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Formulation Development and *In Vitro* Evaluation of Mucoadhesive Buccal tablet Containing Mucolytic Agent

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ABSTRACT

The mucoadhesive buccal tablets with drug Bromhexine Hydrochloride was formulated by employing diverse ratios of excipients and using direct compression method. The polymers like Carbopol 934 p, Pectin, Sodium alignate, HPMC km4 and excipients like Mannitol, Microcrystalline cellulose, Magnesium stearate, and Talc were used in preparation of formulations. The formulated mucoadhesive buccal tablets were assessed for quality attributes like weight variation, hardness, thickness, friability, drug content, moisture absorption, surface pH, swelling index, in vitro drug release studies, and stability studies. Among the various formulations studied formulations F5, F10 and F15 demonstrated comparatively better results. On analyzing regression co efficient values of the optimized batches, it was found that formulations F5, F10, and F15 exhibit Higuchi's release kinetic. The data was fitted into the Korsemeyer- Peppas equation which specifies a coupling of diffusion and erosion mechanism for release of drug. Based on the study results it is concluded that development of mucoadhesive buccal tablets of bromhexine hydrochloride is one of the alternative route of administration to avoid first-pass metabolism and to improve the bioavailability of the drug through buccal mucosa and to improve the release of drug for extensive period of time. In addition, these formulations also reduce the need of frequent administration thereby enhancing the patient compliance. Findings provide evidence that these formulations have a strong prospective as buccal drug delivery system. However, further studies are essential to understand the in vivo performance and permeation aspect of the formulations to finalize the robust formulation.

Keywords: Bromhexine hydrochloride, Buccal drug delivery system Carbopol, Pectin, Sodium alginate, HPMC, Mannitol, MCC, Magnesium stearate, Talc, Moisture absorption, Surface pH, Swelling index, *In vitro* drug release studies, Release kinetics and Stability studies.

INTRODUCTION

Bioadhesive drug delivery formulations were launched around the year 1947 when gum tragacanth and dental adhesive powder mixture is employed for applying penicillin to the oral mucosa; this ultimately became Orabase [1]. The buccal anatomy is as follows, the buccal mucosa lines the inner cheek, and the buccal drug delivery formulations are intended to be placed in the mouth between the upper gingiva (gums) and cheek for the treatment of local and systemic conditions. The buccal route is one of the prospective routes for typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides, as well as conventional small drug molecules. The oral cavity is identified as an effective route for local and systemic drug delivery [2]. In recent years; there has been ever-increasing interest on the use of bioadhesive polymers to control the delivery of biologically active agents systemically or locally. These bioadhesive systems are useful for the administration of drugs, which are susceptible to extensive gastrointestinal degradation and first pass metabolism [3]. Buccal bioadhesive system appears to be attractive because it avoids significant limitations of traditional routes and first pass metabolism. Buccal drug delivery necessitates the use of mucoadhesive polymer, as these dosage forms should ideally adhere to the mucosa and endure salivation, tolerate tongue movement and swallowing conditions for the significant period of time [4].

MATERIALS AND METHODS

Materials

The drug Bromhexine hydrochloride and various polymers, excipients such as Sodium alginate, Carbopol (carbomer 934 p), Pectin, HPMC Km[4] (Hydroxypropyl methyl cellulose), Mannitol, Microcrystalline cellulose, Magnesium stearate, Talc has been procured from Pharmaceutical industry. All other reagents used is of analytical grade.

Equipments used: Electronic weighing balance, Compression machine, Tablet hardness tester, vernier caliper, Friabilator, Melting point determination apparatus, Hot air oven, pH-meter, Dissolution apparatus, UV-Visible spectrophotometer.

EXPERIMENTAL METHODOLOGY

Identification of drug

The melting point of bromhexine Hcl was determined by capillary method [5].

Estimation of bromhexine

Estimation of absorption maxima (λ max): 10 mg of bromhexine Hcl was accurately weighed and transferred to 100 ml volumetric flask. The drug was dissolved in phosphate buffer pH 6.8 and the volume was made up to 100 ml to obtain a stock solution of 100 µg/ml. One ml of this stock solution was again diluted with phosphate buffer pH 6.8 up to 10 ml to obtain a solution of 10 µg/ml. The resulting solution was scanned between 200 nm to 400 nm in a double beam UV-Visible spectrophotometer (Lambda-35).

Preparation of calibration curve in phosphate buffer pH 6.8: 10 mg of bromhexine Hcl was accurately weighed and transferred to 100 ml volumetric flask. The drug was dissolved in 2 ml DMF and the volume was made up to 100 ml using phosphate buffer pH 6.8 to obtain a stock solution of 100 µg/ml (stock solution I). One ml of this stock solution was again diluted with phosphate buffer pH 6.8 up to 10 ml to obtain a solution of 10 µg/ml (stock solution II). From stock solution II aliquots of 2, 4, 6, 8 ml were transferred to a series of 10 ml volumetric flasks. The volume was made up with phosphate buffer pH 6.8 fluids to give 2, 4, 6 and 8 µg/ml of concentration. The absorbance of these solutions was measured at 254 nm against blank.

FORMULATION OF BUCCAL TABLET

Preparation of buccal tablets

The formulations are made by varying the Drug: polymer ratio, the drug quantity is kept constant in all formulations and formulation F1 to F5 contains pectin, formulations F6 to F10 contains sodium alginate and formulations F11 to F15 contains carbopol along with other excipients composition of formulations are presented in (Table 1). The drug-excipient mixture was prepared and compressed using 8 mm die by a tablet press.

Table 1: Composition of Formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Drug: polymer mixture	1:1	1:1.25	1:1.50	1:1.75	1:2	1:1	1:1.25	1:1.50	1:1.75	1:2	1:1	1: 125	1: 1.50	1: 1.75	1:2
Drug (mg)	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Pectin (mg)	4	4	4	4	4	--	--	--	--	--	--	--	--	--	--
Sodium alginate (mg)	--	--	--	--	--	4	4	4	4	4	--	--	--	--	--
Carbopol(mg)	-	-	-	-	-	-	-	-	-	-	4	4	4	4	4
HPMC k4M (mg)	4	6	8	10	12	4	6	8	10	12	4	6	8	10	12
Mannitol(mg)	134	132	130	128	126	134	132	132	128	126	134	132	130	128	126
MCC (mg)	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Magnesium Stearate (mg)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Talc (mg)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Total weight (mg)		200	200	200	200	200	200	200	200	200	200	200	200	200	200

Steps involved in formulation Preparation

• Weighing the calculated quantity of the drug and excipients.

• Mixing of ingredients.

• Lubrication with (magnesium stearate) and glidant (talc).

• Compression of tablets.

EVALUATION TESTS

The drug excipient mixture was subjected for following pre compression evaluations for blend characterization.

Pre Compression Parameters [6]

Bulk density (BD)

Apparent bulk density was determined by using the graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined.

The bulk density was calculated by applying formula=Bulk Density=Weight of powder/bulk volume

Tapped density (TD)

The measuring cylinder with a known mass of blend (M) was tapped for a fixed time (100 taps). The minimum volume (Vt) occupied in the cylinder and weight of the blend was measured. The tapped density (ρt) was calculated using formula=Weight of powder/Tapped volume.

Angle of repose (θ)

Angle of repose is the tan inverse of angle between height of powder pile and the radius of the base of conical pile. Angle of repose was determined using flow through funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) is obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the following equation. Values for angle of repose less than or equal to 30 degrees suggest a free flowing material and values greater than or equal to 40 degrees suggest poorly flowing material.

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

Where, θ is the angle of repose, h is height of pile; r is radius of the base of pile.

Hausner's ratio

Hausner ratio is defined as bulk volume to tapped volume or tapped density to bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Hausner's ratio is determined by the formula: Tapped density/Bulk density.

Carr's index (or) % compressibility

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size distribution of the blend. Blend with compressibility values lesser than about 15% has been found to exhibit good flow properties. Tapped and Apparent bulk density measurements can be used to estimate the compressibility of a material.

Carr's index (or) % compressibility is determined by the formula=[(Tapped density-Bulk density) × 100]/Tapped density.

POST COMPRESSION PARAMETERS

Following Critical Quality attributes were determined after tablet compression process

Physical appearance [7]

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, color,

presence or absence of odor, taste, surface texture and consistency of any identification marks.

Weight variation [8]

The weight variation is a valid indication which helps to determine the related variation in the drug content. Hence, determination of weight is an important assessment.

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of the tablet was determined from the collective weight. The acceptance criteria for the weight variation is kept as-Not more than two tablets deviate from the percentage given below from the average weight and none deviate by more than twice the percentage shown.

Average weight=Weight of 20 tablets/20

Thickness and diameter

The thickness and diameter of the tablet was measured using vernier caliper. 10 tablets were taken from individual formulations, thickness and diameter was measured using vernier caliper in mm.

Hardness

The tablet hardness is the force required to break the tablet. The tablet hardness is the important attribute which determines the dissolution profile and drug release. It is also essential to maintain the strength of tablet until it is consumed. The Pfizer hardness tester was used to determine the tablet hardness. The tablets were held between a fixed jaw and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet is cracked. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.

Friability

Friability of the tablet is determined by using 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 a height of 6 inches in each revolution. Pre weighted sample of 10 tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dedusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage.

$$\%\text{Friability}=\frac{\text{Initial weight}-\text{Final weight}}{\text{Initial weight}} \times 100$$

Drug content

To determine the drug content twenty tablets were weighed and powdered in a mortar. Accurately weighed a quantity of the powder equivalent to about 10 mg of bromhexine Hcl and dissolved by using 2 ml of Dimethyl formamide diluted to 100 ml with phosphate buffer pH 6.8 in 100 ml volumetric flasks. It was shaken for 15 minutes and filtered. 1 ml of the filtrate was diluted to 10 ml with phosphate buffer pH 6.8. The absorbance of the resulting solution was measured at λ-max 254 nm and the content of bromhexine Hcl was calculated from the absorbance obtained.

Moisture absorption study

The moisture uptake studies [9] provided an indication about the relative moisture absorption capacities of polymers and an idea whether the formulations maintain their integrity after absorption of moisture. The study was carried out as per procedure reported earlier (Velmurugan et al.). Briefly, the procedure is as follows agar (5% w/v) was dissolved in hot water, transferred into petriplates and allowed to solidify. Six tablets from each formulation series were placed in vacuum oven overnight prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane. They were then incubated at 37°C for one hour, removed and reweighed.

The percentage moisture absorption was calculated by using the formula.

$$\%\ \text{Moisture absorption}=\frac{\text{Final weight}-\text{Initial weight}}{\text{Initial weight}} \times 100$$

Surface pH study

The surface pH is determined for buccal tablets to investigate the possibility of any side effect *in vivo*. An acidic or alkaline pH may irritate the buccal mucosa, hence the surface pH of tablet ought to be almost neutral. In this method

3 tablets were allowed to swell by placing it in contact with 1 ml of phosphate buffer pH 6.8 for 2 hours at room temperature. The pH was determined by bringing the electrode in contact with the tablet surface and allowing the surface to equilibrate for 1 minute.

Swelling index

Swelling index is studied to understand the swelling behavior, 3 tablets were weighed individually (W1) and then the tablets were placed in agar gel plates 1%-2% in a Petri-dish with the core (drug polymer layer) facing the gel surface, incubated at 37 ± 1°C for up to 6 hrs. At regular intervals of time, the swollen tablets were removed from Petri-dish; the excess water is removed with the help of a filter paper and weighed again (W2). The Swelling Index (SI) was calculated by using the formula.

$$\text{Swelling Index} = \frac{W2 - W1}{W1} \times 100$$

***In vitro* drug release study [10]**

***In vitro* dissolution Procedure:** For the oral dosage forms, the *in vitro* drug dissolution shall be performed in the dissolution medium which simulate the *in vivo* conditions (actual physiological conditions). The *in vitro* drug release studies for the prepared formulations were performed for the period of 8 hours using an electro lab model dissolution tester USP Type-II apparatus (rotating paddle) set at 50 RPM maintaining temperature of 37 ± 0.5°C formulations was placed in 900 ml of the medium (6.8 pH buffer solution). At specified intervals, 10 ml of samples were withdrawn from the dissolution medium and replaced with fresh medium to maintain the constant volume of medium and also to keep up sink condition. The absorbance of the sample solution was measured at 254 nm for the presence of drug, using a UV-visible spectrophotometer.

Calculation for dissolution:

$$\% \text{ Drug release} = \frac{\text{Concentration} \times \text{Dilution factor} \times \text{Volume of media}}{\text{Label claim} \times 1000} \times 100$$

Concentration calculated by: Concentration=Absorbance-Intercept/Slope

RELEASE KINETICS

In order to understand the mechanism [11] and kinetics of drug release, the results of the *in vitro* drug release study were fitted into various kinetic models like zero order (% release *vs* time), first order (log% unrelease *vs* time), Higuchi matrix (% release *vs* square root of time). In order to characterize a model which will stand for a better fit for the formulation. The drug release data further evaluated by applying Korsemeyer Peppas equation, $Mt/M\infty=ktn$, where Mt is the amount of drug released at time t and $M\infty$ is the amount released at time ∞, the $Mt/M\infty$ is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent, a measure of the primary mechanism of drug release. R2 values were calculated for the linear curves obtained by regression analysis of the above plots.

STABILITY STUDY

The stability [12] study was carried out on the optimized formulation as per ICH guidelines Q1C. The Optimized formulations were packed in rubber stoppered vials and loaded in stability chamber. The stability study was performed at 40 ± 2 °C / 75 ± 5 % RH for 1 month. At the end of the study, the samples were examined for drug content, *In vitro* drug release, and swelling index.

RESULTS AND DISCUSSION

Identification of rug

Melting point: The purity of the drug shall be determined by studying the melting point, the melting point of the drug bromhexine hydrochloride was found to be 235°C which was in the range as given in literature; hence the drug could

be confirmed as pure.

Estimation of bromhexine

Determination of absorption maxima: The UV absorption maximum of the drug bromhexine hydrochloride in phosphate buffer pH 6.8 was found to be 254 nm, when scanned between 200-400 nm by UV-visible spectrophotometer.

Calibration curve of bromhexine hydrochloride in phosphate buffer pH 6.8: The calibration curve of the drug bromhexine hydrochloride was prepared by phosphate buffer pH 6.8. The linearity data and calibration curve of the drug is depicted in (Figure 1) and (Table 2) summarizes the concentration and absorbance values. The R2 value is found to be 0.999.

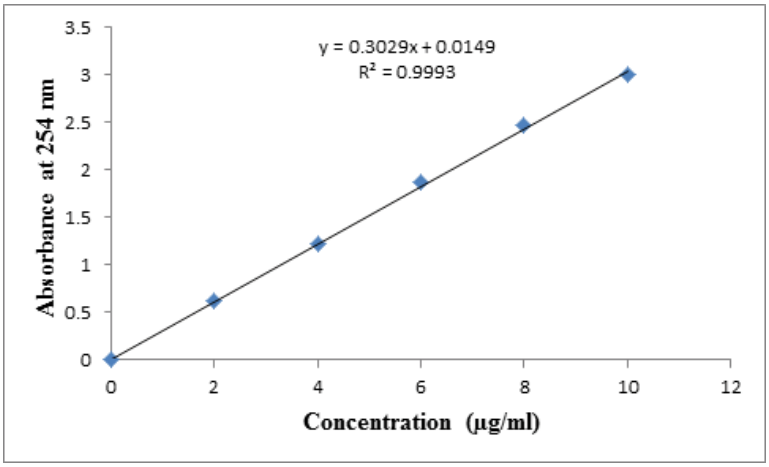

Figure 1: Linearity curve of the drug bromhexine hydrochloride in phosphate buffer pH 6.8.

Table 2: Preparation of standard plot of pH 6.8 phosphate buffer

Sr.No	Concentration (µg/ml)	Absorbance at 254nm
1	0	0
2	2	0.622
3	4	1.216
4	6	1.865
5	8	2.473
6	10	3

Evaluation results of buccal tablet

The blend is evaluated for physical parameters to understand the suitability of the blend for direct compression technique. The precompression attributes and results are summarized in (Table 3). The angle of repose values of the formulations lies within 30 which demonstrate good flowability of the prepared blends. The Carr's index and Hausner's ratio values lies well within limit which indicate that powder blend has good flow property with good compressibility and appropriate for direct compression procedure.

Table 3: Pre Compression Parameters

Batch	Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index %	Hausner's ratio	Angle of repose
F1	P1	0.47	0.57	13.49	1.18	22.13
F2	P2	0.44	0.59	13.21	1.14	24.38
F3	P3	0.38	0.42	15.03	1.09	26.38
F4	P4	0.42	0.48	14.46	1.14	25.51
F5	P5	0.40	0.56	11.5	1.11	26.56
F6	S1	0.46	0.54	14.33	1.17	24.9

F7	S2	0.41	0.48	12.59	1.14	23.05
F8	S3	0.48	0.57	14.89	1.18	25.03
F9	S4	0.47	0.54	13.54	1.24	25.04
F10	S5	0.43	0.53	14.32	1.23	22.06
F11	C1	0.47	0.58	12.82	1.23	24.98
F12	C2	0.45	0.52	15.02	1.15	25.38
F13	C3	0.41	0.49	13.74	1.19	26.14
F14	C4	0.48	0.54	15.09	1.12	25.52
F15	C5	0.40	0.47	14.48	1.17	22.38

POST COMPRESSION PARAMETERS

The compressed tablets were subjected for various evaluations to determine the suitability of the prepared formulations (Figure 2) depicts the physical appearance of the tablets which comprises of different polymers in its composition.

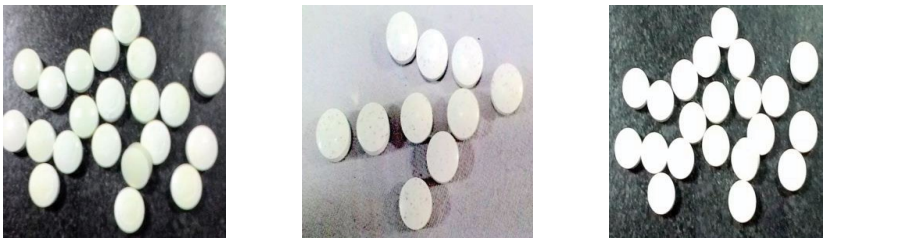

Figure 2: prepared formulations

Physical appearance of the tablet

Color: The color of the tablet was found to be white.

Shape: Shape of the tablet was found to be circular.

Texture: The texture of the tablet was found to be smooth

The hardness of tablets of different formulation (1 to 15) was determined as per standard procedure (Figure 3). The average hardness of tablet was found to be 4.10 to 4.95 kg/ cm^2 results are presented in (Table 4). This confirms that the tablets have sufficient strength to withstand the attritions. The average thickness of tablets was determined and results are presented in (Table 4). The maximum and minimum average thickness of tablet was found to be 3.09 and 3.01 respectively.

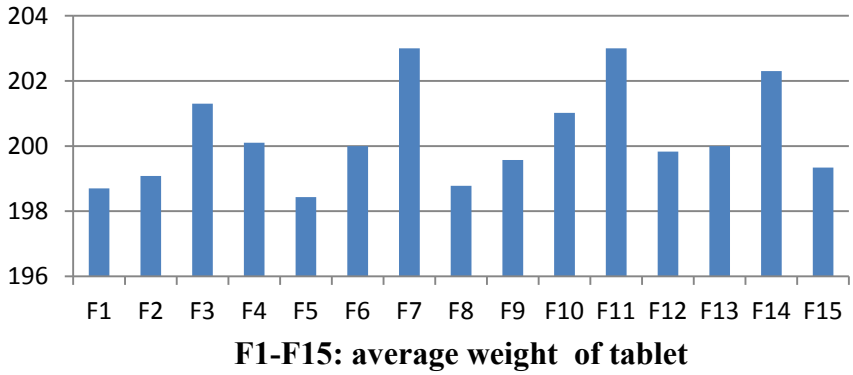

Figure 3: depicts weight variation of formulations F1-F15

It was evident from the above table that all the trial formulations comply with the standard specification mentioned in the USP for average weight, weight variation and friability. Also the thickness and hardness parameters of the prepared

tablets complied within the established In-house specifications. (Figure 4) depicts the physical characterization of tablets.

Table 4: Summarizes physical parameters rsults of prepared table

Batch	Formulation Code	Average weight of tablet(mg)	Average thickness (mm)	Average hardness (kp)	Friability (%)
F1	P1	198.7	3.03	4.57	0.37
F2	P2	199.08	3.01	4.85	0.29
F3	P3	201.3	3.08	4.64	0.22
F4	P4	200.1	3.06	4.67	**0.41**
F5	P5	198.43	3.02	4.1	**0.43**
F6	S1	200	3.01	4.26	**0.22**
F7	S2	203	3.09	4.18	0.28
F8	S3	198.78	3.03	4.89	0.19
F9	S4	199.57	3.05	4.95	0.18
F10	S5	201.02	3.06	4.76	0.26
F11	C1	203	3.06	4.69	0.43
F12	C2	199.83	3.08	4.81	0.37
F13	C3	200	3.07	4.92	0.28
F14	C4	202.3	3.04	4.87	0.24
F15	C5	197.98	3.06	4.65	0.34

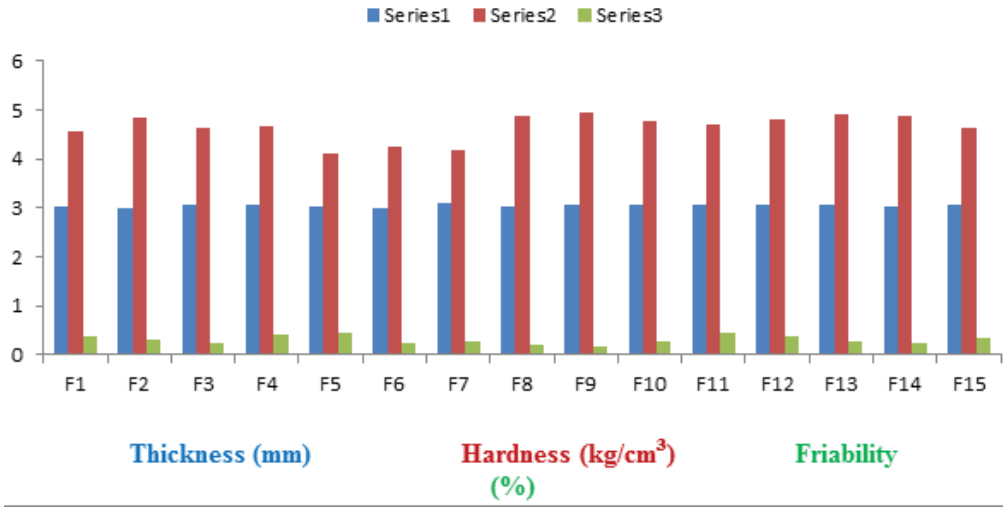

Figure 4: Physical characterizations of tablets F1-F15

Drug content

The drug content of the formulations (F1 to F15) was evaluated and the results are presented in (Table 5 and Figure 5). The maximum drug percentage of drug was found to be 99.59% for formulation F3 and the minimum percentage of drug content was found to be 94.09% for formulation F11. Hence it is concluded that all the formulations have drug percentage within the limits.

Moisture absorption

Moisture absorption studies were performed to evaluate the integrity of the formulation upon exposure to moisture and the results are summarized in (Table 5). The hygroscopic nature of the polymers is one of the important property that affect moisture absorption. The increasing moisture absorption of formulations may be due to the increased concentration of polymer mixture for formulations F5-F15. The moisture absorption was more in formulations containing Carbopol and HPMCK4M group when compared to formulation containing sodium alginate and HPMCK4M, same as Pectin and HPMCK4M. The comparative moisture absorption for formulations was in order of

HPMCK4M+Pectin<HPMCK4M+Sodium alginate<HPMCK4M+Carbopol (Table 5 and Figure 5). This may perhaps be due to the more hydrophilic nature of Carbopol.

Surface pH

Table 5: Evaluation Parameters of formulations F1-F15.

Batch	Formulation code	Drug content %	% Moisture absorbed (8 hours)	Surface pH	Swelling index (6 hours)
F1	P1	97.89	22.73	6.52	73.53
F2	P2	95.57	26.81	6.23	76.08
F3	P3	99.59	28.08	6.56	72.53
F4	P4	97.67	31.23	6.21	76.87
F5	P5	98.52	34.65	6.65	83.52
F6	S1	95.12	29.59	6.35	69.89
F7	S2	97.32	32.12	6.77	75.76
F8	S3	96.56	34.03	6.27	79.64
F9	S4	99.54	34.23	6.18	80.51
F10	S5	95.5	35.15	6.38	83.84
F11	C1	94.08	24.32	6.34	69.84
F12	C2	95.65	26.45	6.23	73.92
F13	C3	97.39	30.03	6.38	80.85
F14	C4	94.98	34.52	6.33	88.64
F15	C5	99.04	35.83	6.4	94.81

The prepared formulations were subjected to surface pH measurement. Tablets showed surface pH values in range of 6.18 to 6.77 (Table 5 and Figure 5) that indicates no risk of mucosal damage or irritation.

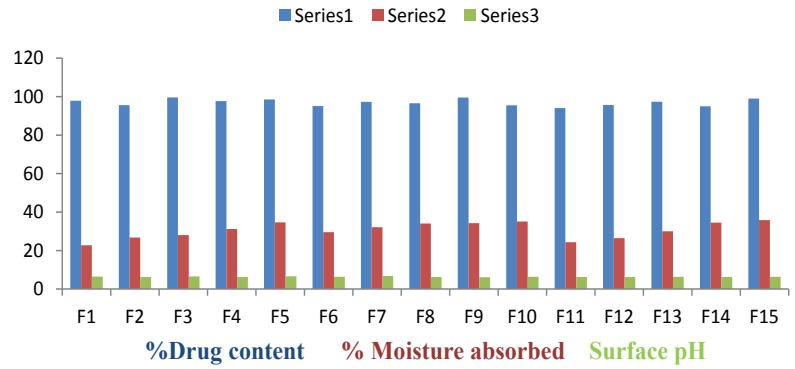

Figure 5: Percentage of Drug content, Moisture absorption and Surface pH of formulations F1-F15.

Swelling index

The swelling index was determined for prepared tablets, swelling index increased proportionally with the weight gain of the tablets, with the increased rate of hydration as shown in (Table 5 and Figure 6). The maximum swelling was seen in formulation F15 containing increased concentration of carbopol polymer.

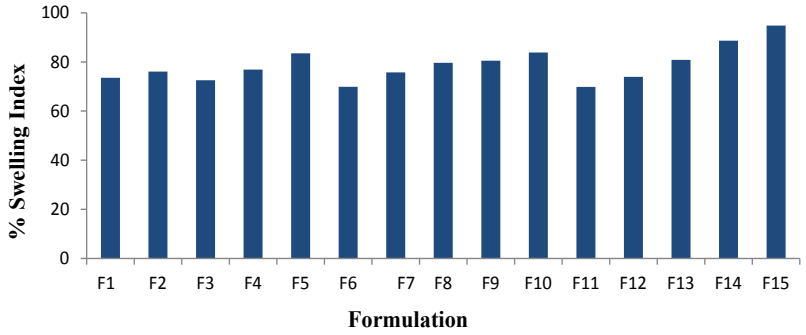

Figure 6: Swelling Index of Formulations F1-F15

In vitro drug release study

In vitro dissolution studies (dissolution profile in pH 6.8 phosphate buffer) (Table 6) summarizes the results observed for formulations at different time points till 8 hrs. Maximum drug release was found in formulation F15 which contains the carbopol polymer and minimum release is observed in formulation F1 which contains pectin polymer. (Figures 7-9) illustrates the release pattern of the tablets.

Table:6 *in vitro* dissolution studies

Time (hr)	% Drug release														
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**
	P1	**P2**	**P3**	**P4**	**P5**	**S1**	**S2**	**S3**	**S4**	**S5**	**C1**	**C2**	**C3**	**C4**	**C5**
0 hour	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1 hour	19.3	23.3	26	28.4	29.21	22.5	31.2	37.7	40.3	43.2	35	36.1	38.5	40.7	47.8
2 hour	27.9	35.9	37.4	42.1	43.54	31.5	39.4	45.4	49	52.1	43	48.7	50.2	68.7	78.1
3 hour	38.5	44.2	49.9	53	56.32	33.8	47.6	53.1	58.3	64.7	57.3	63.2	69.5	75.2	84.2
4 hour	43	51.3	58.2	62.7	64.41	43.2	66.7	71	77.6	80.5	65.9	72.3	76.5	83.1	87
5 hour	49.2	57.2	64.2	70.2	69.87	53.2	73.1	77.2	82.1	85.8	78.4	83.2	85.1	88.7	92.1
6 hour	56.7	62.3	69.6	74.7	75.07	70.8	79	83.1	85.9	87.5	85.2	88.5	90.7	93	95.1
7 hour	67.2	73.8	78.2	80.3	83.12	77.2	83.6	88.3	91.4	93.1	89.29	92.31	94.86	96.1	97.2
8 hour	78.4	80.1	83.4	86	90.14	85.3	89	93.1	95.02	96.9	93.51	95.21	97.36	98.53	99.3

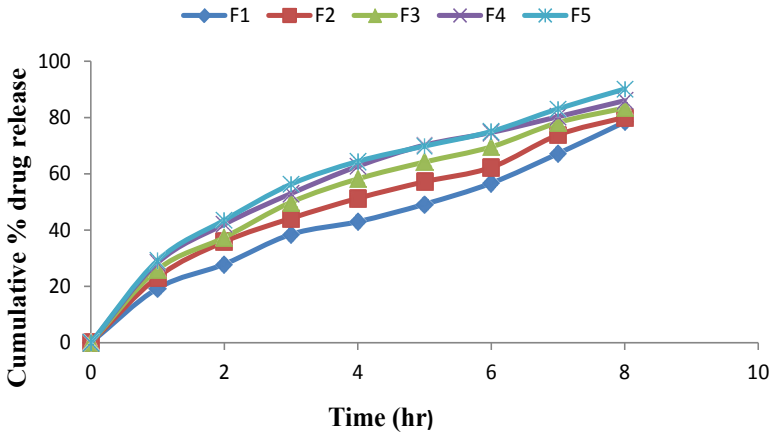

Figure7: Formulation F1-F5 *In vitro* drug release.

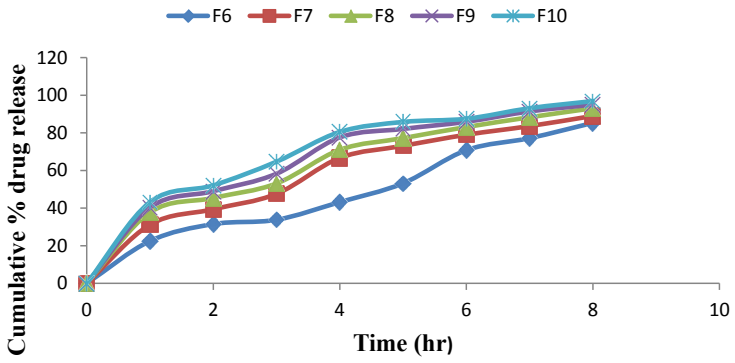

Figure 8: Formulation F6-F10 *In vitro* drug release.

In vitro drug release profile of the identified batches F5, F10 and F15 are shown in (Table 7) and release pattern in depicted in (Figure 10). The formulation F5 with pectin polymer showed maximum drug release. The formulation

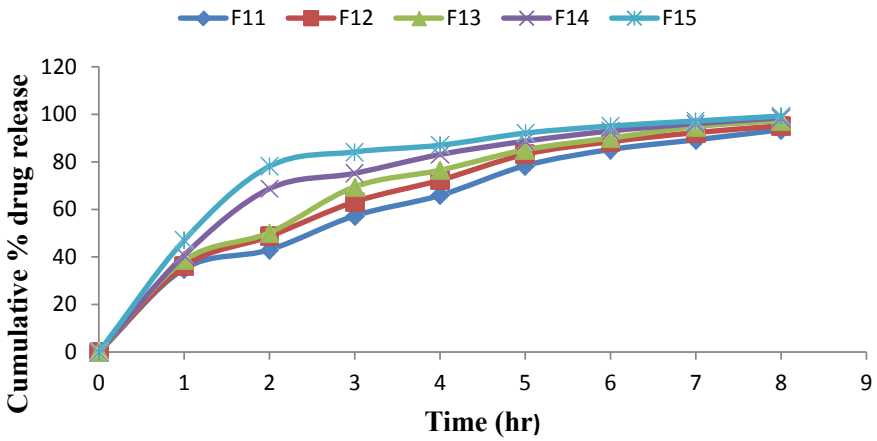

Figure 9: Formulation F11-F15 *In vitro* drug release study.

Table 7: *In vitro* drug release profile of optimized batches.

Time (hours)	F5	F10	F15
0	0	0	0
1	29.21	43.2	47.8
2	43.54	52.1	78.1
3	56.32	64.7	84.2
4	64.41	80.5	87
5	69.87	85.8	92.1
6	75.07	87.5	95.2
7	83.12	93.1	97.2
8	90.14	96.9	99.3

F10 with sodium alginate polymer showed maximum release and the formulation F15 with carbopol polymer showed maximum release.

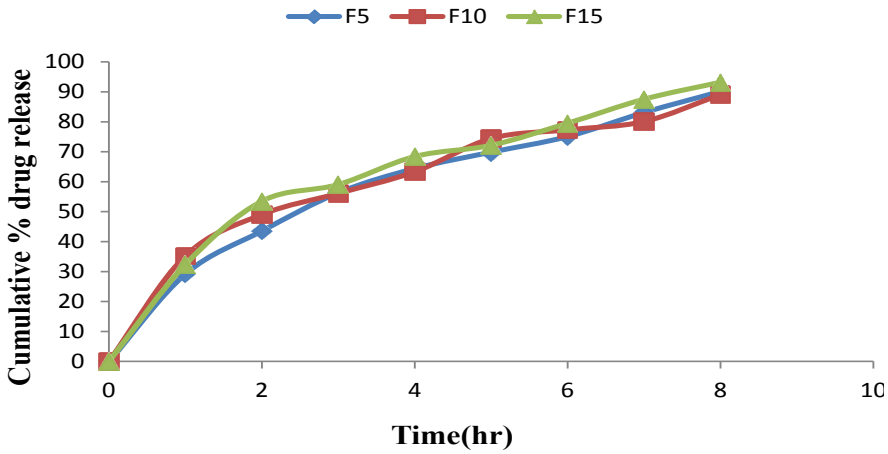

Figure 10: *In vitro* drug release profile of optimized batches.

Release kinetics

The results of curve fitting into the mathematical models are summarized in (Table 8). The results indicate the drug release behavior from the formulations. The *In vitro* release profiles of drug from the optimized batches could be best expressed by Higuchi's equation as the plots showed highest linearity (r2=0.908–0.997).

Stability study results for formulations

The samples of optimized batches (F5, F10, and F15) were kept in accelerated condition (40° ± 2°C/75% ± 5% RH)

Table 8: *In vitro* drug release profile of optimized batches for release kinetic studies.

Batch	Zero order		First order				Higuchi			Korsemeyer- Peppas		
	B	A	R2	B	A	R2	B	A	R2	K	N	R2
F5	9.981	16.92	0.915	0.162	0.93	0.527	31.86	0.748	0.997	1.331	0.554	0.902
F10	10.48	25.14	0.844	0.158	1.018	0.471	34.58	4.566	0.982	1.296	0.493	0.992
F15	9.828	36.24	0.688	0.151	1.095	0.413	34.52	13.13	0.908	1.258	0.444	1.062
B=Slope, A=Intercept , R2=Square of Correlation Coefficient , n=Diffusion exponent												

Table 9: Physical evaluation and assay results for samples drawn from stability study.

Sr.No.	Parameters	Zero time			After 1 month		
		F5	F10	F15	F5	F10	F15
1.	Assay (%)	98.52	95.5	99.04	96.45	94.52	98.79
2.	Friability (%)	0.43	0.26	0.34	0.47	0.32	0.38
3.	Hardness (kg/cm2)	4.1	4.76	4.65	4.02	4.48	4.23

Table 10: *In vitro* dissolution data of batches F5, F10, F15 after accelerated stability study.

Time (hour)	Cumulative % release (Initial			Cumulative % release (After storage at 40° c for 1 month)		
	F5	F10	F15	F5	F10	F15
0	0	0	0	0	0	0
1	29.21	43.2	47	28.85	42	46.1
2	43.54	52.1	78.1	42.96	51.8	77.4
3	56.32	64.7	84.2	54.68	64.2	83.5
4	64.41	80.5	87	63.01	79.6	86.3
5	69.87	85.8	92.1	67.83	84.9	91.5
6	75.07	87.5	95.1	74	86.8	94.8
7	83.12	93.1	97.2	82.03	92.2	96.5
8	90.14	96.9	99.3	88.5	95.3	98.1

for one month. The samples were analyzed for physical evaluation, assay and dissolution. The results are presented in Tables 9 and 10. The results showed that there was no change in physicochemical parameters of tablets. Drug content and friability were found in acceptable limit and similar drug release profiles. Hence the prepared mucoadhesive buccal tablets of Bromhexine hydrochloride were found stable at 40° ± 2°C/75% ± 5% RH.

CONCLUSION

The aim of research work was to formulate and evaluate the "mucoadhesive buccal tablets of Bromhexine Hydrochloride by direct compression technique" by using various polymers and Excipients in order to develop the finest formulation. In the current study an attempt was made to prepare mucoadhesive buccal tablets of the drug Bromhexine Hydrochloride by direct compression method by using various mucoadhesive polymers like pectin, sodium alginate, Carbopol and HPMC k4m. Totally 15 formulations were prepared [Pectin (F1-F5), Sodium alginate (S1-S5) and Carbopol (C1-C5)]. Formulations F5, F10, F15 showed good results for parameters like hardness, friability, drug content, dissolution study, moisture absorption, swelling index, and stability studies. Based on the results obtained, it is concluded that the formulated Bromhexine Hydrochloride tablets encompass a strong potential for use as buccal drug delivery system. However, extensive *in vivo* and stability studies are essential to finalize the robust formulation with desirable quality attribute.

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