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Research

Formulation Development And In-Vitro Evaluation Of Controlled Release Mucoadhesive Buccal Patches Of Candesartan

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Abstract

The present study was aimed to formulate mucoadhesive drug delivery system to enhance bioavailability and avoid pre systemic metabolism. The mucoadhesive patch was fabricated by solvent casting method employing 'O' shape ring placed on a glass surface as substrate by using different polymers such as Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC), Carbopol-P 934 (CP) and Carboxy methyl cellulose (CMC),water is used as the solvents. Propylene glycol serves as the plasticizer as well as penetration enhancer. Triethanolamine was used to neutralize the carbopol polymeric solution. The formulation F4 with Carbopol and HPMC in the ratio 1:4 showed drug release of 88% in 8 hours. The sole purpose of this work is to adhere the buccal film with the mucosa; hence formulation F4 was selected as best formulation. Thus the aim of the present to formulate a buccalmucoadhesive drug delivery system was fulfilled. The further scope of the work requires optimization for scale up and in-vivo animal studies.

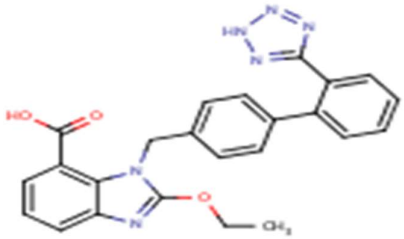
Keywords: Mucoadhesive,

INTRODUCTION

Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs. The mucosa is relatively permeable with a rich blood supply. Theoraltransmucosal drug delivery bypasses liver and avoids pre-systemic elimination in the GI tract and liver (Edith etal.,1999). These Factors make Theoral Mucosaavery attractive and feasible site for systemic drug delivery. Unlike the sublingual mucosa, the buccal mucosa offers many advantages because of its smooth and relatively immobile surface and its suitability for the placement of controlled-release system which is well accepted by patients. The buccal mucosa is relatively permeable, robust in comparison to the other mucosal tissues and is more tolerant to potential allergens which have a reduced tendency to irreversible irritation or damage. The buccal mucosa is a useful route for the treatment of either local or systemic therapies overcoming the drawbacks of conventional administration routes. Buccal route is well vascularized draining to the heart directly via the internal jugular vein[2]. So, it has been largely investigated as a potential site for controlled drug delivery in various chronic systemic therapies. However, salivary production and composition may contribute to chemical modification of certain drugs. Moreover, involuntary swallowing can result in drug loss from the site of absorption. Furthermore, constant salivary

scavenging within the oral cavity makes it very difficult for dosage forms to be retained for an extended period of time in order to facilitate absorption in this site. Bioadhesive polymer can significantly improve the performance of many drugs, as they have prolonged contact time with these tissues. These patient compliance controlled drug delivery products have improved drug bioavailability at suitable cost.

Drug profile
Drug Name:Candesartan
Structure:Candesartan



Synonyms: Candesartan cilexetil
Categories:

- Antihypertensive Agents
- Angiotensin II Receptor Antagonists
- Angiotensin II Type 1 Receptor Blockers

Weight: Average: 440.454
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.

MATERIALS AND METHODS

Materials used

Table 1: List of materials used

S.NO	MATERIALS	MANUFACTURER
1	Candesartan	Provided by Chandra labs, Hyd.
2	Hydroxy propyl methyl cellulose	MYL CHEM Mumbai.
3	Sodium Carboxy methyl cellulose	MYL CHEM Mumbai.
4	Carbopol	MYL CHEM Mumbai.
5	Propylene Glycol	Karnataka fine chem. Industries, Bangalore
6	Potassium dihydrogen phosphate	Hi Pure fine chem. Industries, Chennai
7	Disodium hydrogen phosphate	Qualigens fine chemicals, Mumbai
8	Anhydrous Calcium Chloride (Fused)	Universal laboratories pvt ltd, Mumbai
9	Aluminium chloride (Hydrated)	SD fine chemicals, Mumbai
10	Aspartame	SD fine chemicals, Mumbai

Instruments and apparatus

Table 2: List of instruments used

S.no	Instruments	Manufacturer
4	UV Spectrophotometer	LAB INDIA Instruments Pvt. Ltd. (Model No: 2602)
5	Digital vernier caliper	Absolute Digimate, industrial gin stores, Hyderabad

6	Digital balance	LCGC Chromatographic solution, Hyderabad
7	Remi Magnetic stirrer, Vasai, India	Vasai, India
8	Bath ultra sonicator	LAB INDIA Instruments Pvt. Ltd.
9	pH Meter	Systronics, Hyderabad
10	Centrifuge.	Singhla scientific industries, Ambala.
11	Modified Dissolution Apparatus	LAB INDIA Instruments Pvt. Ltd. UV3000+
12	FT – IR Spectrometer	SHIMADZU FT-IR 8400

METHODOLOGY

Standard curve in 6.8ph phosphate buffer

Stocksolutionof1000µg/mlofCandesartanwaspreparedbydissolving25mgofdruginsmall quantity of methanol and makeup with 6.8pH Phosphate Bufferto 25ml.Fromthistake10mlandmakeupto100mlusing buffer togetastock solution of 100 µg/ml. Fromtheabovesolutiontake 0.4, 0.8, 1.2, 1.6, 2.0ml and dilute to 10 ml with buffertogeta concentrations of 4µg/ml, 8µg/ml, 12µg/ml, 16 µg/ml, 20µg/ml. Theabsorbanceofthedifferentdilutedsolutionswasmeasuredina UVspectrophotometerat255nm.Acalibrationcurvewasplottedbytakingconcentrationofthesolutioninµg/mlonX-axisandabsorbance on Y-axis and correlation co-efficient "r^2" was calculated.

Drug –polymer compatibility studies by ftir

Drug polymer compatibility studies were performed by FTIR[57] (Fourier transform infrared spectroscopy).

Fabrication of candesartan buccal patches

The buccalmucoadhesive patches were prepared by the method of solvent casting technique[54-56] employing 'O' shape ring placed on a glass surface as substrate by using different polymers like Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC), carbopol and Carboxy methyl cellulose (CMC).

The calculated quantities of polymers were dispersed in ethanol (70 % v/v). The carbopol polymeric solution was neutralized using triethanolamine. An accurately weighed 16 mg candesartan was incorporated in polymeric solutions after levigation with 30 % w/w propylene glycol which served the purpose of plasticizer as well as penetration enhancer. The solution was mixed occasionally to get semisolid consistency. Then the solution was subjected to sonication in a bath sonicator to remove the air bubbles Then this were casted on a glass surface employing 'O' shape ring covered with funnel to controlling the evaporation of solvent and allowed to dry at room temperature over night. The dried patches were separated and the backing membrane used was aluminium foil. Then the formulations were stored in desiccators until further use.

Total surface area – 13.45cm^2
patch size = 2*2
total number of patches = ≈4 (3.36)
total amount of drug taken = 4*16mg=64mg

The compositions of formulation of both drug free and candesartan buccal patches were given in Table 3.

Table 3: The Composition Of Buccal Patches Prepared Using Candesartan

Formulation code	Polymers in %			Solvent in %	
	Carbopol	HPMC	CMC	PG*(%)	Aspartame*
F1	5%	-	-	15%	1%
F2	-	5%	-	15%	1%
F3	-	-	5%	15%	1%
F4	1%	4%	-	15%	1%
F5	2%	3%	-	15%	1%
F6	2.5%	2.5%	-	15%	1%
F7	1%	-	4%	15%	1%
F8	2%	-	3%	15%	1%
F9	2.5%	-	2.5%	15%	1%
F10	1%	-	4%	-	1%

Candesartan: 16 mg
Propylene glycol:15% w/w of total weight of the polymer
Aspartame* 1% w/w total weight of the polymer

Stability studies
Following conditions were used for Stability Testing:
1. 21˚C/45% RH analyzed every month for period of three months.
2. 25˚C/60% RH analyzed every month for period of three months.
3. 30˚C/70% RH analyzed every month for period of three months.

RESULTS AND DISCUSSION

Preformulation studies
Solubility studies

Table 4: Showing the solubility of Candesartan (API) in various solvents

S.NO	Test	Specifications	Results
1.	**Description** Colour odour Form	 white odourless amorphous	Complies
2.	**Solubility**	Soluble in methanol,ethanol, slightly soluble in ph6.5 phosphate buffer, HCL,insoluble in water.	Complies

Linearity Curve

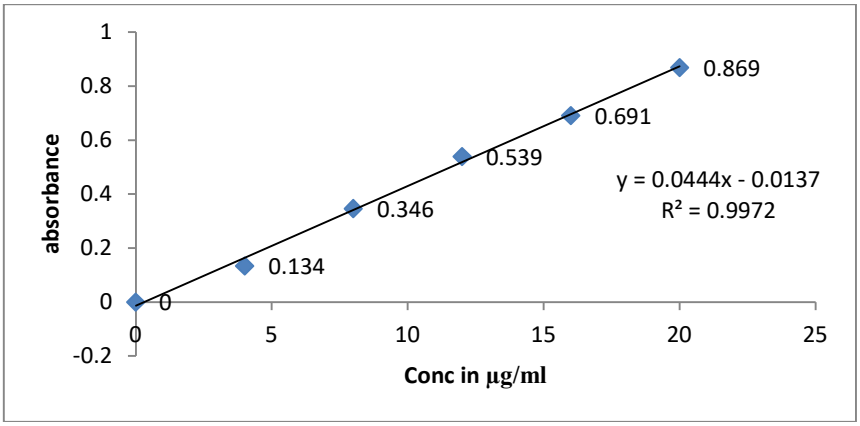


Fig 1: Calibration graph

Compatability Studies

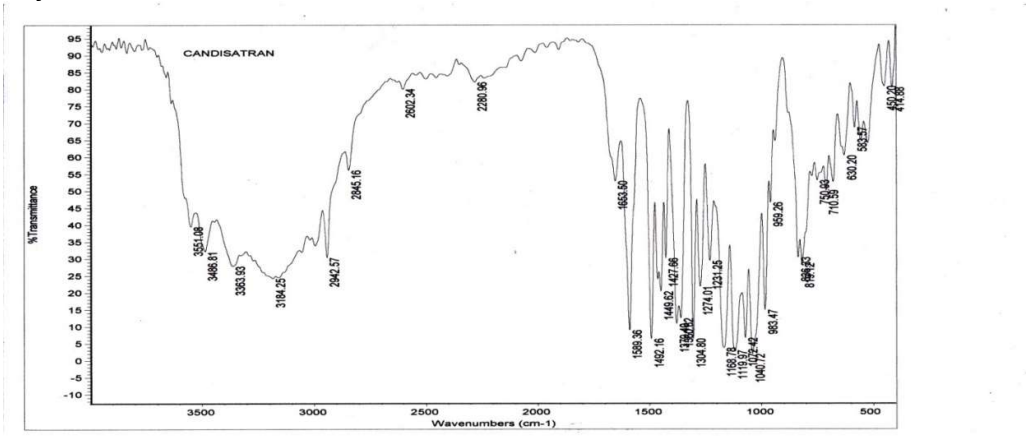


Fig 2: FTIR Spectra of Candisartan

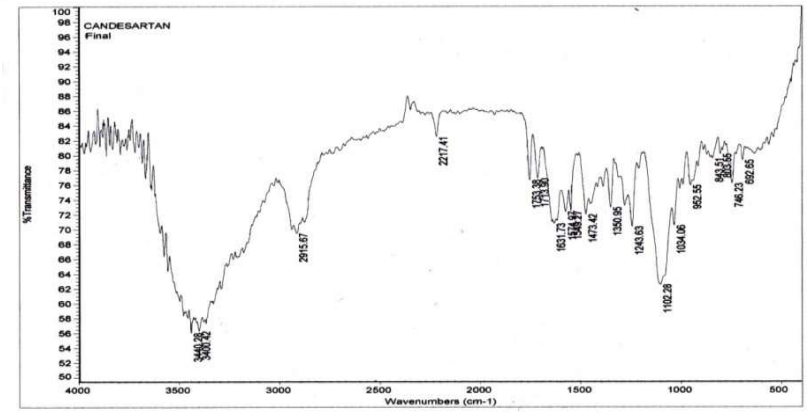


Fig 3: FTIR Spectra of Candisartan final

Physicochemical evaluation

Table 5: Physicochemical evaluation of buccal patches of candesartan

Formulation Code	Surface pH	PMA	PML	Swelling Index	WTR	Thickness (mm)	Weight of patches in mg	Drug Content in mg
F1	6.73	5.21	5.97	69.4	10.18	0.52	187.93	15.87
F2	6.80	7.32	5.14	99.67	7.67	0.51	183.18	15.69
F3	6.71	9.24	4.74	118.4	7.17	0.53	185.53	14.56
F4	6.64	10.32	4.14	124.15	6.4	0.56	186.31	15.89
F5	6.6	12.13	4.08	132.36	5.98	0.55	189.37	15.76
F6	6.52	14.21	3.88	138	5.39	0.53	188.12	15.43
F7	6.57	11.23	5.71	77.9	5.86	0.58	187.9	19.67
F8	6.65	10.26	6.71	73.4	10.21	0.56	184.37	19.71
F9	6.59	12.06	4.47	72.4	6.67	0.54	183.23	19.73
F10	6.63	11.16	5.24	74.6	6.39	0.59	185.03	19.66

***In-Vitro* Drug Release**

Table 6: *In-Vitro* Drug Release Data For Candesartan Buccal Patch

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	**0**	0	0	0	0	0	0
1	9	05	10	**8**	6	9	12	10	13	12
2	14	12	28	**16**	15	17	30	28	26	19
3	23	19	35	**26**	23	24	37	35	33	30
4	36	31	49	**40**	37	39	48	46	45	42
5	42	38	62	**49**	45	43	59	56	57	51
6	52	43	75	**58**	53	49	72	70	69	62
7	60	52	83	**72**	64	57	81	85	80	73
8	76	59	-	**88**	79	68	-	-	-	83

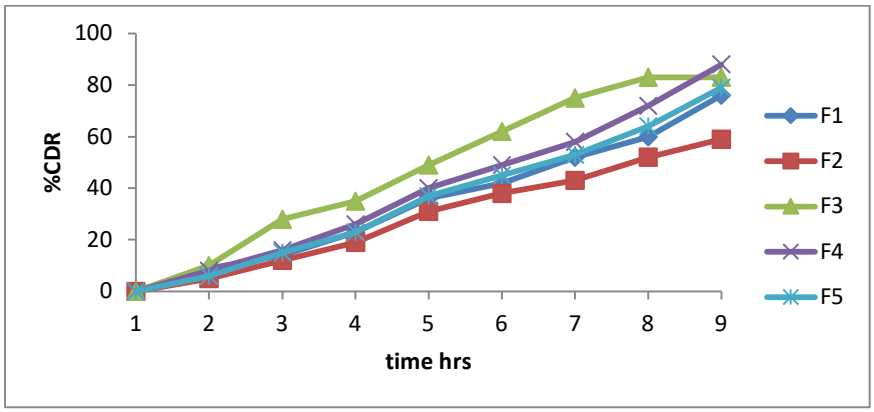


Fig 4: Invitro Drug Release Data For For Formulation F1-F5

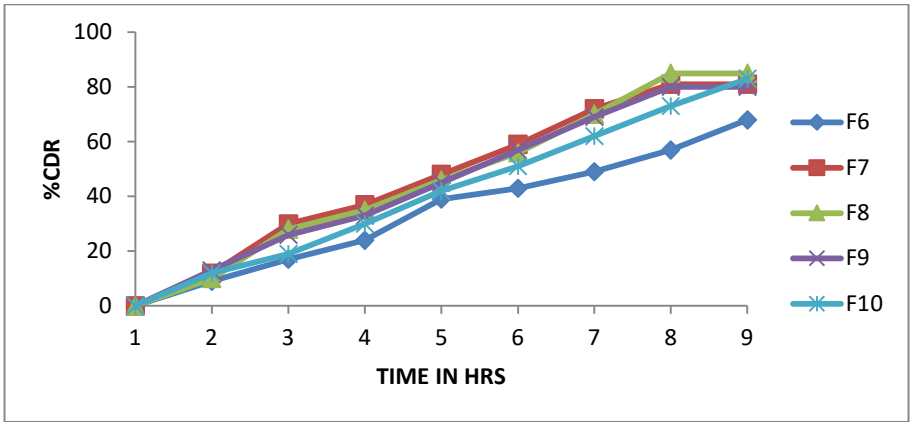


Fig 5: Invitro Drug Release Data For For Formulation F6-F10

Kinetic studies for optimized formulation

Table 7: Kinetic Studies for Optimized Formulation

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	10.85	-0.09994809	30.95630095	1.631549835

Intercept	-3.73333333	2.110082266	-16.4192732	0.540616255
Correlation	0.995454738	-0.92601964	0.931720477	0.916635594
R 2	0.990930135	0.857512379	0.868103047	0.840220813

Stability studies

Table 8: Stability studies

Time	Colour	Assay		Cumulative % drug release at 8 hrs	
		25±2^{0}c and 65±5%RH	**40±2^{0}c and 75±5%RH**	**25±2^{0}c and 65±5%RH**	**40±2^{0}c and 75±5%RH**
First day	White	100	100.50	88.9	88.65
30 days	White	101.88	99.18	88.5	88.12
60 days	White	100.85	98.75	88.24	87.69
90 days	White	99.30	97	87.65	87.32

The Candesartan buccalmucoadhesive patches were prepared by the method of solvent casting technique employing 'O' shape ring placed on a glass surface as substrate by using different polymers such as Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC), Carbopol-P 934 (CP) and Carboxy methyl cellulose (CMC),water is used as the solvents. Propylene glycol serves as the plasticizer as well as penetration enhancer. Triethanolamine was used to neutralize the carbopol polymeric solution.

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy).The prepared Candesartan buccal patches were characterized based upon their physico chemical characteristics like surface pH, PMA, PML, swelling percentage, WVT, thickness, weight, folding endurance and drug content.

The *in- vitro* drug release studies were performed as the release of the drug from the dosage form plays an important role in buccal drug delivery and in determining the therapeutic effect of the drug. The *in- vitro* drug release studies were performed by using a modified dissolution apparatus with donor-receptor compartments.

Drug –polymer compatibility studies by FTIR

The FTIR spectra of Candesartan, HPMC, Carbopol, CMC and the combination of drug and polymers were shows no significant interaction between drug and polymer. The FTIR spectra's of Candesartan , HPMC, Carbopol, CMC , and mixture of drug along with polymers are shown in figure .

Surface pH

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the rate of hydration of the polymers, the surface pH of the patches was determined. The observed surface pH of the formulations was found to be in the range of 6.52to 6.80. The results are found that there is no significant difference of surface pH in all the formulations and the pH range lies within the range of salivary pH i.e. 6.5 to 6.8, hence do not cause irritation and achieve patient compliance. Surface pH values of all the formulations are represented in table no:.

Percentage Moisture Absorption and Percentage Moisture Loss

Checking the physical stability of the patch at high humid conditions and integrity of the patch at dry conditions, the patches were evaluated for PMA and PML. The observed results of PMA and PML were shown in the tabular column. (Table No.). The percentage Moisture uptake in the formulation F6 has shown the highest value of moisture absorption 14.21. The formulation F8 shows higher value of Moisture loss.

Swelling percentage

Table shows the swelling percentage of the formulated buccal patches. The swelling behaviour of the polymer was reported to be crucial for its bioadhesive character. The adhesion occurs shortly after swelling but the bond formed is not very strong. The adhesion increases with the degree of hydration till the point of disentanglement at the polymer tissue surface, which leads to abrupt drop in adhesive strength due to over hydration.

The formulation F6 shows higher value of Swelling percentage 138% which is due to presence of higher concentration of carbopol.

Water Vapour Transmission

Water vapor transmission rate through various patches was given in table. Water vapor transmission studies indicated that all the patches were permeable to water vapour. The formulation F4 has shown maximum water vapor transmission of among all the patches.

The formulation F6 has shown lower water vapor transmission of among all the patches. This may be due to the presence of high amount of carbopol.

Thickness and Weight of patches

The patch thicknesses were observed by using digital vernier caliper and found to be in the range of 0.51mm to 0.59mm. The weight of the patches was found to be in the range of 189.37to 183.18mg.

Folding endurance

The folding endurance was found to be greater than 81 times in case of all the formulations and 23 in case of F10 which was without plasticizer. This makes the system acceptable for movement of mouth, indicating good strength and elasticity. Folding endurance test results indicated that the patches would maintain the integrity with buccal mucosa when applied.

Drug content estimation

The observed results of content uniformity indicated that the drug was uniformly dispersed and with minimum intra batch variability. Recovery was possible to the tune of 14.56 to 15.89.

***In-vitro* drugrelease studies**

Distinguishable difference was observed in the release of candesartan in all formulations. The results and data of *in vitro* studies are shown in the Table No:. Formulations F1containing carbopol alone and Combination of carbopol in F4, F5 and F6 and HPMC gave a reasonable candesartan release up to 8 h.

Formulations,F2 and F3 containing alone HPMC and CMC respectively and F7,F8,F9 nad F10 having combination of HPMC and CMC gave a reasonable candesartan release up to 8 h.

The formulations F1, F2, F3, F4, F5 F6 F7, F8,F9and F10 has shown release 76%,59%,83%,88%,79%68%,81%,85%,80% and 83% respectively. Formulations F4 containing Combination of HPMC, CP gave a reasonable candesartan release up to 8 h.

At pH 6.8, carbopol is present in ionized state and as a result the polymeric network gets loosened comparatively, attributing for the higher drug release. The addition of CMC decreases the candesartan release may be due to enhancement in swelling of the polymer, which in turn increases the barrier effect and decreases the drug release, there by controlling the drug release approximately 8 h.

SUMMARY

The present study was aimed to formulate mucoadhesive drug delivery system to enhance bioavailability and avoid pre systemic metabolism.

The mucoadhesive patch was fabricated by solvent casting method employing ‘O’ shape ring placed on a glass surface as substrate by using different polymers such as Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC), Carbopol-P 934 (CP) and Carboxy methyl cellulose (CMC),water is used as the solvents. Propylene glycol serves as the plasticizer as well as penetration enhancer. Triethanolamine was used to neutralize the carbopol polymeric solution.The formulation F4 with Carbopol and HPMC in the ratio 1:4 showed drug release of 88% in 8 hours. The sole purpose of this work is to adhere the buccal film with the mucosa, hence formulation F4 was selected as best formulation.Thus the aim of the present to formulate a buccalmucoadhesive drug delivery system was fulfilled. The further scope of the work requires optimization for scale up and invivo animal studies.

CONCLUSION

The novel trans-buccoadhesive patches of Candesartan were prepared by solvent casting technique by employing the polymers of HPMC, Carbopol and CMC to obtain Candesartan buccal patches.Details regarding thepreparation and evaluation ofthe formulations have beendiscussedinthe previous chapter. From the study following conclusions couldbedrawn:-

- The Candesartan buccalmucoadhesive patches were prepared by the method of solvent casting technique employing ‘O’ shape ring placed on a glass surface as substrate by using different polymers such as Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC), Carbopol-P 934 (CP) and Carboxy methyl cellulose (CMC) .
- In-vitro drug release decrease with the addition of CMC due to enhancement in swelling of the polymer,

- The prepared Candesartan mucoadhesivebuccal patches were characterized based upon their physico-chemical characteristics like surface pH, swelling percentage, thickness, weight variation.
- Based on the results of evaluation tests formulation coded F4 was concluded as best formulation.

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