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RESEARCH PAPER

Interaction of Verapamil Hydrochloride with Carbopol 934P and Its Effect on the Release Rate of the Drug and the Water Uptake of the Polymer Matrix

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ABSTRACT

In the present study, investigation of the possibility of interaction of verapamil hydrochloride with Carbopol 934P using differential scanning calorimetric analysis and Fourier transform infrared analysis was performed. The effect of the drug-to-polymer ratio, the electrolyte concentration, and the pH of the medium on the extent of interaction of the drug with the polymer using 2^3 *factorial design was investigated. The study also investigated the effect of this interaction on the rate of water uptake of the matrix or the rate of release of verapamil hydrochloride from the swelling polymer matrix. Results revealed that the drug-to-polymer ratio had the most influential effect on both the extent of interaction between the drug and the polymer and the rate of water uptake of the polymer matrix. On the other hand, the pH of the medium had the most significant effect on the rate of drug release. Interaction of the tertiary amine nitrogen of the drug with the anionic carboxyl group on the polymer, forming an insoluble complex, reduced the rate of drug release. This interaction also led to neutralization of the carboxyl group and suppression of the electrostatic repulsion between the anionic groups, which reduced the uncoiling and chain relaxation of the polymer and consequently decreased the swelling of the matrix. The application of the designed experiment allowed the quantification of the effect of each of the studied variables on the investigated responses through the calculation of their coefficient in the response surface equation and checking of their significance.*

Key Words: *Carbopol 934P; Controlled release; Drug-polymer interaction; Verapamil hydrochloride*

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INTRODUCTION

Drug–excipient interactions have been extensively reported in the literature, especially during preformulation studies (1–4). Interaction in the solid state may affect the drug stability (5), drug content (6), or drug bioavailability (7). Drug-polymer interaction is also well known in the literature (8–10). In this matter, the interaction may be physical through hydrogen bonding (11,12) or chemical through the formation of insoluble complexes between either anionic drug and cationic polymer (13) or cationic drug and anionic polymer (14–16). Interaction may not be evident in the solid state, but cannot be avoided when the dosage form comes in contact with the dissolution medium. An interaction under these conditions, whether physical or chemical, may affect the rate and extent of drug release. Yuasa et al. (17,18) and Ozeki et al. (19) reported that there is a linear relationship between the release rate of the medicine and the degree of interaction between the polymer and the medicine. Under these conditions it is expected that some factor would have the greatest effect on the degree of interaction and consequently on the rate of drug release. These factors are either related to the dosage form (mainly, the drug-to-polymer ratio) or to the dissolution medium (mainly, the pH and the ionic strength of the medium).

Carbopol 934P is a vinyl copolymer having a very high molecular weight (about 3 million) (20). This polymer contains acidic carboxyl groups that partially dissociate in water, producing a flexible coil structure (21). It has been used extensively for the preparation of controlled-release peroral dosage forms (22–25), buccoadhesive tablets (26), topical disklike dosage form (27), or gel dosage forms (28). The designed matrix dosage form absorbs water, which is accompanied by polymer chain relaxation in which the drug is entrapped in the gel intramatrix space and released over a long period of time (29). The long entrapment time would allow a good chance for interaction between the carboxylic acid polymer and the drug if its chemical structure favors this interaction. Interaction of Carbopol of different grades with cationic drugs is well reported in the literature (9,16,20,30,31).

Verapamil hydrochloride is a water-soluble calcium channel blocker with class IV antiarrhythmic activity. It is used in the control of supraventricular tachyarrhythmias, in the management of classical and variant angina pectoris, and in the treatment of hypertension. It is soluble in water and will precipitate in alkaline solutions (32). According to its structural formula, it contains tertiary amine nitrogen, which favors interaction with a carboxylic acid polymer.

The present study investigated the interaction of verapamil hydrochloride with Carbopol 934P. Utilizing a designed experiment (2^3 factorial), the effect of the drug-to-polymer ratio, the pH of the medium, and the ionic strength on the extent of interaction was analyzed. The application of a designed experiment allowed the quantification of the effect of each factor on the measured responses through the calculation of its coefficient in the response surface equation. The study also investigated the effect of the previously mentioned factors on the release rate of verapamil hydrochloride from the swelling polymer matrix and the water uptake of the matrix and how they correlate with the extent of drug-polymer interaction.

EXPERIMENTAL

Materials

Verapamil hydrochloride was a generous gift from Adwic Chemicals Company (Cairo, Egypt). Carbopol 934P was donated by Aqualon Company (Delaware). Hydrochloric acid (BDH, Poole, England), disodium hydrogen phosphate, potassium dihydrogen phosphate (Fluka, Buchs, Switzerland), magnesium stearate, and sodium chloride (Merck, Darmstadt, Germany) were used as received.

Design

A 2^3 factorial design (16 runs, duplicate runs of each experiment) was used to study the effect of different variables on the extent of interaction of the drug and the polymer, the release rate of the drug from the swelling polymer matrix, and the water uptake of the matrix. Independent variables included the drug-to-polymer ratio (1 : 1 and 2 : 1) (X_1), the concentration of sodium chloride (as an electrolyte) in the medium (0.25% and 2.5%) (X_2), and the pH of the medium (1.2 and 5) (X_3) (Table 1).

Determination of the Effect of Different Variables on the Extent of Drug-Polymer Interaction

Preparation of the Dialyzing System

A piece of dialyzing membrane (cellulose membrane, molecular weight cutoff 10,000, Spectrapore Arthur H. Thomas Co., Philadelphia, PA) was soaked in distilled water for 24 h. After rinsing with distilled water, the membrane was tied on one end of an open-ended glass tube of 15 cm long and with a 22-mm internal diameter.

Preparation of the Polymer and the Drug Solutions

Polymer solution (0.25%) was prepared by dispersing the appropriate amount of the polymer in distilled water using a mechanical stirrer for 15 min. The obtained polymer dispersion was neutralized with 18% sodium hydroxide solution to pH 7. Drug solutions of two different concentrations (0.25% and 0.5%) were prepared by dissolving the appropriate amount of the drug in distilled water with the aid of a sonicator.

Determination of the Extent of Interaction

To determine the extent of interaction, 5 ml of the polymer solution were mixed with 5 ml of the drug solution in the dialyzing tube according to the design (Table 1). The tubes were leveled inside a baker containing 100 ml of the suitable media (0.1 N hydrochloric acid or Sorensen phosphate buffer of pH 5 containing the suitable concentration of sodium chloride according to Table 1), taking into consideration that the levels of the solution inside and outside the dialyzing tube were the same. Samples were removed after 48 h (a preliminary experiment was done to determine the equilibrium time) and analyzed for drug content. The amount of the free drug was determined; from this, the amount interacted was calculated, and consequently, the amount interacted in milligram of drug per milligram of the polymer was computed. No interaction was observed between the cellulose membrane and verapamil, which was proved by socking a piece of the membrane in a known concentration of the drug for the same period of time. It seems also that the membrane did not interact with Carbopol as it remained clear, transparent, and with the same texture at the end of all the experiment.

Table 1

2^3 Factorial Design of the Selected Variables

Experiment	X_1	X_2	X_3
1	1 : 1	0.25	1.2
a	2 : 1	0.25	1.2
b	1 : 1	2.50	1.2
ab	2 : 1	2.50	1.2
c	1 : 1	0.25	5.0
ac	2 : 1	0.25	5.0
bc	1 : 1	2.50	5.0
abc	2 : 1	2.50	5.0

X_1, the drug-to-polymer ratio; X_2, the concentration of electrolyte; X_3, the pH of the medium.

Physicochemical Characterization of Interaction Product

Differential Scanning Calorimetric Analysis

The DSC thermograms were recorded on a differential scanning calorimeter (DSC-4, Perkin Elmer, Norwalk, CT) calibrated with indium (99.999%). Samples (3 mg) of the pure drug, Carbopol, their physical mixtures (prepared by grinding a 1 : 3 w/w mixture using a mortar and a pestle), and their interaction products (obtained by drying the residues left on the dialyzing membrane) were hermetically sealed in a flat-bottomed aluminum pan. Samples were heated over the temperature range 25°C–350°C under an argon purge at a constant rate of 10°C/min.

Fourier Transform Infrared Analysis

The Fourier transform infrared (FTIR) spectra of pure verapamil hydrochloride and Carbopol, as well as their physical mixtures and interaction products, were measured as potassium bromide disks on a Perkin-Elmer FTIR spectrophotometer (Oak Brook, IL) at a scanning speed of 16×2.0 cm^{-1} in the range 4000–250 cm^{-1} at ambient temperature (25°C).

Effect of Different Variables on the Release Rate of the Drug and the Water Uptake of the Polymer Matrix

Preparation of Tablets

Powders of drug and polymer were blended for 10 min in the ratios 1 : 1 and 2 : 1 drug to polymer using a powder blender (Erweka-Apparatebau, Heusenstamm, Germany). Then, 1% magnesium stearate was added and mixed for an additional 5 min. Tablets were prepared by direct compression of 182 mg of the powder blend, which was assumed to contain 90 mg of drug for the 1 : 1 drug-to-polymer mixture and 120 mg for the 2 : 1 mixture. tablets of 9 mm diameter were compressed on a single-punch tableting machine (Korsch, type EKO, Erweka Apparatebau) to a constant radial crushing strength of 12 ± 0.5 kg.

Determination of Drug Release Rate

The release of verapamil hydrochloride from the prepared tablets was studied using an automated dissolution monitoring system consisting of USP dissolution apparatus no. 1 (SR8 Plus, dissolution test station, Hanson Research, USA) connected to an autosampler (Dissoette 2 autosampler model 27-6AS, Hanson Research, USA). The volume of the dissolution medium was 900 ml of the suitable medium (0.1 N hydrochloric acid or Sorensen phosphate buffer of pH 5 containing the suitable concentration of sodium chloride according to Table 1) maintained at 37°C ± 0.5°C and stirred at 100 rpm. Absorbance was recorded at different time intervals (0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 h) at a wavelength of 229 nm using a Lambda II spectrophotometer (Perkin Elmer Instrument, Norwalk, CT) connected to an IBM computer and using Maestro^{TM} 3.0 software from Hanson Research.

The percentage released was calculated using standard curves developed in the corresponding media and based on the determined drug content (6 replicates for each formula, 1 : 1 and 2 : 1 drug-to-polymer ratios). Data were analyzed according the zero- and first-order equations and according the Higuchi diffusion model. The time for 50% release $t_{50\%}$ was calculated from the best-fit equation. Results are an average of three experiments. Duplicate t_{50} values were used for the response surface analysis.

Determination of the Water Uptake of Matrices

For determination of the water uptake of the matrices, 1 tablet was soaked in 100 ml of the corresponding medium (according to the design of Table 1) at 37°C. At the specified time intervals (0.5, 1, 2.5, 4, 6 h), tablets were removed and placed on tissues to dry their external surface; they were weighed and returned to the medium. The percentage increase in the weight of the original tablet was calculated and plotted versus time to reflect the rate of water uptake (results are an average of three experiments). The extent of water uptake after 6 h (duplicate readings for each combination) was used for the response surface analysis.

Data Analysis of the Factorial Experiments

Data analysis of the extent of interaction (measured as the number of milligrams of drug interacted per milligram of polymer), the rate of drug release (expressed as the time for 50% release of the drug), as well as the water uptake of the matrix (the percentage increase in the tablet weight after 6 h of soaking), was done for duplicate experiments (16 runs for 2^3 factorial) using multiple linear regression analysis. The coefficients of the equation that best fit the previous responses as a function of the level of the studied variables were determined. Analysis of variance was used to check the significance of coefficients in each equation. Equations of the following type were developed:

$$Y = Bo + B_1X_1 + B_2X_2 + \cdots + B_{12}X_1X_2 + B_{13}X_1X_3 + \cdots$$

where Y is the level of the response; B_i and B_{ij} are the regression coefficients; and X_i is the level of the ith independent variable.

The goodness of fit of the equations was checked statistically, taking into consideration the highest correlation coefficient of regression R^2, the lowest standard deviation (SD) about regression, the highest confidence level (CL) of significance of equations, the normal distribution of the residuals, and the highest confidence coefficients of the parameters in each equation.

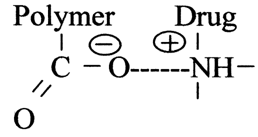
RESULTS AND DISCUSSION

Physicochemical Characterization of the Interaction Product

The precipitate resulting from the interaction of Carbopol 934P and verapamil HCl was white, insoluble in water, and with a melting point higher than 300°C, while the melting point of verapamil hydrochloride was 143.77°C.

Examination of the DSC of the drug, polymer, their physical mixture, and their interaction product (Fig. 1) revealed with no doubt the interaction of verapamil hydrochloride with Carbopol 934P, which was obvious from the disappearance of the endothermic peak of the drug at 143.77°C from the thermogram of the interaction product, but not from that of the physical mixture.

The FTIR spectrum (Fig. 2) of the same materials supported the DSC results. The drug showed a strong band at 2850–2250 cm^{-1} due to the $-\overset{|}{\underset{|}{N}}{}^{+}-H$ stretch of the tertiary amine hydrochloride salt. The same band exists strongly in the physical mixture, but only appeared as a weak band in the interaction product. The disappearance of the strong band at 2850–2250 cm^{-1} suggests the nonexistence of the drug hydrochloride salt in the product, while the appearance of the weak band suggests the formation of a salt between the high molecular weight acidic polymer and the relatively small molecules of the drug according to the following scheme:



Similar results were obtained in the interaction of mebeverine hydrochloride and Carbopol (33).

The Effect of Different Variables on the Extent of Interaction of Verapamil Hydrochloride with Carbopol 934P

The extent of interaction of verapamil hydrochloride with Carbopol 934P expressed as milli-

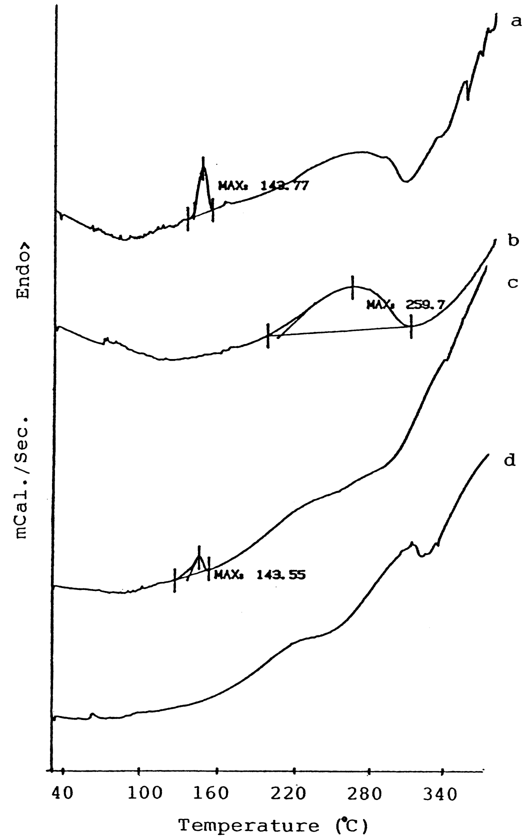


Figure 1. DSC thermograms of (a) verapamil hydrochloride, (b) Carbopol 934P, (c) their physical mixture, and (d) their interaction product.

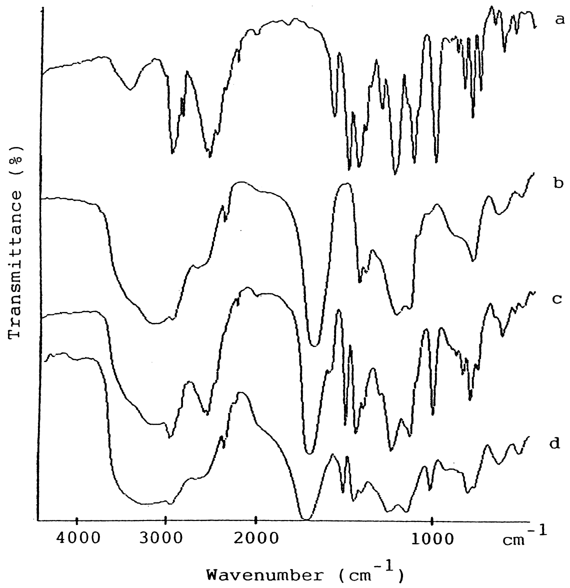


Figure 2. FTIR spectra of (a) verapamil hydrochloride, (b) Carbopol 934P, (c) their physical mixture, and (d) their interaction product.

grams of drug per milligram of the polymer is presented in Table 2. Analysis of the data using multiple linear regression analysis revealed that the most influential effect on the extent of interaction was due to increasing the drug-to-polymer ratio, as shown by the highest coefficient in the response surface equation (B_1) (Table 3 and Fig. 3). This effect can be explained on the basis that the drug, the polymer, and the drug-polymer complex are present in equilibrium in the dialyzing tube. This equilibrium was shifted toward complex formation by increasing the drug-to-polymer ratio and by the formation of the insoluble complex, leading to a higher amount of the drug interacting per milligram of the polymer. A similar finding was observed in the interaction of metoclopramide and poly(D,L-lactide-*co*-glycolide) copolymer (12).

The second factor, which significantly increased the extent of interaction, was increasing the pH from 1.2 to 5, as observed from its coefficient (B_3). This effect may be attributed to the increased dissociation of the polymer-carboxylic groups with increasing pH (33,34), which facilitate more interaction of the anionic carboxyl group with the basic tertiary amine nitrogen of the drug. It may also be due to the decreased solubility of the drug with

Table 2

Effect of Different Variable Combinations on the Extent of Drug-Polymer Interaction, the $t_{50\%}$ *of Drug Release, and the Water Uptake of Matrices*

	Extent of Interaction (mg of Drug/mg of Polymer)		$t_{50\%}$ (h)		Water Uptake After 6 h (% of the Original Tablet Weight)	
Experiment	Run 1	Run 2	Run 1	Run 2	Run 1	Run 2
1	0.515	0.532	10.0	10.5	113.4	120.1
a	0.940	0.961	9.3	9.6	73.5	78.2
b	0.569	0.547	23.9	21.1	66.8	69.2
ab	0.985	1.090	20.9	18.3	45.2	38.5
c	0.733	0.712	140.3	129.1	58.7	62.1
ac	1.358	1.334	129.2	133.9	49.9	46.7
bc	0.568	0.590	163.1	155.3	38.9	41.3
abc	1.100	1.085	161.6	157.2	33.6	36.5

Table 3

Response Surface Data (the Multilinear Regression Parameters of the Factorial Experiment)

Parameters in Equations	Extent of Interaction (mg Drug/mg Polymer)	$t_{50\%}$ (h)	Water Uptake After 6 h (% of the Original Tablet Weight)
B_o	0.002	−27.30	187.10
B_1	0.416	−1.67	−48.06
B_2	0.040	2.87	−29.08
B_3	0.064	32.00	−21.61
B_{12}	—	—	4.83
B_{13}	0.030	—	6.57
B_{23}	−0.031	1.754	2.87
SD	0.038	3.44	3.191
R^2%	98.86	99.81	99.09
CL	99.9	99.9	99.9
DF	10.0	11.0	9.0

B_i and B_{ij} are the multilinear regression coefficients of the equation $Y = B_o + B_1X_1 + B_2X_2 + \cdots + B_{12}X_1X_2 + B_{13}X_1X_3 + \cdots$; SD, standard deviation about the regression, R^2%, explained variation about the mean (R squared); *CL*, confidence level regression equation is nonzero; *dF*, residual degree of freedom.

increasing pH. Under this condition, the formation of an insoluble and stable complex was favorable. Many authors (9,31,33) observed an increase in the interaction of anionic polymers and cationic drugs with increasing pH.

The effect of the ionic strength was dependent on the pH, as observed from the negative coefficient of the antagonistic interaction (B_{23}). Increasing the salt concentration at pH 1.2 increased the amount of interacted drug per milligram of the polymer, while increasing the salt concentration at pH 5 decreased the extent of interaction. This may be explained by the fact that increasing the ionic strength influenced the ionization of the polymer-carboxylic groups. With greater ionic strength, the ionization of the carboxylic groups was shifted toward lower pH, resulting in lower pK_a. Such a shift was considered to be induced by more deprotonation of the polymer in the presence of Na^+ ions (34).

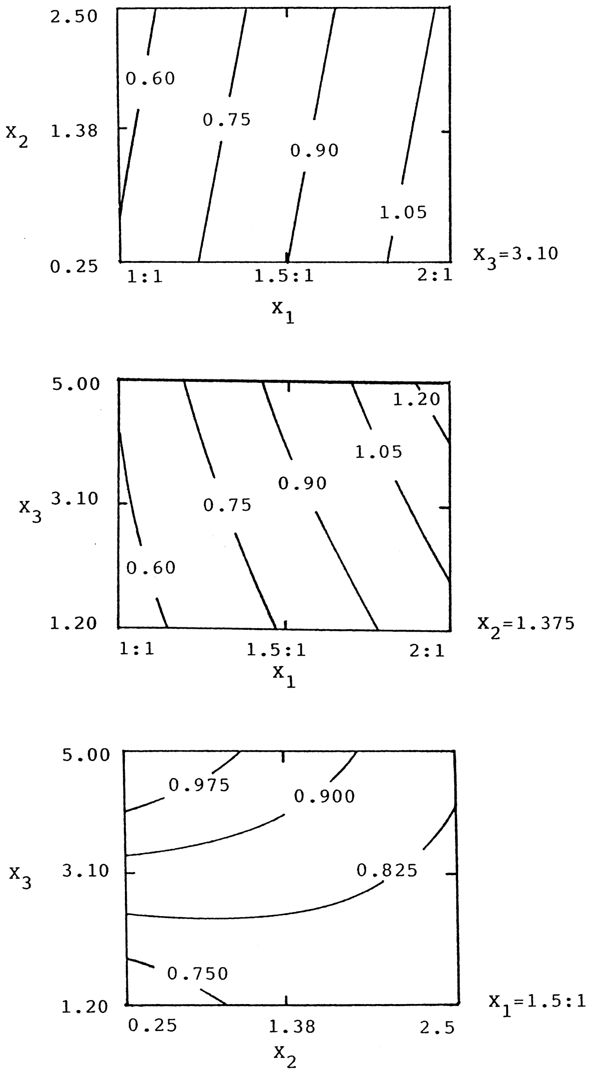


Figure 3. The effect of drug-to-polymer ratio X_1, electrolyte concentration X_2, and pH of the medium X_3 on the extent of interaction of verapamil hydrochloride with Carbopol 934P (mg/mg).

Effect of Different Variables on the Release Rate of the Drug and the Water Uptake of the Polymer Matrix

The release of verapamil hydrochloride from the polymer matrices prepared with 1:1 and 2:1 drug-to-polymer ratios in the previously mentioned media according to Table 1 is presented in Fig. 4. The kinetic treatment of the data revealed that the release of the drug followed the Higuchi diffusion model (Table 4). The $t_{50\%}$ was calculated using the linear regression equation parameters. The effect of different variable combinations on the $t_{50\%}$ is expressed in Table 2.

Response surface analysis revealed that the factor with the most significant effect on the rate of release was the pH, with a highly magnified coefficient in the

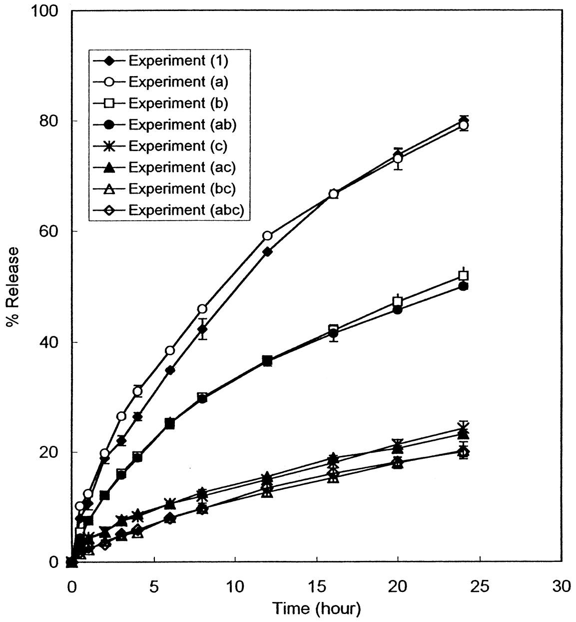


Figure 4. The release rate of verapamil hydrochloride from drug-polymer matrix under different experimental combinations.

Table 4

Higuchi Linear Equation Parameters of the Release of Verapamil Hydrochloride Under Different Experimental Combinations

	Intercept		Slope (Kinetic Release Constant K), $\%/(\mathrm{h})^{1/2}$		Correlation Coefficient R	
Experiment	Run 1	Run 2	Run 1	Run 2	Run 1	Run 2
1	−6.043	−5.793	17.709	17.202	0.993	0.994
a	−2.341	−1.260	17.169	16.529	0.998	0.997
b	−2.200	−2.301	10.675	11.301	0.998	0.998
ab	−4.168	−3.588	11.846	12.527	0.993	0.997
c	−1.764	−2.715	4.370	4.640	0.985	0.988
ac	−1.024	−0.433	4.490	4.358	0.985	0.992
bc	−1.682	−1.975	4.046	4.171	0.993	0.992
abc	−1.071	−1.386	4.017	4.098	0.997	0.996

$t_{50\%}$ equation (B_3) (Table 3 and Fig. 5). This effect could be due in part to decreased solubility of the drug with increasing pH. It could be due in part to the increased interaction of the drug with the polymer with increasing pH, as proven previously, which retards the release of the drug from the insoluble interaction product in the matrix of the polymer. Neau et al. (31) noticed a significant decrease in the release rate of chlorpheniramine from a matrix containing Carbopol 974P with increasing pH from pH 1.5 to pH 7.4 and referred that it was partially due to the increased interaction between the positively charged drug and the negatively charged polymer at higher pH. The effect of pH on the release rate of phenacetin from poly- (ethylene oxide)–carboxyvinylpolymer interpolymer complex was also reported (11). The release rate of the drug increased with increasing pH, which was attributed to the breakdown of the interpolymer complex at the higher pH.

A much lower positive coefficient was observed for the ionic strength, indicating that increasing the concentration of salt decreased the rate of release and consequently increased the $t_{50\%}$. A very small negative coefficient was observed for increasing the drug-to-polymer ratio, indicating a slight decrease in the $t_{50\%}$ and consequently an increase in the rate of release with increasing drug content of the matrix.

Much faster release was expected with decreasing polymer content of the matrix, as reported in many research articles (25,31,35). The more or less similar release patterns of the drug from matrices prepared with different drug-to-polymer ratios (1 : 1 and 2 : 1) may be due to the fact that the expected delaying effect due to increasing polymer content of the

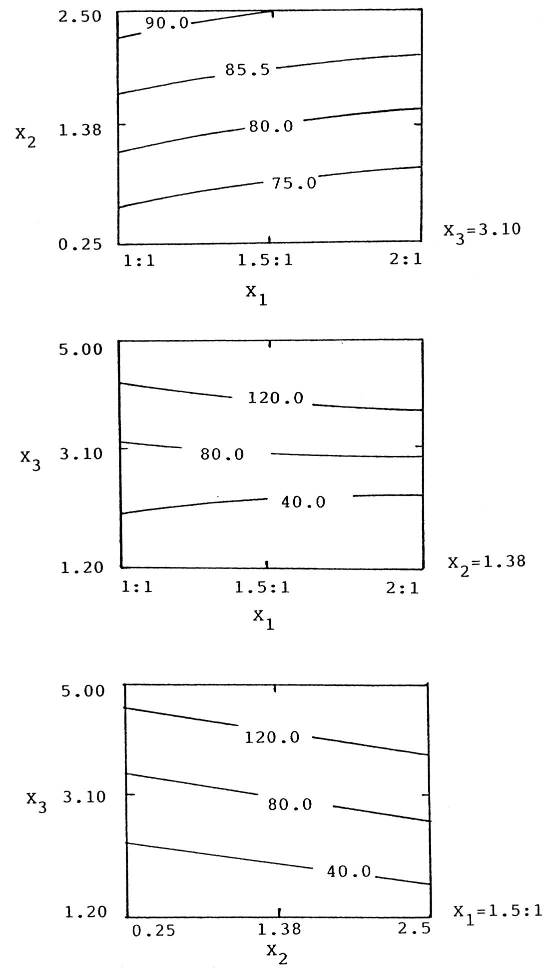


Figure 5. The effect of drug-to-polymer ratio X_1, electrolyte concentration X_2, and pH of the medium X_3 on the rate of release of verapamil hydrochloride $t_{50\%}$.

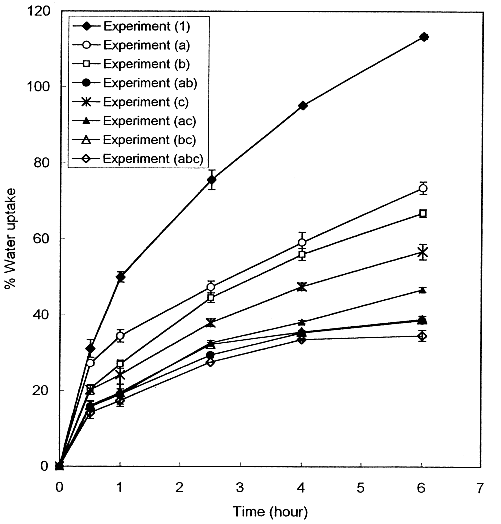


Figure 6. The rate of water uptake as a percentage of the weight of the original tablets under different experimental combinations.

matrix (1 : 1 ratio) was balanced by the increased interaction of the drug and polymer on increasing drug content of the matrix (2 : 1 ratio).

The effect of different variables on the rate of water uptake of the polymer matrix is presented in Table 2 and Fig. 6. The three factors had a decreasing effect on the extent of water uptake of the matrix after 6 h, as observed from the negative coefficients (Table 3). The greatest decreasing effect on the water uptake of the matrix was due to increasing the drug-to-polymer ratio, followed by increasing the electrolyte concentration, and finally by increasing the pH (Fig. 7).

It is well known that the swelling of Carbopol is due to the partial dissociation of the acidic carboxyl group in aqueous solution, producing a flexible coil structure. Gel formation depends on the electrostatic repulsion between the anionic carboxyl groups (21,34,36). The more the dissociation of the carboxyl groups, the more the repulsion and the greater the chain relaxation and swelling of the polymer. From the discussion above, it is obvious that the main reason behind the reduced swelling of the matrix on increasing the drug-to-polymer ratio was the increased interaction of the anionic carboxyl groups with the tertiary amine nitrogen of the drug, forming an insoluble complex.

Increasing the ionic strength decreased the water uptake of the matrix, which was more pronounced at the low pH. It was reported that screening of the carboxyl groups by Na^+ ions at high ionic strength value may influence the viscosity and swelling properties of Carbopol as it does other polyelectrolyte gels (37). Bekturov and Bakauova (38) reported that Carbopol adhesion is very sensitive to the presence of ions. The polymer in solution disentangles due to the action of its partly ionized carboxylic groups. The addition of cations to the solution shields these charges and results in the recoiling of the macromolecules on themselves. Neau et al. (31) replaced water with a strong electrolyte solution, in wetting a mass containing Carbopol 974P, to reduce the tackiness of the mass and facilitate the preparation of extruded and spheronized beads.

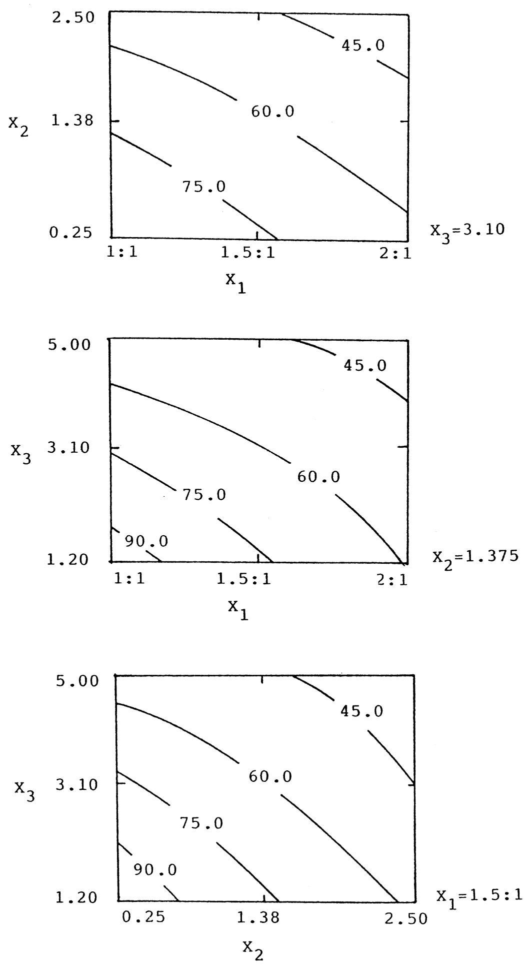


Figure 7. The effect of drug-to-polymer ratio X_1, electrolyte concentration X_2, and pH of the medium X_3 on the extent of water uptake of the polymer matrix after 6 h.

According to Dittmar (39), the carboxyl groups dissociate highly in an alkaline environment, leading to more electronic repulsion between the negatively charged groups, causing more uncoiling and expansion of the molecules and more swelling. However, in the present study, increasing the pH decreased the water uptake and the swelling of the matrix (Fig. 7). This can be partially due to the reduced drug solubility with increasing pH, which reduced the channel porosity of the matrix in media of higher pH. The main reason could be attributed to the fact that increasing the pH facilitated the interaction of the drug with the polymer, leading to more neutralization of the carboxyl group and less repulsion and swelling of the matrix.

In addition, a lake of correlation was observed between the rate of water uptake of the matrices (Fig. 6) and the rate of drug release (Fig. 4), contrary to a previous finding with different polymeric matrices (35). This result can also be attributed to the interaction of the drug with the polymer, which retards the release rate of the drug.

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