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DEVELOPMENT AND CHARACTERIZATION OF MUCOADHESIVE BUCCAL FILMS CONTAINING ANTIHYPERTENSIVE DRUG

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ABSTRACT

Candesartan cilexitil is an Angiotensin II receptor antagonist used in the treatment of hypertension. The conventional formulation of candesartan cilexitil is considered to be low in efficacy, primarily on account of their failure in providing and maintaining effective therapeutic drug levels. It shows low bioavailability due to high hepatic first pass metabolism. Hence, this study aims to focus on development of a mucoadhesive buccal delivery system with an objective of offering a rapid as well as a prolonged delivery coupled with enhanced therapeutic efficacy, patient compliance and the bioavailability. Buccoadhesive films of candesartan were prepared by solvent-casting method using novel and natural mucoadhesive polymers jack fruit gum and tamarind gum along with other polymers. Prepared films were evaluated for their weight, thickness, surface pH, swelling index, drug content uniformity, *in vitro* residence time, folding endurance *in vitro* release and permeation studies. The formulation C11 containing mucoadhesive polymer jackfruit gum was selected to prepare sustained release mucoadhesive films of Candesartan as this formulation retards the release rate upto 8hrs and at the end of 8 hrs the release rate was found to be highest (i.e., 99.6%). Formulation C11showed good swelling, a convenient residence time and promising extended drug release, which can be selected for the development of buccal film for effective therapeutic use. The data observed from this study highlight the feasibility of the buccal route as a viable option for delivery of candesartan cilexitil.

KEYWORDS: Buccal film, Candesartan cilexitil, jackfruit gum, tamarind gum, *ex vivo* studies.

1. INTRODUCTION

Among the various routes of administration oral route is the most convenient, easy and preferred one. However, orally administered drugs are either prone to hepatic first-pass metabolism or metabolism in gastrointestinal (GI) tract or both.[1] Delivery of drugs through various mucosal routes (nasal, rectal, vaginal, ocular and oral mucosa) offer the potential alternative solution for delivery of such types of drugs. These mucoadhesive drug delivery systems delivers the drugs into the systemic circulation by bypassing the hepatic first pass effects and avoiding the pre systemic elimination of the drug within the GI tract and thereby improving the bioavailability of the drug.[2] Out of the various sites available for mucoadhesive drug delivery, buccal mucosa is offers more advantages and is the most suited one for local as well as systemic delivery of drugs due to its anatomical and physiological features. The presence of smooth muscles with high vascular perfusion is the unique feature of buccal mucosa which avoids hepatic first pass metabolism and hence can potentially improve bio availability and this unique feature makes it as an ideal route for mucoadhesive drug delivery.[3] Moreover, these dosage forms are economic and patient-friendly. These systems are designed and formulated with the help of mucoadhesive polymers which are generally of high molecular weight and of high viscosity grades with greater flexibility and optimum chain length. Various mucoadhesive polymers have also been investigated for buccal drug delivery. Among all the mucoadhesive drug delivery systems, buccal films are better drug delivery systems than other mucoadhesive drug delivery systems such as gels and buccal tablets due to relatively longer residence time, more flexibility to cover the buccal mucosa and better comfort.[4]

Candesartan cilexitil is an angiotensin II receptor antagonist used mainly in the treatment of hypertension. It has low bioavailability (15%) due to hepatic first pass metabolism.[5,6] Therefore, to improve its therapeutic efficacy and bioavailability the drug may be administered by buccal route through buccal films. Buccal delivery of Candesartan may circumvent hepatic first pass metabolism and improve bioavailability. Hence the present work deals with the formulation and characterization of mucoadhesive buccal films of Candesartan cilexitil using natural mucoadhesive

polymers like jackfruit gum and tamarind gum along with other polymers.

2. MATERIALS AND METHODS

Candesartan cilexetil was obtained as a gift sample from Natco Pharma Ltd. (Hyderabad). Hydroxy Propyl Methyl Cellulose (HPMC E 50 LV) purchased from Noveon Inc. Carbopol 940 was purchased from Macleod Pharmaceuticals, Baddi. Ethanol and acetone were purchased from S.D. Fine-Chem Limited, Mumbai. Propylene glycol was obtained from Central Drug House Ltd., New Delhi. All other chemicals used were of analytical grade.

2.1 Drug-Excipient compatability studies

Pure drug Candesartan cilexitil and its physical mixture with the polymers is prepared by mixing with spatula followed by mixing in polybag. The samples were packed in vials and charged at 40^0C and 75% RH for 15 days. After 15 days, the samples were examined for DSC and FTIR to find any interaction between the drug and excipients. For FTIR analysis the samples were blended with potassium bromide in1:100 ratio and the blend was made into pellet under high pressure.The pellets were scanned over a wave number range of 4000–400cm-1 using Shimadzu, FTIR instrument. For DSC study 2-5 mg sample was programmed to increase temperature at a rate of 5°C/min from 20°C–500°C using DSC-60 Differential Scanning Calorimeter, Shimadzu.

2.2 Preparation of mucoadhesive buccal films

Mucoadhesive buccal films of Candesartan cilexitil were formulated using natural gums like Jackfruit gum and Tamarind gum as mucoadhesive polymers along with other polymers. Total 12 formulations were developed in which natural gums are used alone and in combination with the HPMC polymer in different ratios. Mucoadhesive buccal films of different formulations were shown in Table 1. Polymeric solutions were prepared by weighing desired quantities of polymers accurately and dissolved in solvents, ethanol and acetone. The beakers containing polymer and solvents were kept aside for 5 min for swelling of the polymer. Then 0.05 ml of propylene glycol was added to the polymer solution. Simultaneously Candesartan cilexitil was accurately weighed in quantity such that 1 cm^2film contained 16 mg and then dissolved in 1 ml of ethanol in another beaker. The drug solution was added to the polymer solution and was mixed thoroughly with the help of a magnetic stirrer. The whole solution was poured into the glass petri plate of size 8.8 cm in diameter and was dried in vacuum oven at 50^0C for 24 h. The backing layer was prepared by ethanolic solution of ethyl cellulose (1%, w/v). The homogenous solution was poured on the dried medicated film. It was dried in vacuum oven at 50^0C for 5 h. After drying, the films were observed and checked for possible imperfections upon their removal from the moulds.The dried bilayer films were cut into square pieces of sides 1 cm containing 16 mg of drug per patch, and then were packed in aluminum foil and stored in desiccator.

Table 1: Composition of various mucoadhesive buccal film formulations.

Ingredients	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
Candesartan cilexitil(mg)	32	32	32	32	32	32	32	32	32	32	32	32
HPMC E50LV(mg)	400	300	250	200	-	300	250	200	-	300	250	200
Carbopol p 940(mg)	-	100	150	200	-	-	-	-	-	-	-	-
Tamarind gum(mg)	-	-	-	-	400	100	150	200	-	-	-	-
Jack fruit gum(mg)	-	-	-	-	-	-	-	-	400	100	150	200
Propylene glycol(ml)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Ethanol(ml)	8	8	8	8	8	8	8	8	8	8	8	8
Acetone(ml)	10	10	10	10	10	10	10	10	10	10	10	10

3. Characterization of Buccal Films[7-11]

a. Thickness and weight

Screw gauge was used to measure the thickness of films. Three films, each of 1 cm^2 surface area were randomly selected and weighed. Then the average weight of the film was calculated.

b. Folding endurance

Number of times a film can be folded at the same place without breaking or cracking gives the value of folding endurance. This was determined by repeatedly folding the films at the same place until they were broke or were folded for 300 times which ever is less.

c. Surface pH

pH of film should be near to 7 or neutral to get absorb through oral mucosa without irritation and toxic effects. Film dissolved in suitable solvent is used to determine surface pH-by-pH meter. The surface pH of the film was determined in order to investigate the possible side effects; since an acidic or alkaline pH may cause irritation to the buccal mucosa. The buccal patch was allowed to swell by keeping it in contact with 5 ml distilled water for one hour at room temperature. The surface pH was measured by placing a pH paper on the surface of the swollen film. The experiment was performed and the average values were calculated.

d. Percent moisture absorption

The buccal films were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of aluminum chloride up to 86% relative humidity. After 3 days, the films were taken out and weighed. Percent moisture absorption determined by formula:

% moisture absorption=
final weight – initial weight/initial weight×100.

e. Percent moisture loss

The buccal films were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed. The percentage moisture absorption and moisture loss were calculated using the formula:
% moisture loss =
Initial weight - final weight /initial weight X 100

f. Swelling Index

Buccal film units were weighed individually, W1, and placed separately on 2% agar gel plates and incubated at $37^0C \pm 1^0C$. At every 30 minutes regular intervals, the films were removed from the gel and adhering gel was removed carefully with tissue paper. The weight of the swollen film was W2. Percentage swelling was calculated using the formula:
S.I=W2-W1/W1 X100
Mean of three determinations was considered. (n=3) Where, S.I = Swelling Index; W2 = Weight of swollen film after time t; W1 = Weight of film before placing in beaker.

g. Determination of in- vitro bio adhesion strength

Mucoadhesive strength was determined by using modified physical balance method for which porcine buccal mucosa was collected from local slaughter house and stored in saline solution. Mucosa layer was stick on the glass slide using double sided sticker which was already stuck on the bottom of 100ml beaker, and this beaker was placed in 1L of beaker. The mucosal and film surface was wetted with few drops of 0.01 N HCl and on the left pan film 50 gm weight was placed for 5 min to allow the initial contact of mucoadhesion. Then drop wise water was added in beaker of right pan till the detachment of tablet from the mucous membrane was observed. Then weight of water present in right pan beaker was determined, using following formula:
Mucoadhesive Strength (gm) = (Weight of beaker +Weight of water) - Weight of empty beaker. After determination of mucoadhesive strength, force of adhesion was calculated using formula, Force of Adhesion (N) = (Mucoadhesive Strength)/1000×9.81

h. Drug Content uniformity

Drug content uniformity was determined by dissolving the buccal film (10 mm in diameter) from each batch by homogenization in 100 ml of an isotonic phosphate buffer (pH 6.8) for 6 h under occasional shaking. The 5ml solution was taken and diluted with isotonic phosphate buffer pH 6.8 up to 20 ml, and the resulting solution was filtered through a 0.45 mm Whatman filter paper. The drug content was then determined after proper dilution at 238 nm using an UV-spectrophotometer. Percent drug content was calculated by
% drug content=
experimental drug content/theoretical drug content×100.

i. In vitro drug release from buccal films

The commercially available dialysis membrane (obtained from Sigma Chemicals) of 200 µm in thickness, pH 5.8 to 8 and porosity 2.4 nm was used as an artificial membrane for preliminary in-vitro studies because of simplicity, homogeneity and uniformity. Dialysis membrane is regenerated seamless cellulose tubing wherein the membrane is partially permeable, having molecular weight cut off between 12,000 to 14,000. This ideal for mimicking in-vivo permeation studies. For the activation of the dialysis membrane tubings were washed in running water for 3-4 hours to remove glycerol followed by treatment of tubing with sodium sulfide solution (0.3% w/v) at 80°C for 1 min to remove sulfur compounds, washed with hot water (60°C) for 2 min, followed by acidification with a 0.2% (v/v) solution of sulfuric acid, then rinse with hot water to remove the acid. Then the dialysis membranes were dipped overnight in the diffusion medium before dialysis for thorough wetting of the tubing.

The in vitro drug release study was carried out using a Franz diffusion cell.[3-5] The effective diffusion area was 1.8 cm^2. The receptor compartment (40 ml) was filled with phosphate buffer saline (PBS), pH 6.8. The films were fitted between the donor and receptor compartments of the diffusion cell. The drug release was performed at 37±0.5°C, at a stirring speed of 50 rpm using a magnetic stirrer. Five milliliters of the sample from receptor medium was withdrawn at regular intervals and replaced immediately with an equal volume of phosphate buffer saline, pH 6.8. The amount of candesartan released into the receptor medium was quantified by using UV–visible spectrophotometer at 238 nm against a blank.

Pharmacokinetics study

Because qualitative and quantitative changes in a formulation may alter drug release and *in vivo* performance, developing tools that facilitate product development by reducing the necessity of bio-studies is always desirable. In order to determine the drug release mechanism that provides the best description to the pattern of drug release, the *in vitro* release data were fitted into various model dependent methods such as zero order, first order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas model. Model dependent methods are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected, the dissolution profiles are evaluated depending on the derived model parameters. The preference of a certain release mechanism was based on the correlation coefficient (r) for the parameters studied, where the highest correlation coefficient is preferred for the selection of the mechanism of release. The release data of LP from different buccal patches prepared was fitted to following mathematical models like:
$Q_t = Q_0 + K_0 t$: Zero order model
$\log C = \log CK^t /2.303$: First order model
$f_t = Q = K_H \times t^{1/2}$: Higuchi model

$M_t/M_\infty = Kt^n$: Korsmeyer–Peppas model

Where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most of the times, $Q_0 = 0$), K_0 is the zero order release constant expressed in units of concentration/time, C_0 is the initial concentration of drug, K is the first order rate constant, K_H is the Higuchi dissolution constant, W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and κ (kappa) is a constant incorporating the surface volume relation, $M_t/M\infty$ is a fraction of drug released at time t, K is the release rate constant and n is the release exponent.

In vitro dissolution has been recognized as an important element in drug development. To analyse the mechanism of the release and release rate kinetics of the formulated dosage form, the data obtained from conducted studies was fitted into Zero order, First order, Higuchi matrix, Korsmeyer-Peppas models.

Stability studies

The optimized film formulation was subjected to stability testing for periods of 2 months at room temperature to simulate patient usage conditions and Refrigerator condition (40^0C). During 2 months of storage, the formulations were examined periodically after 30, 45 and 60 days for physical stability and chemical stability by means of drug content and pH.

4. RESULTS AND DISCUSSION

4.1 Drug excipient compatibility studies

To asses any interaction between the drug and the polymer, FTIR and DSC studies were carried out.The FTIR spectra were shown in "Fig 1(a)-(e)".The FTIR spectra of combination of drug with the polymer did not show any changes in the characteristic peaks of the Candesartan cilexitil. The specific peaks at wave number1665.82 cm^{-1}due to C=O stretching(ketone), 3210.62 cm^{-1} due to O-H stretching (alcoholic), 3320.42 cm^{-1} due to N-H stretching(amine), 1660.09 cm^{-1} aromatic C=C remain unchanged indicating that the drug had not interacted with the polymer.

The DSC thermogram revealed sharp distinct endothermic peak at 174.9°C which remained unchanged when the drug was combined with the polymer. The DSC analysis of the physical mixture of thedrug and the polymer revealed a negligible change in the melting point of Candesartan cilexitil. The DSC thermograms were shown in "Fig 2(a)-(e)".

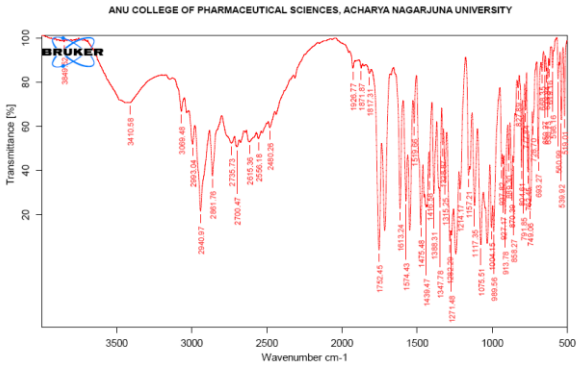

Fig 1(a): FTIR spectra of pure drug Candesartan cilexitil.

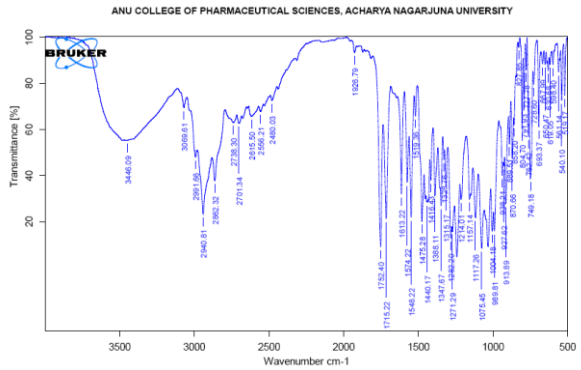

Fig. 1(b): FTIR spectra of Candesartan cilexitil +HPMC.

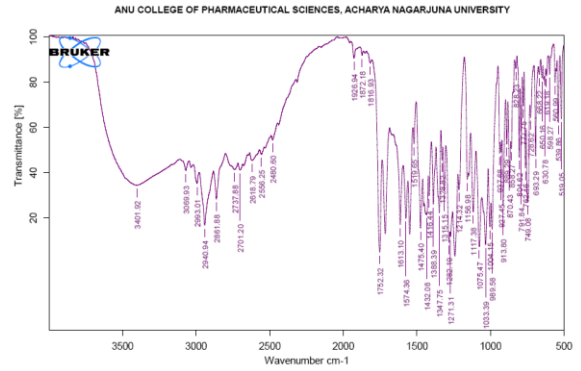

Fig. 1(c): FTIR Spectra of Candesartan and Jackfruit gum.

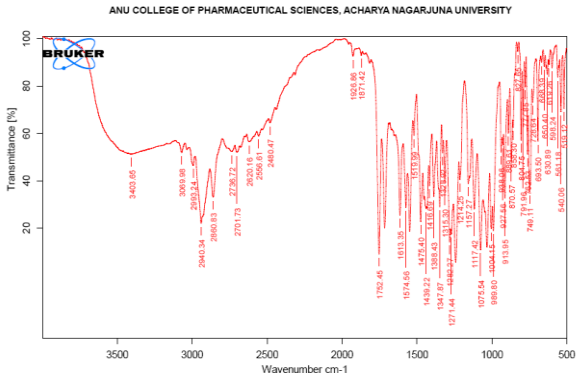

Fig. 1(d): FTIR Spectra of Candesartan cilexitil and Tamarind gum.

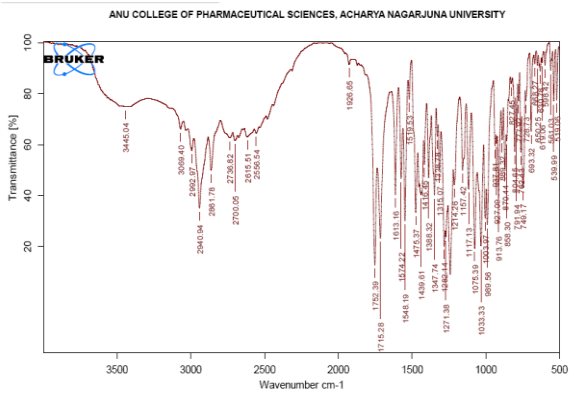

Fig 1(e): FTIR Spectra of Candesartan cilexitil and Carbopol.

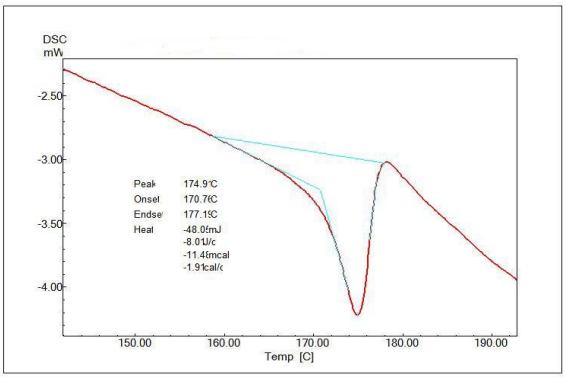

Fig. 2(a): DSC of pure drug Candesartan Cilexitil.

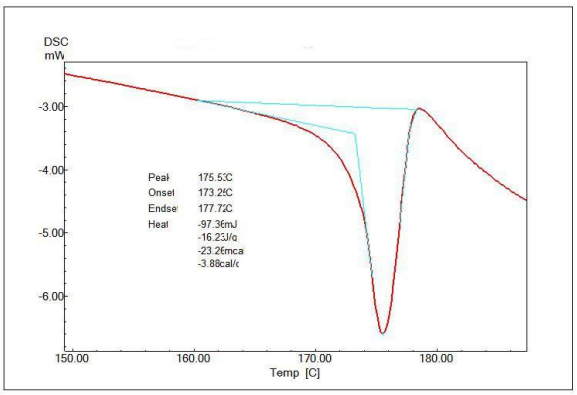

Fig. 2(b): DSC of Candesartan Cilexitil and Jackfruit gum.

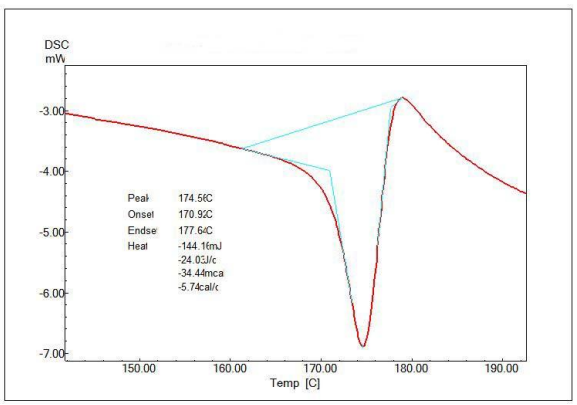

Fig. 2(c): DSC of Candesartan Cilexitil and Tamarind gum.

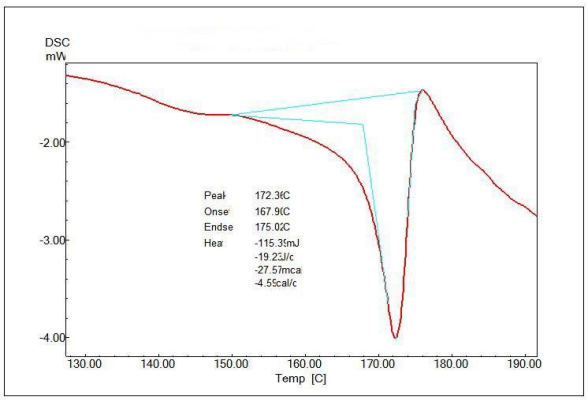

Fig 2(d): DSC of Candesartan Cilexitil and HPMC.

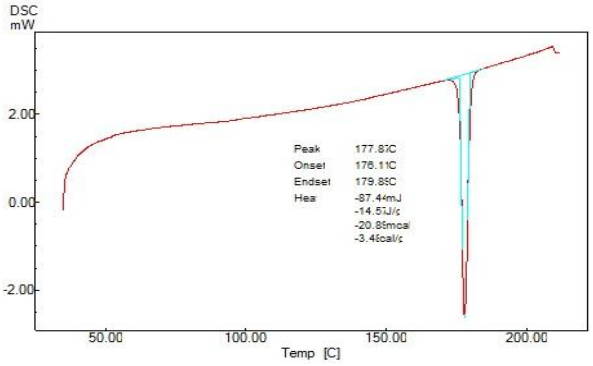

Fig. 2(e): DSC of Candesartan Cilexitil and Carbopol.

4.2 Characterization of buccal films

All the Physico-chemical characteristics of the bilayer films were shown in Table 2.

a. Thickness and weight

The average thickness of all prepared buccal films ranged from 0.17 to 0.26 mm. Weight variation values (g) of film (1 cm^2) for formulations C1 to C12 were found to be between 100 and 164 mg. As the thickness of the films increases, proportional gain in weight of films was observed. This depicts uniform film casting.

b. Folding endurance

As the film forming polymer concentration increases there observed an increase in folding endurance. Folding endurance values for films indicates high mechanical strength of these films. This is highly desirable because it would not allow easy dislocation of the films from the site of application or breaking of film during administration. All the films exhibited folding endurance more than 200 times.

c. Surface pH

The surface pH of the films was determined to examine the possible side effects due to acidic or alkaline pH, which leads to irritation of buccal mucosa. The buccal film was allowed to swell by keeping in contact with 5 ml distilled water for one hour at room temperature. Acidic or alkaline pH may cause irritation to the buccal mucosa and influence the rate of hydration of polymer. The surface pH was measured by placing a pH paper on

the surface of the swollen film. The surface pH of all formulations ranged from 6.3 to 6.81.As the values were near to the neutral pH, no mucosal irritation were expected and ultimately achieve patient compliance.

d. Percent moisture absorption

Moisture interaction studies are necessary to find out the physical stability of the film at high humid conditions and integrity of the film at dry conditions.The percent moisture absorption study was done over a period of 3 days and the results were found to be varied between 4.8% ± 0.02 percentage and 5.4% ± 0.36 percentage. Microbial contaminations and bulkiness of the film can be reduced by presence of low moisture content but low moisture content can make film completely dried and brittle.

e. Percent moisture loss

The results of percent moisture loss varied between 2.40% ± 0.025 percentage and 3.6% ± 0.04 percentage. It is found that increase in the viscosity of the polymer causes retention of moisture capacity and thus slow decline of percent moisture loss. Capacity of excipients to absorb water in vapour form decides percentage moisture absorption. High moisture content in films can be observed by percentage moisture loss. There is inverse relationship between percentage moisture loss and percentage moisture absorption.

f. Swelling Index

The degree of swelling of the bio adhesive polymers is an important factor affecting film bioadhesion. The faster the swelling of the polymer is the faster the initiation of drug diffusion and formation of adhesive bonds resulting in faster initiation of bioadhesion. Maximum hydration was obtained with formulation C11.It may be due to the presence of more amounts of water soluble polymer HPMC than the mucoadhesive polymer Jackfruit gum. Although the marked increase in surface area during swelling can promote drug release but the increase in diffusion path length of the drug may paradoxically delay the release. In addition, the thick gel layer formed on the swollen film surface is capable of preventing matrix disintegration and controlling additional water penetration,So though the swelling index of the formulation C11 is higher it can retard the release rate of the drug upto 8hrs. The swelling index for all the formulations was shown in the "Fig 3".The results indicated that the increase in the polymer concentrations decreased the release rate of the drug higher concentrations of the polymer reduced the diffusion of the drug from the film into the buccal mucosa.

g. Mucoadhesive strength

Buccal film is intended to be delivered by buccal route for either local or systemic action. In either case, it has to be hold on to the buccal mucosa for an extended period of time. Therefore, it must display good mucoadhesive characteristics. Different polymeric combinations showed variations in mucoadhesive strength of films. Mucoadhesive strength also relates to drug release and permeation of drug from buccal mucosa. Highest mucoadhesive strength was observed for the formulation C11 (50.2± 0.026) containing mucoadhesive polymers Jackfruit gum. The result indicated that the jack fruit gum can act as a good mucoadhesive polymer exhibiting good mucoadhesive strength. The mucoadhesive strength of all the formulations was shown in the "Fig 4".

h. Drug Content uniformity

Content uniformity is determined by as per standard assay. The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 88 to 99 %.

i. In-vitro drug release

In vitro drug release study performed up to 8 h provide a clear indication that prepared patches show necessary sustained release profile desired for buccal adhesive drug delivery. In –vitro drug release rate was higher for formulation C1.The drug release rate for formulation C1 was found to be 97.2% within 5 hrs. Though the drug release rate was higher, it failed to sustain the release rate of the drug upto 8 hrs. The Invitro drug release rate of formulations C2, C6 and C10 were also found to be higher but these formulations were also failed to sustain the release rate of the drug upto 8 hrs. Though the release rate retarding polymers were there in the formulations,the concentration of water soluble polymer HPMC was more when compared to these release retarding rate polymers. So the formulation C11 containing mucoadhesive polymer jackfruit gum was selected to prepare sustained release mucoadhesive films of Candesartan as this formulation retards the release rate upto 8hrs and at the end of 8 hrs the release rate was found to be highest (i.e., 99.6%). It indicates the efficiency of mucoadhesive polymers jackfruit gum.

Table 2: Physicochemical characteristics and permeation studies of Candesartan mucoadhesive buccal film formulations.

Formulation	Thickness (mm) ±S.D (n=3)	Weight uniformity (mg) ±S.D (n=3)	Folding endurance	Mucoadhesive strength (gm)±S.D (n=3)	Surface pH ±S.D (n=3)	% Moisture loss ±S.D (n=3)	% Moisture absorption ±S.D (n=3)	Swelling index ±S.D (n=3)	Drug content ±S.D (n=3)
C1	0.22 ± 0.032	80 ± 0.05	> 200	24.3± 0.043	6.5±0.47	1.3±0.055	2.8±0.015	92± 0.02	96±0.32
C2	0.21 ± 0.014	85 ± 0.03	> 200	28± 0.014	6.6±0.32	2.4±0.23	2.9±0.38	88± 0.013	92±0.03
C3	0.17 ± 0.053	150 ± 0.05	> 200	48.5± 0.035	6.3±0.31	2.2±0.54	3.2±0.97	52± 0.004	90± 0.04
C4	0.15± 0.025	100± 0.02	> 200	47.2± 0.002	6.3± 0.012	1.7± 0.12	2.7± 0.12	57± 0.031	95± 0.05
C5	0.19± 0.038	120± 0.04	> 200	32.2± 0.014	6.8± 0.020	1.5±0.005	2.4±0.002	64± 0.024	99± 0.09
C6	0.26 ± 0.076	132 ± 0.012	> 200	30.4± 0.052	6.6±0.024	1.6±0.18	2.7±0.91	74± 0.02	91±0.67
C7	0.24 ± 0.035	144 ± 0.015	> 200	49.5± 0.031	6.3±0.74	1.8±0.263	1.8±0.063	49± 0.012	95±0.34
C8	0.23 ± 0.054	157 ± 0.023	> 200	46.2± 0.039	6.5±0.51	2.3±0.51	3.6±0.049	60± 0.03	94±0.22
C9	0.19 ± 0.021	162 ± 0.003	> 200	38.6± 0.024	6.4±0.36	2.2±0.07	3.2±0.24	62± 0.06	88± 0.067
C10	0.22± 0.020	159± 0.02	> 200	28.6± 0.019	6.5± 0.019	1.7± 0.19	2.3± 0.12	81± 0.022	97± 0.015
C11	0.22± 0.029	164± 0.06	> 200	50.2± 0.026	6.5± 0.014	2.3± 0.07	2.4± 0.03	84± 0.015	99± 0.019
C12	0.21 ± 0.034	160 ± 0.03	> 200	36.6± 0.015	6.6±0.034	1.7±0.23	2.8±0.41	68± 0.012	96±0.23

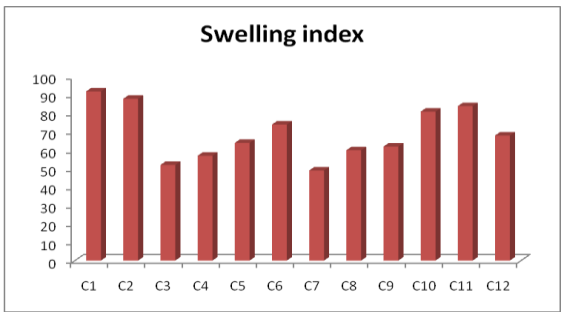

Fig. 3: Swelling index of Candesartan cilexitil buccal film formulations.

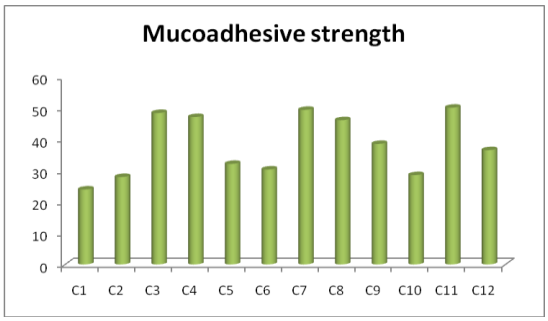

Fig. 4: Mucoadhesive strengths of Candesartan cilexitil buccal film formulations.

Pharmacokinetics study

In-vitro drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetics and according to Higuchi and Peppas models to ascertain mechanism of drug release. The optimized formulation showed 'n' value 1.5722 indicating that drug release by diffusion followed by Supercase II transport mechanism. obtained values of K (kinetic constant), n (diffusional exponent) and r^2 (correlation coefficient) of the *in vitro* release data of Candesartan from mucoadhesive films were presented in Table 3. For all the tested formulations, the values of n on fitting the simple power equation $Mt/M\infty = Kt^n$ were above 0.89 for the release of Candesartan from all the film formulations indicating supercase II transport. The plots were shown in the "Fig 5-8".

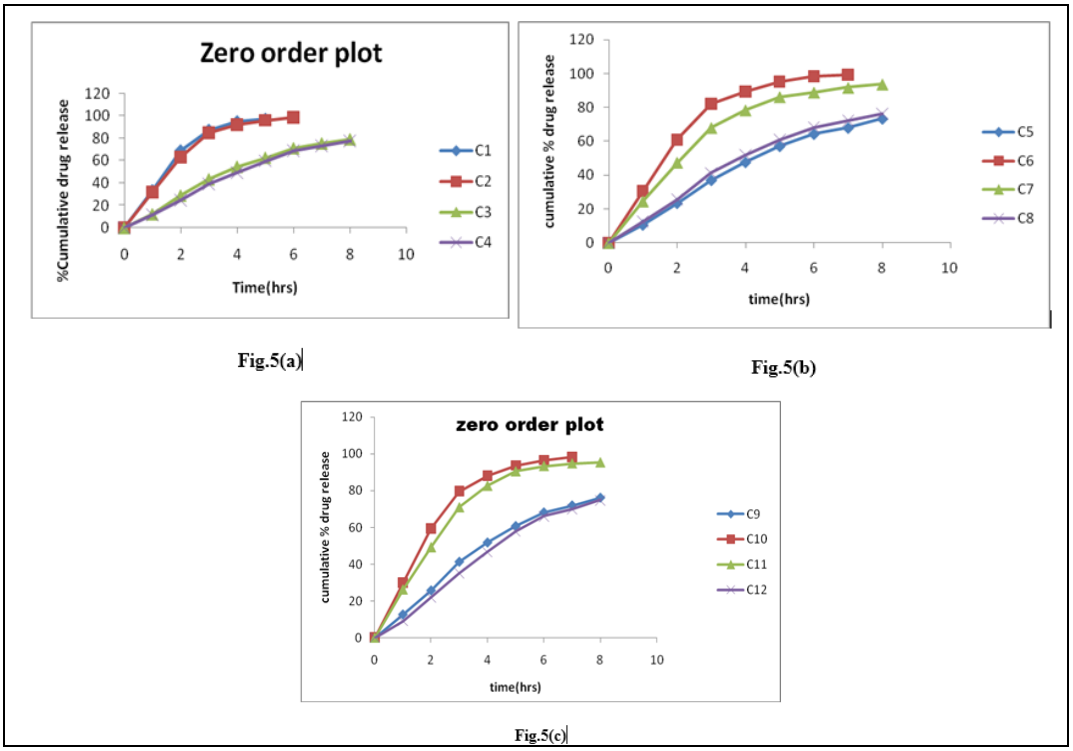

Fig. 5: Zero order plots of Candesartan cilexitil mucoadhesive buccal film formulations.

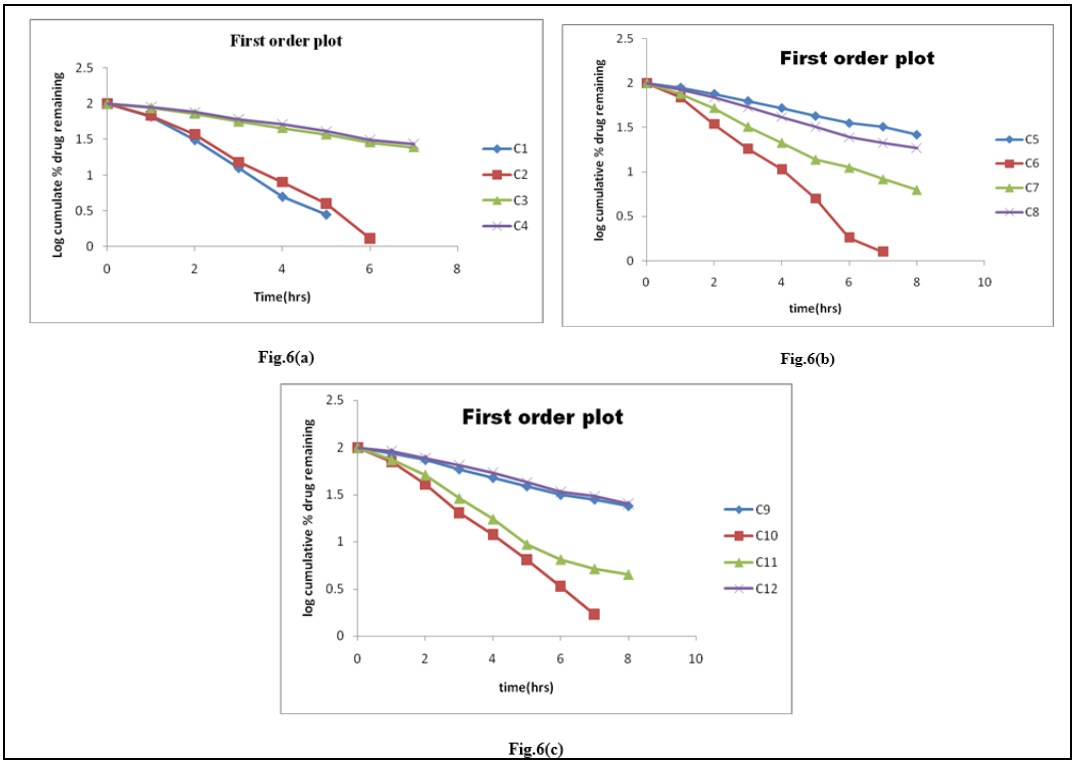

Fig. 6: First order plots of Candesartan cilexitil mucoadhesive buccal film formulations.

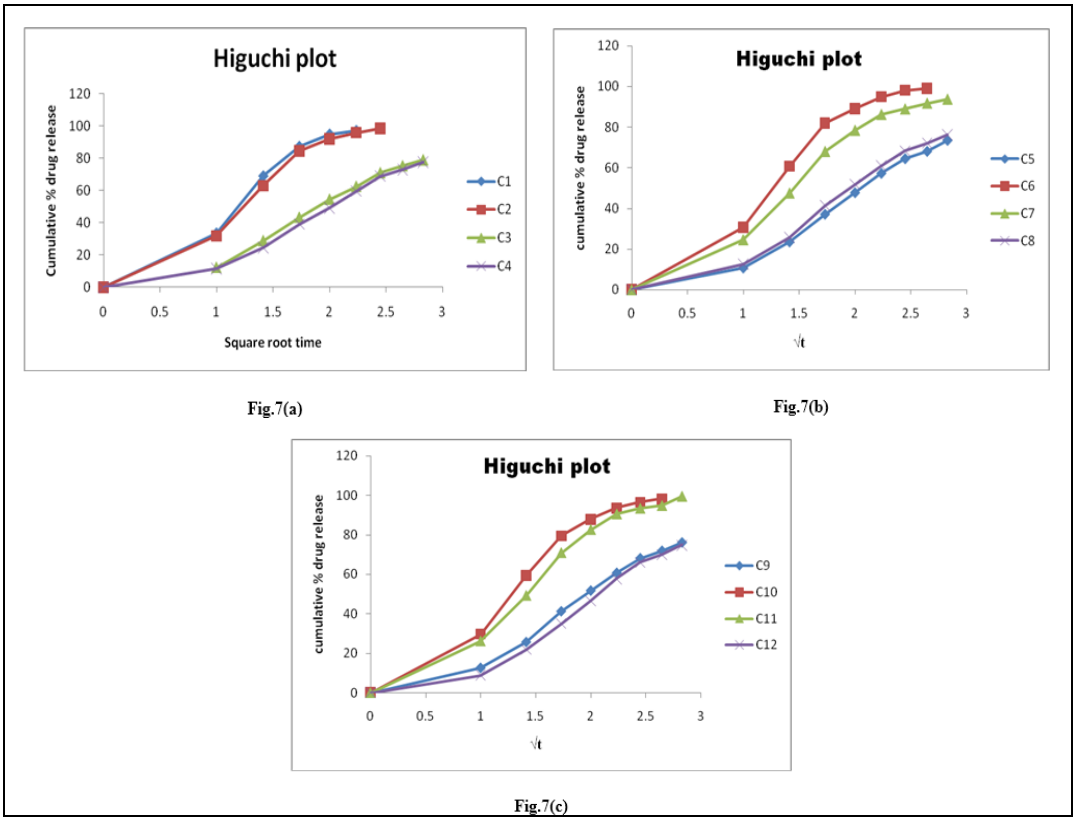

Fig. 7: Higuchi plots of Candesartan cilexitil mucoadhesive buccal film formulations.

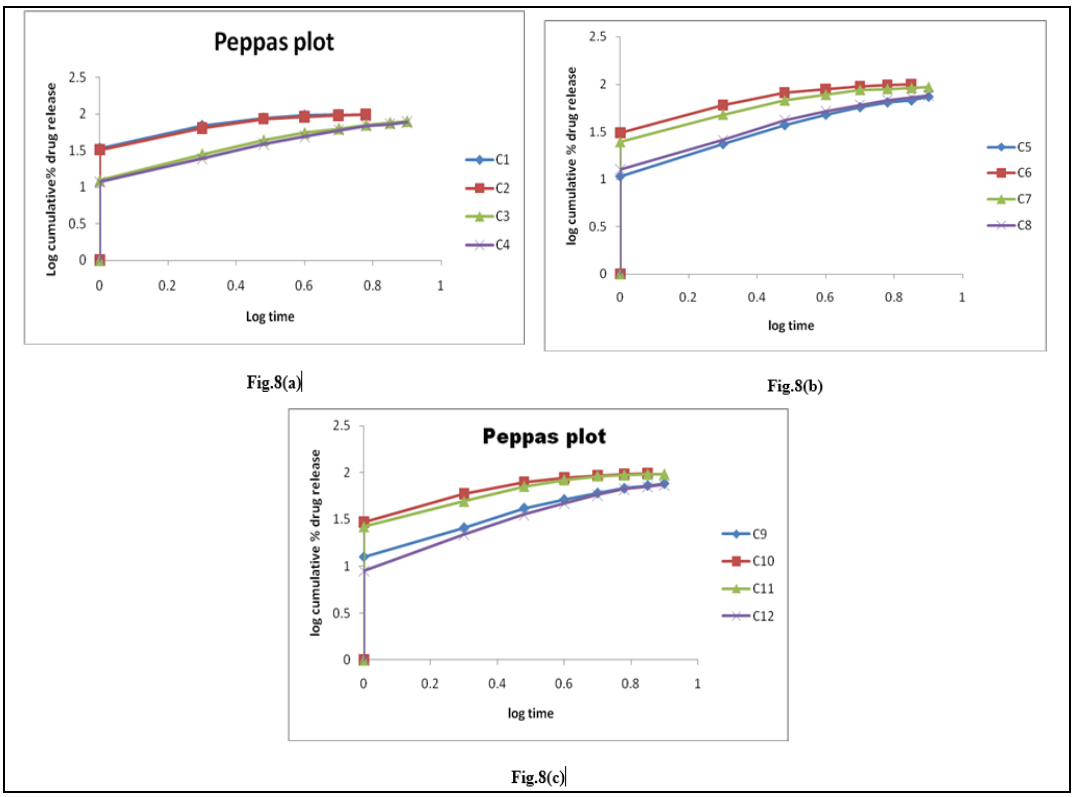

Fig. 8: Peppas plots of Candesartan cilexitil mucoadhesive buccal film formulations.

Table 3: Release kinetics of various formulations for Candesartan cilexitil mucoadhesive buccal films.

Formulation	Zero Order Plot R^2	First Order R^2	Higuchi Plot R^2	Peppas Plot R^2	Peppas Plot n value
C1	0.8844	0.9895	0.966	0.5391	1.6662
C2	0.8608	0.9856	0.9639	0.7237	1.5148
C3	0.9564	0.9964	0.99	0.7422	1.5181
C4	0.9732	0.9913	0.9534	0.7503	1.5127
C5	0.9693	0.996	0.954	0.5492	1.5163
C6	0.8322	0.9906	0.9585	0.5915	1.422
C7	0.858	0.9907	0.9644	0.7215	1.4912
C8	0.9592	0.994	0.9606	0.7219	1.4914
C9	0.9594	0.9952	0.9602	0.5542	1.5163
C10	0.8414	0.9955	0.9613	0.5848	1.4265
C11	0.8431	0.9795	0.9573	0.7864	1.5722
C12	0.9756	0.9932	0.9401	0.5391	1.6662

Stability studies

The packed samples were kept for stability study at 40^0C with 75% RH for 2 months. Sample were collected after every 1 month and evaluated. The drug content and other parameters were compared with initial profile to check the effect of storage on drug release of the formulation. Stability study parameters for optimized C-11 Batch was evaluated. The results were shown in the Table 4.

Table 4: Physico chemical evaluation of formulation C-11 during stability studies at 40 ±2 ^{0}c/75 ±5%RH.

Parameter	0Days	30 Days	45 days	60 Days
Thickness(mm)	0.21±0.053	0.21±0.03	0.21±0.012	0.21±0.053
Folding endurance(times)	>200	>200	>200	>200
Surface pH	6.5±0.37	6.5±0.37	6.5±0.37	6.5±0.37
Swelling index	92± 0.067	94± 0.023	92± 0.017	92± 0.04
Mucoadhesive strength	49.5± 0.0	50.1± 0.0	51.1± 0.0	50.1± 0.0
Drug content	97± 0.080	98± 0.082	97.5± 0.081	98± 0.082

4. CONCLUSION

An attempt to improve the bioavailability of candesartan cilexitil was planned using natural polymers Jackfruit gum and Tamarind gum along with the combination of other polymers. The results of all the physical characterization of all formulations C1-C12were found to be satisfactory. The results of the study show that therapeutic levels of Candesartan cilexitil can be delivered through buccal route. The present study concludes that these erodible mucoadhesive buccal films containing drug can be very promising for effective doses to systemic circulation. These may also provide an added advantage of circumventing the hepatic first pass metabolism. It was concluded that the films containing 16 mg of Candesartan cilexitil in HPMC E50LV and Jackfruit gum (formulation C11) showed good swelling and promising sustained drug release. Thus, C11buccal film can be used for effective therapeutic uses. Buccal films have gained relevance in pharmaceutical industry as a novel, patient-friendly convenient products. The study may be extended for assessing the *in vivo* release and *in vitro–in vivo* correlation. The future scope could be tested in human volunteers to evaluate bioavailability parameters.

5. ACKNOWLEDGEMENT

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