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FACTORIAL DESIGN OF PHENYLPROPANOLAMINE PROLONGED RELEASE TABLETS FORMULATIONS USING FLUID BED DRYER GRANULATOR

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ABSTRACT

A two level factorial design approach was applied to the formulation of prolonged release phenylpropanolamine tablets using three factors: Ethylacrylate-methyl methacrylate co-polymer (Eudragit NE-40D) concentration, Microcrystalline cellulose (Avicel PH102) addition to the tablets formula, and the milling of the granulations before compression. The release rate of the drug was the measured parameter. The rate of drug release was mainly affected by the level of the Eudragit. Avicel promotes the release of the drug, specially at low Eudragit level concentrations. Tablets prepared from unmilled lots showed slower drug release than the corresponding lots of milled granules.

INTRODUCTION

The extended or sustained release of phenylpropanolamine hydrochloride (PPA) was described in several publications (1-6). In these trials, waxes (1), ion exchange resin complexes (2) or microencapsulation techniques (3-6) were applied. They require long processing time and/or solvent exposure. The use of water based film forming dispersions is recommended for environmental concerns and safety measures. The neutral co-polymer of ethyl acrylate - methylmethacrylate esters is available in the market as an aqueous 40% dispersion: Eudragit NE-40D; having an advantage of being neutral and insoluble in the entire physiological pH range (7). The potential possibility of using this polymer with the highly water soluble PPA to prepare sustained release tablets was studied. Factorial design approach was applied to determine other factors such as the incorporation of microcrystalline cellulose in the final tablet formulation and the effect of milling the granules before compression.

EXPERIMENTS

Materials:

Phenylpropanolamine Hydrochloride, Nepera, Harriman, NY.
Eudragit NE-40D, 40% solids, Rhom Pharma.
Microcrystalline Cellulose, Avicel PH102, FMC.
Dibasic Calcium Phosphate Dihydrate, Emcompress, E.Mendell, NY.
Magnesium Stearate, Mallinckrodt.

Equipment:

Fitzmill, model D, 2A screen.
Planetary mixer, Hobart AMF 10 liter mixer.
Fluid Bed Dryer Granulator, Glatt GPCG-5.
Rotary Tablet Press, Manesty Beta Press, 16 stations, 11/31 inch diameter tooling, deep cup punches.

automatic weighing balance. Schleuniger Hardness Tester. Roche Friabilator Vander Kamp. USP disintegration tester, Vander Kamp bath UL 1112 USP dissolution tester, apparatus 2, equipped with an automatic Diode Array UV spectrophotometric analyzer.

Primary Granulation:

The following formula was used to prepare the primary granules for all the lots.

Phenylpropanolamine HCl	100 mg	5.00 kg
Avicel PH102	20 mg	1.00 kg
Emcompress	10 mg	0.50 kg
Eudragit NE-40D	10 mg*	1.25 kg**
	140 mg	7.00 kg

* Solids content.
** Dispersion weight, equivalent to 0.5 kg solids.

The active ingredient was first milled through Fitzmill with 2A screen at high speed, knives forward. The weighed powders were mixed in the Hobart mixer. Eudragit dispersion was first diluted with 500 ml of purified water and mixed with the other ingredients to form a moist mass. That mass was passed through a #12 mesh screen and transferred to the Fluid Bed Dryer. Drying of the fluidized granules was carried out at inlet air temperature 40°C, until the residual moisture (LOD) is 1 $\pm$ 0.3 %.

Granules Coating:

The Eudragit dispersion was weighed and diluted with purified water to bring its solid content to 30%. The diluted dispersion was sprayed through a 1.2 mm diameter nozzle, at a spray rate of 40 ml per minute and inlet air temperature of 30°C. The amount of Eudragit dispersion was calculated for each lot to add 10, 30 or 50% of the solid co-polymer to the granules.

Tablet Compression:

Two sub-lots were prepared from each coated lot: one was blended with 22.5% w/w Avicel for 5 minutes and then was lubricated with 1% w/w magnesium stearate before compression; the other was blended with 1% w/w magnesium stearate for 5 minutes before compression. The tablets lot size was 2 kg each. A 1.8 cu.ft Tote blender was used at 17 rpm speed. The blends were compressed by the rotary tablet press to produce biconvex bevelled tablets, each containing 100±3 mg of PPA.

Granules Evaluation:

Moisture content was determined by loss on drying, using the Computrac at 110°C. Samples of the granules were tested for size distribution, using 100 g samples vibrated over a nest of US standard sieves. The tapped density was checked by using the Vander Kamp tester. The compressibility index was calculated from the relative decrease in bulk density upon tapping.

Tablets Evaluation:

Weight uniformity, thickness and crushing strength were measured during the compression cycle to insure consistent performance. Twenty tablets were used to calculate the Relative Standard Deviation (RSD) for weight and thickness. Ten were tested for the crushing strength using the Schleuniger tester. Friability was carried out on twenty tablets using the friabilator for 4 minutes rotating 25 rpm. Disintegration results were average of 6 tablets. Dissolution rate was tested in the USP paddle dissolution tester, revolving at 50 rpm, 500 ml medium at 37°C. Aliquots were analyzed for PPA content spectrophotometrically at 256 nm. Three dissolution media were tried separately: Hydrochloric acid 0.1 M, purified water, and phosphate buffer of pH 7.5 .

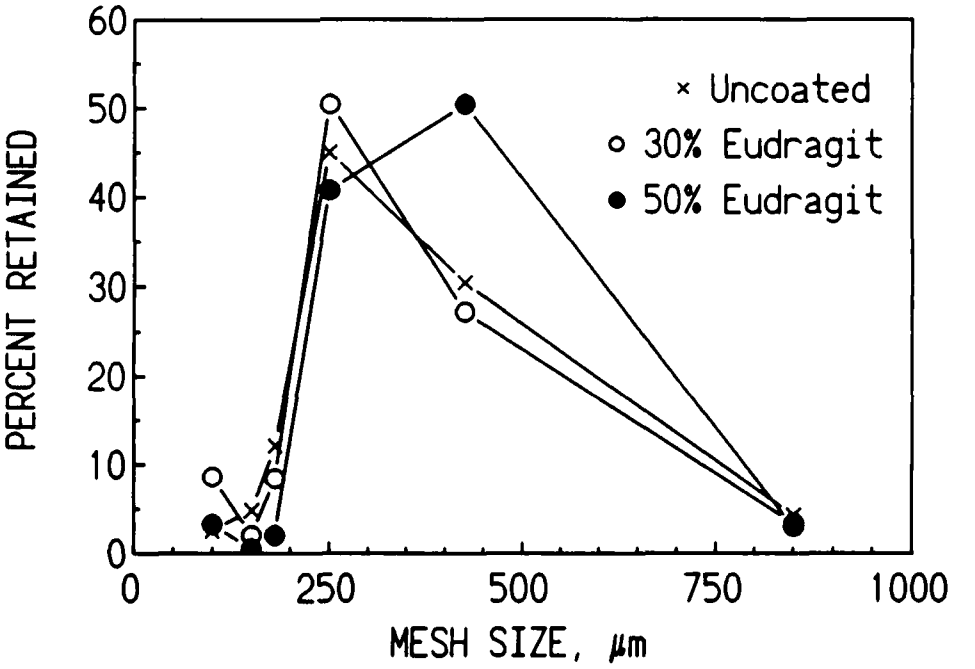

FIGURE 1
Particle Size Distribution of Coated
Phenylpropanolamine Granules

RESULTS and DISCUSSION

Primary granulation had to be performed in a Hobart type mixer to guard against the loss of finely powdered ingredients during fluidization. Segregation because of the density differences was also avoided. Trial of other mixers granulators such as the Gral granulator, resulted in tackiness to the walls and a nonhomogeneous mass. Avicel was added to the formulation to minimize such tackiness. Eudragit dispersion was chosen as a granulating fluid in order to minimize the factors involved in the study. Fluid bed technique was used to dry the granules and for spray coating at the same equipment. Coating

TABLE 1

Compressibility Index, Bulk and Tapped Densities of Phenylpropanolamine HCl and its Blended Granules

Sample	Bulk Density* g/ml	Tapped Density g/ml	Compress. Index* %
Raw Material	0.6814	0.4315	36.7
Primary Granules	0.5182	0.4281	17.4
Lots with 30% Eudragit coating:			
Unmilled, with Avicel	0.5829	0.4948	15.11
Milled, with Avicel	0.6163	0.5233	15.09
Milled, without Avicel	0.5810	0.4910	15.49
Lots with 50% Eudragit coating:			
Unmilled, with Avicel	0.5770	0.4994	13.45
Unmilled, without Avicel	0.5575	0.4780	14.26
Milled, with Avicel	0.6226	0.5338	14.26
Milled, without Avicel	0.6210	0.5321	14.32

* Average of three tests.

results in an increase in particle size of the granules as shown in Fig.1.

The compressibility index was lower for the coated granules (Table 1), indicating better flow properties.

All compressed tablets were of good uniformity (Table 2). The weight and thickness values for relative standard deviation (RSD) did not exceed 2%; indicating good uniformity of the blends. The mechanical strength of the tablets, monitored by the hardness and friability values in Table 2, is much higher for tablets with Avicel.

TABLE 2

Physical Properties of Phenylpropanolamine Tablets

Eudragit %	Weight*±RSD mg	Thickness* in	Hardness Kp	Friab. %loss
Formulations With Avicel:				
30%, Unmilled	222.5±0.75	0.174	7.13±0.73	0.42
30%, Milled	220.8±1.07	0.168	5.35±0.38	0.65
50%, Unmilled	256.8±1.20	0.187	6.67±0.38	0.55
50%, Milled	259.0±0.95	0.189	7.10±0.78	0.38
Formulations Without Avicel:				
30%, Unmilled	181.5±1.12	0.149	3.65±0.44	0.71
30%, Milled	186.8±0.88	0.152	3.68±0.20	0.72
50%, Unmilled	210.0±0.98	0.168	2.67±0.33	0.72
50%, Milled	210.7±1.95	0.169	1.57±0.42	0.92

* Weight and Thickness data are average of 20 tablets. Standard deviation of thickness ranged from 0.0007 in most cases, to 0.0012 in case of milled lot with 50% Eudragit coat.

Correction for differences in tablets size, by dividing the measured force by the area of the tablet, will bring the values of crushing strength closer. The percent loss in weight of tablets during friability testing was insignificant for all lots.

Tablets containing Avicel resulted in faster disintegration and dissolution. The disintegration time for the 10% Eudragit coated lots was 21 minutes in water. All lots with 30 or 50% Eudragit required more than an hour for disintegration, except those lots with Avicel and 30% Eudragit in the coating: they disintegrated in 25 minutes or less.

Release rate studies of Phenylpropanolamine HCl from tablets of different Eudragit contents, with or without Avicel, milled or unmilled are represented in Figures 2-6. The presence of Eudragit at 50% level in the coating step significantly reduces the rate of drug release compared to the lots coated with 30% level of Eudragit. Dissolution testing was extended for up to eight hours for tablets containing 50% of Eudragit, while release of PPA from tablets coated with 30% Eudragit was complete in much shorter time. Only 90 minutes were sufficient to obtain complete release of the drug from tablets coated with 10% Eudragit.

Avicel promotes dissolution when added in the final blend before compression. Although no complete disintegration of the tablets was observed, lots of tablets containing Avicel were swollen and soft, small erosion was also noticed after one hour of dissolution. Differences in drug release rates between lots with Avicel and lots without Avicel could be observed (Fig. 2-6), considering the differences in scales during plotting. Analysis of Variance, ANOVA test, revealed highly significant differences in the amount dissolved in three hours, when comparing lots with Avicel and lots with no Avicel.

Milling of the granules before compression intended to illustrate the role of coating integrity on the release performance of the tablets. Figures 2-4 show that the unmilled lots of 30% Eudragit coat, release the drug faster than the milled lots. In case of lots with 50% Eudragit coating, the milling accelerated the drug release. The milling in the 30% lots seams to result in better sealing of the supporting polymer skeleton that retard the drug release. The lots with 50% Eudragit already having enough polymer for prolonging the release, milling in such case resulted in more drug exposure and faster release. Additional support of these assumption may be required to its validation.

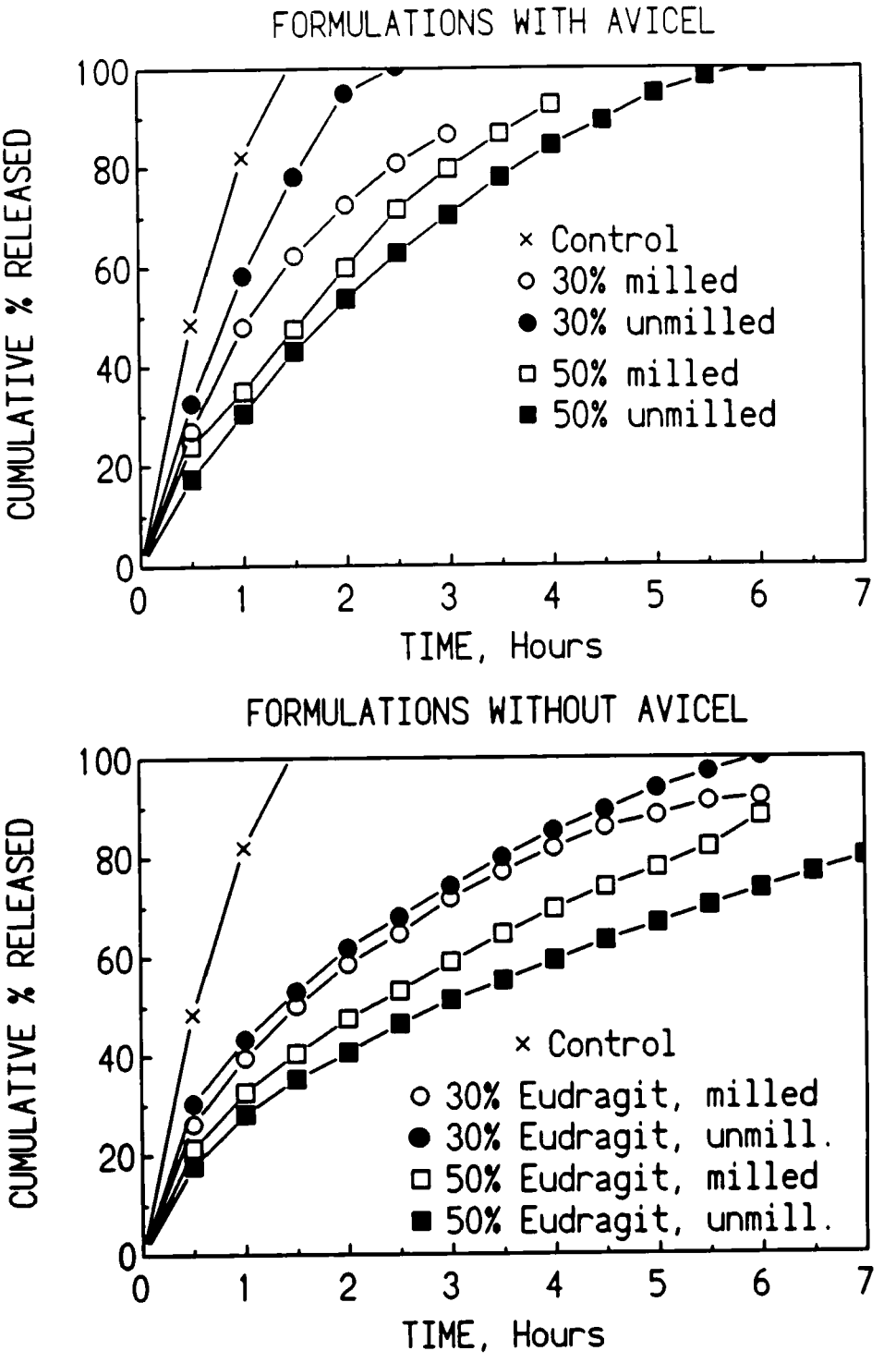

FIGURE 2

Effect of Eudragit Coat Content and Milling of the Granules on the Rate of Phenylpropanolamine Release from Compressed Tablets in Water

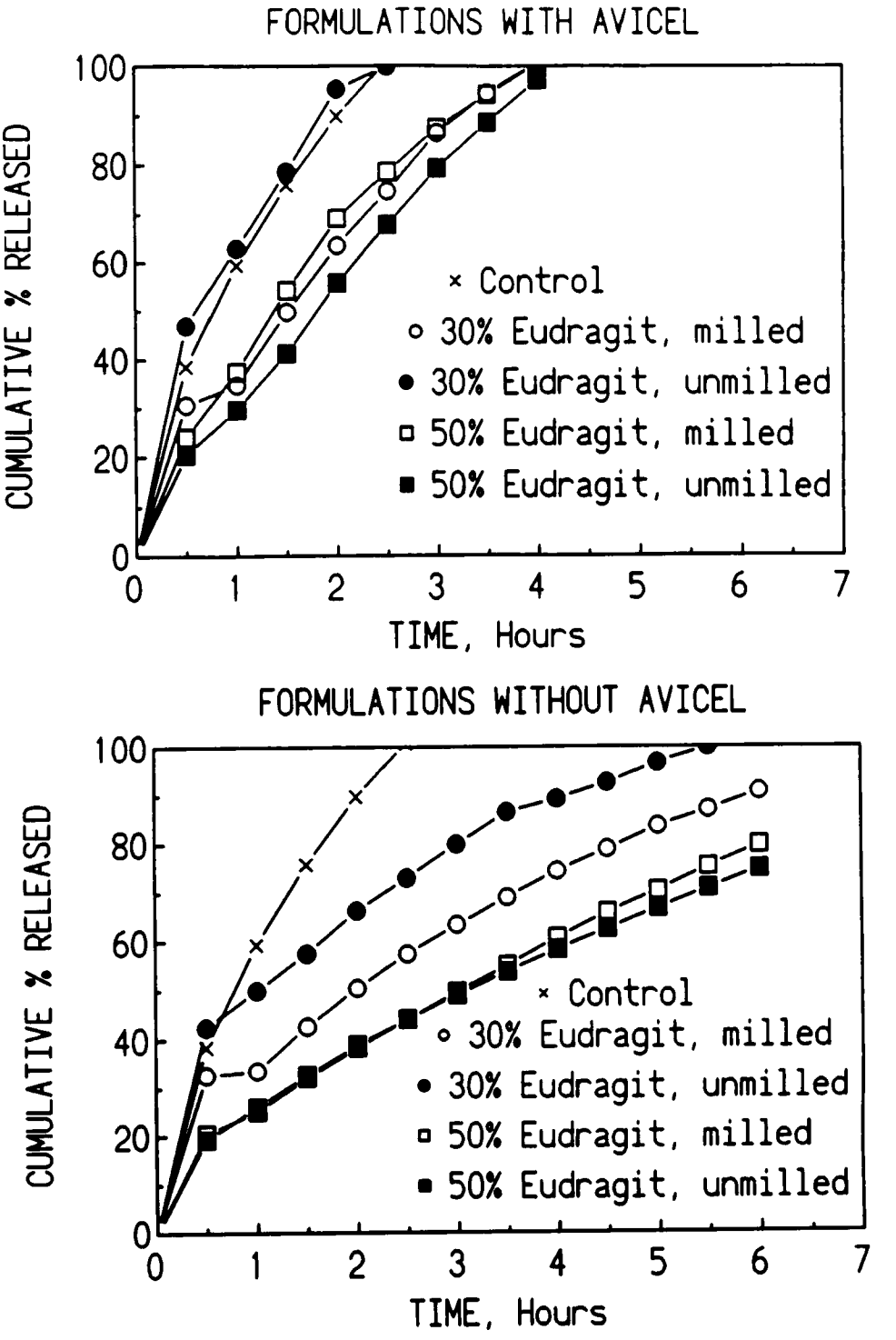

FIGURE 3

Effect of Eudragit Coat Content and Milling of the Granules on the Rate of Phenylpropanolamine Release from Compressed Tablets in Phosphate Buffer pH 7.5

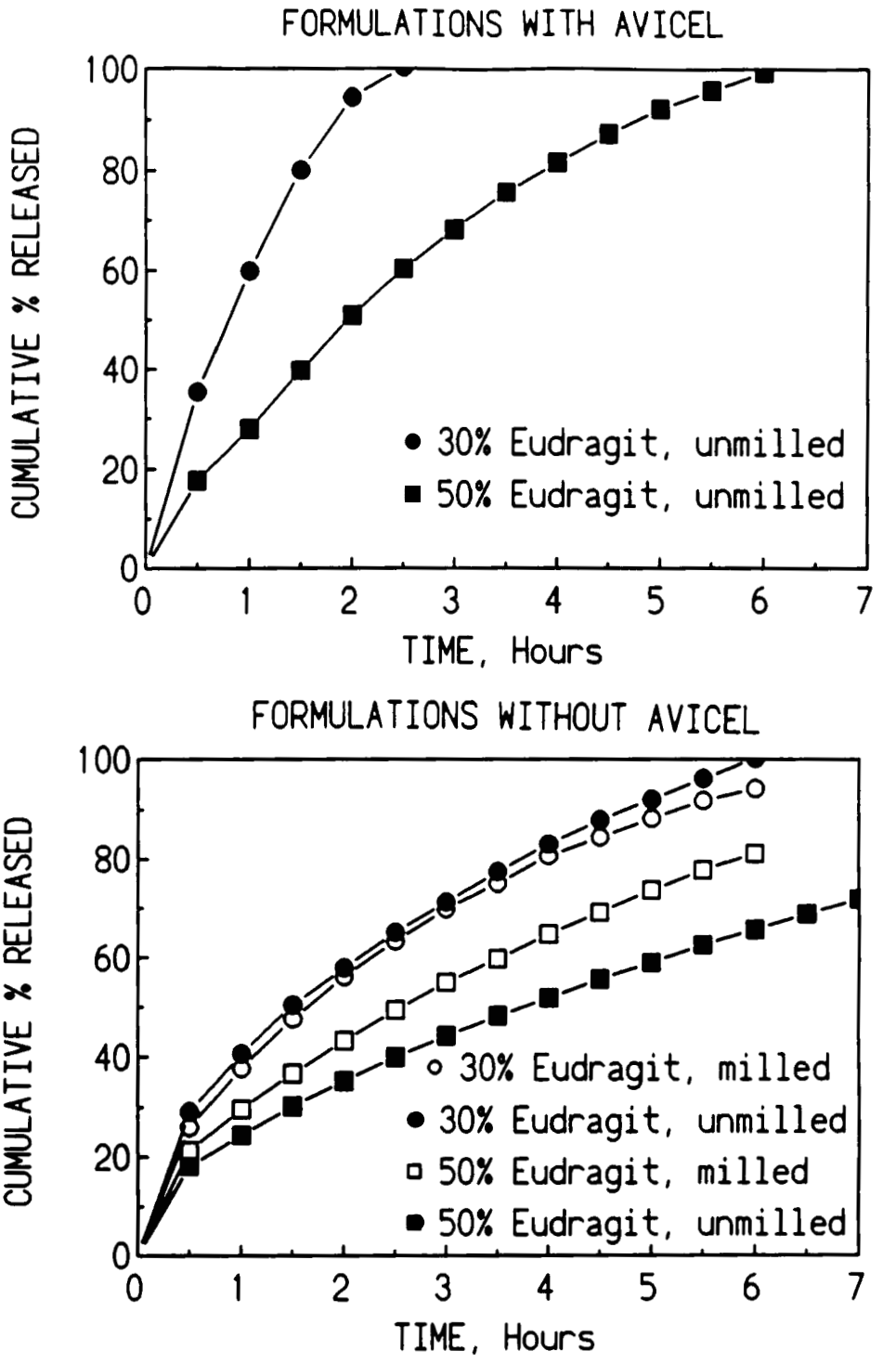

FIGURE 4

Effect of Eudragit Coat Content and Milling of the Granules on the Rate of Phenylpropanolamine Releasefrom Compressed Tablets in 0.1 M Hydrochloric Acid

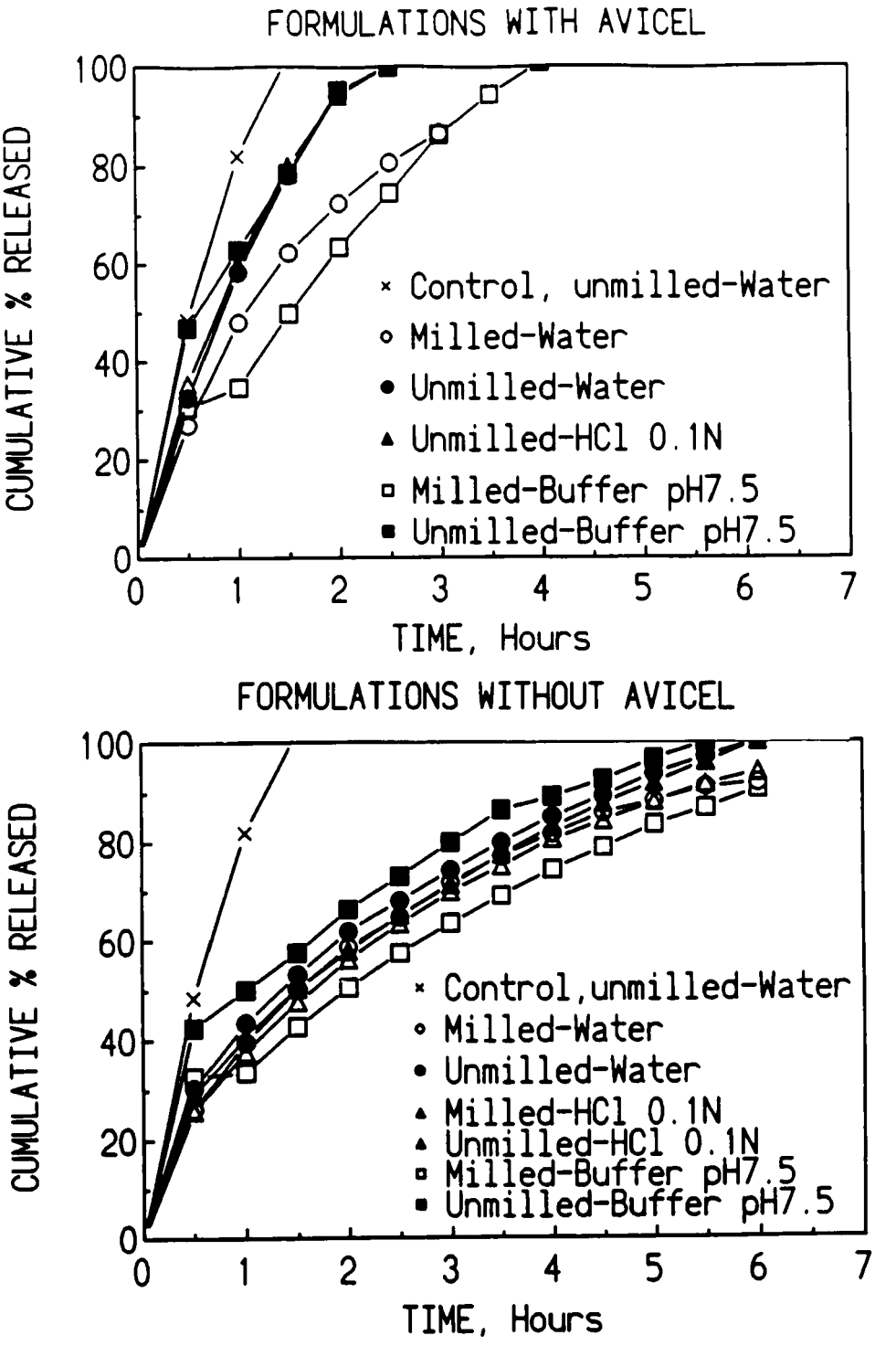

FIGURE 5

Effect of Dissolution Media on the Rate of Phenylpropanolamine Release from Compressed Tablets Lots with 30% Eudragit.

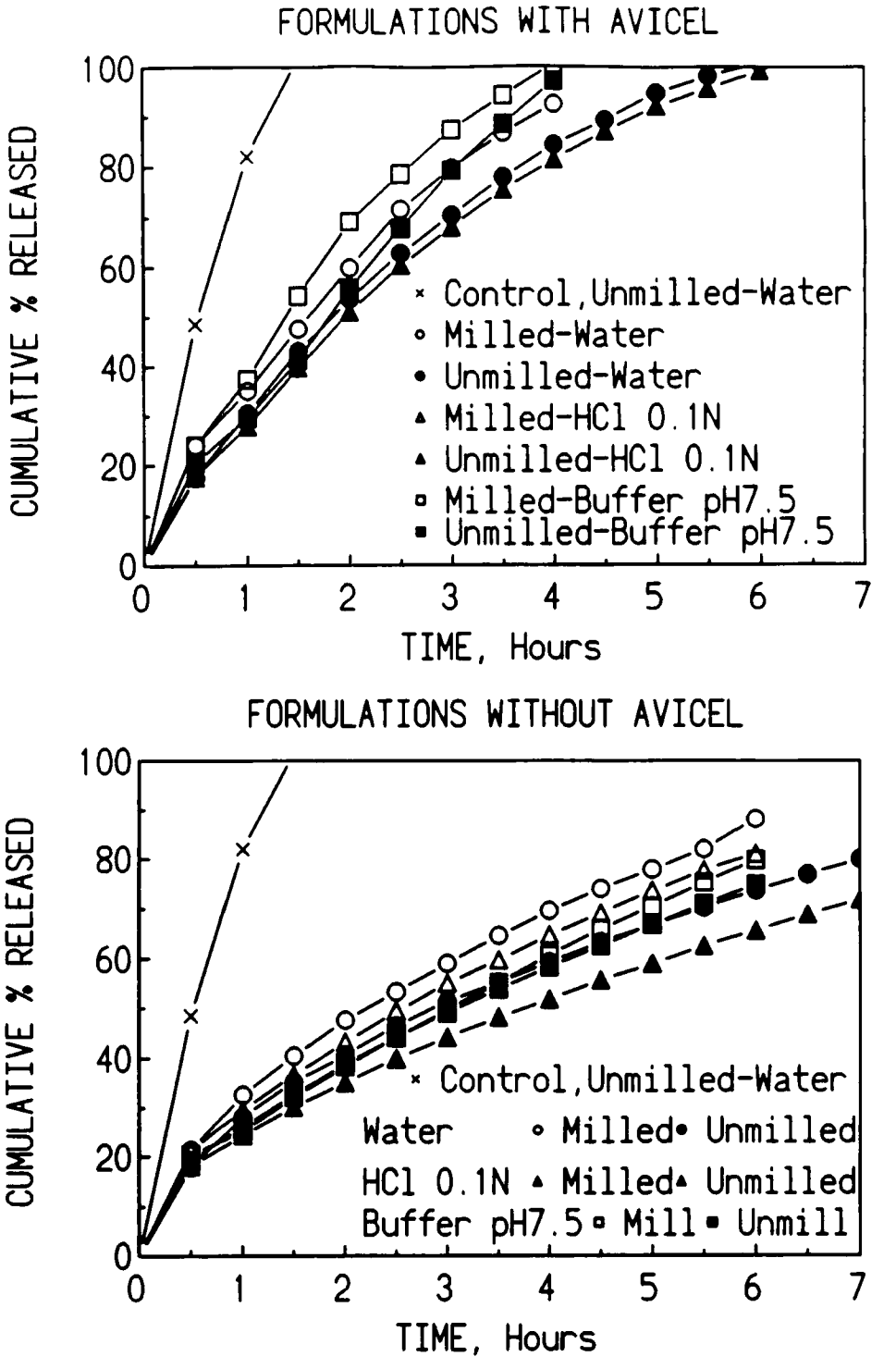

FIGURE 6

Effect of Dissolution Media on the Rate of Phenylpropanolamine Release from Compressed Tablets

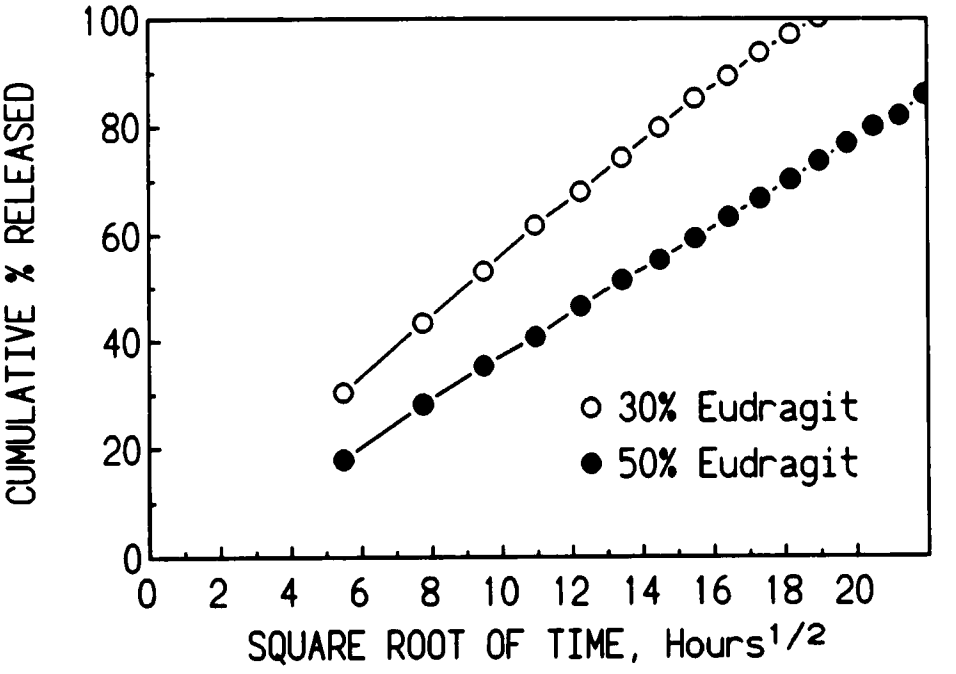

FIGURE 7

Cumulative Percent Phenylpropanolamine Released in Water as a Function of the Square Root of Time Lots with Unmilled Granules and No Avicel.

No consistent differences were observed between the three dissolution media studied: water, 0.1M HCl and phosphate buffer of pH 7.5 (Figure 5 and 6). For lots of relatively faster release, Eudragit 30% and Avicel containing formulas, the release is faster in the acid medium than the buffer system. The drug having a pK_a of 9.4 is expected to be more soluble in the HCl medium. The lots of high Eudragit content or no Avicel they released the drug slowly. The dissolution rate in these cases depend more on the penetration of the dissolution medium through the matrix of the tablet to dissolve the drug. The mixed factors such as milled or unmilled granules also contributed to these variations.

TABLE 3

Factorial Design Evaluation of Phenylpropanolamine Release in Water

(Three factors, two level factorial design for Dissolution Test)
Time: 180 minutes

TRIAL NO.	MEAN	X_1	X_2	X_3	X_1X_2	X_1X_3	X_2X_3	$X_1X_2X_3$	RESPONSE Y_i	LOT NO.
1	+	-	-	-	+	+	+	-	74.2	3A W/O A
2	+	+	-	-	-	-	+	+	103.9	3A W A
3	+	-	+	-	-	+	-	+	75.2	4A W/O A
4	+	+	+	-	+	-	-	-	86.6	4A W A
5	+	-	-	+	+	-	-	+	26.3	3B W/O A
6	+	+	-	+	-	+	-	-	42.5	3B W A
7	+	-	+	+	-	-	+	-	61.7	4B W/O A
8	+	+	+	+	+	+	+	+	79.6	4B W A
SUM +	550.0	312.6	303.1	210.1	266.7	271.5	319.4	285.0		
SUM -	0	237.4	246.9	339.9	283.3	278.5	230.6	265.0		
CHECK SUM	550.0	550.0	550.0	550.0	550.0	550.0	550.0	550.0		
DIFFERENCE	0550	-75.20	-56.20	129.80	16.6	7.0	-88.8	-20.0		
EFFECT	-68.75	-18.8	-14.05	32.45	-4.15	1.75	-22.2	-5.0		

NOTE: CONFIDENCE INTERVALS COULD NOT BE CALCULATED DUE TO LACK OF REPLICATION OF RUNS. THERE IS ONE EXPERIMENT MODEL COEFFICIENT DESCRIBED BY:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

X_1 = Avicel [Yes (18.1%)/No (0%)]
X_2 = Milling (Yes/No)
X_3 = Eudragit Concentration - (30% - 50%)

TABLE 4

Factorial Design Evaluation of Phenylpropanolamine Release in Phosphate Buffer

(Three factors, two level factorial design for Dissolution Test)

Time: 180 minutes

TRIAL NO.	MEAN	X_1	X_2	X_3	X_1X_2	X_1X_3	X_2X_3	X_1X_2X3	RESPONSE Y_1	LOT NO.
1	+	-	-	-	+	+	+	-	62.3	3A W/O A
2	+	+	-	-	-	-	+	+	69.0	3A W A
3	+	-	+	-	-	+	-	+	70.3	4A W/O A
4	+	+	+	-	+	-	-	-	85.3	4A W A
5	+	-	-	+	+	-	-	+	39.5	3B W/O A
6	+	+	-	+	-	+	-	-	43.0	3B W A
7	+	-	+	+	-	-	+	-	68.6	4B W/O A
8	+	+	+	+	+	+	+	+	70.2	4B W A
SUM +	508.23	267.53	294.4	221.3	257.30	245.80	270.13	249.03		
SUM -	0	240.70	213.83	286.93	250.93	262.43	238.10	259.20		
CHECK SUM	508.23	508.23	508.23	508.23	508.23	508.23	508.23	508.23		
DIFFERENCE	508.23	-26.83	-80.57	65.63	-6.37	16.63	-32.03	10.17		
EFFECT	-63.53	-6.70	-20.14	16.40	-1.59	4.16	-8.00	2.54		

NOTE: FACTORIAL DESIGNS STUDIES FOR WATER AND BUFFER MEDIUMS RESULTS WERE PERFORMED WITH INITIAL DISSOLUTION DATA FOR SCREENING OF LOTS RELEASE.

DISSOLUTION TEST WERE REPEATED FOR ACCURACY AND EVALUATED BY ANOVA TEST.

X_1 = Avicel [Yes (18.1%)/No (0%)]
X_2 = Milling (Yes/No)
X_3 = Eudragit Concentration - (30% - 50%)

The two lots with slowest dissolution rates were selected for further analysis of the release mechanism. The percent cumulative drug released was plotted versus the square root of time (Fig.7). A linear relationship was found indicating a diffusion mechanism as derived by Higuchi (8) for inert porous matrix.

The dissolution behavior of tablets in water and phosphate buffer was evaluated with a three factors two levels design for the initial dissolution results at 3 hour interval (Table 3,4). Computed effects from factorial design are considered as "real" if they are "large" in absolute value. A close to zero effect is not considered reliable or accurate.

The effects of the three factors considered in this study may be evaluated by ranking according to the magnitude. A ranking of the assign factor effect by magnitude from largest to smallest in absolute value establishes the probable relative importance of the factors. If this principle is applied to the dissolution testing performed in water, the sustained release of phenylpropanolamine HCl will be mainly influenced by the concentration of Eudragit NE. Positive sign of the effect is an indication of direct relationship between the increase of Eudragit content and the prolongation of the drug release. Effect of Avicel concentration is also large in absolute value.

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