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Optimization of process variables for the preparation of ibuprofen coprecipitates with Eudragit S100

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Summary

The objective of this study was to optimize the technique used to prepare extended release coprecipitates of ibuprofen with Eudragit S100. The technique involved dissolution of ibuprofen and Eudragit S100 in alcohol USP followed by the addition of cold water with agitation for a specified length of time. A four-factor full factorial design with agitation time and speed and volumes of alcohol and water was used for optimization. The dependent variables were percent recovery of ibuprofen, flowability index and geometric mean diameter of the coprecipitated granules. Mathematical relationships and response surface plots were obtained to relate the dependent and independent variables. Optimization was performed by the grid search and computer methods.

Introduction

Coprecipitation of poorly soluble drugs with polymers has been attempted in order to improve their dissolution and absorption (Simonelli et al., 1969; Sugimoto et al., 1980). More recently, this technique has been modified to prepare extended release preparations (Hassegawa et al., 1985; Bodmeier and Chen, 1990; Malamataris and Avgerinos, 1990; Kawashima et al., 1992). While several methods have been reported for coprecipitation, the present method involved the dissolution of drug and polymer in a common solvent followed by the addition of a non-solvent with agitation. The coprecipitate obtained was filtered and dried. Kislalioglu et al. (1991) prepared and characterized the coprecipitates of ibuprofen with several acrylate polymers by using this method. The method was simple, practical and required only very small amounts of polymers to retard the release of drugs like ibuprofen which require a high dose.

In developing extended release solid dosage forms, it is important that the coprecipitates have predictable properties such as the percent recovery of the drug, flowability index and size of the coprecipitated granules. These properties may be controlled by factors such as agitation time and

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speed, and volumes of the solvent and non-solvent needed for coprecipitation. The present investigation dealt with preparing coprecipitates of ibuprofen with the acrylate polymer, Eudragit S100, using alcohol USP as the solvent and water as the non-solvent. Ibuprofen was chosen because it has a short half-life of about 2 h, high dose requirements, gastrointestinal side effects, is readily soluble in alcohol USP and practically insoluble in water. Valle-Jones et al. (1984) have indicated that although ibuprofen is one of the safest of the NSAI drugs, its efficacy and tolerance may be improved by sustained release formulations. Eudragit S100 was used since it has been shown to retard the dissolution of ibuprofen, it does not interact with ibuprofen and does not need any additive such as emulsifying agents to give microsphere-like granules (Khan and Kislalioglu, 1987; Kawashima et al., 1989; Kislalioglu et al., 1991). The main objective of the study was to statistically determine the levels of factors which yield coprecipitates with the highest percent recovery of ibuprofen, best flow properties and predictable size of the coprecipitated granules. This optimization process may be used to prepare extended release coprecipitates with predictable properties which can be easily formulated as solid oral dosage forms.

Materials and Methods

Materials

Ibuprofen was kindly provided by Boots Pharmaceutical Inc. (Shreveport, LA), and Eudragit S100 was a gift from Röhm Pharma (Weiterstadt, Germany). Water used in all the experiments was deionized and distilled. All other chemicals were used as received.

Methods

Preparation of coprecipitates

Preliminary experiments indicated that ibuprofen and Eudragit S100, in a ratio of 6:1, form coprecipitates which have good flow properties, percent recovery, potential to sustain the release of ibuprofen and give microsphere-like structures whose size can be controlled. Therefore, this ratio was kept constant throughout the study. 10 g of ibuprofen and 1.67 g of Eudragit S100 were dissolved in alcohol in an amount ranging from 20 to 40 ml. To this alcoholic solution, water was added under stirring at a specified rate for a specified length of time. The water temperature was maintained at 5°C to ensure that precipitation was complete and that the granule size was more uniform. The resultant precipitates were filtered out using Whatman no. 4 qualitative filter paper, collected in an evaporating dish and dried at 40°C until they reached a constant weight. The coprecipitates were then packed in screw-capped amber bottles.

Determination of drug content and percent recovery

An HPLC method was used to assay the ibuprofen content in coprecipitates. The isocratic method described in the USP monograph of ibuprofen was modified to use methanol instead of acetonitrile. The conditions which gave optimum resolutions between the drug ibuprofen and the internal standard, valerophenone, included a 0.75 ml/min flow rate, 254 nm wavelength, 10 μl sample size, 15×0.45 cm C_{18} column and a mobile phase containing 28:72 of 4% chloroacetic acid aqueous solution:methanol.

To determine the drug content, 50 mg of coprecipitate was dissolved in 20 ml of methanol. 2 ml of internal standard solution (1 mg/ml of valerophenone in methanol) and 25 ml of distilled water were added to this solution and sufficient methanol was added to make up the volume to 100 ml. Peak area ratio of the drug and internal standard was compared with standard values to obtain the amount of ibuprofen present in the coprecipitate. Percent recovery of ibuprofen was computed by multiplying the amount of ibuprofen in 50 mg of coprecipitate with the total weight of copreciptate obtained and taking its percentage.

Determination of the flow properties

The following methods have been used for determining the flow parameters for Carr's (1965) flowability index values.

TABLE 1

Variables in the factorial design

Independent variables
X_1 = agitation time; 5 and 15 min
X_2 = agitation rate; 200, 500 and 800 rpm
X_3 = alcohol USP volume; 20, 30 and 40 ml
X_4 = water volume; 50, 125 and 200 ml
Dependent variables
Y_1 = percent recovery (%)
Y_2 = flowability index
Y_3 = geometric mean diameter (mm)

Angle of repose (AR)

10 g of the coprecipitated granules were allowed to pass through a funnel of 12 cm, fixed at a height of 8 cm from the surface of a table. The angle of repose, which is the angle formed by the material heap, was measured by a protractor. The experiment was repeated twice.

Angle of spatula (AS)

A steel spatula of 10×2.2 cm was inserted flat at the bottom of the heap formed for AR measurements and withdrawn vertically. The angle that the material heap formed on the flat spatula was measured by the protractor.

Compressibility ratio (CR)

CR was a numerical value obtained by using tapped (T) and untapped (U) volumes of 12 g of the coprecipitated granules. It is obtained by using the formula:

$$CR = (U - T) \cdot 100/U$$

Uniformity coefficient (UC)

This was determined by sieve analysis. US standard sieves were stacked in the ascending order of sieve number, no. 8, 12, 20, 60 and fines. 10 g of the coprecipitated granules were allowed to pass through the sieves by vibration at a setting of 5 for 2 min in a sieve shaker (CSC Scientific Co., Fairfax, VA). UC was obtained as the ratio of the sieve through which 60% of the material passed to that through which 10% of the material passed.

Experimental design

A four-factor full factorial was employed. The variables and levels are shown in Table 1. All 54 of the possible combination of levels of the factors were examined in randomized order.

Results and Discussion

The experimental runs and responses observed for the first 10 formulations are listed in Table 2. The range of the responses can be seen from the complete table. The maximum recovery was 99.8% in experiment FD10 and the minimum recovery was 73.7% in experiment FD26. Only the water volume was different, amounting to 50 ml in FD10 and 200 ml in FD26. The stirring time was only 5 min in both the experiments. The low recovery of ibuprofen might have been due to increased solubility and filtration of ibuprofen before the polymer crystallized out completely.

TABLE 2

Observed values of the responses for the full factorial design

Run no.	Factors				Responses		
	X_1	X_2	X_3	X_4	Y_1	Y_2	Y_3
FD1	15	500	30	125	8.88	86.14	1.40
FD2	15	200	20	200	9.25	81.80	8.40
FD3	15	800	20	50	9.56	88.28	0.78
FD4	5	800	20	125	9.10	90.66	1.60
FD5	15	200	30	125	9.13	86.70	7.20
FD6	15	200	30	50	9.59	80.30	5.50
FD7	5	500	40	50	9.69	77.64	1.20
FD8	15	500	20	200	8.66	84.03	4.00
FD9	5	200	20	125	9.71	86.24	9.20
FD10	5	500	20	50	9.98	87.29	0.78

The rate of polymer crystallization was found to be much slower than that of the drug. Therefore, by a careful selection of the factor choices, drug recovery can be improved considerably. The flowability index value was maximum with 90.68 in experiment FD18 and minimum with a value of 65.67 in experiment FD29. A flowability index of greater than 80 is considered excellent (Carr, 1965). Both preparations were agitated for 15 min, but all the other three factors were at different levels. The increase in flowability might be related to the uniformity of coprecipitated granules that resulted from increased stirrer speed and hydro-alcoholic volumes. Geometric mean diameter and standard deviations in FD18 and FD29 were found to be 0.56 ± 0.2 and 1.35 ± 1.2, respectively. Moreover, observation under a light microscope indicated a microsphere-like appearance of the coprecipitate in FD18 and loose aggregates in FD29. The last column of Table 2 shows the variation in the geometric mean diameter. The diameter was as high as 9.2 mm in FD9 and as low as 0.53 mm in FD33. All the four factors were at different levels. The reduction in geometric mean diameter is quite obvious as the increased speed and time of agitation provide an increased shear on the coprecipitates. Moreover, increased volumes of the two media provides a greater opportunity for the coprecipitated granules to disperse and therefore the degree of aggregation is less in FD33.

In order to determine the levels of the factors which yield optimum values of the responses, mathematical relationships were generated between the dependent and independent variables, which in the present investigation, was performed with a statistical package, X-Stat®. The resultant polynomial equations of all the responses are given below:

$$Y_1 = 6.16 + 0.133X_1 + 0.003X_2 + 0.097X_3 + 0.006X_4 - 0.005X_1^2 - 0.002X_3^2 \quad (1)$$

$$Y_2 = 105.48 + 1.488X_1 - 0.012X_2 - 1.252X_3 - 0.127X_4 + 0.001X_1X_2 + 0.035X_1X_3 + 0.002X_1X_4 + 0.002X_3X_4 - 0.164X_1^2 + 0.015X_3^2 \quad (2)$$

$$Y_3 = 4.049 + 0.129X_1 - 0.020X_2 - 0.071X_3 + 0.090X_4 + 0.001X_1X_3 - 0.002X_3X_4 + 0.001X_3^2 \quad (3)$$

Eqns 1–3 represent the quantitative effect of the process variables on the three responses Y_1, Y_2 and Y_3 respectively. The values of the coefficients X_1–X_4 relate to the effects of these variables on the particular response.

TABLE 3

Observed and predicted values of the responses

Expt	Y_1			Y_2			Y_3		
	Obs.	Pred.	Resi.	Obs.	Pred.	Resi.	Obs.	Pred.	Resi.
FD1	88.80	95.72	−6.92	86.14	80.77	5.37	1.40	2.15	−0.75
FD2	92.50	85.06	7.44	81.80	77.02	4.78	8.40	7.13	1.27
FD3	95.60	91.57	4.03	88.28	85.39	2.89	0.78	−0.32	1.10
FD4	91.00	89.42	1.58	90.66	84.00	6.66	1.60	2.57	−0.97
FD5	91.30	92.22	−0.92	86.70	79.38	7.32	7.20	4.91	2.29
FD6	95.90	88.82	7.08	80.30	80.07	0.23	5.50	3.91	1.59
FD7	96.90	89.04	7.86	77.64	79.23	−1.59	1.20	0.86	0.34
FD8	86.60	87.07	−0.47	84.03	80.69	3.34	4.00	3.85	0.15
FD9	97.10	88.15	8.95	86.24	83.83	2.41	9.20	5.80	3.40
FD10	99.80	91.57	8.23	87.29	85.69	1.60	0.78	0.55	0.23

Coefficients with more than one factor term represent the interaction terms and coefficients with higher order terms indicate the quadratic nature of the relationship. A positive sign indicates a synergistic effect while a negative sign represents an antagonistic effect. To justify the use of polynomial equations, values of X_1–X_4 were substituted in Eqns 1–3 to obtain the theoretical values of Y_1, Y_2 and Y_3. The theoretical (predicted) values were compared with the observed values and were found to be in good agreement. The observed, predicted and residual values of the first 10 formulations are shown in Table 3.

The relationships between the dependent and independent variables can be further understood by contour plots. Fig. 1 shows the effect of X_1 and X_2 on Y_1. At very low agitation time and speed, represented by B in Fig. 1, recovery of ibuprofen was 91.5% and at high agitation time and speed a recovery of 93–94% was observed. However, the recovery was highest in region F with intermediate agitations and speed. At low agitation times it is likely that all the drug crystallized out completely, resulting in a greater loss in the filtrate. On the other hand, an increase in time of agitation would cause more drug to crystallize out. However, the crystallized drug may

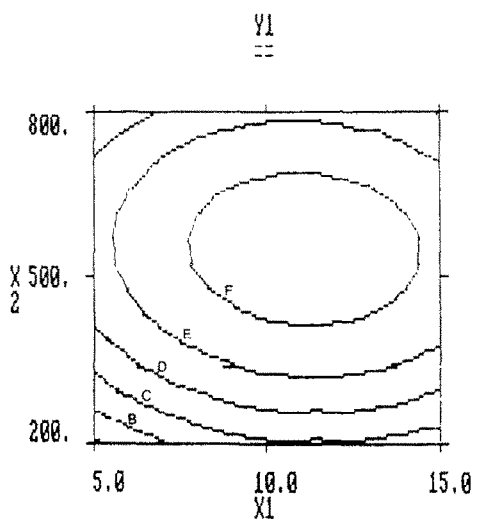

Fig. 1. Effect of agitation time and rate on the recovery of ibuprofen (in g). (B) 9.2; (C) 9.3; (D) 9.4; (E) 9.5; (F) 9.6.

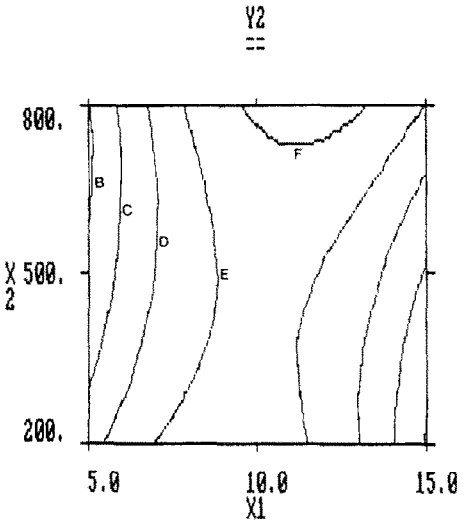

Fig. 2. Effect of agitation time and rate on the flowability index of coprecipitated granules. (B) 79.5; (C) 81.0; (D) 82.5; (E) 84.0; (F) 85.5.

resolubilize with a simultaneous increase in agitation speed. Therefore, at intermediate levels the recovery was good. The explanation given above is valid only when the alcohol and water volumes are at their medium levels of 30 and 125 ml, respectively.

Fig. 2 shows the effect of X_1 and X_2 on the response Y_2. When the agitation time was 8–12 min and the speed was between 750 and 800 rpm, the flowability index value was at a maximum of 85.5 where the shape of the agglomerates has been found to be near spherical. At very low times of agitation, irrespective of the agitation rate, the flowability index was very low which may again be due to incomplete aggregation of the drug and polymer.

Fig. 3 depicts the geometric mean diameter of the coprecipitated granules as a function of X_1 and X_2. Irrespective of the agitation time, the coprecipitates decrease in size as the speed of agitation increases. This can be easily explained by the decrease in size of the aggregates with increased shear stress.

Figs 4–6 show the effect of factors X_3 and X_4 on the responses Y_1, Y_2 and Y_3, respectively, when the other two factors are at their medium levels. Region E in Fig. 4 shows that a recovery of

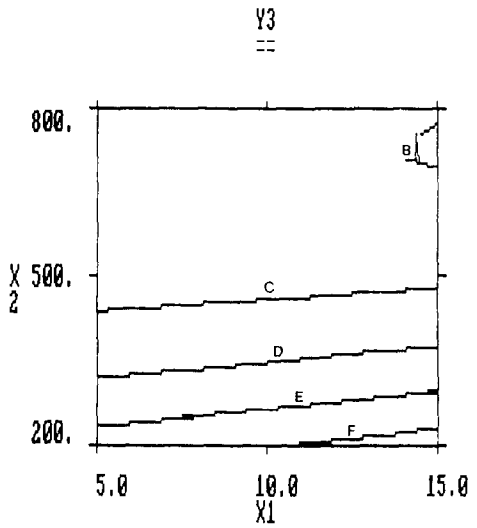

Fig. 3. Effect of agitation time and rate on the geometric mean diameter of the coprecipitated granules. (C) 2.25; (D) 3.00; (E) 3.75; (F) 4.50.

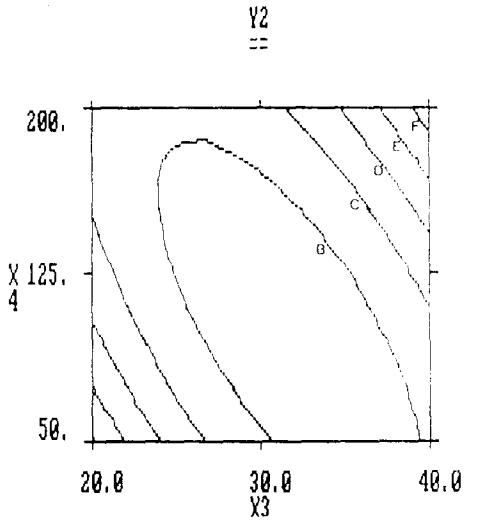

Fig. 5. Effect of alcohol and water volumes on the flowability index of coprecipitated granules. (B) 84.75; (C) 85.5; (D) 86.25; (E) 87.00; (F) 87.75.

94% can be achieved at low, medium and even high levels of alcohol volumes, provided that water volume is less than 180 ml and the factors X_1 and X_2 are at their medium levels. When the alcohol volume is very low and the water volume increases from 50 to 200 ml, the recovery decreases from 94 to 88% which may again be due to the increased solubility and loss due to filtration as the overall volume of hydro-alcoholic media increase. Fig. 5 shows that the flowability index was 84 or greater, irrespective of the levels of X_3 and X_4. However, at high levels of X_3 and X_4 the flowability index value was as high as 87.75. A possible explanation can be provided on inspection of Fig. 6 which demonstrates the relationship of X_3 and X_4 with the geometric mean diameter of the coprecipitated granules. As the levels of alcohol and water were increased, the aggregate size was decreased which may have resulted in more uniform size of the granules and hence increased flowability index.

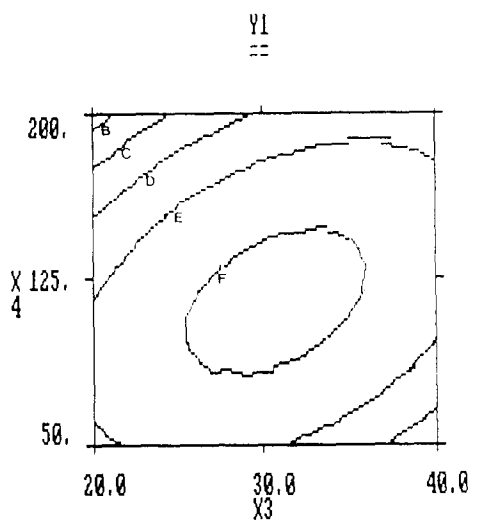

Fig. 4. Effect of alcohol and water volumes on the recovery of ibuprofen. (B) 8.8; (C) 9.0; (D) 9.2; (E) 9.4; (F) 9.6.

After generating the polynomial equations to relate the dependent and independent variables, the levels of four factors which yielded the optimum values of Y_1 and Y_2 and a controlled size of the granules (between 0.425 and 0.85 mm) were determined. This size was chosen as it was very easy to compress the granules without any need for further screening. Optimization was achieved either by superimposing the contour plots or by using the statistical package X-Stat®.

The contour plot method, also called the grid search method, involves the superimposition of contours. Two sets of contours were plotted. The

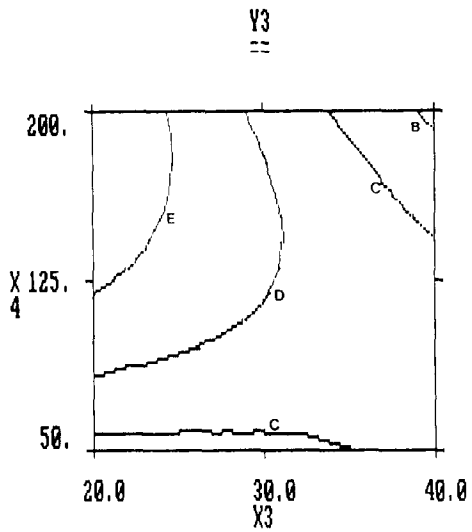

Fig. 6. Effect of alcohol and water volumes on the geometric mean diameter of the coprecipitated granules. (B) 0.00; (C) 1.00; (D) 2.00; (E) 3.00.

first set contained contours of the responses Y_1 obtained as a function of X_1 and X_2 at all combinations of levels of X_3 and X_4. The superimposition of these plots provided an X_1 range of 10.2–11 min, and X_2 range of 620–640 rpm for optimum Y_1. The second set of contours contained plots of Y_1 as a function of X_3 and X_4 at all combinations of levels of X_1 and X_2. The superimposition of such plots provided an X_3 range of 25–32 ml and X_4 range of 68–130 ml.

The computer optimization was performed to search for the levels of X_1–X_4 to maximize Y_1 by introducing the following constraints;

$$Y_2 > 80;\ 0.425\ mm \leq Y_3 \leq 0.85\ mm$$

Under these conditions, the values obtained for X_1, X_2, X_3 and X_4 were 10.5 min, 634 rpm, 27.8 ml and 69.6 ml, respectively. By substituting these values into the polynomial equations (Eqns 1–3), the predicted values of the responses were found to be 9.57 g, 85.6 and 0.85 mm for Y_1, Y_2 and Y_3, respectively. In order to test these values, two new formulations were prepared with the optimum values of the factors. The average observed values were 93.7%, 89.83 and 0.97 for the percent recovery, flowability index and geometric mean diameter, respectively.

Conclusions

Coprecipitates of ibuprofen and Eudragit S100 were prepared by using a 6:1 ratio of drug to polymer. The process variables agitation time, stirring speed, volume of alcohol and water affected the quality of the resultant product. The quantitative effect of these factors on the loading efficiency of coprecipitated granules, their flow properties and geometric mean diameter could be predicted by using polynomial equations. Levels of the process variables were predicted to obtain the optimum values of the responses.

Optimized formulations prepared according to the predicted levels provided responses which were close to those predicted. Studies on the development of its dosage form and performance in human volunteers will be reported in subsequent publications.

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