ORIGINAL ARTICLE

Enhancing the Performance of Paroxetine Hydrochloride Mucoadhesive Buccal Tablets for Anti-depression Treatment: A Response Surface Methodological Approach

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Abstract

Objective: This study aimed to find a way to make buccal tablets of Paroxetine Hydrochloride (PRX) that stick to mucous membranes effectively and have a controlled release. **Materials and Methods:** Response surface approach, notably a three-level strategy, and Design Expert® software were used to develop and optimize Paroxetine Hydrochloride buccal tablets for oral medication delivery. PRX's unidirectional mucoadhesive buccal tablets were prepared by direct compression using Carbopol 934P and HPMC K15M as mucoadhesive controlled release agents. The developed formulations were assessed for a variety of characteristics before and after compression, as well as for surface pH, swelling, *ex vivo* mucoadhesive strength, and *in vitro* and *ex vivo* drug release. **Results:** The Fourier-transformed infrared spectrum and differential scanning calorimetry peak of Paroxetine Hydrochloride indicated that there was no interaction between the drug and the used excipients. Swelling index research found that polymer concentration is directly correlated with swelling. Formulation F4 Paroxetine Hydrochloride exhibited the highest mucoadhesive strength (0.93 ± 0.06N) with the highest ratio of carbopol 934P and HPMC K15M (2:5), while formulation F11 had the weakest force (0.68 ± 0.04N) due to higher and lower polymer quantities. In *in vitro* release trials, tablet formulation F9 demonstrated superior release characteristics (95.57 ± 0.42%, 8 h) compared to other formulations due to carbopol 934P and HPMC K15M swelling, drug release was slow (0–63.34%) for the first 4 h. Drug release increased from 4 to 8 h, reaching 95.57 ± 0.42% by the end. *Ex vivo* permeation research using drug release experiments identified formulation F9 as the best, with a 70.88 ± 2.65% drug release compared to 42.65 ± 2.52%. **Conclusion:** The ideal controlled release system would release the medication at the right time and keep it at the therapeutic level for as long as possible. According to dissolving profiles and swelling data, mucoadhesive buccal tablets released Paroxetine Hydrochloride mostly due to the quickly hydrating polymer. This study aimed to bypass first-pass metabolism and increase Paroxetine Hydrochloride bioavailability.

Key words: First-pass metabolism, mucoadhesive buccal tablets, Paroxetine Hydrochloride, selective serotonin reuptake inhibitor

INTRODUCTION

Physicians generally prescribe oral medication administration for most therapeutically active medicines. Some medications are impacted by gastrointestinal (GI) tract physiological circumstances, including digesting enzymes, poor absorption efflux by P-glycoprotein, and first-pass metabolism by liver-related enzymes. Many mucoadhesive formulations have been studied for buccal

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administration, usually with permeability enhancers. Taste masking components may be used to disguise medication or excipient tastes.[1]

The buccal mucosa, the lining of the oral cavity, is an attractive site for drug administration due to its high vascularity and, importantly, its easy accessibility, making it a confident choice for various dosage forms. Tablets, patches, films, and semisolid gels have been developed as solid buccal mucoadhesive dosage forms for more extended medication administration. Buccal transbuccal medication delivery has more potential than oral administration because it eliminates first-pass destruction and GI drug clearance.[2]

The anionic polymer carbopol 934P has remarkable bioadhesive strength. However, its mucoadhesive qualities are adequate when used alone. Hence, hydroxypropyl methylcellulose must be mixed with anionic polymers to lengthen the mucoadhesion duration and improve medication absorption across buccal mucosa.[3]

Anxiety, major depressive disorder, obsessive-compulsive disorders, and other mental illnesses may be treated with Paroxetine Hydrochloride, the most potent antidepressant in the family of selective serotonin reuptake inhibitors. Paroxetine has a limited oral bioavailability of around 30–50% due to its poor water solubility and substantial liver metabolism despite its good GI tract absorption.[4,5] Paroxetine Hydrochloride is an excellent choice for buccal administration due to its physicochemical features, a short molecular weight of 329.36, Cmax attained 2–8 h after an oral dose and half-life of approximately 17 h. The medicine is sold as regular, sustained-release, and oral solutions; no buccal dosage forms are available now. With the promise of a quick start of action and the ability to avoid hepatic metabolism, developing mucoadhesive buccal tablets of Paroxetine Hydrochloride is a priority in the pharmaceutical industry and a possible step forward.[6-8]

MATERIALS AND METHODS

Materials

Paroxetine Hydrochloride is a gift sample from Hetero, Hyderabad. Carbopol 934P, hydroxypropyl methyl cellulose (HPMC K15M), and Microcrystalline cellulose were obtained from Loba Chemicals, Mumbai. The rest of the ingredients were purchased from commercial enterprises and were of analytical quality.

Experiment design (Response surface methodology [RSM])

RSM, specifically employing a three-level approach, was utilized for experimental design and formulation optimization of Paroxetine Hydrochloride buccal tablets intended for oral drug delivery. Design Expert® software (Version 13.0.5.0, State-Ease Inc., and India) was employed for this purpose. Considering the previous literature and formulation variables, the central composite design emerged as the most suitable design for analyzing quadratic response surfaces, linear responses, two-factorial interactions, and polynomial models. This design enabled process optimization with the minimum number of runs, comprising 12 runs, including 3 replicated center points. A computer-generated non-linear, polynomial model quadratic equation was developed to elucidate the three-factor three-level design. This comprehensive approach facilitated the optimization of the mucoadhesive tablets formulation parameters with a focus on achieving desired characteristics for buccal drug delivery.

$$\text{Polynomial equation } (Y) = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_{12} + b_{22}X_{22} + b_{33}X_3$$

In the developed model, Y represents the dependent variable, with b_0 representing the intercept, and b_1 to b_{33} denoting the regression coefficients obtained from the observations of individual responses. The independent variables are represented by X_1 to X_3, which correspond to the coded levels of prefixed variables. Specifically, X_1 represents the percentage weight of carbopol 934P, X_2 represents and HPMC K15M. Furthermore, terms like X_i^2 (where i = 1, 2, or 3) depict the interaction of independent variables, while the quadratic terms are denoted by X_1^2. The encoded values of the various independent and dependent variables, along with their respective levels, are defined in Tables 1 and 2. This structured approach facilitates the interpretation and manipulation of variables in the regression analysis, aiding in the optimization of the buccal formulation process.

Preparation of mucoadhesive buccal tablets of Paroxetine Hydrochloride

Paroxetine Hydrochloride mucoadhesive buccal tablets were prepared to utilize carbopol 934 and HPMC K15M as polymers using the direct compression technique. Particle size uniformity was achieved by passing all components, including excipients, polymer, and Paroxetine Hydrochloride, through sieve 60 after precise weighing per the batch formula. Transfer the drug and all other components (except lubricants and glidants) to a sheet of butter paper using a stainless steel spatula. In a mortar, combine the ingredients for 10–15 min in the order of their increasing weights. After everything was well combined, the remaining materials were added and blended once more for 5 min. A multi-station tablet punching machine (Shakti, SLP-1-8D) was used to compress each formulation [Table 3] produced into pills using an 8 mm punch.

Table 1: Paroxetine Hydrochloride buccal tablets: Model variables and central composite design coded levels

Name of variables			
In dependent (% w/v)	**Carbopol 934P (X_1)**	**HPMC K15M (X_2)**	
Dependent (Responses)	**Swelling index % (Y_1)**	**Drug release at 4 h (Y_2)**	**Drug release at 8 h (%) (Y_3)**
Coded levels	Low	Centre	High
	−1	0	+1
A: Carbopol 934P (X_1)	20	30	40
B: HPMC K15M (X_2)	50	75	100

Table 2: Proto-type experimental runs of Paroxetine Hydrochloride buccal tablets using central composite design

Run	Independent variables (%w/v)	
	A: Carbopol 934P (X_1)	**B: HPMC K15M (X_2)**
1	20	100
2	30	100
3	40	75
4	40	100
5	30	75
6	30	50
7	30	75
8	30	75
9	20	75
10	40	50
11	20	50
12	30	75

Evaluation of mucoadhesive buccal tablets of Paroxetine Hydrochloride

Drug excipients compatibility study by Fourier-transformed infrared (FTIR)

The research was conducted using FTIR spectroscopy to determine the potential drug-excipient interaction. The KBr disk method was used to capture the drug, polymer, and formulation Fourier transform infrared (FTIR, Bruker-210329) spectra. The five medication mixes subjected to FTIR analysis included pure Paroxetine and a physical combination of Paroxetine Hydrochloride with polymers, as well as a better formulation. Two or three milligrams of sample and the same weight of dry potassium bromide were compressed to form a KBr disk. Spectrums recorded through disk scanning fell within the 4000–400/cm range.[9,10]

Differential scanning calorimetry (DSC) analysis

DSC analysis was performed using a PerkinElmer Thermal Analysis differential scanning calorimeter. The samples, ranging from 1 to 5 mg, were heated in an aluminum pan in a nitrogen environment at a rate of 10°C/min, with indium in the reference pan. The DSC studies were performed for the Paroxetine Hydrochloride, the excipients mentioned above, and the drug-excipient powder mixtures.[11]

Physical characterization of mucoadhesive buccal tablets of Paroxetine Hydrochloride

The developed mucoadhesive buccal tablets were checked for thickness, weight variation, hardness, friability, and content uniformity. Six tablets' thicknesses were measured using a micrometer. In accordance with the British Pharmacopoeia, an electronic balance (Sartorius, M22, Germany) was used to ascertain the weight of 20 tablets and the weight variation was then computed. Using a hardness tester, the severity of six tablets was ascertained. The friability test was conducted per the British Pharmacopoeia, which included precisely weighing ten tablets and placing them in a tablet Roche Friabilator drum spun at 25 rpm for 4 min. The next step was to take the tablets out of the drum, dust them, and then weigh them precisely. A weight loss percentage was determined. To find the percentage of uniformity in the content, five tablets were mortared at random in a mortar. Then, 100 mL of a buffer solution (pH 6.8) was used to extract powder equal to one dosage of the medicine. One milliliter of filtrate was diluted to 5 mL using a buffer solution with a pH of 6.8. The aliquot solution was then passed through a 0.45 Millipore filter and analyzed spectrophotometrically at 260 nm after sufficient dilution with buffer solution (pH 6.88). A total of three sets of tests were conducted.[12-14]

Surface pH

The potential for *in vivo* side effects was investigated by determining the surface pH of the produced buccal tablets. Because changes in pH might irritate the buccal mucosa, we performed everything possible to keep it neutral. A composite glass electrode was used to accomplish this. For 1 h at room temperature, the tablet was let to swell by being in touch with 2 mL of buffer (pH 6.8 ± 0.5). After putting the electrode into touch with the tablet's surface and giving it 1 min to acclimate, the pH was measured. Tablet surface pH was measured in triplicate and calculated as mean ± SD.[15]

Swelling index (SI)

The mucoadhesive buccal tablet's SI was measured 3 times, and the average plus or minus the standard deviation was

Table 3: Formulation of mucoadhesive buccal tablets of Paroxetine Hydrochloride

Formulation code (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Paroxetine Hydrochloride	25	25	25	25	25	25	25	25	25	25	25	25
Carbopol 934P	20	30	40	40	40	30	30	30	20	40	20	30
HPMC K15M	100	100	75	100	75	50	75	75	75	50	50	75
Microcrystalline cellulose	75	65	80	55	80	115	90	90	100	105	125	90
Aspartame	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

computed. The buccal tablets were measured individually (W_1) and then set aside on 2% agar gel plates. They were then incubated at a temperature of 37 ± 2°C. The tablet was gently removed from the petri dish, and any extra surface water was carefully blotted out using filter paper at regular intervals of 1–8 h. The SI was determined by reweighing the enlarged tablet (W_2) and using the following calculation.[16]

$$\text{Swelling Index} = (W_2 - W_1)/W_1$$

Mucoadhesion strength

A modified two-armed physical balance was used to test the mucoadhesive force of the developed buccal tablets, as shown in Figure 1. After being collected from a nearby slaughterhouse and kept in normal saline at 4°C, freshly excised swine buccal mucosa was used as a model tissue, and all fats and debris were removed beforehand. Applying cyanoacrylate glue, the porcine buccal mucosa (B) was secured to the glass platform (C). Slowly raising the glass stage (C) brought the surface of the developed tablet (D) into touch with the buccal mucosa after it had been mounted to the balancing pan. The 50 g(E) preload was placed on top of the tablet on the balance pan for 5 min after being taken off. The tablet was separated from the buccal mucosa by raising the weights (F). The mucoadhesive strength was determined by weighing the tablet down to its lowest point, in grams, when removed from the membrane surface.[17,18] The following equation was used to determine the adhesion force.

Force of adhesion (N) = (Mucoadhesive strength/100) × 9.81

Ex vivo mucoadhesion time

In a beaker, a piece of recently sliced porcine buccal mucosa was adhered to the glass surface using cyanoacrylate glue. After 2 mL of buffer was applied to one side of each tablet, the buccal tissue was firmly connected to it with a gentle pressure applied with a fingertip for 20 s. After 500 mL of buffer was added to the beaker and maintained at 37 ± 1°C for 2 min, the buccal cavity was mimicked by swirling at 100 rpm. The time it took for the mucoadhesive to dissolve or wear off was recorded. The average mucoadhesion time ± standard deviation was determined after it was repeated 3 times.[19]

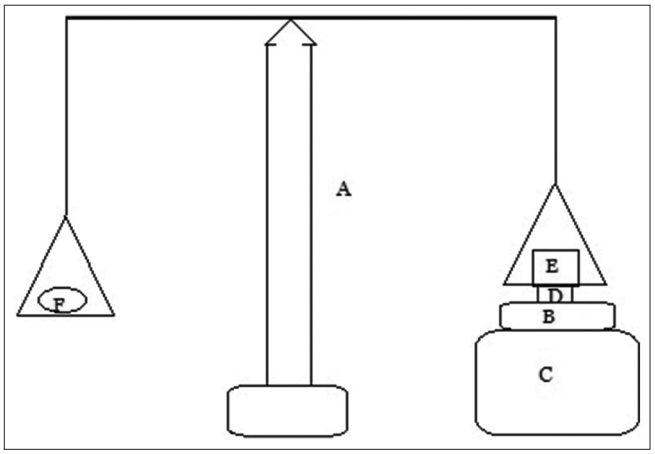

Figure 1: Modified physical balance

In vitro drug release studies

The *in vitro* release of Paroxetine Hydrochloride from prepared mucoadhesive buccal tablets was studied on a rotating paddle (USP-II) dissolution apparatus (EDT-08LX, Electrolab). Using cyanoacrylate adhesive, the Paroxetine Hydrochloride mucoadhesive buccal tablets' backing layer (n = 6) was fastened to a glass slide. The slide was then placed in the bottom of the dissolution vessel, which contained 500 mL of phosphate buffer (pH 6.8) as the dissolution medium. The dissolution medium was stabilized at 37 ± 0.5°C and stirred at 50 rpm. At set intervals, 5 mL of the fluid was removed using syringe filters with a pore size of 0.45 µm, and the same amount of fluid was added back in to keep the sink condition constant. The amount of Paroxetine Hydrochloride released from mucoadhesive buccal tablets was determined spectrophotometrically at 260 nm.[20]

Kinetics for drug release mechanism

The release data were thoroughly kinetically analyzed using Excel 2007 (Microsoft software) to determine the mechanism and order of drug release from different formulations. Zero-order, first-order, Higuchi, and Korsmeyer–Peppas models were exhaustively used to analyze the release kinetics.[21]

Ex vivo permeation studies

A Franz diffusion cell was used to conduct the *ex vivo* buccal drug permeation research at 37°C ± 0.5°C. After being

collected from the nearby butcher, the buccal mucosa of swine was swiftly transferred to the lab in a chilled standard saline solution. The buccal mucosa was delicately detached from the surrounding fat and muscles using a tiny, sharp blade. The buccal mucosal epithelium was used in <1 h. The buccal mucosa was placed between donor and receptor compartments. The receiver chamber contained a pH 6.8 phosphate buffer. The buccal mucosa stabilized for 30 min. In the donor chamber, 2 mL of buffer solution (pH 6.8) was poured, the Paroxetine Hydrochloride buccal tablet was put with the core facing the mucosa, and the compartments were clamped. Continuous stirring with a magnetic bead at a consistent speed maintained hydrodynamics in the receiving compartment throughout the research. Samples were taken at set times. The quantity of medication that penetrated the buccal mucosa was measured using a 260 nm UV spectrophotometer (Shimadzu, UV-1900, Japan).[22]

RESULTS AND DISCUSSION

FTIR study

The FTIR spectrum of pure Paroxetine Hydrochloride showed intense bands at 3334.00 cm^{-1}, 2922.59 cm^{-1}, and 1121.28 cm^{-1} corresponding to the functional groups NH, C-H, and C-F bending, as shown in Figure 2a. The FTIR spectrum of optimized formulation showed intense bands at 3349.46 cm^{-1}, 2916.23 cm^{-1}, and 1109.58 cm^{-1}, indicating no change in the functional groups NH, C-H, and C-F as shown in Figure 2b and confirming that there was no shift or considerable changes in the IR peaks in the peak position of Paroxetine Hydrochloride in spectra of drug and excipients, which proved that drug and excipients were compatible.

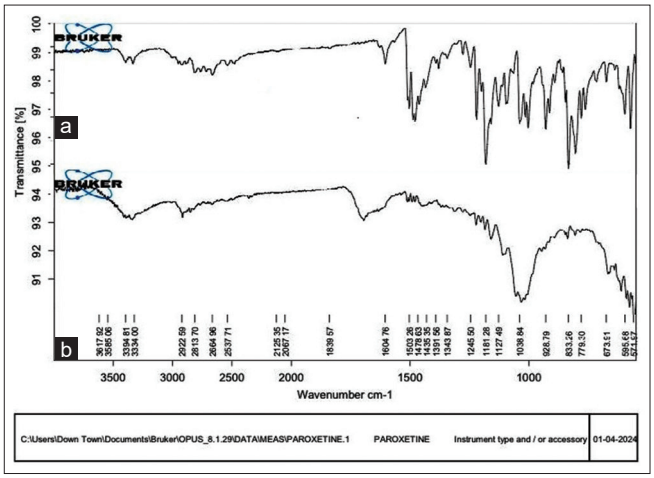

Figure 2: Fourier-transformed infrared spectrum of (a) pure drug Paroxetine Hydrochloride, (b) Optimized formulation

DSC study

Pure Paroxetine Hydrochloride exhibited an endothermic peak of 151°C corresponding to its melting point. The DSC peak of Paroxetine Hydrochloride was preserved in its physical mixtures with each of the aforementioned excipients, indicating that there was no interaction between the drug and the used excipients [Figure 3]. The reduction in Paroxetine Hydrochloride peak intensity in some thermograms was probably attributed to the dilution factor of the mixing process.

Characterization of mucoadhesive buccal tablets of Paroxetine Hydrochloride

Characterization plays an essential role in pharmaceutical invention and quality assurance. This method is necessary to gain insights into tablets' physicochemical properties, guarantee uniform quality, meet regulatory criteria, and safely and efficiently deliver the prescribed dosage to patients.

Weight variation, hardness, thickness, friability and drug content

Table 4 shows that the mucoadhesive buccal tablet thickness and weight variation values are within the limitations specified for oral tablets in the pharmacopoeia. The mass might be anything between 222.8 ± 1.47 and 229.6 ± 0.46 mg. There was a range of 2.70 ± 0.19 mm to 2.77 ± 0.33 mm in tablet thickness. The pills' hardness varied between 3.23 ± 0.12 and 3.96 ± 0.13 kg/cm^2. The hardness, thickness, and mass of all

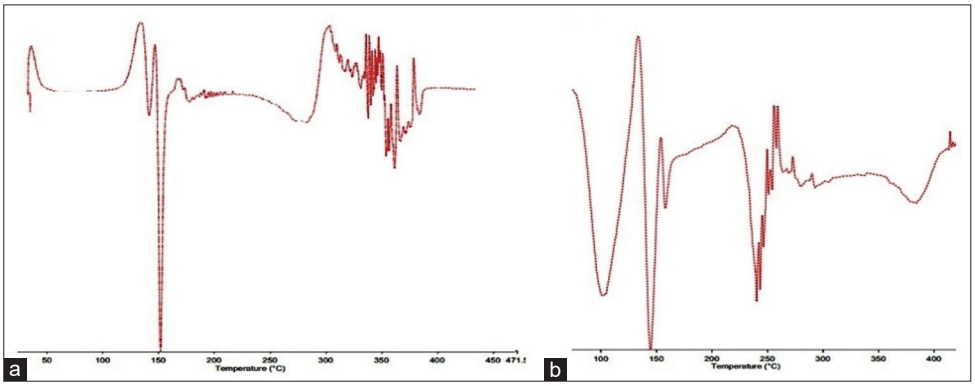

Figure 3: Differential scanning calorimetry thermograms of (a) Pure Paroxetine Hydrochloride, (b) Optimized formulation

compressed tablets did not exceed the limitations set by USP. The drug content ranged from in all formulations F1 to F12, 98.88 ± 0.74 to 101.23 ± 1.46, and the friability ranged from 0.46 ± 0.16 to 0.66 ± 0.33. Friability and drug content of all compressed tablets were within the limits as per USP.

Surface pH study and SI

All of the formulations had surface pH values that were near neutral, falling between 6.5 and 6.9. These findings show that within the salivary pH range of 6.5–6.9, all of the formulations provide a satisfactory pH. They did not locally irritate the mucosal pathway. According to Table 5, all the tests indicated before have been completed.

The swelling behavior of a buccal bioadhesive system is an essential property of uniform and prolonged release and effective mucoadhesion. The SI study indicated that the swelling rate was directly proportional to polymer content. The SI was calculated over time. The SI indicates the relative moisture absorption capacities of polymers and whether the formulations maintain their integrity after moisture absorption. The results of the present formulation are tabulated in Table 5.

Mucoadhesion strength

The concentration and kind of mucoadhesive polymers used in Paroxetine Hydrochloride tablets influenced their mucoadhesion strength attribute. Table 5 shows the mucoadhesion force of different mucoadhesive buccal tablets of Paroxetine Hydrochloride formulations. Formulation F4 Paroxetine Hydrochloride mucoadhesive buccal tablets containing carbopol 934P and HPMC K15M at the ratio of 2:5 (F4) exhibited the highest mucoadhesive strength (0.93 ± 0.06N), whereas formulation F11 showed the weakest

Table 4: Tableting evaluation parameters of the prepared formulations

Formulation	Hardness*	Thickness*	Weight variation†	Friability*	Drug content*
F1	3.46±0.18	2.75±0.12	226.5±1.14	0.55±0.14	99.63±1.25
F2	3.59±0.14	2.77±0.33	224.3±0.18	0.56±0.13	99.33±1.13
F3	3.43±0.17	2.70±0.19	225.8±0.63	0.55±0.13	99.45±0.56
F4	3.29±0.19	2.76±0.14	228.5±1.19	0.49±0.22	98.88±0.74
F5	3.43±0.14	2.72±0.13	225.6±0.83	0.51±0.23	99.36±0.82
F6	3.52±0.12	2.72±0.16	223.5±0.16	0.63±0.15	101.23±1.46
F7	3.38±0.11	2.73±0.13	224.7±0.18	0.55±0.23	98.95±1.93
F8	3.32±0.16	2.73±0.19	222.8±1.47	0.66±0.15	99.49±0.73
F9	3.96±0.13	2.75±0.16	226.8±0.25	0.66±0.33	100.15±0.96
F10	3.88±0.18	2.76±0.15	224.5±0.64	0.65±0.22	99.76±0.73
F11	3.23±0.12	2.76±0.14	229.6±0.46	0.46±0.16	100.8±1.15
F12	3.39±0.15	2.75±0.13	224.2±1.16	0.49±0.22	99.33±0.66

*Each value of 3 mean±SD. †Weight variation limit: ±0.16–1.47%

Table 5: Tableting evaluation parameters of the prepared formulations

Formulation	Surface pH*	Swelling index*	Mucoadhesion strength (N)*	*Ex vivo* mucoadhesion time (h)*
F1	6.9±0.05	53.4±0.32	0.83±0.03	7.3±0.36
F2	6.7±0.04	55.2±0.53	0.86±0.05	7.6±0.89
F3	6.5±0.04	57.7±0.42	0.90±0.02	>8
F4	6.7±0.03	53.5±0.28	0.93±0.06	>8
F5	6.8±0.05	55.5±0.77	0.76±0.07	>8
F6	6.9±0.06	58.4±0.22	0.71±0.05	4.5±0.33
F7	6.7±0.03	57.2±0.59	0.76±0.03	6.5±0.26
F8	6.5±0.05	54.9±0.37	0.75±0.08	7.2±0.45
F9	6.7±0.06	56.3±0.29	0.72±0.03	7.8±0.13
F10	6.5±0.06	57.1±0.63	0.71±0.05	8.3±0.28
F11	6.5±0.05	58.5±0.29	0.68±0.04	6.6±0.59
F12	6.6±0.04	53.9±0.33	0.76±0.07	7.5±0.31

*Each value of 3 mean±SD

mucoadhesion force (0.68 ± 0.04N) with the buccal mucosa when compared with other formulations due to a higher and lower amount of polymers respectively. However, optimized formulation F9 showed 0.72 ± 0.03N good mucoadhesive strength with swine buccal mucosa due to swelling and contact time.

Ex vivo mucoadhesion time

By comparing the *ex vivo* mucoadhesion time of Paroxetine Hydrochloride mucoadhesive buccal tablets, Table 5 shows that carbopol 934P and HPMC K15M mucoadhesive buccal tablets F3, F4, and F5 showed the longest mucoadhesion time (>8 h), while formulations F6 and F11 showed the shortest ranging from 4.5 ± 0.33 and 6.5 ± 0.59 h, respectively. Formulations F1, F2, F7, F8, and F12 buccal tablets had moderate adhesion time ranging from 6.5 ± 0.26 to 7.6 ± 0.33 h, while F9 and F10 buccal tablets showed very moderate mucoadhesion time ranging from 7.8 ± 0.13 and 8.3 ± 0.28 h, respectively. As the concentration of carbopol 934P increased with decreasing HPMC K15M secondary polymer, the retention time increased. This test reflects the mucoadhesive capacity of polymers used in formulations. The results revealed that F9 formulations showed better mucoadhesion time than all others.

Optimization of Paroxetine Hydrochloride buccal tablets by RSM

To assess the significance of factors and their interactions on the SI of buccal tablets, ANOVA was conducted. ANOVA is a statistical method used to determine significant differences between group means. In this study, it helps assess the effect of independent variables (X) and their interactions on the Paroxetine Hydrochloride buccal tablets (Y), identifying key factors that influence the outcome and optimizing the formulation for desired characteristics.

Influence of independent variables on SI (Y_1)

From the ANOVA data, the comparison of mean square values and F values of all the two selected independent variables was made. From the values authors were observed that the HPMC K15M value highest mean square value 23.60 and F value could be 15.68, rather than the other variables, and also the observed *P*-value of HPMC K15M was less than 0.05, would suggesting the percentage weight of HPMC K15 was promising and significantly more influence the response of SI. The hypothetical relation of selected independent variables on SI was revealed by given polynomial equation as below.

$$\text{Swelling index } Y_1 = +55.97 + 0.0617X_1 + 4.98X_2 + 1.325X_1X_2$$

From the equation, the authors observed that the co-efficient value of HPMC K15M was positive and carbopol 934P remain constant. It means that the amount of HPMC K15M as increases, the SI of the Paroxetine Hydrochloride buccal tablets were increased due to, when HPMC K15M comes into contact with water, it absorbs large amounts of water and swells significantly. This is due to the hydrophilic nature of the carboxyl groups (-COOH) present in its polymeric structure and also the ionization of carboxyl groups leads to electrostatic repulsion between the negatively charged polymer chains. This causes the polymer to expand even more, further increasing its swelling and forming a gel-like structure. This swelling and gel formation mechanism makes carbopol 934P an excellent thickening, suspending, and stabilizing agent in pharmaceutical buccal formulations, especially in controlled-release systems.

The R-squared (R^2) value of 0.952 indicates that 95.01% of the variation in the response variable is explained by the model, showing a good fit. The small difference between the adjusted and predicted R^2 values (<0.2) further supports the model's accuracy. In addition, the non-significant lack of fit ($P = 0.6869$) confirms that the data fits the linear model well. The interactions of the independent variables on swelling are illustrated in 2D contour and 3D RSM plots, as shown in Figures 4 and 5.

Influence of independent variables on parentage drug release after 4 h (Y_2)

The ANOVA data shows that HPMC K15M had the highest mean square value (636.75) compared to carbopol 934P (289.95), with an F value of 19.50, indicating its greater influence on drug release. The *P*-value for HPMC K15M (0.0017) was <0.05, confirming its significant impact on the percentage of drug release at the desired time intervals. The relationship between the selected independent variables and the SI is expressed through the following polynomial equation.

$$\text{Percentage drug release after 4 h } (Y_2) = +55.31 - 6.95X_1 - 10.30X_2$$

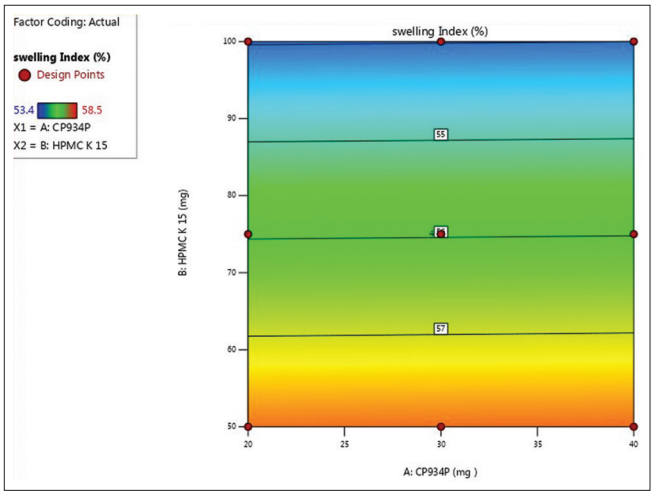

Figure 4: 2D Contour plots of all independent variables on swelling index (Y_1)

The equation shows negative coefficient values for HPMC K15M (10.30) and carbopol 934P (6.95), indicating that as the concentration of these polymers increases, drug release from Paroxetine Hydrochloride buccal tablets decreases.

This is because carbopol 934P, with its higher swelling capacity and strong mucoadhesive properties due to its cross-linking and carboxyl groups, forms a tighter gel, prolonging adhesion to the buccal mucosa and slowing drug release. HPMC K15M also contributes to mucoadhesion but is less effective than carbopol 934P in this regard.

The R-squared (R^2) value of 0.963 indicates that 96.30% of the variation in the response is explained by the model, demonstrating a good fit. The small difference between the adjusted and predicted R^2 values (<0.2) confirms its accuracy. The non-significant lack of fit (*P*=0.8935) shows that the data fits the linear model well. The interactions between the independent variables on drug release are depicted in the 2D contour and 3D RSM plots in Figures 6 and 7.

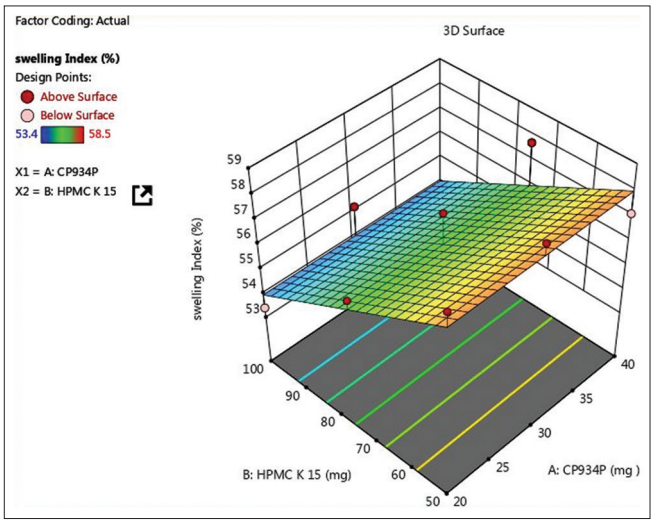

Figure 5: 3D response surface methodology plots of all independent variables on swelling index (Y_1)

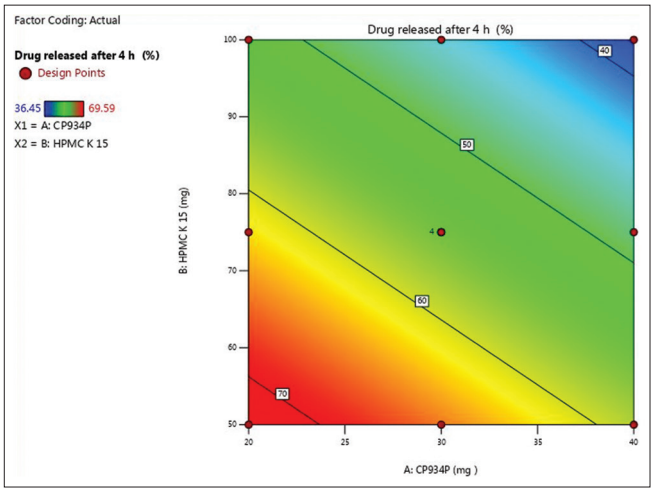

Figure 6: 2D Contour plots of all independent variables on drug release at 4 h (Y_2)

Influence of Independent variables on parentage drug release after 8 h (Y_3)

The ANOVA data reveals that HPMC K15M, with the highest mean square value of 578.01 compared to carbopol 934's 310.18, has a stronger influence on drug release, as indicated by its F value of 7.59. The *P*-value for HPMC K15M (0.0023), being below 0.05, confirms its significant effect on drug release at the desired time intervals. The relationship between the independent variables and the drug release is expressed through the following polynomial equation.

$$\text{Percentage drug release after 8 h } (Y_3) = +88.39 - 7.19\,X_1 - 9.82\,X_2$$

The equation shows negative coefficient values for HPMC K15M (9.82) and carbopol 934P (7.19), indicating that as the concentration of these polymers increases, drug release from Paroxetine Hydrochloride buccal tablets decreases. This is because at 4 h, the drug release is slower, primarily controlled by the strong swelling and gel-forming properties of HPMC K15M, with carbopol 934P adding to the sustained release but to a lesser extent. At 8 h**,** the drug release is significantly reduced, as both polymers have created a thick gel barrier, with HPMC K15M playing a dominant role in maintaining controlled drug release and carbopol 934P was supporting the extended-release over time. Finally, the use of these two independent variables ensures prolonged and controlled drug release, with a gradual increase over time, aligning with the goals of a buccal delivery system.

The R-squared value of 0.957 shows that 95.7% of the response variation is explained by the model, indicating a good fit. The small difference between adjusted and predicted R^2 (<0.2) confirms accuracy. The non-significant lack of fit (*P* = 0.8975) suggests the linear model fits well. Interactions on drug release after 8 h are shown in 2D contour and 3D RSM plots [Figures 8 and 9].

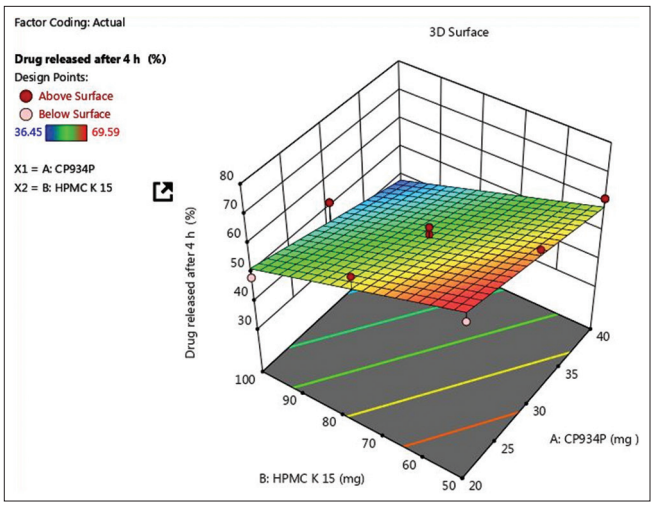

Figure 7: 3D RSM plots of all independent variables on drug release at 4 h (Y_2)

Numerical and graphical optimization

The optimization of Paroxetine Hydrochloride buccal formulations aimed to achieve key characteristics like SI and controlled drug release over time. This process was guided by specific constraints and study goals, focusing on enhancing the formulation's performance. The data were depicted in Table 6.

The authors identified 100 potential optimization solutions that met the established constraints. These solutions were ranked by desirability scores, with the highest score indicating the optimized formulation [Figure 10].

In this study, a formulation with 22.42 units of carbopol 934P and 90.34 units of HPMC K15M achieved a SI of 54.73 ± 0.15, 54.25 ± 0.23% drug release at 4 h, and 87.80 ± 0.25% at 8 h. With a desirability score of 1.000, it was identified as the optimal formulation [Figure 11]. Desirability scores helped compare formulations, with blue indicating low desirability and red highlighting areas of increasing desirability, peaking at one.

The selected formulations were experimentally validated for practical use. Graphical optimization, shown in the overlay plot [Figure 12], was used to optimize the SI and drug release at 4 and 8 h. Red data points represent various experimental conditions, while the yellow-shaded region highlights the optimal area where the desired criteria are met. Specific points in this area show exact values for carbopol 934P and HPMC K15M. Contour plots helped identify the best formulation for further development of the buccal tablet.

In vitro dissolution studies

This study aimed to develop a buccal tablet formulation for Paroxetine Hydrochloride capable of sustaining drug release over 8 h. The tablets, tested in a phosphate buffer (pH 6.8), successfully released 95.57 ± 0.42% of the drug within the

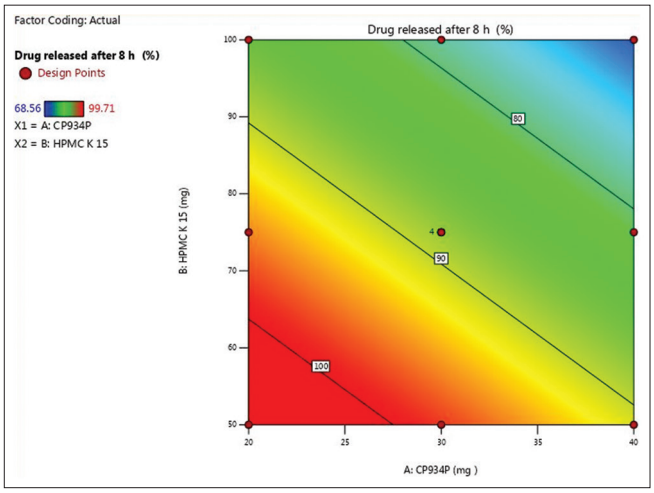

Figure 8: 2D contour plots of all independent variables on drug release at 8 h (Y_3)

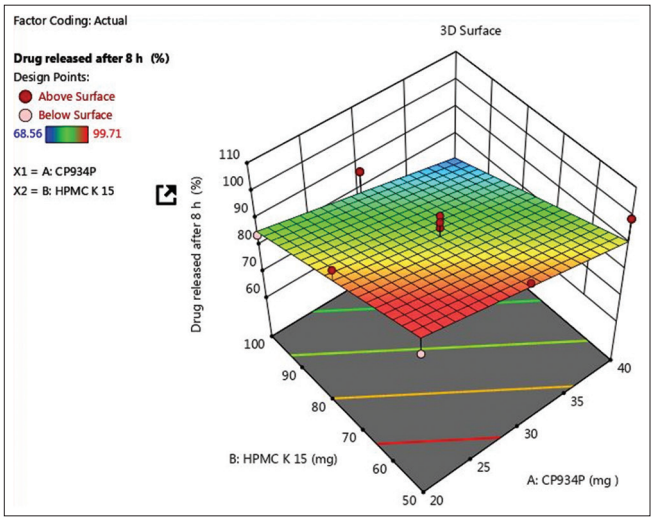

Figure 9: 3D response surface methodology plots of all independent variables on drug release at 8 h (Y_3)

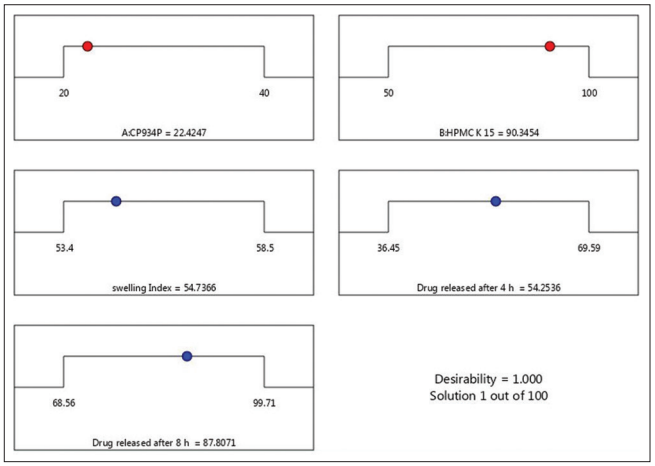

Figure 10: Composition of selected independent variables for optimized Paroxetine Hydrochloride buccal tablets batch

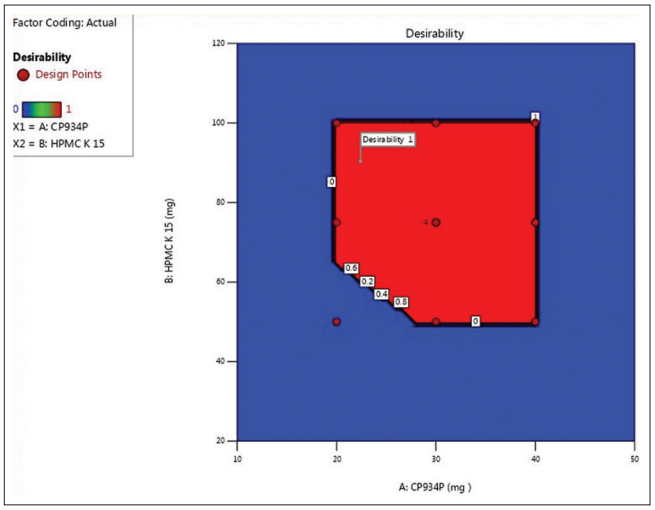

Figure 11: Desirability plot for optimization of Paroxetine Hydrochloride buccal tablets

Table 6: Constraints and goals for Paroxetine Hydrochloride buccal tablets

Name of variables	Goal	Lower limit	Upper limit	Importance
Carbopol 934P (X_1)	In range	20	40	+++
HPMC K15M (X_2)	In range	50	100	+++
Swelling index (X_3)	In range	53.4	58.5	+++
Drug release at 4 h (Y_1)	In range	36.45	69.59	+++
Drug release at 8 h (Y_2)	Minimize	70.12	99.71	+++++

Table 7: *In vitro* release kinetics of the formulation F1-F12

Formulation codes	Zero-order model	First-ORDER MODEL	Higuchi model	Korsmeyer Peppas model
F1	0.989	0.956	0.948	0.988
F2	0.979	0.960	0.931	0.955
F3	0.981	0.996	0.952	0.995
F4	0.991	0.976	0.931	0.975
F5	0.985	0.992	0.942	0.992
F6	0.956	0.821	0.979	0.995
F7	0.981	0.948	0.953	0.993
F8	0.983	0.933	0.945	0.994
F9	0.949	0.795	0.990	0.998
F10	0.978	0.788	0.969	0.997
F11	0.933	0.823	0.988	0.994
F12	0.973	0.906	0.974	0.997

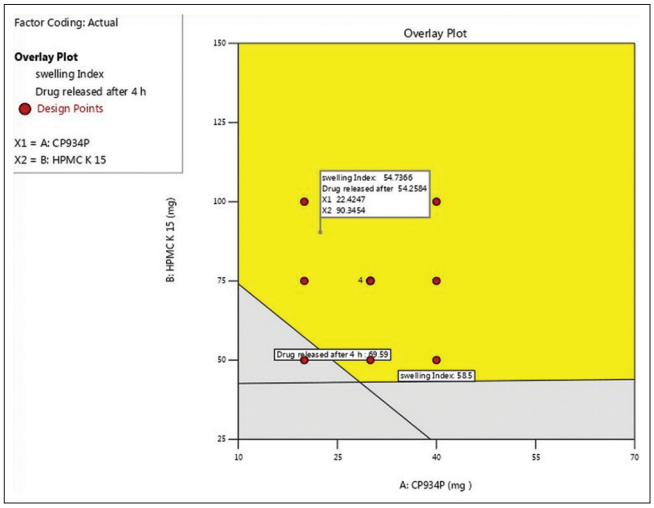

Figure 12: Overlay plot for optimization of Paroxetine Hydrochloride buccal tablets

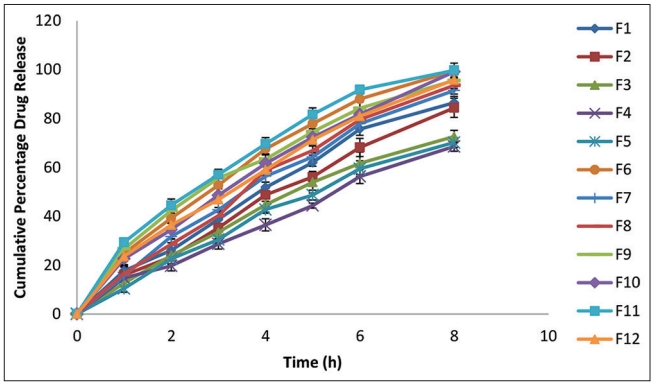

Figure 13: *In vitro* dissolution profile of optimized Paroxetine Hydrochloride buccal tablets

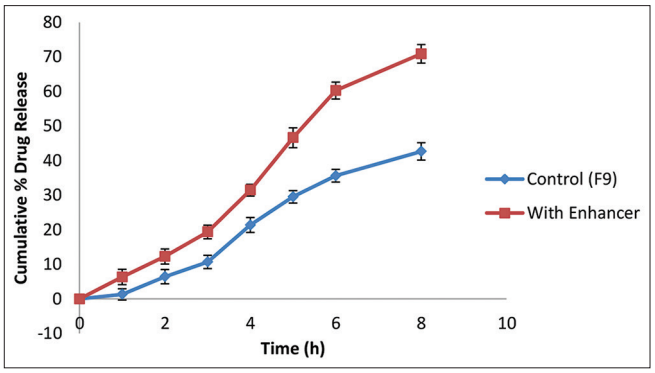

Figure 14: *Ex vivo* permeation studies of formulation F9

desired period [Figure 13], offering an extended-release profile suitable for once-daily dosing.

During the first 4 h, the drug release rate was slow (0–63.34%), controlled by the swelling of carbopol 934P and HPMC K15M. These polymers form a gel barrier on hydration, regulating drug diffusion and preventing a rapid release. The gel thickens over time, ensuring a steady release of Paroxetine.

Between 4 and 8 h, the drug release rate increased, reaching 95.57 ± 0.42% by the end. This acceleration is due to further polymer swelling, increased matrix porosity, and erosion, which facilitate faster drug diffusion. In conclusion, the formulation demonstrated effective sustained release, improving patient compliance and maintaining therapeutic efficacy over an extended period.

Kinetics for drug release mechanism

The formulation F9, which shows higher R^2 values for Higuchi and Peppas (0.990 and 0.998), suggests that the drug release follows a kinetic diffusion mechanism. The Peppas model was applied when the release mechanism was unknown or more than one type of release could be involved [Table 7].

Ex vivo permeation studies

Based on the drug release profile, an *ex vivo* study was conducted using an F9 formulation with PEG 6000 as a permeation enhancer and a control (without enhancer). The *ex vivo* permeation research is based on drug release experiments, which led to the selection of formulation F9 as the optimal formulation. The test drug release was 70.88 ± 2.65% as against 42.65 ± 2.52% [Figure 14]. Permeation of the medication across the buccal membrane was consistent and sluggish, with a maximum of 70.88 ± 2.65% of the Paroxetine Hydrochloride being able to pass through in 8 h.

CONCLUSION

There was no evidence of drug-excipient interaction in the Paroxetine Hydrochloride FTIR spectra and DSC peak. Research on the SI has shown a direct correlation between the concentration of polymers and swelling. The mucoadhesive strength was highest (0.93 ± 0.06 N) in formulation F4 Paroxetine Hydrochloride, which had the highest carbopol 934P and HPMC K15M (2:5) ratio, and lowest (0.68 ± 0.04 N) in formulation F11, which had lower and higher polymer quantities, respectively. Tablet formulation F9 outperformed other formulations in *in vitro* release trials, showing superior release characteristics (95.57 ± 0.42%, 8 h). The drug release was slow (0–63.34%) for the first 4 h because of the swelling of carbopol 934P and HPMC K15M. By the end of the 8 h, the drug release had increased to 95.57 ± 0.42%. The most effective formulation, F9, was determined through *ex-vivo* permeation research utilizing drug release experiments; it achieved a drug release rate of 70.88 ± 2.65%, surpassing the previous best of 42.65 ± 2.52%.

The ANOVA study showed that the R^2 of 0.952 for SI and 0.957 ± 0.42% for drug release agreed with the slight difference between the adjusted and predicted R^2 values (<0.2), supporting the model's accuracy. In addition, the non-significant lack of fit (P = 0.6869) and (P = 0.8975) confirms that the data fits the linear model well for swelling and drug release, respectively. This model can thus be utilized for the design development process. Since the desirability result was determined to be 1, the results were considered valid. In a perfect scenario, a controlled release system would release the medication at the precise moment needed to reach the therapeutic level and keep it there for as long as possible. The overarching goal of this study was to find a way to bypass first-pass metabolism and boost Paroxetine Hydrochloride bioavailability.

AUTHOR CONTRIBUTIONS

The authors confirm their contribution to the article as follows: Study conception and design: KSS, SP, SA; data collection: KSS, SA, SP; analysis and interpretation of results: KSS, SP, CT; draft manuscript preparation: KSS, CT, SA. All authors reviewed the results and approved the final version of the manuscript.

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