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Design, Development and Optimization of Controlled Release Microcapsules of Diltiazem Hydrochloride

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Diltiazem is frequently recommended to be administered as a controlled release formulation. The current study aims at development and optimization of controlled release microcapsules of diltiazem hydrochloride. The microcapsules were formulated as per factorial design taking rate controlling coat polymer (ethylcellulose) and emulgent (Span 80) as the factors at three level each. The formulations were tested for drug release, entrapment efficiency, size and surface topography using Scanning Electron Microscopy. A polynomial equation for each response variable was constructed. The resultant data were critically analyzed to locate the composition of optimum formulations, the corresponding microcapsules were formulated and thoroughly evaluated. The microcapsules were topographically regular with over 90% encapsulation efficiency. The release profile using optimized formulation was found to be quite regulated for controlled release purposes ($t_{80\%}$ ≈ 9.5 h) with little dose dumping (release upto 16 h ≈ 99%). All the predicted values of response variables demonstrated close agreement with the experimental data.

Of late, systematic optimization techniques have been frequently employed for design and development of controlled release (CR) pharmaceutical dosage forms[1,2]. Such studies are usually carried out using Response Surface Methodology (RSM) where the selected responses are recorded for a set of pre-planned studies to predict an optimum formulation[3,4]. This tends to require fewer experimental trials yielding the best solution in the presence of competing objectives thus making problem tracing and rectification quite easier. The recent literature is replete with reports on application of RSM optimization for microcapsule formulations[5-9].

Diltiazem hydrochloride, a calcium channel antagonist, is a drug of choice in the treatment of angina pectoris and mild to moderate systemic hypertension, with a favourable adverse effect profile[10]. The dosage schedule for diltiazem *viz.* three times daily for prolonged antihypertensive therapy has been rated as quite cumbersome using conventional formulations[11]. The short biological half-life (3-4 h) and low dose (30-60 mg) of diltiazem coupled with the pharmacodynamic requirement of sustenance of blood pressure fall in hypertensive patients call for its once-a-day CR formulation[11,12].

The objective of the present study is to design, develop and optimize the CR diltiazem microcapsules using RSM. Albeit some work has been under taken on development of CR microcapsules of diltiazem hydrochloride[13,14], yet little literature information is available on the effect of procedural variables on the microencapsulation process. Ethylcellulose (EC) was employed as the release rate controlling polymer for micrcapsule coating and Span 80 was taken as the emulgent. The current study investigates the effect of two independent variables, i.e., mass ratio of EC to drug and concentration of Span 80 on the varied response variables, *viz.* Percent entrapment efficiency (entr), $t_{80\%}$, release up to 16 h (rel_{16h}) and the microcapsule size. A factorial design (FD) for two factors at three levels (3^2 design) was chosen for RSM, as it has an added advantage of determining quadratic re-

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sponse surface[4,15]. In a recent study[16] carried out in our laboratories on controlled release buccoadhesive hydrophilic matrices of diltiazem hydrochloride, this 3^2 design was found to be extremely useful in detecting nonlinearity in the response(s) and predicting the performance of the optimized formulation(s) with high degree of prognosis.

MATERIALS AND METHODS

Diltiazem hydrochloride was obtained from M/s Cipla Ltd., Mumbai, ethylcellulose (14 Cp) was procured from S.D. Fine Chemicals Ltd., Boisar and Span 80 was purchased from Koch-Light Laboratories, Coinbrook Bucks, UK. All other materials used in the study were of analytical grade. The major pieces of equipment employed in the study encompassed, Dissolution Tester (PTW-II Pharma Test, Switzerland), Spectrophotometer (λ 15, Perkin Elmer, Switzerland), Rotavapor Film Evaporator (461, Buchi, Switzerland), Sonicator (3210, Bransons, USA) and Scanning Electron Microscope (JSM 6100 SEM. JEOL, Japan).

Experimental design:

An FD with two independent variables at three levels with three replicates each was employed in the study. Table 1 indicates the factor combinations used along with the translation of their coded levels in the studies. A second order regression model using multiple linear regression analysis (MLRA) was developed for the various responses in the form of equation as, $\mathbf{Y} = \beta_0 + \beta_1 \mathbf{X}_1 + \beta_2 \mathbf{X}_2 + \beta_{12} \mathbf{X}_1 \mathbf{X}_2 + \beta_{11} \mathbf{X}_1^2 + \beta_{22} \mathbf{X}_2^2$, where. **Y** is the measured response, X_1 and X_2 are the coded levels of the two factors, β_0 is the coefficient of the intercept term, β_1 and β_2 are the coefficients of the two factors, β_{11} and β_{22} are the coefficients of the corresponding quadratic terms, and β_{12} is the coefficient of the interaction term.

TABLE 1: SELECTED FACTOR COMBINATIONS AS PER THE FACTORIAL DESIGN FOR 2 FACTORS AT 3 LEVELS EACH.

Experimental Trial No.	Factor levels*	
	Factor 1	Factor 2
1	-1 (1.0)	-1 (0.2)
2	-1 (1.0)	0 (0.6)
3	-1 (1.0)	1 (1.0)
4	0 (1.5)	-1 (0.2)
5	0 (1.5)	0 (0.6)
6	0 (1.5)	1 (1.0)
7	1 (2.0)	-1 (0.2)
8	1 (2.0)	0 (0.6)
9	1 (2.0)	1 (1.0)

*The parentheses in the data indicate the decoded values of factor levels. Factor 1 is the ratio of amount of ethylcellulose to drug and factor 2 is percentage (w/v) of Span 80 in the external phase.

Formulation of microcapsules:

A modification of emulsion solvent evaporation method for microencapsulation was employed[17]. A solution of EC was constituted in acetone and the drug was homogeneously dispersed in it. The dispersion was added to liquid paraffin containing Span 80 in varied concentration(s), while stirring (1500 rpm). The emulsion was stirred for 5-6 h at 25-30° to facilitate the evaporation of solvent and formulation of microcapsules. Subsequently, a suitable amount of petroleum ether was added to the dispersion, the microcapsules were filtered and dried at ambient temperature. The resultant microcapsules were washed with demineralized water and re-washed with petroleum ether to remove the traces of liquid paraffin and desiccated under vacuum. As per factorial design, a total of nine microcapsule formulations (Table 1) were finally prepared with varying levels of surfactant and polymer to drug mass ratio.

Drug content:

An accurately weighed amount of microcapsules was added to dichloromethane (10 ml) to dissolve the EC coat. Ten ml of phosphate buffer (pH 6.8) was added to it and dichloromethane was evaporated at 32-34° using rotary film evaporator. The dispersion was filtered and residue washed with phosphate buffer. The spectrophotometric absorbance of the filtrate was measured at 236 nm after appropriate dilution and the drug content determined. Percent entrapment efficiency was computed from the ratio of assayed drug content to that of drug amount incorporated in the microcapsules.

Optical microscopy:

The size distribution analysis of the microcapsule polydisperse phase was carried out using optical microscopy. The projected diameter of a total of 400 microcapsules was observed for all the formulations. The size data were attempted to be fitted into normal and log-normal distribution using χ^2 test of goodness of fit[18]. Based on the value of χ^2 statistic, the size distribution was characterized to be log-normal ($p<0.01$) and equivalent spherical diameters on sur-

face number basis (d_{sn}) were computed using Hatch-choate equations[19].

***In vitro* release studies:**

Dissolution studies were carried out in triplicate for all the formulations, employing USP XXIII Apparatus 1 (basket method) at 100 rpm and 37±0.5° using phosphate buffer (pH 6.8) as the dissolution medium. An aliquot of the sample was periodically withdrawn at suitable time intervals and the volume replaced with fresh dissolution medium. The samples were analyzed spectrophotometerically at 236 nm and the absorbance data was appropriately corrected for loss of drug during sampling using mathematical relationship proposed earlier[20].

The raw dissolution data was analyzed using ZOREL software that has the in-built provisions for calculating the values of amount of drug dissolved, percent release, rate of drug release and log fraction released at varied times[21]. Using the software, the kinetic constant (k) and diffusional release exponent (n) were also computed based upon the logarithmic transformation of the relationship proposed by Peppas and Sahlin[22], i.e., log (M_t/M_∞) = log k + n log t. Also, the values of the statistical parameters for release kinetics data of each formulation were calculated and based on the phenomenological analysis, the type of release, whether Fickian, non-Fickian (anomalous) or zero-order, was predicted. The values of time taken for 50%, 60%, 70% and 80% release as described by $t_{50\%}$, $t_{60\%}$, $t_{70\%}$ and $t_{80\%}$, respectively were calculated by Stineman interpolation using GRAPH software (MicroMath Inc., USA, Ver. 2).

Scanning electron microscopy (SEM) analysis:

The microcapsule samples were observed both pre-dissolution and post-dissolution under SEM at 5-10 k V by sprinkling sample on the aluminum stubs having double adhesive tape, and subsequent evaporation of gold palladium alloy in the ion sputter unit. The microphotographs of suitable magnifications were obtained for surface topography.

Response surface analysis:

The response variables considered for optimization were $t_{80\%}$, entr. efficiency, rel_{16h} and microcapsule size. For the studied design, MLRA was applied to fit second-order polynomial equation to correlate the studied responses with the examined variables[14]. The computation for current RSM optimization study was carried out using an in-house built software, FACTOP[23]. Only those coefficients, which were found to be statistically significant using Student's t-test, were considered in framing the polynomial equation(s). Also, the statistical parameters of the polynomials like coefficient of determination (R^2), standard error of estimate (s), Fisher's significance criterion (F ratio) were computed. The statistical significance of the polynomials was declared by comparison of the latter values with that of the standard tabulated ones at appropriate degrees of freedom. The polynomial regression results were demonstrated using 3-D graphs and contour plots, both drawn using MS-Excel employing the output files generated with the help of FACTOP software. Finally, the prognosis of optimum formulation was conducted in two stages. First, a feasible space was located amongst the response values at varied levels of each factor. Subsequently, a grid search was conducted in the narrower region to predict the possible compositions. Two, optimum microcapsule compositions were chosen by the critical evaluation of grid search values, the formulations prepared, evaluated for performance and the results compared with the predicted ones.

RESULTS AND DISCUSSION

It is vivid from SEM microphotograph at low magnification of 60X (fig. 1a) that the microcapsules are distinctly spherical with little variation in size. Fig 1b depicts that at moderate resolution (550X), the surface of microcapsules is primarily smooth and regular. At higher magnification of 5000X (fig. 1c), distinct pores are evident on the polymeric wall of the microspheres. Following *in vitro* dissolution, the microcapsule structure gets constricted and shrunk (fig. 1d) without losing the surface porosity. It is quite obvious that the drug may have diffused out of microcapsule pores and channels leaving behind the collapsed EC coat.

In the current study, the values of release rate exponent (n) were found to range between 0.251 and 0.346 for all the nine formulations (Table 2) and the values for the optimized formulations were 0.330 and 0.334. For a sphere, a value of n≤0.43 is known to indicate predominantly Fickian drug release[24]. Accordingly in the current study, the mechanism of drug release from spherical microcapsules is distinctly Fickian diffusion. Fig. 2 indicates the significant decreasing influence of the polymer on the release profiles of the microcapsule formulations at a fixed level (0.6% w/v) of Span 80. The prominence of initial burst effect in the first two hours followed with a relatively regulated drug release for the remaining dissolution period is also apparent in the corresponding inset profile. The initial rapid drug release may be attributable to the presence of loose crystals on the surface, characteristic of drug release kinetics from microca-

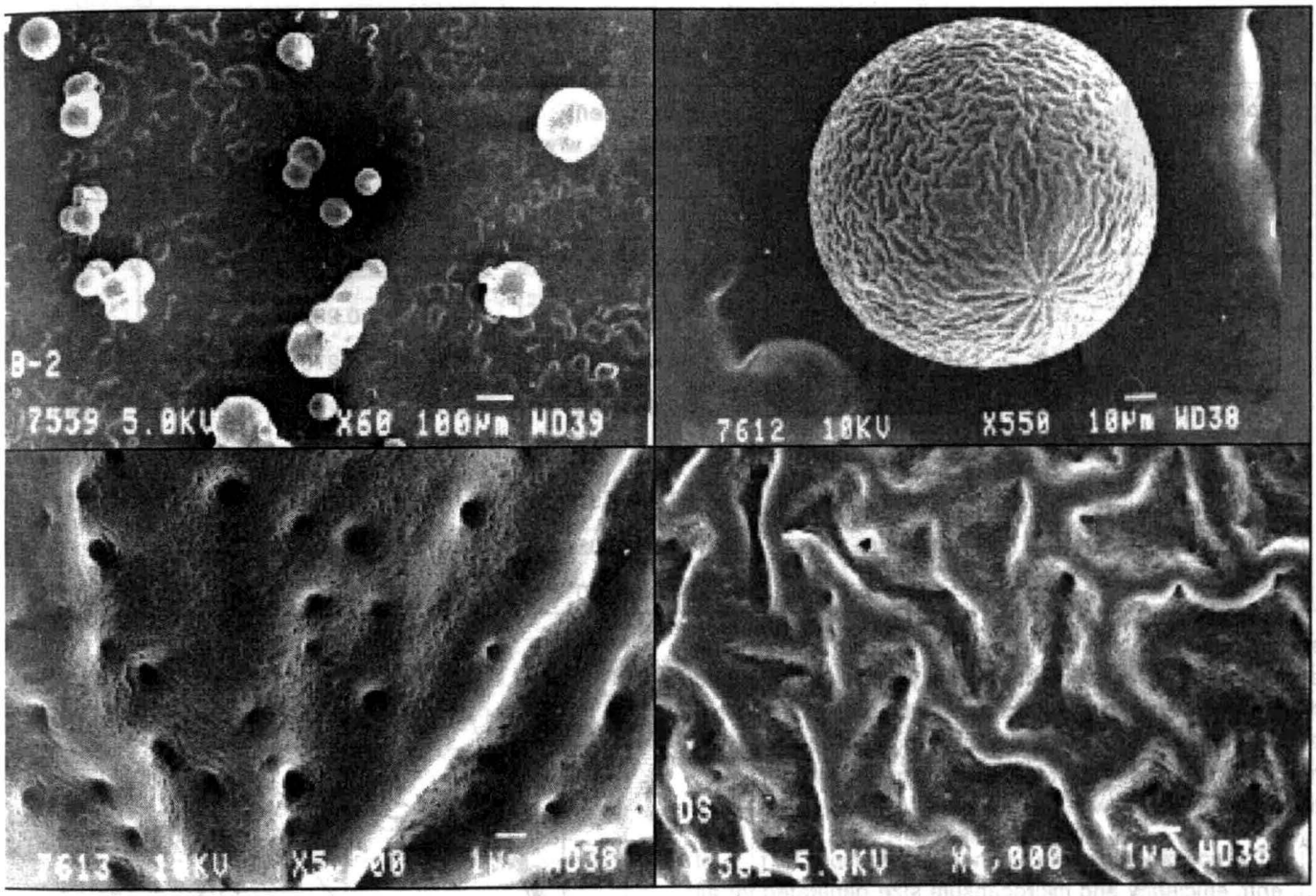

Fig 1: Scanning electron microphotograph of the optimized microcapsules loaded with drug at (a). low resolution (60 X). (b). moderate resolution (550 X). (c). high resolution (5000 X) before dissolution, (d). high resolution (5000 X) following dissolution.

psules[25]. Analogous release patterns observed for all the studied formulations may account for the high magnitude of relative variability (S.E.M.) in the overall rate of drug release (Table 2). The values of kinetic constant (k) varied notably from 0.358 to 0.485 with a distinct decreasing trend discernible with increasing levels of either EC or Span 80. It is already documented in literature[26] that k is a characteristic function of polymer properties such as solubility, viscosity and molecular weight.

Table 2 portrays an increasing trend in the values of $t_{80\%}$ with an increase in the ratio of polymer to drug at constant levels of surfactant. Thus it can be deciphered that the microcapsules composed of higher polymer content provided slower drug release rate. The retardation in release rate may be imputed to a thicker water-insoluble polymeric coating of microcapsules. The data also depicted that the entrapment increases with increasing amount of total polymer for all the formulations. Such relationships between drug loading into microcapsules and polymer amount are previously reported[27]. The size of microcapsules was found to augment with an increasing amount of polymer. This can be ascribed to an increase in the viscosity of the internal phase leading subsequently to an increase in microcapsule size[28].

The influence of Span 80 on percent drug release and rate of drug release has been shown in Table 2. The table depicts a marginal declining trend in the percent drug release with increasing amount of the emulgent. Span 80 is known to be a relatively lipophilic surfactant with HLB of 4.3. Its increased concentration may have accounted for decreased microcapsule porosity leading subsequently to diminution in drug release. Entrapment efficiency showed an increasing trend with increasing Span 80 levels, as presented in Table 2. It is already known that Span 80 tends to decrease interfacial tension amongst the emulsion phases and

TABLE 2: MICROCAPSULE CHARACTERISTICS AND DISSOLUTION PARAMETERS FOR ALL THE NINE FORMULATIONS PREPARED AS PER FACTORIAL DESIGN (n=3)

Polymer to drug ratio	Span 80 (% w/v)	Particle size (μm) mean±SD	Entrapment efficiency (% w/w) mean±SD	k	n	$t_{80\%}$ (h)	rel_{16h} (%)
1:1	0.2	94.89±1.25	75.15±2.45	0.485	0.260	6.83	99.17
1:1	0.6	94.73±0.95	79.23±0.89	0.481	0.251	7.59	98.84
1:1	1	90.66±1.48	83.18±2.38	0.424	0.297	8.47	97.92
1.5:1	0.2	110.48±1.27	84.45±1.45	0.457	0.270	7.92	98.92
1.5:1	0.6	105.40±2.45	86.15±1.90	0.455	0.267	8.31	98.46
1.5:1	1	97.25±0.84	87.5±1.75	0.450	0.267	8.63	95.99
2:1	0.2	110.89±1.39	89.27±1.30	0.417	0.298	8.87	97.46
2:1	0.6	110.66±1.06	90.58±2.35	0.401	0.300	9.96	92.95
2:1	1	109.39±0.68	94.85±1.50	0.358	0.346	10.20	92.99

stabilize the emulsions with oily continuous phase[18]. The augmentation of entrapment efficiency seems to be due to the improvement in emulsion stability at higher Span 80 levels. As indicated in Table 2, the microcapsule size (d_{sn}) significantly decreased with increasing surfactant concentration, in accordance with literature[16].

The coefficients of the polynomial equations for $t_{80\%}$, rel_{16h}, entr. efficiency and microcapsule size generated for all the formulations using MLRA and presented in equations 1 to 4 along with the values of statistical parameters *viz.* R^2, s, and level of statistical significance. High values of R^2 ranging between 0.965 to 0.997 and statistical significance ($p<0.01$) coupled with low magnitudes of s ranging between 0.19 to 0.99 ratify the validity of the response surface relationships. Using MLRA, a total of six coefficients were calculated, leaving the added interaction terms, as irrational inclusion of greater number of terms often lead to a reduction in F value at higher numerator degrees of freedom and insignificant t values for various individual coefficients, thereby making the equation statistically invalid. Only those coefficients which were statistically significant at 5% levels or higher were taken for subsequent feasibility and grid searches.

$$t_{80\%} = 8.559 + 0.977\ X_1 + 0.612\ X_2 - 0.082\ X_1X_2 + 0.413\ X_1^2 - 0.222\ X_2^2 \quad ...(1)$$

($R^2 = 0.971$, s = 0.19, $p < 0.01$).

$$entr = 86.89 + 6.502\ X_1 + 2.528\ X_2 - 0.807\ X_1\ X_2 - 1.0178\ X_1^2 - 0.078\ X_2^2 \quad ...(2)$$

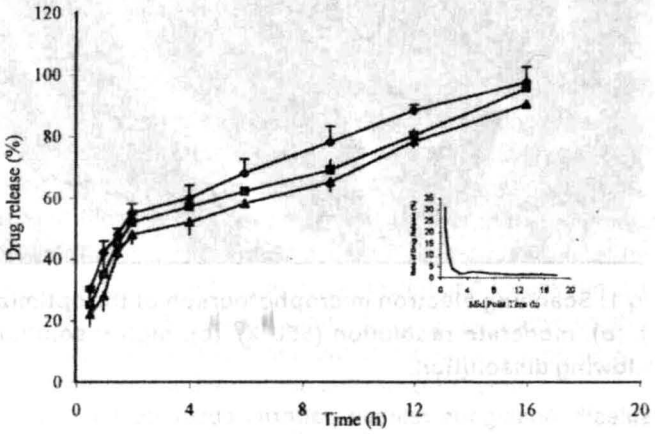

Fig 2: Diagram depicting influence of polymer to drug ratio on mean percent release at fixed level of Span 80 (0.6% w/v). The inset shows the corresponding plot between rate of drug release and mid points of time intervals. (●● 1.0/1.0; ■■ 1.5/1.0; ▲▲ 2.0/1.0)

($R^2 = 0.977$, s = 0.99, $p < 0.01$)

$$rel_{16h} = 98.244 - 1.917\ X_1 - 1.177\ X_2 - 0.377\ X_1\ X_2 - 0.983\ X_1^2 - 0.213\ X_2^2 \quad ...(3)$$

($R^2 = 0.965$, s = 0.30, $p < 0.01$)

$$d_{sn} = 93.206 + 23.215\ X_1 - 7.012\ X_2 - 4.795\ X_1\ X_2 + 13.938\ X_1^2 - 1.962\ X_2^2 \quad ...(4)$$

($R^2 = 0.997$, s= 0.19, $p < 0.01$)

The response surface graphs shown in fig. 3 to fig. 6 facilitate an understanding of the contribution of the vari-

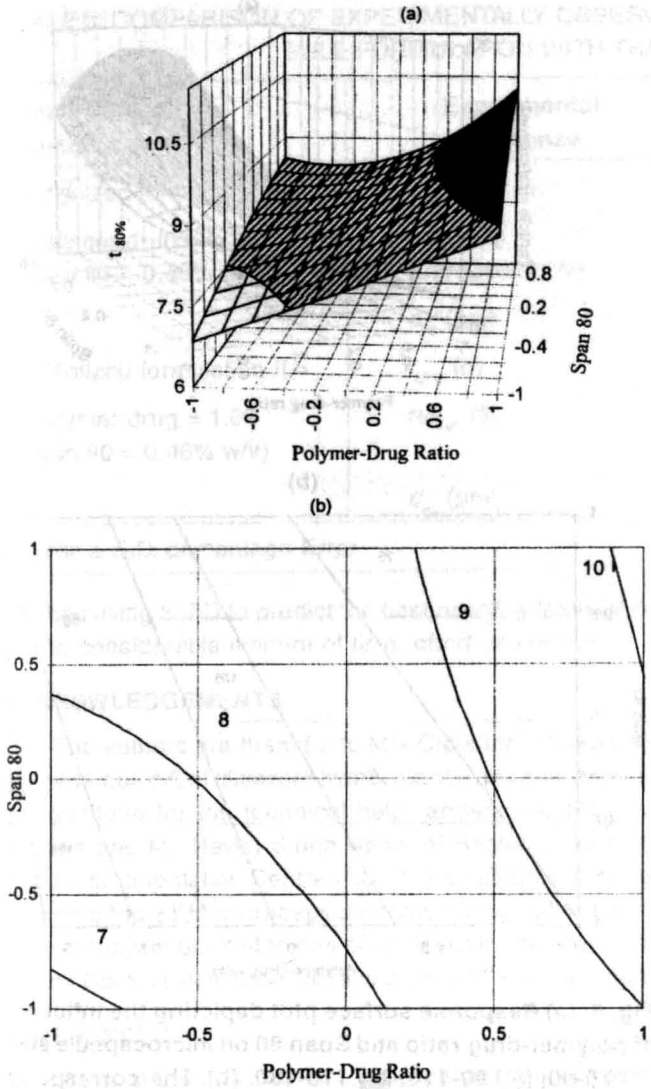

Fig. 3: (a) Response surface plot depicting the influence of polymer-drug ratio and Span 80 on $t_{80\%}$. ☐ 6-7.5; ▒ 7.5-9; ■ 9-11. (b).The corresponding map showing contour lines at the fixed values of $t_{80\%}$.

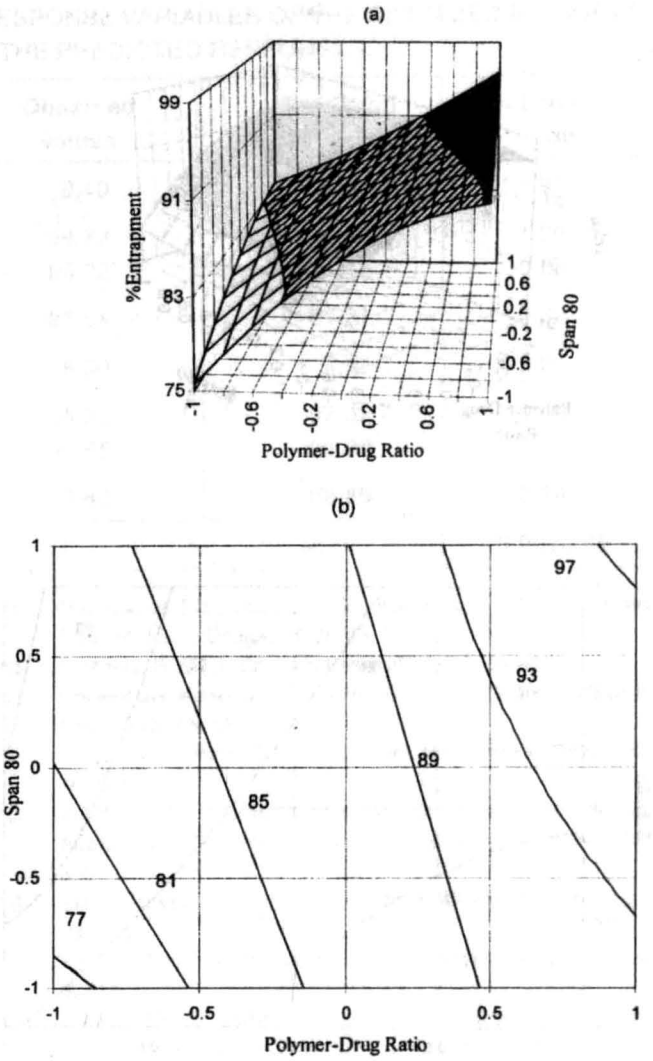

Fig. 4: (a) Response surface plot depicting the influence of polymer-drug ratio and Span 80 on entrapment efficiency. ☐ 75-83; ▒ 83-91; ■ 91-99. (b).The corresponding map showing contour lines at the fixed values of percent entrapped drug.

ables and their interactions. Fig. 3a evidently illustrates that $t_{80\%}$ augments with increasing levels of both polymer and Span 80. The corresponding contour plot (fig. 3b) depicts an approximate inverse linear relationship with Span 80 levels. However, to maintain $t_{80\%}$ at a high value of 10 h, a high polymer amount has to be coupled with moderate concentrations of the emulgent.

Similarly, as it is observed from fig. 4a, an increase in the amount of polymer as well as Span 80, tends to improve the drug loading. Therefore, as shown in fig. 4b, to achieve high drug entrapment, moderately high levels of both polymer and surfactant are required. Fig. 5a depicts the nonlinear descending trends for the extent of drug release (rel_{16h}) with increasing polymer amount and Span 80. The corresponding contour map (fig. 5b) corroborates the nonlinear trend at all levels of Span 80. Fig. 6a portrays a linear increase in microcapsule size with increasing polymer to drug ratio. On the other hand, with increasing surfactant concentration at low polymer concentrations, the size tends to decrease. The linearity of contour lines (fig. 6b) evidently reveal that higher microcapsule size can be attained using high polymer to drug ratio and intermediate levels of surfactant. However, smaller microcapsules can be obtained by

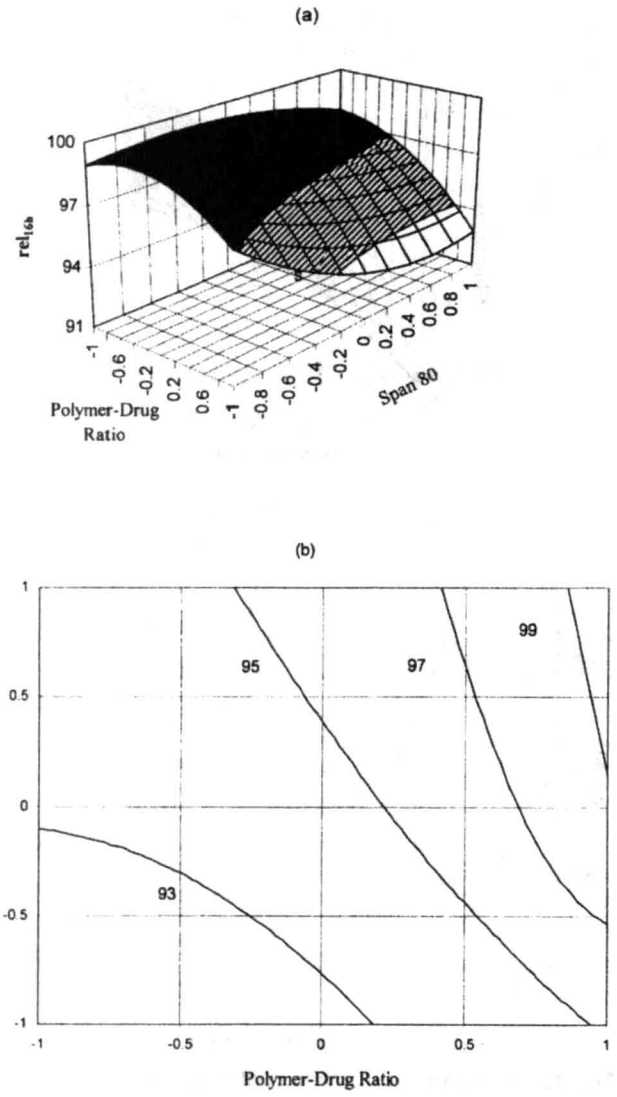

Fig. 5: (a) Response surface plot depicting the influence of polymer-drug ratio and Span 80 on rel_{16h}. ☐ 91-94; ☐ 94-97; ■ 97-100. (b). The corresponding contour map showing contour lines at the fixed values of rel_{16h}.

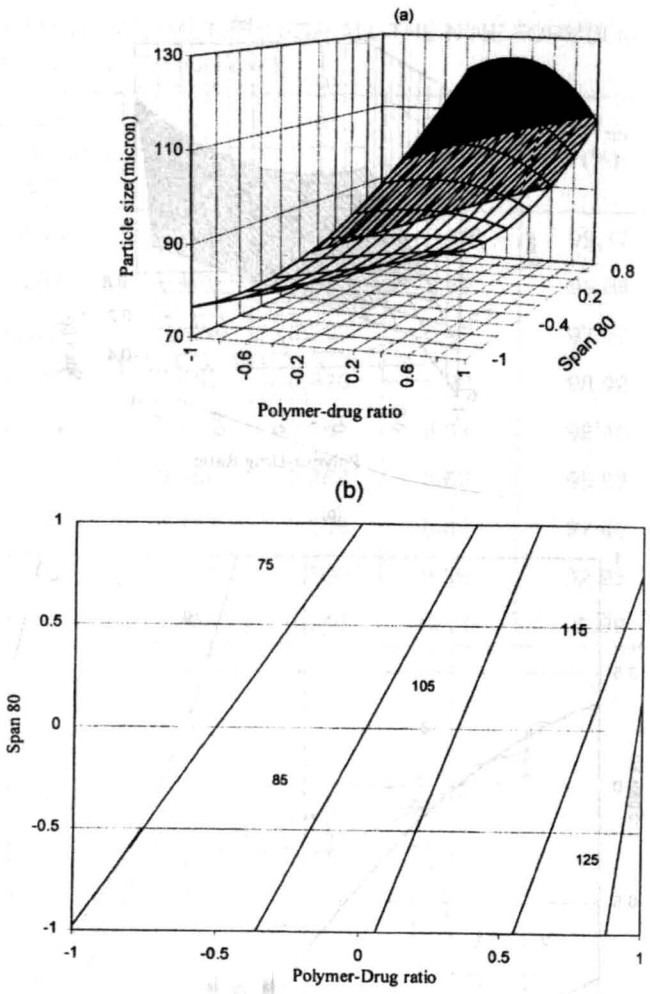

Fig. 6: (a) Response surface plot depicting the influence of polymer-drug ratio and Span 80 on microcapsule size. ☐ 70-90; ☐ 90-110; ■ 110-130. (b). The corresponding contour map showing contour lines at the fixed values of d_{sn}.

complimenting low polymer levels with low Span levels or intermediate polymer levels with high levels of surfactant.

Table 3 enlists the values of the observed response variables and those predicted using MLRA method along with the percentage prediction errors. The prediction error for the response variables ranged between 0.24 to 2.01 % with the mean ± SD of the absolute error as 0.96 ± 0.65%. The low magnitudes of error construe high prognostic ability of the RSM, i.e., factorial design coupled with MLRA. Model simplification using MLRA by eliminating insignificant parameters with $p>0.05$ has already been reported to result in better prognosis of the performance of optimized formulation[29]. Our results are in clear agreement with the same.

Significant entrapment of diltiazem hydrchloride into ethylcellulose microcapsules and subsequent considerable prolongation of drug release was attained by optimizing various formulation variables. The mechanism for controlled release of drug was found to be predominantly Fickian diffusion. The 3D-response surfaces and 2D-contour maps provided a critical insight into the effects of the factors, i.e., coating polymer and emulgent on the chosen response variables. The predicted outcomes of RSM were in marked consonance with the observed experimental findings. Thus, the current study ratifies the rational use of optimization meth-

TABLE 3: COMPARISON OF EXPERIMENTALLY OBSERVED RESPONSE VARIABLES OF THE OPTIMIZED MICROCAPSULE FORMULATION WITH THAT OF THE PREDICTED RESPONSES.

Formulation Composition	Experimental Response	Observed values	Predicted values	% Error
Optimized formulation I	$t_{80\%}$ (h)	9.40	9.23	1.91
(Polymer:drug = 1.70	rel_{16h} (%)	98.73	97.68	1.06
Span 80 = 0.40% w/v)	Entrapment (%)	90.72	91.17	-0.50
	d_{sn} (μm)	91.51	91.21	0.32
Optimized formulation II	$t_{80\%}$ (h)	9.50	9.32	2.01
(Polymer:drug = 1.68	rel_{16h} (%)	98.90	97.32	1.59
Span 80 = 0.46% w/v)		90.85	91.80	1.04
	d_{sn} (μm)	86.86	86.65	0.24
Mean ± S.D. percentage Error				0.96±0.65

odology using 3^2 FD to predict the best possible formulation saving considerable amount of time, effort and money.

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