ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 14, Issue 1, 2021

Online - 2455-3891
Print - 0974-2441

Research Article

FORMULATION AND EVALUATION OF BUCCOADHESIVE TABLETS OF BUSPIRONE HYDROCHLORIC ACID

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Received: 28 August 2019, Revised and Accepted: 29 October 2020

ABSTRACT

Objective: The aim of the study was to prepare and evaluate buccal-adhesive tablets of buspirone hydrochloric acid (HCl) that avoids gastric degradation and first-pass metabolism, thereby increasing the drug bioavailability and onset of action. Buspirone HCl belongs to a class anxiolytic agent and a serotonin receptor agonist belonging to the azaspirodecanedione class of compounds.

Methods: In the present work, different ratios of Gantrez MS 955 along with Carbopol 934 were studied to give bioadhesive strength. A 3^2 full factorial design was applied to investigate the combined effect of Gantrez MS 955 concentration (X1) and Carbopol 934 concentration (X2).

Results: Results of the multiple regression analysis revealed that the independent variables significantly affected the dependent variables (bioadhesive strength [Y1], Q2 [Y2], Q3 [Y3], Q4 [Y4]). On the basis of multiple linear regression analysis and contour plot evaluation, it was found that the combination of two polymers possessed excellent mucoadhesive properties allowing ease of application and removal of the tablets from the buccal mucosa.

Conclusion: The formulation batch A9 fulfilled all the criteria set from the desirability search. From the *in vitro* diffusion study, flux was calculated for the optimized batch. A study of the effect of tablet diameter and the environmental factors on the bioadhesion of the tablet was done. To study the environmental factor on bioadhesion, prehydration time and contact time were considered. Results found that increase in prehydration time decrease in bioadhesive strength and increase in contact time increased bioadhesive strength. Thus, a stable buccoadhesive formulation optimized for formulation ingredients and process parameters was prepared successfully.

Keywords: Buccal adhesive tablets, Buspirone hydrochloric acid, Anti-Anxiety, Anxiolytic agent, Gantrez MS 955, Carbopol 934, Buccoadhesive tablet.

 DOI: http://dx.doi.org/10.22159/ajpcr.2021v14i1.39567. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Buccal mucosa is an attractive route for systemic delivery of drugs as it is relatively permeable with a rich blood supply. Moreover, it has high robustness and accessibility. A drug can be easily applied and localized at the application site and can also be removed from there if necessary [1-3]. The buccal mucosa has been investigated for local and systemic delivery of therapeutic peptides and other drugs that are subjected to the first-pass metabolism or are unstable within the rest of the gastrointestinal tract. Buccal delivery for the transmucosal absorption of drugs into the systemic circulation offers a number of advantages over oral delivery, especially for those drugs that have poor oral bioavailability and/or those drugs that suffer from extensive first-pass metabolism in the liver. Conceivably, buccal delivery systems provide ease of administration and thereby increase patient compliance [4-6]. Buspirone hydrochloric acid (HCl) is an anxiolytic agent and a serotonin receptor agonist belonging to the azaspirodecanedione class of compounds. It is used in the treatment of generalized anxiety, where it has advantages over other anti-anxiety drugs because it does not cause sedation (drowsiness) and does not cause tolerance or physical dependence. Buspirone hydrochloride binds to 5-HT type 1A serotonin receptors on presynaptic neurons in the dorsal raphe and on postsynaptic neurons in the hippocampus, thus inhibiting the firing rate of 5-HT-containing neurons in the dorsal raphe. Buspirone also binds at dopamine (DA) type 2 receptors, blocking presynaptic DA receptors. It increases firing in the locus ceruleus, an area of brain where norepinephrine cell bodies are found in high concentration. The net result of buspirone actions is that serotonergic activity is suppressed while noradrenergic and dopaminergic cell firing is enhanced [7,8]. In this study, an attempt has been made to develop buspirone hydrochloride buccal adhesive tablet to avoid first-pass metabolism and increase the bioavailability of the drug. There are two prime considerations in the design of buccal adhesive tablet of Buspirone HCl, One is to attach firmly to the buccal mucosa and other in case of buspirone hydrochloride the extensive first-pass metabolism. There are various bioadhesive polymers present which are polyacrylic acid derivatives such as polycarbophil and other polymers such as sodium alginate, Chitosan, HPC, HEC, sodium carboxymethylcellulose, polyethylene oxide, and hydroxypropyl methylcellulose (HPMC). In the present work, Gantrez MS 955 and Carbopol 934 were selected for the adhesive dosage form. Carbopol 934 (carbomers) is polyacrylic acid and Gantrez MS 955 is polyacrylic acid derivative, having both anion and cation [9,10].

METHODS

Buspirone HCl was obtained as a gift sample from Astron Pharmaceuticals, Ahmedabad, India. Gantrez MS 955 was obtained from ISP India Ltd., India. Carbopol 934, HPMC K4M, HPMC K15M, sodium alginate, sodium carboxymethylcellulose, microcrystalline cellulose, mannitol, lactose, magnesium stearate, and talc were purchased from S.D. Fine Chemicals Ltd., Mumbai, India. Ethylcellulose was purchased from Asha Cellulose Pvt. Ltd., Valsad, India, all ingredients were of analytical grade.

Work was carried out during M. Pharm project in 2013-2014 at S. K. Patel College of Pharmaceutical Education and Research, Kherva.

Preformulation Study

Pre-formulation studies to generate supportive data were performed to understand the physicochemical behavior of a drug and the necessary

modifications needed to design, develop, and evaluate dosage forms. The preformulation studies performed were:

1. Ultraviolet (UV). spectroscopy of buspirone HCl
2. DSC [11-13]
3. Excipient compatibility with the drug using Fourier-transform infrared (FTIR) [14-20].

Results are discussed in result and discussion.

Formulation of buccal tablets

Bilayered tablets of a backing layer and adhesive drug reservoir layer were prepared by covering one side of a single-layer tablet with a layer of ethylcellulose. Ethylcellulose was selected as a hydrophobic polymer that has very low water permeability, thus providing an impermeable backing layer that can prevent drug loss in the oral cavity.

Drug containing layer of the tablets was prepared by direct compression of drug blended with Carbopol-934, Gantrez MS-955, and other excipients using 8 mm flat-faced punches at a lower hardness then the backing layer of ethyl cellulose was compressed with a final hardness to obtain the final Bilayered tablets [21].

Experimental Design

On the basis of the preliminary trials, a 3^2 full factorial design was employed to study the effect of independent variables, that is, amount of Carbopol-934 (X1) and the amount of Gantrez MS-955 (X2), in terms of ratio against 1 part of drug on dependent variables such as bioadhesion strength (Y1) and % drug release Q2 (Y2), Q4 (Y3), and Q6 (Y4). A statistical model (equation below) incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y= b0 +b1X1+b2X2+b12X1X2+b11X12+b22X22$$

Where, Y is the dependent variable

b0 is the arithmetic mean response of the nine runs

b1 is the estimated coefficient for the factor X1

The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1X2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X12 and X22) are included to investigate non-linearity. The design matrix for the experiment is shown in Table 2.

Evaluation of buccoadhesive tablets

In-vitro dissolution study

Drug release was studied using the USP XIII dissolution test apparatus using a rotating basket at 37±0.5°C at 100 rpm. Tablet was added to 900 ml of phosphate buffer of 6.4 pH. The backing layer of buccal tablet was attached to the vessel with instant adhesive (cyanoacrylate adhesive). Samples were withdrawn at specified time intervals and replaced with fresh dissolution medium (phosphate buffer pH 6.4). The amount of drug released was determined spectrophotometrically at 239 nm. The release rate study was carried out for 6 h. Cumulative percentage of drug release was calculated using the equation obtained from the standard curve. The drug in phosphate buffer (pH 6.4) followed Beer Lambert's law in the range of 0–12 µg/ml with correlation coefficient of 0.9951.

In vitro diffusion study

The *in-vitro* buccal drug permeation study of buspirone hydrochloride through sheep buccal mucosa was performed using at 37±0.2°C, mucosa mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the membrane and the compartments clamped together. The donor and receptor compartments were filled with phosphate buffer pH 6.4 and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm. One milliliter sample was withdrawn at predetermined time intervals and analyzed for drug content at 239 nm using UV spectrophotometer.

The cumulative amount of permeated drug was plotted versus time and the steady-state flux was calculated using the formula:

$$J_{SS=}\Delta M/(A.\Delta t)$$

Where ΔM is the amount of drug transported across the membrane during the time Δt and A is the diffusional area.

Bio adhesive strength

A modified balance method was used to determining the *ex vivo* mucoadhesive strength. Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer (pH 6.4) at 37°C. The sheep buccal mucosa was cut into pieces and washed with phosphate buffer (pH 6.4). A piece of buccal mucosa was tied to glass slide which was fixed on plank and the plank was assembled with a crown block. After hydrating the mucosa with distilled water, the tablet was brought in contact with the mucosa by applying little force for a minute. After the initial contact, the tablet was encircled by a thread which fastened a light plastic beaker through the crown block. Then, water was dropped into beaker until the tablet and sheep mucosa were pulled apart by the gravity of water. The beaker containing water was weighed and minimum detachment force was calculated accordingly. The experiments were performed and average values with standard deviation were reported. This detachment force gives the mucoadhesive strength of the buccal tablet in grams [22]

Table 1: Composition of buspirone hydrochloride buccal adhesive tablets

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	9.40	9.40	9.40	9.40	9.40	9.40	9.40	9.40	9.40
HPMC K4M	20	-	-	-	10	-	-	10	-
HPMC K15M	-	20	-	-	-	-	-	-	-
Gantrez MS-955	-	-	20	-	-	-	-	10	10
Carbopol-934	-	-	-	20	10	-	-	-	10
Sod. CMC	-	-	-	-	-	20	-	-	-
Sod. Alginate	-	-	-	-	-	-	20	-	-
MCC	14.6	14.6	14.6	14.6	14.6	14.6	14.6	14.6	14.6
Mannitol	4	4	4	4	4	4	4	4	4
Mg. Stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Ethyl cellulose	50	50	50	50	50	50	50	50	50
Color	Sunset yellow								
Total weight	100	100	100	100	100	100	100	100	100

*All quantities are in mg. Sod. CMC: Sodium carboxymethylcellulose

Table 2: Factorial design and values of independent variables

	Independent variable		Dependent variable			
Formulation code	**X_1**	**X_2**	**Y_1 (bioadhesion strength dynes)**	**Y_2 (Q2) %**	**Y_3 (Q4) %**	**Y_4 (Q6) %**
A1	−1	−1	13.416	64.667	75.934	83.129
A2	−1	0	13.634	58.547	72.570	85.517
A3	−1	+1	13.923	55.431	74.787	87.839
A4	0	−1	12.021	49.937	70.412	84.771
A5	0	0	11.385	55.124	72.232	86.683
A6	0	+1	13.002	49.432	71.994	89.549
A7	+1	−1	13.053	41.213	60.378	85.475
A8	+1	0	13.669	42.215	61.231	88.523
A9	+1	+1	13.778	45.006	65.023	93.964

Translation of coded levels in actual units

Independent variable	Real value		
	Low (−1)	**Medium (0)**	**High (+1)**
Carbopol-934 (X1)	5	7.5	10
Gantrez MS-955 (X2)	10	12.5	15

Table 3: Calibration curve of buspirone hydrochloride

Concentration (mcg/ml)	Absorbance (nm)
0	0
4	0.237±0.021
6	0.4±0.025
8	0.571±0.017
10	0.684±0.022
12	0.865±0.011

Table 4: Evaluation parameter of batches for optimization of mucoadhesive polymers and excipients (trial 1 with lactose)

Batch code	Bioadhesion strength (dynes)	% Cumulative release at 6 h (%)	Drug content (%)
F1	6.889±0.05	61.781±0.03	97.560±0.01
F2	6.671±0.03	55.997±0.02	99.000±0.06
F3	3.626±0.02	61.316±0.03	98.000±0.05
F4	14.504±0.02	57.460±0.03	98.100±0.05
F5	8.702±0.01	57.061±0.04	97.750±0.03
F6	7.252±0.10	57.992±0.05	98.640±0.01
F7	10.152±0.01	68.630±0.05	98.300±0.09
F8	5.801±0.15	64.906±0.01	97.560±0.01
F9	8.122±0.01	67.433±0.03	99.010±0.01

Force of detachment (dynes) = Actual wt for detachment (g) × g

Where g= acceleration due to the gravity (980 cm/s^2)

Kinetics of drug release

The *in vitro* release data of buspirone from different batches of tablets were fitted using the zero-order, first-order, and Higuchi diffusion models as well as the Korsmeyer–Peppas equation to determine the model that best describes drug release from pellet formulations. The preference of the release mechanism is based on the value of the correlation coefficient. The data revealed a good fit to the Korsmeyer–Peppas equation, indicating combined effects of diffusion and erosion mechanisms for drug release. In addition, the release exponent (n) was calculated from the Korsmeyer equation.

Stability studies

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. Formulations were selected for stability on the basis of the *in vitro* drug release profile. The formulations were subjected to accelerated stability studies as per ICH guidelines, that is, 40°C temperature and 75% RH in aluminum foil for 1 month in thermostated ovens. The samples were taken at 0 and 30 days. Tablets were evaluated for the different physicochemical parameters.

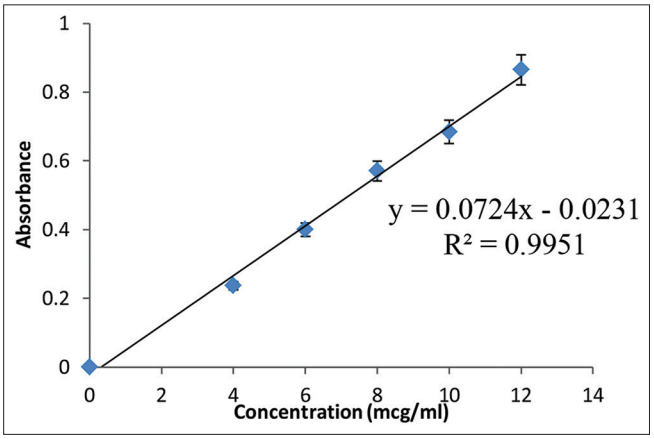

Fig. 1: Calibration curve of buspirone hydrochloride

RESULTS AND DISCUSSION

Spectral analysis of buspirone hydrochloride

Determination of λmax

The standard solution of concentration 10 µg/ml of buspirone hydrochloride was prepared in pH 6.4 phosphate buffers to obtain the desired concentration and subjected for UV scanning in the range of 200–400 nm using a double beam UV-visible spectrophotometer.

Construction of calibration curve of buspirone hydrochloride

Aliquots of concentrations 4, 6, 8, 10, and 12 µg/ml were prepared from standard solution with Phosphate buffer pH 6.4. The absorbance of the prepared solutions was measured at 239 nm using UV/visible spectrophotometer.

FTIR study

FTIR spectra of buspirone hydrochloride were found to be similar as that of P203 polymorph. It has strong additional bands in the range of 2600–2400 cm^{-1}, at 1350 and 1450 cm^{-1} which is absent in P-188 form as per literature. The spectra for Buspirone HCl is shown in Fig. 2 and Buspirone HCl with excipients is shown in Fig. 3.

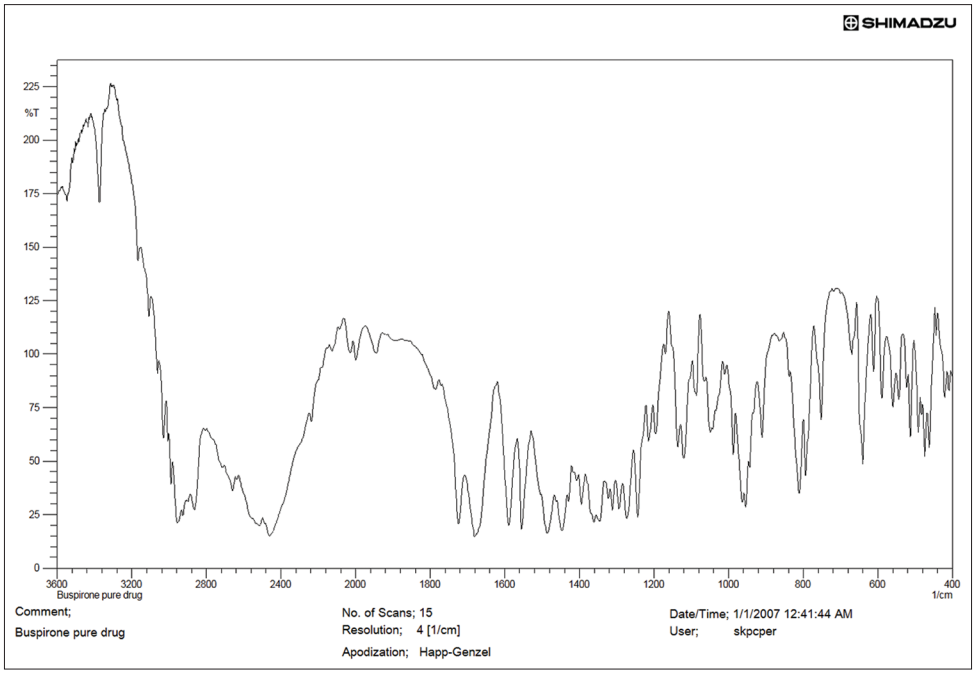

Fig. 2: Fourier-transform infrared of buspirone hydrochloride

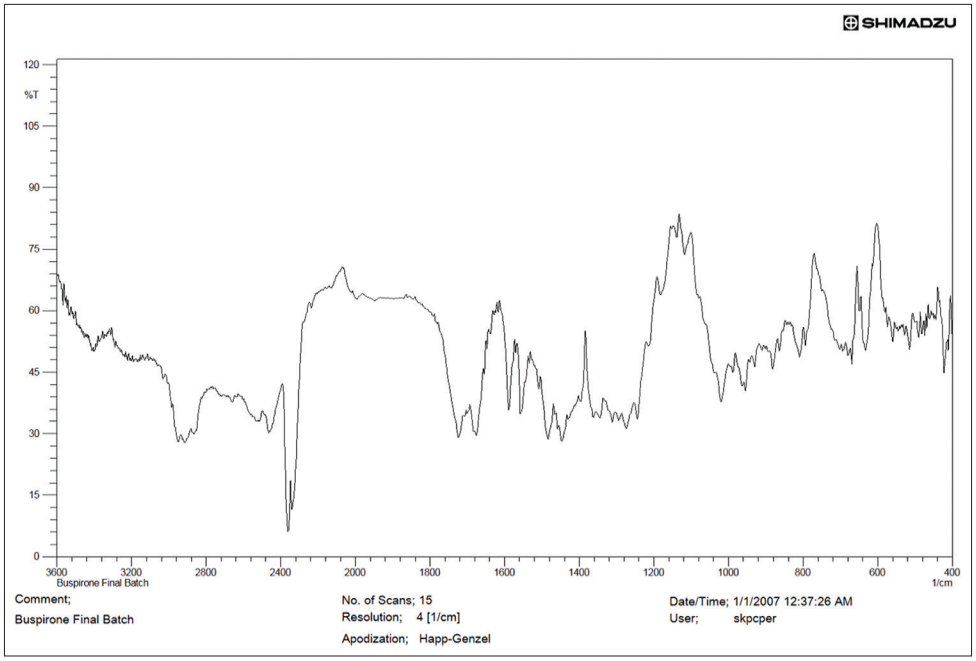

Fig. 3: Fourier-transform infrared of buspirone hydrochloride with excipients

DSC study

DSC spectra of buspirone HCl plain drug show an endothermic peak at 205°C. When the spectra of the mixture were taken there was no change in peak observed which shows that drug and polymers are compatible with each other.

Buspirone HCl may appear in two polymorphic forms:

- Low melting point form described in P188 described in U.S. Patent 4,810,789 having a melting point 192°C then converted into higher melting polymorph at 205°C
- Higher melting point form P203 described in U.S. Patent 3,717,634 having a melting point 203–205°C. It also has strong additional bands in the range of 2600–2400 cm^{-1}, at 1350 and 1450 cm^{-1}.

Optimization of mucoadhesive polymers and excipients

Different batches were prepared to optimize mucoadhesive polymers and other excipients. Various polymers such as HPMC K4M, HPMC K15, Carbopol 934, Gantrez MS 955, sodium alginate, and sodium carboxymethyl cellulose were taken along with the excipients such as mannitol and lactose for optimization.

In this study, an attempt has been made to develop buspirone hydrochloride buccal adhesive tablets to avoid the first-pass metabolism and to increase the bio-availability of the drug. Two prime considerations in the design of buccal adhesive tablets, one is to attach firmly to the buccal mucosa and other in case of buspirone bio-availability of drug (% drug release). Here, in the preliminary

study, batch F4, F6, F7, and F9 show the good release of the drug, but when release pattern is considered, it is well observed in batch F7 and F9. In trial-2, with mannitol increase in drug release profile was observed then lactose. Hence, mannitol was selected instead of lactose and when bioadhesive strength and dissolution profile both factors are considered it is well observed in batch F9 and F18 (Carbopol-934 and Gantrez MS-955). Finally, for factorial design Carbopol-934, 5-7.5-10 mg and Gantrez MS-955 10-12.5-15 mg were considered.

Powder blend property

The micromeritic properties of the powder blend of the formulations were checked, angle of repose was found to be around 19–29°, which shows good to average flowing properties of the powder blend. The loose bulk and tapped density were found around 0.395–0.486 and 0.504–0.593 g/cc, respectively. Carr's index was observed between 16.23% and 23.39% and Hausner's ratio was between 1.16 and 1.23. The drug content was found to be between 95.23% and 99.02%, which passes the official requirement. This ensured the uniformity of the drug content in the tablets. Weight variation data of the prepared tablets indicated no significant difference in the weight of individual tablet from the average value. Hardness and the thickness of the prepared tablets were observed within the range of 3.8–4.2 kg/cm^2 and 1.99–2.2 mm, respectively.

***In-vitro* dissolution**

Fig. 6 and Table 5 show the *in-vitro* drug release studies performed for A1–A9 formulations using pH 6.4 phosphate buffers as dissolution medium and measuring drug concentration UV spectrophotometrically at 239 nm. The studies were performed for 6 h.

***In-vitro* bioadhesive strength**

Fig. 7 and Table 6 show the result of *in-vitro* bioadhesive strength of formulated tablets of batches A1–A9 using sheep buccal mucosa.

Statistical analysis of factorial design batches

The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (positive or negative). Consequently, the equations may be used to obtain estimates of response as a relative small error of variance was noticed in the replicates. The data transformation simplifies the calculations for model development. The data generated by the experimental design were utilized for drawing contour plot, to obtain an optimized region within the factorial space, and thereby produce an optimized formulation.

Effect of variable on bio-adhesion

Regression statistics	
Multiple R	0.934
R square	0.874
Adjusted R square	0.664
Standard error	0.500
Observations	9

Coefficients

Coefficient	**Coefficient value**	**p-value**
b_0	11.934	0.013
b_1	−0.079	0.072
b_2	0.378	0.016
b_{11}	1.442	0.084
b_{22}	0.302	0.264
b_{12}	0.054	0.452

Equation:

$Y=11.93-0.079X_1+0.37X_2+0.054X_1X_2+1.44X_1^2+0.30X_2^2$

Coefficients with one factor represent the effect of that particular factor on responses, while the coefficients with more than one factor and those with second-order terms represent the interaction between

Table 5: Evaluation parameter of batches for optimization of mucoadhesive polymers and excipients (trial 2 with mannitol)

Batch code	**Bioadhesion strength (dynes)**	**% Cumulative release at 6 h (%)**	**Drug content (%)**	**% drug diffuse at 6 h (%)**
F10	4.900±0.01	61.813±0.03	97.560±0.02	61.852±0.02
F11	12.936±0.04	56.000±0.08	98.995±0.08	55.997±0.05
F12	4.352±0.02	61.316±0.05	98.000±0.09	61.349±0.03
F13	14.504±0.01	57.500±0.04	98.560±0.04	57.461±0.02
F14	6.526±0.03	57.100±0.03	96.750±0.05	68.231±0.06
F15	13.416±0.03	58.992±0.02	98.640±0.01	57.992±0.08
F16	9.790±0.01	63.930±0.02	95.300±0.02	68.632±0.02
F17	7.252±0.02	66.906±0.01	96.560±0.02	64.901±0.01
F18	13.770±0.01	69.433±0.01	98.010±0.03	67.433±0.01

Table 6: Formulation and optimization of buccoadhesive tablets using 3^2 full factorial design

Formulation code	**Independent variable**		**Dependent variable**			
	X_1	**X_2**	**Y_1 (Bioadhesion strength dynes)**	**Y_2 (Q2) %**	**Y_3 (Q4) %**	**Y_4 (Q6) %**
A1	−1	−1	13.416	64.667	75.934	83.129
A2	−1	0	13.634	58.547	72.570	85.517
A3	−1	+1	13.923	55.431	74.787	87.839
A4	0	−1	12.021	49.937	70.412	84.771
A5	0	0	11.385	55.124	72.232	86.683
A6	0	+1	13.002	49.432	71.994	89.549
A7	+1	−1	13.053	41.213	60.378	85.475
A8	+1	0	13.669	42.215	61.231	88.523
A9	+1	+1	13.778	45.006	65.023	93.964

Translation of coded levels in actual units

Independent variable	**Real value**		
	Low (−1)	**Medium (0)**	**High (+1)**
Carbopol-934	5	7.5	10
Gantrez MS-955	10	12.5	15

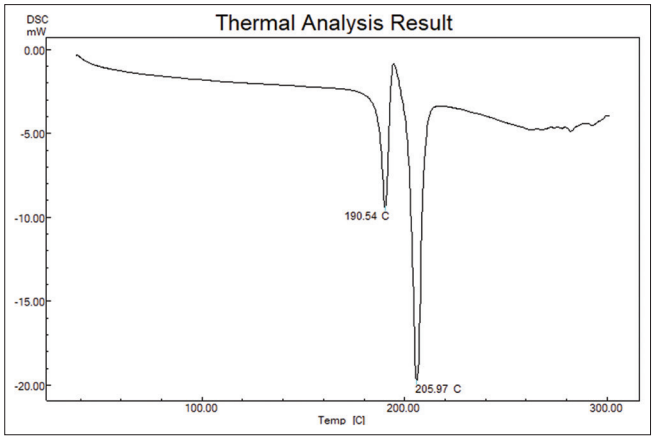

Fig. 4: DSC spectra of pure drug

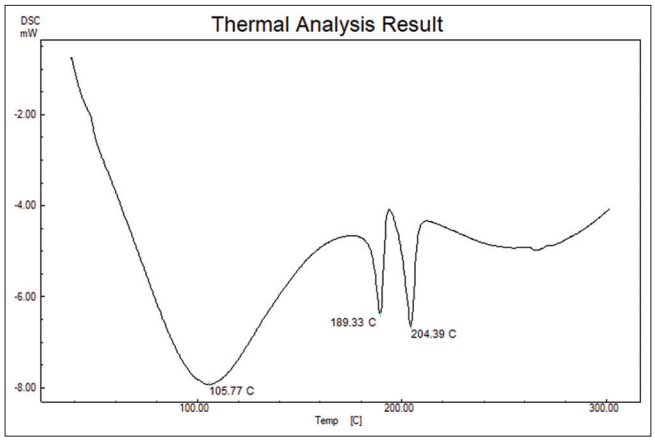

Fig. 5: DSC spectra of mixture

those factors and the quadratic nature of the phenomena, respectively. Positive sign in front of the terms indicates a synergistic effect, while a negative sign indicates an antagonistic effect upon the responses. For response Y1 (bio-adhesion) mathematical model was used, omitting the insignificant terms ($p>0.05$) by adopting multiple regression analysis. The effect of X1 and X2 was found significant ($p<0.05$).

The high p-value of X_1 and X_2 suggests that the interaction between X_1 and X_2 is not significant. The combined effect of factors X_1 and X_2 can further be elucidated with the help of response surface and counter plots which demonstrate that Y_1 varies in a linear fashion with the amount of both polymers.

Effect of variable on % cumulative release at 2 h (Q2)

Regression statistics	
Multiple R	0.978
R Square	0.956
Adjusted R square	0.884
Standard error	2.667
Observations	9

Coefficients		
Coefficient	**Coefficient value**	**p-value**
b_0	52.173	0.0001
b_1	−8.368	0.004
b_2	−0.991	0.429
b_{11}	−0.317	0.876
b_{22}	−1.014	0.628
b_{12}	3.257	0.092
Equation: $Y=52.173-8.368X_1-0.991X_2+3.257X_1X_2-0.317X_1^2-1.014X_2^2$		

The quadratic model for Q2 (release at 2 h) was found to be significant with F value of 13.462. The variable had a significant effect on % drug release. A relationship was obtained between the fraction of

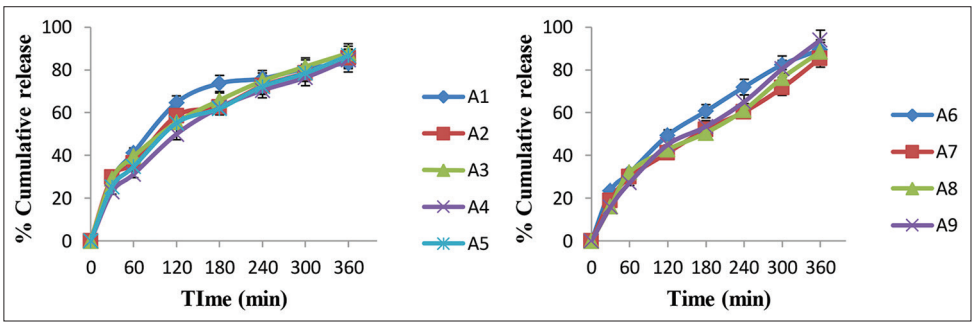

Fig. 6: % Cumulative release of factorial batches

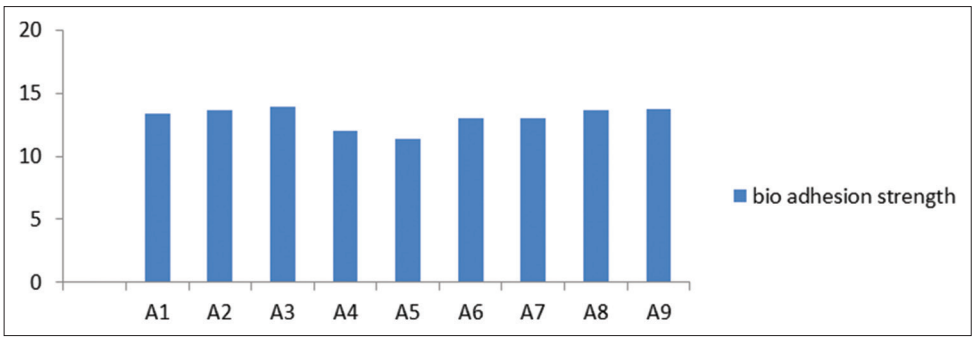

Fig. 7: *In-vitro* bioadhesion of factorial batches

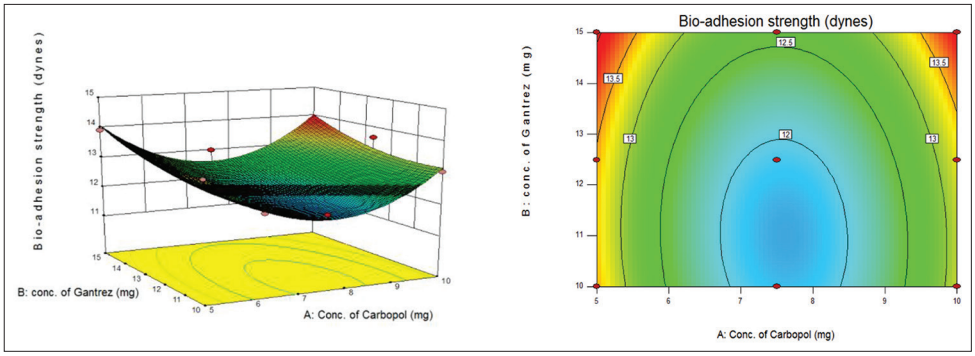

Fig. 8: Counter Plot (3-D) graph of Y1 (bioadhesion strength)

Table 7: Micromeritic properties of powder blends of different batches

Batch code	Angle of repose (°)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner's ratio	Drug content (%)
A1	19±1.05	0.486±0.01	0.593±0.12	16.23±1.20	1.18±0.18	97.63±0.01
A2	25±1.23	0.432±0.01	0.504±0.45	16.46±1.56	1.20±0.32	98.09±0.04
A3	29±1.85	0.395±0.06	0.568±0.39	23.39±1.88	1.16±0.24	95.23±0.02
A4	25±1.63	0.420±0.04	0.518±0.21	18.51±1.28	1.23±0.06	98.15±0.01
A5	21±1.25	0.490±0.03	0.598±0.09	18.04±1.36	1.13±0.09	97.00±0.06
A6	23±1.29	0.482±0.02	0.588±0.33	16.76±1.43	1.24±0.85	98.32±0.03
A7	22±1.32	0.420±0.01	0.528±0.20	13.73±1.09	1.29±0.26	95.32±0.05
A8	29 ±1.22	0.418±0.04	0.530±0.19	18.91±1.25	1.10±0.47	98.14±0.02
A9	20±1.08	0.497±0.01	0.521±0.05	12.90±1.04	1.03±0.05	99.02±0.01

Table 8: Evaluation of buccoadhesive tablets for buspirone hydrochloride

Formulation code	Average wt of tablets (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
A1	98.9±2.50	2.2±0.02	4.0±0.01	0.44±0.02	97.63±0.01
A2	99.8±1.23	1.9±0.01	3.8±0.05	0.50±0.02	98.09±0.04
A3	99.0±1.00	2.1±0.01	4.2±0.02	0.42±0.01	95.23±0.02
A4	101.0±2.09	2.0±0.00	4.0±0.01	0.38±0.03	98.15±0.01
A5	97.0±4.26	1.8±0.02	3.5±0.65	0.36±0.05	97.00±0.06
A6	98.2±2.45	2.0±0.00	3.9±0.55	0.50±0.04	98.32±0.03
A7	95.0±5.69	2.0±0.00	4.0±0.02	0.32±0.05	95.32±0.05
A8	105.0±5.03	2.1±0.01	4.5±0.06	0.35±0.06	98.14±0.02
A9	99.8±1.09	2.0±0.00	4.1±0.01	0.51±0.01	99.02±0.01

Table 9: % Cumulative release of factorial batches

Time (Min.)	A1	A2	A3	A4	A5	A6	A7	A8	A9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30	28.83±0.08	29.89±0.05	29.07±0.02	22.98±0.02	25.37±0.02	23.36±0.04	18.9±0.18	16.09±0.03	15.85±0.08
60	41.29±0.03	36.40±0.08	39.54±0.04	31.20±0.3	34.74±0.08	31.80±0.04	29.93±0.09	32.13±0.01	27.22±0.06
120	66.6±0.05	58.5±0.05	55.43±0.69	49.93±0.05	55.12±0.06	49.43±0.03	41.21±0.25	42.77±0.03	45.00±0.01
180	73.68±0.07	62.68±0.36	65.80±0.03	62.32±0.06	61.94±0.08	60.68±0.02	52.21±0.06	50.58±0.03	53.51±0.02
240	75.93±0.06	72.5 ±0.25	74.78±0.09	70.41±0.03	72.23±0.02	71.99±0.01	60.37±0.03	61.23±0.02	65.02±0.01
300	80.50±0.09	78.60±0.07	81.55±0.01	76.43±0.01	78.49±0.06	82.41±0.05	71.66±0.03	76.22±0.02	80.50±0.06
360	83.10±0.01	85.51±0.01	87.83±0.01	84.77±0.01	86.68±0.08	89.54±0.02	85.47±0.04	88.52±0.02	93.96±0.01

Table 10: *In-vitro* bioadhesive strength

Formulation	Force for detachment (dyne)
A1	13.416
A2	13.634
A3	13.923
A4	12.021
A5	11.385
A6	13.002
A7	13.053
A8	13.669
A9	13.778

Table 11: Coefficients and their p-values

Coefficients	Y1 (bioadhesion strength)	Y2 (Q2)	Y3 (Q4)	Y4 (Q6)
Bo	0.013	0.0001	0.008	0.009
b1	0.072	0.004	0.001	0.007
b2	0.016	0.429	0.207	0.0021
b11	0.084	0.876	0.324	0.490
b22	0.264	0.628	0.038	0.369
b12	0.452	0.092	0.111	0.082

Carbopol-934 and Gantrez MS 955, and it was observed that % drug release increase with an increase in the amount of both the polymers.

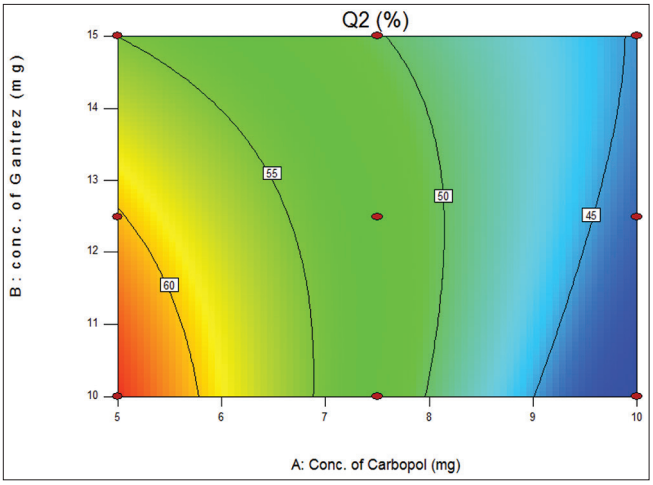

Fig. 9: Surface response graph of Y2 (Q2)

This effect was seen in the drug release at all three points (Q2, Q4, and Q6).

Effect of variable on % cumulative release at 4 h (Q4)

Regression statistics		
Multiple R	0.978	
R Square	0.956	
Adjusted R square	0.884	
Standard error	2.667	
Observations	9	
Coefficients		
Coefficient	**Coefficient value**	**p-value**
b_0	70.830	0.008
b_1	−6.110	0.001
b_2	0.850	0.207
b_{11}	−3.230	0.324
b_{22}	1.080	0.038
b_{12}	1.450	0.111
Equation: $Y=70.830-6.110X_1+0.850X_2+1.450X_1X_2-3.230X_1^2+1.080X_2^2$		

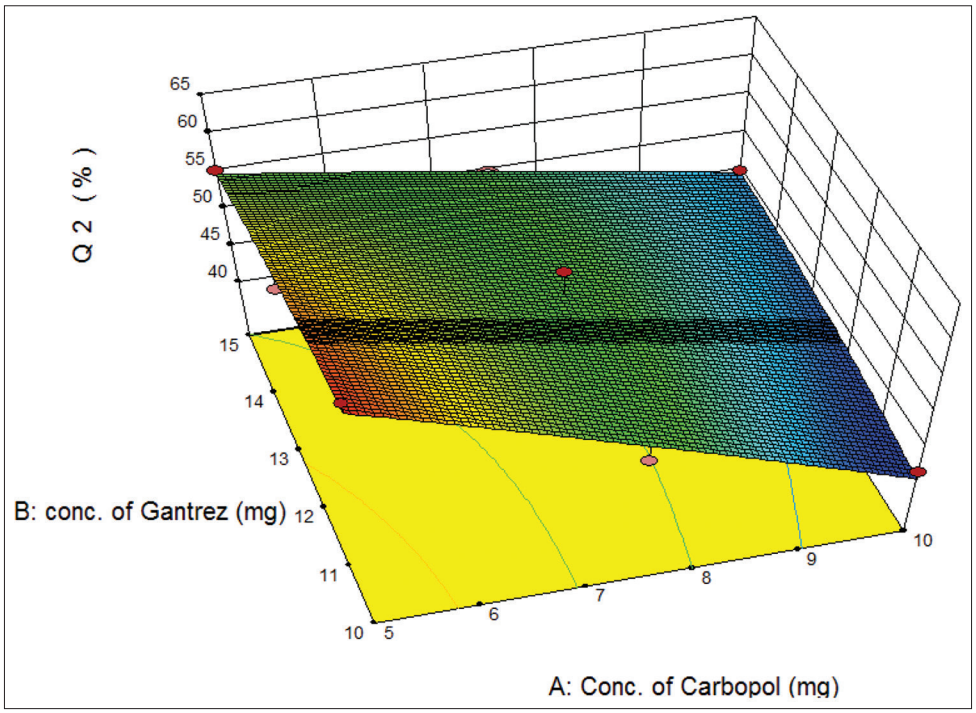

Fig. 10: Counter plot (3-D) graph of Y2 (Q2)

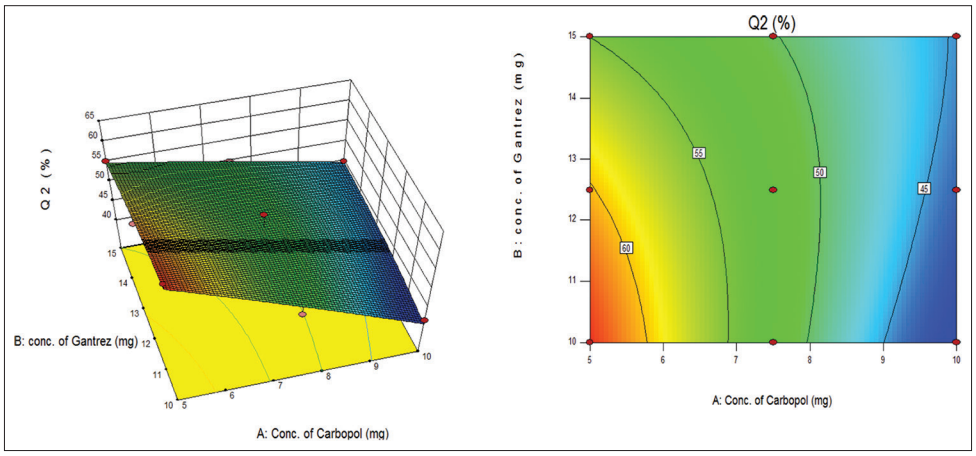

Fig. 11: Counter plot (3-D) graph of Y2 (release at 2 h [Q2])

Effect of variable on % cumulative release at 6 h (Q6)

Regression statistics	
Multiple R	0.990
R square	0.980
Adjusted R square	0.947
Standard error	0.733
Observations	9

Coefficients

Coefficient	Coefficient value	P-value
b_0	86.640	0.009
b_1	1.910	0.007
b_2	3.000	0.0021
b_{11}	0.410	0.490
b_{22}	0.550	0.369
b_{12}	0.940	0.082

Equation:

$Y=86.640+1.910X_1+3.000X_2+0.940X_1X_2+0.410X_1^2+0.550X_2^2$

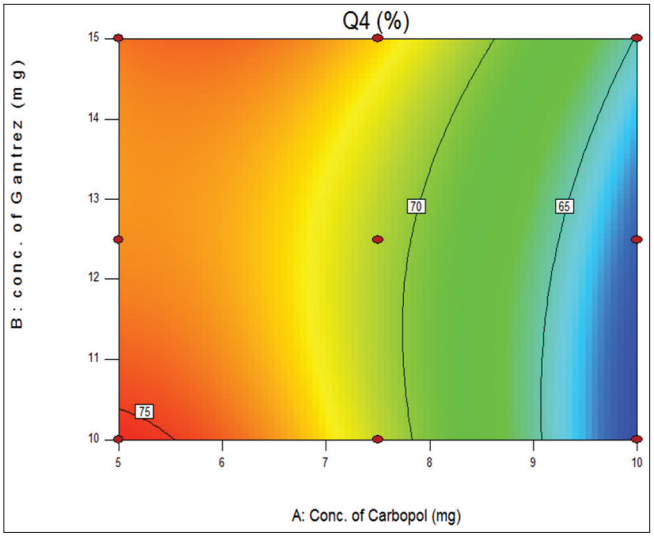

Fig. 12: Counter plot (3-D) graph of Y3 (release at 4 h Q4)

The p-value shows that X1 and X2 variables, that is, concentration of Carbopol 934 and Gantrez MS 955, respectively, were significantly affecting the Q2, Q6, and Q10 values.

Selection of optimized batch

A numerical optimization technique by the desirability approach was used to generate the optimum settings for the formulation. The process was optimized for the dependent variables Y1, Y2, Y3, and Y4 arrived at by keeping the bioadhesion force greater than 11.462 dynes/cm^2 and % drug release Q6 between 84% and 95%. The formulation batch A9 fulfilled all the criteria set from the desirability search. To gain say desirability of the response surface model, a new optimized formulation was prepared according to the predicted model and evaluated for the

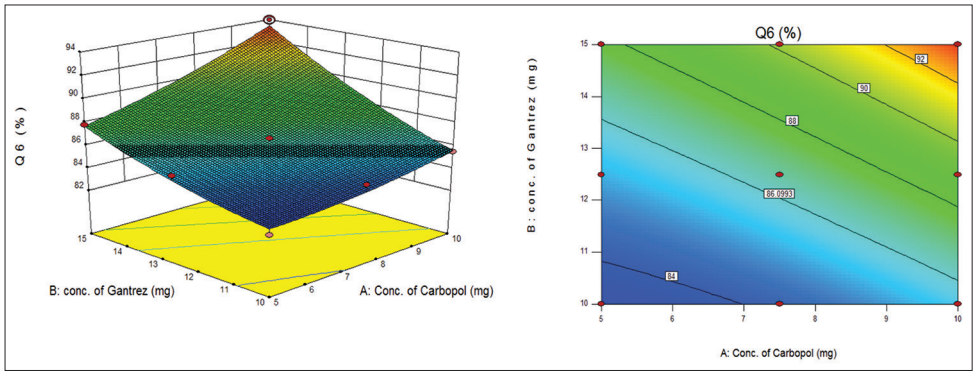

Fig. 13: Counter plot (3-d) graph of Y4 (release at 6 h Q6)

Table 12: Selection of optimized batch

	Y1 (bio-adhesion)	Y2 (Q2)	Y3 (Q4)	Y4 (Q6)
Predicted	14.18	44.62	67.37	98.23
Observed	13.98	46.50	68.02	94.96
Predicted error	1.40	3.48	0.96	3.32

Predicted error (%) = (observed value-predicted value)/predicted value × 100%

Table 13: Dissolution kinetic model data of buspirone HCL

Dissolution models		Batch codes								
		A1	A2	A3	A4	A5	A6	A7	A8	A9
Higuchi	R^2	0.9494	0.9849	0.9441	0.9963	0.9959	0.9952	0.9809	0.9683	0.9596
Zero-order	R^2	0.5040	0.6734	0.7034	0.8133	0.7619	0.8593	0.9901	0.9161	0.9500
Korsmeyer–Peppas	R^2	0.9763	0.9934	0.9950	0.9967	0.9965	0.9993	0.9933	0.9878	0.9950
	n	0.3790	0.4270	0.4410	0.5190	0.4800	0.5590	0.6110	0.6450	0.7060
Hixson–Crowell	R^2	0.8745	0.8954	0.9208	0.9571	0.9377	0.9739	0.9634	0.9653	0.9821
First-order	R^2	0.9414	0.9445	0.9622	0.9832	0.9717	0.9865	0.9722	0.9681	0.9752

R= correlation coefficient

n = the release exponent obtained from Korsmeyer–Peppas equation

HCl: Hydrochloric acid

Table 14: Stability study parameters for optimized batch

Parameters	Time (days)	
	0 day	30 days
% Drug content	98.23±0.01	97.65±0.02
Bioadhesive strength (dynes/cm$^{2)}$	13.77	12.62
% Drug release (after 6 h)	93.964±0.02	93.562±0.02

responses. Predicted value and observed values are illustrated in the table below which shows good relationship between the observed and predicted values.

Kinetics of drug release

The *in vitro* release data of buspirone from different batches of tablets were fitted using the zero-order, first-order, and Higuchi diffusion models [23] as well as the Korsmeyer–Peppas equation to determine the model that best describes drug release from pellet formulations. Preference of the release mechanism is based on the value of the correlation coefficient. The data revealed a good fit to the Korsmeyer–Peppas equation, indicating combined effects of diffusion and erosion mechanisms for drug release. In addition, the release exponent (n) was calculated from the Korsmeyer equation [24-26].

The calculated values of n indicated are more than 0.45 and <0.89 in Korsmeyer–Peppas model; means it follows Anomalous (non-Fickian) diffusion. R2 value was nearer to 0.9821 in Hixson–Crowell model in optimized batch which means it follows Hixson–Crowell model of dissolution kinetic models [27]. Release mechanism from polymer follows Hixson–Crowell up to an extent.

Stability study

After 30 days of stability of the optimized batch, values of all parameters like % drug content, bioadhesive strength, and were almost similar to the initial values as seen in Table 3. The result also showed that there is no change in tablet shape and color. The drug dissolution and diffusion profile were just the same of the initial profile (Fig. 5). There was not any significant change in any value, so the formulation is stable. This study is in agreement with the ICH guideline Q1A (R2), that is, no significant change (5%) [28].

CONCLUSION

The study suggests that the hydrophilic bioadhesive tablets of buspirone HCl can be designed using Carbopol 934 and Gantrez MS 955. The matrices demonstrated adequate bioadhesion with buccal mucosa. Moreover, *in-vitro* bioadhesive strength versus time measurements demonstrated that the combination of two polymers possessed excellent mucoadhesive properties allowing ease of application and removal of the tablets from the buccal mucosa. The mechanism of bioadhesion may potentially result from the interpenetration and physical entanglement of Gantrez with mucus layer. The rate of release of the drug substance as well as the bioadhesive bond strength of the formulation can be modulated by varying the amount of Gantrez and Carbopol included in the tablets. The mucoadhesive buccal tablets evaluated in the present study were easy to formulate, inexpensive, provide easy application, and convenient removal from the mucosal surface and did not irreversible damage the underlying tissue. Therefore, such tablets containing polyacrylic acid bioadhesive polymers along with carbomers may represent an improved buccal delivery system for a variety water-soluble, low molecular weight drugs.

ACKNOWLEDGMENT

I am thankful to the Department of Industrial Pharmacy and Pharmaceutics, Shree S. K. Patel pharmaceutical College of Education and Research, Ganpat University, Kherva, for their approval and permission in collecting the data and carrying out this study smoothly.

AUTHORS' CONTRIBUTIONS

All the authors contributed to the preparation of the final manuscript.

CONFLICTS OF INTEREST

There are no conflicts of interest regarding the publication of this article.

AUTHORS' FUNDING

The authors did not receive any funding for this research work.

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