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EFFECTS OF COMPRESSION FORCE AND TYPE OF FILLERS ON RELEASE OF DICLOFENAC SODIUM FROM MATRIX TABLETS

Narong Sarisuta and Pilawan Mahahpunt*

Department of Manufacturing Pharmacy
Faculty of Pharmacy, Mahidol University
Bangkok, Thailand

*Jawa Manufacturing Ltd., Bangkok, Thailand

ABSTRACT

The influence of compression force and type of fillers on the release pattern of diclofenac sodium from wet-granulated tablet matrices containing Emcompress and lactose as fillers with Eudragit RSPM as a matrix additive was determined. The release pattern of diclofenac sodium from these matrices in USP phosphate buffer pH 7.2 at 37 °C were found to be independent of compression forces whereas the ratios of insoluble (Emcompress) to soluble filler (lactose) appeared to greatly influence the drug release rate as evidenced in the increased release rate with decreasing Emcompress content. The kinetics of drug release was determined and found to precisely comform to the Higuchi's planar matrix model. A theoretical approach to predict the drug release rate from a designed system was presented and found to be satisfactorily predictive.

INTRODUCTION

Although the factors influencing release of solid drug dispersed in inert matrices have been thoroughly investigated in numerous publications [1-10], very limited number was done upon effects of some process variables such as compression force, additive ratios in the matrix, etc. The drug release rates from elastic matrices such as polyvinyl chloride were found to be independent of the compression forces which was attributed to its constancy of porosity within the matrix.[3] Similar results were obtained in the case of compressed hydrophilic matrix, *i.e.*, hydroxypropylcellulose, which was rationalized on the basis that the release rate is governed by the swellable gel surrounding the tablet instead of its porosity.[7] Cameron and McGinity [9] have currently reported that compaction pressure as well as tablet hardness played minimal role within the range of 6.8-15 kg on release rate of theophylline from tablets containing a combination of cationic (Eudragit RSPM) and anionic (Eudragit L100) acrylic resins. Another report recently proposed by Martinez-Pacheco *et al.* [11, 12], however, revealed that the dissolution rate of cephalexin from double-layer tablets containing various proportions of Eudragit E or RS was significantly affected by compression pressure.

In this study the release patterns of diclofenac sodium tablet matrices prepared by wet granulation with various additive ratios and compressed at 3 different forces were examined. Other properties such as porosity, solubility, and diffusion coefficient were also determined.

MATERIALS

Diclofenac sodium was obtained from Chemische Fabrik Schweizerhall, Italy. Eudragit RSPM and lactose were from Rohm Pharma and Meggle, Germany, repectively. Unmilled dibasic calcium phosphate dihydrate (Emcompress), Edward Mendell, U.S.A. Magnesium stearate and talcum were from Volovskoya, Yugoslavia. Ethanol absolute and potassium dihydrogen phos-

TABLE 1. The Formulations of Diclofenac Sodium Matrix Tablets at Various Ratios of Emcompress to Lactose

Compositions (mg)	Ratios of Emcompress to Lactose				
	1:0	8:2	1:1	2:8	0:1
Diclofenac sodium	100.0	100.0	100.0	100.0	100.0
Eudragit RSPM	30.0	30.0	30.0	30.0	30.0
Emcompress	162.5	130.0	81.25	32.5	-
Lactose	-	32.5	81.25	130.0	162.5
Talcum	4.5	4.5	4.5	4.5	4.5
Magnesium stearate	3.0	3.0	3.0	3.0	3.0

phate were from E. Merck and Riedel-De Haen Ag Seelze, Germany, respectively. Benzoic acid, BDH Chemicals Ltd., England.

METHODS

Preparation of Tablet Matrix: Tablets containing 100 mg diclofenac sodium were prepared by means of wet granulation with compositions presented in TABLE 1. The fractions of drug, lactose, and Emcompress that passed through a 60-mesh sieve were mixed with Eudragit RSPM in a planetary mixer (Kitchen Aid Model K5SS, U.S.A.) for 5 min and wet granulated with 95 % w/w ethanol. The wet mass was passed through a 18-mesh sieve and dried at 60 °C for 8 hr in a tray dryer (Kan Model HA-40). The dried granulation was then rescreened through 20-mesh sieve, mixed with talcum and magnesium stearate for 5 min in tumbling mixer(Rotomixer,

U.K.) and compressed into flat-faced tablets having a diameter of 8.0 mm and a weight of 300 mg. The compressions were made at 3 different upper punch forces, *i.e.*, 300, 450, and 600 kg using instrumented single punch tablet press (Diaf Model TM 206, Denmark) equipped with dynamic strain amplifier (Kyowa Model DPM-612A, Japan), preamplifiers (Gould Model 210-310031-1, U.S.A.), and strip chart recorder (Gould Model SC27X, U.S.A.).

Studies of Drug Release from Tablet Matrix: A USP XXII dissolution test apparatus 2 (Hanson Model QC72RB,U.S.A.) was used to examine the release characteristics of diclofenac sodium matrix tablets. The paddle was immersed in 1,000 ml of USP phosphate buffer pH 7.2 being maintained at 37 ± 0.5 °C and the rotating speed was 50 ± 1 rpm. The withdrawn samples were analyzed spectrophotometrically for diclofenac sodium at 276 nm.

Determination of Tablet Porosity: From knowledge of tablet volumes and compositions, along with densities of drug and matrix material, calculation of maximum possible porosity during release of drug contributed by air, soluble excipients, and the drug itself was carried out. The tablet dimensions were determined with a micrometer, and the true density of each component was determined with pycnometer.

In another method for estimating porosities the tablets were completely leached of the solute by dissolution medium at 37 °C for 8 hr, and consequently dried and weighed. The weight loss was conferred to the weight of dissolved drug and lactose. The amount of drug dissolved at 8-hr interval was analyzed spectrophotometrically at 276 nm. The amount of lactose dissolved at 8 hr could be determined from the difference between weight loss of leached tablet and the amount of drug dissolved out. The void volume occupied by drug and lactose particles could be easily deduced from the true density of each component.

Determinations of Diffusion Coefficient and Solubility: The details of the diffusion cell used have been described previously.[13] The diffusion coefficient and solubility of diclofenac sodium in phosphate buffer pH 7.2 at 37 °C were determined as reported earlier.[14]

RESULTS AND DISCUSSION

Effect of Compression Force: The release of diclofenac sodium in USP phosphate buffer pH 7.2 from matrices containing Emcompress and lactose at various ratios and compressed at 3 different forces (600, 450, and 300 kg) are plotted against $t^{1/2}$ and shown graphically in FIGURE 1 for the ratio of 8:2. It obviously shows the applicability of Higuchi's matrix model to the systems studied with the correlation coefficients of more than 0.997 for all filler ratios and compression forces. All formulations exhibit retardation ability of release up to 8 hours at various degrees depending on filler compositions. In contrast, tablet compression forces were shown to have minimal effect on release characteristics at every filler ratio. Release curves nearly fall on the same line, indicating that compression pressure as well as tablet hardness are not important factors in modifying the release pattern of the drug from this type of matrix within the range of 300-600 kg forces and 4-10 kg tablet hardnesses. These results are in accords with those previously reported by Cameron and McGinity [9], which was explained that as the compaction force was increased up to a certain critical limit, the compact mass would elastically deform so that the porosity fell to a minimal value and remained constant thereafter.

For the discussing case, it is valid to assume that variation in compression forces should be closely related to a minor change in air porosity of tablet as illustrated in TABLE 2. The volume of air is expectedly decreased with increased compression forces but to a small degree in terms of percentage contributed to total void volume. This pos-

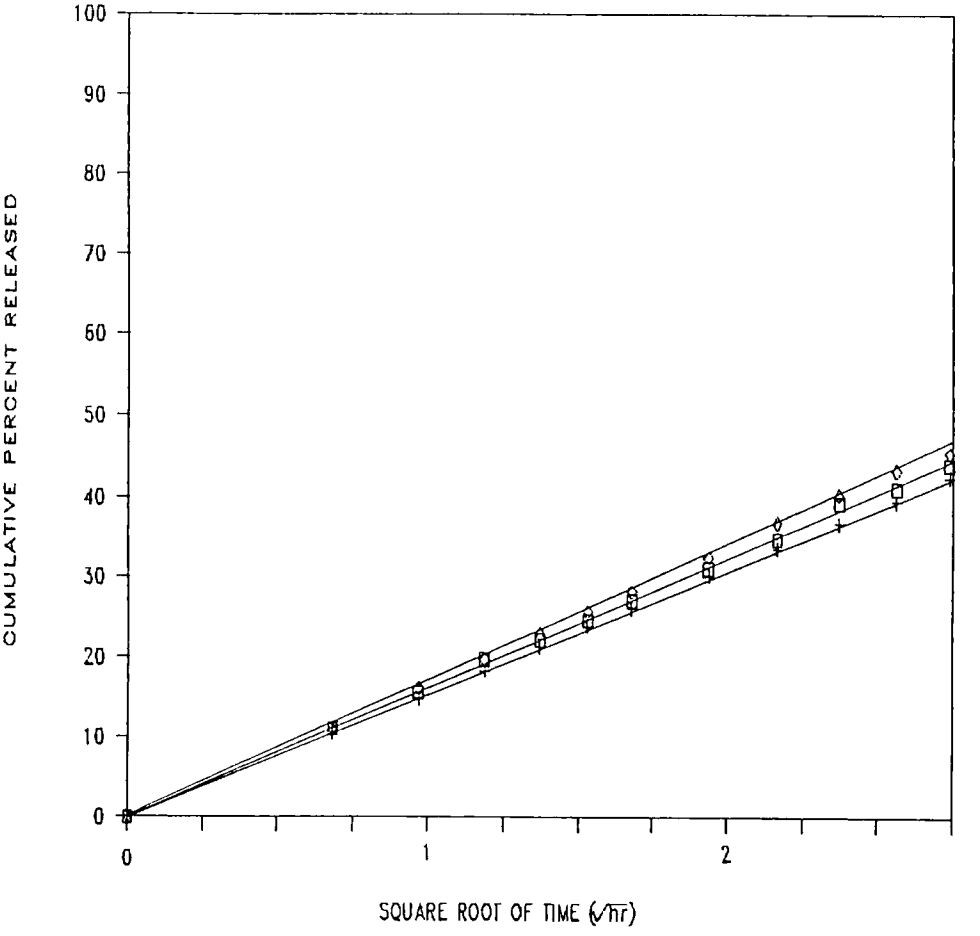

FIGURE 1

Plots of diclofenac sodium release against square root of time for tablets with Encompress to lactose ratio of 8:2 at compression forces of: □ , 600 kg; + , 450 kg; ◇ , 300 kg (average from 6 tablets).

TABLE 2. Percentage of Volume of Air Contributed to Total Void Volume of Diclofenac Sodium Tablets at Different Compression Forces

E:L Ratio	600 kg Force			450 kg Force			300 kg Force		
	vol. of air (ml)	% of vol. of air	tablet porosity	vol. of air (ml)	% of vol. of air	tablet porosity	vol. of air (ml)	% of vol. of air	tablet porosity
0:1	0.0377	18.22	0.8961	0.0441	20.77	0.8988	0.0542	24.10	0.9025
2:8	0.0347	18.82	0.8291	0.0433	22.52	0.8354	0.0499	25.36	0.8407
1:1	0.0236	16.58	0.7083	0.0337	22.14	0.7220	0.0513	30.09	0.7429
8:2	0.0237	21.49	0.5848	0.0274	23.87	0.5924	0.0351	28.89	0.6090
1:0	0.0243	26.24	0.4947	0.0317	31.99	0.5151	0.0321	32.46	0.5170

tulate is numerically supported by invariation in porosity of tablets when the compression force is increased as shown in TABLE 2. Such behavior is thought to be specifically associated with their nature of compaction especially when brittle fracture taking place. This, however, contrasts with the results of the other previous study by Martinez-Pacheco *et al.*[12] as already mentioned.

Effect of Filler Ratios: Since it is likely to assume that the insoluble network structure in tablets formed by Encompress and Eudragit RSPM remained intact during solvent leaching, the soluble portion consisted of diclofenac sodium and lactose would solely determine the void space in

the depletion zone. This ratio of insoluble to soluble fillers would be directly related to porosity term in Higuchi's equation. The Higuchi's plots of diclofenac sodium released from tablets with various ratios of Emcompress to lactose at 600 kg compression forces are shown in FIGURE 2 with correlation coefficients of more than 0.997. Slopes of these Q *versus* $t^{1/2}$ plots were found to decrease by the same factor as the decrease in square root of porosity as the ratios of Emcompress were increased regardless of compression forces applied.

Theoretical Prediction of Release Rate: Close examination of Higuchi's equation would suggest that the most likely term to be significantly affected by filler types and compositions as well as compression forces is porosity of the matrix. Careful consideration involving volumes occupied by all soluble and insoluble ingredients in matrix would provide transformation of porosity term into their mass fractions *via* Eq. 1

$$\epsilon = \left[(\rho_l x_d + \rho_d x_l)/\rho_l \rho_d\right]\rho_{tab} \qquad (1)$$

where ρ_l, ρ_d, and ρ_{tab} are the densities of soluble filler, active drug, and tablet, x_d and x_l are the mass fractions of drug and soluble filler, respectively.

This situation is valid only if the soluble part of excipients dissolves and diffuses out faster than the diffusion of drug molecules from matrix, producing specific porosity and tortuosity in the depletion zone. This has been verified by leaching diclofenac sodium tablets in dissolution medium at 37 °C for 8 hr as already described under the determination of porosity. The amount of dissolved drug and lactose are shown in TABLE 3 which indicate much more rapid release of lactose from matrix when compared with that of diclofenac sodium. After 8 hr of leaching,

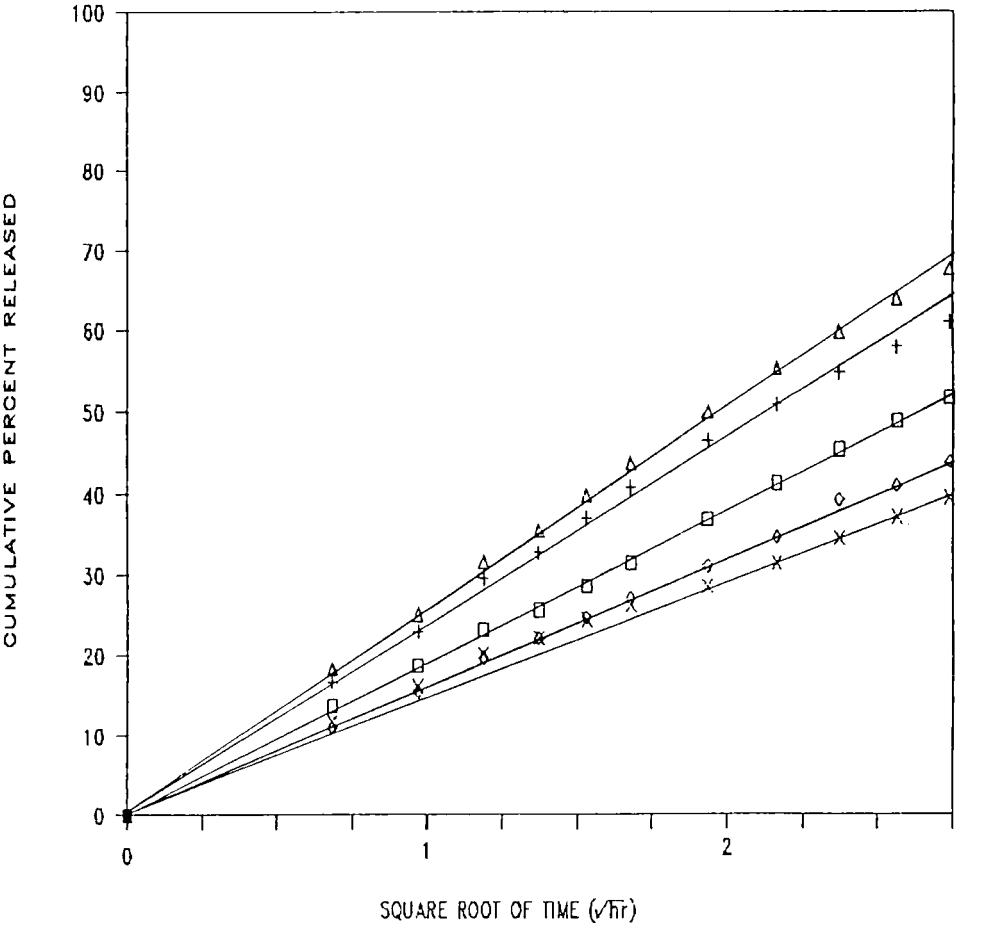

FIGURE 2

Plots of diclofenac sodium release against square root of time for tablets compressed at compression force of 600 kg with Encompress to lactose ratios of: △, 0:1 ; +, 2:8 ; □, 1:1 ; ◇, 8:2 ; ×, 1:0 (average from 6 tablets).

TABLE 3. Percentage of Diclofenac Sodium and Lactose Released from Tablets in Phosphate Buffer pH 7.2 after 8 hr, and Porosity Values for Tablets with Various Ratios of Encompress to Lactose at Three Different Compression Forces Determined by Physical Measurement and Calculated from Equation 1

E:L Ratio	Compression Force (kg)	Percent of[a] Drug Released(SD)	Percent of[a] Lactose Released(SD)	Porosity by[a] Physical Measurement	Porosity by Calculation
0:1	600	54.79(1.49)	91.79(0.38)	0.8961	0.8831
	450	57.08(2.13)	93.53(0.69)	0.8988	
	300	54.40(0.72)	92.34(0.79)	0.9025	
2:8	600	51.10(3.16)	91.19(3.91)	0.8291	0.8186
	450	51.52(1.30)	97.23(0.30)	0.8354	
	300	51.81(1.96)	95.10(2.96)	0.8407	
1:1	600	39.65(0.57)	88.17(2.90)	0.7083	0.6982
	450	40.38(1.33)	91.45(1.45)	0.7220	
	300	41.55(1.10)	92.17(1.99)	0.7429	
8:2	600	32.23(0.23)	98.62(1.00)	0.5848	0.5495
	450	31.16(1.21)	97.71(3.68)	0.5924	
	300	34.96(1.04)	100.00(0.00)	0.6090	
1:0	600	27.47(0.39)	-	0.4947	0.4346
	450	31.59(0.23)	-	0.5151	
	300	27.20(0.97)	-	0.5170	

[a] Average of three determinations

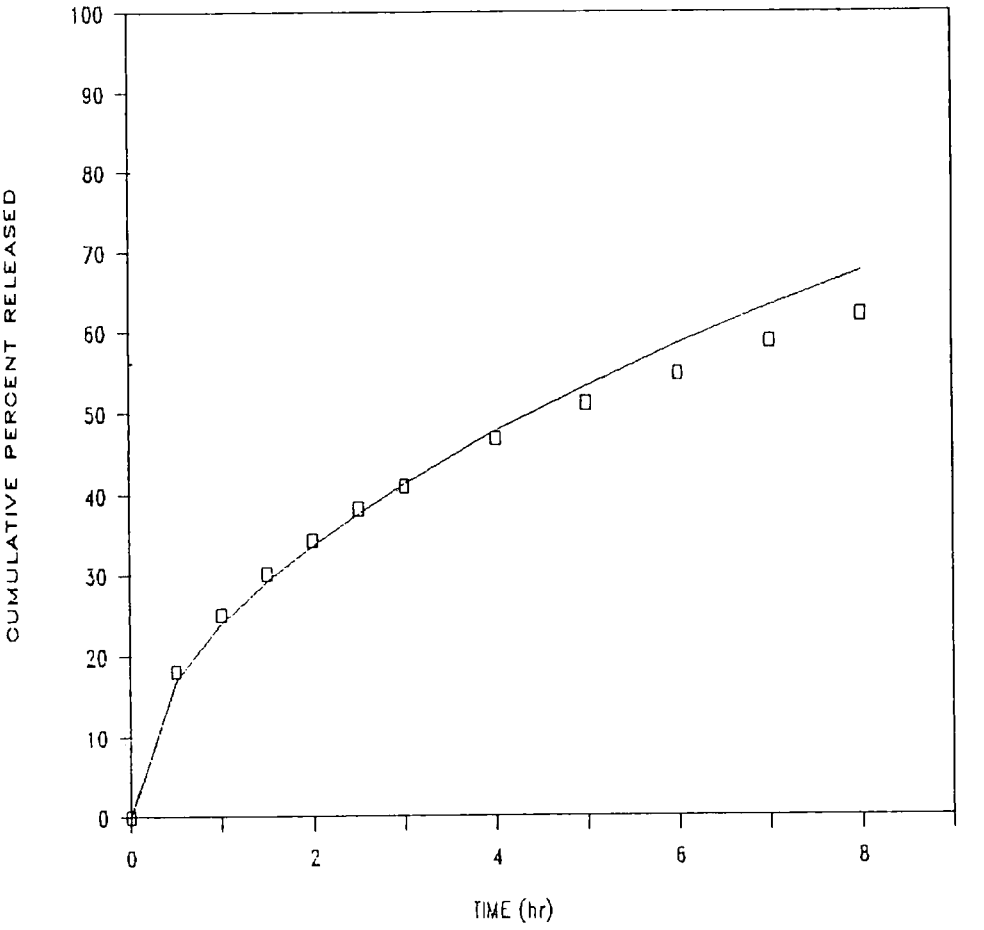

FIGURE 3

Comparisons between the observed release rate of diclofenac sodium tablets with 2:8 ratio of Emcompress to lactose at 450 kg compression force in phosphate buffer pH 7.2 and the calculated values represented by the solid line.

almost all of lactose in formulation (more than 90 %) was released where as considerable amount of drug still remained within the matrix.

By using Eq. 1 with substitution of suitable mass fraction of soluble filler in the matrix, porosity value required to yield the desired drug release rate *via* Higuchi's equation may be obtained, provided the densities of soluble filler, drug, and tablet are known. The density of tablet may be estimated by using the weighed average basis of the true density of each ingredient in the tablet matrix. Values of porosity calculated by this means along with those determined by physical measurement for various filler ratios and compression forces in the case studied are also tabulated in TABLE 3. It is, however , important to emphasize that these calculated magnitudes of porosity are merely the estimate values since they do not include the porosity occupied by air. As a matter of fact, it is not possible to know the air porosity without performing the direct physical measurements of tablet. Therefore, the calculated values minimally differ from those obtained by direct physical measurements.

The predicted amount of diclofenac sodium released from tablet matrices for Emcompress to lactose ratio of 2:8 at 450 kg compression forces calculated in this manner at all time intervals are shown along with the experimental values in FIGURE 3. The comparisons show good agreement between the calculated and the observed values so that this theoretical approach seems to be satisfactorily predictive and valid in designing and manufacturing the controlled release drug delivery using inert matrix system.

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