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Original research paper

Formulation development of oral controlled release tablets of hydralazine: Optimization of drug release and bioadhesive characteristics

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The current study involves development of oral bioadhesive hydrophilic matrices of hydralazine hydrochloride, and optimization of their *in vitro* drug release profile and *ex vivo* bioadhesion against porcine gastric mucosa. A 3^2 central composite design was employed to systematically optimize the drug delivery formulations containing two polymers, *viz.*, carbomer and hydroxypropyl methyl cellulose. Response surface plots were drawn and optimum formulations were selected by brute force searches. Validation of the formulation optimization study indicated a very high degree of prognostic ability. The study successfully undertook the development of an optimized once-a--day formulation of hydralazine with excellent bioadhesive and controlled release characteristics.

Keywords: hydralazine, experimental design, bioadhesive, response surface methodology, gastrointestinal therapeutic system, hydrophilic matrices

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Oral controlled release (CR) systems constitute the most »sought after« route of drug administration since they obviate the need of frequent dosage administration and fluctuating blood levels characterized by saw-tooth kinetics, and hence improve the patient compliance (1). The success of CR devices is invariably hindered by their inability to localize in the selected region(s) of the gastrointestinal (GI) tract (2). Mucoadhesive drug delivery systems (DDS) offer a promising approach for controlled and site-specific delivery to the GI tract by attaching the devices to the mucus and mucosa of the tract *via* the process of bioadhesion. These mucoadhesive systems are also known to provide intimate contact between the dosage form and the absorptive mucosa, resulting in high drug flux through the absorbing tissue with improved bioavailability (3).

Hydralazine (HZ), a directly acting vasodilator, is widely prescribed in the treatment of hypertension and congestive heart failure. Albeit the drug is readily absorbed following oral administration, it is subjected to significant first-pass metabolism (4). Oral bio-

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availability of the drug has been reported to range between 10 and 35 %, depending upon the extent of acetylation. HZ has a short biological half-life (2–4 h), low dose (50–100 mg) and high physicochemical stability. Owing to these favorable properties, several researchers have reported once-a-day CR formulation of HZ (5–8). No attempts, however, have been reported to date on formulation optimization of its CR bioadhesive system.

The objective of the current study was to develop mucoadhesive CR tablet formulations of HZ hydrochloride and optimize their bioadhesive and drug release characteristics employing the benefits of the 'Design of Experiments' (DoE) methodology (9).

EXPERIMENTAL

Chemicals and reagents

HZ hydrochloride was provided *ex gratis* by M/s Sarabhai Chemicals Ltd., India. Methocel K4M (hydroxypropylmethyl cellulose, HPMC) and Carbopol 971P (CP) were obtained as gift samples from M/s Dow Chemical Company, USA and M/s B.F. Goodrich Ltd., USA, respectively. Dibasic calcium phosphate ($CaHPO_4$, DCP) and magnesium stearate (MS) were obtained from M/s Namco Laboratories, India and Loba Chemie Ltd., India, respectively. All other materials used in the current study were of analytical grade and were used as received.

Formulation

Different mucoadhesive tablet formulations of HZ hydrochloride were formulated using varying amounts of polymers (CP and HPMC) and DCP as the inert diluent, along with a fixed quantity of MS as the glidant and lubricant. Table I lists the various compositions employed during the study. HZ hydrochloride and the polymers, *viz.*, CP and HPMC, were screened through a # 80 mesh sieve (size: 180 μm) and DCP and MS were screened through a # 120 mesh sieve (size: 125 μm) prior to use. All materials were accurately weighed and mixed intimately in a polyethylene bag for 10 minutes. The blended mix was subsequently compressed into 400 mg tablets using flat-faced and round punches (12.8 mm diameter) fitted in a single-punch manual compression machine (Cadmach, India).

Table I. Composition of hydralazine hydrochloride tablets

Ingredient	Mass (mg)
Hydralazine hydrochloride	50
CP 971P	50–150
HPMC K4M	60–180
Magnesium stearate	5
Dibasic calcium phosphate	q.s. to 400

q.s. quantum satis

Experimental design

A central composite design (CCD) for two factors at three levels each (with $\alpha = 1$) was selected to optimize the varied response variables. The two factors, *viz.* polymer X_1 (CP) and polymer X_2 (HPMC) of each polymer blend, were varied as required by the experimental design and the factor levels were suitably coded (Table II). The amount of MS was kept constant at 1.25 % (*m*/*m*), while DCP was taken in a sufficient quantity to maintain a constant tablet mass of 400 mg. Time taken to release 50 % of the drug (t_{50}), extent of release until 18 hours (ext_{18}), diffusional release exponent (n), and bioadhesive strength (ρ) were taken as the response variables.

Tablet assay and physical evaluation

Ten tablets were powdered and a quantity equivalent to 20 mg of HZ hydrochloride was extracted with 60 mL of methanol. The resultant suspension was heated at 60 °C and shaken for 15 minutes. The contents were cooled and diluted up to 100 mL with methanol and filtered. Absorbance of the filtrate was measured at λ_{max} of 265 nm using a double beam UV/Vis spectrophotometer (140 A, Shimadzu, Japan) and the drug content was determined using the standard calibration equation taking the molar absorption coefficient (ε) as 1.0107×10^4 L mol^{-1} cm^{-1}. Tablets were also evaluated for hardness ($n = 6$) using a Monsanto type hardness tester (Campbell, India), friability ($n = 6$) using a Roche Friabilator (Tropical Lab Equipments, India), mass variation ($n = 10$) using an electronic balance (Mettler, Switzerland), and thickness ($n = 10$) using Vernier Callipers (Baker Gauges Ltd., India).

Table II. Factor combinations as per the chosen experimental design

Formulation code	Trial No.	Coded factor levels	
		X_1	X_2
F1	1	–1	–1
F2	2	–1	0
F3	3	–1	1
F4	4	0	–1
F5	5	0	0
F6	6	0	1
F7	7	1	–1
F8	8	1	0
F9	9	1	1
Translation of coded levels in actual units			
Coded level	–1	0	1
X_1: CP (mg)	50	100	150
X_2: HPMC (mg)	60	120	180

In vitro *drug release studies*

Dissolution studies were carried out on all the formulation combinations in triplicate, employing the USP 27 (10) paddle method (Apparatus 2, Pharma Test, USA) at 50 rpm and 37 ± 0.5 °C using phosphate buffer (PB) pH 6.6 as the dissolution medium. An aliquot of sample was withdrawn periodically at suitable time intervals and the volume was replaced with an equivalent volume of plain dissolution medium. Samples were analyzed spectrophotometrically at 260 nm. Drug release data obtained from *in vitro* dissolution were analyzed using the ZOREL software (11) with in-built provisions for applying the correction factor for volume and drug losses during sampling (12). Drug release data were fitted into the Korsemeyer-Peppas model (13):

$$\frac{M_t}{M_\infty} = k_1 t^n + k_2 t^{2n}$$

where M_t is the amount of drug released at time t, M_∞ is the amount of drug released at an infinite time, k_1 and k_2 are the magnitudinal contributions of diffusion and polymer relaxation mechanism, and n is the Fickian diffusion coefficient.

Based on the phenomenological analysis, the type of release, *i.e.*, whether Fickian, non-Fickian (anomalous) or zero-order, was predicted. The value of t_{50} was calculated using the Stineman interpolation option of the GRAPH software (Version 2, Micromath Inc., USA). Dissolution studies employing graded concentrations of DCP and without DCP were carried out earlier to ratify its inertness on drug release kinetics.

Ex vivo *bioadhesion studies*

Bioadhesion studies were conducted employing a slightly modified version of an in-house fabricated bioadhesion assembly (3, 14). Porcine gastric mucosa was used as the model membrane. The mucosa was kept frozen in PB pH 7.4 and thawed to room temperature before use. The mucosal membrane was excised by removing the underlying connective and adipose tissue and was equilibrated at 37 ± 1 °C for 30 min in buffer (PB pH 6.6) before the bioadhesion evaluation study. The tablet (n = 3) was lowered onto the mucosa under a constant weight of 49 N for a total contact period of 1 min. Bioadhesive strength was assessed in terms of weight, in N, required to detach the tablet from the membrane.

Bioadhesive strength of the optimized formulation was also investigated as a function of pH using eight buffers (0.1 mol L^{-1}) with pH ranging between 1.2 and 8.0.

Optimization data analysis

For the studied design, the multiple linear regression analysis (MLRA) method was applied using the Design Expert software version 6.0.10 (Stat-Ease, USA) to fit the full second-order polynomial equation with added interaction terms. Polynomial regression results were demonstrated for the studied responses. Finally, the prognosis of optimum formulation was conducted in two stages; first, a feasible space was located and second, an exhaustive grid search was conducted to predict the possible solutions.

DoE validation and selection of optimum formulation

Eight formulations were selected as check-points to validate DoE optimization. Mucoadhesive tablet formulations were compressed using the chosen optimal composition and evaluated for physical tests, tablet assay, dissolution performance and bioadhesion, as described earlier. The observed and predicted responses were critically compared. Linear correlation plots were constructed for the eight chosen optimized formulations. Residual graphs between predicted and observed responses were also constructed separately and the percent bias (error) was calculated with respect to the observed responses. Amongst the formulations selected for validation (n = 8) and prepared as per the experimental design (n = 9) one was carefully chosen as the optimum formulation by »trading off« the values of response parameters. Values of t_{50}, ext_{18}, ρ and n were maximized within the available domain.

RESULTS AND DISCUSSION

Selection of polymers and suitable experimental design

The polymers, *viz*. CP and HPMC, were selected owing to their excellent bioadhesive strength, release rate controlling ability (15), non-toxicity, non-irritancy, stability at GI pH and compatibility with the drug. Successful use of the polymer combination of an ionic polymer (like CP) and a nonionic polymer (like HPMC) is known to provide the formulation with controlled drug release along with desired mucoadhesive properties (14, 16).

A CCD for two factors at three levels with α = 1, equivalent to 3^2 factorial design (FD), was chosen as the experimental design. This is an effective second-order experimental design associated with a minimum of experiments to estimate the influence of individual variables (main effects) and their second-order effects (14, 17 18). Further, this design has an added advantage of determining the quadratic response surface, not estimable using an FD at two levels (19).

Drug content and physical evaluation

The content of drug in formulations varied between 98.5 and 100.2 % (m/m) (mean ± SD = 99.3 ± 0.7 %). Tablet mass varied between 399.09 and 403.06 mg (401.08 ± 1.62 mg), thickness between 2.51 and 2.91 mm (2.71 ± 0.17 mm), hardness between 4.67 and 7.04 kg cm^{-2} (5.86 ± 1.16 kg cm^{-2}), and friability ranged between 0.51 and 0.76 % (m/m) (0.64 ± 0.12 %). Thus, all physical parameters of the compressed matrices were within the permissible limits of USP (10).

In vitro *drug release studies*

Addition of either water-soluble or insoluble diluents in large quantities can markedly increase the release rate of hydrosoluble active principles (20). Preliminary studies carried out at graded DCP levels, *viz.*, 1:1, 1:3 and 1:5, and without DCP indicated near

superimposability in the dissolution curves with values of the similarity factor (f_2) ranging between 89.9 to 97.8 (21). This analogy of dissolution profiles ratifies the inertness of DCP in the present drug release studies.

As evident from the diverse nature of dissolution profiles (Fig. 1), the influence of polymer levels seems to be vital in regulating the drug release. Drug release rate curves (Fig. 1, inset) of all the formulations portray an initial burst release of the drug, characteristic of most hydrophilic matrices (3, 14, 22). Summary of the drug release parameters (Table III) shows that the value of n varies from 0.4653 to 0.6618, distinctly delineating the non-Fickian release behaviour of all formulations. Values of the kinetic constant, k, showed a declining trend with an increase in the level of each polymer, construing an appreciable change in the polymer matrix with a change in the polymer composition. Relatively high magnitudes of the Fickian diffusion constant, k_1, *vis-à-vis* the polymer relaxation constant, k_2, clearly show that the drug release was predominantly determined by Fickian diffusion, with negligible contribution of polymer relaxation. This is in consonance with several research findings that a mixture of HPMC with CP results in the reduction of polymer viscosity owing to reduced hydration of the matrix and facilitating drug diffusion through the polymer hydrogel (14, 16, 23, 24). Table III reveals that the overall rate of drug release tended to decrease with an increase in concentration of HPMC or CP. The values of t_{50} were found to rise markedly from 3.49 to 18.11 h from the lowest to the highest level of both polymers, respectively. In contrast, the values of ext_{18} decreased significantly with an increase in the content of either polymer. Nearly 50 % of the drug remained captive in the hydrophilic matrix up to 18 hours at the highest levels of both polymers, which may lead to appreciable diminution in the extent of drug absorption. Moderate levels of polymers should, therefore, be employed to yield an apt value of t_{50} and ext_{18}.

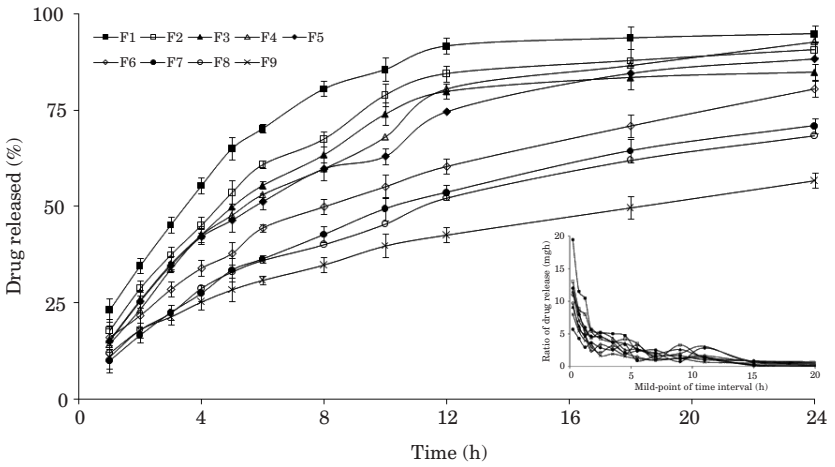

Fig. 1. Dissolution profiles of various mucoadhesive tablet formulations (F1 to F9) of hydralazine hydrochloride prepared as per the experimental design (n = 3). The crossbars indicate ± 1 SD. The inset shows the corresponding drug release rate profiles.

Table III. Drug release parameters of various mucoadhesive formulations prepared as per the experimental design[a]

Formulation code	Formulation composition		Release exponent (n)	Kinetic constant (k)	Fickian diffusion constant (k_1)	Polymer relaxation constant (k_2)	Extent of drug release till 18 hours (ext_{18}, %)	t_{50} (h)	Rate of drug release (mg h^{-1})
	CP (mg)	HPMC (mg)							
F1	50	60	0.4653	0.271	1.334	–0.0052	93.71	3.49	3.68 ± 3.31
F2	50	120	0.5331	0.208	1.240	0.0088	87.73	4.64	3.31 ± 2.53
F3	50	180	0.6092	0.165	1.172	0.0226	83.45	5.01	3.62 ± 2.52
F4	100	60	0.6017	0.166	1.179	0.0206	88.25	5.47	3.11 ± 2.03
F5	100	120	0.5433	0.182	1.202	0.0113	84.51	5.81	2.94 ± 2.22
F6	100	180	0.5131	0.165	1.777	0.0076	70.87	8.03	2.52 ± 2.16
F7	150	60	0.6618	0.103	1.093	0.0239	64.40	10.24	2.48 ± 1.55
F8	150	120	0.5607	0.125	1.129	0.0118	61.99	11.33	2.13 ± 1.53
F9	150	180	0.5041	0.121	1.130	0.0037	49.71	18.11	1.72 ± 1.47

[a] Mean ± SD; n = 3

Ex vivo *bioadhesive strength determination*

Fig. 2 construes an increasing trend in the bioadhesive strength with an increased amount of either polymer, in agreement with the literature (3, 14, 25). Hydrogels are known to swell readily on contact with the hydrated mucous membrane (14). This glass-rubbery transition provides hydrogel plasticization, resulting in a large adhesive surface for maximum contact with mucin and flexibility to the polymer chains for interpenetration with mucin. Increasing the polymer amount may provide more adhesive sites and polymer chains for interpenetration with mucin, resulting in augmentation of bioadhesive strength. Although the maximum value of bioadhesive strength is attained at the highest levels of both polymers, the effect of CP was found to be distinctly more pronounced than that of HPMC.

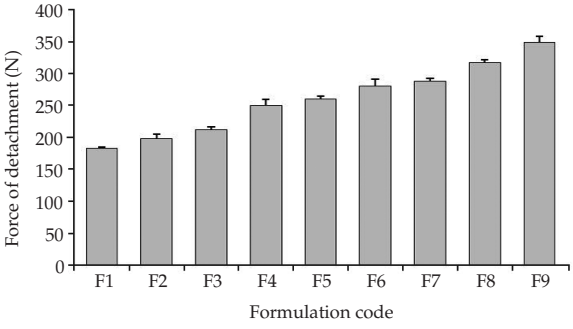

Fig. 2. Bar diagram showing bioadhesive strength determined as the force of detachment of mucoadhesive tablet formulations (F1 to F9) of hydralazine hydrochloride prepared as per central composite design (n = 3). The crossbars indicate + 1 SD.

The bioadhesive strength tends to rise uptill pH 5 and reaches almost plateau levels thereafter. The results are in agreement with earlier reports that optimum gel strengthening of mucoadhesive polymers occurs in weakly acidic environments, where both the polymer and the mucus have their optimum spatial conformation and thereby, improved viscoelasticity (26). Thus, it can be concluded that the optimized formulation has a distinct bioadhesive potential throughout the pH environment of the GI tract. Such optimized mucoadhesive tablets offer an economical and simpler technology as a once-a--day GI retentive CR formulation system of the drug.

Exploration of polymer mechanism using RSM

Quite high values of R^2 of the MLRA coefficients for all four responses, ranging between 0.9946 and 0.9999, vouch high prognostic ability of the RSM polynomials:

$$Y = \beta_o + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1 X_2^2 + \beta_7 X_2 X_1^2$$

Seven coefficients (β_1 to β_7) were calculated representing β_0 as the intercept, and β_3 to β_7 various quadratic and interaction terms.

Figs. 3a to 6a portray the 3-dimensional response surface plots for the studied response properties, *viz.*, t_{50}, ext_{18}, ρ and n while Figs. 3b to 6b depict the corresponding contour plots. Fig. 3a shows a nonlinear trend in the values of t_{50}, markedly increasing with the augmentation of CP levels. With HPMC, the values of t_{50} tend to rise nonlinearly, followed by an asymptote at the low levels of CP. The same is evident from the corresponding contour plot (Fig. 3b), showing somewhat declining nonlinear contour lines. Figs. 4a and 4b reveal a sharp decline in the value of ext_{18} with an increase in the amount of each of the polymers, *i.e.*, CP and HPMC, the influence of CP being much more pronounced. Nonlinear descending contour lines in Fig. 4b further show that the variation in ext_{18} is a complex function of the polymer levels, the effect of HPMC being less prominent. Fig. 5a shows a nearly linear ascending pattern for the values of bioadhesive strength, as the content of either polymer is increased, the effect being much more prominent with CP than with HPMC. Maximum bioadhesive strength is observable at the highest levels

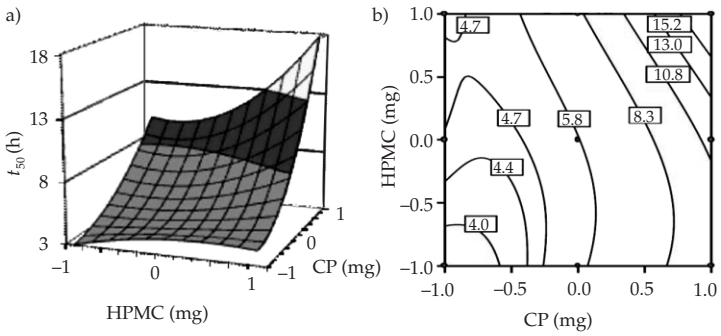

Fig. 3. a) Response surface plot showing the influence of CP and HPMC on the value of t_{50} of mucoadhesive tablet formulations of hydralazine hydrochloride; b) the corresponding contour plot.

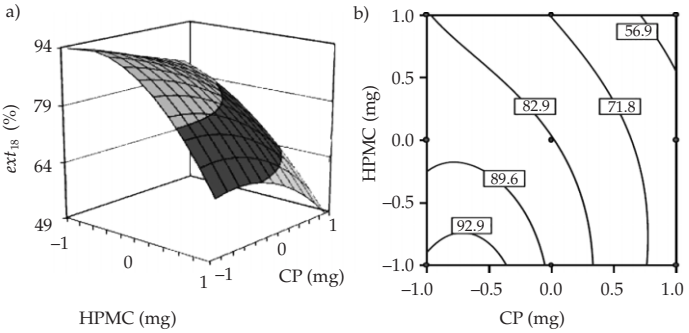

Fig. 4. a) Response surface plot showing the influence of CP and HPMC on the value of the extent of drug release up to 18 h (ext_{18}) of mucoadhesive tablet formulations of hydralazine hydrochloride; b) the corresponding contour plot.

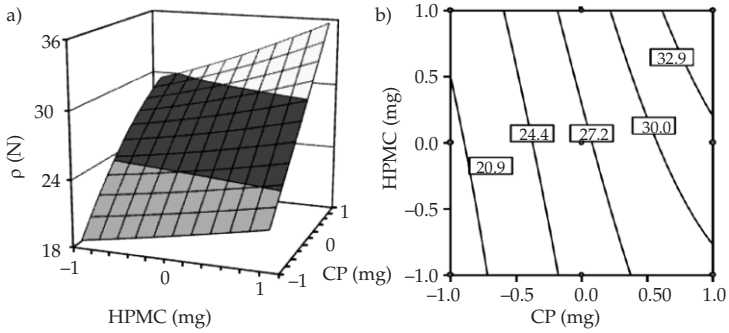

Fig. 5. a) Response surface plot showing the influence of CP and HPMC on the value of bioadhesive strength (ρ) of mucoadhesive tablet formulations of hydralazine hydrochloride; b) the corresponding contour plot.

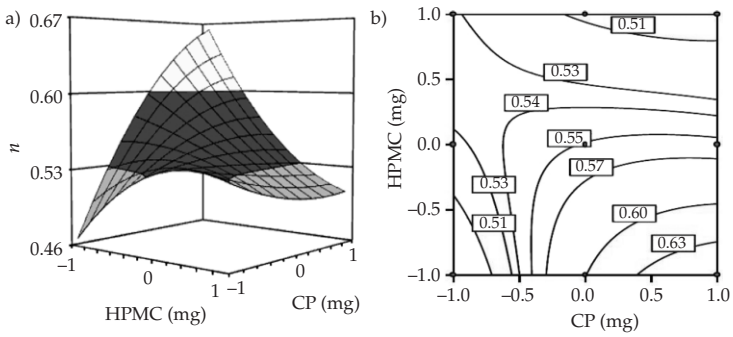

Fig. 6. a) Response surface plot showing the influence of CP and HPMC on the value of the release exponent (n) of mucoadhesive tablet formulations of hydralazine hydrochloride; b) the corresponding contour plot.

of both polymers, *viz.*, CP and HPMC. Nearly vertical contour lines (Fig. 5b) corroborate the markedly significant influence of CP on ρ values *vis-a-vis* HPMC. Fig. 6a portrays a twisted nonlinear relationship of n with increasing amounts of HPMC and CP. At low

Table IV. Comparison of the experimental results with the predicted responses

Formulation composition CP/HPMC (mg)	Response variable	Experimental value	Predicted value	Percentage bias (%)
50/68.4	t_{50} (h)	5.29	5.07	4.2
	ext_{18} (%)	91.51	90.75	0.8
	ρ (N)	254.89	252.94	0.8
	n	0.6302	0.6054	3.9
94/64.8	t_{50} (h)	5.07	5.18	–2.2
	ext_{18} (%)	91.13	89.60	1.7
	ρ (N)	258.13	258.43	–0.1
	n	0.6071	0.6052	0.3
86/64.8	t_{50} (h)	5.03	5.12	–1.8
	ext_{18} (%)	87.12	88.94	–2.1
	ρ (N)	258.72	260.48	–0.7
	n	0.6053	0.5955	1.2
60/67.2	t_{50} (h)	5.25	5.17	1.5
	ext_{18} (%)	88.10	87.63	0.5
	ρ (N)	251.06	252.05	–0.4
	n	0.5789	0.5588	3.5
102/74.4	t_{50} (h)	5.10	5.09	0.2
	ext_{18} (%)	87.71	87.13	0.7
	ρ (N)	246.17	248.63	–1.0
	n	0.5619	0.5482	0.6
110/180	t_{50} (h)	12.36	12.27	0.7
	ext_{18} (%)	61.31	60.93	0.6
	ρ (N)	320.56	322.03	–0.5
	n	0.5571	0.5421	2.7
130/144	t_{50} (h)	9.17	9.32	–1.6
	ext_{18} (%)	70.49	70.09	0.6
	ρ (N)	298.99	297.62	0.5
	n	0.5393	0.5232	3.0
140/168	t_{50} (h)	15.08	15.56	–3.2
	ext_{18} (%)	54.52	54.65	–0.2
	ρ (N)	337.02	335.35	0.5
	n	0.5128	0.5049	1.5
Mean (± SD) percent			0.3 ± 1.8	

HPMC levels, the value of n increases nonlinearly with an increase in CP. On the other hand, the value of n at low levels of CP increases to an asymptote with an increasing amount of HPMC. Thus, the current results seem to be in agreement with the findings of Nokhodchi *et al.* (24), indicating an ambiguous relationship of n with the change in polymer composition. The corresponding contour plot (Fig. 6b) also shows an unambiguous nonlinear trend with a »saddle point« at the low levels of CP and high levels of HPMC (9).

DoE validation and selection of optimum formulation

Upon comparison of the observed responses with those of the anticipated ones (Table IV), the prediction error varied between –3.2 and 4.2 % (mean ± SD = 0.32 ± 1.8 %). Linear correlation plots drawn between the predicted and observed responses after forcing the line through the origin, also demonstrated high values of R (0.9771 to 0.9989), indicating excellent goodness of fit ($p < 0.001$). The corresponding residual plots show nearly uniform and random scatter around the mean values of response variables.

The optimum formulation was selected by »trading off« various response variables and adopting the following maximizing criteria: $t_{50} > 4.5$ h; $ext_{18} > 80$; $0.57 < n < 0.89$; $\rho > 235.2$ N. Upon comprehensive evaluation of grid searches, the formulation (CP: 50.0 mg and HPMC: 68.4 mg) fulfilled the optimal criteria of best regulation of the release rate and bioadhesive strength with t_{50} of 5.29 h, ext_{18} of 91.51 %, n of 0.6302 and ρ of 254.9 N.

CONCLUSIONS

The current studies are aimed at successful development and optimization of a once-a-day formulation of HZ hydrochloride with high regulation of the release rate and bioadhesive strength. Suitable balancing between the levels of two polymers (CP and HPMC) is imperative to acquire maximum extension in drug release and adequate bioadhesion. The bioadhesive nature of formulation may prolong the GI retention in an actual *in vivo* situation and eventually augment the extent of release and absorption. Miniscule bias between the observed and predictive responses confirms the high prognostic ability of the study design. The study offers a platform technology, the results of which can be successfully extrapolated to the soluble salts of other basic drugs as well.

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S A Ž E T A K

Razvoj tableta hidralazina s kontroliranim oslobađanjem za oralnu uporabu: Optimizacija oslobađanja ljekovite tvari i bioadhezivnih svojstava

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Istraživanje uključuje razvoj bioadhezivnih hidrofilnih matriksa hidralazin hidroklorida za oralnu uporabu, optimizaciju oslobađanja ljekovite tvari *in vitro* i bioadhezivnih svojstava *ex vivo* na sluznici želuca svinje. 3^2 dizajniranje korišteno je za sistematsko optimiranje formulacija koje u sastavu imaju dva polimera, karbomer i hidroksipropilmetilcelulozu. Nacrtane su krivulje ovisnosti i grubo odabrane optimalne formulacije. Validacija optimiranih formulacija ukazuje vrlo visoki stupanj predvidljivosti. Razvijena je optimirana formulacija hidralazina koja se dozira jednom dnevno, a ima izvrsnu bioadhezivnost i sposobnosti kontroliranog oslobađanja.

Ključne riječi: hidralazin, dizajniranje eksperimenta, bioadhesivnost, metoda površina, gastrointestinalni terapijski sustav, hidrofilni matriksi

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