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DEVELOPMENT AND EVALUATION OF MUCOADHESIVE TABLETS CONTAINING BROMHEXINE HYDROCHLORIDE IN β- CYCLODEXTRIN COMPLEX FOR BUCCAL DELIVERY

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ABSTRACT

Bromhexine hydrochloride, a potent mucolytic for respiratory disorders, exhibits low oral bioavailability (22–27%) due to extensive hepatic first-pass metabolism. This study aimed to develop and evaluate mucoadhesive buccal tablets of bromhexine hydrochloride in beta-cyclodextrin to bypass pre-systemic clearance and optimize drug delivery through the oral mucosa. Inclusion complexes of the drug with β-cyclodextrin prepared to enhance solubility of drug. Tablets containing 8 mg of the active drug were formulated using Hydroxypropyl Methylcellulose, and Carbopol as bio adhesive polymers, with microcrystalline cellulose as the filler. A 13-run Central Composite Design was applied to optimize the polymeric matrix designed with the help of Design Expert software. The formulations were evaluated for flow properties, hardness, thickness, surface pH, weight variation, drug content uniformity, swelling index, and in vitro dissolution behaviour. Among the prepared batches, the optimized formulation demonstrated superior performance. It exhibited a surface pH compatible with salivary conditions, ensuring minimal mucosal irritation. The swelling index was successfully maintained below 100%, preventing rapid matrix erosion while preserving structural integrity. In vitro dissolution studies confirmed a controlled and sustained drug release profile. FT-IR analysis verified structural compatibility between the drug and excipients. 90-day stability study showed no significant changes in quality or release behaviour. The optimized buccal tablet offers a viable approach for delivering bromhexine hydrochloride, providing a promising strategy to avoid first-pass metabolism, enhance systemic availability, and improve clinical outcomes.

KEYWORDS: Bromhexine hydrochloride, β-cyclodextrin, buccal tablet, mucoadhesive polymer, bioavailability, solubility.

1. INTRODUCTION

Buccal drug delivery systems mark a significant advancement in pharmacology and therapeutics by offering an alternative route for drug administration through the buccal mucosa, the inner cheek lining. This approach has several benefits compared to traditional oral and injectable methods, making it appealing for both patients and healthcare providers. The buccal mucosa is richly vascularized, allowing drugs to be absorbed quickly and efficiently into systemic circulation while bypassing the gastrointestinal tract and first-pass liver metabolism. This is especially useful for drugs that have poor gastrointestinal absorption, are unstable in stomach acid, or undergo extensive liver metabolism. As a result, buccal delivery can improve bioavailability, lower required doses, and reduce systemic side effects. Various dosage forms, such as tablets, films, patches, and gels, are designed to stick to the buccal mucosa and release medication in a controlled way. Mucoadhesive polymers are often added to enhance adhesion and prolong retention, ensuring steady drug release.[4] This route is particularly beneficial for patients who struggle with swallowing, including the elderly, children, and those with specific medical conditions. Administering a drug via a buccal tablet allows it to be absorbed directly into the systemic circulation from the deeply vascularized mucosal lining of the cheek.[5,4]

Bromhexine Hydrochloride is a widely prescribed mucolytic agent used in the treatment of respiratory disorders associated with viscid or excessive mucus, such as bronchitis and chronic obstructive pulmonary disease (COPD). It helps thin and loosen mucus, making it easier to cough up and clear from the airways. It belongs to BCS Class II drug, exhibiting poor aqueous solubility and undergoing extensive hepatic first-pass metabolism when administered through conventional oral routes. Cyclodextrins are cyclic oligosaccharides capable of forming non-bonded inclusion complexes with hydrophobic drug molecules within their lipophilic central cavities. The formation of a Bromhexine Hydrochloride, beta-cyclodextrin complex remarkably enhances the aqueous solubility, dissolution rate, and subsequent permeability of the drug.

2. MATERIALS AND METHODS

2.1 Determination of melting point[3]

Melting point was determined by capillary method, a small amount (0.1-0.2g) of pure drug was transferred onto a watch glass. One end of capillary tube of 5cm long was sealed and the solid was introduced into a capillary tube and packed to a height of 3 cm. Then the capillary tube was placed in melting point apparatus and the temperature at which the melting of drug started was noted by using the thermometer placed in the apparatus.

2.2 Solubility studies[3]

Solubility of bromhexine hydrochloride was observed in different solvents such ethanol, water, phosphate buffer pH 6.8, and propylene glycol.

2.3 Drug and excipient compatibility study[18]

Fourier Transform Infra-Red Spectroscopy (FT-IR) analysis was carried out on pure substances and their physical mixtures. FT-IR spectra of pure drug, excipients and their physical mixtures were taken by direct method between 400-4000 cm^{-1}. The peaks of pure drug, excipient and physical mixtures were compared for incompatibility.

2.4 Determination UV λmax

Dissolve accurately weighed 50mg of bromhexine hydrochloride in 100 ml of Phosphate buffer (pH-6.8) in 100ml standard flask to get 1mg/ml from the stock solution of bromhexine hydrochloride, I ml is pipetted out and diluted to 100ml with phosphate buffer to get 10µg/ml solution. The absorption maximum of standard solution of bromhexine hydrochloride is determined by scanning the resulting stock solution in UV spectrometer at 200-400 nm. The absorption maxima obtained is compared with reference standard for the value.

2.5 Preparation of standard calibration curve of Bromhexine hydrochloride in phosphate buffer (6.8)

In a 100 ml volumetric flask, standard solution was prepared by dissolving 100 mg of bromhexine hydrochloride in phosphate buffer (pH-6.8) and make up to the volume with phosphate buffer. From the standard solution, 1 ml was taken and the volume was made up to 100 ml with phosphate buffer and labelled as stock (10µg/ml). From this stock solution, serial dilutions were made by withdrawing 2ml, 4ml, 6 ml, 8 ml and 10 ml and transferred individually into 10 ml standard flask and the volume was made up to the mark using phosphate buffer. The absorbance of the samples was observed using UV spectrophotometer at a wavelength of 253nm and a graph is plotted between concentration taken on x- axis and absorbance taken on y-axis.

2.6 Precompression parameters of powder blend

The powder blend was analysed for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

2.6.1 Bulk density

Bulk density was determined by placing the powder blend in a measuring cylinder and the total volume was noted. The weight of powder bed was determined. Bulk density was calculated by using the formula.

$$\text{Bulk density} = \frac{\text{Total weight of powder/granules}}{\text{Total volume of powder/granules}}$$

2.6.2 Tapped density

The powder blend carefully introduced into graduated measuring cylinder. The cylinder was tapped on surface 100times from a height of 1 inch. After tapping volume was noted. Tapped density can be calculated by using following formula.

$$\text{Tapped density} = \text{weight of powder} / \text{Tapped volume}$$

2.6.3 Angle of repose

Angle of repose was determined by measuring the height and radius of the heap of the powder bed. A cut stem funnel was fixed to a stand and bottom of the funnel was fixed at a height of 3 cm from the plane. Powder was placed in the funnel and allowed to flow freely. The height and radius of the heap were measured and noted.

$$\theta = \tan^{-1} (h / r)$$

2.6.4 Compressibility Index

The Carr's compressibility index, also known as the Carr index. It is calculated based on the bulk density and tapped density of the powder and provides insights into its flowability and compaction characteristics.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped desnsity}} \text{X } 100$$

2.6.5 Hausner's ratio

It is the ratio of tapped density to bulk density. Hausner's ratio is an ease of powder flow. Hausner's ratio= Tapped density / Bulk density

2.7 FORMULATION OF BROMHEXINE HYDROCHLORIDE BUCCAL TABLETS

2.7.1Preparation of bromhexine hydrochloride- β-Cyclodextrin Inclusion Complex

The inclusion complex of the drug with beta-cyclodextrin (β-cyclodextrin) was prepared using the kneading method. The active pharmaceutical ingredient (API) and beta-cyclodextrin were accurately weighed in a 1:1 molar ratio. To initiate the process, a homogeneous paste of beta-cyclodextrin was formed by adding a solvent mixture consisting of ethanol and water in an appropriate ratio. The weighed drug was then incorporated into the paste, and the mixture was continuously and thoroughly kneaded for 30 to 40 minutes to ensure optimal complexation. Following the kneading process, the resulting wet mass was dried in an oven maintained at approximately 50°C for 2 hours, or until it achieved complete dryness. The dried inclusion complex mass was subsequently pulverized and passed through a #60 mesh sieve to obtain a uniform, free-flowing powder suitable for further formulation processing.

2.7.2 Formulation and Compression of Mucoadhesive Buccal Tablets

Mucoadhesive buccal tablets were prepared using the direct compression method. First, the drug-cyclodextrin complex and all other ingredients were accurately weighed. The complex was then mixed thoroughly with the mucoadhesive polymer to ensure uniform distribution. Next, the filler and glidant were added, and the mixture was blended gently. Finally, the resulting powder blend was compressed directly into tablets using a tablet compression machine.

Table no. 1: Formulation table of bromhexine hydrochloride tablet designed using Design Expert (Stat ease Version 13.0.7.0).

FORMULATION	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Bromhexine hydrochloride (mg)	8	8	8	8	8	8	8	8	8	8	8	8	8
Beta-cyclodextrin (mg)	22	22	22	22	22	22	22	22	22	22	22	22	22
HPMC K4M (mg)	40	80	40	80	31.72	88.28	60	60	60	60	60	60	60
Carbopol (mg)	10	10	30	30	20	20	5.86	34.14	20	20	20	20	20
Mannitol (mg)	98.99	74.99	86.99	62.99	91.96	58.03	83.48	66.51	74.99	74.99	74.99	74.99	74.99
Microcrystalline cellulose(mg)	66	50	58	42	61.31	38.69	55.65	44.34	50	50	50	50	50
Talc (mg)	4	4	4	4	4	4	4	4	4	4	4	4	4

2.8 EVAULATION OF BROMHEXINE HYDROCHLORIDE BUCCAL TABLET

2.8.1 Thickness[5]

Thickness of tablets was measured by using micro meter

2.8.2 Hardness/Crushing strength[5]

Hardness or tablet crushing strength i.e. the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

2.8.3 Friability[4]

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each

revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed.

2.8.4 Weight Variation[4]

20 Tablets were randomly selected and individually weighed and calculated the average weight and compared the individual tablet's weight to the average weight.

2.8.5 Drug Content[6]

Twenty tablets were taken, powdered and the powder equivalent to one dose each was transferred to a 100 mL volumetric flask and phosphate buffer (pH-6.8) was added. The volume was then made up to the mark with phosphate buffer. The solution was filtered and diluted suitably and drug content in the samples was estimated using UV- Visible spectrophotometer at 253nm.

2.8.6 Surface pH[5]

The formulated tablet was kept in of phosphate buffer for 2 hours at room temperature. The surface of the tablet was placed in contact with a glass electrode, and the pH was measured after allowing it to equilibrate for 1 minute.

2.8.7 Swelling Index[6]

The swelling index of the buccal tablet was determined in phosphate buffer pH 6.8 The initial weight of the tablet was determined and then tablet was placed in 15 ml phosphate buffer pH 6.8 in a Petri dish and then was incubated at 37 ± 1°C. The tablet was removed at different time intervals (1, 2, 3, 4, 5, 6 hrs) blotted with filter paper and reweighed (W2). The swelling index is calculated by using he formula.

$$\text{Swelling index} = 100\ (W2-W1) / W1$$

Where, W1 = Initial weight of the tablet. W2 = Final weight of tablet.

2.9 In-vitro Dissolution Studies[9]

The in-vitro dissolution was performed for the single unit tablets using USP Type II dissolution apparatus (Paddle type). Tablet was placed in the dissolution apparatus containing 900 ml of Phosphate buffers pH 6.8 and the paddle was rotated at 50 rpm at a temperature of 37±0.5°C. Samples of 5 ml were collected at different time intervals up to 6 hours and analysed by spectrophotometer at 253nm. Then the cumulative amount of drug release from the prepared tablets at different time intervals was calculated, the average of triplicate measurement was used as the final value and dissolution profile was plotted.

2.10 Formulation Optimization via DOE[6]

A computer aided optimization approach employing a statistical design of experiments was used to identify critical factors, their interactions, and the optimal process conditions necessary to achieve the targeted results. Design Expert Stat Ease Software was utilized to determine the optimal formulation. The optimization process utilized a central composite design, concentration mucoadhesive polymer HPMC and Carbopol were selected as the two independent variables, while in-vitro drug release and swelling index were considered as the two response variables. As a result, thirteen experimental trials were performed. Contour plots were created, and the optimal formulation was chosen based on the established optimization criteria.

2.11 Kinetic studies

To determine the drug release mechanism, the dissolution data were fitted to various kinetic models, including Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models.

2.12 Stability studies

The accelerated stability studies were carried out according to ICH guidelines on optimized formulation for the period of 3 months. The Tablet was evaluated before and after 3 months for change in appearance, Hardness, drug content and In vitro release.

3. RESULT AND DISCUSSION

3.1 Determination of melting point

Melting point of bromhexine hydrochloride was determined by capillary rise method and it was found to be 237± 0.45°C, which complies with official standards.

3.2 Solubility studies

Solubility studies were carried out in different solvents and it was found that bromhexine hydrochloride was sparingly soluble in ethanol and propylene glycol, very slightly soluble in water, practically insoluble in phosphate buffer pH 6.8 which complies with the pharmacopeial specifications.

3.3 Drug – excipient compatibility

Compatibility study was done by FT-IR spectroscopic method.

During FT-IR studies the peak of bromhexine hydrochloride was obtained at peak 690 cm^{-1}, 1303cm^{-1}, 163cm^{-1}, 2932cm^{-1}, 3297cm^{-1}. It has been found in this investigation that there is no chemical interaction between the excipients and bromhexine hydrochloride. The major peak in the drug and excipient mixture was found to remain unchanged, indicating that there was no physical interaction due to bond formation between the substances.

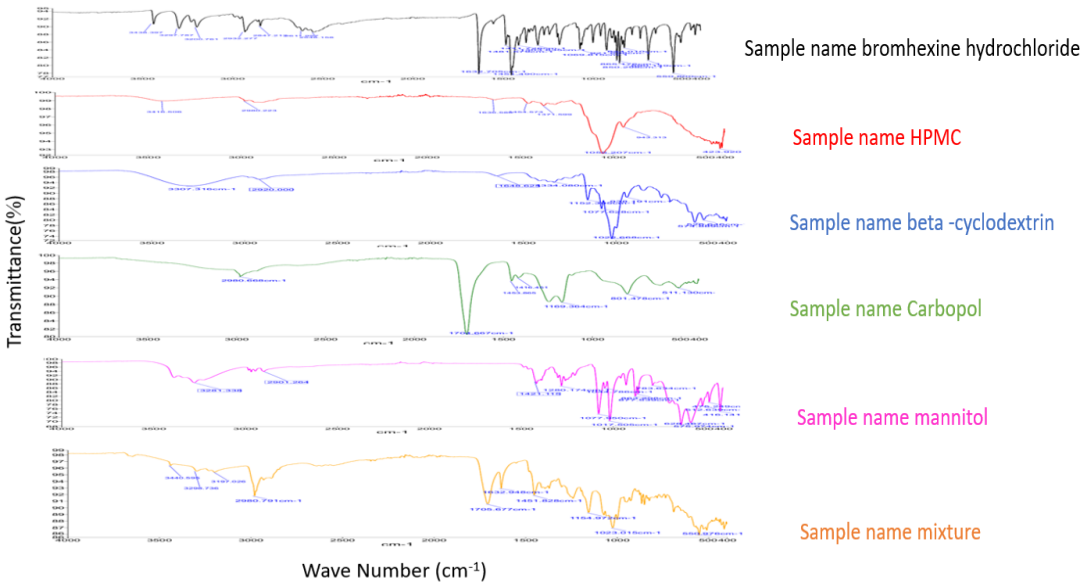

Figure no 1: FTIR spectrum of drug+ beta-cyclodextrin +HPMC + Carbopol+ mannitol.

Table no 2: Calibration curve data of bromhexine hydrochloride.

Concentration (µg/ml)	Absorbance
0	0
2	0.131±0.002
4	0.259±0.0032
6	0.387±0.0021
8	0.514±0.004
10	0.624±0.003

All values expressed as mean of ± SD, n = 3

3.3.1 Standard calibration curve of bromhexine hydrochloride

The λ_{max} of bromhexine hydrochloride in phosphate buffer pH 6.8 found to be 253 nm. The curve was found to be linear and obeys Beer- Lambert's law in the range of 1- 10 µg/ml with regression co-efficient 0.9994. The absorbance values are tabulated in the Table 2.

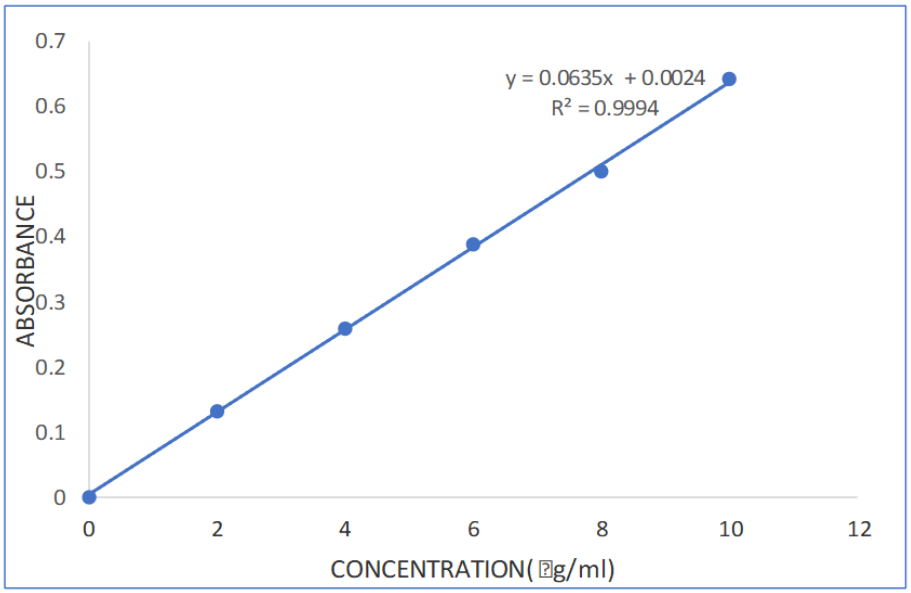

Fig no. 2: Standard calibration curve of bromhexine hydrochloride in Phosphate buffer (pH 6.8) at 253nm.

3.4 Pre-compression parameters

The precompression parameters of the formulations are shown in the table no.3. All the formulations exhibited good flow properties of powder blend. Bulk density values for all batch beads were obtained in the range from 0.29-0.39 kg/cm^3 and the tapped density values obtained in the range from 0.40- 0.45 kg/cm^3. The angle of repose values range in between 25.8°-33.58° indicating that the powder blend has good flow property for compression. Carr's index value for all batch beads was found in the range of 13.3-22.5, indicating excellent to good flow properties for all batches.

Hausner's ratio for all batch beads was found between 1.15- 1.37showing excellent flow properties of beads of all batches.

Table no. 3: Precompression parameters of different batches of formulation formulation.

Formulation	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index	Hausner's ratio	Angle of repose (°)
F1	0.38±0.02	0.44±0.014	13.63±0.52	1.15±0.02	26.42±0.45
F2	0.34±0.01	0.42±0.022	17.04±0.088	1.23±0.03	29.85±0.61

F3	0.32±0.02	0.41±0.031	20.95±0.074	1.28±0.02	31.24±0.55
F4	0.30±0.01	0.40±0.033	21.33±0.112	1.33±0.02	33.58±0.38
F5	0.39±0.02	0.45±0.022	13.33±0.041	1.15±0.01	25.88±0.38
F6	0.31±0.01	0.41±0.012	21.39±0.095	1.32±0.03	32.15±0.84
F7	0.37±0.01	0.43±0.012	13.95±0.063	1.16±0.02	27.56±0.49
F8	0.29±0.02	0.40±0.021	22.50±0.145	1.37±0.05	33.22±0.25
F9	0.35±0.02	0.42±0.023	16.66±0.038	1.20±0.01	28.52±0.22
F10	0.32±0.03	0.4±0.023	16.76±0.056	1.21±0.01	28.43±0.24
F11	0.25±0.02	039±0.022	15.66±0.024	1.10±0.02	27.58 ±0.16
F12	0.33±0.02	0.42±0.022	16.43±0.012	1.140±0.01	29.52±0.26
F13	0.34±0.02	0.4±0.024	16.66±0.039	1.450±0.02	28.89±0.32

All values expressed as mean of ± SD, n = 3

3.5 EVALUATION OF BROMHEXINE HYDROCHLORIDE BUCCAL TABLETS

3.5.1Post – Compression Parameters

3.5.1.1Thickness

All the formulation showed uniform of thickness of 3.47- 3.83mm.

3.5.1.2 Hardness

The hardness of tablets ranged from 4.5-6.97kg/cm².

3.5.1.3 Friability

The friability test was performed on the formulations. Friability of all prepared tablets were founded in the range of 0.25%-0.38% indicating the tablet prepared were of sufficient strength.

3.5.1.4 Drug Content

Drug content of all formulations was tested and was found to be within the pharmacopeial limit. This ranges between 96.72%-98.63%.

3.5.1.5 Weight Variation

The weight variation test was performed. The weight variations of the sample were found to be within the range of 248 mg- 252mg. All formulations complied with the test for weight variation according to the pharmacopeial specifications.

3.5.1.6 Surface pH

The surface pH of the prepared mucoadhesive tablets was determined to evaluate any potential in vivo side effect. The surface pH of all formulation was found to be in the range of pH6.5 to 6.9, which is close to the salivary pH, indicating that all formulation is safe and are not expected to produce any local irritation in the oral cavity.

Table no: 4 Post compression parameters of different batches of formulation.

Formulation	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Weight Variation (mg)	Drug Content (%)	Surface pH
F1	5.34±0.83	3.58±0.02	0.31±0.23	250.2±0.72	97.75±0.41	6.5±0.54
F2	6.46±0.63	3.53±0.069	0.29±0.33	251±0.54	98.63±0.43	6.53±0.21
F3	5.89±0.77	3.47±0.034	0.32±0.19	249.5±0.68	97.13±0.33	6.7±0.41
F4	6.93±0.93	3.65±0.08	0.25±0.37	249±0.72	98.58±0.23	6.64±0.12
F5	4.5±0.38	3.48±0.05	0.38±0.42	250±0.39	97.52±0.34	6.9±0.68
F6	6.97±0.82	3.83±0.03	0.26±0.58	251±0.07	97.32±0.35	6.67±0.31
F7	5.11±0.12	3.67±0.07	0.30±0.95	252.5±0.03	98.38±0.23	6.7±0.23

F8	5.86±0.17	3.53±0.34	0.31±0.64	248±0.087	98.39±0.38	6.82±0.42
F9	5.42±0.94	3.54±0.91	0.29±0.75	249±0.011	96.72±0.42	6.72±0.23
F10	5.62±0.94	3.54±0.91	0.29±0.75	249±0.011	97.32±0.35	6.72±0.23
F11	5.62±0.94	3.54±0.91	0.29±0.75	249±0.011	97.35±0.46	6.72±0.23
F12	5.62±0.94	3.54±0.91	0.29±0.75	249±0.011	98.42±0.43	6.72±0.23
F13	5.62±0.94	3.54±0.91	0.29±0.75	249±0.011	98.32±0.38	6.72±0.23

All values expressed as mean of ± SD, n = 3

3.5.2 Swelling index

The swelling index for the 13 formulation batches ranged from 45.2% (F1) to 78.5% (F4). This difference is directly caused by the concentration of the polymers used in each batch. Formulations like F4 and F6 contained a higher concentration of hydrophilic polymers (Carbopol and HPMC), which allowed them to absorb water rapidly. A higher swelling index is highly desirable for buccal delivery because it creates a thick, flexible gel layer that helps the tablet stick tightly and securely to the mucosal lining. Most of the other batches maintained a moderate swelling profile (between 55% and 62%). This moderate polymer concentration provides the perfect balance.it gives the tablet excellent stickiness while ensuring it remains strong enough to not dissolve or break apart too quickly in the mouth.

Table no 5: Swelling index of different batch of formulation.

Formulation	Swelling index after 6hours
F1	45.2±0.21
F2	62.4±0.32
F3	58.1±0.32
F4	78.5±0.43
F5	51.3±0.52
F6	72.6±0.24
F7	55.4±0.26
F8	69.8±0.35
F9	58.65±0.22
F10	60.65±0.22
F11	59.32±0.32
F12	58.4±0.34
F13	60.42±0.32

All values expressed as mean of ± SD, n = 3

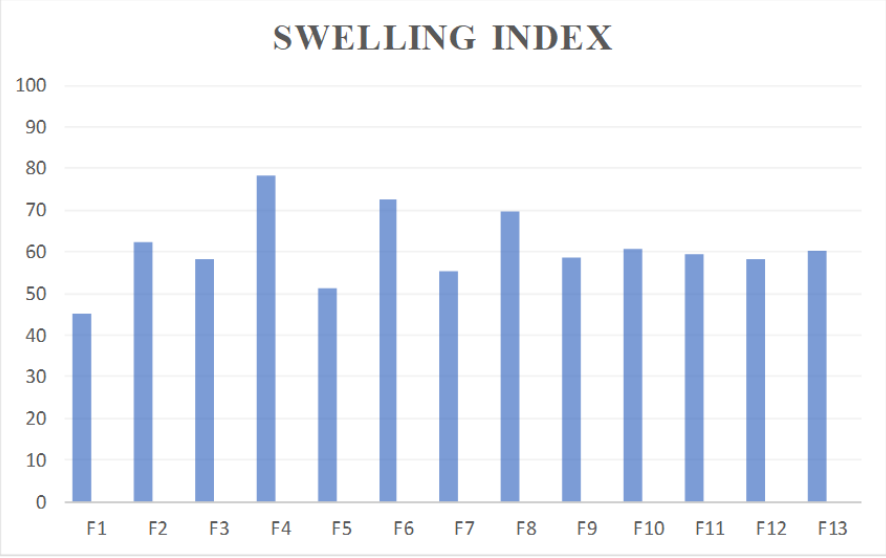

Figure no 4: Graphical representation of swelling index in different batches of formulation.

3.5.3 In-vitro release studies

Table no 6: In vitro drug release profile for F1 to F13 formulation for 6 hours.

Formulation	0hr	1hour	2hour	3hour	4hour	5hour	6hour
F1	0	15.40 ± 0.12	32.10 ± 0.18	48.50 ± 0.22	64.80 ± 0.15	80.20 ± 0.19	92.41 ±0.15
F2	0	11.20 ± 0.14	24.50 ± 0.11	36.80 ± 0.19	48.20 ± 0.16	59.40 ± 0.22	69.60 ± 0.18
F3	0	12.80 ± 0.16	27.40 ± 0.21	41.50 ± 0.13	55.20 ± 0.20	68.10 ± 0.14	79.57 ± 0.23
F4	0	9.50 ± 0.11	20.80 ± 0.15	31.40 ± 0.24	42.10 ± 0.18	51.50 ± 0.12	60.10 ± 0.21
F5	0	16.20 ± 0.19	33.40 ± 0.25	50.90 ± 0.17	67.50 ± 0.21	82.90 ± 0.16	95.67 ± 0.28
F6	0	9.20 ± 0.13	20.10 ± 0.17	30.50 ± 0.11	41.20 ± 0.15	50.30 ± 0.20	58.90 ± 0.16
F7	0	14.80 ± 0.15	31.20 ± 0.20	47.10 ± 0.16	63.40 ± 0.22	78.50 ± 0.11	90.32 ± 0.24
F8	0	12.10 ± 0.11	25.80 ± 0.19	38.90 ± 0.23	51.60 ± 0.14	63.20 ± 0.17	74.01 ± 0.19
F9	0	14.50 ± 0.17	30.80 ± 0.14	46.20 ± 0.21	61.90 ± 0.18	77.10 ± 0.15	89.20 ± 0.17
F10	0	14.90 ± 0.21	31.40 ± 0.16	47.30 ± 0.19	63.20 ± 0.25	78.80 ± 0.13	91.23 ± 0.22
F11	0	14.60 ± 0.18	31.00 ± 0.22	46.50 ± 0.15	62.10 ± 0.19	77.40 ± 0.21	89.52 ± 0.25
F12	0	13.80 ± 0.12	29.20 ± 0.15	43.90 ± 0.17	58.50 ± 0.20	72.90 ± 0.14	84.23 ± 0.19
F13	0	14.90 ± 0.19	31.50 ± 0.11	47.40 ± 0.22	63.30 ± 0.16	78.90 ± 0.18	91.25 ± 0.21

All values expressed as mean of ± SD, n = 3

The in-vitro drug release profiles of the thirteen batches (F1–F13) were evaluated over a period of 6 hours, revealing a progressive increase in cumulative drug release over time was observed. At the final 6-hour interval, the cumulative percentage of drug release varied significantly across the batches, ranging from a minimum of 58.90 ± 0.16% in formulation F6 to a maximum of 95.67 ± 0.28% in formulation F5.The lower drug release observed in F6 can be attributed to the higher concentrations of polymers such as HPMC and Carbopol, which form a viscous gel barrier upon hydration that increases the diffusion path length, whereas the composition of F5 allowed for a more rapid and nearly complete drug dissolution by the end of the study. Furthermore, the replicate centre points of the experimental design (F9 to F13) yielded tightly clustered final release values between 84.23% and 91.25%, demonstrating minimal variance and confirming the high reproducibility of the preparation methodology and the stability of the experimental framework.

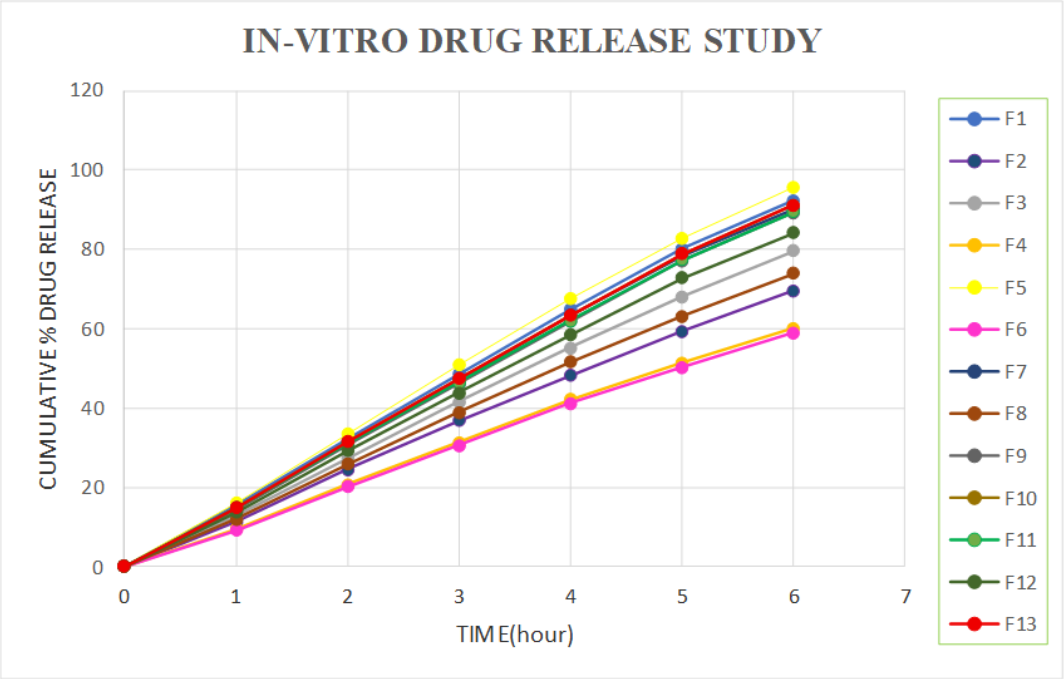

Figure no 5: Graphical representation of in-vitro drug release in different batches of formulation.

3.6 Optimization by Design Expert Software

Optimization was done by Design Expert software (Version 13.0.7.0, Stat-Ease). 2 factors were selected for optimizing the formulation, weight HPMC and Carbopol. To determine the best formulation, 2 responses i.e., in-vitro drug release and swelling index were considered. 13 formulations were suggested by the software and Central composite design was used to investigate the effect of the two independent variables and their potential interaction.

On the basis of the fit summary, a Quadratic model was chosen to be the best fit for in-vitro drug release, and a Linear model was chosen as the best fit for swelling index as suggested by the software. The outcomes of ANOVA indicated that the selected models were significant ($p < 0.05$) and the lack of fit (LOF) values were not significant (P Value > 0.05), indicating the reliability of the models. Specifically, the in-vitro release quadratic model showed an F value of 30.79 ($p = 0.0001$), a non-significant lack of fit ($p = 0.2601$), an Adjusted R^2 of 0.9254, and a Predicted R^2 of 0.7880 .For the swelling index, the linear model demonstrated an F value of 92.11 ($p < 0.0001$), a non-significant lack of fit ($p = 0.6231$), an Adjusted R^2 of 0.9382, and a Predicted R^2 of 0.9132.The numerical optimization tool provided 25 sets of optimal solutions among which 62.57 mg of HPMC and 18.43mg of Carbopol was selected by the software as the optimized concentration with a desirability of 1.000. The predicted values of response variables at this optimum were 88.21 % for in-vitro release and 59.19 for swelling index.

Table no. 5: Numerical test results of model adequacy checking for influence of independent variables on response variables.

Response	Suggested Model	Sequential p-value	Lack of Fit p-value	R^2	Adjusted R^2	Predicted R^2	Adequate Precision
In-Vitro Release	Quadratic	0.0016	0.2601	0.9565	0.9254	0.7880	16.0851
Swelling Index	Linear	<0.0001	0.6231	0.9485	0.9382	0.9132	27.9122

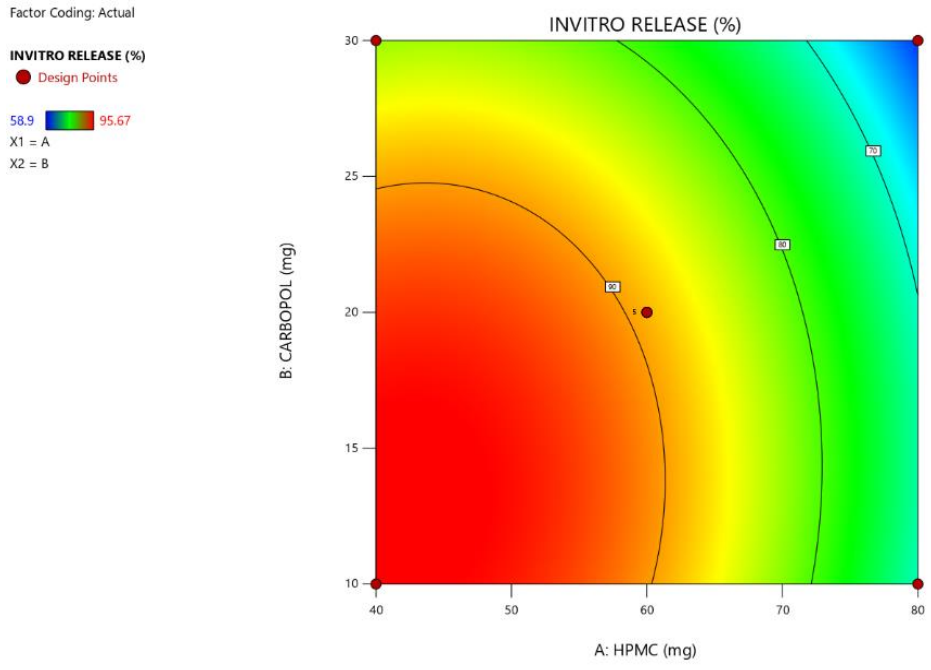

Figure no 6: Contour plot for In-vitro drug release.

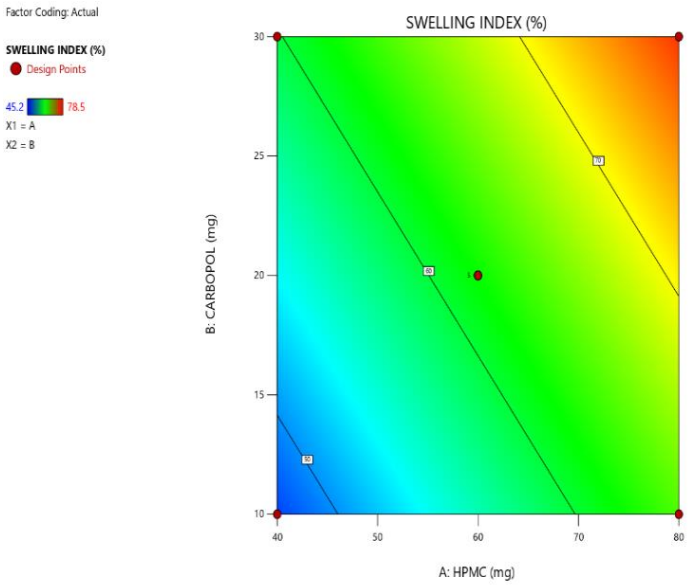

Figure no 7: Contour plot for swelling index.

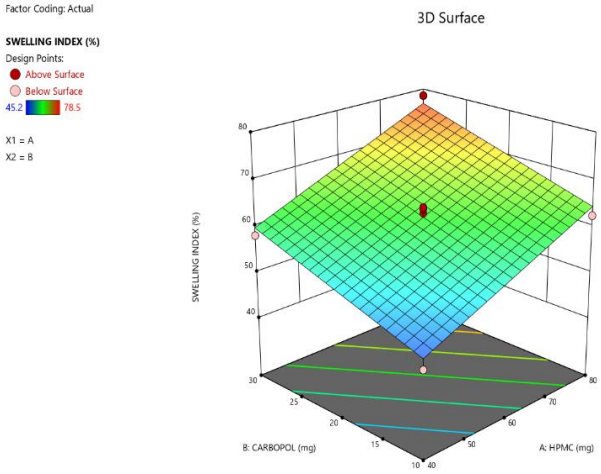

Figure no 8: 3-D response surface plot for swelling index.

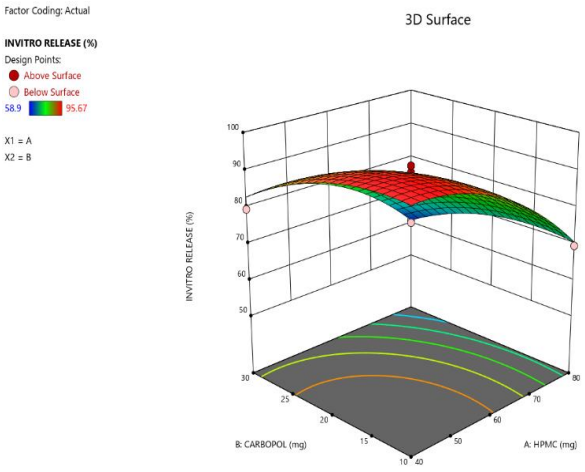

Figure no 9: 3-D response surface plots for in vitro release.

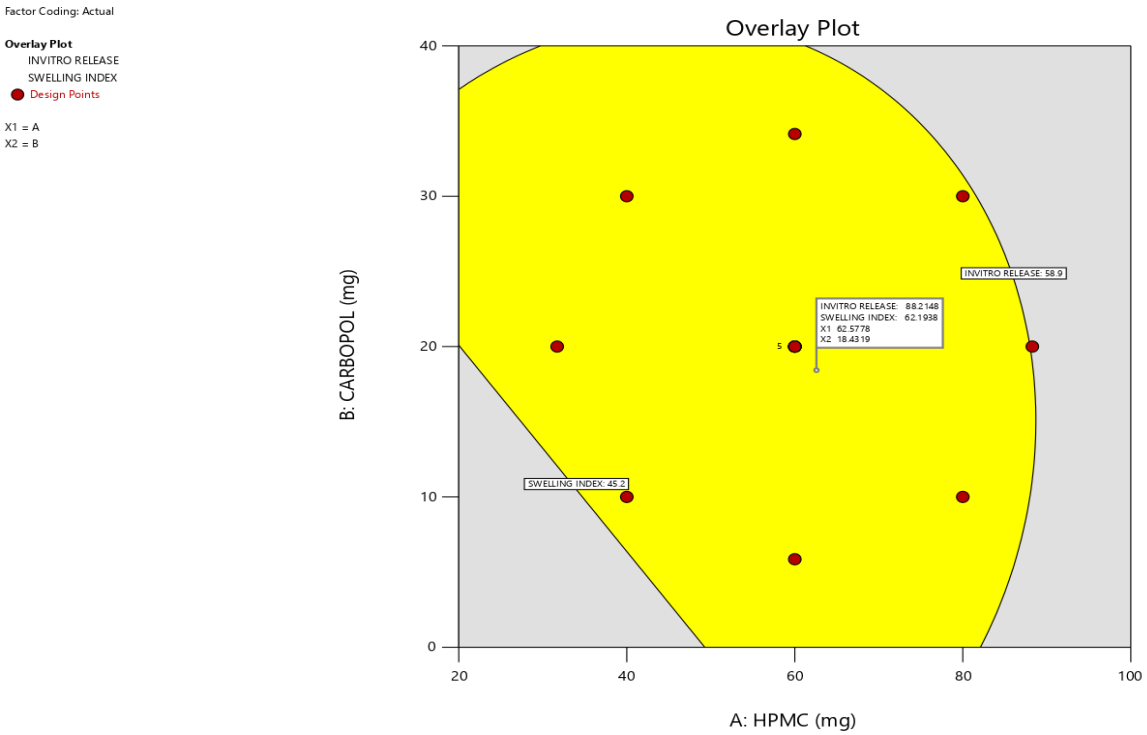

Figure no 10: overlay plot of optimized formulation of bromhexine hydrochloride buccal tablet.

Table no 6: Response value of predicted, experimental and percentage error obtained at optimal level of the factors.

Response	Predicted	Experimental	% Error
DRUG RELEASE	88.21	89.2	0.99
SWELLING INDEX	59.19	58.65	0.54

3.7 Kinetic studies

The in-vitro dissolution profile of the optimized mucoadhesive formulation was mathematically fitted into various kinetic models (Zero-order, First-order, Higuchi, and Korsmeyer-Peppas) to evaluate the mechanism of drug release.

The linear regression coefficient (R^2) was used to evaluate the best-fit model. The calculated R^2 values were found to be 0.9989 for Zero-order, 0.9563 for First-order, and 0.9184 for the Higuchi diffusion model. The formulation displayed the highest mathematical linearity with the Korsmeyer-Peppas model (R^2= 0.9995). The release exponent (n) derived from the slope of the Korsmeyer-Peppas plot was 1.0381. An exponent value of n > 0.89 confirms Super Case II transport, indicating that the drug release mechanism is regulated by a combination of polymer swelling, matrix erosion, and relaxation of the mucoadhesive chains.

Table no 7: Drug release kinetics of optimized formulation.

Zero order R^2	First order R^2	Higuchi R^2	Korsmeyar – Peppas R^2	n
0.9989	0.9563	0.9184	0.9995	1.03

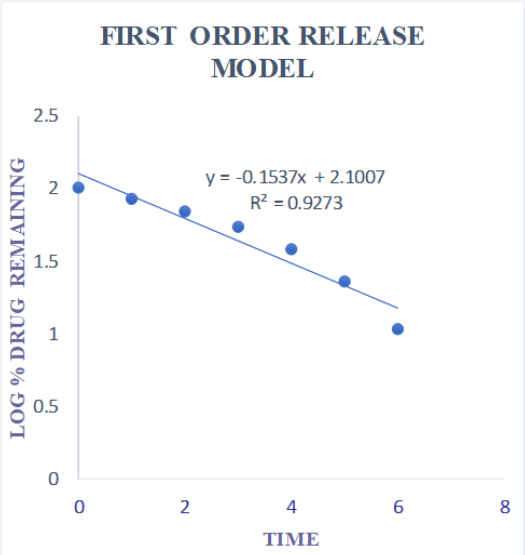

Fig no 11: Zero order release model.

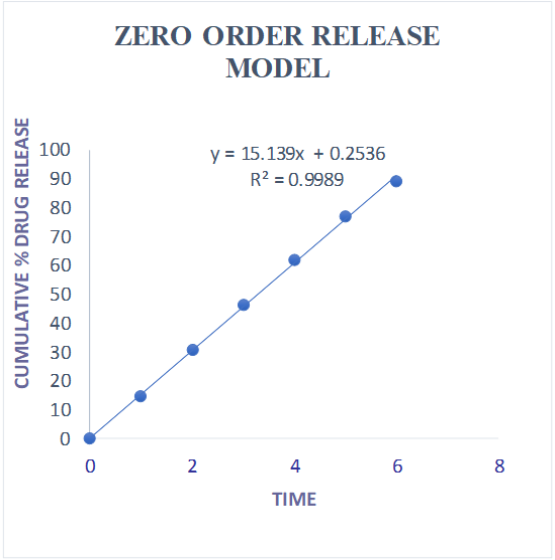

Fig no 12: First order release model.

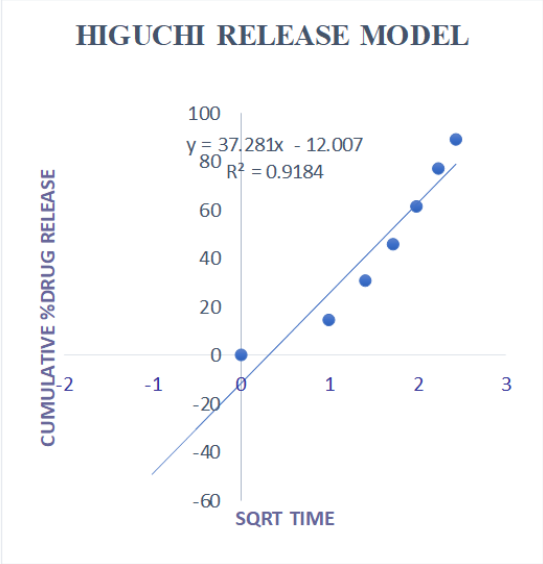

Fig no. 13: Higuchi release model.

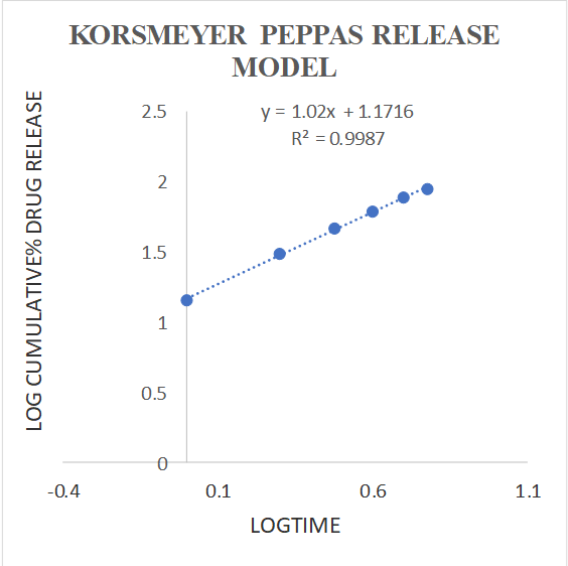

Fig no. 14: Korsmeyer Peppas release model.

Table no 8: Result of stability studies.

3.8 Stability studies

Storage condition	Sampling interval	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	In-vitro drug release (%)	Swelling index
40˚C ±2˚C at 75%±5% RH	Initial Study	5.42±0.94	0.29±0.75	96.86± 0.42	89.2±0.17	58.65±0.22
	30 days	5.34±0.23	0.28±0.02	96.81± 0.031	89±0.112	58.63±0.113
	90 days	5.3±0.39	0.22±0.01	96.75± 0.091	87.263±0.21	58.59±0.214
25˚C ±2˚C at 60%±5% RH	Initial Study	5.42±0.42	0.29±0.025	96.86± 0.061	89.2±0.31	58.63±0.313
	30 days	5.42±0.17	0.28±0.015	96.83± 0.11	89.1±0.01	58.62±0.15
	90 days	5.39±0.25	0.24±0.017	96.81± 0.15	88.9±0.37	58.6±0.12
5˚C ±3˚C	Initial Study	5.42±0.21	0.29±0.013	96.86± 0.15	89.2±0.13	58.63±0.34
	30 days	5.41±0.14	0.28±0.054	96.85± 0.15	89.1±0.161	58.62±0.21
	90 days	5.4±0.11	0.27±0.16	96.83±0.15	87.9±0.161	58.61±0.12

All values expressed as mean of ± SD, n = 3

The optimized formulation was subjected for stability studies as per ICH Guidelines 3 months. It showed that the prepared tablets passed stability studies with not much significant changes in hardness, friability, drug content, in-vitro drug release, swelling index. The results of stability data were shown in Table no 8.

4. CONCLUSION

In the study successfully developed mucoadhesive buccal tablets containing bromhexine hydrochloride in beta-cyclodextrin inclusion complex to overcome the challenges of poor aqueous solubility, slow dissolution, and low oral.

Bioavailability caused by extensive hepatic first-pass metabolism. Various formulations were prepared using distinct ratios of bio adhesive polymers. The selected formulation exhibited a high degree of experimental precision, yielding a verified drug release of 89.2% and a swelling index of 58.65, alongside an ideal surface pH.

The findings demonstrate that complexation with beta-cyclodextrin significantly enhances the solubility and dissolution characteristics of bromhexine hydrochloride within the buccal matrix. Direct absorption across the buccal mucosa successfully bypasses hepatic first-pass pathways, thereby markedly improving drug bioavailability. Consequently, this system offers a potential reduction in dosing frequency and a more rapid, consistent therapeutic response compared to conventional oral administration. This formulation is highly advantageous for patients requiring efficient mucolytic therapy for respiratory disorders, providing an effective route of administration that eliminates the need for swallowing.

Ultimately, the straightforward and stable preparation methodology makes this buccal delivery system a practical, and patient-compliant alternative to traditional solid dosage forms.

5. ACKNOWLEDGEMENT

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