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An Investigation into the Factors Influencing Drug Release from Hydrophilic Matrix Tablets Based on Novel Carbomer Polymers

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Drug release from hydrophilic matrix tablets can be strongly influenced by the proportion of matrix forming polymer and the dimensions and geometry of the tablets. A complete two-factor, three-level factorial design, followed by multiple regression analysis and response surface methodology, was applied to investigate the influence of polymer level and tablet size on drug release kinetics from hydrophilic matrix tablets prepared with Carbopol 971P and Carbopol 71G. Tablet diameter, radius-to-height ratio, tablet surface area, and surface-area-to-volume ratio were evaluated as independent variables in terms of their applicability to characterize tablet size and geometry. The results indicate that it may be possible to control the rate of drug release by modifying the proportion of carbomer in tablets and tablet dimensions. The practical benefit of these simulations is to optimize the geometry and dimensions of a controlled release device and reduce the number of experiments involved in the development of new controlled release dosage forms.

Keywords Carbomer, Dissolution, Drug Delivery, Hydrophilic Matrix Tablet, Paracetamol, Sustained Release

Hydrophilic matrix tablets are among the most widely used controlled release dosage forms for oral delivery due to their low cost and ease of fabrication. Drug release from hydrophilic matrix tablets upon contact with dissolution media or physiological fluids involves hydratation of tablet surface and formation of the gel layer that swells imbibing additional amount of water. The dissolved drug diffuses through the gel layer and hydratation and swelling progress into the tablet core. It could be expected that these processes are dependent on the type and proportion of the polymer used as a controlled release agent, as well as the tablet geometry and dimensions. The subject of tablet size and shape should be considered both from the physiological and the manufacturers point of view.

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Channer and Virjee (1986) investigated the influence of tablet size and shape on transit time through the esophagus and found that large oblong tablets had significantly lower transit time compared with large plain tablets, whereas the transit time of small and medium tablets was lower than that for large tablets irrespective of their shape. Also, the residence time of dosage form in stomach could depend on the size of the dosage form (Wilson 1998). From the formulators point of view, tablet size and shape should be evaluated regarding required dose of the active substance, content of excipients, mechanical characteristics of the tablets, accessibility of tableting tools of different sizes and shapes, and above all the targeted drug release profile.

Several researchers (Siepmann et al. 1998, 2000; Siepmann, Streubel, and Peppas 2002; Reynolds, Mitchell, and Balwinski 2002; Karasulu, Ertan, and Kose 2000; Kim 1995) investigated the effect of matrix geometry on drug release from sustained release dosage forms. They have mostly focused on application and evaluation of hydroxypropylmethylcellulose (HPMC) as a controlled release agent. The selection of the parameter that appropriately characterizes the tablet geometry is questionable. Tablet size is usually expressed by the tablet radius or tablet weight, but it appears that tablet height as well as the tablet surface area and volume should be evaluated. Siepmann et al. (2000) examined the effect of the aspect ratio (radius/height) and the size of cylindrical matrices on drug release and reported that release from small tablets is faster than from large cylindrical tablets due to the higher relative surface area (absolute surface area/absolute volume). Reynolds et al. (2002) studied the effect of relative surface area of the tablets on drug release pattern and concluded that this parameter is valuable when comparing relative drug release from tablets of varying shapes.

Considering the apparent differences in the behavior of hydrophilic matrices prepared with HPMC and carbomer polymers upon contact with dissolution medium, i.e., the extensive swelling of carbomer matrices, the effect of polymer concentration, and matrix geometry for tablets based on carbomer resins should be evaluated. Some authors evaluated the effect

of polymer level on drug release, from carbomer matrix tablets, without considering the effect of tablet size (Khan and Zhu 1999; Huang and Schwartz 1995; Fereira et al. 1995; Perez-Marcos et al. 1995).

Carbomers, synthetic high molecular weight acrylic acid polymers cross-linked with polyalkenyl polyether and commercially available under the brand name of Carbopol®, are not new in sustained release technology but are still interesting. Most of the work done on the evaluation of carbomers used the Carbopol 934 and Carbopol 974P polymers. Novel, toxicologically preferred Carbopol 971P and technologically improved Carbopol 71G polymers were used in this study.

The nonsalicylate analgesic and antipyretic drug, paracetamol, which is voluminous and poorly compressible, was used as a model substance. Paracetamol is generally classified as a drug with high solubility that shows high permeability throughout the intestinal tract, meeting the criteria as a class I drug according to the Biopharmaceutics Classification System (Amidon and Lobenberg 2000). The absorption of class I drugs should depend on their in vivo dissolution, controlled by the kinetics of drug release from the dosage form.

To statistically evaluate the effect of polymer content and tablet size, factorially designed experiments were conducted, followed by multiple regression analysis and response surface methodology (Box, Hunter, and Hunter 1978; Montgomery 1997).

MATERIALS AND METHODS

The following materials were obtained from commercial suppliers and used as received: paracetamol (Merck, Germany), Carbopol 971P, Carbopol 71G (BFGoodrich, USA), lactose monohydrate (Fluka Chemie, Switzerland), polivinylpirolidone (Kollidon 30, BASF, Germany), microcrystalline cellulose (Emcocell XLM 90, Penwest, USA), collodial silicium dioxide (Aerosil 200, Degussa, Germany), and sodium stearyl fumarate (Pruv, Penvest, USA).

Experimental Design

Two separate experimental runs including 9 samples were performed according to the 3^2 experimental design. Additionally, the central experiment was done in triplicate to determine validity of the obtained mathematical models. The independent variables were proportion of Carbopol 971P or Carbopol 71G (X_1) and tablet size (X_2). The proportion of polymer was 7.5, 15.0, or 22.5%. Tablet size was expressed as tablet radius, radius-to-height ratio (aspect ratio), tablet surface area, and surface-area-to-volume ratio (designated as relative surface area). The selected response variable (Y) was percent of drug released after 5 hr of investigation (D_{5h}). The experimental matrix, real and coded values of investigated factors, and response variable are presented in Tables 1 and 2 for samples prepared with Carbopol 971P and Carbopol 71G, respectively.

After performing the experiments, multiple linear regression was applied to evaluate the regression coefficients of the mathematical model that included the linear and quadratic terms of both factors investigated, as well as the interaction factor:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1^2 + b_4X_2^2 + b_5X_1X_2 \quad [1]$$

Student's *t*-test was applied to each term of the quadratic model to evaluate their significance. Only terms that were significant were included in the final model. An experimental matrix was, after the estimation of regression coefficients, used to characterize the results by response surface methodology. Response surface and contour plots were drawn to visualize the effect of investigated factors.

Preparation of Tablets

Tablet samples were prepared using conventional wet granulation method. A paracetamol–lactose mixture (80:20) was granulated using 5% polyvinylpyrrolidone aqueous dispersion. The sustained release agent was added extragranularly, as well as

TABLE 1
Experimental matrix with the real and coded values of investigated factors and response variable for samples prepared with Carbopol 971P

Factor levels											
Sample	X_1 Coded	X_1 Real	X_2 Coded	X_2 Real							Y D_{5h} (%)
				m (mg)	d (mm)	h (mm)	r/h	P (mm^2)	V (mm^3)	P/V	
P1	−1	7.5	−1	275	9	4.24	1.0613	246.99	269.60	0.9161	96.08
P2	0	15	−1	275	9	4.26	1.0563	247.56	270.87	0.9139	66.24
P3	1	22.5	−1	275	9	4.66	0.9657	259.00	296.62	0.8736	50.51
P4	−1	7.5	0	550	12	4.39	1.3667	391.50	496.24	0.7889	44.73
P5	0	15	0	550	12	4.46	1.3453	394.13	504.16	0.7817	37.78
P6	1	22.5	0	550	12	4.96	1.2097	412.97	560.68	0.7365	28.79
P7	−1	7.5	1	825	15	4.44	1.6892	562.37	784.22	0.7171	43.12
P8	0	15	1	825	15	4.60	1.6304	569.91	812.48	0.7014	34.75
P9	1	22.5	1	825	15	4.88	1.5369	583.10	861.93	0.6765	26.28

TABLE 2
Experimental matrix with the real and coded values of investigated factors and response variable for samples prepared with Carbopol 71G

Factor levels											
Sample	X_1 Coded	X_1 Real	X_2 Coded	X_2 Real							Y D_{5h} (%)
				m (mg)	d (mm)	h (mm)	r/h	P (mm^2)	V (mm^3)	P/V	
G1	−1	7.5	−1	275	9	3.85	1.1688	235.97	244.80	0.9639	97.52
G2	0	15	−1	275	9	3.85	1.1688	235.97	244.80	0.9639	74.30
G3	1	22.5	−1	275	9	3.9	1.1538	237.38	247.98	0.9573	47.68
G4	−1	7.5	0	550	12	4.45	1.3483	393.76	503.03	0.7828	47.79
G5	0	15	0	550	12	4.5	1.3333	395.64	508.68	0.7778	37.15
G6	1	22.5	0	550	12	4.55	1.3187	397.52	514.33	0.7729	27.90
G7	−1	7.5	1	825	15	4.49	1.6704	564.73	793.05	0.7121	45.69
G8	0	15	1	825	15	4.44	1.6892	562.37	784.22	0.7171	31.97
G9	1	22.5	1	825	15	4.4	1.7045	560.49	777.15	0.7212	27.30

other excipients, mixed and compressed in an excenter tablet machine (Erweka Korsch EK0, Germany) using flat round punches of various diameters (9, 12, and 15 mm). The compression pressure was adjusted to provide tablets with hardness between 50 and 60 kN. The set of tablet samples prepared with Carbopol 971P was designated as samples P1-P9, while tablet formulations containing Carbopol 71G were designated as samples G1-G9. To evaluate the effect of tablet height, additional samples of tablets containing 22.5% of Carbopol 71G, with diameters of 12 mm and 3 mm (sample G63), 5 mm (sample G65), and 6 mm (sample G66) tablet height were prepared.

Drug Release Study

The release experiments were conducted in the rotating paddle apparatus (Erweka DT 70, Germany), in 1000 ml of distilled water 37°C, at 50 rpm. Then 3-ml samples were withdrawn at 1 hr intervals, filtered, properly diluted, and assayed UV-spectrophotometrically (spectrophotometer Cary 50, Varian, Australia) at 243 nm. Six tablets were studied for each formulation. Upon formation of the gel layer at the tablet surface, tablets stuck to the vessel of the dissolution apparatus, which significantly decreased the drug release rate as the surface area of the matrix exposed to the medium was reduced. To prevent such sticking, wire helix was used that did not restrict the contact of the tablet with the dissolution medium.

Drug release kinetics were evaluated using the following exponential equation proposed by Ritger and Peppas (1987):

$$M_t/M_\infty = kt^n \quad [2]$$

where M_t/M_∞ is the fraction of drug released at time t, k is the kinetic constant (drug release rate constant), which incorporates structural and geometrical characteristics of the controlled release system, and n is the diffusional release exponent indicative of the release mechanism. The experimental data were fitted to the proposed equation using nonlinear regression (Levenberg-Marquardt algorithm, Microcal Origin 5.0).

RESULTS AND DISCUSSION

Drug release profiles obtained for tablet samples prepared with Carbopol 971P (samples P1-P9) and Carbopol 71G (samples G1-G9) are presented in Figures 1 and 2, respectively. More homogenous and uniform matrix swelling was observed in the tablets prepared with Carbopol 971P, whereas with Carbopol 71G matrices, the disentanglement of polymer chains was much more pronounced as well as more intensive swelling in axial direction. An overall trend of more sustained drug release could be observed in Carbopol 971P tablets during the first hours of investigation, while Carbopol 71G, used as a controlled release agent, tended to maintain the integrity of the matrix and thus prolong drug release. Complete drug release (i.e., >80%) during 8 hr of investigation was observed in "small" tablets and medium and large tablets containing 7.5% of Carbopol 71G. The drug release was prolonged over 10 hr in medium and large tablets containing 22.5% of Carbopol 71G and medium and large tablets containing both 15% or 22.5% of Carbopol 971P.

The obtained values of diffusional exponent (n) varied from 1.1818 to 2.2613 for tablets prepared with Carbopol 971P and from 1.5412 to 2.6443 for Carbopol 71G tablets. Considering the cylindrical shape of the tablets, the n value of 0.89 indicates the zero-order drug release kinetics, while $n > 0.89$ denotes super case II transport (Ritger and Peppas 1987). According to the obtained n values, the drug release kinetics could be described as swelling and relaxation of the polymer controlled following the super case II transport.

Multiple regression analysis and analysis of variance revealed that within the investigated experimental field, the effect of both polymer content and tablet size significantly influenced the

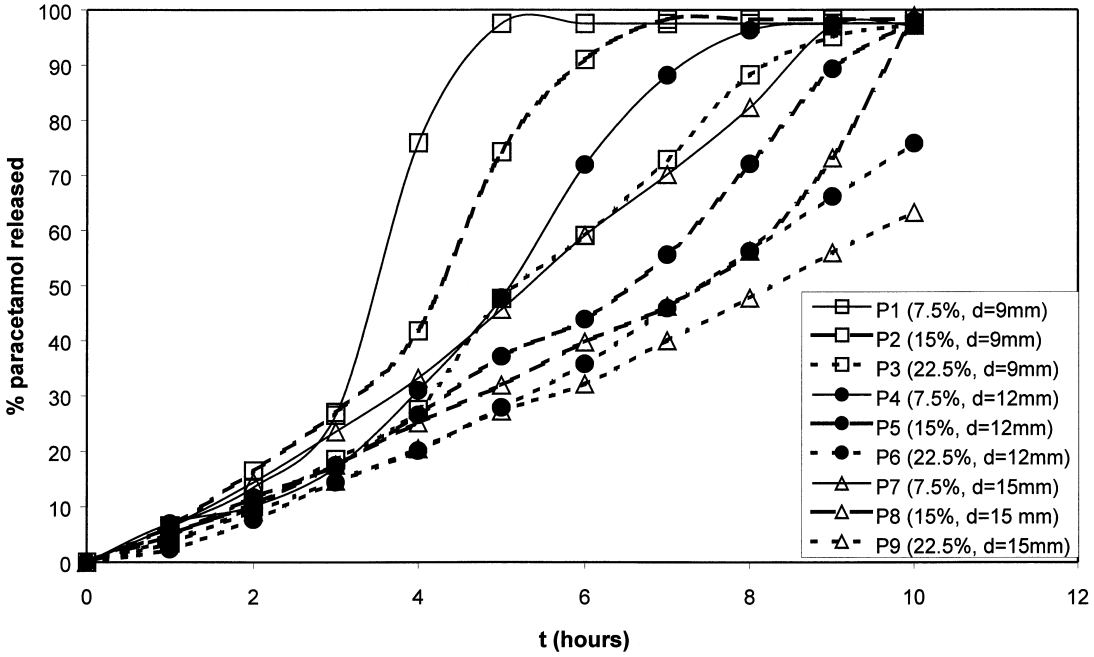

FIG. 1. Drug release profiles obtained for tablets with varying polymer content and tablet size prepared with Carbopol 971P (samples P1-P9).

percent of drug released after 5 hr of investigation. The effect of concentration was linear, while the tablet size exhibited both the linear and quadratic effect. The effect of interaction factor also was significant in the majority of studied cases. The regression coefficients of quadratic models calculated by multiple regression were found to be significant ($p < .05$) and coefficients of determination for each model are reported in Tables 3 and 4 for series of tablets prepared with Carbopol 971P and Carbopol 71G, respectively. The highest coefficient of determination for the samples prepared with Carbopol 971P was obtained when aspect ratio was selected as the parameter of tablet size, while for the samples prepared with Carbopol 71G, the best fit was obtained for model in which relative surface area was used to characterize the tablet size.

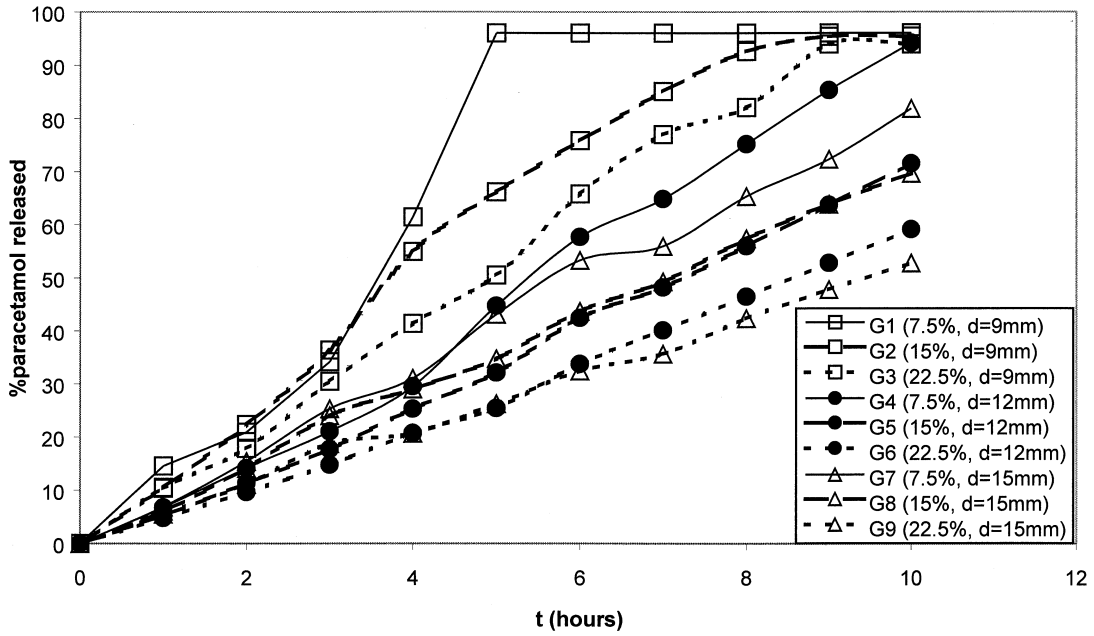

FIG. 2. Drug release profiles obtained for tablets with varying polymer content and tablet size prepared with Carbopol 71G (samples G1-G9).

TABLE 3
Summary of the multiple regression analysis for tablet samples prepared with Carbopol 971P (samples P1-P9)

Regression coefficient	Tablet dimensions evaluated as X_2 factor			
	Diameter	Radius/height	Surface area	Surface area/volume
b0	491.187	670.294	242.147	845.330
b1	−5.647	−10.590	−1.727	−1.43
b2	−60.817	−755.649	−0.783	−2140.310
b3	—	—	—	—
b4	2.083	226.373	0.0008	1446.60
b5	0.319	6.373	—	—
R^2	0.9789	0.9938	0.9402	0.9507

The mathematical models obtained for these two sets of tablets, based on tablet diameter and tablet surface area, were almost identical in regard to the calculated set of regression coefficients. Although high coefficients of determination were obtained for model based on the tablet diameter as parameter describing the tablet size, it would not allow the accurate prediction of drug release from matrices of different height. Thus, aspect ratio and relative surface area as parameters encountering both tablet diameter and height should be further evaluated.

The response surface and contour plots of drug released after 5 hr versus polymer content versus tablets aspect ratio for set of tablets prepared with Carbopol 971P and Carbopol 71G are given in Figures 3a and 4a, respectively. Accordingly, the relationship between percent of drug released after 5 hr versus polymer content versus relative surface area of the tablets is presented through the response surface and contour plots presented in Figures 3b and 4b, for the two set of tablets.

The drug release profiles observed when studying the effect of tablet height are presented in Figure 5. Although the percent of drug released from samples with various tablet heights (and weights) were different as illustrated in Figure 5b, the actual amounts of drug released were almost identical during the first 5 hr of investigation (Figure 5a). These results were inconsistent with those reported by Siepmann et al. (2000) for hydroxypropylmethylcellulose matrix tablets, in which, with respect to variable tablet height, similar results were obtained for percent of drug released, while the amounts of drug released were markedly different.

In the case of "thin" (h = 3 mm) tablets, complete drug release and disintegration of matrix occurred after 6 hr, while in the case of "thicker" tablets, with 5 mm and 6 mm tablet height, drug release proceeded until 12 hr or 14 hr of investigation, respectively.

These results indicate that in the case of Carbopol 71G matrix tablets, within the usual range of radius/height ratio, the effect of more intensive axial than radial swelling resulted in superimposable drug release profiles during first hours of investigation, regardless of tablet height. However, tablet height was the factor determining the time interval in which the integrity of the matrix remained intact, thus influencing the overall sustained release period.

To evaluate the predictability of the obtained mathematical models, the internal and external predictability values were assessed according to the percent prediction error:

$$\%PE = [|Y_{obs} - Y_{pred}|/Y_{obs}] \times 100 \quad [3]$$

TABLE 4
Summary of the multiple regression analysis for tablet samples prepared with Carbopol 71G (samples G1-G9)

Regression coefficient	Tablet dimensions evaluated as X_2 factor			
	Diameter	Radius/height	Surface area	Surface area/volume
b0	469.660	956.440	253.212	314.849
b1	−6.152	−2.250	−4.463	5.121
b2	−55.507	−1183.350	−0.726	−853.553
b3	—	—	—	—
b4	1.829	389.51	0.0006	676.723
b5	0.349	—	0.0064	−8.571
R^2	0.9808	0.8769	0.9599	0.9866

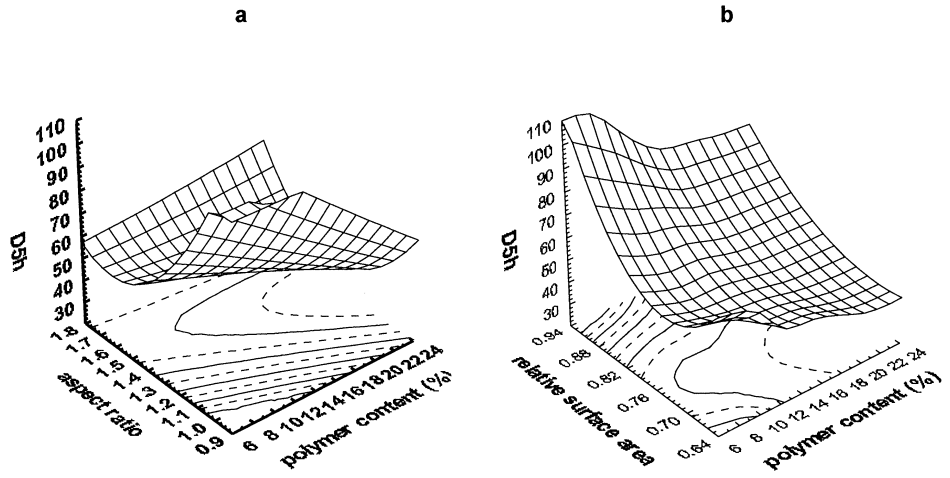

FIG. 3. Response surface and contour plot of (a) D_{5h} vs. polymer content vs. aspect ratio; (b) D_{5h} vs. polymer content vs. relative surface area for samples prepared with Carbopol 971P.

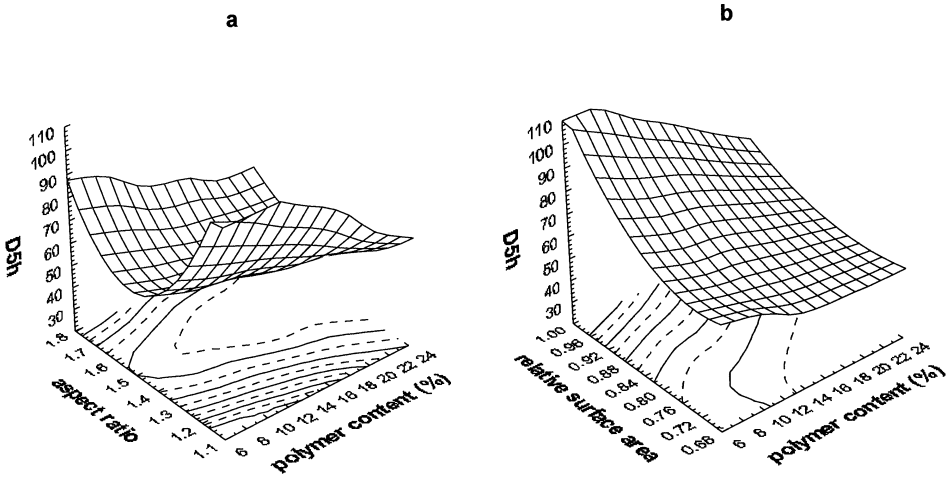

FIG. 4. Response surface and contour plot of (a) D_{5h} vs. polymer content vs. aspect ratio; (b) D_{5h} vs. polymer content vs. relative surface area for samples prepared with Carbopol 71G.

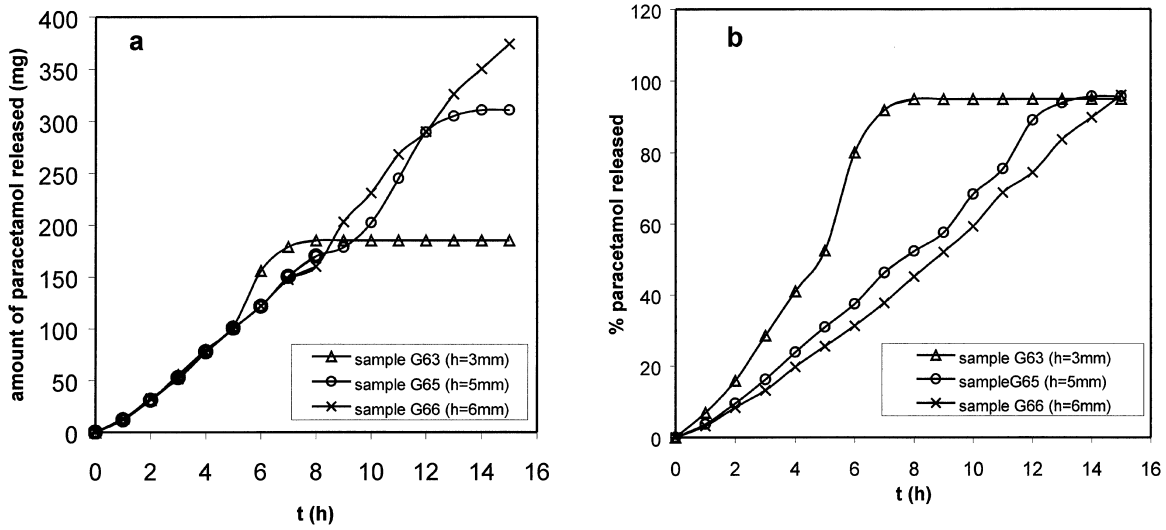

FIG. 5. Effect of the initial tablet height on the (a) resulting absolute amounts of drug released; (b) resulting relative amounts (%) of drug released from Carbopol 71G matrix tablets of various height. △: 3 mm, ○: 5 mm; ×: 6 mm.

TABLE 5
Predicted and observed values of D_{5h} for samples with different tablet heights

Sample	Predicted D_{5h} values (%PE)				Experimentally observed D_{5h} values
	Based on d	Based on r/h	Based on P	Based on P/V	
G6	22.76 (18.42)	22.82 (18.21)	16.25 (41.76)	25.56 (8.39)	27.90
G63	22.76 (56.70)	97.16 (84.86)	24.45 (53.48)	60.39 (14.90)	52.56
G65	22.76 (53.62)	52.88 (70.80)	14.36 (53.62)	27.10 (12.47)	30.96
G66	22.76 (52.93)	125.31 (389.88)	12.04 (52.93)	28.31 (10.67)	25.58
G8	34.82 (8.91)	35.20 (10.10)	21.73 (32.03)	35.38 (10.67)	31.97

where Y_{obs} is the experimentaly observed value of the response variable and Y_{pred} is the value predicted according to the proposed mathematical model. The internal predictability was estimated from the results used to develop the mathematical model (samples G6 and G8). The external predictability was anticipated using data from the additional samples of tablets with various tablet height (G63, G65, G66). The predicted values of percent of drug released after 5 hr of investigation calculated according to the proposed mathematical models and percent prediction error calculated for each example, as well as the observed values, are presented in Table 5. Good agreement between theory and experiment was observed in the mathematical model based on relative surface area as the parametar describing tablet dimensions, quantified by a percent prediction error ranging from 8.39 to 14.90%

CONCLUSION

Our results indicate that it may be possible to control the rate of drug release by modifying the proportion of carbomer in tablets and tablet dimensions. The kinetics of drug release depended on the type of polymer, as well as on the polymer content and tablet geometry. Although chemically identical, Carbopol 971P and Carbopol 71G exhibit different drug release patterns due to the technological modifications involved in the manufacture of Carbopol 71G. The present results suggest that the release kinetics are mostly regulated by a swelling-controlled diffusion process, because most of the drug is released while a large portion of the polymer matrix remains intact.

Both the content of polymer and tablet geometry and dimensions should be evaluated to optimize the formulation with the targeted drug release pattern. Although the tablet diameter seems to be the prevalent tablet size parameter determining the drug release rate, we found that relative surface area is a more relevant term for comparison of tablets of varying height, which also is expected to be useful for comparison of tablets of different shape. The practical benefit of these simulations is to optimize the geometry and dimensions of a controlled release device and reduce the number of experiments involved in the development of new controlled release dosage forms.

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