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Optimization and characterization of controlled release multi-particulate beads coated with starch acetate

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Abstract

The objectives of the present study were (1) to model the effects of process and formulation variables on in vitro release profile of a model drug dyphylline from multi-particulate beads coated with starch acetate (SA); (2) to validate the models using R^2 and lack of fit values; (3) to optimize the formulation by response surface methodology (RSM); (4) to characterize the optimized product by thermal, X-ray and infrared spectroscopic analyses. Dyphylline loaded inert beads were coated using organic solution of SA with high degree of substitution. A three-factor, three-level Box–Behnken design was used for the optimization procedure with coating weight gain (X_1), plasticizer concentration (X_2) and curing temperature (X_3) as the independent variables. The regression equation generated for Y_5 (cumulative percent drug released after 12 h) was $Y_5 = 89.83 - 11.98X_1 + 2.82X_2 - 4.31X_1^2 + 1.90X_1X_2$. Optimization was done by maximizing drug release in 12 h and placing constraints at dissolution time points of 0.5, 1, 4 and 8 h. The drug release data of the optimized product were close to that predicted by the model. The models could explain 99% of variability in responses. Thermal, X-ray and infrared analyses suggested absence of any significant interaction of the drug with the excipients used in the formulation. SEM photographs showed the integrity of the coating layer.

Keywords: Starch acetate; Multi-particulate coated beads; Box–Behnken optimization design; Controlled release; Excipient compatibility; Mathematical modeling

1. Introduction

Starch acetate (SA) is a relatively new polymer used as an excipient in controlled release pharmaceutical dosage forms (Korhonen et al., 2000, 2002; Pohja et al., 2004). It was shown to have good film forming properties (Tarvainen et al., 2002) and recently drug release patterns from SA films were reported (Tuovinen et al., 2003). However, SA has not been used as a con-

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trolled release film former on tablets, pellets or other solid dosage forms. It was evident that SA has different solubility properties than native starch (Kruger and Rutenberg, 1967) and the degree of substitution (dS) with acetyl moiety in starch has great influence on solubility as well as on other mechanical and physicochemical properties (Korhonen et al., 2000, 2002). The degree of acetylation was also shown to affect the rate of drug release substantially and the relation was reciprocal (Korhonen et al., 2000). Therefore, SA with high dS-value was used in the present study.

Oral controlled drug delivery systems offer better patient compliance, less fluctuation in plasma drug level and reduced cost for the overall treatment compared to conventional drug delivery systems (Lordi, 1986; Khan et al., 1995). Multi-particulate dosage form is an efficient drug delivery system for controlled drug delivery since it provides many advantages over other immediate or modified release dosage forms. Some of these advantages are more predictable gastric emptying (Davis, 1986), minimizing local concentration of drug (Eskilson, 1985), less likelihood of dose dumping (Sam, 1985) and lower incidence of inter- and intra-subject variability (Butler et al., 1998; Kyroudis et al., 1989).

In the present investigation, dyphylline, a xanthine analog with peripheral vasodilatation and bronchodilator actions (Hanson, 1995) was taken as the model drug. The reasons for that were its good aqueous solubility (0.33 g/ml) (Hanson, 1995) and simplicity of analytical method (USP, 2000). It has also some other advantages as a model drug in controlled release preparations. Those include its moderately low half-life (1.8–2.1 h), predictable and dose related plasma levels and almost exclusive elimination by the kidneys (PDR, 1997).

Response surface methodology has been successfully utilized in several studies to optimize process and formulation variables and to obtain product with desired properties (Singh et al., 1995; Karnachi and Khan, 1996; Nazzal et al., 2002). RSM provides rapid method and reliable design.

The present study was carried out mainly to investigate the prospect of SA as a controlled-release coating agent. For this purpose, SA coated dyphylline multiparticulate beads were prepared and optimized using Box–Behnken design and the optimized formulation was characterized by thermal, X-ray and IR analyses to find out drug compatibility with the formulation excipients. SEM analysis was performed to observe the integrity of the film-coated layer.

2. Materials and methods

2.1. Materials

The following materials were obtained as gifts: Pure-Dent® B700 from Grain Processing Corporation (Muscatine, IA), dyphylline from BASF Corporation (Mount Olive, NJ), 18/20 Nu-Pareil® KY White from Chr. Hansen Inc. (Mahwah, NJ), Opadry II® Beige from Colorcon (West Point, PA), Triacetin, USP from Eastman Chemical Company (Kingsport, TN). Pyridine, acetone, ethanol and chloroform were purchased from Fisher Scientific (Fair Lawn, NJ) and talc and acetic anhydride from Spectrum Chemical Mfg. Corp. (Gardena, CA).

2.2. Experimental design

In preliminary studies, we identified the three most important factors affecting dyphylline release from a multi-particulate drug delivery system coated with SA. Those were coating weight gain, plasticizer concentration and curing temperature. Several other factors, such as SA concentration, inlet temperature, atomizing pressure and curing time were found to have less influence on drug dissolution from the beads. Therefore, these factors were kept constant throughout the batches of the present study. A three-factor, three-level Box–Behnken design was used for the optimization process using a statistical software, Statgraphics® Plus, version 4.1 (Manugistics Inc., MD). The non-linear quadratic model generated by the design is of the form:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{23}X_2X_3 + b_{13}X_1X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2$$

where Y represents the response associated with each factor level combination, b_0 an intercept and b_1–b_{33} are the regression coefficients of the factors, X_1–X_3 (Box and Behnken, 1960). A description of the dependent and independent variables are given in Table 1. A total of 15 runs (Table 2) with triplicate center points were

Table 1
Variables in Box–Behnken design

Factor	Level used		
	−1	0	1
X_1 = coating weight gain (%)	7	10	13
X_2 = plasticizer concentration (%)	40	55	70
X_3 = curing temperature (°C)	40	45	50

Response	Constraints
Y_1 = cumulative % drug released in 0.5 h	2–10
Y_2 = cumulative % drug released in 1 h	10–15
Y_3 = cumulative % drug released in 4 h	35–50
Y_4 = cumulative % drug released in 8 h	70–80
Y_5 = cumulative % drug released in 12 h	90–100

generated. The models were evaluated in terms of statistically significant coefficient, standardized main effects (SME) and R^2-values.

2.3. Synthesis of SA

Pure-Dent® B700, a native corn starch containing about 25% amylose (Young, 1984) was acetylated using the paste disintegration technique as described elsewhere (Wolff et al., 1951; Ogawa et al., 1999) to obtain SA with high dS. Pregelatinization was performed by boiling starch in water at a temperature just below 100 °C for 20 min. The jelly-like mass was precipitated with anhydrous alcohol using a high shear homogenizer. The precipitate was washed with sufficient acetone, dried in air and sieved through mesh #60 or lower. The acetylation of 50 g pregelatinized starch was done with 200 g of acetic anhydride in a medium of 400 g of pyridine. The reaction was carried out in a flask under a reflux condenser at 100 °C for 4 h. The product was precipitated with enough alcohol, filtered and washed several times with alcohol, dried in air and passed through a sieve #60 or lower.

The dS-value was calculated using the equations reported earlier (Ogawa et al., 1999; Bello-Perez et al., 2002). The molecular weight of SA was determined by gel permeation chromatography using PL-GPC 220 with two PLgel Mixed-B columns (Polymer Labs Inc., Amherst, MA), calibrated with polystyrene molecular mass standard. The mobile phase, a mixture of dimethyl acetamide and sodium nitrate was used at 100 °C at a flow rate of 1.0 ml/min. Elutes were detected with an RI detector.

2.4. Preparation of drug loaded beads

Loading of dyphylline on Nu-Pareil® KY White inert beads of mesh size 18/20 was performed using a drug loading suspension with the composition of dyphylline, the drug (20%, w/w), Opadry II®, a binding agent (6%, w/w) and talc, an anticaking agent (2%, w/w) in deionized water. The components were mixed together with continuous stirring at medium speed of

Table 2
Observed responses from randomized runs in Box–Behnken design

Run	Factor			Response				
	X_1	X_2	X_3	Y_1	Y_2	Y_3	Y_4	Y_5
1	0	−1	1	4.18	10.05	37.99	72.52	88.19
2	1	0	−1	3.02	6.88	27.00	56.30	75.11
3	0	0	0	5.50	13.24	45.33	78.54	88.38
4	−1	0	1	27.12	37.60	79.22	95.01	98.56
5	1	1	0	3.44	7.89	30.88	61.87	79.00
6	1	0	1	2.79	5.10	27.35	51.79	74.66
7	0	1	−1	8.99	17.21	55.22	85.21	95.88
8	0	1	1	6.85	15.80	50.02	83.00	94.50
9	−1	−1	0	23.12	33.33	72.11	92.29	98.09
10	−1	1	0	29.90	42.17	87.80	98.30	99.50
11	0	0	0	4.80	12.88	44.08	77.87	90.07
12	1	−1	0	2.19	4.23	24.32	47.74	70.01
13	−1	0	−1	28.37	37.94	83.00	95.99	98.50
14	0	0	0	5.22	13.41	45.78	78.74	91.03
15	0	−1	−1	5.09	11.30	41.20	75.77	90.00

Table 3
Process parameters used in drug loading and polymer coating

Processing condition	Drug loading	Seal coating	Controlled release coating
Bead bed size (g)	200	200	200
Inlet temperature (°C)	43	45	37
Outlet temperature (°C)	42	43	36
Air volume (M^3/h)	120	120	120
Atomizing pressure (bar)	0.6	0.8	1
Blow out pressure (bar)	2.0	2.5	1.5
Coating solution flow rate (ml/min)	2	2	2
Spray nozzle diameter (mm)	0.8	0.8	0.8

a Pro 250® homogenizer (Pro Scientific Inc., Monroe, CT). Drug loading was done using a Wurster type spray (bottom spray) in a Strea-1® fluid bed coater (Niro Inc., Columbia, MD). After obtaining an appreciable extent of drug loading, the beads were seal coated. Seal coating suspension was identical to the drug loading suspension except that the drug is absent in the former. Seal coating was applied until a 2% of weight gain to the drug loaded beads was obtained. The process parameters used in drug loading and seal coating are presented in Table 3. Following the seal coating, beads were dried in the coating chamber at 45 °C for 20 min and subsequently transferred into an oven at 37 °C and kept there for 6 h. Drug loss by attrition of the beads with the coating chamber or by leaching of the drug through the fresh solvent during controlled release coating process can be prevented by seal coating.

2.5. Controlled release coating

SA, synthesized before was dissolved in chloroform to obtain a 2% solution. Depending on the levels used in a particular batch, either 40 or 55 or 70% (w/w) of plasticizer (triacetin) based on SA concentration was added to the solution and stirred for 2 h. Coating was performed in a Strea-1® fluid bed coater. The process parameters are listed in Table 3. Following coating, the beads were dried in the coating chamber at 37 °C for 20 min and later on cured in an oven at either 40 or 45 or 50 °C for 16 h. Beads from the optimized formulation were of the mesh size 14/16.

2.6. Content analysis

The initial steps of content analysis are the extraction of the drug, which was performed by crushing accurately 100 mg of coated beads taken from each batch in a mortar containing 100 ml of water, transferring into an Erlenmeyer flask and sonicating for 30 min. The other steps of analysis were filtration, appropriate dilution and spectroscopic measurement of drug content using a GBC 918 UV–vis Spectrophotometer (Dandenong, Victoria, Australia) at 273 nm.

2.7. In vitro dissolution testing

Coated beads, containing 300 mg of dyphylline (624.9–659.7 g total weight depending on batches), were subjected to dissolution study to calculate in vitro drug release profile. An automated USP apparatus II, VK 7000 (Vankel Technology Group, Cary, NC), with the paddle speed of 50 rpm and 900 ml of deionized water as the dissolution medium at 37 °C was employed. Samples were withdrawn at different time points (0.5, 1, 2, 4, 6, 8, 10 and 12 h), suitably diluted with water and assayed spectrophotometrically at 273 nm. Cumulative percent release of the drug was calculated from the concentration of the diluted sample. Each run was duplicated and the mean values were used in the design. Among the samples, the ones at 0.5, 1, 4, 8 and 12 h were used in the design.

2.8. Thermal analysis

Thermal behavior of the optimized formulation was studied by differential scanning calorimetry (DSC) using DSC 7 (Perkin-Elmer, Norwalk, CT). The instrument was calibrated using indium standards. Accurately weighed samples (5–10 mg) were hermetically sealed in flat bottom aluminum pans and heated from 100 to 200 °C at a rate of 10 °C per min under an

atmosphere of nitrogen. Melting endotherms of the drug and the excipients used in the formulation were also determined in the same way. Thermograms were normalized and rescaled as needed before overlapping.

2.9. X-ray diffraction study

X-ray powder diffraction study was performed by a Philips Norelco Diffractometer (Eindhoven, The Netherlands) equipped with a graphite monochromator. Nickel filtered Cu-Kα radiation operated at 40 kV and 20 mA was used as the radiation source. Samples were scanned between 2° and 27° (θ) at a speed of 1 °/min. Before analysis, the optimized beads and Nu-Pareil® inert beads were crushed separately to obtain fine powder suitable for the test.

2.10. Fourier transform infrared spectroscopy (FTIR)

Powdered optimized beads and the ingredients used in drug loading were subjected to FTIR with a Nexus 470 FTIR (Thermo Nicolet Corporation, Madison, WI). Background spectrum was collected before running each sample. The samples were analyzed between wavenumbers 4000 and 600 cm^{-1}.

2.11. Scanning electron microscopy

The surface topography of the uncoated and coated (optimized) beads and cross section of optimized beads were examined under a JEM-100 CX Analytical Electron Microscope (Jeol Inc., Japan) interfaced with KEVEX Image Analyzer. The samples were loaded on copper sample holder and sputter coated with carbon followed by gold.

3. Results and discussion

3.1. Synthesis of SA

SA with high dS is not available commercially. Therefore, it was synthesized in our lab. Since, viscosity is a major concern during coating process in a fluid bed coater, corn starch was preferred to other starch sources as SA from corn starch has been shown to be less viscous than that from potato or tapioca starch in organic solutions (Mullen and Pacsu, 1942). The method reported by Ogawa et al. (1999) was found to yield the desired product, and therefore, this method was followed with suitable modifications. The dS-value was found to be 2.9 (acetyl content 43.94%). The weight average molecular weight of SA was determined to be 780,357.

3.2. Experimental designs and the fitted models

A three-factor three-level Box–Behnken design as the RSM requires 15 experiments. The independent variables of the 15 experimental runs and their responses are given in Table 2. Nine batches showed at least 90% drug release at 12 h (Y_5) and the range of Y_5 of all batches was 74.66–99.50%. The ranges of the other responses, Y_1–Y_4 (drug release in 0.5, 1, 4 and 8 h, respectively) were 2.19–29.90, 4.23–42.17, 24.32–87.80 and 47.74–98.30, respectively. Uncoated beads completely released the drug before 1 h. The fitted models can be viewed as regression equations as in Table 4, generated by the software. Only statistically significant ($p < 0.05$) coefficients are included in the equations. Positive sign before a factor in polynomial equations represents that the response increases with the factor. On the other hand, a negative sign means the response and factors have reciprocal relation. It is clear that coating weight gain (X_1) and curing tempera-

Table 4
Regression equations of the fitted models[a]

$$Y_1 = 5.17 - 12.13X_1 + 1.83X_2 - 0.57X_3 + 9.27X_1^2 + 0.88X_3^2 - 1.38X_1X_2$$
$$Y_2 = 13.18 - 15.87X_1 + 3.02X_2 - 0.60X_3 + 8.51X_1^2 - 1.30X_1X_2 - 0.36X_1X_3$$
$$Y_3 = 45.06 - 26.57X_1 + 6.04X_2 - 1.48X_3 + 8.37X_1^2 - 2.28X_1X_2$$
$$Y_4 = 78.38 - 20.49X_1 + 5.01X_2 - 1.37X_3 - 3.84X_1^2 + 2.03X_1X_2 - 0.88X_1X_3$$
$$Y_5 = 89.83 - 11.98X_1 + 2.82X_2 - 4.31X_1^2 + 1.90X_1X_2$$

[a] Only the terms with statistical significance are included.

Table 5
Standardized main effects of the factors on the responses[a]

	Standardized main effect (SME)				
	Y_1	Y_2	Y_3	Y_4	Y_5
X_1	63.10	191.34	60.54	137.59	33.26
X_2	9.52	36.41	13.76	33.64	7.83
X_3	2.96	7.23	3.37	9.20	–
$X_1 \times X_1$	32.76	69.71	12.96	17.52	8.13
$X_2 \times X_2$	–	–	–	–	–
$X_3 \times X_3$	3.11	–	–	–	–
$X_1 \times X_2$	5.08	11.08	3.67	9.64	3.73
$X_1 \times X_3$	–	3.07	–	4.18	–
$X_2 \times X_3$	–	–	–	–	–
R^2	99.90	99.99	99.88	99.98	99.61
p-Value of lack of fit	0.2410	0.6801	0.2863	0.6121	0.8306

[a] Only the terms with statistical significance are included.

ture (X_3) have negative effects on the responses Y_1–Y_5, whereas, the plasticizer concentration (X_2) has positive effects. Increasing coating weight gain increased the physical barrier between the drug in the beads and the dissolution medium, and that produced the slow rate of drug release. During the coating process, the inlet temperature of the coating chamber evaporates the bulk of the solvent and thus polymer accumulates on the substrates (beads). However, film formation is completed only after curing of the products. Curing helps gradual coalescence of the polymers on the substrate, which leads to smooth and homogeneous film (Bodmeier et al., 1997). Higher temperature helps the curing process of the film and slowed drug release rate. Plasticizers increase free volume in polymeric film, which positively affects drug release (Sastry et al., 1998; Sinko and Amidon, 1989). Besides, the moderate solubility of triacetin in water (ICSC, 1994) should also have facilitated the release of a water-soluble drug, such as dyphylline.

Coefficients with higher order terms or more than one factor term in the regression equation represent quadratic relationships or interaction terms, respectively. This means the relation between responses and factors are not always linear. A factor can produce different degree of effects on a response when used at different levels. Similar situation may arise when more than one factors are changed at the same time. The equations show interaction effect of factors X_1 and X_2 on Y_1 through Y_5. X_1 also showed quadratic effect on all the responses. This could be due to its (X_1) much higher effects compared to the other two factors on the responses.

3.3. Standardized main effects, reliability of the models

SME, presented in Table 5 were calculated by dividing the main effects with the standard error of the main effects. Only statistically significant ($p < 0.05$) values are given. The larger SME of X_1 suggests the paramount importance of coating weight gain on drug release. R^2-value signifies the percentage of variability in responses that are explained by the models. In the present study, the high R^2-values (>99%) represented reliability of the design. Besides, the p-value for lack of fit for all models in Table 5 are greater than 0.05, suggesting absence of

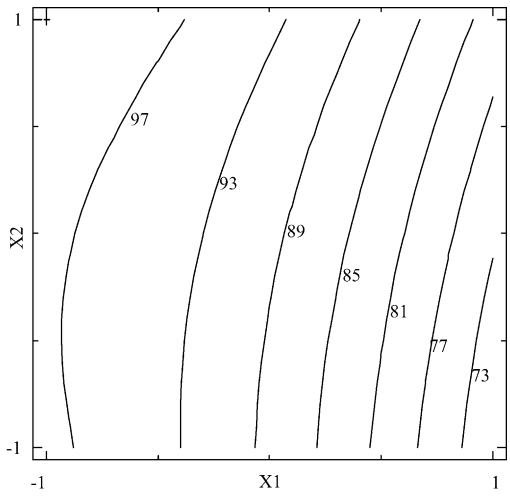

Fig. 1. Contour plot showing the effects of coating weight gain (X_1) and concentration of plasticizer (X_2) on response Y_5.

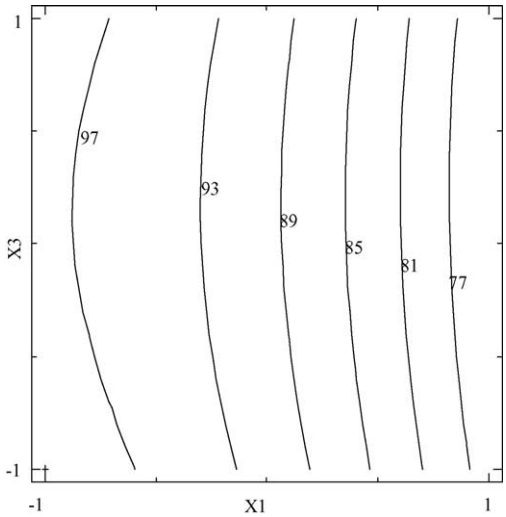

Fig. 2. Contour plot showing the effects of coating weight gain (X_1) and curing temperature (X_3) on response Y_5.

any lack of fit of the models and that also strengthened the reliability of the models.

3.4. Contour and response plots

Two-dimensional contour plots and three-dimensional response surface plots, as presented in Figs. 1–6, are very useful to see interaction effects of the factors on the responses. These types of plots

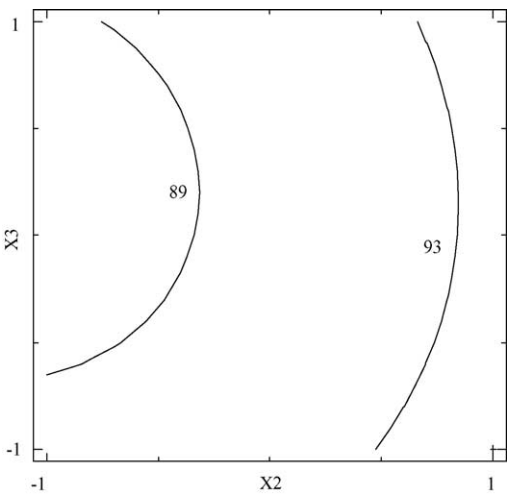

Fig. 3. Contour plot showing the effects of concentration of plasticizer (X_2) and curing temperature (X_3) on response Y_5.

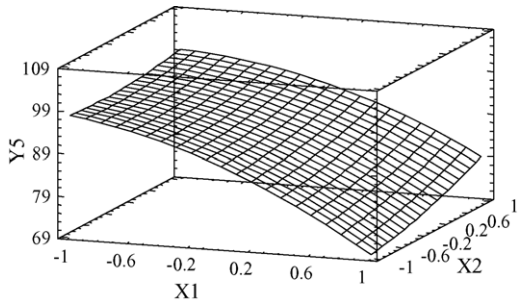

Fig. 4. Response surface plot of coating weight gain (X_1) and concentration of plasticizer (X_2) on response Y_5.

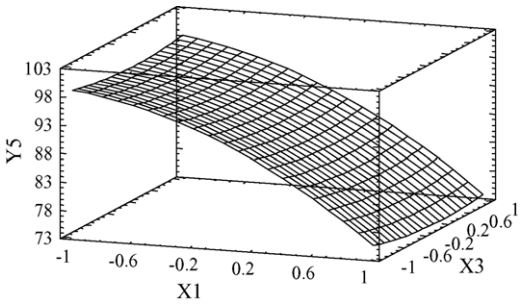

Fig. 5. Response surface plot of coating weight gain (X_1) and curing temperature (X_3) on response Y_5.

show effects of two factors on the response at a time. In all the presented figures, the third factor was kept at level zero. The almost straight lines in the Figs. 1 and 2 predicted nearly linear relationship of factor X_1 with factors X_2 and X_3. As for example, more than 97% of drug release after 12 h was achievable if the coating weight gain had been kept below approximately 7.5%, irrespective of the curing temperature used in the design. Factors X_2 and

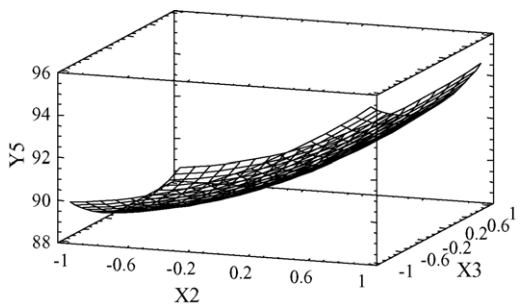

Fig. 6. Response surface plot of concentration of plasticizer (X_2) and curing temperature (X_3) and on response Y_5.

Table 6
Equations used in the dissolution model study[a]

Model	Equation
Zero-order	$m_0 - m = kt$
First-order	$\ln m = kt$
Second-order	$-\frac{1}{m} = kt$
Hixson–Crowell	$m_0^{1/3} - m^{1/3} = kt$
Baker–Lonsdale	$\frac{3}{2}(1-(1-(m_0-m))^{2/3}) - \frac{m_0-m}{100} = kt$
Higuchi's	$m_0 - m = kt^{1/2}$
Two-third	$m_0^{2/3} - m^{2/3} = kt$
Bamba	$\ln(m_0 - m) = kt$

[a] m_0 is the initial drug amount (100%, when represented as percentage); m the amount of drug remaining at a specific time (calculated as percentage of m_0); k the rate constant; t is the time.

X_3 have non-linear relationship. However, response surface plots show the scenario more clearly. Fig. 4 shows that about 99% drug would be available when the coating weight gain is kept at the lowest level, regardless of the plasticizer concentration. However, at the highest coating level (13%) drug release increased linearly with plasticizer concentration. This indicates slight non-linear relation between factors X_1 and X_2. Factors X_1 and X_3 have almost linear relationship as evident from Fig. 5. Fig. 6 shows quite interesting interrelationship between factors X_2 and X_3. Drug release was higher at both low and high levels of curing temperature at any level of plasticizer concentration and it is the lowest at the moderate values of curing temperature. However, the overall drug release increased with increased plasticizer concentration provided the curing temperature was kept constant.

Table 8
Optimized formulation: expected and observed dissolution values

Factor	Optimized level of factor	
Coating weight gain (%)	10	
Plasticizer concentration (%)	55	
Curing temperature (°C)	45	
Response	**Expected**	**Observed**
Cumulative % drug released in 0.5 h	5.17	5.20
Cumulative % drug released in 1 h	13.18	13.42
Cumulative % drug released in 4 h	45.06	45.82
Cumulative % drug released in 8 h	78.38	78.02
Cumulative % drug released in 12 h	89.83	90.58

3.5. Mechanism of drug release

Several dissolution models were applied to investigate the release mechanism of the 15 different formulations. The models included zero-, first- and second-order, Hixson Crowell, Baker Lonsdale, Higuchi's, two-third and Bamba model. The equations used to determine the appropriate models are presented in Table 6.

Table 7 shows the mean and standard deviation of R^2-values of all 15 runs of the design plugged into some common release patterns. Overall, these showed best fit in first-order model. In first-order system, drug release is dependent on the remaining concentration of drug in the bead. However, Hixson–Crowell model also fitted well to the experimental batches. The mathematical expression of Hixson–Crowell model is:

$$m_0^{1/3} - m^{1/3} = kt$$

Table 7
Dissolution models fitted with R^2-values of release profiles

Model	R^2-value			
	15 runs	4 runs with 70–80% drug release at 12 h	2 runs with 80–90% drug release at 12 h	9 runs with ≥90% drug release at 12 h
Zero-order	0.9252 ± 0.0851	0.9951 ± 0.0046	0.9658	0.8851 ± 0.0891
First-order	0.9917 ± 0.0049	0.9867 ± 0.0054	0.9922	0.9938 ± 0.0035
Second-order	0.8893 ± 0.0416	0.9117 ± 0.0197	0.9332	0.8695 ± 0.0396
Hixson–Crowell	0.9834 ± 0.0240	0.9953 ± 0.0022	0.9936	0.9758 ± 0.0289
Baker–Lonsdale	0.9590 ± 0.0265	0.9254 ± 0.0208	0.9679	0.9720 ± 0.0163
Higuchi's	0.9588 ± 0.0170	0.9449 ± 0.0083	0.9671	0.9632 ± 0.0184
Two-third	0.9579 ± 0.0557	0.9981 ± 0.0013	0.9839	0.9343 ± 0.0616
Bamba	0.8025 ± 0.0420	0.8533 ± 0.0082	0.8080	0.7787 ± 0.0327

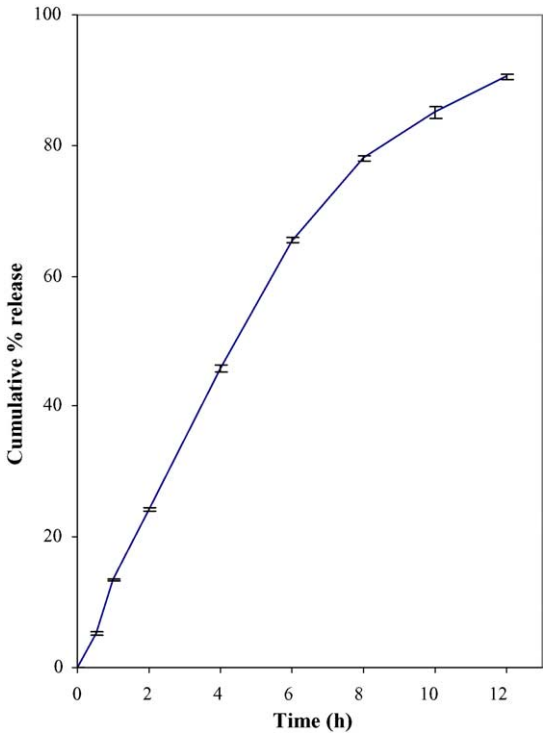

Fig. 7. Dissolution profile of the optimized formulation.

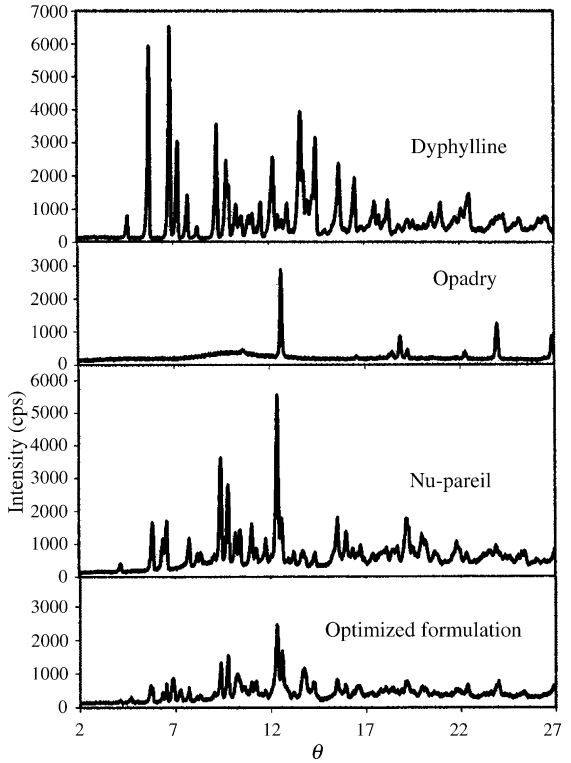

Fig. 9. X-ray diffraction patterns of the optimized formulation and the ingredients.

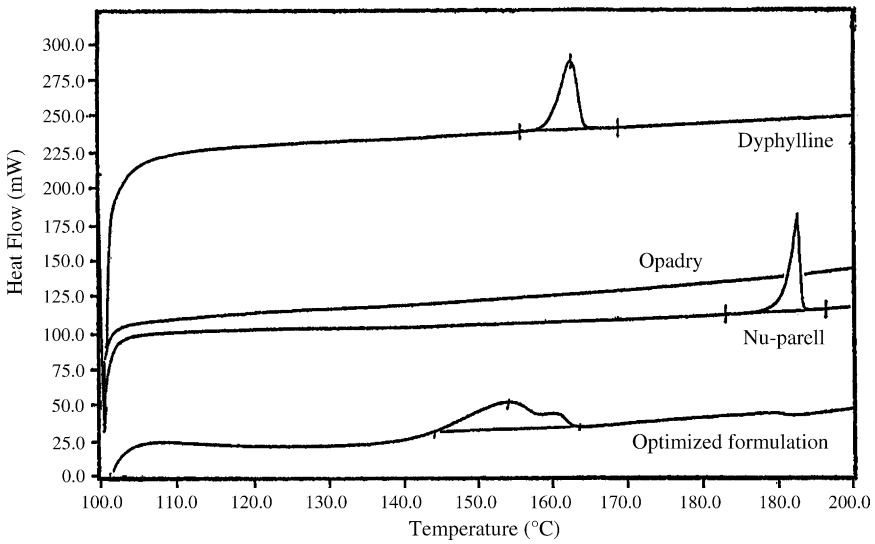

Fig. 8. DSC thermograms of the optimized beads and the ingredients.

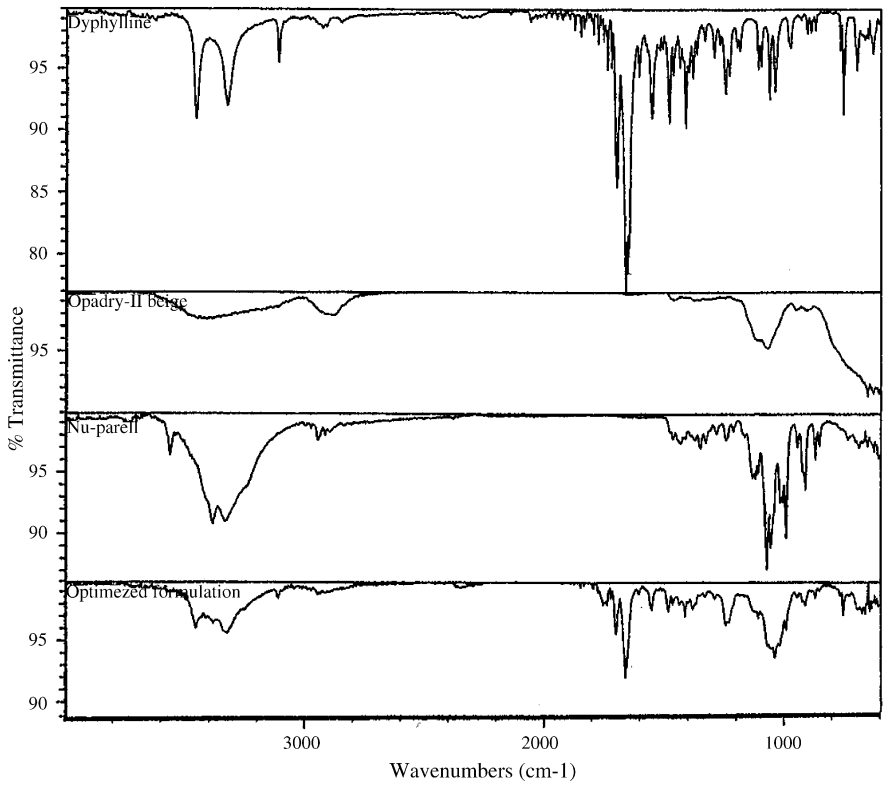

Fig. 10. FTIR spectra of the optimized beads and the ingredients.

where m is the amount of drug left undissolved (Hixson and Crowell, 1931). It is noteworthy that as we shifted from batches with slower release to faster release, first-order model fitted better but Hixson–Crowell model tended to deviate.

Zero-order release provides constant drug release over time irrespective of the formulation and environmental components. Therefore, it should be the ideal model for drug release. Our 15 runs could explain 92.52% variability of the results by zero-order model. It is clear from the last three columns of Table 7 that batches with slow release tended to show zero-order release, which deviates as drug release increased. Since, coating weight gain had the greatest influence on drug release it can be concluded that in general, batches with higher coating should show zero-order release.

Zero-order model was fitted to the release profile of non-osmotic, membrane controlled, spherical multi-particulate dosage forms by several investigators (Frohoff-Hulsmann et al., 1999; Wang et al., 1997). The mathematical modeling of such time independent reservoir systems (Peppas, 1995) would be:

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{\Delta C 4\pi\, DKr_{\mathrm{e}}r_{\mathrm{i}}}{r_{\mathrm{e}} - r_{\mathrm{i}}}$$

where $\mathrm{d}m/\mathrm{d}t$ is the release rate, ΔC the difference in concentration between two sides of the membrane, D the diffusion coefficient of drug through the membrane, K the partition coefficient of the drug between the membrane and the reservoir, r_{i} the internal radius and r_{e} is the external radius of the bead.

3.6. Optimization

Most of the experimental batches, especially those with higher drug release showed the best fit with first-order kinetics. Response Y_5 was maximized and other responses were minimized within the constraint limits to exclude outliers, if any. The variables and the responses are shown in Table 1. The optimized for-

mulation generated by the design is given in Table 8 and turned out to be identical with one of the batches of the design. Even though, for confirmation a fresh batch was prepared with the optimized formulation and studied for drug release in triplicate. The expected and observed results of the responses are presented in Table 8. Those are in close agreement. The dissolution profiles of the observed and the expected data were compared using two fit factors f_1 and f_2 (Moore and Flanner, 1996). These fit factors provide a single number describing two curves that consist of several points to reduce the complexity of curve comparison. The fit factors f_1 and f_2 are zero and 100, respectively, if the two curves are identical and change up to 100 and zero, respectively, as those become completely dissimilar. The calculated values of f_1 and f_2 were 0.61 and 97.44, respectively, suggesting the closeness of observed and predicted values. The complete dissolution profile of the optimized formulation is shown in Fig. 7. The release pattern of the optimized formulation was best fitted to both first-order and Hixson–Crowell kinetics with R^2-value of 0.9962.

3.7. Thermal analysis

Thermal analysis of a formulation could show any, few or all of the following changes: eutectic interactions, solid solution formation, polymorphic transitions and physical interaction between the ingredients. Thus, the interpretation of thermograms is complex in nature. Fig. 8 shows the DSC thermograms of dyphylline, formulation components and the optimized formulation. Broadening of the drug peak is related more to the impurities than physical interaction of the drug with the components. This is confirmed by X-ray, IR and content analysis of the formulation that showed no significant drug interaction.

3.8. X-ray analysis

X-ray powder diffractometry can be used to study the solid-state reactions of two or more samples (Suryanarayanan, 1995). The X-ray diffraction patterns presented in Fig. 9 showed that the sharp peaks of dyphylline were maintained in the formulation suggesting no change in drug crystalinity. Moreover, all the peaks of dyphylline, especially those at 13.675° and 14.450° are retained in the X-ray diffraction pattern of the formulation. Also, the evidence of the appearance of no new peak proves absence of drug interaction with the excipients. The reduction of the intensity of the peaks is only due to the reduction of drug concentration in the optimized formulation.

3.9. FTIR

FTIR spectra of dyphylline, formulation excipients and the optimized formulation are presented in Fig. 10.

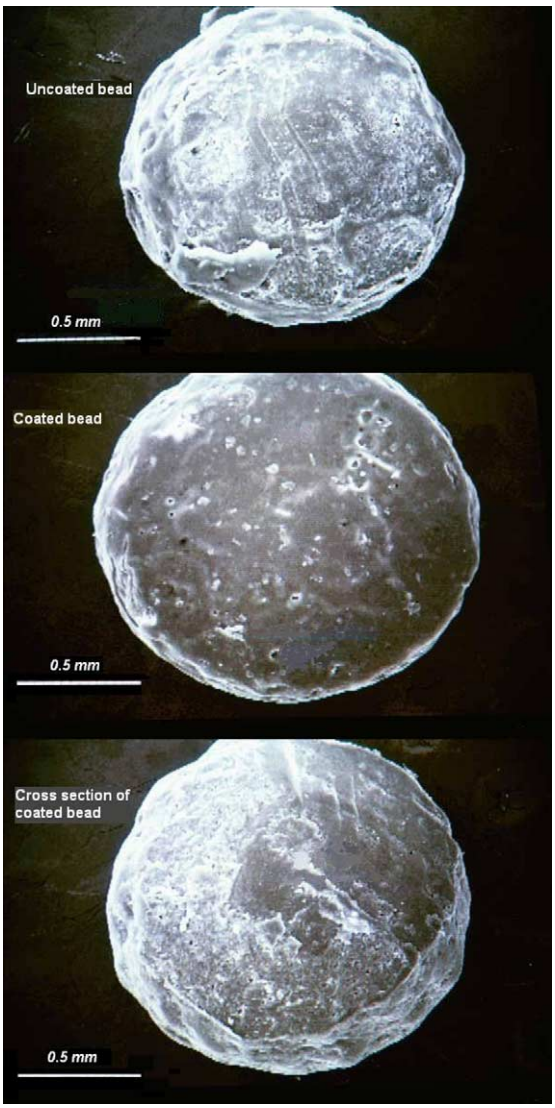

Fig. 11. SEM pictures of uncoated and coated beads and cross section of coated bead.

Dyphylline showed some prominent peaks at 3460, 3320, 3110, 1705 and 1660 cm^{-1}, which could be assigned to the stretching vibrations of intramolecularly hydrogen bonded OH groups, ≡CH, hydrogen bonded NH, non-conjugated C=O and amide moieties, respectively. In the optimized formulation, all those peaks were present explaining no drug degradation or appearance of any new product. All the above analyses prove the integrity of the optimized formulation.

3.10. SEM

Scanning electron microscopic pictures of uncoated and coated beads as well as the cross section of the coated bead are presented in Fig. 11. Uncoated bead appeared to have rough surface, which became smooth on getting coating on it. The cross section of the coated bead shows the core of inert bead, drug layer surrounding the core and outermost intact, uniform polymer coating layer that provided controlled drug release.

4. Conclusions

An optimized multiparticulate drug delivery system of dyphylline coated with SA, customized in our lab was prepared. The design could explain over 99% variability in the models. The optimized formulation showed first-order release kinetics. DSC, X-ray, FTIR and SEM studies showed no change in drug content and integrity of the coated bead. Therefore, SA could be a nice candidate as a coating agent in controlled release drug delivery systems.

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