FORMULATION AND EVALUATION OF BUCCOADHESIVE TABLETS OF BUSPIRONE HYDROCHLORIC ACID

JIGNYASA RAVAL¹, ANKITA YAGNIK²*

¹Department of Industrial Pharmacy, Shree S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Mehsana, Gujarat, India. ²Department of Pharmaceutics, Akshar-Preet Institute of Pharmacy, Jamnagar, Gujarat, India. Email: yagnikanikita.07@gmail.com

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 3² 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.

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 noradrenergic 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 polycrylic 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 polycrylic acid and Gantrez MS 955 is polycrylic 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 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 ethylcellulose was compressed with a final hardness to obtain the final Bilayered tablets [21].

**Experimental Design**
On the basis of the preliminary trials, a 3² 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) show how the response changes when one factor at a time from its low to high value. The interaction (X1X2) terms show how the response changes when two factors are simultaneously changed. The polynomial terms (X1² and X2²) show how the response changes when one factor at a time from its low to high value. The interaction (X1X2) terms show how the response changes when two factors are simultaneously changed.

**Evaluation of buccoadhesive tablets**

*In-vitro diffusion 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 0.9951.

**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 | -  | -  | -  | -  |
| HPMC K15M    | -  | 20 | -  | -  | -  | -  | -  | -  | -  |
| Gantrez MS-955 | -  | -  | 20 | -  | -  | -  | -  | 10 | 10 |
| Carbopol-934 | -  | -  | -  | 20 | 10 | -  | -  | -  | -  |
| Sod. CMC     | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| 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*
Force of detachment (dynes) = Actual wt for detachment (g) × g

\[ g = \text{acceleration due to the gravity (980 cm/s}^2) \]

**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.

**RESULTS AND DISCUSSION**

**Spectral analysis of buspirone hydrochloride**

**Determination of \( \lambda_{\text{max}} \)**

The standard solution of concentration 10 \( \mu \)g/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 \( \mu \)g/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 polymer ph. 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.
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 tablets from the average value. Hardness and the thickness of the prepared tablets were observed within the range of 3.8–4.2 kg/cm² 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.

### 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±0.08              |
| 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 3² full factorial design

| Formulation code | Independent variable | Dependent variable |
|------------------|----------------------|--------------------|
|                  | X₁                  | X₂                | Y₁ (Bioadhesion strength dynes) | Y₂ (Q2) % | Y₃ (Q4) % | Y₄ (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)             | 5          |
| Medium (0)           | 10         |
| High (+1)            | 15         |

### 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        | 0.050       |
| Observations          | 9           |

| Coefficients         | Coefficient value | p-value |
|----------------------|-------------------|---------|
| b₀                   | 11.934            | 0.013   |
| b₁                   | -0.079            | 0.072   |
| b₂                   | 0.378             | 0.016   |
| b₃                   | 1.442             | 0.004   |
| b₄                   | 0.302             | 0.264   |
| b₅                   | 0.054             | 0.452   |

Equation:

\[ Y = 11.93 - 0.079X₁ + 0.37X₂ + 0.054X₁X₂ + 1.44X₁^2 + 0.30X₂^2 \]
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 X1 and X2 suggests that the interaction between X1 and X2 is not significant. The combined effect of factors X1 and X2 can further be elucidated with the help of response surface and contour plots which demonstrate that Y1 varies in a linear fashion with the amount of both polymers.

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

| Coefficient | Coefficient value | p-value |
|-------------|-------------------|---------|
| b0          | 52.173            | 0.0001  |
| b1          | −8.368            | 0.004   |
| b2          | −0.991            | 0.429   |
| b11         | −0.317            | 0.876   |
| b22         | −1.014            | 0.628   |
| b12         | 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...
Carbopol-934 and Gantrez MS 955, and it was observed that % drug release increase with an increase in the amount of both the polymers.

| 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             | 0.48±0.01           | 0.59±0.12             | 16.2±1.20        | 1.18±0.18       | 97.6±0.01        |
| A2         | 25±1.23             | 0.43±0.01           | 0.50±0.45             | 16.4±1.56        | 1.20±0.32       | 98.0±0.04        |
| A3         | 29±1.85             | 0.39±0.06           | 0.56±0.39             | 23.9±1.88        | 1.16±0.24       | 95.3±0.02        |
| A4         | 25±1.63             | 0.42±0.04           | 0.58±0.21             | 18.5±1.20        | 1.23±0.06       | 98.1±0.01        |
| A5         | 21±1.25             | 0.49±0.03           | 0.59±0.09             | 18.0±1.36        | 1.13±0.09       | 97.0±0.06        |
| A6         | 23±1.29             | 0.48±0.02           | 0.58±0.33             | 16.7±1.43        | 1.24±0.85       | 98.3±0.03        |
| A7         | 22±1.32             | 0.42±0.01           | 0.52±0.20             | 13.7±1.09        | 1.29±0.26       | 95.3±0.05        |
| A8         | 29±1.22             | 0.41±0.04           | 0.53±0.19             | 18.9±1.25        | 1.10±0.47       | 98.1±0.02        |
| A9         | 20±1.08             | 0.49±0.01           | 0.52±0.05             | 12.9±1.04        | 1.03±0.05       | 99.0±0.01        |

**Table 7: Micromeric properties of powder blends of different batches**

| Formulation code | Average wt of tablets (mg) | Thickness (mm) | Hardness (kg/cm²) | Friability (%) | Drug content (%) |
|------------------|---------------------------|---------------|-------------------|---------------|-----------------|
| A1               | 98.9±2.50                 | 2.2±0.02      | 4.0±0.01          | 0.4±0.02      | 97.6±0.01       |
| A2               | 99.8±1.23                 | 1.9±0.01      | 3.8±0.05          | 0.5±0.02      | 98.0±0.04       |
| A3               | 99.0±1.00                 | 2.1±0.01      | 4.2±0.02          | 0.4±0.01      | 95.2±0.02       |
| A4               | 101.0±2.09                | 2.0±0.00      | 4.0±0.01          | 0.38±0.03     | 98.1±0.01       |
| A5               | 97.0±4.26                 | 1.8±0.02      | 3.5±0.65          | 0.36±0.05     | 97.0±0.06       |
| A6               | 98.2±2.45                 | 2.0±0.00      | 3.9±0.55          | 0.50±0.04     | 98.3±0.03       |
| A7               | 95.0±5.69                 | 2.0±0.00      | 4.0±0.02          | 0.32±0.05     | 95.3±0.05       |
| A8               | 105.0±5.03                | 2.1±0.01      | 4.5±0.06          | 0.35±0.06     | 98.1±0.02       |
| A9               | 99.8±1.09                 | 2.0±0.00      | 4.1±0.01          | 0.51±0.01     | 99.0±0.01       |

**Table 8: Evaluation of buccoadhesive tablets for buspirone hydrochloride**

**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          | 28.8±0.08| 29.8±0.05| 29.0±0.02| 22.9±0.02| 25.3±0.02| 23.3±0.04| 18.9±0.18| 16.0±0.03| 15.8±0.08|
| 60          | 41.2±0.03| 36.4±0.08| 39.5±0.04| 31.2±0.3| 34.7±0.08| 31.8±0.04| 29.9±0.09| 32.1±0.01| 27.2±0.06|
| 120         | 66.6±0.05| 58.5±0.05| 55.4±0.69| 49.9±0.05| 55.1±0.66| 49.4±0.13| 41.2±0.25| 42.7±0.03| 45.0±0.01|
| 180         | 73.6±0.07| 62.6±0.36| 65.8±0.03| 62.3±0.06| 61.9±0.08| 60.6±0.02| 52.2±0.06| 50.5±0.03| 53.5±0.02|
| 240         | 75.9±0.06| 72.5±0.25| 74.7±0.09| 70.4±0.3| 72.3±0.02| 71.9±0.01| 60.3±0.03| 61.2±0.02| 65.0±0.01|
| 300         | 80.5±0.09| 78.6±0.07| 81.5±0.01| 76.4±0.31| 78.4±0.06| 82.4±0.05| 71.6±0.03| 76.2±0.02| 80.5±0.06|
| 360         | 83.1±0.01| 85.5±0.01| 87.8±0.01| 84.7±0.01| 86.6±0.08| 89.5±0.02| 85.4±0.04| 86.5±0.02| 93.9±0.01|

**Table 10: In-vitro bioadhesive strength**

**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.
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 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:

\[ Y = 70.830 - 6.110X_1 + 0.850X_2 + 1.450X_1X_2 - 3.230X_1^2 + 1.080X_2^2 \]
Effect of variable on % cumulative release at 6 h (Q6)

Regression statistics

| Multiple R | 0.990 |
| R square   | 0.980 |

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_3         | 0.410            | 0.490   |
| b_4         | 0.550            | 0.369   |
| b_5         | 0.940            | 0.082   |

Equation:

\[ Y = 86.640 + 1.910X_1 + 3.000X_2 + 0.410X_1X_2 + 0.550X_2^2 + 0.940X_1^2 \]

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/cm² 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

| Predicted | 14.18 |
| Observed  | 13.98 |
| Predicted error | 3.48 |

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

Table 12: Dissolution kinetic model data of buspirone HCl

| Dissolution models | Batch codes | R² | A1 | A2 | A3 | A4 | A5 | A6 | A7 | A8 | A9 |
|--------------------|-------------|----|----|----|----|----|----|----|----|----|----|
| Higuchi            |             |    | 0.9494 | 0.9849 | 0.9441 | 0.9963 | 0.9959 | 0.9952 | 0.9809 | 0.9683 | 0.9596 |
| Zero-order         |             |    | 0.6734 | 0.7034 | 0.8133 | 0.7619 | 0.8593 | 0.9910 | 0.9161 | 0.9500 |
| Korsmeyer–Peppas   |             |    | 0.9763 | 0.9934 | 0.9950 | 0.9967 | 0.9965 | 0.9993 | 0.9933 | 0.9878 | 0.9950 |
| Hixson–Crowell     |             |    | 0.3790 | 0.4270 | 0.4410 | 0.5190 | 0.4800 | 0.5590 | 0.6110 | 0.6450 | 0.7060 |
| First-order        |             |    | 0.8745 | 0.8954 | 0.9206 | 0.9571 | 0.9377 | 0.9739 | 0.9634 | 0.9653 | 0.9821 |

n = the release exponent obtained from Korsmeyer–Peppas equation

HCl: Hydrochloric acid
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 Hixon–Crowell model in optimized batch which means it follows Hixon-Crowell model of dissolution kinetic models [27]. Release mechanism from polymer follows Hixon-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 irreversibly damage the underlying tissue. Therefore, such tablets containing polyacrylic acid bioadhesive polymers along with carboxymethyl 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 Pharmacaceutics, 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.

### REFERENCES

1. Fatma AI, Noha AN, Boraie NA, Mortada LM. Mucoadhesive buccal patches of miconazole nitrate, in-vitro/in-vivo performance and effect aging. Int J Pharm 2003;264:1-14.
2. Pankil AG, Patel MR, Patel KR, Patel NM. A review article on mucoadhesive buccal drug delivery system. Int J Pharm Res Dev 2011;3:159-73.
3. Gandli SD, Priyanka RP, Rahul U, Tambawala T, Shah MA. Mucoadhesive drug delivery systems an unusual maneuver for site specific drug delivery system. Int J Pharm Sci 2011;3:851-71.
4. Jain NK. Controlled and Novel Drug Delivery. 1st ed. New Delhi: CBS Publishers and Distributors; 1997. p. 52-81.
5. Patel KV, Patel ND, Dodiya HD, Shelat PK. Buccal bioadhesive drug delivery system, an overview. Ind J Pharm Bio Arch 2011;2:600-9.
6. Shojai AH. A systemic drug delivery via the buccal mucosal route. Pharm Tech 2001;25:70-81.
7. Tripathi KD. Essential of Medical Pharmacology. 6th ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2008. p. 171-2, 435,465-8.
8. Available from: https://www.drugbank.ca/drugs/DB00490. [Last accessed on Dec 2013].
9. Raymond CR, Paul JS, Owen SC. Handbook of Pharmaceutical Excipients. 5th ed. London, United Kingdom: Pharmaceutical Press; 2009.
10. Nazila SM, Montakam C, Thomas PJ. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev 2005;57:1666-91.
11. Lee VH, Robinson JR. Sustained and Controlled Release Drug Delivery System. New York: Marcel Dekker; 2009. 71-121, 138-71.
12. Ahlineck C, Zograf G. The molecular Basis of moisture effects on the physical and chemical stability of drugs in the solid state. Int J Pharm 1990;62:87-95.
13. Chatwal G, Anand. S. Instrumental methods of chemical analysis. In: Analytical Chemistry. 5th ed., Vol. 82. Karnataka: Himalaya Publishing House; 2002. p. 29-30.
14. Silverstein RM, Bassler GC, Morrill TC. Spectrometric Identification of Organic Compounds. 4th ed. New York: John Wiley and Sons, Inc.; 1981. p. 95.
15. Bellamy LJ. In the Infrared Spectra of Complex Organic Molecules. 2nd ed. New York: John Wiley and Sons, Inc.; 1958. p. 1.
16. Adnan A, Lina N, omari A. Pantoprazole sodium. In: Analytical Profile of Drug Substances and Excipients. Vol. 29. Amsterdam, Netherlands: Elsevier; 2005. p. 213-57.
17. Mills T, Roberson JC, Simon MJ. Instrumental Data for Drug Analysis. 3rd ed., Vol. 2. Milton Park, Abingdon-on-Thames: Taylor and Francis; 2009. p. 1362-3.
18. Prasad RY, Krishnaiah R, Satyanarayana S. In vitro evaluation of guar gum as a carrier for colon specific drug delivery. J Control Rel 1999;51:281-7.
19. Juraitat N, Kampanhat H, Satit P. Development of time pH, and enzyme-controlled colonic drug delivery using spray-dried chitosan acetate and hydroxypropyl methylcellulose. Eur J Pharm Biopharm 2008;68:253-9.
20. European Medicines Agency. ICH Topic Q 3 C (R3) Impurities: Residual Solvents, Note For Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95), March 1998. CPMP/ICH/283/95. Amsterdam, Netherlands: European Medicines Agency; 1998.
21. Raval JA, Modi SV, Shah NP. Formulation and process optimization of buccoadhesive tablet of rabeprazole. Int J Pharm Chem Sci 2012;1:277-86.
22. Udigar BK, Hiremath SN, Rao KS, Pawar D. Buccoadhesive tablets containing ketonozalone inclusion complex with β-cyclodextrin. Res J Pharm Tech 2009;4:396-404.
23. Higuchi T. Mechanism of sustained action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963;52:1145-9.
24. Korsmeyer R, Gurny R, Peppas N. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm 1983;15:25-35.
25. Peppas NA. Analysis of fickian and non-fickian drug release from polymers. Pharm Acta Helv 1985;60:110-1.
26. Harland RS, Gazzaniga A, Sangalli ME. Drug/polymer matrix: Swelling and dissolution. Pharm Res 1988;5:488-94.
27. Hixon AW, Crowell JH. Dependence of reaction velocity upon surface and agitation. Ind Eng Chem 1931;23:923-31.
28. ICH Harmonised Tripartite Guideline: Stability Testing of New Drug Drug Substances and Products Q1A(R2) Current Step 4 Version; 2003. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-1-r2-stabilitytesting.