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Optimization and characterization of controlled release pellets coated with an experimental latex: I. Anionic drug

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Abstract

The aim of the present study was to evaluate the suitability of an experimental latex as a controlled release coating dispersion by preparing, optimizing and characterizing pellets of ibuprofen. A laboratory size fluidized bed coating machine (Uniglatt M-2817) was used to coat ibuprofen loaded beads with the experimental latex to release 400 mg of ibuprofen in a 12 h period in pH 7.2 phosphate buffer. Independent variables such as solids content, volume of coating dispersion, and plasticizer concentration were optimized using a three-factor, three-level Box-Behnken design. The response studied was cumulative percentage dissolved in 12 h with constraints on 1, 6 and 12 h. Surface response plots were utilized to relate the dependent and the independent variables. The optimization procedure generated a maximum of 86% release in 12 h when the levels of solids content, volume of coating dispersion and plasticizer concentration were 11.06% w/w, 113.7 ml, and 26.59% w/w respectively. The optimized pellets prepared based on the predicted levels yielded response values which were close to the predicted values. The kinetics of release was shown to follow Baker-Lonsdale model. The formulations were characterized using DSC, SEM and X-ray diffraction studies. Comparative evaluation with other commercial preparations indicated that the experimental latex provides a more efficient release of the anionic drug, ibuprofen.

Keywords: Controlled release; Pellet; Coating; Latex; Optimization; Ibuprofen; Box-Behnken design; Dissolution; X-ray diffraction

1. Introduction

Polymeric film coating has been used for years as a means of developing controlled release dosage forms. However, not until recently have scientists shifted focus from organic-solvent based to water-based coating. This has been primarily due to explosion hazard, potential toxicity, strict air quality controls instituted by federal agencies and the expense associated with organic solvents and their recovery systems (Banker and Peck, 1981). Currently, much focus is on multiparticulate dosage forms because of their several advantages over single unit dosage forms (Follonier and Doelkar, 1992). These include reduced risk of systemic toxicity due to dose dumping, reduced risk of local irritation and predictable gastric emptying. Multiparticulate dosage forms are

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commonly coated in fluidized bed granulators and agglomeration of the beads during coating is a common problem. Therefore, a polymer latex which provide an efficient and predictable release of drugs with minimal agglomeration should be of considerable interest.

In the present study a novel latex comprising of ethylacrylate(EA) and methylmethacrylate(MMA), which has a very little tendency for agglomeration, has been evaluated for its controlled release properties.

Ibuprofen [2-(4-isobutylphenyl)propionic acid], is a widely used nonsteroidal anti-inflammatory drug (NSAID). It is weakly acidic with a pK_a of 5.3 and solubility of 0.016 mol per l at pH 7.5. It is rapidly absorbed after oral administration and has a half-life of 1.8–2 h (Hertzfeldt and Kummel, 1983). This short half-life and increased need for patient compliance, especially in the management of rheumatoid arthritis, suggests the need of a controlled drug delivery.

The objectives of the present study were to investigate the effects of formulation variables on the in-vitro release of ibuprofen from beads coated with the experimental latex and compare its performance with the commercially available dispersions such as, Aquacoat®, Surelease® and Eudragit RS and RL 30D®.

1.1. Experimental design

A 3-factor, 3-level Box-Behnken design (Box and Behnken, 1960) was used to construct a second order polynomial model for the optimization process. This response surface design provided an empirical mathematical model to describe the effect of formulation variables on the product characteristics. The model generated contained quadratic terms which explained the non-linear nature of responses. This design also resolves the 2-factor interaction effects from the individual terms and allows a mid-level setting (0) for a combination of factors. The model is of the form,

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1X_2 + b_5X_2X_3 + b_6X_1X_3 + b_7X_1^2 + b_8X_2^2 + b_9X_3^2 + E$$

where b_1–b_9 are the coefficients of the respective variables and their interaction terms, and E is an error term.

Preliminary studies provided a setting of the levels for each formulation variable. The studied factors were polymer concentration or total solids (X_1), volume of coating dispersion (X_2) and plasticizer concentration (X_3). An orthogonal design was used such that the factor levels were evenly spaced and coded for low, medium and high setting as −1, 0 and 1, respectively. Table 1 summarizes the factors and their levels. Table 2 shows the responses studied and the constraints used. Table 3 shows the experimental design in a randomized form.

Table 1
Independent variables: Factors and their levels for Box-Behnken design

Factors	Levels		
	−1	0	1
Solids content (% w/w) (X_1)	5	12.5	20
Volume of coating (ml) (X_2)	50	125	200
Plasticizer concentration (% w/w) (X_3)	8	24	40

Table 2
Dependent variables and the constraints used

	Dependent variables/responses	Constraints
Y_1	cumulative % dissolved in 1 h	$10 \geq Y_1 \leq 30$
Y_2	cumulative % dissolved in 6 h	$45 \geq Y_2 \leq 65$
Y_3	cumulative % dissolved in 12 h	$80 \geq Y_3 \leq 100$

2. Materials and methods

2.1. Materials

Ibuprofen USP (Albemarle Co., Baton Rouge, LA) was used as the model drug. Nupareil seeds (mesh no. 30/35, Ingredient Technology, NJ) was used to prepare the pellets. Opadry® (YS-1-7472, Colorcon Inc., PA) was used for seal coating. Triethyl citrate (Morflex Chemical Co., Greensboro, NC) was used as plasticizer. Eudragit RS 30D and RL 30D® (Rohm Tech, Weiterstadt, Germany) were received as sample gifts. Tita-

nium dioxide was used as an opacifier (Warner Jenkins Co.). Talc was purchased from Spectrum Chemical Co. Alcohol USP was purchased from Aaper Alcohol and Chemical Co., Shelbyville, KY. Water, used in all experiments, was deionized and distilled. All other chemicals were used as received.

2.2. Methods

2.2.1. Preparation of experimental latex

An aqueous latex (Ex-913-509-1291) of acrylate and methacrylate copolymers was prepared by emulsion polymerization. The total solids content was 30.1% w/v and the pH of the latex was 2.6. The viscosity obtained with a Brooksfield viscometer was 12.5 cp. The residual acrylate monomers were kept below 400 ppm.

2.2.2. Drug layering

500 g of Nu-pareil sugar beads (mesh no. 30–35) was used as initial cores to achieve 60% or greater drug loading. Ibuprofen was passed through US sieve no. 20 and mixed with distilled water. Opadry® was used as a binder. 20 g of talc was added to the above dispersion as an anti-adherent to prevent particulate aggregation during the coating process. Finally, Tween 20 was added and the slurry was mixed properly for 2 h prior to use in a high speed mixer and filtered through a 30 mesh screen filter.

A laboratory size Uniglatt fluidized bed coating machine (model no. 2817) was used for coating the drug suspension using a 1.2 mm insert. The flow rate was maintained constant such that no agglomeration of the beads occurred during the coating process. The air flap was kept between 60 and 90° to achieve good drying efficiency. During the layering process, the beads were intermittently dried for 15 min at room temperature. After layering, the beads were collected in a tray and dried at 37°C in an oven.

2.2.3. Seal coating

Preliminary studies indicated that the seal coating does not hinder diffusion of drug. Seal coating was applied to the layered pellets prior to applying the controlled release coating to minimize leaching of drug into the latex and also to prevent mechanical abrasion of the layered drug. Opadry® was used as the permeable seal coating polymer.

2.2.4. Controlled release coating

Preliminary experiments were performed to select the levels of experimental latex to result in

Table 3
Experimental runs and observed responses (randomized)

Run	Controlled factors			Measured responses		
	X_1	X_2	X_3	Y_1	Y_2	Y_3
1	20	200	24	0	5.62	12.06
2	20	50	24	67.31	92.34	94.31
3	5	200	24	50.15	87.8	89.19
4	5	50	24	95.84	96.18	101.9
5	20	125	40	23.69	50.42	67.64
6	20	125	8	11.42	25.0	33.34
7	5	125	40	82.39	96.29	98.78
8	5	125	8	71.0	96.31	100.7
9	12.5	200	40	6.78	33.89	52.46
10	12.5	200	8	7.03	18.18	33.05
11	12.5	50	40	68.49	89.42	91.55
12	12.5	50	8	77.77	94.71	95.71
13	12.5	125	24	13.8	54.57	74.80
14	12.5	125	24	18.10	54.72	72.92
15	12.5	125	24	14.21	57.20	86.08

a fast and reproducible coating process. Based on the experimental design and the factors to be studied, 15 formulations were prepared. The experimental latex was diluted to the desired solids content and plasticized before use. Table 4 summarizes the coating conditions for the controlled release coating.

2.2.5. Sieve analysis

After coating the 15 batches of formulations, the beads were dried and sieved. Then they were subjected to sieve analysis using a nest of U.S. standard sieves (3.36, 2.38, 1.68, 1.19, 1.0, 0.84, 0.71 mm openings). For each formulation, a weighed amount of beads were placed on the top sieve and the nest was placed on a Retsch sieve shaker at a fixed setting of 20 for 5 min. Pellets collected on top of each size range were weighed and used to calculate the cumulative percent oversize. The geometric mean diameter (d_g) and the geometric standard deviation (σ_g) were calculated (using log-probability plots) and the values are shown in Table 5. All fines and agglomerates were discarded. The fraction of beads remaining between sieve no. 16 and 20 were collected and used for further characterization of the formulation.

2.2.6. Content uniformity

Accurately weighed samples of the coated pellets (100 mg) from all the formulations were dissolved in alcohol USP., filtered and analyzed spectrophotometrically for ibuprofen content at 266 nm. A calibration curve was used based on standard solutions in alcohol USP. The latex and all other excipients used in the coating did not interfere with the analysis at this wavelength. All experiments were performed in triplicate.

Table 4
Conditions for fluidized bed coating

Inlet air temperature (°C)	35–40
Outlet air temperature (°C)	25
Atomising air pressure (psig)	40–45
Spray nozzle diameter (mm)	1.20
Batch size (g)	500
Spray rate (ml/min)	10
Binder solution	5–6% w/v Opadry in water
Air flap (°)	60–90
Filter shaking interval and duration	every 10 s for 5 s

Table 5
Geometric mean diameters and standard deviation of the formulations for Box-Behnken design

Run	Geometric mean diameter (μm)	Geometric standard deviation (μm)
1	1096.48	0.871
2	1258.93	0.933
3	1174.90	0.832
4	1258.93	0.794
5	1202.26	0.831
6	1230.27	0.813
7	1258.93	0.832
8	1288.25	0.832
9	1318.26	0.851
10	1288.25	0.831
11	1318.25	0.794
12	1412.54	0.794
13	1288.25	0.851
14	1412.54	0.812
15	1288.25	0.831

2.2.7. Dissolution studies

Coated pellets equivalent to 400 mg of ibuprofen were used for determining the in-vitro release of drug. The USP Paddle Apparatus was used with 900 ml of phosphate buffer (pH 7.2) at 37°C and 100 rpm. Samples (5 ml) were withdrawn at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 h and were assayed spectrophotometrically at 266.5 nm. From the absorbance values, the cumulative percent of ibuprofen released was calculated. All the experiments were performed in triplicate.

For all the 15 formulations, the measured response selected was cumulative percent dissolved in 12 h with constraints at 1 and 6 h. Figs. 1, 2 and 3 show the dissolution profiles of the 15 formulations over a 12 h period.

2.2.8. Infrared spectroscopy

Infrared spectra of the pure drug, excipients and the optimized formulation were determined from KBr pellets using an infrared spectrophotometer, model MX-S (Nicolet Analytical Instruments). The scanning range used was 4000–400 cm^{-1}.

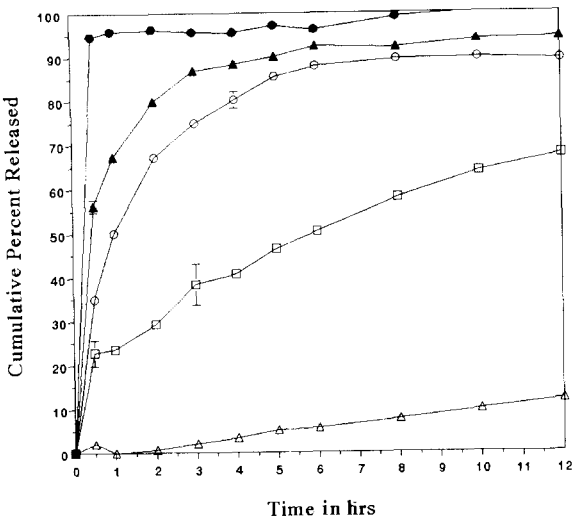

Fig. 1. Dissolution profiles of ibuprofen from pellets coated with experimental latex. (△) Form 1, (▲) form 2, (○) form 3, (●) form 4, (□) form 5.

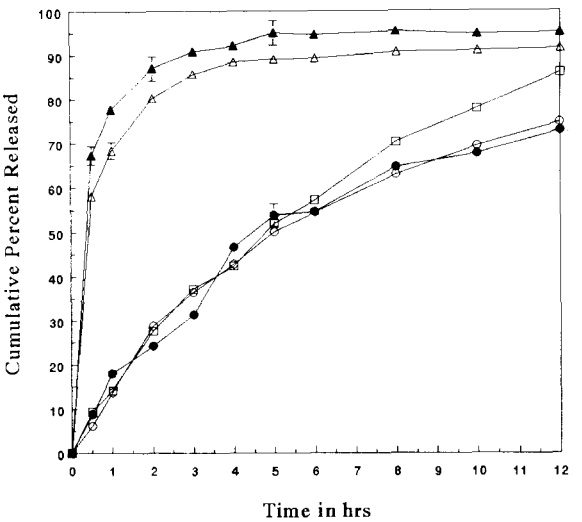

Fig. 3. Dissolution profiles of ibuprofen from pellets coated with experimental latex. (△) Form 11, (▲) form 12, (○) form 13, (●) form 14, (□) form 15.

2.2.9. *X-ray diffraction study*

Qualitative and quantitative X-ray diffraction studies were performed using a Philips X-Ray diffractometer, Model 1840. Measurements were carried out at 40 kV and 35 mA current at a continuous scan rate of one second per step. Finely ground samples were scanned from 10° to 40° 2θ. Diffractogram of pure Ibuprofen was used as a reference for qualitative studies. In the quantitative studies a standard plot of the peak height ratio (I/I_0) of pure Ibuprofen to internal standard, sodium chloride, was constructed (Kislalioglu et al., 1991). The degree of crystallinity was estimated using this plot.

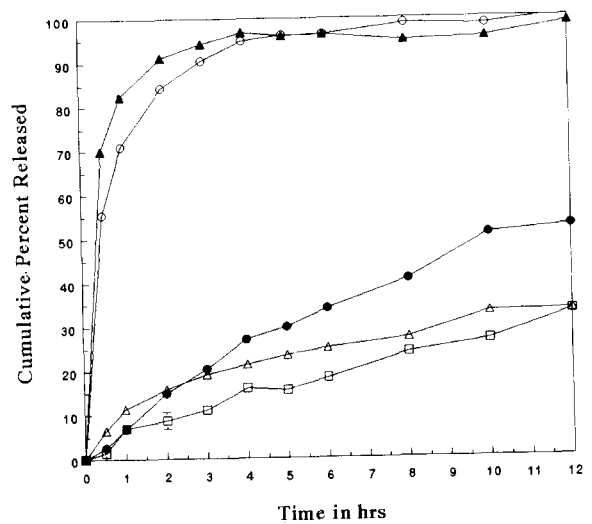

Fig. 2. Dissolution profiles of ibuprofen from pellets coated with experimental latex. (△) Form 6, (▲) form 7, (○) form 8, (●) form 9, (□) form 10.

2.2.10. *Differential scanning calorimetry (DSC)*

DSC scans were performed using a Perkin Elmer DSC-7 to obtain the melting endotherms of pure Ibuprofen, opadry and latex and the optimized formulation. The instrument was calibrated using indium standards. About 5–12 mg of each sample was weighed into small aluminum pans. Samples were heated from 25 to 200°C at a rate of 10°C per min in an atmosphere of nitrogen. Thermograms were normalized and autoscaled before overlapping. Also, DSC was used to find the glass transition temperature (T_g) of the unplasticized latex, plasticizer and the plasticized film.

2.2.11. *Scanning electron microscopy (SEM)*

The surface topography of the optimized formulation was examined under a Phillips model

505 SEM. The optimized beads were loaded on studs and sputter coated with gold for 105 s at 20 mA under a pressure of 0.1 Torr. The coated beads were scanned and the micrographs were examined for the effect of the formulation variables on the surface morphology of the latex coating. Pictures of the intact bead and a cross-section were taken to determine the integrity of the film.

3. Results and discussion

In order to determine the levels of factors which yield optimum values of dissolution responses, mathematical relationships were generated between the dependent and independent variables using the statistical package X-Stat 2.0® (X-Stat version, 1993). The resultant equations of all the responses are given below:

$$Y_1 = 222.25 - 12.14X_1 - 11.02X_2 - 1.88X_3 + 0.40X_1^2 + 0.04X_3^2 \quad (1)$$

$$Y_2 = 154.78 - 5.41X_1 - 0.20X_2 - 0.94X_3 - 0.03X_1X_2 + 0.05X_1X_3 + 0.20X_1^2 \quad (2)$$

$$Y_3 = 117.21 - 1.75X_1 + 0.17X_2 - 0.34X_3 - 0.03X_1X_2 + 0.08X_2X_3 + 0.03X_1^2 - 0.02X_3^2 \quad (3)$$

The coefficients of the Xs in the above equations are corrected to two decimal places. Eq. 1–3 represent the quantitative effect of the formulation variables on the three responses Y_1–Y_3 respectively. The values of the coefficients X_1–X_3 relate to the effects of these variables on the corresponding response. Coefficients with more than one factor term represent the interaction terms and coefficients with higher order terms indicate the quadratic (non-linear) nature of the relationship. A positive sign indicates a synergistic effect while a negative sign represents an antagonistic effect. To justify the use of the polynomial equations, values of X_1–X_3 were substituted in Eq. 1–3 to obtain the theoretical values of Y_1–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 for the dependent variable Y_3 are shown in Table 6.

Table 6
Residual table for predicted response Y_3

Run	Observed	Predicted	Residuals
1	12.06	9.49	2.57
2	94.31	93.44	0.87
3	89.91	90.06	−0.87
4	101.9	104.47	−2.57
5	67.64	67.22	0.42
6	33.34	37.2	−3.86
7	98.78	94.92	3.86
8	100.7	101.12	−0.42
9	52.46	55.45	−2.99
10	33.05	31.76	1.29
11	91.55	92.84	−1.29
12	95.71	92.72	2.99
13	74.80	77.93	−3.13
14	72.92	77.93	−5.01
15	86.08	77.93	8.15

Two-and three-dimensional plots for the measured responses were formed based on the model to assess the change of the response surface. Also the relationship between the dependent and independent variables can be further understood by these plots. Fig. 4 shows the effect of X_2 and X_3 on Y_3. The constraints for Y_1 and Y_2, are shown

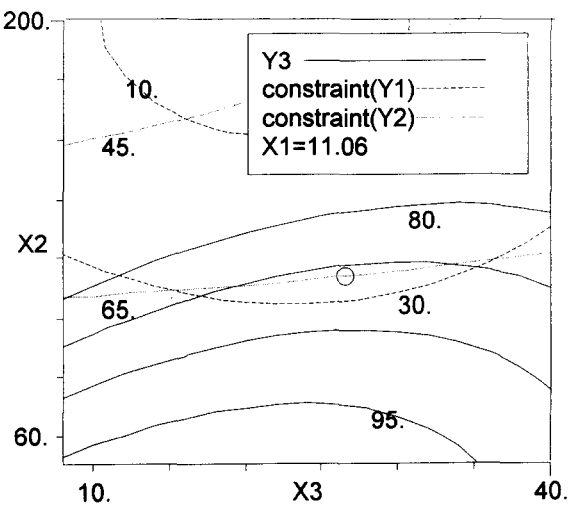

Fig. 4. Contour plot showing the effect of volume of coating (X_2) and plasticizer concentration (X_3) on the response Y_3.

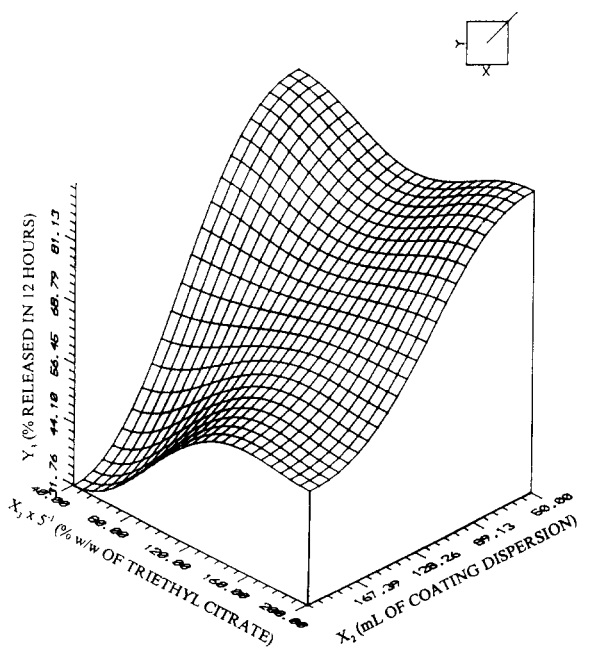

Fig. 5. Response surface plot (3D) showing the effect of volume of coating (X_2) and plasticizer concentration (X_3) on the response surface Y_3.

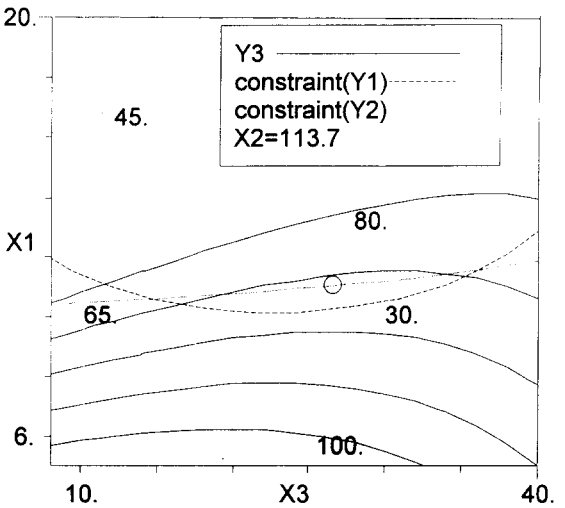

Fig. 6. Contour plot showing the effect of solids content (X_1) and plasticizer concentration (X_3) on the response Y_3.

by the different type of contour lines. These are also listed in Table 2. The maximized points are indicated by small circles. Fig. 5 is the corresponding response surface plot. At high volume of coating (X_2), the increase in dissolution with an increase in the plasticizer level from 8 to 20% is much more pronounced than the low volume of coating. The plasticizer softens the polymer spheres in the latex, facilitating coalescence to form a coherent film and also reduces the minimum film-forming temperature (MFT) of the latex. However, an increase in plasticizer level with insufficient polymer levels causes an incomplete formation of film resulting in faster drug release. Increasing the latex coating volume with an increase in the plasticizer forms a smooth but thick membrane resulting in slow drug release.

Fig. 6 shows the effect of X_1 and X_3 on the response Y_3. The figure shows that at a fixed ($X_2 = 113.7$ ml) the response Y_3 is maximized at plasticizer levels of 25–30% w/w and polymer concentration of 10–12% w/w. Fig. 7 shows that with an increase in the total solids of the latex (X_1) dissolution is decreased, and this effect was found to be pronounced at low levels of plasticizer. The release at low solids content of the

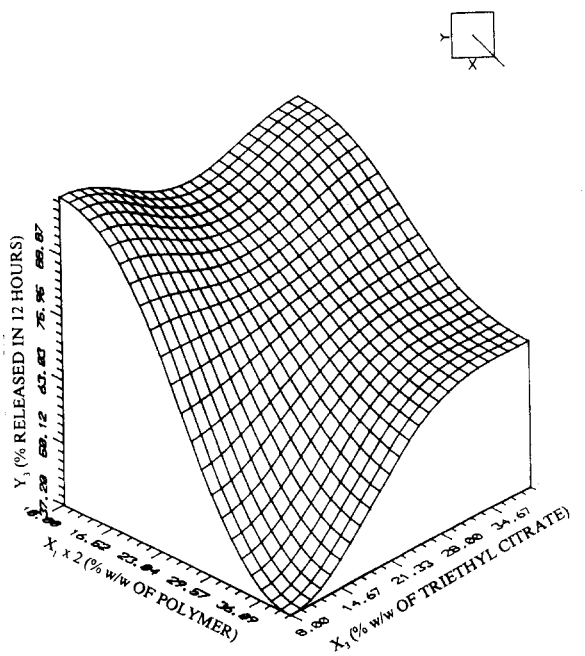

Fig. 7. Response surface plot (3D) showing the effect of solids content (X_1) and plasticizer concentration (X_3) on the response surface Y_3.

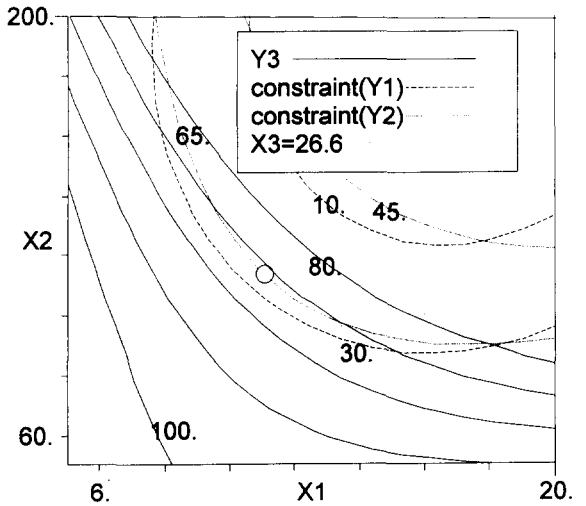

Fig. 8. Contour plot showing the effect of solids content (X_1) and volume of coating (X_2) on the response Y_3.

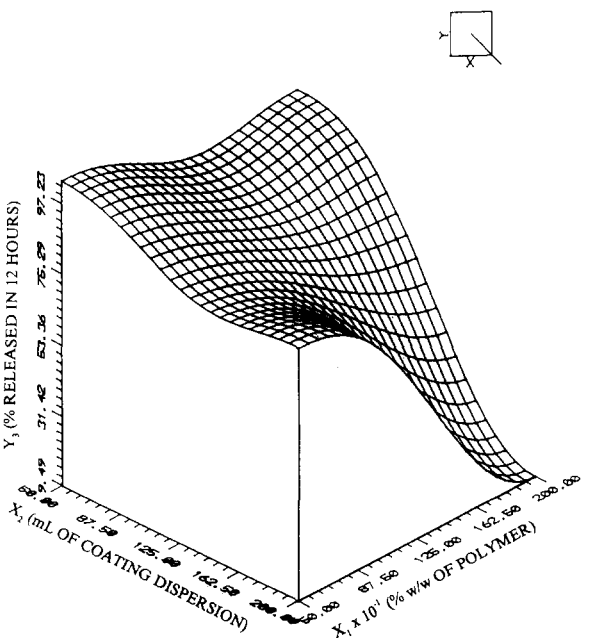

Fig. 9. Response surface plot (3D) showing the effect of solids content (X_1) and volume of coating (X_2) on the response surface Y_3.

latex was faster than at high solids content. Latex used at high concentration of polymer causes relatively more retardation in the drug release.

Similarly, Fig. 8 demonstrates the effect of X_1 and X_2 on the response Y_3. As shown in the figure, the response Y_3 is maximized at a solids content of 10–12% w/w and a volume of coating between 100 and 200 ml. Fig. 9 depicts the surface response to these factors. At high solids content, dissolution decreases considerably as the volume of latex increases from 50 to 200 ml. However, the decrease in dissolution is much less pronounced at low solids content for the same increase in the volume of coating dispersion. Higher coating volume increases coating thickness and decreases drug release. Conversely, at low volume of coating and solids content, the release of ibuprofen increased drastically. The low polymer concentration and thickness of coat increases the drug release.

After generating the polynomial equations to relate the dependent and independent variables, the process was optimized for response Y_3. Optimization involves maximizing or minimizing a certain response. In this study optimization was performed with constraints on Y_1 and Y_2 to maximize the response Y_3, i.e., cumulative percentage released in 12 h. This was done with the help of X-Stat® package. The optimization procedure generated maximum of 86% of drug release after 12 h. The levels of X_1, X_2 and X_3 which maximize Y were 11.06%, 113.7 ml and 26.59%, respectively. To check the validity of the optimization procedure, a fresh batch of ibuprofen pellets coated with the above conditions resulted in 84% of ibuprofen released in 12 h. Table 7 illustrates the predicted and observed responses for the optimum formulation.

A comparative evaluation of the sustained release coating by the experimental latex and other commercial dispersions such as, Aquacoat®, Surelease®, Eudragit RS 30D® and Eudragit RL 30D®, prepared under identical conditions, is

Table 7
Response after maximizing

Responses	Predicted	Observed
Y_1	26.23	27
Y_2	65.00	65.48
Y_3	85.91	84.75

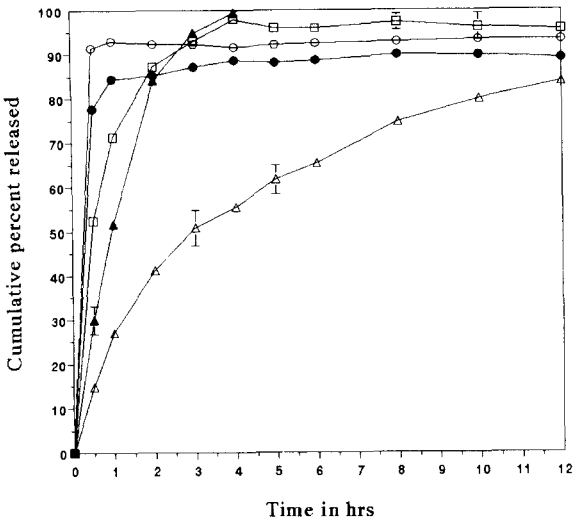

Fig. 10. Comparative ibuprofen release profiles of the experimental latex with some commercial preparations. (△) Experimental latex, (▲) Aquacoat, (○) Eudragit RL-30D, (●) Eudragit RS-30D, (□) Surelease.

shown in Fig. 10. Clearly, the latex provides a more sustained release. Moreover, the amount of talc needed during the coating process to prevent agglomeration was 5.3, 8.1, 12.9, 15.1 and 20.2 g for the experimental latex, Aquacoat®, Surelease®, Eudragit RS 30D® and Eudragit RL 30D® coatings, respectively.

IR spectra of the pure drug and optimized formulation showed a characteristic absorption stretch for C = O group (carboxylic acid) 1770 cm^{-1} and also a C-H stretch at 3000 cm^{-1}. Also, strong broad absorptions in the range of 3000–2500 cm^{-1} were observed due to O-H stretching vibrations (carboxylic acid groups). Although inconclusive without further characterization, there was no sign of interaction between the drug and the excipients used for coating.

X-ray diffraction patterns are shown in Fig. 11. Qualitative comparison between the pattern A (pure drug) and pattern B (optimized formulation) suggests a reduction in peak intensity for the optimum formulation. This could be due to the retardation of ibuprofen crystallization by the coated polymer (Sekikawa et al., 1978). To study the relationship between the drug content and crystallinity quantitatively, a standard curve was plotted for peak intensity ratio of drug (I) to internal standard (I_0) vs drug concentration. Sodium chloride was used as the internal standard. Physical mixtures of drug and dried ground latex with the internal standard were run and the peak intensity, the angle 2θ and the d values

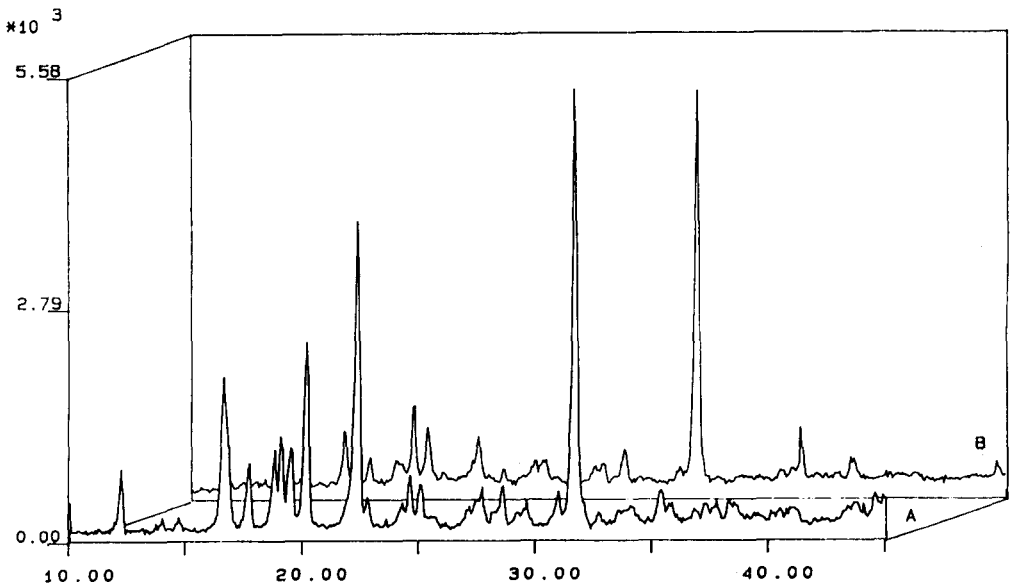

Fig. 11. Qualitative X-ray diffractograms of (A) pure drug and (B) optimized formulation.

Table 8
Peak intensity ratios of drug and optimum formulation with sodium chloride

Sample	I/I_0		2θ		d values	
	P_1 [a]	P_3 [a]	P_1 [a]	P_3 [a]	P_1 [a]	P_3 [a]
Pure drug	0.36	0.70	16.57	22.29	5.35	3.98
Opt. form.	0.17	0.16	16.65	22.29	5.32	3.98

[a] P_1 and P_3: peaks 1 and 3, respectively.

were obtained. A linear relationship of I/I_0 was observed with increasing drug concentrations ($r = 0.9984$). Two peaks at 16.5 (P_1) and 22.29 2θ (P_3), characteristic of ibuprofen were used for quantification (Suryanarayan, 1991) since they were most sensitive to changes in drug concentration. As observed in Fig. 11, there is a significant reduction on the crystallinity of the optimized formulation. The I/I_0 values in Table 8 show a drastic reduction in the peak intensity I/I_0 for the formulation as compared to the pure drug. The d values are quite similar for the pure drug and the formulation indicating lack of interaction between the drug and the coated latex. However, there is a marked reduction in the degree of crystallinity of the optimized formulation which may be because of the reduced proportion of drug in the total sample on the X-ray diffraction plate.

The DSC scan of Ibuprofen, the seal coat material Opadry®, and the optimum formulation is shown in Fig. 12. Ibuprofen has a sharp melting point at 76.81°C, and Opadry® has the melting point at 52°C. Preliminary studies indicated that the latex formulation does not show any endothermic peaks between 25 and 200°C. Therefore, the peak appearing at 71.11°C in the optimum formulation appears to be due to an interaction between the Opadry® and ibuprofen. The nature of interaction and its consequence on the stability of ibuprofen is currently under investigation. The other additives did not show any interaction. The heat of fusion (ΔH_f) for ibuprofen was 111.4 J/g whereas the ΔH_f for the optimized formulation was 39.5 J/g. The glass transition

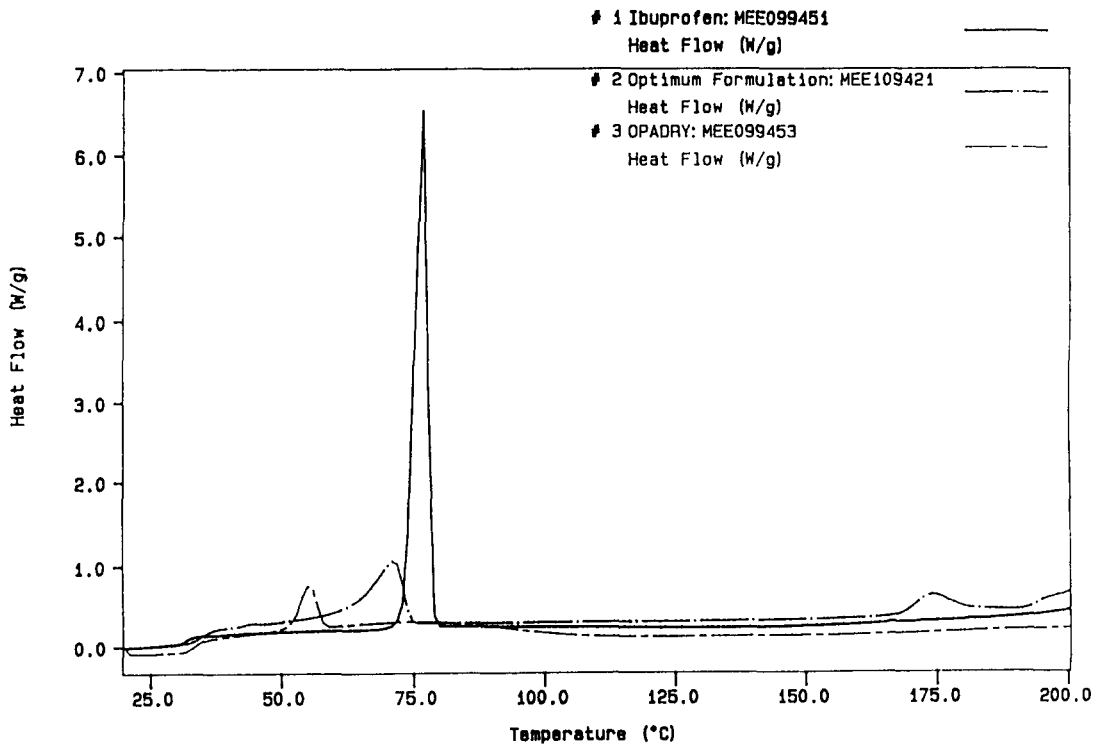

Fig. 12. DSC thermograms (————) ibuprofen, (—— · ——) optimized formulation and (—— - - ——) Opadry.

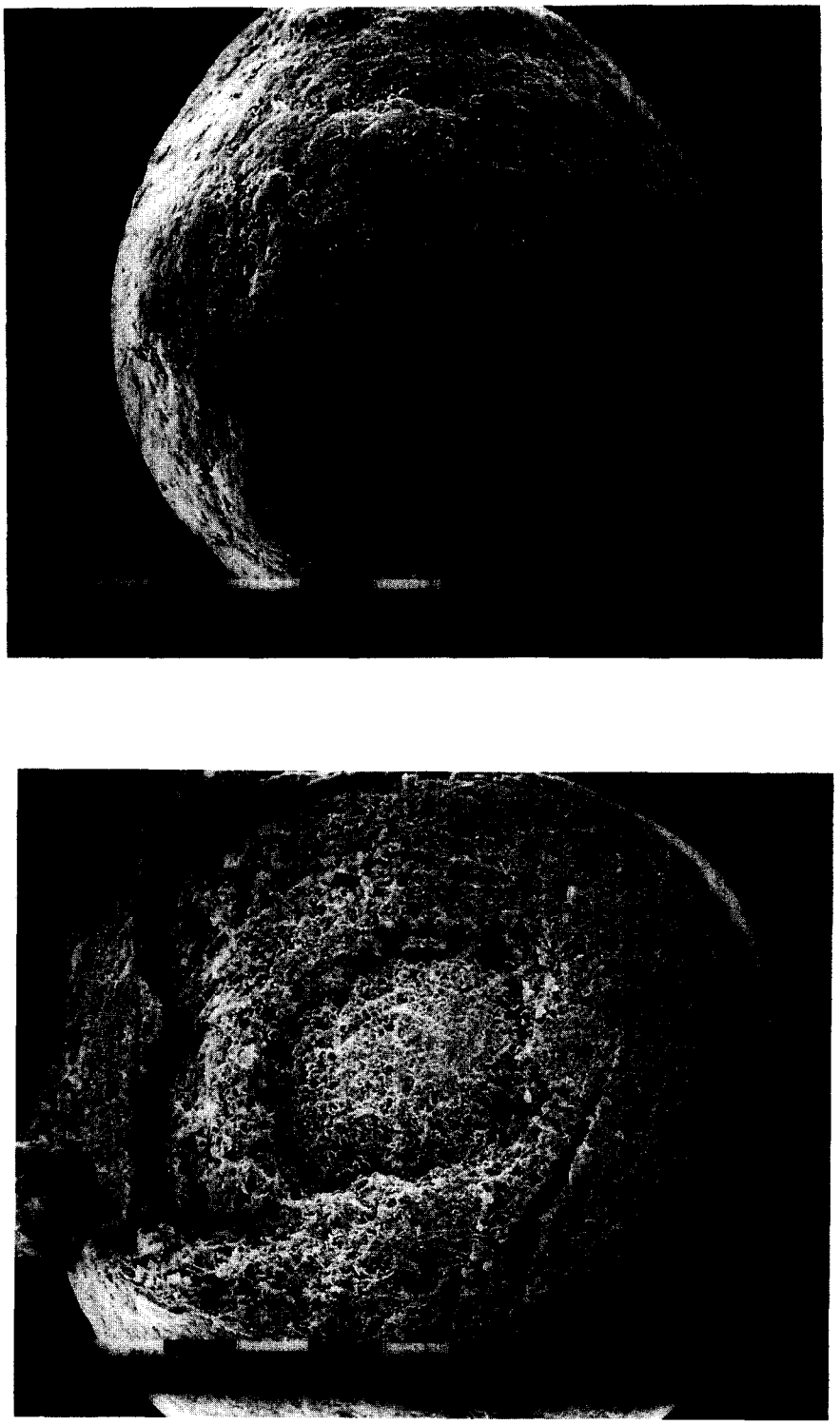

Fig. 13. SEM pictures of beads coated with experimental latex (IBU1) and cross-section of the coated bead (IBU3).

temperature (T_g) of unplasticized latex and the plasticizer, TEC, were found to be 49.3 and 10.7°C, respectively. The plasticized latex showed a T_g of 27.5°C.

SEM pictures (Fig. 13) of the optimized bead shows a uniform and intact coating of the latex. The surface appeared rough due to presence of talc used as an anti-adherent. The cross-section shows the porous core structure with a coherent film at the boundary. This film formation may be due to the reduction of T_g of the latex by the plasticizer.

To understand the mechanism of drug release, various models were used to fit the dissolution kinetics of the pellets. The model for diffusion controlled release given by Higuchi (1963) is $100 - M = kt^{1/2}$, where M is the percentage of drug undissolved, k the dissolution rate constant, and t the time of dissolution. The equation proposed by Bamba et al. (1979), $\ln M = kt$, assumes that the drug molecule diffuse out through a dissolving gel-like layer formed around the drug during the dissolution process. The equation $m_o^{1/3} - m^{1/3} = kt$, proposed by Hixon and Crowell (1931) for the dissolution of powders, assumes that the dissolution of powder is independent of the initial particle diameter (m in this equation refers to the amount of drug left undissolved). The equation $m_o^{2/3} - m^{2/3} = kt$ is the 'two-third root' or the modified cube-root equation, which takes into account the changing surface area of the beads during dissolution (Niebergall and Goyan, 1963). The Baker-Lonsdale model (Baker and Lonsdale, 1987) is given by the equation $Y = 3/2[1 - (1 - F)^{2/3}] - F = k't$, where F is the fraction of the drug released and $k' = 3DC_s/r_o^2C_0$. D is the diffusion coefficient, C_s the saturation solubility, C_o the total concentration of the drug dispersed and dissolved and r_o the initial radius. This model is also referred to as $t^{-1/2}$ law. For the dissolved drug, the fraction released at any given time is independent of initial loading whereas, for dispersed drug, the fraction released at a given time decreases with increasing drug loading. However, for both types the release follows the $t^{-1/2}$ law approximately to the first 50% of the drug. Table 9 shows the least square parameters of the model equations applied to the optimized ibuprofen pellets. The Baker-Lonsdale model appears to provide the best correlation.

Table 9
Least-square parameters applied to dissolution of optimized formulation

Dissolution models	Dissolution rate constant (k)	r^2
Higuchi's square-root model	25.1796	0.9919
Bamba's model	0.1462	0.9900
First-order model	0.1180	0.8403
Hixon-Crowell cube root model	0.2276	0.7175
Two-third model	1.2534	0.8592
Baker-Lonsdale model	0.0186	0.9984

4. Conclusions

The formulation variables, solids content, volume of coating, and the plasticizer concentration affected the release of the drug from the formulation and was found to be non-linear (quadratic in nature). The quantitative effect of these variables could be predicted using polynomial equations. Levels of these formulations were predicted to obtain the optimum levels of the responses. Optimum formulation prepared according to the predicted levels provided responses which were close to those of the predicted responses. The experimental latex can be useful for controlled delivery of drugs, like ibuprofen. Comparative evaluation with commercially available latexes indicated a more efficient release at the levels used. X-ray diffraction studies showed a reduction in crystallinity of the drug in the optimum formulation. DSC studies revealed an interaction between the drug and the excipient, Opadry®. SEM pictures revealed the uniformity of the coat structure.

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References

Baker, R.W. and Lonsdale, H.K., *Controlled Release of Biologically Active Agents*, Wiley, New York, 1987, pp. 15–71.

Bamba, M., Puisieux, F., Marty, F. and Cartensen, J.T., Physical model for release of drug from gel forming sustained release preparations. *Int. J. Pharm.*, 2 (1979) 307–315.

Banker, G.S. and Peck, G.E., The new, water-based colloidal dispersions. *Pharm. Technol.*, 5 (1981), 55–61.

Box, G.E.P. and Behnken, D.W., Some new three level designs for the study of quantitative variables. *Technometrics*, 2 (1960) 455–475.

Follonier, N. and Doelkar, E., Biopharmaceutical comparison of oral multiple-unit and single-unit sustained-release dosage forms. *STP Pharm. Sci.*, 2 (1992) 141–158.

Hertzfeldt, C.D. and Kummel, R., Dissociation constants, solubilities and dissolution rates of some selected nonsteroidal antiinflammatories. *Drug Dev. Ind. Pharm.*, 9 (1983) 767–793.

Higuchi, T., Mechanism of sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.*, 52 (1963) 1145–1149.

Hixon, A.W. and Crowell, J.H., Dependence of reaction velocity upon surface and agitation: I. Theoretical considerations. *Ind. Eng. Chem.*, 23 (1931) 923–931.

Kislalioglu, M.S., Khan, M.A., Blount, C., Goettsch, R.W. and Bolton, S., Physical characterization and dissolution properties of ibuprofen: Eudragit coprecipitates. *J. Pharm. Sci.*, 80 (1991) 799–804.

Niebergall, P.J. and Goyan, J.E., Dissolution rate studies: I. Continuous recording technique following rapid reactions in solution. *J. Pharm. Sci.*, 52 (1963) 29–33.

Sekikawa, H., Nakano, M. and Arita, T., Inhibitory effect of polyvinylpyrrolidone on the crystallization of drugs. *Chem. Pharm. Bull.*, 26 (1978) 118–126.

Suryanarayan, R., Quantification of carbamazepine in tablets by X-ray diffractometry. *Adv. X-ray Anal.*, 34 (1991) 417–427.

X-Stat, Version 2.0® software, Wiley, New York, 1993.