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Development & *In-Vitro* Characterization of candesartan Muco-Adhesive Buccal Tablets

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A B S T R A C T

Mucoadhesive drug delivery systems are the systems which utilize the property of mucoadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time. Candesartan is an angiotensin-receptor blocker (ARB) that may be used alone or with other agents to treat hypertension. Nine different formulations were prepared by using different constituents. Then the tablets were evaluated for various physicochemical properties and stability. They were also evaluated for in vitro drug release, swelling index and release kinetics. Among all the formulations, the F6 formulation with API and Carbopol 934 in the ratio of 1: 7 exhibited significant moisture absorption properties with optimum release profile.

Keywords: Mucoadhesive drug delivery systems, Candesartan, swelling index, Carbopol-934

A R T I C L E I N F O

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1. Introduction

Mucoadhesive Drug Delivery System:

Mucoadhesive drug delivery systems are the systems which utilize the property of mucoadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time [1].

Advantages of mucoadhesive buccal drug delivery:

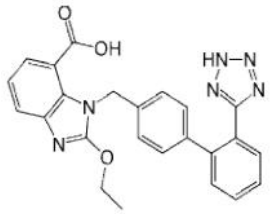
a. Drug administration via the oral mucosa offers a number of advantages
b. Offers an superb route for the systemic delivery of drug which by passes first pass metabolism, thereby offering a greater bioavailability.
c. It satisfies a number of futures of the controlled release system.
d. The oral mucosa lacks prominent mucus secreting goblet cells and therefore there is no problem of diffusion limited mucus build up beneath the applied dosage form.
e. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes [2,3].

Limitations of Buccal Drug Administration:

- Drugs which are unstable at buccal pH cannot be administered.
- Eating and drinking may become restricted.
- There is an ever present possibility of the patient swallowing the dosage form.
- Drugs contained in the swallowed saliva follows the pre-oral and advantages of buccal route are lost [4]

Drug Profile of Candesartan [5]:

Structure:



Chemical Formula: $C_{24}H_{20}N_6O_3$

IUPAC Name: 2-ethoxy-1-({4-[2-(2H-1,2,3,4-tetrazol-5-yl) phenyl] phenyl}methyl)-1H-1,3-benzodiazole-7-carboxylic acid

Molecular weight: 440.45

Category: Antihypertensive agent

2. Materials and Methods

Table 1: Composition of Mucccoadhesive Buccal Tablets of Candesartan

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Candesartan	8	8	8	8	8	8	8	8	8
Manitol	113.5	97.5	81.5	113.5	97.5	81.5	113.5	97.5	81.5
HPMC K4M	24	40	56	-	-	-	-	-	-
Carbapol 934p	-	-	-	24	40	56	-	-	-
HEC	-	-	-	-	-	-	24	40	56
Aspartame	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
Magnesium sterate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total (mg/tab)	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Preparation of Mucco-adhesive Baccal tablets: The buccoadhesive tablets were prepared by direct compression method. all the ingridients were mixed in formulated proportion and lubricants was added and punched using 16 stations mult punch tablet compression machine. Each tablet contained 150 mg of Candesartan the batch size for each formulation was 50 tablets.

3. Results and Discussion

Melting Point: Melting point values of Candesartan sample were found to be 1690C.

Calibration Curve of Candesartan:

Table 2: Data of concentration and absorbance for Candesartan in Phosphate buffer pH 6.8

S. No	Concentration (µg/ml)	Absorbance
1	0	0
2	20	0.0968
3	40	0.1963
4	60	0.2861
5	80	0.3758
6	100	0.4794

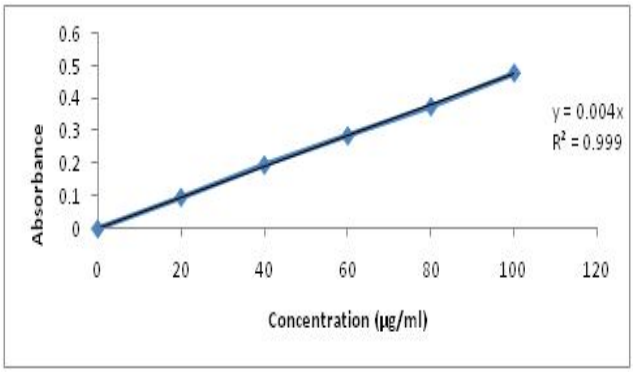


Figure 1: Standard graph of Candesartan in Phosphate buffer pH 6.8

Evaluation of Micromeritic Properties of Powder Blend:
Discussion: The press coated tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and drug content. Angle of repose was less than 35° and Carr's index values were less than 12 for the raw material of all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

Table 3: Evaluation studies of Candesartan tablets

Formulation Code	Hard ness (kg/cm^2)	Thickness (mm)	Weight variation	Fraibility(%)	Drug content (%)
F1	6.3±0.60	2.55±0.03	150.74±0.61	0.21	99±0.05
F2	6.8±0.16	2.54±0.02	150.38±0.71	0.25	99±0.01
F3	7.0±0.30	2.51±0.02	150.45±0.64	0.81	98±0.01
F4	6.8±0.16	2.31±0.01	149.91±1.01	0.66	99±0.06
F5	6.3±0.12	2.35±0.03	149.98±0.82	0.55	100±0.12
F6	7.1±0.02	2.12±0.01	148.42±0.61	0.74	100±0.56
F7	6.3±0.17	2.54±0.03	151.98±1.01	0.94	100±0.14
F8	6.8±0.13	2.42±0.01	150.74±0.75	0.64	99±0.25
F9	6.1±0.10	2.51±0.06	150.38±0.71	0.13	100±0.31

Where, All values are mean ±S.D,n=20

Disscussion:
All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 99 and 100 mg. The hardness of the tablets ranged from 6.1 to 7.1 Kg/cm2 and the friability values were less than 1% indicating that the matrix tablets were compact and hard. The thickness the tablets ranged from 2.12 to 2.55 mm. All the formulations satisfied the content of the drug as they contained 90 to 101 % of Candesartan and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practice within control.

Table 4: Swelling Index of Candesartan Mucco adhesive buccal tablets

Time (hrs)	Swelling Index (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	52.12	36.23	26.35	46.27	35.06	36.55	36.5	33.68	35.21
2	63.52	46.61	35.62	63.51	49.18	45.92	43.1	56.33	49.35
3	71.32	53.24	33.21	76.81	53.34	69.37	62.6	75.92	72.31
4	83.61	63.53	46.41	83.56	66.29	79.11	72.8	83.29	86.35
5	86.15	76.62	56.10	84.17	79.14	86.54	86.3	86.16	78.03
6	66.24	58.8	48.23	60.43	55.55	78.44	72.1	70.13	68.32
7	36.32	34.14	42.11	33.98	46.18	52.15	62.35	56.24	52.42
8	19.25	23.23	36.87	14.26	22.46	32.29	25.6	27.35	24.35

Disscussion :
All the formulations were hydrated generally by keeping the tablets in contact with water for 1 h to 8 h. The highest hydration (swelling) i.e. 86.54% was observed with the formulation F6. This may be due to quick hydration of polymers Carbopol 934p. The swelling rate of tablets increased in the case of formulation F6 containing Carbopol 934p.

Table 5: Evaluation tests of Candesartan Mucco-adhesive buccal tablets surface ph & Mucco-adhesive strength.

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	23	26	30	27	25	29	23	28	29
2	27	30	37	41	39	44	38	47	41
4	39	44	52	52	55	58	57	61	48
6	48	53	59	61	64	72	64	72	55
7	59	63	69	74	77	84	76	79	64
8	67	74	79	85	87	93	78	80	82

Disscussion :

Surface pH of all the formulations F1 to F9 was found to be 5.7 to 6.82, which is well within the limit of acceptable salivary pH range of 5.69 to 6.34. Hence, it was concluded that all formulations could not produce any local irritation to the mucosal surface. Increase in concentration of polymer increases bio-adhesive strength of formulation. The *Ex vivo* residence time was determined by using specially designed apparatus. Formulations F8 to F9 showed lower residence time when compared to the formulations F1 to F7. As the concentration of Muco-adhesive material increased, the *ex vivo* residence time also increased. This test reflects the adhesive capacity of polymers used in formulations. The results revealed that the mixture of carbopol 934 containing formulations showed better residence time than the mixture of and HPMC K4M and HEC formulations. The formulations F1, F2, F3 containing drug, HPMC K4 M polymers in the 16% , 26.6% , 37.3% and ratio was 1:3,1:5,1:7 respectively. The *in vitro* cumulative drug release profile of formulations F1, F2, F3 and F4 showed 64%, 74%, 79% respectively. Among these four formulations, F3 was found to be highest percentage drug release. During the study it was observed that the tablets were initially swell and no erodible over the period of 8 h. Similarly the formulations F4, F5, F6 drug, containing Carbopol 934p polymers in the 16% , 26.6% , 37.3% and ratio was 1:3,1:5,1:7 respectively. The *in vitro* cumulative drug release profile of formulations F4, F5, F6 showed 85%, 87%, 93% respectively. Among these four formulations, F6 was found to be highest percentage drug release. During the study it was observed that the tablets were initially swell and non-erodible over the period of 8 h. Similarly the formulations F7, F8, F9 drug, containing HEC polymers in the 16% , 26.6% , 37.3% and ratio was 1:3,1:5,1:7 respectively. The *in vitro* cumulative drug release profile of formulations F7, F8, F9 showed 78%, 80%, 82% respectively. Among these four formulations, F6 was found to be highest percentage drug release. During the study it was observed that the tablets were initially swell and non-erodible over the period of 8 h. From the overall data it was found that the formulation F6 showed the maximum percentage of drug release i.e. 93% at the end of 8 h. Finally polymer concentration is increased. This showed 93% drug released in 8hr. where perfect match with the Marketed product product was (90%) obtained. So F6 was considered as optimized formulation.

Dissolution Study of Marketed product Product:

Table 6: *In-vitro* Dissolution profile of Candesartan from optimized formulation F6and marketed product

Time in (hr)	1	2	4	6	8	12
Marketed product	14.4	23.4	36.3	50.3	62.7	90
F6	29	44	58	72	84	93

Kinetic Analysis of Dissolution Data:

Table 7: Drug Release Kinetics of Batch (F6) Candesartan Muco-adhesive buccal Tablets Mathematical modeling and drug release kinetics of F6 optimized formulation.

Time	Log Time	Square root of Time	Cumulative % Drug Released	Log Cumulative % Drug Released	Cumulative % Drug Remained	Log Cumulative % Drug Remained
0	0	1	-	-	100	2
1	1	0	24	1.3802112	76	1.880813592
2	1.414214	0.30103	44	1.6434527	56	1.748188027
4	2	0.60206	58	1.763428	42	1.62324929
6	2.44949	0.778151	72	1.8573325	28	1.447158031
7	2.645751	0.845098	84	1.9242793	16	1.204119983
8	2.828427	0.90309	93	1.9684829	7	0.84509804

Stability Study:

After storage, the optimized formulation (F6) was analyzed for various physical parameters No major difference was found between evaluated parameters before and after storage and all are in acceptable limits. The tablets showed satisfactory physical stability at 40^0C at 75 % RH.

4. Conclusion

The overall results indicated that the polymers API and Carbopol 934 in the ratio of 1: 7 showed satisfactory muco-adhesive properties. Among all the formulations, the F6 formulation using these polymers in the above ratio with drug exhibited significant moisture absorption properties with optimum release profile. The optimized formulation F6 also showed satisfactory surface pH and physical parameters, effective *in vitro* permeation, satisfactory stability in human saliva. Hence it can be concluded that the formulation F6 will be useful for buccal administration of Candesartan. The in vitro drug release of F6 shows improved percentage releasing in comparison with Marketed product.

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