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Box-behnken design for the optimization of formulation variables of indomethacin coprecipitates with polymer mixtures

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Abstract

Numerous reports explain the dissolution release mechanisms and certain matrix type formulations follow the Higuchi's square root of time model. Earlier screening experiments have shown that compression of indomethacin coprecipitates prepared using Eudragit polymer mixtures yielded matrix tablets which release 80% of the drug in 24 h. The present study deals with optimization of formulation variables to improve dissolution characteristics of the matrix formulation. A three-factor, three-level Box-Behnken design with drug to polymer ratio (X_1), polymer to polymer ratio (X_2) and solvent ratio (X_3) as the independent variables were selected for the study. The dependent variable was cumulative percent of drug released in 24 h. As a novel approach, constraints were placed on the dependent variable such that the ideal release characteristics of a matrix formulation would be obtained for the 24-h release formulation. Based on the experimental design, different indomethacin release rates and profiles were obtained. The dependent and independent variables were related using mathematical relationships and surface response plots. The model predicted a 100.7% release with the X_1, X_2 and X_3 levels of 7.813, 0.9586 and 1.5, respectively. The optimized formulation prepared according to predicted levels provided release rates which were close to predicted values. Also, the observed and predicted response values fell in the range of calculated values as obtained from the Higuchi's model. Further, the optimized formulation was compared with solid dispersions and physical mixtures. All the formulations were characterized by X-ray diffraction, IR DSC and dissolution studies.

Keywords: Coprecipitates; Optimization; Indomethacin; Box-Behnken design; Dissolution; X-ray diffraction; Differential scanning calorimetry

1. Introduction

Coprecipitation technique reported by Simonelli et al., 1969 and Sugimoto et al., 1980 has been used to improve the dissolution and absorption of poorly soluble drugs. However, the recent trend is to modify this technique to sustain the release of therapeutic agents (Karnachi et al., 1995a,b, Khan et al., 1995, 1994; Kislalioglu et al., 1991; Malamataris and Avgerinos, 1990;

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Kawashima et al., 1989). Karnachi et al., 1995b prepared and characterized coprecipitates of indomethacin using acrylate polymers. The method was simple, practical and required small quantities of polymers to retard the release of drugs such as indomethacin. Alvan et al., 1975 have reported that a high initial plasma concentration after oral administration of indomethacin produces adverse reactions. Administration of indomethacin-controlled release capsules produced longer, smoother plasma levels as compared to conventional capsules that produced strong peaks and troughs. Tablet dosage forms have been reported to possess less tendency to adhere to the oesophagus. The present investigation was directed towards the development of sustained release tablets of indomethacin by compressing its coprecipitates with a mixture of Eudragit polymers, RS100 and L100. Indomethacin was chosen as the model drug as it has a short half life, gastrointestinal effects, is soluble in alcohol USP and practically insoluble in water. Eudragit RS100 and L100 were used since it has been shown to retard the dissolution of indomethacin in very small amounts (Karnachi et al., 1995a). In developing sustained release solid dosage forms, it is important that these coprecipitates have predictable release behavior. This may be controlled by certain formulation and process variables which need to be determined and quantified. Prior work, based on a Plackett-Burman screening design, was used to isolate the critical formulation parameters affecting the final product characteristics (Karnachi et al., 1995a). The formulation variables with maximum influence on the release were drug to polymer ratio (X_1), polymer to polymer ratio (X_2) and solvent ratio (X_3). These factors resulted in a formulation that followed the Higuchi's square root of time model, suggesting a matrix tablet formulation (Karnachi et al., 1995b). However, the formulation released only 80% drug in 24 h. Further optimization was required to achieve 100% release in 24 h. Since it was known that the formulation follows Higuchi's square root of time model, a novel optimization procedure based upon the Higuchi's model values of cumulative percent released with high and low constraints at different time points have been employed. Therefore, the objective of this study was to study the effect of formulation variables on cumulative percent of drug released, statistically determine the levels of these factors and optimize the product using mathematical equations and response surface plots. The optimization procedure would aid in preparing controlled release coprecipitates with predictable properties. Further, a comparative evaluation of optimized tablets prepared with coprecipitates, solid dispersions and physical mixtures with respect to their dissolution, IR, crystallinity index and thermal changes was performed.

2. Experimental design

A three-factor, three-level Box Behnken design (Box and Behnken, 1960) was used for the optimization procedure. This design is suitable for exploration of quadratic response surfaces and constructs a second order polynomial model, thus helping in optimizing a process using a small number of experimental runs. The design consists of replicated center points and the set of points lying at the midpoints of each edge of the multidimensional cube that defines the region of interest. The model constructed is as follows: $-Y = a_o + a_1X_1 + a_2X_2 + a_3X_3 + a_4X_1X_2 + a_5X_2X_3 + a_6X_1X_3 + a_7X_1^2 + a_8X_2^2 + a_9X_3^2 + E$ where a_o to a_9 are the regression coefficients; X_1, X_2 and X_3 are the factors studied; Y is the measured response associated with each factor level combination; and E is the error term. The independent factors and measured responses are listed in Table 1.

3. Materials and methods

3.1. Materials

The following chemicals were obtained from commercial suppliers; Indomethacin (Spectrum chemicals, USA), Eudragits RS100 and L100 (Rohm Pharma, Weiterstadt, Germany), and alcohol USP (Fisher scientific, USA). All ingredients were used as received. Water used was deionized and distilled.

Table 1
Variables in the Box-Behnken design

	Independent variables
X_1 =	Drug : Polymer ratio
X_2 =	Polymer : Polymer ratio (RS100 : L100)
X_3 =	Solvent ratio (water : alcohol)
	Dependent variables
Y_1 =	Release after 1 h
Y_2 =	Release after 3 h
Y_3 =	Release after 6 h
Y_4 =	Release after 12 h
Y_5 =	Release after 24 h

3.2. Methods

3.2.1. Preparation of coprecipitates and tablets

Coprecipitates and their tablets were prepared as reported (Karnachi et al., 1995b). Briefly, the drug and polymers were dissolved in alcohol USP and precipitated using distilled water reduced to pH 1.2 at 4°C. The formulation and process conditions are summarized in Table 2. Solid dispersions and physical mixtures were also prepared as reported earlier (Karnachi et al., 1995b).

3.2.2. Drug loading efficiency

Accurately weighed samples of coprecipitates (50 mg) were dissolved in alcohol USP and assayed spectrophotometrically for indomethacin content at 317 nm. A calibration curve was used based on standard solutions in alcohol USP. The polymers did not interfere with the analysis at this wavelength. The indomethacin concentration was calculated and expressed as percent drug loading efficiency.

3.2.3. Infrared spectroscopy

Nicolet analytical infrared spectrophotometer (model MX-S) was used to obtain IR spectra of pure drug, physical mixtures, solid dispersions and coprecipitates (KBr tablets). The scanning range used was 4000–400 cm^{-1}.

3.2.4. Qualitative X-ray diffraction study

Qualitative X-ray diffraction studies were performed as reported (Karnachi et al., 1995b) using a Philips X-ray diffractometer model, PW 1840.

3.2.5. Dissolution studies

Dissolution experiments were performed with tablets equivalent to 75 mg indomethacin in 900 mL medium. The tablets were exposed to pH 1.2 for 1 h followed by changing the medium to pH

Table 2
Observed values of responses for the Box-Behnken design.

Form No.	X_1	X_2	X_3	Y_1	Y_2	Y_3	Y_4	Y_5
1	12.6	1.09	1	9.43	21	34.32	52.29	75.66
2	7.6	1.09	0.5	8.4	19.97	31.85	53.48	79.88
3	17.6	0.59	1	4.67	10.07	28.56	56.76	83.08
4	12.6	1.09	1	9.43	21.18	34.32	52.29	75.66
5	12.6	0.59	1.5	11.12	24.71	44.19	79.1	96.12
6	17.6	1.09	1.5	11.83	31.37	43.09	70.78	88.35
7	7.6	1.59	1	8.46	18.23	1.04	49.72	75.72
8	7.6	0.59	1	9.72	23.86	44.25	75.91	100.6
9	12.6	1.59	0.5	9.53	21.56	37.31	58.87	84.99
10	17.6	1.09	0.5	11.73	23.48	43.79	76.04	101.6
11	17.6	1.59	1	4.7	10.33	27.28	53.19	77.03
12	12.6	1.59	1.5	10.12	23.53	39.88	62.73	87.77
13	12.6	0.59	0.5	10.43	27.18	48.21	80.53	98.94
14	12.6	1.09	1	9.43	21.18	34.32	52.29	75.66
15	7.6	1.09	1.5	10.58	23.54	41.31	66.44	94.6

7.2. The study was then carried out for 24 h. The dissolution medium was maintained at a temperature of 37°C ± 0.5°C (USP XXII rotating basket method, at 100 rpm). At suitable time points, 5 mL of the medium was withdrawn and analyzed spectrophotometrically at 318 nm. Equivalent amount of medium was added as replacement. Experiments were performed in triplicate.

3.2.6. Differential scanning calorimetry (DSC)

DSC was carried out using a Perkin-Elmer (DSC-7) instrument to obtain the melting endotherms of indomethacin and the optimized formulations of coprecipitates, solid dispersions and physical mixtures. Formulations containing approximately 5 mg of indomethacin were scanned in sealed aluminum pans from 100 to 180°C at a rate of 10°C/min under nitrogen atmosphere. All the DSC curves were normalized and autoscaled before overlapping.

4. Results and discussion

The experimental runs and the observed responses for the 15 formulations are shown in Table 2. The dependent variable studied was cumulative percent released in 24 h with constraints at different time points to yield the Higuchi's square root of time profile (Higuchi, 1963). Based on the experimental design, the factor combinations resulted in different indomethacin release rates. The range of the responses were 101.6% in formulation No. 8 (maximum) and 75.66% in formulation Nos. 1, 4, 14 (minimum). Dissolution profiles of all the 15 formulations are shown in Figs. 1–3. The dependent and independent variables were related using mathematical relationships obtained with the statistical package, X-Stat® (John Wiley and Sons, New York). The polynomial equation obtained was: $Y_5 = 179.54 - 3.10X_1 - 83.09X_2 - 63.65X_3 + 1.88X_1X_2 - 2.80X_1X_3 + 5.6X_2X_3 + 0.152X_1^2 + 18.56X_2^2 + 46.62X_3^2$.

The equation represents the quantitative effect of process variables (X_1, X_2 and X_3) and their interactions on the response (Y_5). The values of the coefficients X_1 - X_3 are related to the effect of these variables on the response (Y_5). Coefficients with more than one factor term and those with higher order terms represent interaction terms and quadratic relationships. A positive sign represents a synergistic effect while a negative sign indicates an antagonistic effect. The values of X_1 - X_3 were substituted in the equation to obtain the theoretical values of Y_5. The theoretical (predicted) values were compared with the observed values and were found to be in reasonably close agreement. Table 3 shows the observed, predicted and residual values.

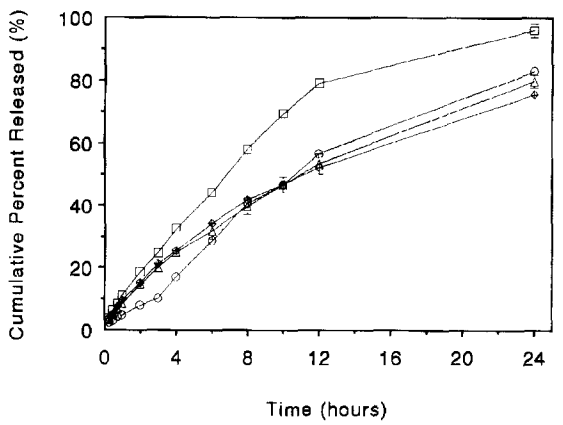

Fig. 1. Dissolution profiles of indomethacin coprecipitate tablets of (1) Form 1 -+- (2) Form 2 -△- (3) Form 3 -○- (4) Form 4 -◇- (5) Form 5 -□-.

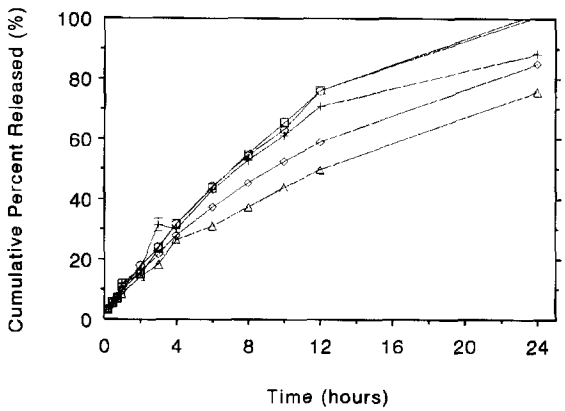

Fig. 2. Dissolution profiles of indomethacin coprecipitate tablets of (1) Form 6 -+- (2) Form 7 -△- (3) Form 8 -○- (4) Form 9 -◇- (5) Form 10 -□-.

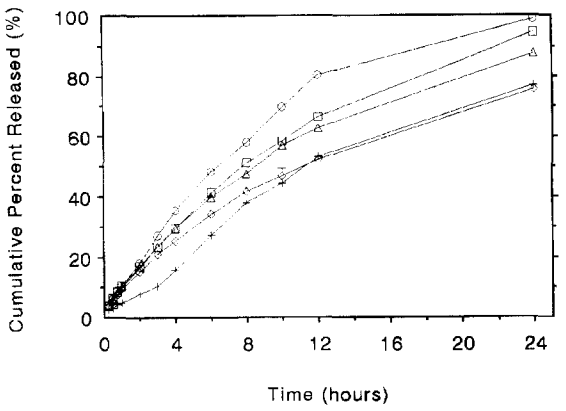

Fig. 3. Dissolution profiles of indomethacin coprecipitate tablets of (1) Form 11 -+- (2) Form 12 -△- (3) Form 13 -○- (4) Form 14 -◇- (5) Form 15 -□-.

The relationship between the dependent and independent variables were further elucidated using contour plots. Figs. 4, 6 and 8 show the effect of factors X_1, X_2 and X_3 on the response Y_5. The small circles indicate levels at which maximum response would be observed. Fig. 4 shows the effect of X_1 and X_2 on Y_5 at a fixed level of X_3 (1.5). Fig. 5 shows the effect of X_1 and X_2 and their interaction on Y_5. At low levels of X_2 (polymer to polymer ratio), Y_5 is increasing from 83 to 100% when the drug to polymer ratio (X_1) is

Table 3
Observed and Predicted values of the response <TB3>

Form No.	Observed (h)	Predicted (h)	Residuals
1	75.66	75.66	-0.
2	79.88	84.03	-4.15
3	83.08	85.95	-2.87
4	75.66	75.66	-0.
5	96.12	97.4	-1.28
6	88.35	84.2	4.15
7	75.72	72.85	2.87
8	100.6	95.57	5.03
9	84.99	83.57	1.27
10	101.6	97.84	3.76
11	77.03	82.06	-5.03
12	87.77	86.89	0.88
13	98.94	99.82	-0.88
14	75.66	75.66	-0.
15	94.66	98.42	-3.76

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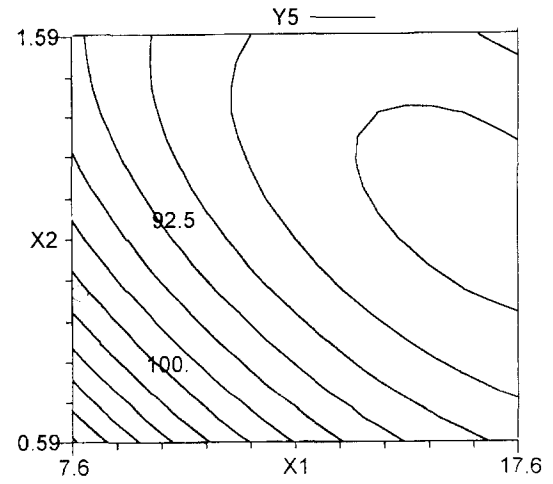

Fig. 4. Contour plot showing the effect of drug to polymer ratio (X_1) and polymer to polymer ratio (X_2) on the response Y_5.

decreasing from 17.6 to 7.6. Conversely, at high levels of X_2, Y_5 is decreasing when the drug to polymer ratio (X_1) is decreasing from 17.6 to 7.6. The possible explanation for this is that at low levels of X_2, the polymer Eudragit L100 concentration is more. This polymer being more soluble

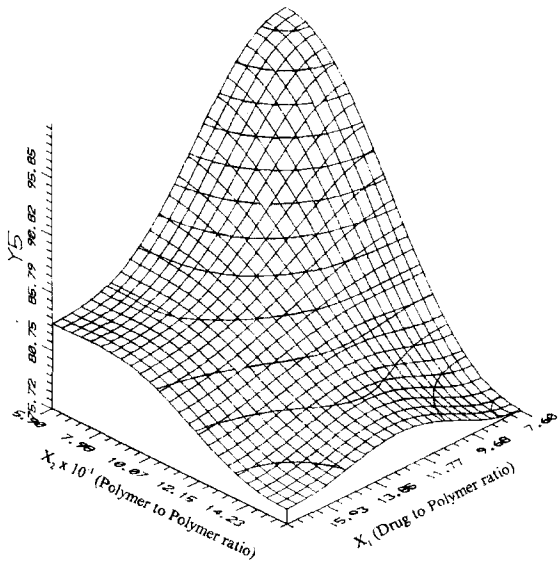

Fig. 5. Response surface plot (3D) showing the effect of drug to polymer ratio (X_1) and polymer to polymer ratio (X_2) on the response surface Y_5.

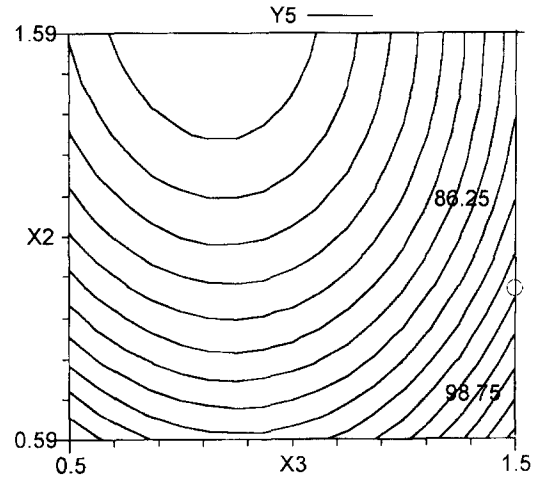

Fig. 6. Contour plot showing the effect of polymer to polymer ratio (X_2) and solvent ratio (X_3) on the response Y_5.

than Eudragit RS100, provides pores and channels for the drug to diffuse out more efficiently resulting in higher drug release. Other information which can be derived from Fig. 5 is that at low drug to polymer ratio (X_1), Y_5 decreases from 100 to 75% as X_2 increases from 5.9 x 10^{-1} to 15.9 x 10^{-1}. This is because at low X_1 level the amount of polymer is more compared to drug and also the ratio of Eudragit RS100 polymer is more as compared to Eudragit L100 polymer due to high X_2 levels. Thus, the dissolution rate is decreased. However, for the same X_2 level increase, Y_5 decreases only from 82 to 75% at high X_1 levels. This is because the amount of total polymer concentration is less as compared to drug and the level of Eudragit RS100 polymer is more. Fig. 6 is a contour plot that shows the effect of X_2 and X_3 on Y_5. As seen from the figure, the response Y_5 is maximized at polymer to polymer ratio of 0.9586 and solvent ratio of 1.5. The role of solvent ratio (X_3) and its interaction with X_2 (polymer to polymer ratio) on the release of indomethacin (Y_5) can be discussed with the help of Fig. 7. As seen from the figure, at low solvent ratio, Y_5 increased from 85 to 100% when the X_2 levels decreased from 15.9 x 10^{-1} to 5.9 x 10^{-1}. The release (Y_5) increased from 88 to 97% at high solvent ratio and with the same decrease in X_2 levels from 15.9 x 10^{-1} to 5.9 x 10^{-1}. Further, there is a slight increase in Y_5 with an increase in solvent ratio from 5.9 x 10^{-1} to 15.9 x 10^{-1} at high X_2 (polymer to polymer ratio) levels. At low levels of X_2, the release is higher at both high and low levels of X_3 (solvent ratio). This is because the polymer Eudragit RS100 is less as compared to L100 which leads to faster release. Also at high levels of X_3, there is complete precipitation of drug along with the polymers and RS100 polymer being in lesser concentration, the dissolution is faster. Fig. 8 shows the effect of X_1 and X_3 on Y_5. The small circle represents the maximized response Y_5 at specified levels of X_1 and X_3. It can be seen in Fig. 9 that at high drug to polymer ratio (X_1), Y_5 has increased from 88 to 94.66% when the solvent ratio decreased from 15 x 10^{-1} to 5 x 10^{-1}. Conversely, at low drug to polymer ratio (X_1), Y_5 decreased from 87 to 80% for the same decrease in solvent ratio from 15 x 10^{-1} to 5 x 10^{-1}. Possible explanation for this behavior is provided by the fact that at low solvent ratio there is incomplete precipitation of polymers along with drug. Hence, the encapsulating efficiency decreases resulting in an increase in dissolution rates.

After generating the polynomial equations relating the dependent and independent variables,

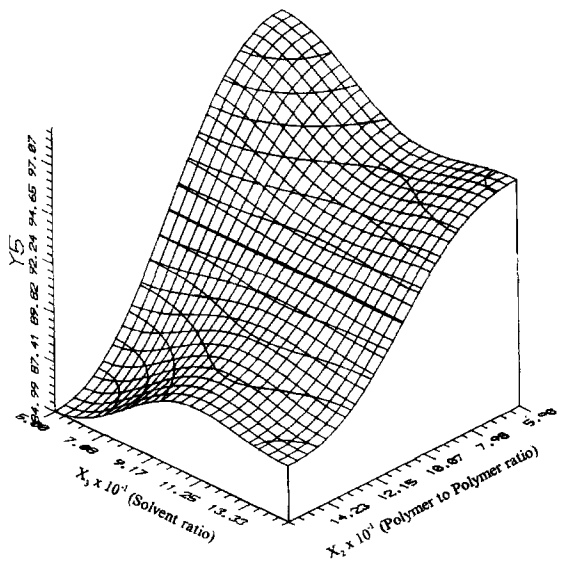

Fig. 7. Response surface plot (3D) showing the effect of polymer to polymer ratio (X_2) and solvent ratio (X_3) on the response surface Y_5.

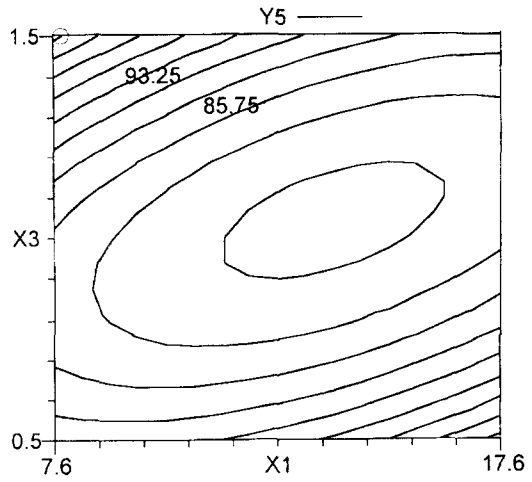

Fig. 8. Contour plot showing the effect of drug to polymer ratio (X_1) and solvent ratio (X_3) on the response Y_5.

the process was optimized for response Y_5. Optimization was performed to search for the levels of X_1–X_3 which maximize Y_5, by introducing the following constraints; $10 < Y_1 < 30$; $45.5 < Y_3 < 54.5$; $65.5 < Y_4 < 74.5$; $95.5 < Y_5 < 104.5$. Under these conditions, the model predicted a Y_5 of 100.7% at X_1, X_2 and X_3 values of 7.813, 0.9586

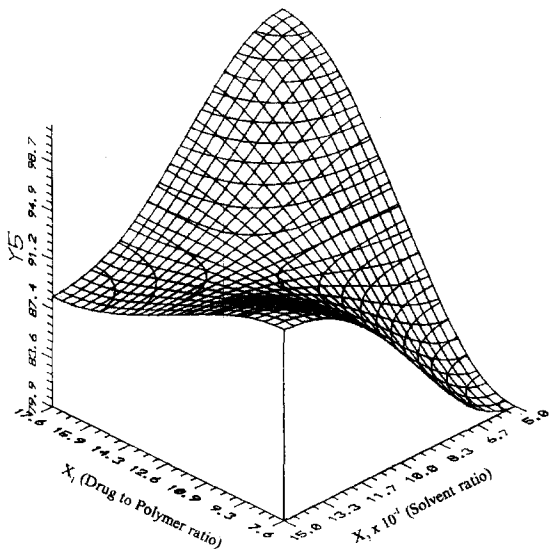

Fig. 9. Response surface plot (3D) showing the effect of solvent ratio (X_3) and drug to polymer to polymer ratio (X_1) on the response surface Y_5.

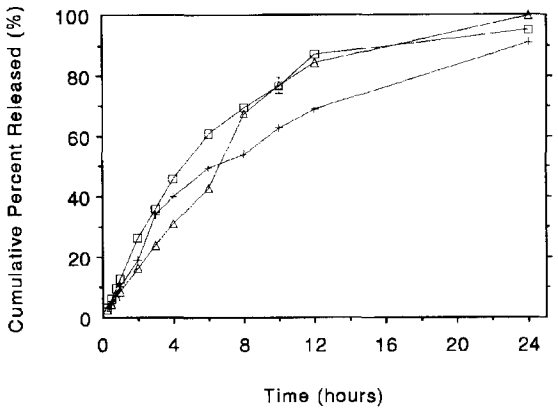

Fig. 10. Comparative dissolution profiles of indomethacin tablets of coprecipitates (+), solid dispersions (△) and physical mixtures (□).

and 1.5, respectively. To verify these values, two optimum formulations were prepared with the above values of the factors. The Y_5 values obtained were 90.91 and 91.0%. This demonstrates the reliability of the optimization procedure. As a comparative evaluation, the dissolution profiles of the optimized coprecipitates along with solid dispersions and physical mixtures prepared under similar conditions is shown in Fig. 10. The average observed values were 91% for coprecipitates, 99.72% for solid dispersions and 95.03% for physical mixtures (Fig. 10). All further characterization was performed using the optimized formulations.

The IR spectra of the drug and the physical mixtures showed characteristic absorption for the C=O group (carboxylic acid) at 1713 cm^{-1} and C=O group (amide) at 1692 cm^{-1}. Strong broad absorptions in the range of 3000 to 2500 cm^{-1} were observed for the O–H stretching vibrations (carboxylic acid group). For the coprecipitates and solid dispersions, there is no change in the characteristic peaks indicating a lack of strong interaction between indomethacin and the polymers, Eudragit RS100 and L100.

X-ray diffraction patterns is shown in Fig. 11. Both polymers used are amorphous in nature. Comparison of X-ray diffraction patterns of indomethacin, coprecipitates, solid dispersions and physical mixtures showed a significant reduction of crystallinity in the case of coprecipitates and

solid dispersions. This could be due to retardation of indomethacin crystallization by the polymers. In the case of solid dispersions, the solvent evaporates at a faster rate which does not provide sufficient time for the drug molecules to come closer in an ordered manner to form crystal lattices resulting in reduced crystallinity. For coprecipitates, the drug and polymers precipitate out initially to form a film on the outer surface of the coacervate droplet. This film later solidifies on drying due to diffusion of ethanol out of the droplet to produce a polymer matrix surrounding the drug. Hence X-ray diffraction patterns show reduced crystallinity for coprecipitates.

Typical DSC thermograms of indomethacin, physical mixtures, solid dispersions and coprecipitates are shown in Fig. 12. The endothermic peaks show a reduction in the intensity of indomethacin peaks for physical mixtures, solid dispersions and coprecipitates as compared to pure indomethacin drug. Moreover, there is a considerable shift in the endothermic peaks of solid dispersions and coprecipitates. The location for maximum peaks have shifted from 161°C to 153°C and 154°C in solid dispersions and coprecipitates. There is no shift of peaks in physical mixtures. Two polymorphic forms of indomethacin, Form I (melting point 160–161°C) and Form II (melting point 153–154°C) have been reported (O'Brien et al., 1984). Data in Fig. 12 clearly suggests that indomethacin exists as Form II in the case of coprecipitates and solid dispersions. The heats of fusion ($\triangle H$) for the respective samples are as follows: 88.238 J/g (indomethacin), 69.244 J/g (coprecipitates), 68.607 J/g (solid dispersions) and 76.191 J/g (physical mixtures). Further studies regarding the nature of this conversion from Form I to Form II and its effect on dissolution upon long term storage at elevated conditions of temperature and humidity are in progress.

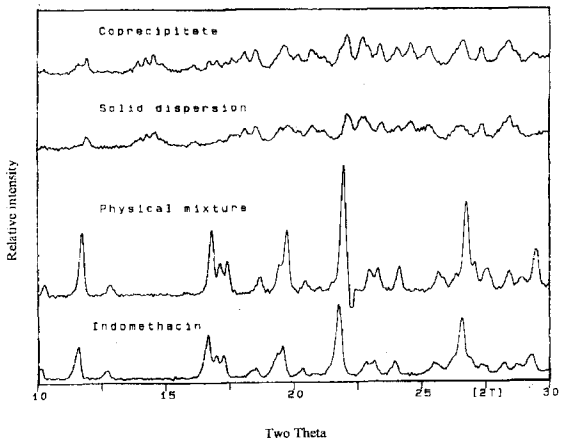

Fig. 11. Qualitative X-ray diffractograms of (1) indomethacin (2) physical mixture (3) solid dispersion and (4) coprecipitate.

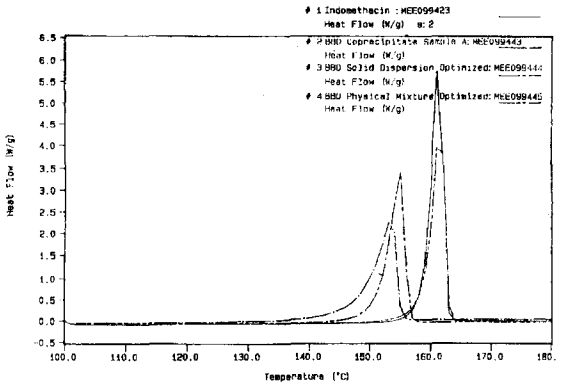

Fig. 12. DSC thermograms showing melting peak of (1) —— indomethacin (2) —.— coprecipitate (3) —— — —— solid dispersion and (4) —— — — —— physical mixture.

5. Conclusions

Coprecipitates of indomethacin with Eudragit RS100 and L100 with optimum matrix properties were prepared using the coprecipitation technique. A three-factor, three-level Box-Behnken design with drug to polymer ratio, polymer to polymer ratio and solvent ratio was employed. The quantitative effect of these factors at different levels on the release rates could be predicted by using polynomial equations. The levels of these factors were predicted to obtain maximized response. Observed responses were close to the predicted values for the optimized formulations. The IR data did not indicate a significant drug-polymer interaction. X-ray diffraction showed a reduction in crystallinity for the coprecipitates and solid dispersions. DSC revealed the conversion of indomethacin from Form I to Form II in solid dispersions and coprecipitates.

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