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COMMUNICATION

The Contributions of Erosion, Swelling, and Porosity to Theophylline Release Kinetics from *Cissus populnea* Polymer Matrices

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ABSTRACT

The variable factors of erosion rate, swelling rate, and porosity were used in studying the release patterns of theophylline from our Cissus populnea *polymer (CPP) matrices under the different factor combinations given by a simple 2^n factorial experimental design. The zero-order slopes and correlation coefficients representing release rate and linearity, respectively, as obtained from both the nonsteady state and steady state were statistically treated. It appears that the nonsteady-state analysis is more suitable for studying the effects of individual factors, while the steady-state analysis appears more suitable for studying interaction effects of the factors. The study also showed that erosion is the main mechanism by which theophylline is released from the matrices, while swelling is responsible for maintaining linearity in the zero-order release curves. A careful examination of the statistical results shows some functional relationships between the factors, which should be considered in designing more detailed factorial experiments to enable the establishment of equation models for predicting the release profile of theophylline from our CPP matrices under any given dissolution condition.*

Key Words: Cissus populnea *polymer matrices; Contributions of factors; Theophylline release kinetics.*

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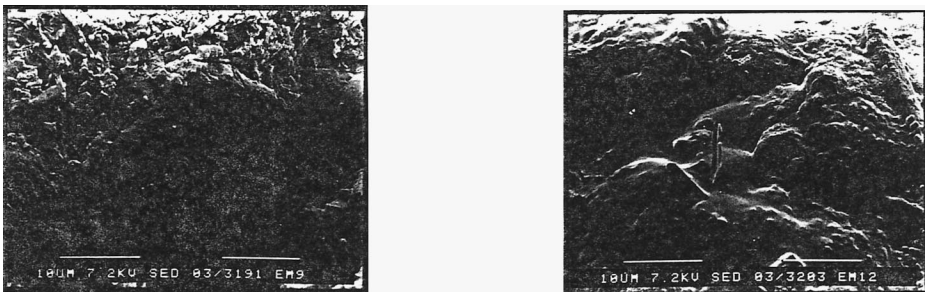


(a) **(b)**

Figure 1. Scanning electron micrographs of the surface of (a) F1, high-porosity matrix, and (b) F2, low-porosity matrix, after 1-hr dissolution test (2500 × 0.65 enlargement).

INTRODUCTION

Drug release kinetics from erodible or swellable polymer matrices are further complicated by the presence of a second moving boundary, namely, the eroding or swelling polymer front (1) in addition to the moving diffusional front. Ganderton (2) also reported the influences of porosity, erosion, and swelling on drug release from matrix devices.

This study investigated the contributions of erosion, swelling, and porosity to the theophylline release profile from novel *Cissus populnea* polymer (CPP) matrices under nonsteady-state and steady-state statistical analyses. Such analyses will give the needed prior knowledge for designing more detailed factorial experiments for the establishment of equation models for predicting drug release from the complex systems of matrices under any given condition. CPP is a polysaccharide hydrocolloid

Table 1

Release Responses from Different Factor Combinations

			Responses	
	Sample	Combination	Release Rate ($\%min^{-1}$)	Correlation Coefficient
Non-steady-state (entire release profile)	1	abc	0.0515	0.9874
	2	Abc	0.0586	0.9882
	3	aBc	0.0403	0.9962
	4	abC	0.0578	0.9821
	5	ABc	0.0849	0.9997
	6	AbC	0.1339	0.9973
	7	ABC	0.0539	0.9989
	8	ABC	0.0769	0.9995
Steady-state phase (linear portion)	1	abc	0.0411	0.9994
	2	Abc	0.0468	0.9999
	3	aBc	0.0362	1.0000
	4	abC	0.0450	1.0000
	5	ABc	0.0830	0.9999
	6	AbC	0.1260	0.9999
	7	ABC	0.0511	0.9999
	8	ABC	0.0752	0.9997

Table 2

Summary of Effects of Factors

		Effect on		Calculated *t*-Value for	
	Factor	Release Rate	Correlation Coefficient	Release Rate	Correlation Coefficient
Non-steady-state	Erosion (*a*,*A*)	0.0378	0.0050	2.600	1.2253
	Swelling (*b*,*B*)	−0.0115	0.0098	0.599	3.4930
	Porosity (*c*,*C*)	0.0218	0.0016	1.198	0.3534
Steady state phase	Erosion (*a*,*A*)	0.0394	0.00003	2.7266	0.1517
	Swelling (*b*,*B*)	−0.0034	0.00008	0.1675	0.6202
	Porosity (*c*,*C*)	0.0226	0.00008	1.2226	0.6187

Critical *t*-value (at $\phi = n_1 + n_2 - 2 = 6$ and $P = 5\%$) = 2.45.

obtained from the stem bark of *Cissus populnea* of the family Amplidaceae (Vitaceae). Ibrahim et al. (3), in pharmacognostic studies, reported that the polymer consists of D-glucuronic acid and the sugars galactose and xylose.

EXPERIMENTAL

Materials

The materials used were CPP (as extracted with an IMS-acetone mixture), lactose (Whey Products, Ltd., DairyCrest, Surrey, England), theophylline anhydrous (Sigma Chemical Co., St. Louis, MO), magnesium stearate (Boots Co., Ltd., industrial methylated spirit, Nottingham, England), IMS (Hays, Ltd., London, England), acetone, potassium dihydrogen orthophosphate, and disodium hydrogen orthophosphate (BDH, Poole, England).

Methods

Preparation of Tablets

Granules were prepared by the wet granulation method using a number 40 sieve (420 μm). The granules were then mixed with the desired quantity of magnesium stearate and compressed at 2 tons on an RIIC manual single-punch tableting machine (Research and Industry Instruments Company, England). Two types of tablets were prepared, one having 25% w/w lactose (F1: ''high'' porosity, i.e., C) and the other having no lactose (F2: ''low'' porosity, i.e., c) (Fig. 1).

Erosion Studies

Six individually weighed tablets were put into six vessels of a USP paddle dissolution apparatus (Copley Instruments, Ltd., Nottingham, England); at 1-hr intervals,

Table 3

Summary of Effect of Interactions Between Factors

		Difference Being Tested		Calculated *t* Value for	
	Interaction	Release Rate	Correlation Coefficient	Release Rate	Correlation Coefficient
Non-steady-state phase	Erosion and swelling	−0.0039	−0.0030	−0.202	0.6897
	Swelling and porosity	−0.0190	−0.0003	−1.056	0.0671
	Erosion and porosity	0.0119	0.0029	0.620	0.6654
Steady-state phase	Erosion and swelling	−0.0040	−0.00018	0.1958	1.5437
	Swelling and porosity	−0.0190	−0.00023	1.0048	2.095
	Erosion and porosity	0.0132	−0.00018	0.6737	1.5437

Critical *t* value (at $\phi = n_1 + n_2 - 2 = 6$ and $p = 5\%$) = 2.45.

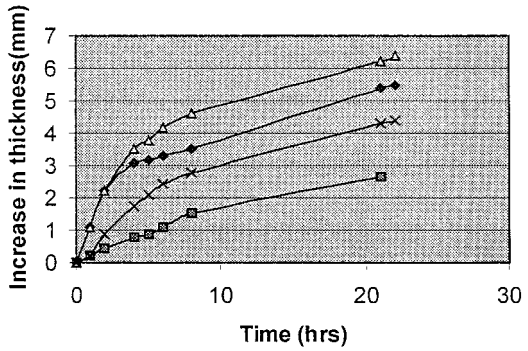


Figure 2. Increase in tablet thickness with time as a function of immersion medium, showing the conditions for ''high'' and ''low'' swelling intensities. ◆, F1 in D/water; ■, F1 in pH 7.2 medium; △, F2 in D/water; ×, F2 in pH 7.2 medium.

1 tablet was removed, weighed, and dried to constant weight. The difference between the dried, eroded tablet and its initial weight represents the erosion. The study was conducted using 50 rpm (''low'' erosion, i.e., a) and 100 rpm (''high'' erosion, i.e., A).

Swelling Studies

The thicknesses of the tablets were measured using calipers. The tablets were then placed on a stage in either pH 7.2 buffer solution (''low'' swelling rate, i.e., b) or distilled water (''high'' swelling rate, i.e., B). The increase in thickness of each tablet was followed with time and represents the swelling. The following eight-factor combinations, as given by a simple 2^3 factorial design, were used for the dissolution studies: abc, Abc, aBc, abC, ABc, AbC, aBC, and ABC. The results are shown in Table 1 for both the nonsteady and steady states.

Dissolution Tests

Theophylline release from each of the eight factor combinations was studied using a calibrated computer-automated dissolution system.

RESULTS AND DISCUSSION

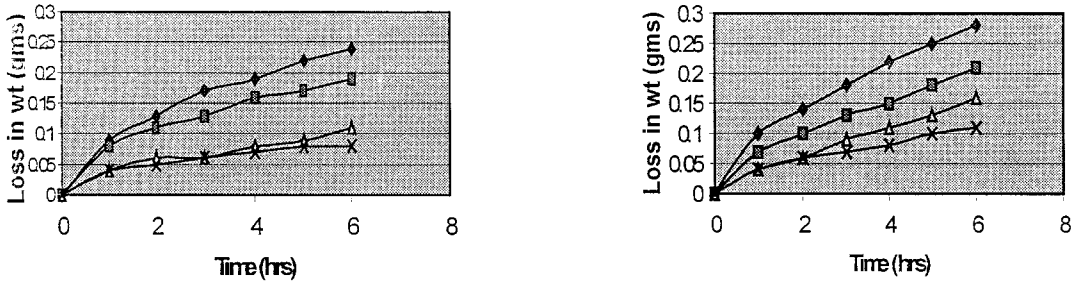
Contributions of Factors

From Table 2, it can be seen that, in both nonsteady and steady states, increasing either erosion or porosity increases the theophylline release rate, due most likely to increased exposed surface area. On the other hand, increasing the swelling rate decreased the release rate, presumably due to the development of a viscous gel barrier.

In the nonsteady-state analysis (Table 2), two factors showed significant influences: the influence of erosion on release rate (calculated $t = 2.6 >$ tabulated $t = 2.45$) and the influence of swelling on linearity (i.e., correlation coefficient [calculated $t = 3.49 >$ tabulated $t = 2.45$]). When considering only the steady-state phase, the influence of swelling on linearity was no longer significant (calculated $t = 0.62 <$ tabulated $t = 2.45$), as shown in Table 2. The influence of erosion on release rate became the only significant factor. The nonsteady-state analysis may therefore be more sensitive for studying the effects of the individual factors.

Contributions of Interactions of Factors

Table 3 shows that none of the interactions was significant in both nonsteady and steady states. However, Figs. 2 and 3 show that an increase in porosity reduced



(a) **(b)**

Figure 3. Weight loss of tablets as a result of erosion with time at (a) 50 rpm and (b) 100 rpm, showing the conditions for low and high erosion using the paddle method at 37°C. ◆, F1 in D/water; ■, F1 in pH 7.2 medium; △, F2 in D/water; ×, F2 in pH 7.2 medium.

swelling (F1 swells less than F2), but increased erosion (F1 loses more weight than F2). The higher *t* values in the steady-state analysis could be an indication that the steady state is more suitable for studying the effects of interactions of the factors. It appears that if wider differences between the low and high levels of the factors are used, significant interactions might be observed for the steady-state analysis.

A more detailed factorial design, such as that described by Bolton (5), should take into consideration these functional relationships to enable the establishment of equation models based on additive and/or multiplicative interactions of factors for predicting theophylline release profiles from our CPP matrices under any given dissolution conditions.

CONCLUSIONS

Erosion is the main mechanism by which theophylline is released from CPP matrices, while swelling is responsible for imparting linearity to the release profile. Some functional relationships appear to exist among erosion, swelling, and porosity. The nonsteady-state analysis appears more suitable for studying the individual effects of these factors, while the steady-state analysis looks more suitable for studying their interaction effects.

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