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Captopril gastrointestinal therapeutic system coated with cellulose acetate pseudolatex: evaluation of main effects of several formulation variables

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Abstract

Maintenance of constant drug levels in the body for those drugs that are used in management of hypertension is extremely beneficial. This can be successfully achieved by delivering the antihypertensives as osmotically-controlled drug-delivery system that essentially eliminates the influence of pH on the drug release. The main objective of this study was to evaluate the main effects of the formulation variables on the release of captopril from osmotically-controlled drug-delivery system coated with a custom-made cellulose acetate (CA) pseudolatex reported earlier. A secondary objective was to identify a suitable antioxidant for incorporating in the formulation as the drug undergoes metal-catalyzed oxidative degradation. The drug showed good stability ($\geq 90\%$ intact captopril) in solution in the presence of ascorbic acid for a period of 48 h. A seven-factor, 12-run Plackett–Burman screening design was employed to study the main effects of amounts of Polyox® N10 and N80, Carbopol® 934P and 974P, sodium chloride, orifice size, and % coating weight gain. The response variable was cumulative percent of drug released in 12 h, Y_3, with constraints on lag time Y_1 and time for 50% drug released Y_2. Quantitative evaluation of the screening design variables revealed that Polyox® N10, Carbopol® 974P, and % coating weight gain had a greater influence on the drug release than the rest of the factors. The main effects decreased in the order: Polyox® N10 (-8.07) = % Coating weight gain (-8.07) > Carbopol® 974P (6.83) > Carbopol® 934P (-5.3) > Polyox® N80 (5) > orifice size (2.6) > amount of sodium chloride (1.97). © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Captopril; Experimental design; Formulation variables; Gastrointestinal therapeutic system; Pseudolatex

1. Introduction

Over the past 30 years several new drug entities were introduced for the cure of various diseases and disease states. Concomitantly, the therapeutic

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advantages of controlled drug delivery were also recognized. As a result, various controlled drug-delivery devices such as matrix and diffusion-controlled systems are currently available (Grass and Robinson, 1990). It is well recognized that by controlled drug delivery, steady therapeutic efficacy with reduced or no risk of side effects can be achieved. Besides, spatial and temporal delivery of drugs is possible by appropriately-designed controlled drug-delivery systems (Chiao and Robinson, 1995). Amongst all the controlled drug-delivery systems, oral-controlled drug delivery has received major attention because of its greater popularity (Banakar, 1987; Khan et al. 1994, 1995). Despite several advantages, drug release from oral-controlled release dosage forms may be affected by pH, gastric motility, and the presence of food (Jonkman, 1989). One practical approach with the potential to overcome these disadvantages is the osmotic drug-delivery system.

Captopril, an orally-active angiotensin-converting enzyme inhibitor, has proven to have excellent clinical effectiveness in the treatment of essential hypertension. It has been a drug of choice in hypertension management. However, after single oral dosing of the drug, the antihypertensive action is only effective for 6–8 h. Hence, clinical use requires a daily dose of 37.5–75 mg to be taken three times in divided doses (Martindale, 1977; Duchin et al., 1982). Development of a controlled delivery system for captopril would bring many advantages to patients. A coated controlled release captopril oral delivery system is not available in the market. In addition, the literature search also did not indicate studies directed towards the development of an optimized captopril osmotically-controlled delivery system coated with cellulose acetate (CA) pseudolatex. One of the difficulties of captopril formulations has been reported to be its instability in aqueous solutions. The metal-catalyzed oxidative degradation was found to be the cause for inactive captopril disulphide formation (Timmins et al., 1982). In another reported study dealing with the identification of a suitable dissolution medium for testing captopril-sustained release dosage form, oxidative degradation was reduced by citrate buffer solutions (Chen et al., 1995).

The present study was conducted to determine the main effects of formulation variables for the development of an osmotically-controlled drug-delivery system for captopril coated with CA pseudolatex. Since the aqueous dispersion of CA coating system was proposed for the development of captopril, the stability of the drug in the presence of different antioxidants was also evaluated.

2. Materials and methods

2.1. Materials

The following materials were received as gifts: captopril from Invamed Inc (Dayton, NJ, USA); Polyox® N10 and Polyox® N80 from Union Carbide Corporation (Danbury, CT, USA); cellulose acetate (39.8% acetylation) from FMC Corporation (Philadelphia, PA, USA); Carbopol® 934P and 974P from B.F. Goodrich Company (Cleveland, OH, USA); FD and C red (No.27 HT23) from Colorcon (West Point, PA, USA); ascorbic acid from Takeda USA Inc (Orangeburg, NY, USA); lactose from Foremost (Baraboo, WI, USA) and diacetin from CP Hall Company (Chicago, IL, USA). Destab™ for placebo tablets was obtained from Particle Dynamics (St Louis, MO, USA). Sodium chloride, sodium citrate, citric acid, phosphoric acid, and magnesium stearate were purchased from Mallinckrodt Specialty Chemical Company (Paris, KT, USA), and methanol and hydrochloric acid from Spectrum Chemical Mfg. Corporation (Gardena, CA, USA). All materials were used as received.

3. Methods

3.1. HPLC analytical method development for the assay of captopril samples

Captopril was assayed by employing a Novapak C-18, 15 × 3.9 cm column with a particle size of 4 μm. The HPLC system included an isocratic pump (model 2350) with ISIS autosampler, an autoinjector with a Valco valve, an UV detector (Waters, model 484) and an integrator (Shimadzu

CR-501). The wavelength used was 220 nm. The mobile phase consisted of a 72.5:27.5 mixture of 0.1% phosphoric acid and methanol. An injection of 10 μl sample was used for the analysis. The captopril solutions were employed as external standards. The retention time for captopril was 4.9 min. Fig. 1 shows the representative chromatogram for captopril analysis. The peak areas obtained from chromatograms were used to calculate the concentration values of captopril in the tested sample solutions.

3.2. Captopril solution stability studies

Stability of captopril was evaluated in four types of solutions at 37 and 60°C. Solutions of captopril with 1 mg/ml concentration were made in the following systems: (1) distilled water; (2) 0.05 M and pH 6 citrate buffer; (3) Ascorbic acid solution with a concentration of 5 milligrams per milliliter; and (4) combined solution of citrate buffer (0.05M and pH 6) and ascorbic acid (5 mg/mg captopril). These captopril solutions were poured into scintillation vials and kept at 37 and 60°C. Two milliliter samples ($n = 3$) were collected at 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 h time points and analyzed by HPLC. The solutions showing presence of $\geq 90\%$ captopril was considered stable for the drug stability.

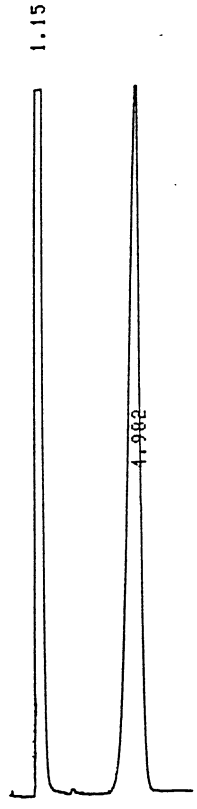

Fig. 1. Representative chromatogram of captopril HPLC analysis.

3.3. Calibration curves for assay of captopril solution stability and dissolution samples

Captopril, 100 mg, was dissolved in different stability solutions in a 100 ml volumetric flask to give stock solutions. The stock solutions were suitably diluted to give 0.1, 0.5, 0.75, 1.0, and 1.5 mg/ml of captopril standard solutions. Each standard was analyzed in duplicate by HPLC method at 220 nm. The mobile phase used was 72.5% of 0.1% H3PO4 and 27.5% of methyl alcohol. A calibration plot of concentration versus peak area of captopril yielded a straight line each with r^2 of 0.999.

The calibration curve for captopril dissolution sample analysis was also constructed as above. The standard solutions used were 1, 5, 10, 20, and 40 μg/ml of captopril and 0.25 mg/ml of ascorbic acid. External standards were employed for the entire analysis.

3.4. Plackett–Burman screening design

Plackett–Burman factorial designs can identify main factors from large number of suspected contributor factors for the desired response variables. Therefore, these designs are extremely useful in preliminary studies where the aim is to identify formulation variables that can be fixed or eliminated in further investigation. The model is of the form:

$$Y = A_0 + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_4 + \ldots\ldots\ldots\ldots\ldots + A_nX_n$$

where Y is the response, A_0 is a constant and A_1–A_n are the coefficients of the response values. The design analyzes the input data and presents a

Table 1
Formulation factors of captopril GITS for Plackett–Burman screening design

Independent factors	Levels used	
	Low	High
X_1 = Amount of Polyox®N10	100 mg	250 mg
X_2 = Amount of Polyox®N80	100 mg	250 mg
X_3 = Amount of Carbopol®934P	0 mg	5 mg
X_4 = Amount of Carbopol®974P	0 mg	5 mg
X_5 = Amount of NaCl	20 mg	60 mg
X_6 = Orifice size	0.014 inches	0.02 inches
X_7 = Coating % weight gain	10%	16%
Dependent factor		
Y_3 = Cumulative percent of drug released in 12 h		
Constraints		
Y_1 = Lag time $0 < Y_1 < 0.5$		
Y_2 = Time for 50% drug dissolved $5 < Y_2 < 7$		

Table 2
Processing conditions for latex coating

Tablet bed size	500 g
Inlet temperature	80 ± 2°C
Outlet temperature	60 ± 2°C
Inlet air pressure	9.9 psig
Atomizing pressure	0.67 kp/cm^2
Coating spray rate	7–10 g/min
Proportionating pump speed	2
Air flap opening	30°
Processing conditions for seal coating	
Tablet bed size	500 g
Inlet temperature	50 ± 2°C
Outlet temperature	45 ± 2°C
Inlet air pressure	20 psig
Atomizing pressure	1.2 kp/cm^2
Coating spray rate	7–10 g/min
Proportionating pump speed	2
Air flap opening	45°

rank ordering of the variables with magnitude of effect, and designates signs to the effects to indicate whether an increase in factor value is advantageous or not (Murray, 1994). The dependent and independent variables are listed in Table 1, and the processing conditions in fluid-bed coating are shown in Table 2. A seven-factor 12-run Plackett–Burman screening design, Table 3, was generated using X-Stat®.

3.5. Preparation of captopril bilayerd osmotic tablets

The drug layer was comprised of 37.5 mg of captopril and 100 or 250 mg of Polyox® N10, 0 or 5 mg of Carbopol®934P, 187.5 mg of ascorbic acid, 5 mg of lactose, and 0.8 mg of magnesium stearate. The osmotic layer was comprised of 100 or 250 mg Polyox® N80, 0 or 5 mg of Carbopol® 974P, 20, or 60 mg of sodium chloride, 0.8 mg of magnesium stearate, and 0.4 mg of FD&C red color. Both layers were mixed separately. Bilayered, standard convex tablets of half-inch diameters were prepared using a carver press (model C) attached to a carver semiautomatic compression accessory (model No.2729). The compression pressure was adjusted so that the average hardness of tablets after compression was 7–8 kp. This hardness was selected to avoid very high pressures that may damage the punches in eventual high speed production.

3.6. CA pseudolatex coating

Initially the tablets were seal coated with a 2% w/v CA solution in acetone to prevent the highly water-swellable carbopols and polyox resins from coming in contact with water. Following this seal coating, pseudolatex coating was provided. The pseudolatex was warmed to room temperature before the addition of plasticizer. Diacetin (160% w/w based on solids content of pseudolatex) was dispersed in water and slowly added to the pseudolatex with mild stirring. Additional volume of water was added to adjust the final solids content of plasticized pseudolatex to 8.1% w/v. The seal coated experimental captopril osmotic tablets were mixed with placebo tablets of Destab™ in a

laboratory model Uni–Glatt fluidized-bed coater (Model 2817). The nozzle employed had 1.0 mm diameter. The processing conditions for both seal coating and pseudolatex coating are shown in Table 2. The tablet bed was warmed for 5 min before the pseudolatex was sprayed. The outlet temperature and spray rates were maintained at 60 ± 2°C and 7–10 gm/min, respectively, during the entire coating process. The spraying was interrupted whenever the outlet temperature dropped below 58°C. Following coating, the experimental tablets were dried in an oven at 45°C for 48 h and stored in a closed amber colored container at room temperature. An orifice of 0.014 or 0.02 inch diameter was drilled into the drug layer before the dissolution testing. The depth of orifice was maintained constant at 0.06 inches.

3.7. In vitro dissolution testing

The tablets were subjected to dissolution studies using USP Paddle Method, employing distilled water as the medium. The temperature was maintained at 37°C and the paddle speed used was 100 rpm. At predetermined times, samples were withdrawn and analyzed by the HPLC method reported in previous section.

4. Results and discussion

The concentration of captopril present in different solutions at 37 and 60°C is presented in Table 4. Captopril showed good stability in all solutions at 37°C except citrate buffer and ascorbic acid. However, this behavior is not consistent with solutions kept at 60°C with the exception of solution containing ascorbic acid. Overall $\geq 90\%$ of captopril was found to be intact in solutions with ascorbic acid at both tested temperatures at the end of 48 h. Captopril showed good stability in the presence of citric acid at 37 but not at 60°C. Chen et al. (1995) have revealed that captopril degrades faster at higher temperatures even in the citric acid buffer. In the present study, coating of the captopril GITS with CA pseudolatex was carried out at high inlet and outlet temperatures. Furthermore, the presence of citric acid may not prevent the oxidative degradation of captopril. Besides, the stability study also showed a decrease in captopril concentration at elevated temperatures. Therefore, ascorbic acid was used as an antioxidant in the development of captopril GITS in the present investigation.

Preliminary studies were carried out to identify low and high levels of the factors selected for

Table 3
Captopril GITS-randomized runs and the response[a]

Run	X_1	X_2	X_3	X_4	X_5	X_6	X_7	Y_1	Y_2	Y_3
1.	1	−1	1	−1	−1	−1	1	0.56	10.15	57.90
2.	1	1	−1	1	−1	−1	−1	0.32	6.40	79.50
3.	−1	1	1	−1	1	−1	−1	0.50	5.60	80.10
4.	1	−1	1	1	−1	1	−1	0.21	6.75	75.70
5.	1	1	−1	1	1	−1	1	0.23	6.80	78.30
6.	1	1	1	−1	1	1	−1	0.27	5.70	74.10
7.	−1	1	1	1	−1	1	1	0.33	6.40	77.80
8.	−1	−1	1	1	1	−1	1	0.47	7.60	72.40
9.	−1	−1	−1	1	1	1	−1	0.12	5.40	90.70
10.	1	−1	−1	−1	1	1	1	0.44	7.80	64.20
11.	−1	1	−1	−1	−1	1	1	0.37	6.20	79.10
12.	−1	−1	−1	−1	−1	−1	−1	0.11	6.10	78.00

[a] X_1 to X_7 see Table 1.

Table 4
Captopril stability in different solutions (mg/ml)[a]

Time (h)	A_1	A_2	A_3	A_4	B_1	B_2	B_3	B_4
0.0	1.10	1.20	1.10	1.10	1.10	1.20	1.10	1.20
0.5	0.99	1.05	1.05	1.02	1.01	1.04	1.04	1.00
1.0	0.97	1.03	1.03	1.00	1.00	1.02	1.03	0.99
2.0	0.98	0.99	1.02	0.98	0.99	1.01	1.01	0.97
4.0	0.96	0.98	1.08	0.98	0.98	0.99	1.01	0.96
8.0	0.96	0.95	1.01	0.96	0.98	0.98	1.01	0.89
12.0	0.95	0.92	0.98	0.94	0.98	0.98	1.01	0.91
24.0	0.94	0.80	0.99	0.85	0.98	0.99	1.02	0.87
36.0	0.94	0.91	0.99	0.81	0.99	0.99	1.01	0.85
48.0	0.93	0.84	0.99	0.62	0.99	0.99	1.01	0.85
60.0	0.92	0.77	0.97	0.33	0.95	0.99	1.00	0.60
72.0	0.92	0.77	0.97	0.30	0.95	0.99	0.99	0.59

[a] Solutions: A_1, A_2, A_3 and A_4 at 60°C; solutions: B_1, B_2, B_3 and B_4 at 37°C; A_1 and B_1, water; A_2 and B_2, cikate buffer; A_3 and B_3, ascorbic acid in water; A_4 and B_4: ascorbic acid in citrate buffer.

screening. The factor combination helped in the preparation of captopril GITS with desired response. The formulation variables and their levels used in the study are presented in Table 1. The 12-run Plackett–Burman screening design consisting of seven-factors at two levels is shown in Table 3. The response studied was cumulative percent captopril released in 12 h with constraints on lag time and time for 50% (t_{50}) drug release. The response values are also shown in Table 3.

The dissolution profiles of captopril osmotic tablets obtained for the 12 runs are presented in Figs. 2 and 3. Different factor combinations yielded response of varying magnitudes. The values of response Y_3 ranged from 57.9% (run 1) to 90.7% (run 9).

4.1. Polynomial equation

To understand the mathematical relationship between independent and dependent (response Y_3) factors studied, a polynomial equation was generated. The polynomial equation obtained is as follows:

$$Y_3 = 76.7 - 4.03\ _1 + 2.50\ X_2 - 2.65\ X_3 + 3.42\ X_4 + 0.98\ X_5 + 1.28\ X_6 - 4.03\ X_7.$$

Where Y_3 is cumulative percent dissolved in 12 h.

The above equation presents the direction and magnitude of the factors (X_1–X_7) on response Y_3. Therefore, it is obvious from the equation that factors with large coefficient values have profound effect on the response Y_3. Factors with positive coefficients (X_2, X_4, X_5, and X_6) influence response Y_3 synergistically, whereas factors with negative coefficients (X_1, X_3, and X_7) show antagonistic effect on response. The significance of the ratio of

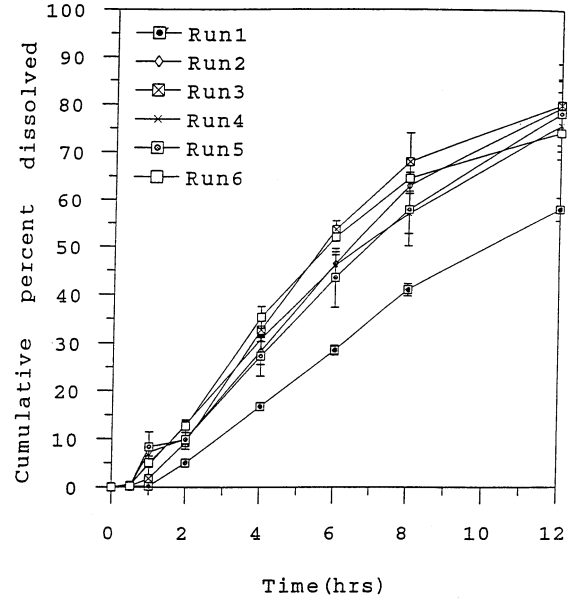

Fig. 2. Dissolution profiles of captopril osmotic tablets for runs 1–6.

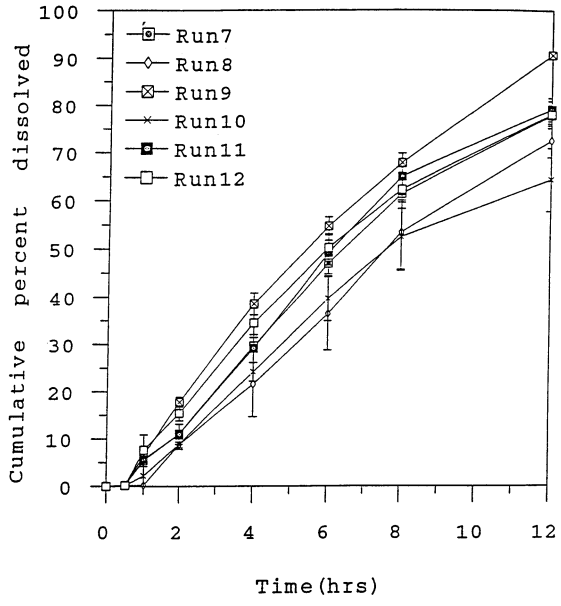

Fig. 3. Dissolution profiles of captopril osmotic tablets for runs 7–12.

mean square variation as a result of regression and residual error was tested using ANOVA. The test indicated a significant ($P < 0.05$) effect of factors on responses [F_{cal} (14.62) > F_{crit} (6.09)].

Table 6
Magnitude and direction of variables on the response of captopril GITS

Factors	Main effects (Y_3)
X_1	−8.07
X_2	5.00
X_3	−5.30
X_4	6.83
X_5	1.97
X_6	2.60
X_7	−8.07

The theoretical (predicted) values were obtained by substituting the factor levels in the polynomial equation. The predicted and observed values, Table 5, were found to be in close agreement.

The main effects with their magnitude and direction are obtained from the model for each factor and are listed in Table 6. Amongst the seven factors studied, the factors X_2, X_4, X_5, and X_6 showed positive main effects. The factors X_2 and X_4 showed a strong main effect on response Y_3, indicating directly proportional relationship. However, factors X_1, X_3, and X_7 have a large negative main effect on response Y_3.

Table 5
Captopril GITS-observed and predicted values of response (Y_3)

Run	Observed (%)	Predicted (%)	Residuals	
1.	57.90	56.75	1.15	
2.	79.50	81.95	−2.45	
3.	80.10	79.85	0.25	
4.	75.70	74.22	1.48	
5.	78.30	75.85	2.45	
6.	74.10	74.35	−0.25	
7.	77.80	79.22	−1.42	
8.	72.40	73.62	−1.22	
9.	90.70	89.55	1.15	
10.	64.20	66.58	−2.38	
11.	79.10	77.68	1.42	
12.	78.00	78.18	−0.18	
ANOVA for Y_3				
Source	DF	SS	MS	F-ratio
Total (corrected)	11	749.3		
Regression	7	721.1	103	
Residual	4	28.18	7.05	14.62
Explained variation about the mean = 96.2%				

4.2. Contour plots

Contour plots were obtained to understand the effect of factors on response Y_3 more clearly. Effect of factors X_1 (Polyox® N10) and X_2 (Polyox® N80) on response is shown in Fig. 4. Both Polyox® N10 and N80 are nonionic polyethylene oxide water-soluble resins. These resins are very hydrophilic and hydrate rapidly to form a gel. The highly-viscous gel and entrapped drug in this gel is released through the orifice at slow rates (Union Carbide, 1993). Therefore, an increase in Polyox® N10 from 100 to 250 mg decreased the response Y_3. However, an increase in Polyox® N80 increased the response. The reason may be the swelling nature of Polyox® N80 that was present in the osmotic layer. It is obvious that more drug will be pushed out when the osmotic compartment swells.

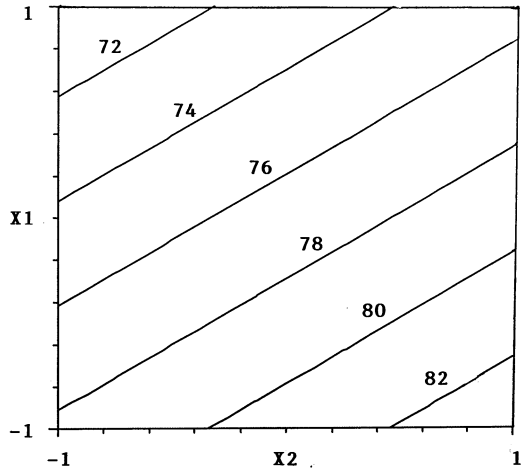

Fig. 4. Contour plots showing the effect of Polyox® N10 (X_1) and Polyox® N80 (X_2) on response Y_3.

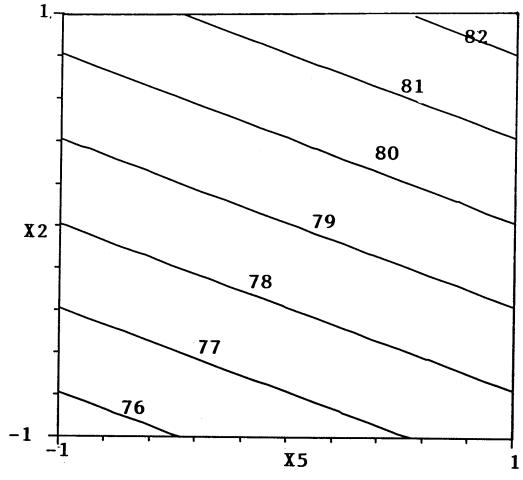

Fig. 5. Contour plots showing the effect of Polyox® N80 (X_2) and sodium chloride (X_5) on response Y_3.

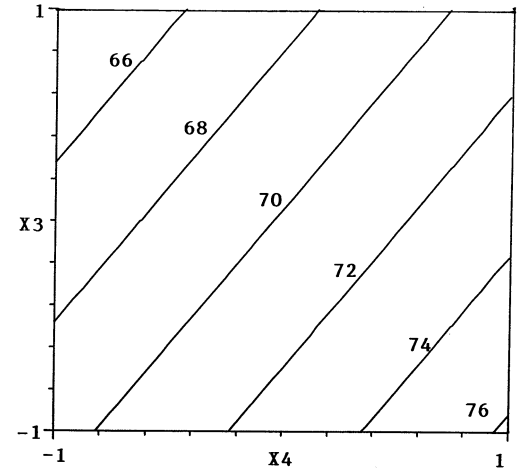

Fig. 6. Contour plots showing the effect of Carbopol® 934P (X_3) and Carbopol® 974P (X_4) on response Y_3.

The positive influence of Polyox® N80 (X_2) and sodium chloride (X_5) is presented in Fig. 5. An increase in Polyox® N80 from 100 to 250 mg increased the response as seen in Fig. 5. The response Y_3 increased when the amount of sodium chloride increased from 20 to 60 mg. The increase in sodium chloride pulls more water into the osmotic layer aiding in increased drug delivery (Theeuwes, 1975).

The negative effect of Carbopol 934P on captopril drug release, and the positive effect of Carbopol 974P are shown in Fig. 6. The presence of Carbopol 934P in the drug layer is in agreement with its general drug dissolution retardant properties. However, the positive main effect of Carbopol 974P is probably because of its presence in the osmotic layer. Because of this polymer as well as the Polyox, the osmotic layer swells and pushes the drug layer which in turn forces the drug out of the orifice.

The effects of the amount of sodium chloride (X_5) and the % coating weight gain (X_7) on response Y_3 is shown in Fig. 7. An increase in the amount of sodium chloride from 20 to 60 mg increased the response Y_3 through increased osmotic pressure influence as seen in Fig. 5. Conversely, the increase in coating weight gain from 10 to 16% decreased the response Y_3. The reason for this condition is the increased hindrance on water permeation by increased thickness of osmotic membrane (Swanson et al., 1987).

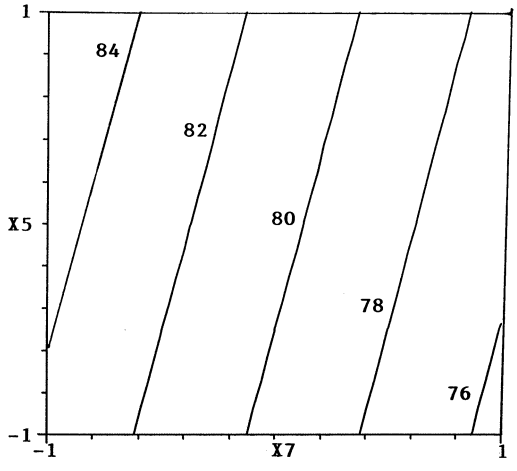

Fig. 7. Contour plots showing the effect of sodium chloride (X_5) and percent coating weight gain (X_7) on response Y_3.

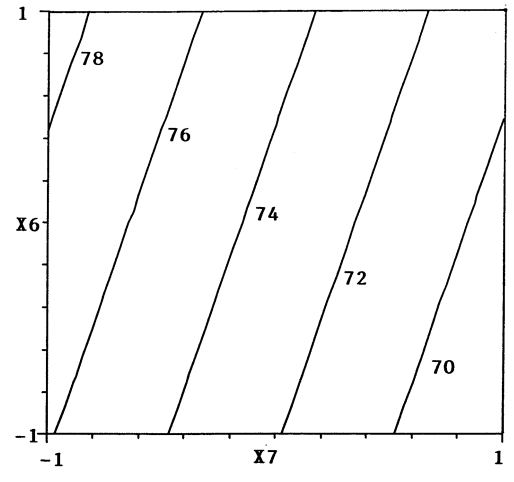

Fig. 8. Contour plots showing the effect of orifice size (X_6) and percent coating weight gain (X_7) on response Y_3.

The effect of orifice size (X_6) and coating percent weight gain (X_7) are shown in Fig. 8. The increase in orifice size increases the drug release regardless of the extent of coating weight gain. However, an increase in coating weight gain has been found to decrease the drug release.

5. Conclusions

Captopril showed good solution stability at both 37 and 60°C in the presence of 1:5 drug to ascorbic acid ratio over a period of 48 h. The captopril stability was shown to decline in plain distilled water, citrate buffer, and a mixture of citrate buffer and ascorbic acid. Screening of formulation variables, amounts of Polyox® N10 and N80, Carbopol® 934P and 974P, sodium chloride, orifice size and % coating weight gain using Plackett–Burman screening design revealed that Polyox® N10, Carbopol® 974P, and % coating weight gain had more influence as compared to the other factors on captopril release from osmotic tablets coated with CA pseudolatex. The main effects decreased in the order Polyox® N10 (-8.07) = % coating weight gain (-8.07) > Carbopol® 974P (6.83) > Carbopol® 934P (-5.3) > Polyox® N80 (5) > orifice size (2.6) > amount of sodium chloride (1.97). In conclusion, the significant main factors such as Polyox N10, % coating weight gain, Carbopol 974P, and Carbopol 939P can be judiciously used in a further optimization study to obtain captopril osmotically-controlled bilayered tablets with desired drug-release properties.

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