layer

Active (Dyphylline)	10.7 mg
Calcium carbonate	109.3 mg
Lanolin	20.0 mg
Gum arabic powder	20.0 mg
Total	160.0 mg

The active (Dyphylline), calcium carbonate, and gum arabic powder are mixed. The lanolin is dispersed in alcohol and mixed together with the powders. The total mixture is dried, sized, and granulated with water. After drying and sizing again, this material is compressed over the tablet core A to a diameter of 3/8 in.

C. Second Compressed Layer

Active (Dyphylline)	10.7 mg
Kaolin	189.3 mg
Lanolin	30.0 mg
Gum arabic powder	40.0 mg
Total	270.0 mg

The same procedure is followed as with the core (A), and the material is compressed over tablet (B) to a diameter of 15/32 in.

Volume changes, moisture penetration, and gelation rates for the standard formulation are shown in Figs. 11–13. Measurements were made in exact accordance with the procedures set forth by Carstensen and Bamba (2,3).

RESULTS AND DISCUSSION

Figure 1 illustrates the release profile for the triple-pressed tablet described in the Experimental section. A single-phase sustained-release tablet of identical composition and size, but with active evenly distributed, is also shown in Fig. 1 for comparison. Figure 2 shows the dissolution profile of the core, and the double-pressed and triple-pressed tablet. A closer look at the dissolution profile of the triple-phase tablet is shown in Fig. 3, and a sinusoidal effect is evident from the data points. The reason for this is partly due to discontinuities in the concentration, but the thickness of the tablet also plays a role. The curvature in the early release is likely due to the gelation rate of the system. Preceding gel formulation, the drug is released quite rapidly. This appears to primarily affect release for the first half-hour. The initial release can be slowed or even delayed with a placebo coating. Figure 4 demonstrates this effect.

Although tablet machines are available for three-phase press-coated tablets, two-phase or double-pressed tablet machinery is more common. An attempt to fabricate a two-phase system is shown in Fig. 5. The results are not as satisfactory (regarding release times) as those from three-phase tablets but are still surprisingly linear.

Figure 6 depicts the core and the double-pressed and triple-pressed release profiles using the active ingredient diethylpropion hydrochloride. Figure 7 demon-

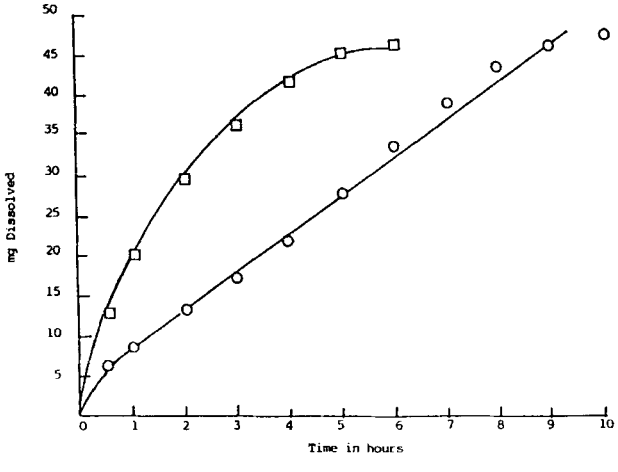

Figure 1. Release of 1-(4-fluorophenyl-4-(-4-methyl-1-piperidinyl)-1-butanone hydrochloride (active 1) from a 50-mg triple-pressed system, ○; and from a single-pressed tablet, □.

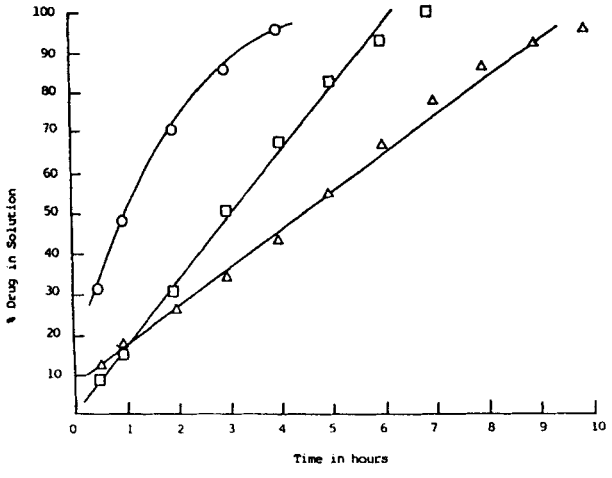

Figure 2. Release of active 1 from core, ○; double-pressed, □; and completed triple-pressed tablet, Δ.

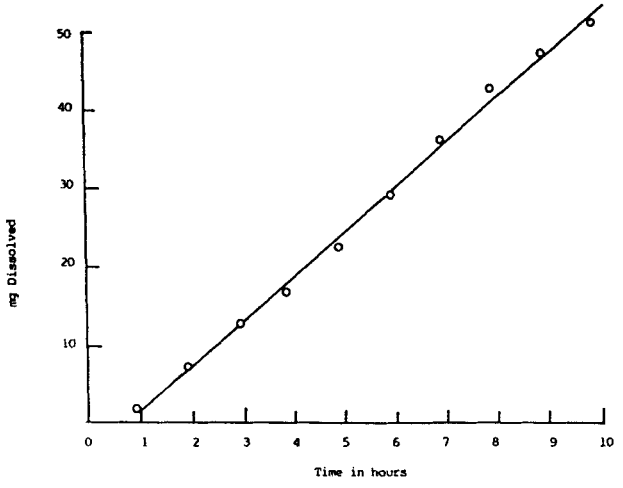

Figure 4. Release of active 1 from a four-phase tablet with outer press coat as placebo.

strates the versatility of the standard triple-pressed formulation which linearizes the release of Dyphylline (50 mg). Figure 8 illustrates release of Dyphylline from a triple-pressed tablet with a placebo second press coat. Figure 9 shows release of Dyphylline from a triple-pressed tablet with placebo first and second press coats. Note the increasing lag time prior to release as consecutive placebo press coats are added, Figs. 8 and 9.

Release of Dyphylline (50 mg) from the comparative formulation (8) is shown in Fig. 10. This profile is reminiscent of standard diffusion controlled formulations.

Volume change of the triple-press-coated gel-type (standard formulation) controlled-release tablet (placebo) is given in Fig. 11. The rate of hydration of the triple-press-coated gel-type (standard formulation) controlled-release tablet (placebo) is given in Fig. 12. Figure 13 depicts the rate of gelation of the triple-pressed-coated gel-type (standard formulation) controlled-release tablets (placebo).

Figures 8 and 9 reestablish the findings of Fig. 4. This is that a placebo coat delays the initial release of active. In Fig. 8, where the second press coat is replaced

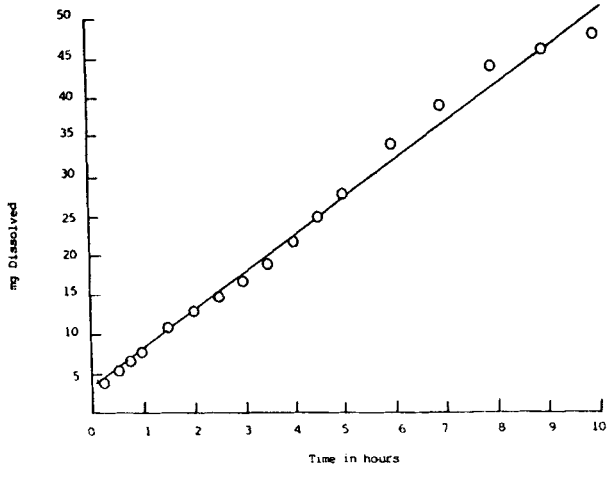

Figure 3. Release of active 1 from a triple-pressed tablet in more detail.

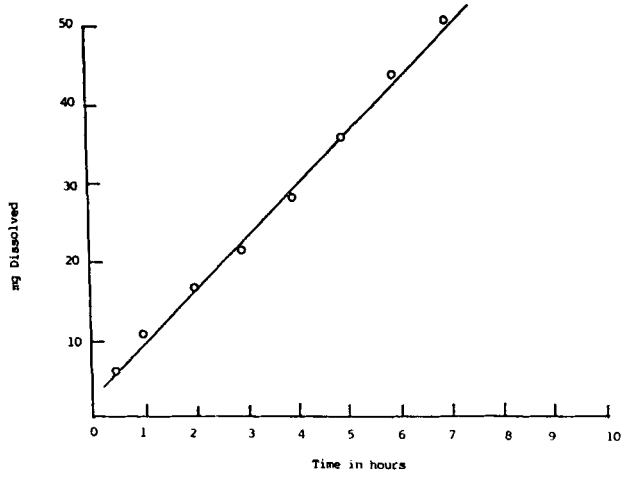

Figure 5. Release of active 1 from a two-phase (double-compressed) tablet. Tablet consists of B (13.64 mg active) pressed over A (36.36 mg active).

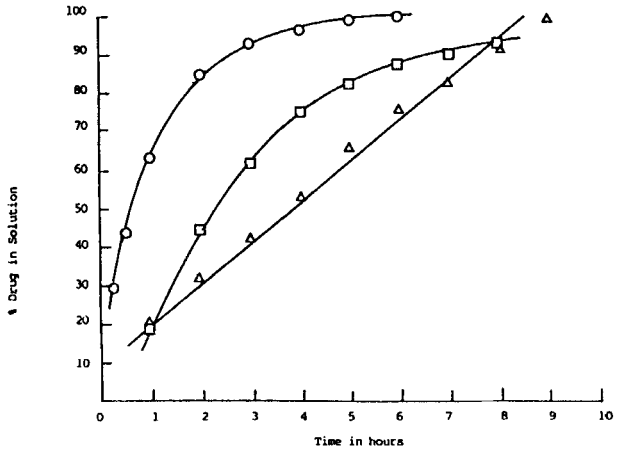

Figure 6. Release of diethylpropion HCl from core, ○; double-pressed, □; and completed triple-pressed tablet, Δ.

by placebo coat (standard formulation without active), it is apparent, after the initial lag time, the remaining amount of active is released in an almost linear manner. In Fig. 9, both the first and second press coats are replaced with placebo. Again, the delay is followed by linear release for most of the remaining amount of active.

There is a suggestion here of saturation kinetics. Once the gel barrier is formed, it may possibly become saturated with active to achieve a "steady-state" situation resulting in apparent zero-order (linear) kinetics.

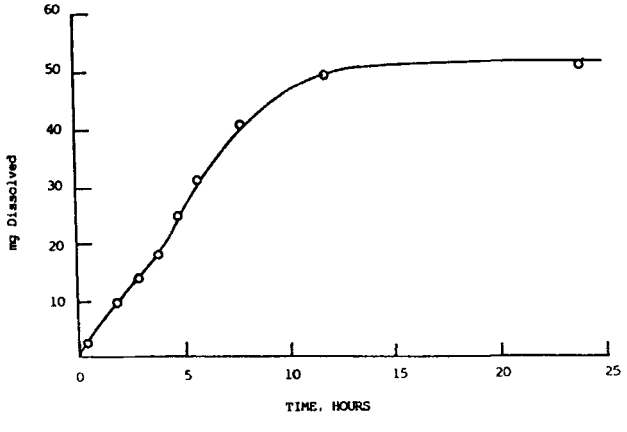

Figure 7. Release of Dyphylline from a triple-pressed tablet.

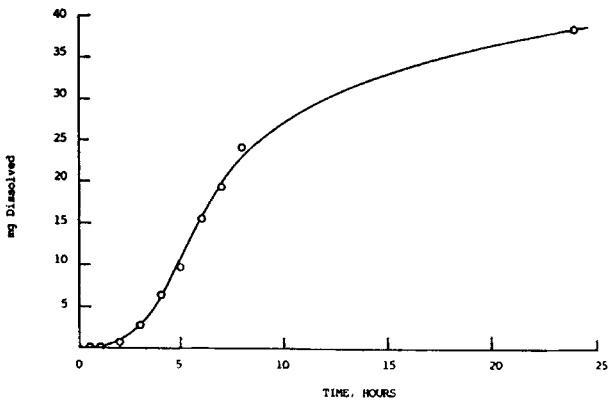

Figure 8. Release of Dyphylline from a triple-pressed tablet with placebo second press coat.

Layer 1:	Layer 2:	Layer 3:
Interior of tablet with higher concentration of drug than gel saturation level.	Gel layer saturated with active.	Dissolution medium

The gel layer, when observed in this way, could be considered a rate-limiting, almost membrane structure, leading to apparent zero-order kinetics. This is not meant to imply that the total mechanism leading zero-order kinetics can be explained in this way. If the mechanism of gel saturation were true in total, ordinary, nongradient, tablet gel types of tablets should release drug by a zero-order process. If one examines the standard triple-pressed for-

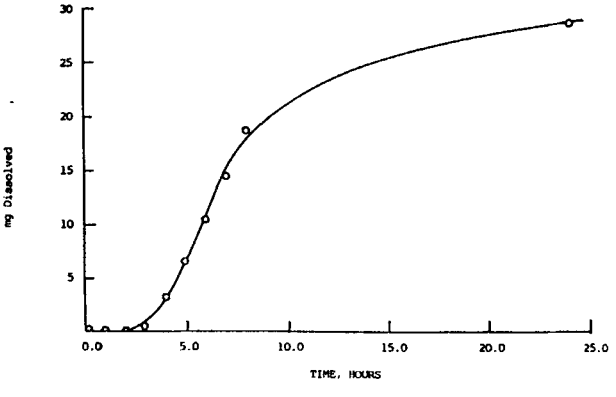

Figure 9. Release of Dyphylline from a triple-pressed tablet with placebo first and second press coats.

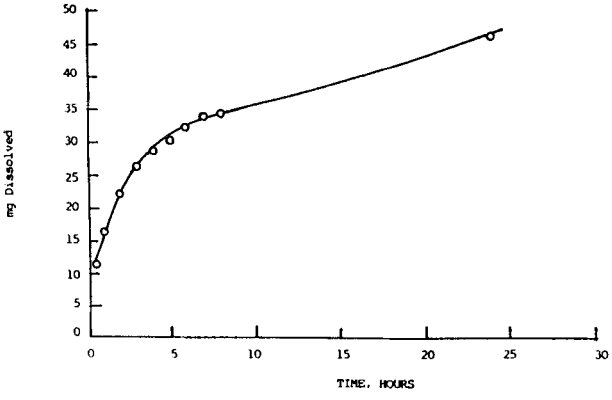

Figure 10. Release of Dyphylline from comparative formulation.

mulation, the second press coat, which represents 250/530 × 100 = 47.2% of the total tablet weight, includes 10.7 mg of active. In a conventional uniform concentration tablet this layer would contain 0.472 × 50 = 23.6 mg of active. The outermost active layer releases drug by a $t^{1/2}$ or Higuchi square root mechanism (1). Examination of the graphs (for example, Fig. 1) shows an initial dumping or high rate of release. By reducing the amount of drug in the second press coat from 23.6 mg to 10.7 mg for a triple-pressed tablet, this dumping effect before gelation is probably minimized. A comparative formulation from the patent literature (8) was tested for release order/profile. Although the patent (8) claims zero-order release, the triple-pressed tablet did not release drug as claimed. It appears that Higuchi kinetics ($t^{1/2}$) apply here. Also implied is that this matrix formulation will not change the order of drug release by redistribution of the drug; i.e., comparative formulation composition.

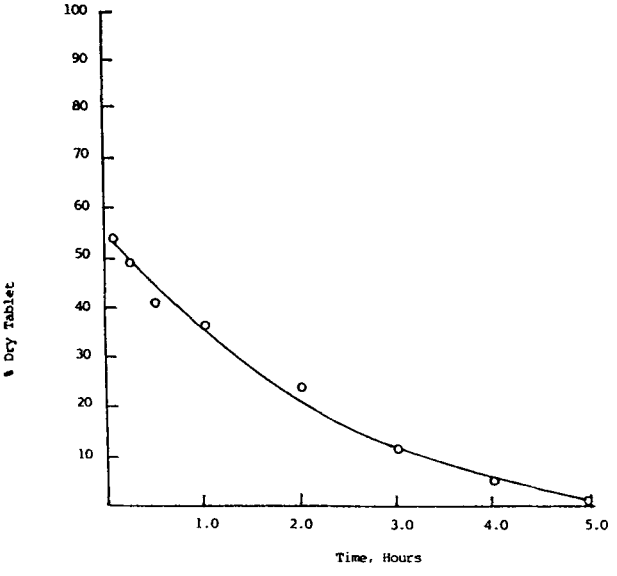

Figure 12. Rate of hydration of triple-press-coated gel-type (standard formulation) controlled-release tablet (placebo).

Figures 11, 12, and 13 illustrate physical changes occurring in the triple-pressed, synthetic gel systems. In Fig. 11 the rapid increase in volume of the tablets immersed in dissolution media is obvious. Figure 12 shows the initially rapid phase of hydration followed by a second, slower phase of hydration. In Fig. 13, gelation is observed as a

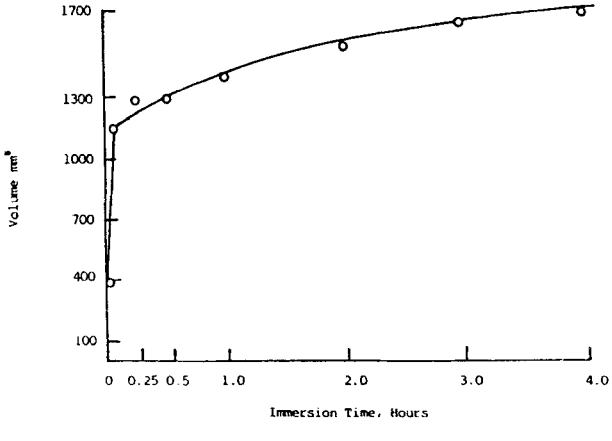

Figure 11. Volume change of triple-press-coated gel-type (standard formulation) controlled-release tablet (placebo).

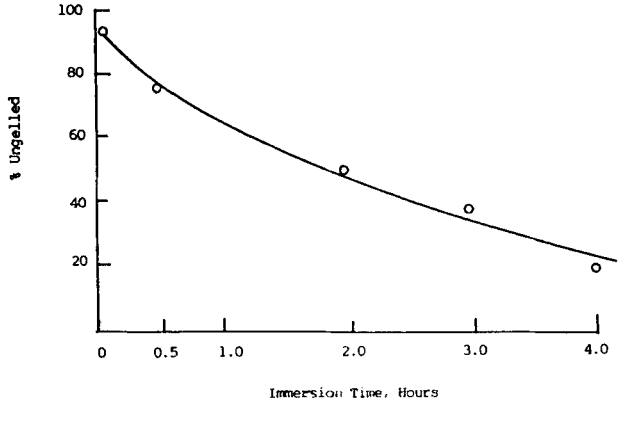

Figure 13. Rate of gelation of triple-press-coated gel-type (standard formulation) controlled-release tablet (placebo).

generally slower process than either hydration or volume increase and hydration, Figs. 11 and 12. This could lead to redistribution of the drug in the system before any significant amount of drug release occurs. The nature of this proposed redistribution of drug might be to enhance the drug distribution expressed by $c = \alpha/r^2$, Eq. (1), and smooth out the discontinuities introduced by the use of $M_l = \Delta r/r_o \times C_o$, Eq. (3).

Controlled swelling can be found in the literature (9). Studies have been reported that use controlled swelling to redistribute drug in a dosage form in order to obtain a desired release. The mechanistic suggestions that have been presented are not aimed at explaining the total mechanistic picture for triple- or double-pressed gradient concentration tablets. They are mentioned so that readers of this article might carry out further studies aimed at disclosing a correct mathematical model for the systems described in this paper.

REFERENCES

1. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).
2. M. Bamba and J. T. Carstensen, Int. J. Pharm., 2, 305 (1979).
3. M. Bamba and J. T. Carstensen, Int. J. Pharm., 3, 87 (1979).
4. M. A. Zoglio and J. T. Carstensen, Int. J. Pharm. Tech. Prod. Mfr., 5(4), 1 (1984).
5. J. T. Carstensen, *Theory of Pharm. Systems. II. Heterogenous Systems,* Academic Press, New York, 1972, p. 285.
6. J. T. Carstensen, *Solid Pharm. Mechanical Properties and Rate Phenomena*, Academic Press, New York, 1981, p. 231.
7. R. L. Juliano, *Drug Delivery Systems, Characteristics and Biomedical Applications,* Oxford Univ. Press, New York, 1980.
8. British Patent 233055, May 26, 1971 (Example 3) (filed June 15, 1967). For copies: Patent Office, 25 Southampton Buildings, London WC2A 1AY.
9. J. R. Robinson and V. H. Lee, *Controlled Drug Delivery*, 2nd ed., Marcel Dekker, New York, 1987.