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Statistical Optimization of Ketoprofen-Eudragit® S100 Coprecipitates to Obtain Controlled-Release Tablets

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ABSTRACT

Coprecipitates of ketoprofen and Eudragit® S100 have been prepared by a recently reported technique and compressed as tablets to release 75 mg of the drug in phosphate buffer (pH 7.2) medium in a 12-hour period. A second-order Box-Behnken design has been employed to optimize the independent variables that include the level of polymer Eudragit® S100 used, the level of diluent lactose used, and the applied compressional pressure. The design included a total of 15 experiments for the three variables at three levels each. Tablets containing 75 mg of ketoprofen were compressed according to the design. Dissolution experiments were run by the USP basket method at 100 rpm. Dissolution half-time (t_{50}) was recorded from the plot of cumulative percent of ketoprofen dissolved as a function of time. Hardness and thickness of the tablets were also recorded. A mathematical relationship and response surface plots were generated to determine the relationship between t_{50} and the independent variables with constraints on the hardness and the thickness. Levels of the independent variables were predicted to obtain the optimum response. The optimization procedure predicted a t_{50} of 4.81 hours, hardness of 18 kg, and thickness of 0.41 cm when the levels of polymer, diluent, and compressional pressure were 22.86%, 36.92 mg, and 0.97 tons respectively. New formulations that were made accordingly yielded t_{50} values that were very close to the predicted values.

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INTRODUCTION

Coprecipitates of drugs and polymers have been studied extensively for enhancing the dissolution of poorly soluble compounds (1–3) and for providing sustained drug delivery (4–6). Coprecipitates have been synonymously used with solid dispersions, although there are clear differences between them (7). Traditionally, solid dispersions have been prepared by the fusion or solvent evaporation method, whereas the coprecipitation involves dissolution of drug and polymers in an organic solvent followed by the addition of a nonsolvent under agitation (7). Khan et al. (8) reported the effects of process variables on the flow characteristics of ibuprofen-Eudragit® S100 coprecipitates. After obtaining the coprecipitates, a suitable formulation has to be made, and surprisingly, only a very few reports are available in the literature to provide a sustained-release dosage form of coprecipitates. Formulation of sustained-release suspensions (9), capsules (10), and directly compressible tablets (11) are a few examples of the reported studies. The present study deals with an optimization procedure to prepare sustained-release tablets of a nonsteroidal drug, ketoprofen, from its coprecipitate with the acrylic and methacrylic acid polymer, Eudragit® S100.

The drug ketoprofen was selected because of its low plasma half-life of 2–4 hours (12), low water solubility, and high solubility in alcohol USP. The latter two properties are very helpful for the preparation of coprecipitates. The polymer Eudragit® S100 was used based on some preliminary studies that indicated an efficient release profile of ketoprofen with very small amounts of the polymer. The overall objectives of the present study were to prepare coprecipitates of ketoprofen with Eudragit® S100 by the recently reported method (8), and compress them as tablets. The procedure was simple, practical, and provided controlled release of ketoprofen with low levels of Eudragit® S100. As a part of this preparation procedure, a second-order Box-Behnken design was applied to optimize the dosage forms with constraints on the tablet hardness and thickness. The independent variables for the present study were polymer and diluent ratios in the formulation, and the applied compressional pressure. The dependent variable selected was the dissolution t_{50}.

MATERIALS AND METHODS

Ketoprofen was purchased from Sigma Chemicals; Eudragit® S100 was obtained as a gratis supply from Rohm Pharma (Weiterstadt, Germany). All other chemicals were used as received.

Preparation of Coprecipitates

Ten grams of ketoprofen and the required amount of Eudragit® S100 (depending on the experimental run) were dissolved in 27.8 mL of alcohol USP. To this alcoholic solution, water (maintained at 5°C) was added while stirring at a rate of 634 rpm, and the stirring was continued for 10.5 minutes. The resultant precipitate was filtered using Whatman #4 qualitative filter paper, collected in an evaporating dish, and dried at 40°C until it reached a constant weight. The coprecipitate was then passed through a #20 mesh and stored in amber-colored bottles.

Drug Loading Efficiency

Fifty milligrams of the copreciptate was dissolved in 100 mL of alcohol USP, and after suitable dilutions, absorbance was recorded in a DU-8 Beckman spectrophotometer at 299.6 nm. From a standard Beer's plot, concentration was determined from the observed absorbance values and expressed as the percent drug loading efficiency.

Compression of Coprecipitates

Appropriate amount of the coprecipitates containing 75 mg of ketoprofen was passed through USP standard sieve #20 and mixed with diluent lactose in an amount ranging from 35 to 105 mg per tablet depending on the experimental run presented in Table 1. Talc and magnesium stearate were added as glidant and lubricant respectively in a concentration of 1% each and mixed in a plastic bag for 1 minute. The resultant mixture was then compressed in a semiautomated Carver Press by using 6 mm biconvex punches. The compressional pressure ranged from 0.5 to 1.5 tons.

Dissolution Studies

Dissolution was carried out using a USP Basket method at 37°C and 100 rpm. Nine hundred milliliters of pH 7.2 phosphate buffer was used as the dissolution medium. Before beginning the dissolution in pH 7.2 medium, the tablets were soaked in simulated gastric fluid for an hour. An automated dissolution tester (Vankel dissolution apparatus, manostat peristaltic pump, and

Table 1

Experimental Runs and Observed Responses of Ketoprofen Coprecipitates with Eudragit®

Experiment Number	X_1	X_2	X_3	Y_1	Y_2	Y_3
BB1	11	70	1.50	2.60	9.35	0.39
BB2	22	70	1.00	4.20	11.60	0.45
BB3	22	105	1.50	2.40	22.70	0.50
BB4	22	105	1.50	2.20	11.90	0.50
BB5	11	105	1.00	1.60	13.60	0.40
BB6	33	70	0.50	2.60	17.30	0.57
BB7	22	70	1.00	4.20	11.55	0.45
BB8	33	105	1.00	3.20	24.40	0.53
BB9	22	35	1.50	3.80	18.50	0.39
BB10	11	70	0.50	2.60	18.30	0.43
BB11	11	35	1.00	3.80	13.20	0.36
BB12	22	70	1.00	4.00	11.60	0.43
BB13	33	35	1.00	4.60	27.70	0.45
BB14	33	70	1.50	4.00	29.50	0.51
BB15	22	35	0.50	4.60	26.20	0.39

Beckman model 35 UV-spectrophotometer with controller for automatic sampling) was programmed to record absorbance peak heights at predetermined time intervals. The absorbance peak heights were then converted to cumulative percent dissolved using a standard plot. All the experiments were performed in triplicate.

Hardness and Thickness

Hardness and thickness were measured by a Stokes hardness tester and Vernier calipers respectively. The average of five measurements for each parameter was recorded.

Experimental Design

A second-order Box-Behnken design was employed to maximize the dissolution t_{50} values of the tablets with constraints on tablet hardness and thickness. The independent variables and their levels and the dependent variables are given below:

Independent Variables

X_1 = Polymer to drug ratio (%) = 11%, 22%, and 33%

X_2 = Amount of diluent per tablet = 35, 70, and 105 mg

X_3 = Compressional pressure = 0.5, 1, and 1.5 tons

Dependent Variables

Y_1 = Dissolution t_{50}

Y_2 = Tablet hardness (kg)

Y_3 = Tablet thickness (cm)

The mathematical relationship between dependent and independent variables is given by the following equation:

$$Y = B_0 + B_1X_1 + B_{11}X_1^2 + B_2X_2 + B_{22}X_2^2 + B_{12}X_1X_2 + B_3X_3 + \ldots$$

where Y is the dependent variable, X_1, X_2, and X_3 are the independent variables, B_1 is the coefficient of variable X_1, and B_{12} is the coefficient of interaction of X_1 and X_2. The higher-order terms show the quadratic nature of the relationships. The total number of experiments required must be greater than or equal to the number of coefficients in the model. The ratio of number of experimental runs to the maximum number of experimental runs gives the redundancy of the model. Box-Behnken design requires fewer runs than the full-factorial design and therefore provides less redundancy. However, some information on the three-level interactions is lost. Generally, the design consists of a replicated center point and a set of points at the midpoint of each edge of a multidimensional cube that defines the region of interest. For the three-factor and three-level design, a total of 15 experimental runs are needed. These runs, along with the response variables of disso-

lution t_{50}, tablet hardness, and thickness, are presented in Table 1.

RESULTS AND DISCUSSION

The experimental runs, their randomized order, and the responses observed are shown in Table 1. The experimental order was completely randomized to minimize the bias in the observed values. The dissolution profiles of all the experimental runs are shown in Figures 1–3. The t_{50} values were obtained as the time corresponding to 50% release of the drug, ketoprofen. Further, it can be seen from Table 1 that the experimental runs 13 and 15 showed maximum sustaining action with a t_{50} of 4.6 hours while experiment number 5 yielded tablets with a minimum t_{50} of 1.6 hours. With no constraints on hardness and thickness, experiments 13 and 15 should be the best choice for sustained-release ketoprofen tablets with the present variables. However, the average hardness of the tablets in experiments 13 and 15 was 27.7 and 26.2 kg respectively, which may damage the punches and tablet presses if operated at high speeds. Therefore, it was decided to optimize the formulation to obtain maximum t_{50} with constraints on hardness (less than or equal to 18 kg) and thickness (less than or equal to 0.5 cm). Under these constrained conditions, mathematical relationship between the independent variables and dissolution t_{50} was obtained in the form of a polynomial equation, and is given below:

$$Y_1 = 2.4 + 0.01X_1 - 0.02X_2 + 3.43X_3 + 0.06X_1X_3 + 0.02X_2X_3 - 3.05X_3^2$$

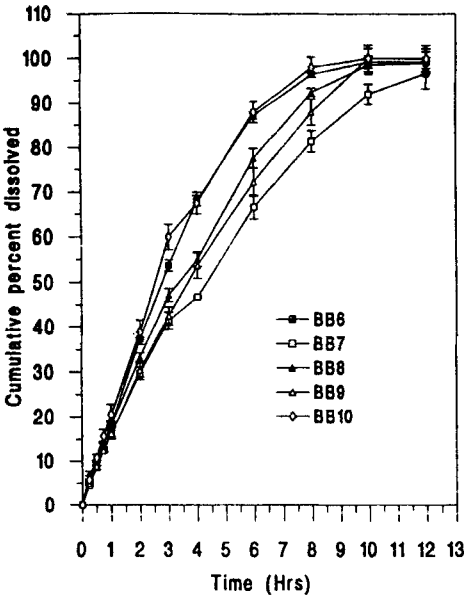

Figure 2. Dissolution profiles of ketoprofen tablets obtained from the coprecipitates by the Box-Behnken design experiments 6–10.

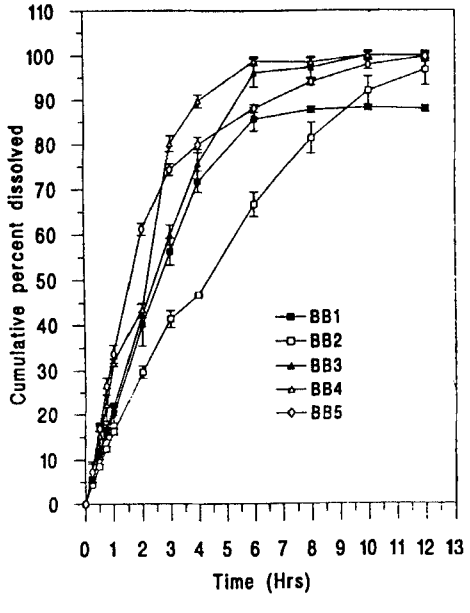

Figure 1. Dissolution profiles of ketoprofen tablets obtained from the coprecipitates by the Box-Behnken design experiments 1–5.

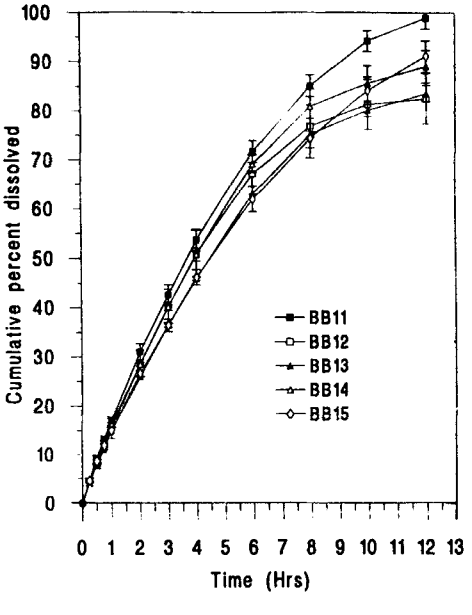

Figure 3. Dissolution profiles of ketoprofen tablets obtained from the coprecipitates by the Box-Behnken design experiments 11–15.

The polynomial equation is shown after correcting for the insignificant terms and reducing the coefficients to two decimal places. From the equation, it can be interpreted that the dissolution t_{50} increases with polymer ratio (X_1) and compression pressure (X_3), and decreases with an increase in the level of lactose (X_2). The lactose, being soluble in the dissolution medium, may be acting as a channeling agent, thereby allowing more drug to dissolve. It can also be interpreted from the equation that there is a synergistic action between the levels of polymer and compression pressure, possibly because of increased bulk resulting in greater hardness and slower dissolution. The positive synergistic effect is also seen by a combined action of lactose content and compression pressure. To justify the use of polynomial equation, values of X_1, X_2, and X_3 from all the experimental runs were substituted in the above equation to obtain the predicted values of the dissolution t_{50}. These values are shown in Table 2. It can be seen that the residual values are indicating a fairly good agreement between the observed and the predicted response.

To further understand the relationship between dependent and independent variables, contour plots were generated using the statistical package X-Stat® and are shown in Figures 4–6. As demonstrated in Figure 4, at high lactose levels, dissolution t_{50} values decreased to 2 hours when the polymer Eudragit S100 concentration was below 15%. Dissolution t_{50} of 4.5 hours was obtained at higher X_1 and low X_2 levels.

When the compression pressure was between 1.45 and 1.5 tons and the polymer concentration was less than 13%, the dissolution t_{50} was least with a value of

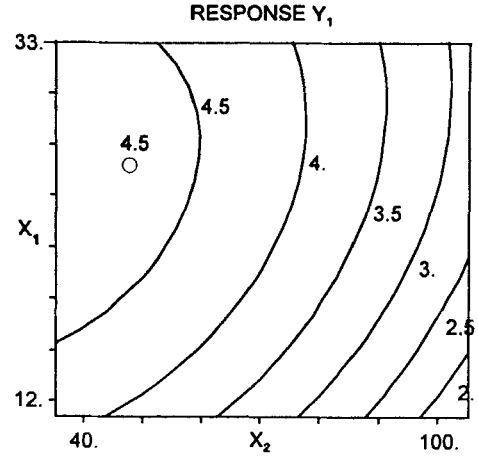

Figure 4. Contour plot showing the effect of polymer concentration (X_1) and diluent level (X_2) on the dissolution t_{50} of ketoprofen.

3.2 hours. This can be seen in Figure 5. The central large region of the same contour plot shows a dissolution t_{50} of 4.73 hours when the compression pressure was between 0.7 and 1.2 tons and the polymer concentration was greater than 15%. The increase in the t_{50} was probably due to increased compression on a greater bulk, and the corresponding increase in the tablet hardness.

Figure 6 shows the effect of factors X_2 and X_3, and their interaction on the response Y_1. The dissolution t_{50} was maximum when the lactose level was less than 50%, and the compression pressure was between 0.5

Table 2

Observed and Predicted Values of Ketoprofen Coprecipitates with Eudragit® S100

Experiment Number	Observed t_{50} (hr)	Predicted t_{50} (hr)	Residuals
BB1	2.6	2.304	0.296
BB2	4.2	4.133	0.067
BB3	2.4	2.471	-0.071
BB4	2.2	2.471	-0.271
BB5	1.6	1.554	0.046
BB6	2.6	2.896	-0.296
BB7	4.2	4.133	0.067
BB8	3.2	2.904	0.296
BB9	3.8	3.800	0.000
BB10	2.6	2.646	-0.046
BB11	3.8	4.096	-0.296
BB12	4	4.133	-0.133
BB13	4.6	4.646	-0.046
BB14	4	3.954	0.046
BB15	4.6	4.257	0.343

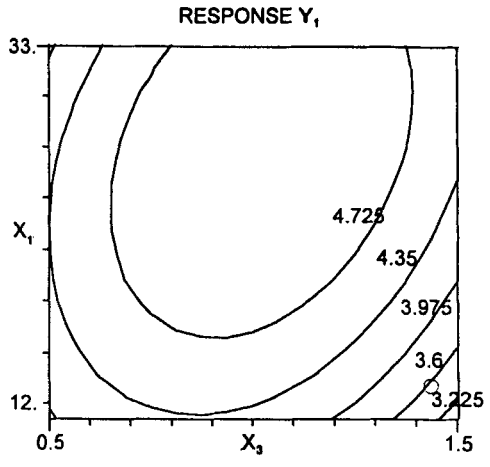

Figure 5. Contour plot showing the effect of polymer concentration (X_1) and compression pressure (X_3) on the dissolution t_{50} of ketoprofen.

and 1.2 tons. Very high compression pressures yielded tablets that were capping, which might have been the reason for decreased t_{50}. The decreased t_{50} at higher X_2 levels was probably because of the increased channeling effect of lactose.

Having studied the effect of independent variables on the responses, it was then desired to obtain the levels of independent variables that would provide the maximum t_{50} with constraints on the hardness and the thickness. By the computer optimization process, X_1, X_2, and X_3 levels of 22.86, 36.92, and 0.965 respectively predicted the response values Y_1, Y_2, and Y_3 of 4.81 hours, 18 kg, and 0.41 cm respectively. As a confirmation process, a fresh batch of ketoprofen tablets prepared with the above independent variable levels yielded tablets with the dissolution t_{50}, hardness and thickness of 4.65 hours, 17.6 kg, and 0.4 cm respectively.

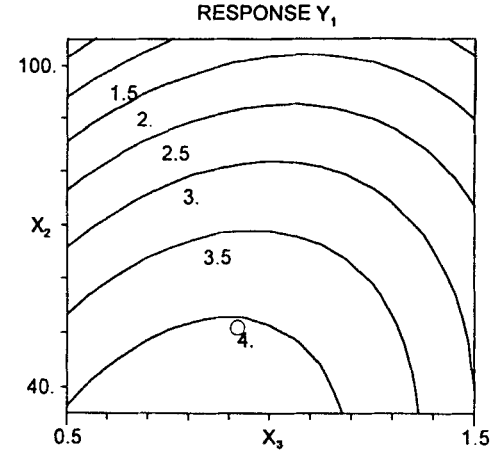

Figure 6. Contour plot showing the effect of diluent level (X_2) and compression pressure (X_3) on the dissolution t_{50} of ketoprofen.

CONCLUSIONS

Controlled-release coprecipitates of ketoprofen have been formulated by using a recently reported technique of coprecipitation. The technique was simple, practical, and eliminates the need of toxic organic solvents or heating to prepare extended-release preparations. Ketoprofen coprecipitates were successfully compressed to obtain tablets of predictable dissolution t_{50}. The second-order Box-Behnken design with 15 experimental runs for three factors at three levels was adequate to obtain the levels of Eudragit® S100, lactose, and compressional pressure in the optimization process. Theoretically predicted t_{50} values were compared with the observed values and were found to be close.

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