FORMULATION DEVELOPMENT AND EVALUATION OF CANDESARTAN BUCCAL TABLETS

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ABSTRACT

Among the various routes of drug delivery oral route is the most widely accepted route by the patients for delivery of therapeutically active drugs. So buccal route was widely used and convenient method for drug administration. Aim of the present study was to prepare and characterize mucoadhesive buccal tablets of Candesartan by direct compression method using different mucoadhesive polymers such like carbopol, hydroxypropyl methylcellulose and sodium alginate. Nine formulations were prepared while (F1) to (F3) were prepared by taking individual concentrations whereas all the remaining formulations prepared by taking combinations of polymers. Formulations (F4) to (F6) were composed of carbopol, hydroxypropyl methylcellulose and sodium alginate in ratio of 1: 2. Formulations (F7) to (F9) were composed by taking polymers like carbopol, hydroxypropyl methylcellulose and sodium alginate in 1.5: 1.5 ratios. Candesartan is an angiotensin II receptor antagonist which is widely used for the treatment of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction following myocardial infraction and heart failure. The prepared buccal tablets were characterized for thickness, hardness, weight variation, drug content, friability and *in vitro* drug release. Among all the formulations the (F3) formulation with sodium alginate showed 93% drug release, while (F7) with equal ratios 1.5:1.5 ratios of hydroxypropyl methylcellulose and sodium alginate showed 98% drug release within 8 hrs. All the formulations were following zero order release kinetics.

***Key words*:** Buccal tablet, Candesartan, Carbopol, Hydroxypropyl methylcellulose, Sodium alginate.

INTRODUCTION

Historically the oral route of drug administration has been the one used most for both conventional as well as novel drug delivery.[1] The concept of mucosal adhesion or mucoadhesive was introduced into controlled drug delivery area in the early 1980's, which is become a major part of novel drug delivery system in the recent era. Some of the potential sites for attachment of any mucoadhesive system are included in buccal cavity, nasal cavity, eyes, vagina, rectal, sublingual route and gastrointestinal area.[2] The term bioadhesion is typically used to describe the adhesion between polymer either synthetic of natural to soft tissue. In instances when bond is formed between mucus membrane and polymer the term "mucoadhesion" is used. Mucus membrane is one in which the goblet cells are present for the secretion of mucus which is composed of glycoprotein mucin.[3] Buccal mucosa is a potential site for the delivery of drugs to the systemic circulation. A drug administered through the buccal mucosa enters directly to systemic circulation, thereby minimizing the first pass hepatic metabolism and adverse gastrointestinal effect. Buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally to prevent accidental swallowing. Therefore adhesive mucosal dosage forms were suggested for oral delivery. Buccal mucosa makes a more appropriate choice of site if prolonged drug delivery is desired because buccal site is less permeable than the sublingual site.[4] Candesartan a non peptide angiotensin II type 1(AT1) receptor antagonist used in the treatment of hypertension and congestive heart failure. The aim of this work was to develop Candesartan buccal tablets for the treatment of hypertension and congestive heartfailure.[5]

MATERIALS AND METHOD

Materials

Candesartan was a gift sample from Aurobindo Pharma Ltd, Hyderabad. Carbopol, hydroxy propyl methylcellulose and sodium alginate were received from Loba Chemicals, Mumbai. Sodium saccharine, talc, magnesium stearate and mannitol were procured from S.D. Fine Chemicals, Mumbai.

Methods

Mucoadhesive buccal tablets preparation

Candesartan mucoadhesive buccal tablets were prepared by direct compression method. All the powders were passed through a 60 mesh sieve. The required quantity of drug and various polymers in individual and combinations were taken and mixed thoroughly. The blend was lubricated with magnesium stearate for 3-5 minutes by adding talc as glidant. The powder blend was evaluated for the pre-compression studies and then directly compressed using 12 station compression machine (Sai Pharmatech Ltd, India) to obtain tablet weight of 100 mg [6]. The formulations composition was shown in Table1.

Table 1: Formula of Candesartan buccal tablets

Ingredients	CBF1	CBF2	CBF3	CBF4	CBF5	CBF6	CBF7	CBF8	CBF9
Candesartan	30	30	30	30	30	30	30	30	30
Carbopol	30	-	-	10	-	10	15	-	15
HPMC	-	30	-	20	10	-	15	15	-
Sodium alginate	-	-	30	-	20	20	-	15	15
Sodium saccharine	5	5	5	5	5	5	5	5	5
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2
Mannitol	30	30	30	30	30	30	30	30	30
Totalweight(mg)	100	100	100	100	100	100	100	100	100

Evaluation of powder blends of Candesartan formulation

The powder blends of Candesartan formulations were evaluated before compression to assess the flow properties of the powder.[7,8,9]

Angle of repose: It is direct measure of flow property of powders. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal plane. The results are given in Table 2.

$$\text{Angle of repose } (\theta) = \text{Tan}^{-1} (h/r)$$

Where h = height of pile, r = radius of pile.

Bulk density: 25gm of powder blend was weighed accurately which was previously passed through 30# sieve and transferred in 100 ml graduated cylinder. Carefully measure powder level without compacting and read the unsettled apparent volume (Vo). Calculate the apparent bulk density in gm/ml by following formula. The results are given in Table 2.

Bulk density = Weight of powder /Bulk volume

Tapped density: 25gm of drug was weighed accurately, which was previously passed through 30# sieve and transferred in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density apparatus (Electro Lab, Mumbai, India). The cylinder was tapped for 500 times initially and tapped volume (V_1) was measured to the nearest graduated units. Tapping was repeated an additional 750 times and the tapped volume (V_2) was measured. The tapped bulk density was measured in gm/ml by the following formula. The results are given in Table 2.

Tapped density = Weight of powder /Tapped volume

Carr's index: The simplest way of measurement of free flow property of powder is compressibility an indication of the ease with which a material can be induced to flow is given by % compressibility that is calculated by the following formula.

Carr's index = Tapped density - bulk density/ Tapped density X100

Hausner's ratio: It is an indirect index of ease of powder flow. It is calculated by the following formula. Lower value of hausner ratio (< 1.25) indicates better flow properties than higher ones (>1.25). The results are given in Table 2.

Hausner's ratio = Tapped density / Bulk density

Evaluation of Candesartan buccal tablets:

Weight variation

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. [10]

Thickness

Ten tablets from the representative samples were randomly taken and their thickness was measured by using Vernier Caliper (Pharma Labs, Ahmedabad, India) and the reading was recorded in millimetres.[11]

Hardness

The hardness of tablet is directly proportional to friability loss and convenient in handling the tablets. Breaking under the condition of transportation and handling before the use depends on its hardness. Monsanto hardness tester (E 30 Dwaraka Mai, Hyderabad, India) was used to measure the hardness of tablets of each batch. The hardness expressed in terms of kg/cm^2.[12]

Drug Content

The content uniformity of Candesartan buccal tablet was determined. From each batch ten tablets were weighed and finely powdered. An amount of powder equivalent to 4mg of powder was accurately weighed and dissolved in pH 6.8 phosphate buffer. The resulting solution was suitably diluted with pH 6.8 phosphate buffer and analysed by using UV - Visible Spectrophotometer (Shimadzu 2060 - Plus, Ahmedabad, India) at 233 nm. The results are given in Table 3 and 4.

Friability

Ten tablets were weighed (W_0) and placed in the Roche friabilator (PSM- 02 Electro Lab, India) and was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again (W). The percentage friability was measured by the following formula. [13]

$$\text{Percentage friability} = 1 - (W/W_0) \times 100$$

Where, W_0 = Initial weight of tablet, W = Weight of tablet after revolution**.**

Swelling Studies

Buccal tablets were weighed individually (W_1) and placed separately in petridish containing 15 ml of pH 6.8 phosphate buffer. At regular time intervals (1, 2, 3, 4, 5, 6, 7 and 8 hr) the buccal tablets were removed from the petridish and excess surface water was removed carefully with the filter paper. The swollen tablets were then reweighed (W_2**)**. This experiment was performed in triplicate. The swelling index (water uptake) was calculated according to the following equation**.**[14]

$$\text{Swelling index} = [(W_2 - W_1)/W_1]$$

Where, W_1 = Initial weight of tablet, W_2 = Weight of tablet after swelling**.**

***In vitro* drug release study**

The tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. *In vitro* drug release studies were carried out in 900 ml of pH 6.8 phosphate buffer for 8 hr using a USP Dissolution Paddle apparatus Type II (Electro Lab, Mumbai, India) at 50 rpm and 37 ± 0.5°C. At predetermined time intervals samples were withdrawn and replaced with fresh medium. The samples were filtered, diluted suitably and then analyzed by using UV–Visible Spectrophotometer (Shimadzu 2060-Plus, Ahmedabad, India) at 233 nm. All dissolution studies were performed in triplicate. The mechanism of drug release from the buccal tablets was determined by finding the best fit of the release data to Zero order, First order, Higuchi and Korsmeyer-Peppas plots.[15] The results are given in Table 5 and 6.

Water absorption ratio and wetting time

A piece of tissue paper folded twice was placed in a petridish containing 5ml of water. A pre weighed tablet (W_B) was placed on the paper and the time for complete wetting was measured which is characterized by colouring of tablet. The wetted tablet was then reweighed (W_A). Water absorption ratio R was determined according to the following formula.[16] The results are given in Table 3 and 4.

$$R = (W_A - W_B / W_B) X100$$

Where,

W_A = weight of tablet after absorption of water,

W_B = weight of tablet before absorption of water

Determination of surface pH

The surface pH of the prepared Candesartan buccal tablets was determined to evaluate the possible irritation effects on the mucosa. The buccal tablets were placed in glass tubes and allowed to swell in contact with distilled water (12 ml) and the pH was measured by bringing the pH paper, in contact with the surface of the tablet and allowing it to equilibrate for 1 minute.[17]

RESULTS AND DISCUSSION

In the present work, Candesartan buccal tablets were prepared by using direct compression method as it was feasible and simple. The best parameters obtained for Candesartan buccal tablets were evaluated based on drug release.

Evaluation of powder blends of Candesartan buccal tablets

In the present study direct compression method was employed for preparation of Candesartan buccal tablets. The flow properties of the powder blends were checked by studying the angle of repose, compressibility index, Hausner's ratio. The powder blends were found to have good flow properties within the limits and the values were given in Table 2.

Table 2: Evaluation data of powder blend of Candesartan buccal formulations

Powder characteristics	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
CBF1	19.03±0.11	0.562±0.02	0.636±0.02	11.62 (Good)	1.131 (Good)
CBF2	19.03 ± 0.11	0.566±0.06	0.647± 0.03	15.91 (Good)	1.189 (Good)
CBF3	17.17±0.11	0.540±0.06	0.642±0.06	15.85 (Good)	1.189 (Good)
CBF4	20.55±0.51	0.549±0.05	0.623±0.05	11.85 (Good)	1.134 (Good)
CBF5	19.03 ± 0.11	0.500±0.06	0.647 ± 0.03	15.91 (Good)	1.189 (Good)
CBF6	17.17 ±0.11	0.540±0.06	0.642± 0.06	15.85 (Good)	1.189 (Good)
CBF7	20.55±0.51	0.549±0.05	0.623±0.05	11.85 (Good)	1.134 (Good)
CBF8	19.01 ± 0.11	0.546±0.05	0.640 ± 0.03	11.15 (Good)	1.189 (Good)
CBF9	17.17±0.11	0.640±0.06	0.642±0.06	15.85 (Good)	1.189 (Good)

Bulk density was found to be in the range of 0.500 - 0.640 (gm/ml) and tapped density between 0.623 - 0.647 (gm/ml) for all the formulations. The % compressibility index was calculated by using the density data. The obtained values 11.15 - 15.91 % which were found to be good flow and the Hausner's ratio values were in the range of 1.131- 1.189 for all powder blends. This was further supported by the angle of repose values between 17.17 - 20.55°. As it was below 30° it indicated good flow properties of powder blend.

Preparation and evaluation of Candesartan buccal formulations

Candesartan buccal tablets were prepared by employing direct compression method to find the comparative effect for release of the drug by using different concentration ranges of polymers in controlled manner.

Table 3: Evaluation data of Candesartan buccal formulations (CBF1- CBF4)

Evaluation Parameters	CBF1	CBF2	CBF3	CBF4
Weight Variation (mg)[a]	99±0.86	97.1 ± 1.16	106 ± 3.57	102 ± 0.88
Thickness(mm)[b]	4.40 ±0.01	4.59 ± 0.05	5.32 ± 0.01	4.38 ± 0.07
Friability (%)[b]	0.192±0.57	0.198±0.12	0.218 ±0.17	0.236±0.27
Hardness (Kg/cm^2)[c]	4.10±0.23	4.85 ± 0.25	5.41 ± 0.05	4.22 ± 0.15
Content Uniformity(%)[c]	98.4±0.73	101 ± 1.61	99.2 ± 0.12	99.1 ± 0.40
Swelling index(%)[c]	72.28±0.04	63.58 ± 0.69	68.15 ±1.58	69.03±0.91
Surface p^{H} [c]	6.6±0.34	6.5±0.07	6.7±0.07	6.9±0.01
Water absorption ratio (%)[c]	15.4±0.34	17.5±0.24	33.77±0.14	38.77±0.34

Each value is an average of twenty determinations [a]

Each value is an average of ten determinations [b]

Each value is an average of three determinations [c]

Table 4: Evaluation data of Candesartan buccal formulations (CBF5- CBF9)

Evaluation Parameters	CBF5	CBF6	CBF7	CBF8	CBF9
Weight variation(mg)[a]	105 ± 0.88	106 ± 3.57	102 ±0.88	97.1 ±1.16	106 ± 3.57
Thickness (mm)[b]	4.18 ±0.07	5.32 ±0.01	4.38 ±0.07	5.22 ±0.01	4.18 ±0.07
Friability (%)[b]	0.216±0.07	0.116±0.07	0.198±0.12	0.218±0.17	0.216±0.07
Hardness (Kg/cm^2)[c]	4.15 ±0.15	4.15 ±0.15	4.85±0.25	4.41 ±0.05	4.15 ±0.15
Content uniformity(%)[c]	99. 02±.12	99.2 ±0.12	99.1 ±0.40	98.4 ±0.73	98.4 ±0.73
Swelling index (%)[c]	67.90±0.48	65.92±0.74	53.14±1.99	63.70±1.81	66.04±0.12
Surface p^{H} [c]	6.9±0.09	6.8±0.10	6.6±0.20	6.7±0.46	6.9±0.12
Water absorption ratio(%)[c]	15.41±0.44	38.4±0.34	36.2±0.34	23.1±0.24	35.46±0.14

Each value is an average of twenty determinations [a]

Each value is an average of ten determinations [b]

Each value is an average of three determinations [c]

All the tablets were having beveled edged flat surface in round shape with white color. The average weight of tablets was in the range of 97-106 mg. Thickness of the tablets was in range of 4.18 -5.32 mm. The hardness of tablets was determined and found in the range of 4.10 – 5.41Kg/cm^2. As the aim of study to release the drug slowly, the hardness was kept in the higher range. The friability of all tablets was less than 1% in the range of 0.116– 0.236 % which is in the acceptable limits which indicates formulations have good mechanical strength. All the formulations are subjected for content uniformity and were in the range of 98.4 - 101 %. It was observed that all the formulations were as per I.P. specification limits (90.0 to 110.0 %) of tablet. The swelling index of tablets were determined and it was found that the tablet containing the combination of carbopol and hydroxypropyl methylcellulose polymer in ratio of 1: 2 and 1.5 : 1.5 have shown highest swelling index. Swelling index

indicates the uptake of water into tablet matrix producing an increasing in weight. The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity. The surface pH of the buccal tablets depends on the nature and composition of mucoadhesive polymers. Surface pH of the all the formulation were found to be in the range of 6.5 to 7.0. This pH is near to the neutral, so the buccal tablet does not cause any irritation on the mucosa. The swelling state of polymer in formulations was reported to be crucial for its boiadhesive behaviour. Adhesion occurs shortly after the beginning of swelling but the bond formed between the mucosal layer and polymer is not very strong. The adhesion will increase with degree of hydration until point where over hydration leads to an abrupt drop in adhesive strength due to disentanglement at polymer/ tissue interface. Individual carbopol concentration (F1) has high swelling index with low water absorption ratio. Combination of carbopol and hydroxypropyl methylcellulose (F4) obtained swelling index and water absorption ratio values at a higher extent. Individual concentration of sodium alginate (F3) obtained high drug release. But drug release of hydroxypropyl methylcellulose (F2) was nearer to sodium alginate in individual concentrations. While low concentration of carbopol and high concentration of hydroxypropyl methylcellulose in combinations (F4) gave 86% drug release and with equal ratios of carbopol and hydroxypropyl methylcellulose (F7) gave 88% drug release. But low concentration of hydroxypropyl methylcellulose and high concentration of sodium alginate (F5) in combination form gave 95% drug release. While equal ratios of both hydroxypropyl methylcellulose and sodium alginate in combination (F8) gave 98% drug release. The % drug release data and plot which were obtained for the Candesartan buccal tablets by direct compression in phosphate buffer pH 6.8 was shown in Table 5 and 6 and Figure 1 and 2 respectively.

Table 5: Cumulative % drug release data of Candesartan buccal formulations in phosphate buffer pH 6.8 (CBF1- CBF5)

Batch no Time (hr)	CBF1	CBF2	CBF3	CBF4	CBF5
0	**0**	**0**	**0**	**0**	**0**
1	20±0.01	28±0.06	25±0.04	23±0.08	27±0.05
2	32±0.05	39±0.02	34±0.02	39±0.06	34±0.01
3	48.2±0.02	43.2±0.09	38.4±0.06	46.4±0.04	43.6±0.03
4	53±0.08	58.2±0.01	42.7±0.03	52.2±0.02	56.4±0.07
5	67±0.03	62.9±0.07	58.5±0.05	66.8±0.05	65.3±0.04
6	72.8±0.01	73.77±0.06	64.3±0.01	79.2±0.01	71.8±0.02
7	78.5±0.03	87.3±0.02	76±0.09	82.3±0.06	76.2±0.08
8	81.2±0.04	92±0.05	93±0.01	86±0.03	95±0.05

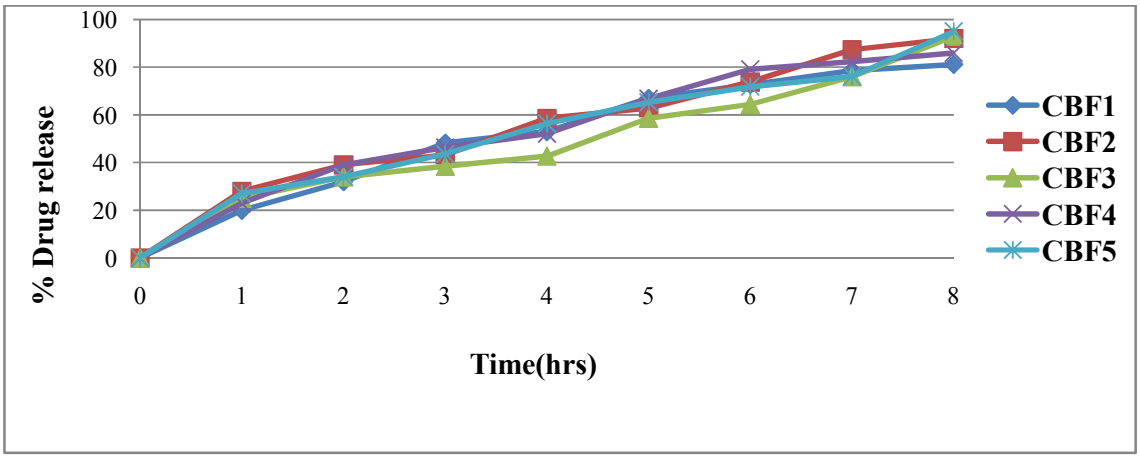

Figure1: % Cumulative drug release plot of Candesartan buccal tablets in phosphate buffer pH 6.8 (CBF1- CBF5)

Table 6: Cumulative % drug release data of Candesartan buccal tablets in phosphate buffer pH 6.8 (CBF6- CBF9)

Batch no Time (hr)	CBF6	CBF7	CBF8	CBF9
0	0	0	0	0
1	21±0.09	24.6±0.09	28.6±0.01	26.6±0.08
2	27±0.01	31.2±0.01	31±0.06	32±0.06
3	34.4±0.06	42.8±0.04	39±0.08	46±0.01
4	58.7±0.03	56.5±0.03	43.4±0.06	54.2±0.03
5	64.9±0.07	67.7±0.05	58.8±0.03	66.8±0.05
6	72.7±0.02	73±0.01	61.5±0.04	72.5±0.04
7	75±0.08	83±0.06	75.4±0.01	78.7±0.07
8	87±0.01	86±0.09	98±0.02	89±0.06

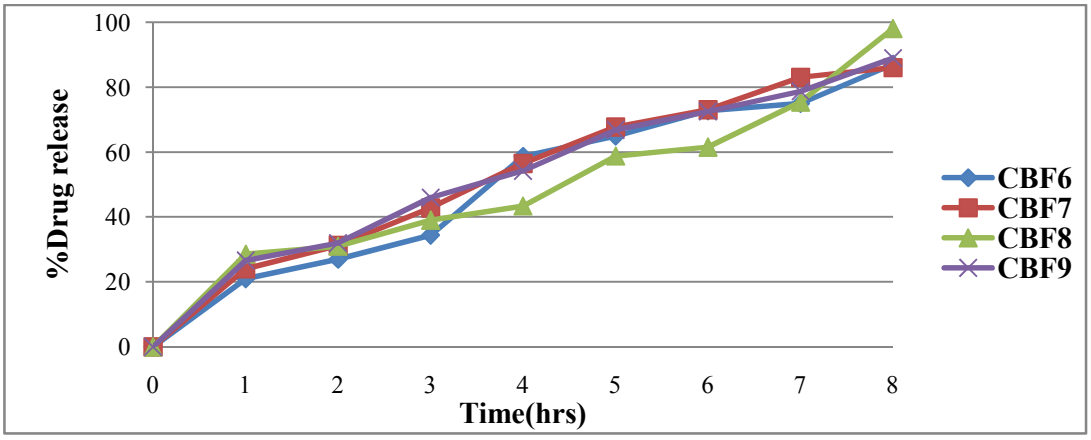

Figure 2: % Cumulative drug release plot of Candesartan buccal tablets in phosphate buffer pH 6.8 (CBF6- CBF9)

Table 7: Kinetics data of Candesartan buccal tablet

Batch no	Zeroorder (R^2)	Firstorder (R^2)	Higuchi (R^2)	Korsmeyer-Peppas(R^2)	n
CBF1	0.998	0.945	0.922	0.999	0.898
CBF2	0.997	0.957	0.886	0.997	0.958
CBF3	0.993	0.970	0.901	0.977	0.879
CBF4	0.982	0.908	0.865	0.992	0.939
CBF5	0.997	0.933	0.899	0.993	0.961
CBF6	0.996	0.955	0.930	0.993	0.841
CBF7	0.991	0.975	0.902	0.997	0.903
CBF8	0.992	0.962	0.885	0.994	0.935
CBF9	0.995	0.975	0.937	0.995	0.925

CONCLUSION

In the present work, an attempt was made to develop mucoadhesive buccal dosage form tablets of Candesartan to improve better patient compliance. From the tablets prepared the following conclusions are drawn. Buccal tablets of Candesartan were prepared using different polymers such as hydroxypropyl methylcellulose, sodium alginate and carbopol by changing the polymer quantities in individual ratios and combinations to study effect of these polymers on the physico chemical characters, swelling index, surface p^H, content uniformity, water absorption ratio and *in vitro* drug release. Among all the nine formulations carbopol (F1) showed maximum swelling index value. Finally the formulations (F8) with hydroxypropyl methylcellulose and sodium alginate in equal ratios gave 98% drug release which was most suitable for preparing buccal tablets and all the formulations were following zero order release kinetics.

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