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Research Article

FORMULATION AND OPTIMIZATION BY APPLYING 3^2 FULL FACTORIAL DESIGN OF MUCOADHESIVE MICROSPHERES OF NIFEDIPINE

CHIMAN LAL[1]*, RAJEEV GARG[2], GHANSHYAM DAS GUPTA[3]

[1]Department of Research and Development, I. K. G. Punjab Technical University, Kapurthala, Punjab, India. [2]Department of Pharmaceutical Research, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar, Punjab, India. [3]Department of Pharmaceutics, I.S.F. College of Pharmacy, Moga, Punjab, India. Email: chimanberi22@gmail.com

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ABSTRACT

Objective: The purpose of this research work is to formulate and optimize mucoadhesive microspheres of nifedipine using Carbopol 934P as mucoadhesive and ethyl cellulose as a carrier polymer for controlling the release of nifedipine.

Methods: The emulsion solvent evaporation technique was used for the preparation of microspheres and the 3^2 full factorial designs were employed for optimization of microspheres. The developed microspheres were characterized for percent yield, entrapment efficiency, particle size, *in vitro* release study, percent mucoadhesion, surface morphology, and stability study.

Results: Evaluating outcomes of preliminary batches indicated that 100 ml volume of processing medium, 5 h stirring time and 2% concentration of emulsifying agent were suitable for spherical, free-flowing microspheres and high percentage drug entrapment efficiency. The optimized batch exhibited 84.35% drug entrapment efficiency, 61.78% mucoadhesion and drug release were also sustained for more than 12 h. Scanning electron microscopy study revealed that produced microspheres were spherical in shape.

Conclusion: Experimental responses of the optimized batch have close proximity with the predicted value and stability study of the optimized formulation proved the formulation is stable for a long period of time; hence, it is an excellent alternative over the conventional delivery system.

Keywords: Mucoadhesive microspheres, nifedipine, Carbopol 934P, ethyl cellulose, factorial design.

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INTRODUCTION

Nifedipine [Dimethyl 1,4–dihydro–2,6–dimethyl–4-(2-nitrophenyl) pyridine–3,5–dicarboxylate] is one of the drugs which is most effective and extensively used in the management of angina (especially in Prinzmetal's angina) and hypertension. It is also commonly helpful to control the blood pressure in an effective manner during pregnancy [1,2] and in a small subset of pulmonary hypertension patients whose symptoms respond to calcium channel blockers [3]. Nifedipine tablet is eliminated rapidly due to its short biological half-life about 2 h [4] and shows irregular bioavailability due to its high first pass effect [5]. The conventional dosage form has several side effects such as an increase in heart rate, palpitation, and flushing [6], that is, why it is requisite to develop a new kind of dosage form for the nifedipine to overcome these side effects and multiple dose intervals.

In the design of drug delivery systems, mucoadhesive microspheres are a contemporary topic of interest to prolong the residence time of the dosage form on the site of application or absorption [7]. For the enhancement of bioavailability of the drug, it facilitates the intimate contact of the dosage form with the underlying absorption surface [8]. The interactions of bio-adhesive polymers to the mucin layer of the mucous membrane are referred to as mucoadhesion [9]. It can be achieved by the specific and nonspecific interaction of bioadhesive polymer with a mucus layer [10]. When the mucoadhesive microspheres of poorly soluble drugs are prepared, they are highly dispersed in the inner part of the microspheres or adsorbed at the surface of microspheres, which may assist to enhance the bioavailability of drugs [11]. The complex phenomenon of mucoadhesion is based on the different types of theories such as electronic, wetting, adsorption, and diffusion theory [12]. The adhesion of microspheres with a mucus layer achieved by two stages, first wetting of the microspheres after that, the establishment of adhesive interaction [13,14].

The purpose of this work is to formulate and optimize the mucoadhesive microspheres of nifedipine using the Carbopol 934P as mucoadhesive and ethyl cellulose as carrier polymer. A 3^2 full factorial design was employed to study the effect of independent variables such as the amount of ethyl cellulose and amount of Carbopol 934P on the physicochemical characteristics drug entrapment efficiency, Q_1h (% cumulative drug release at 1 h), and $t_{90\%}$ and mucoadhesion of the mucoadhesive microspheres of nifedipine.

MATERIALS AND METHODS

Materials

Nifedipine was obtained from Macleods Pharmaceutical Ltd. (Mumbai, India). Carbopol 934P was purchased from Sigma-Aldrich Pvt. Ltd. Ethylcellulose, light liquid paraffin, Span 80, Ethanol 95%, petroleum ether, and methanol were purchased from Loba Chemie Pvt., Ltd., Mumbai. Hydrochloric acid (HCl) was purchased from Thermo Fisher Scientific India Pvt., Ltd., Mumbai. All other chemicals were of analytical grade.

Preparation of microspheres

The emulsion solvent evaporation technique was used to prepare mucoadhesive microspheres of nifedipine. Ethyl cellulose was dissolved in 95% ethanol; Carbopol 934P and nifedipine powder were dispersed in ethyl cellulose solution under magnetic stirring for 2 h. Then, this suspension was dispersed dropwise in light liquid paraffin containing span 80 as surfactant with continuous stirring on Remi mechanical stirrer at 1000 rpm. After 5 h of stirring, ethanol was evaporated gradually and microspheres were produced. These prepared microspheres were washed with petroleum ether, filtered and dried at room temperature for 24 h and then stored in the desiccators until used.

Determination of percentage yield
The percentage of production yield was calculated from the weight of dried microspheres (W1) and the sum of the initial dry weight of starting materials (W2) as the following equation [15,16].

$$\%\text{yield} = \frac{\text{Total amount of dried microspheres (W1)}}{\text{Total weight of raw material (W2)}} \times 100 \quad (1)$$

Determination of drug content and entrapment efficiency
An appropriate amount of microspheres of nifedipine was crushed to fine powder, extracted with methanol for 24 h and then filtered. After filtration, absorbance measured spectrophotometrically at 235 nm for drug content. The drug entrapment efficiency was calculated using the following equation [17,18].

$$\%\text{Entrapment efficiency} = \frac{\text{Practical drug loading}}{\text{Theoretical drug loading}} \times 100 \quad (2)$$

Determination of particle size of microspheres
The freshly prepared microsphere was examined with an optical microscope and the size of the microspheres was measured using a pre-calibrated ocular micrometer and stage micrometer. About 200–300 particles of each formulation were observed and counted [19-21].

***In vitro* release study**
USP type II dissolution test apparatus was used for studying the drug release properties of the microspheres. An appropriate amount of microspheres of nifedipine was taken in muslin cloth and tied on the paddle which was suspended in the media under test. The test was carried out in 0.1 N HCl (pH 1.2) (900 ml) equilibrated at 37 ± 0.5°C. The paddles were rotated at 50 rpm. At specific time points, 5 ml of dissolution media was withdrawn and replaced with 5 ml of fresh dissolution medium [22,23]. The collected samples were analyzed spectrophotometrically at 238 nm for their absorbance. Concentrations were calculated using calibration curves developed in respective media. Taking into account, the loss of the drug in aliquot replaced, the correction factor was used, as shown in Equation 3 [24].

$$C_i = Ai + \frac{Vs}{Vt}\sum_{i=1}^{n-1} Ai\left(\frac{Vt}{Vt - Vs}\right) \quad (3)$$

Where, C_i = Corrected absorbance, V_s = Sample of dissolution media withdrawn, V_t = Total volume of dissolution media.

Dissolution release profiles were plotted with percentage drug released at different time intervals. The average value of $t_{90\%}$ for all batches was calculated from the dissolution data.

***In vitro* wash-off test**
In vitro wash-off test was used to evaluate the mucoadhesive property of microspheres. The rats were sacrificed by cervical dislocation. The abdomen was opened and the stomach was excised [25]. A 1-cm by a 1-cm piece of rat stomach mucosa was cut and tied on a glass slide (3-inch by 1-inch) with thread. Approximately 100 microspheres were spread onto the wet rinsed tissue specimen and hanging prepared slide onto the grooves of a USP tablet disintegrating test apparatus. After that, the disintegrating test apparatus was switched on, and tissue specimen was given up and down movements for 10 h in a beaker containing simulated gastric fluid (pH 1.2). The microspheres remaining on the surface of the gastric mucosa were counted after 10 h and the percentage mucoadhesion was calculated by the formula shown in Equation 4 [26,27].

$$\text{Percent mucoadhesion} = \frac{\text{Weight of adhered microspheres}}{\text{Weight of applied microspheres}} \times 100 \quad (4)$$

Release kinetics and mechanism
To know the release mechanism and kinetics of nifedipine, all formulations were attempted to fit into mathematical models. r^2 value of zero-order, first-order, and Higuchi model and n, r^2 values for Korsmeyer–Peppas models were calculated [28].

Determination of surface morphology
The surface characteristics of microspheres were studied by scanning electron microscope (JEOL JSM-6100 scanning microscope, Japan). Sample of microspheres was mounted on a stub and coated with a layer of gold using a sputter coater (JFC-1100). The samples were scanned at 5 kV and photomicrograph at different magnification ratio [29,30].

RESULTS AND DISCUSSION

Preliminary studies
During the preliminary trials, the volume of processing medium is the one important factor related to microspheres. Three different volumes of light liquid paraffin 50, 100, and 150 ml were selected. Irregular microspheres are obtained when 50 ml of light liquid paraffin was used and spherical and the free-flowing microspheres are obtained when 100 and 150 ml of processing medium were used, so 100 ml of processing medium was selected for maximum sphericity.

Preliminary batches C_1 to C_{12} were prepared to study the effect of the concentration of emulsifying agents and stirring time on the percent yield, particle size, drug entrapment efficiency, mucoadhesion, and shape of the microspheres.

The concentration of emulsifying agent varied from 1 to 2.5% and stirring time 3-7 h. Spherical and free-flowing microspheres were obtained using more than 2%, and irregular microspheres were obtained using <2% emulsifying agent. The drug entrapment efficiency, mucoadhesion, and particle size were also affected by the concentration of an emulsifying agent. Increases the emulsifying agent was inversely affected the drug entrapment efficiency, however, mucoadhesion and particle size considerably increases. Hence, the 2% emulsifying agent was selected for further studies. Increases the stirring time (3–7 h) were inversely affected the drug entrapment efficiency although, increased the percentage yield and mucoadhesion so that 5 h stirring time was used for the preparation of microspheres.

Experimental design
On the basis of preliminary study, a 3^2 full factorial design was used to determine the effects of independent variables X_1 (amount of ethyl cellulose) and X_2 (amount of carbopol934P) on dependent variables percent entrapment efficiency, percent mucoadhesion, Q_1h and $t_{90\%}$. The selection of independent and dependent variables is given in Table 1, although all the batches were prepared according to the experimental design listed in Table 2.

Percentage yield and entrapment efficiency
The percentage yield of coded batches varies from 64.56 to 89.63%. The minimum percentage yield was 64.56% of batch N_1, whereas maximum 89.63% for N_9 batch. The results are given in Table 3.

The entrapment efficiency of batches varies from 50.23 to 86.45%, as shown in Table 3. The maximum entrapment efficiency was 86.45% of batch N_9. It shows entrapment efficiency is increased due to an increase in the concentration of ethyl cellulose and Carbopol 934P. The entrapment efficiency depends on the type and amount of polymers used. It was found that, if increasing the amount of ethyl cellulose and Carbopol 934P the entrapment efficiency was increased.

Size of microspheres
The microspheres of coded batches are spherical and free-flowing and the size varies from 71.32 to 126.75 um. The size also depends on the concentration of the polymer solution. The results showed that by increasing the concentration of polymers obtained microspheres were more spherical and the size of microspheres was also increased.

In vitro drug release study

In vitro drug release study carried on all the formulations. Q_1h and $t_{90\%}$ was calculated. The values of Q_1h of prepared formulations are 21.60–33.81% and $t_{90\%}$ in the range of 464–705 min, as shown in Table 4. The amount of ethyl cellulose inversely affects the Q_1h, although increasing the concentration of Carbopol 934P Q_1h is also increased.

Batch N_7 shows drug release for a long time and batch N_3 shows 90% drug release in 464 min. It shows that by increasing the amount of ethyl cellulose, the microspheres released drug for a long time while increasing the amount of Carbopol 934P the drug release reduced. The drug release curves of all the batches are shown in Fig. 1.

Table 1: Independent and dependent variables

Independent variable	Variable level		
	Low (−1)	Medium (0)	High (1)
Amount of ethyl cellulose (mg)	100	150	200
Amount of carbopol 934P (mg)	50	100	150
Dependent variables			
Y_1=Percent entrapment efficiency			
Y_2=Q_1 h (percent CDR at 1 h)			
Y_3=$t_{90\%}$			
Y_4=Percent mucoadhesion			

CDR: Cumulative drug release

Table 2: 3^2 full factorial design matrix

Batches	X1	X2	X12	X11	X22
N_1	−1	−1	1	1	1
N_2	−1	0	0	1	0
N_3	−1	1	−1	1	1
N_4	0	−1	0	0	1
N_5	0	0	0	0	0
N_6	0	1	0	0	1
N_7	1	−1	−1	1	1
N_8	1	0	0	1	0
N_9	1	1	1	1	1
N_{10}*	0	0	0	0	0
N_{11}*	0	0	0	0	0

*Center point batch

Table 3: Results of percentage yield, entrapment efficiency, and particle size of microspheres

Batch number	Percent yield	Percent entrapment efficiency*	Particle size* (um)
N_1	64.56	50.23±2.36	71.32±3.88
N_2	69.24	52.64±3.24	72.65±2.54
N_3	76.14	53.94±1.12	74.41±2.98
N_4	72.21	54.56±3.14	95.21±1.96
N_5	81.45	61.23±3.08	98.16±2.82
N_6	85.23	63.14±2.66	97.32±3.16
N_7	76.21	76.23±1.34	112.56±2.76
N_8	74.05	83.23±4.08	116.98±4.28
N_9	89.63	86.45±3.78	126.75±1.32
N_{10}*	78.82	61.94±2.64	96.86±2.68
N_{11}*	80.26	60.83±3.64	102.35±3.21

*Mean±SD, (n=3). SD: Standard deviation

Table 4: Results of Q1 h, $t_{90\%}$ and mucoadhesion

Batch number	Q1 h (Percent CDR)*	$t_{90\%}$	Mucoadhesion
N_1	31.00 ± 0.63	594	60
N_2	32.42 ± 1.58	558	68
N_3	33.81 ± 1.36	464	76
N_4	22.38 ± 1.38	680	55
N_5	26.83 ± 0.97	634	64
N_6	33.15 ± 1.16	471	71
N_7	21.60 ± 1.36	705	49
N_8	22.00 ± 1.22	671	57
N_9	22.70 ± 1.02	514	68
N_{10}*	27.17 ± 0.55	648	60
N_{11}*	25.83 ± 1.10	641	65

*Mean ± SD, (n = 3). SD: Standard deviation, CDR: Cumulative drug release

Mucoadhesion

In vitro wash-off test for percentage, mucoadhesion varied from 49 to 76%. Results indicated that the amount of ethyl cellulose has a negative effect on percent mucoadhesion. Batch N_3 have a maximum percent mucoadhesion because of less concentration of ethyl cellulose. The results are depicted in Table 4.

Release kinetics and mechanism

The different kinetics equations are applied on all the formulations of nifedipine microspheres such as zero-order, first-order, Higuchi, Hixon Crownwell, and Korsmeyer–Peppas. The R^2 values of all formulations are shown in Table 5.

The R^2 value of all formulations is >0.90 and best fit in Korsmeyer–Peppas model (R^2 > 0.997). The values of release exponent for the batch N_2, N_3, and N_6 are <0.5 indicate Fickian diffusion, and all the other batches show non-Fickian diffusion.

Data fitting to the model

Full factorial design as the response surface methodology (RSM) requires nine batches with two center point batches (N_1-N_{11}). The responses of all the prepared formulations were simultaneously fit to quadratic modal using Design Expert 11. The positive values of the coefficient stand for an effect in favors and the negative values oppose factors and response. Polynomial equations generated by Design Expert were established on the basis of ANOVA. The statistical analysis suggests that the independent variables significantly affected dependent variables.

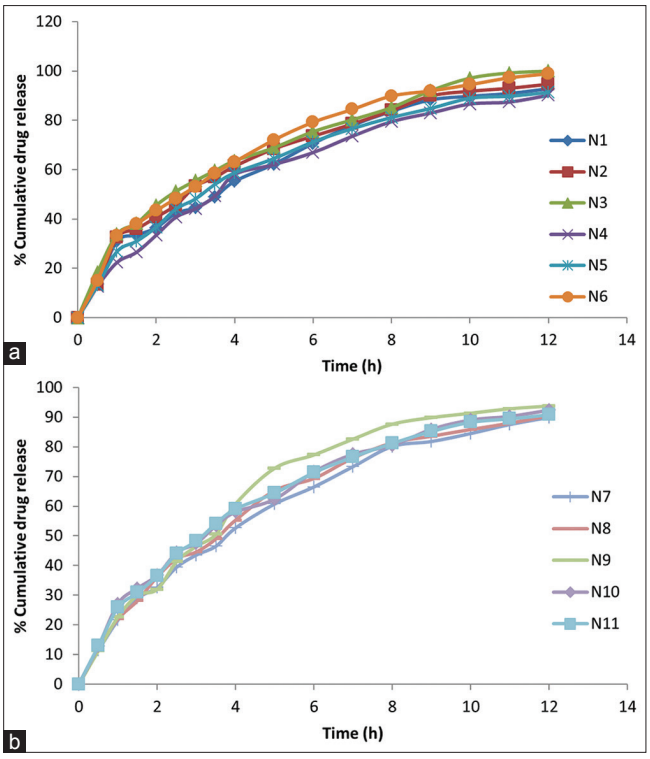

Fig. 1: Percent cumulative drug release of batches (a) N_1 – N_6 (b) N_7 – N_{11}

Factorial equation for drug entrapment efficiency

Assessing the drug loading capacity of microspheres, the drug entrapment efficiency is important variable. The following polynomial equation was derived from multiple regression analysis of the data.

$$Y_1 = +61.07 + 14.85X_1 + 3.75X_2 + 1.63X_1X_2 + 7.27X_1^2 - 1.82X_2^2$$

The percentage drug entrapment of all the 11 batches varied from 50.23% to 86.45% has shown good correlation coefficient 0.9980. Y_1 is strongly affected by the independent variables. The equation of drug entrapment efficiency reflects the wide range of values of various coefficients. Out of two independent variables X_1(14.85) and X_2(3.75), the X_2 has a lower value of the coefficient. p value of X_1 and X_2 is 0.0001 found to be significantly affected Y_1. The interaction of both the independent variables has significantly affected by positive value (+1.63). This showed that the amount of ethyl cellulose has prominent effects on entrapment efficiency as compared to the amount of Carbopol 934P. Contour plot and response surface graph for drug entrapment efficiency is shown in Fig. 2.

Factorial equation for percent cumulative drug release in 1 h

$$Y_2 = +27.37 - 5.15X_1 + 2.82X_2 - 0.9898X_1X_2 - 0.3735X_1^2 + 0.3962X_2^2$$

The values of Q_1 for all the batches varied from 21.60 to 33.81%. Y_2 is affected by the independent variable with good correlation coefficient 0.9123. The value of X_1 and X_1^2 interaction has a negative value indicating undesirable effects on Y_2. The value of X_2 (+2.82) has a positive effect indicating that the X_2 has favorable effects on Y_2. Both the independent variables (X_1, X_2) were also significantly ($p < 0.05$) affected the Y_2. All the results of Q_1 showed that the Carbopol 934P has a positive effect on dissolution after 1 h. Contour plot and response surface graph for percentage mucoadhesion are shown in Fig. 3.

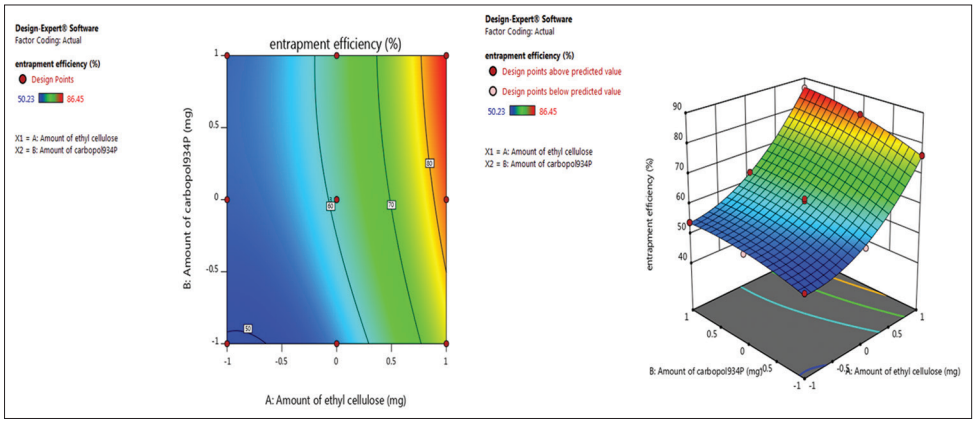

Fig. 2: Contour and three-dimensional surface plot for entrapment efficiency

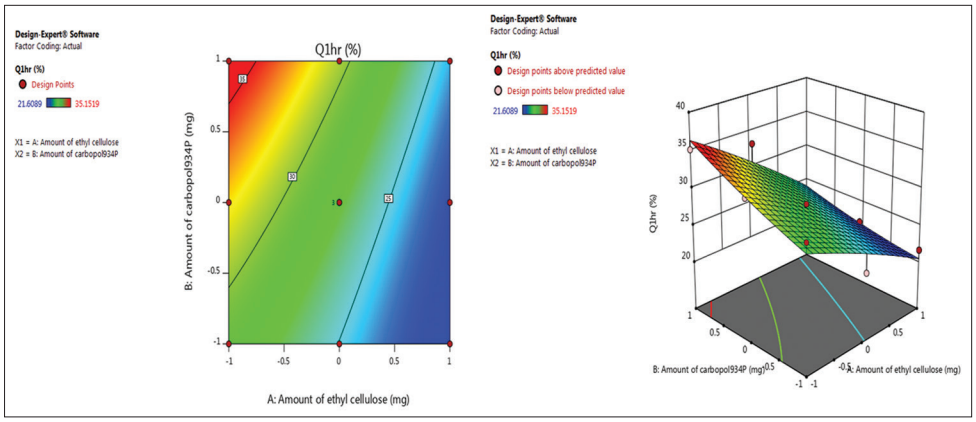

Fig. 3: Contour and three-dimensional surface plot for Q_1h

Table 5: Release kinetic data for the batch N_1–N_{11}

Batch number	Zero-order kinetics R^2	First-order kinetics R^2	Higuchi kinetics R^2	Hixon-Crownwell R^2	Korsmeyer–Peppas	
					R^2	n
N_1	0.939	0.984	0.989	0.990	0.977	0.519
N_2	0.904	0.987	0.991	0.987	0.992	0.485
N_3	0.901	0.923	0.995	0.975	0.997	0.461
N_4	0.935	0.996	0.990	0.991	0.989	0.610
N_5	0.919	0.996	0.993	0.990	0.993	0.545
N_6	0.903	0.991	0.966	0.964	0.960	0.486
N_7	0.932	0.995	0.991	0.991	0.995	0.604
N_8	0.928	0.997	0.989	0.988	0.990	0.603
N_9	0.926	0.993	0.977	0.987	0.980	0.648
N_{10}	0.923	0.994	0.994	0.990	0.995	0.535
N_{11}	0.908	0.998	0.993	0.989	0.993	0.554

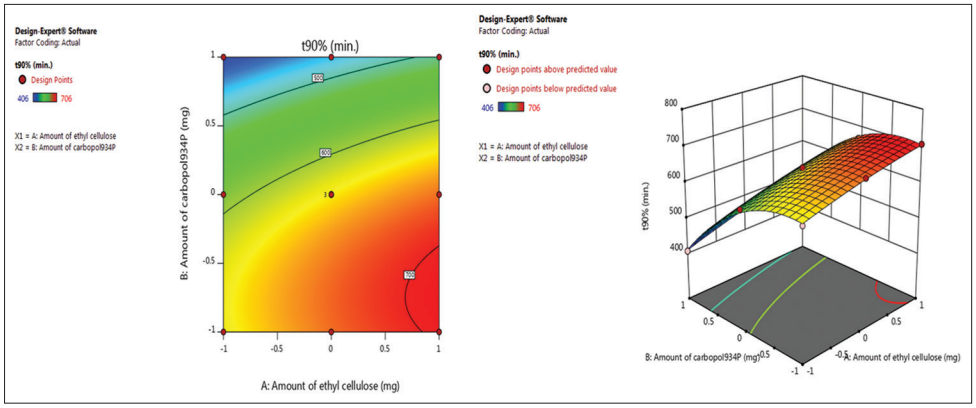

Fig. 4: Contour and three-dimensional surface plot for $t_{90\%}$

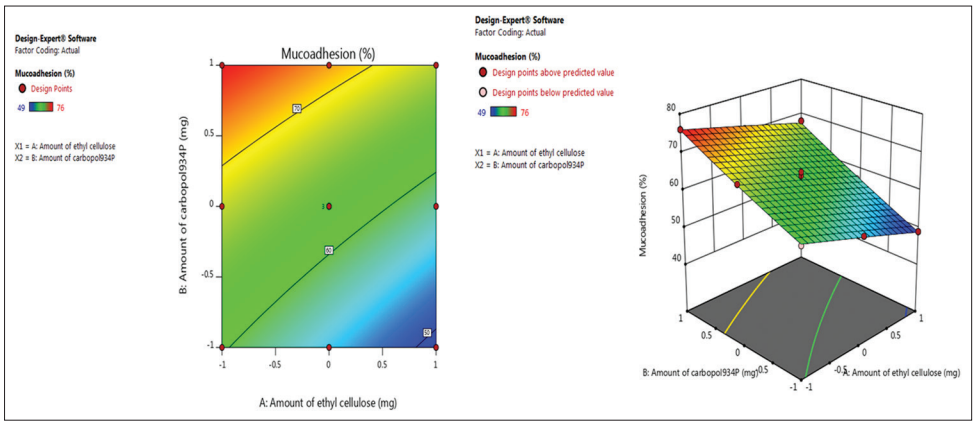

Fig. 5: Contour and three-dimensional surface plot for percent mucoadhesion

Factorial equation for $t_{90\%}$

$$Y_3 = +636.11 + 43.50X_1 - 103.83X_2 + 6.00X_1X_2 - 6.76X_1^2 - 66.76X_2^2$$

The $t_{90\%}$ of the batches varied from 464 to 705 min. Y_3 is strongly affected by the independent variables with a good correlation coefficient 0.9973. The batches N3, N6, and N9 had the lower time required for achieving the $t_{90\%}$ (<514 min). From the independent variables, X_1(+43.50) has a positive effect and X_2 (-103.83) has a negative effect on $t_{90\%}$. The independent variables significantly ($p < 0.01$) affecting the drug release. This showed that the amount of ethyl cellulose has a prominent effect, although the amount of Carbopol 934P had unfavorable effects on $t_{90\%}$. Batch N7 exhibited a higher $t_{90\%}$ of 706 min and seems to be a promising candidate for achieving drug release up to 12 h. Contour plot and response surface graph for $t_{90\%}$ is shown in Fig. 4.

Factorial equation for percentage mucoadhesion

$$Y_4 = +62.82 - 5.00X_1 + 8.50X_2 + 0.75X_1X_2 - 0.1053X_1^2 + 0.3947X_2^2$$

The values of *in vitro* wash-off test for percentage mucoadhesion varied from 49 to 76. Y_4 is strongly affected by the independent variable with good correlation coefficient 0.9770. The batches N_3, N_6, and N_9 showed higher percentage mucoadhesion (<68%) and the batches N_1, N_4, and N_7 showed <60% percent mucoadhesion. The value of X_1(-5.00) has a negative effect and X_2(+8.50) has a positive effect on percent mucoadhesion, indicating that the X_1 has favorable and X_2 has unfavorable effects on Y_3. Both the independent variables (X_1, X_2) were also significantly ($p < 0.01$) affecting the Y_3. All the results of percent mucoadhesion showed that the Carbopol 934P is mainly responsible for mucoadhesion. Contour plot and response surface graph for percentage mucoadhesion is shown in Fig. 5.

Optimization of formulation

The optimized formulation was selected based on the criteria of attaining completed and controlled release with highest possible entrapment efficiency and mucoadhesion. On "trading off" various response variables, optimum batch (O_1) was prepared using 200 mg amount of ethyl cellulose and 127 mg of Carbopol 934P as determined by the optimization technique. The experimental value of drug entrapment efficiency is about 84.35%, Q_1h about 23.25% $t_{90\%}$ of about 618 min and the percent mucoadhesion about 61.78%, as shown in Table 6 and the release curve with extrapolation is shown in Fig. 6.

Table 6: Results of the optimized batch for response variables

Response variables	PV	EV
Y_1=Entrapment efficiency	85.56	84.35
Y_2=Q_1 h=Percent CDR after 1 h	22.95	23.25
Y_3=$t_{90\%}$	599.9	618
Y_4=Percent mucoadhesion	62.87	61.78

CDR: Cumulative drug release, EV: Experimental value, PV: Predicted value

To determine the mechanism of drug release from the optimized batch, the release profile fitted to zero-order, first-order, and Higuchi equation, the "R^2" value was found to be 0.937, 0.996, and 0.989, respectively. The release profile fitted to Korsmeyer–Peppas equation, the "R^2" value was found to be 0.993 and "n" value was 0.603 for the optimized batch. It showed that the mechanism of drug release was non-Fickian diffusion. It may be due to swelling of the microspheres.

Surface morphology

Scanning electron microscopy analysis of the optimized batch (O_1) revealed that the microspheres were discrete and spherical. It appeared to have smooth surfaces at higher magnification, as shown in Fig. 7.

Validation of design

Additional three random batches (V_1, V_2, and V_3) of mucoadhesive microspheres were prepared for the validation of the experiment

Table 7: Formulation composition, predicted, and experimental values of checkpoint batche

Batch number	Formulation composition (X_1, X_2)	Entrapment efficiency		Q_1 h (percent CDR)		$t_{90\%}$		Percent mucoadhesion	
		PV*	EV*	PV*	EV*	PV*	EV*	PV*	EV*
V_1	175:125 (0.5:0.5)	72.13	71.26	25.96	24.52	589	562	64.85	63.44
V_2	125:75 (−0.5:−0.5)	53.53	54.14	28.29	29.04	650	664	61.35	62.32
V_3	175:75 (0.5:−0.5)	67.57	67.76	23.63	22.48	690	676	55.97	54.89

*PV: Predicted value, *EV: Experimental value, CDR: Cumulative drug release

Table 8: Accelerated stability studies of optimized batch

Response	Initial	After 3 months
Entrapment efficiency	84.35	84.24
Q_1 h=Percent CDR after 1 h	23.25	22.62
$t_{90\%}$	618	612
Percent mucoadhesion	61.78	60.56
Particle size	114.18	113.98
Shape of microspheres	Spherical and free flowing	Spherical and free-flowing

CDR: Cumulative drug release

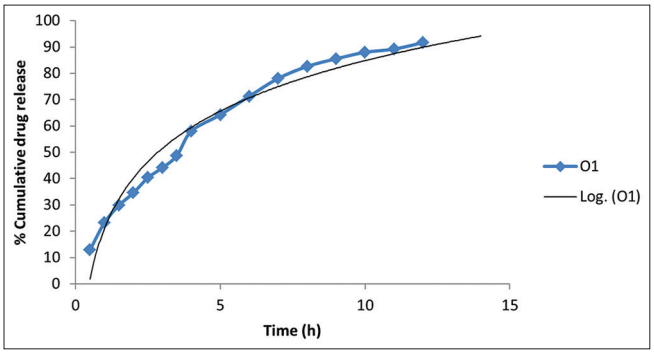

Fig. 6: Percent cumulative drug release of optimized batch (O_1)

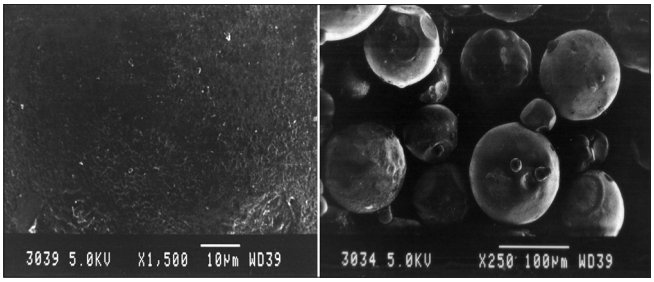

Fig. 7: Surface morphology of optimized batch

design and polynomial equations. These additional batches are also known as checkpoint batches. The predicted values of these checkpoint batches are compared with the experimental results and the percent prediction error (%PE) in prognosis was calculated. The results are shown in Table 7.

The prediction error is helpful for the validity of generating equations. It found to vary between −5.87 and −2.58 of the checkpoint batches. A low range of error proves the high prognostic ability of RSM.

Stability study of optimized batch (O_1)

The formulation is stored for three months on 40 ± 2°C temperature and 75 ± 5% relative humidity. It was found to be stable after 3 months. The results are shown in Table 8.

The effects of independent variables on the response parameters were visualized from the response surface graphs. Numerical optimization using the desirability approach was employed to locate the optimal settings of the formulation variables so as to obtain the desired response. An optimized formulation was developed by setting constraints on the dependent and independent variables. The formulation developed was evaluated for the responses, and the experimental values obtained were compared with those predicted by the mathematical models generated.

CONCLUSION

The results of 3^2 full factorial design of mucoadhesive microspheres of nifedipine using ethyl cellulose as carrier polymer and Carbopol 934P as mucoadhesive polymer (independent variables) significantly affected the dependent variables such as entrapment efficiency, Q_1h, $t_{90\%}$, and percent mucoadhesion. The optimized batch exhibited a high entrapment efficiency and good mucoadhesion. Moreover, drug release of mucoadhesive microspheres >12 h indicates that the microspheres have sustained release. Experimental responses of the optimized batch have close proximity with the predicted value and stability study of the optimized formulation proved that the formulation is stable for a long period of time; hence, it is an excellent alternative over the conventional delivery system.

CONFLICTS OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

This work is carried out in collaboration between all authors and all are equally contributed to do this research work.

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