**FORMULATION DEVELOPMENT & EVALUATION OF CANDESARTAN CILEXITIL
MUCOADHESIVE BUCCAL FILMS****K. Prema Kumari*, T. Malyadri and P. Sreenivasaprasana**

Department of Pharmaceutics, M.L. College Pharmacy, Singarayakonda A.P- 101.

***Corresponding Author: K. Prema Kumari**

Department of Pharmaceutics, M.L. College Pharmacy, Singarayakonda A.P- 101.

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ABSTRACT

Candesartan cilexetil useful in the treatment of hypertension having Angiotensin II receptor antagonist activity. Buccoadhesive films of candesartan were prepared by solvent-casting method using novel polymers to improve the efficacy and bioavailability than the conventional formulations. The prepared buccal 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 contains polyox to prepare sustained release mucoadhesive films of Candesartan as this formulation retards the release rate up to 8 hrs and at the end of 8 hrs the release rate was found to be highest (i.e., 99.6%). Formulation C11 showed 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 cilexetil.

KEYWORDS: Buccal film, Candesartan cilexetil, 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 deliver 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 bioavailability 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 cilexetil 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 cilexetil with other polymers.

2. MATERIALS AND METHODS

Candesartan cilexetil was obtained as a gift sample from commercial labs. 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 compatibility studies

Pure drug Candesartan cilexetil 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°C 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 in 1:100 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.

2.2 Preparation of mucoadhesive buccal films

Mucoadhesive buccal films of Candesartan cilexetil were formulated using polyox polymer 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 cilexetil was accurately weighed in quantity such that 1 cm² film 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°C 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°C 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 cilexetil(mg) | 32 | 32 | 32 | 32 | 32 | 32 | 32 | 32 | 32 | 32 | 32 | 32 |
| Polyox | 100 | 75 | 50 | 25 | - | 75 | 50 | 25 | - | 75 | 50 | 25 |
| HPMC E50LV(mg) | 400 | 300 | 250 | 200 | - | 300 | 250 | 200 | - | 300 | 250 | 200 |
| Carbopol p 940(mg) | - | 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 cm² 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:

$$\% \text{ moisture absorption} = \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \times 100.$$

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:

$$\% \text{ moisture loss} = \frac{\text{Initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

f. Swelling Index

Buccal film units were weighed individually, W1, and placed separately on 2% agar gel plates and incubated at 37°C ± 1°C. 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.

$$S.I = \frac{W2 - W1}{W1} \times 100$$

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.⁷ 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 X 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.^[1,3,4] The effective diffusion area was 1.8 cm². 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:

$$Q_t = Q_0 + K_0 t \quad : \text{Zero order model}$$

$$\log C = \log CK^t / 2.303 \quad : \text{First order model}$$

$$f_t = Q = K_H \times t^{1/2} \quad : \text{Higuchi model}$$

$$M_t/M_\infty = Kt^n \quad : \text{Korsmeyer-Peppas model}$$

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_∞ 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°C). 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 assess any interaction between the drug and the polymer, FTIR was 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 cilexetil. The specific peaks at wave number 1665.82 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 the drug and the polymer revealed a negligible change in the melting point of Candesartan cilexetil. The DSC thermograms were shown in “Fig 2(a)-(e)”.

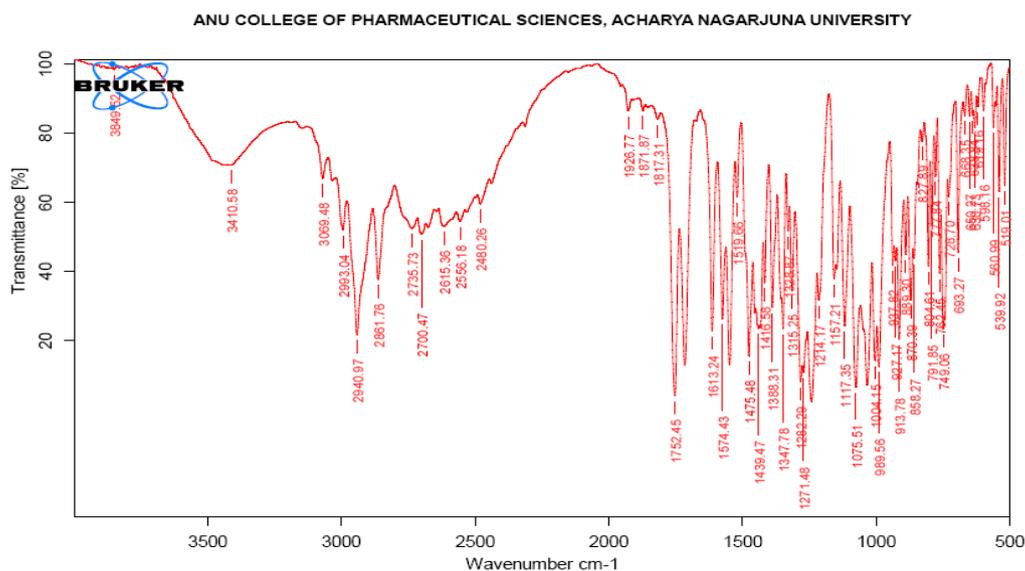


Fig. 1(a): FTIR spectra of pure drug Candesartan cilexetil.

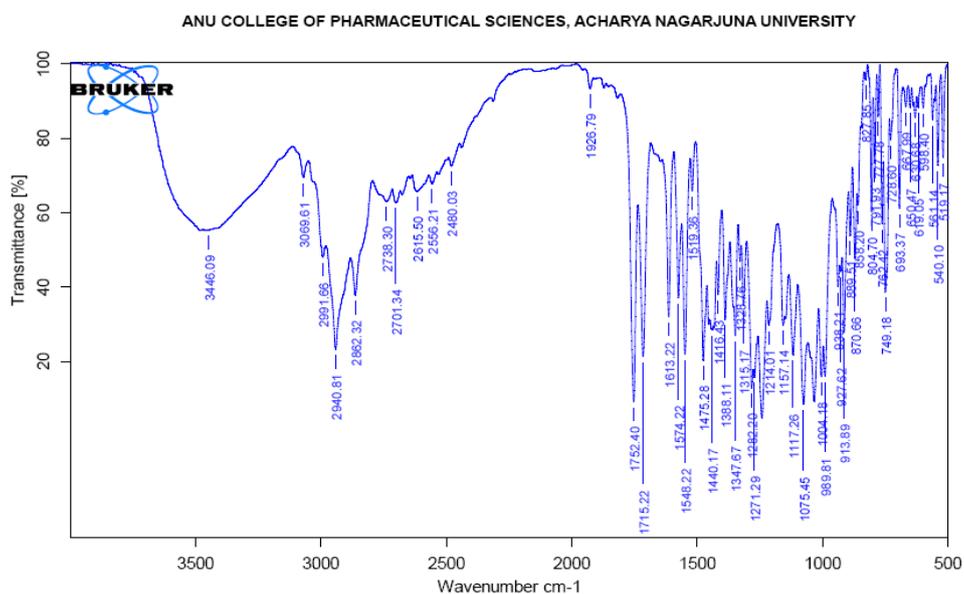


Fig. 1(b): FTIR spectra of Candesartan cilexetil + HPMC.

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 cm²) 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. 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 polyox gum. The result indicated that the polyox 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 *In vitro* 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 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 at this concentration.

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 | 23.3± 0.043 | 6.5±0.47 | 1.3±0.055 | 2.8±0.015 | 93± 0.02 | 96±0.32 |
| C2 | 0.21 ± 0.014 | 85 ± 0.03 | > 200 | 27.5± 0.014 | 6.6±0.32 | 2.4±0.23 | 2.9±0.38 | 87± 0.013 | 92±0.03 |
| C3 | 0.17 ± 0.053 | 150 ± 0.05 | > 200 | 47.5± 0.035 | 6.3±0.31 | 2.2±0.54 | 3.2±0.97 | 54± 0.004 | 90± 0.04 |
| C4 | 0.15± 0.025 | 100± 0.02 | > 200 | 46.2± 0.002 | 6.3± 0.012 | 1.7± 0.12 | 2.7± 0.12 | 58± 0.031 | 95± 0.05 |
| C5 | 0.19± 0.038 | 120± 0.04 | > 200 | 32.7± 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 | 30.6± 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 | 49.7± 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 | 45.2± 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 | 38.4± 0.024 | 6.4±0.36 | 2.2±0.07 | 3.2±0.24 | 64± 0.06 | 88± 0.067 |
| C10 | 0.22± 0.020 | 159± 0.02 | > 200 | 28.8± 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 | 50.8± 0.026 | 6.5± 0.014 | 2.3± 0.07 | 2.4± 0.03 | 88± 0.015 | 99± 0.019 |
| C12 | 0.21 ± 0.034 | 160 ± 0.03 | > 200 | 36.9± 0.015 | 6.6±0.034 | 1.7±0.23 | 2.8±0.41 | 68± 0.012 | 96±0.23 |

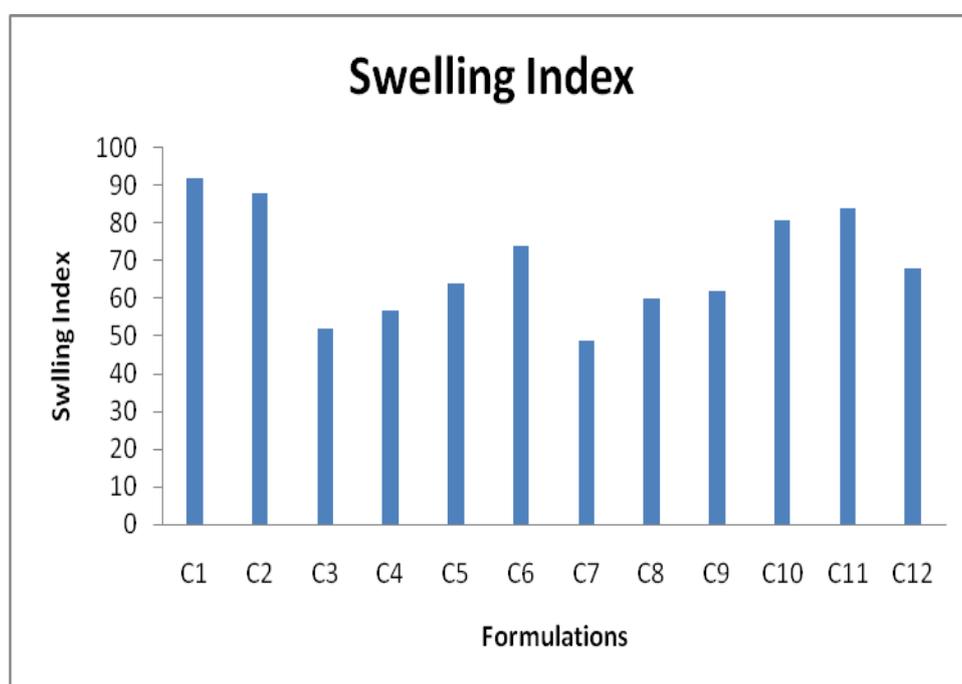


Fig. 3: Swelling index of Candesartan buccal film formulations.

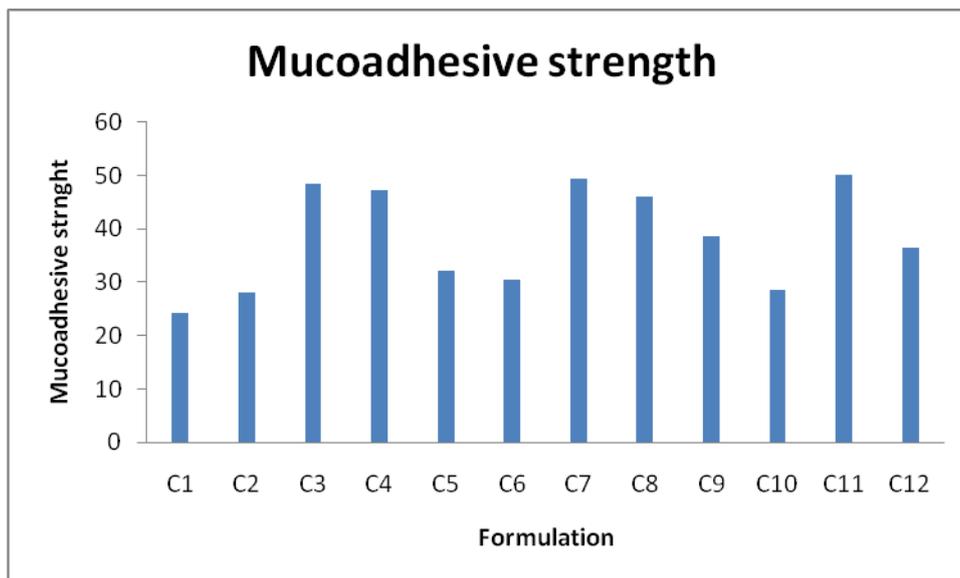


Fig. 4: Mucoadhesive strengths of Candesartan cilexetil buccal film formulations.

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”.

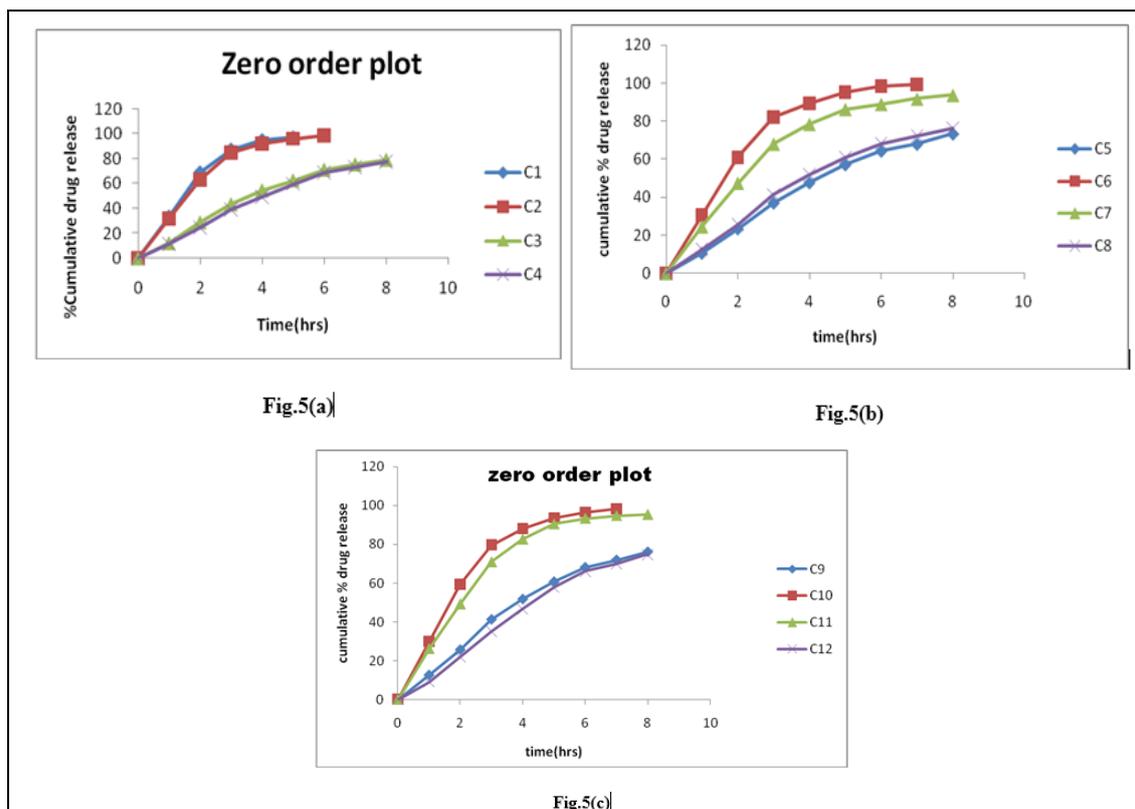


Fig. 5: Zero order plots of Candesartan cilexetil mucoadhesive buccal film formulations.

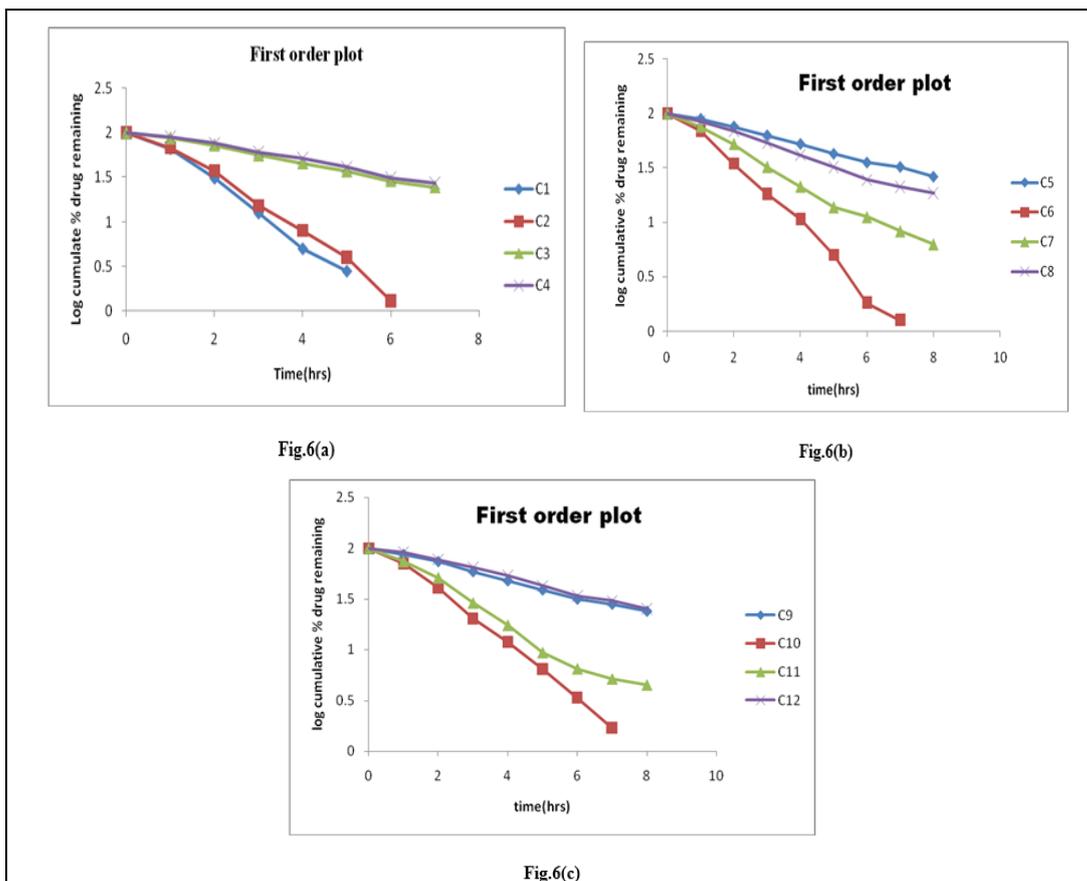


Fig. 6: First order plots of Candesartan cilexetil mucoadhesive buccal film formulations.

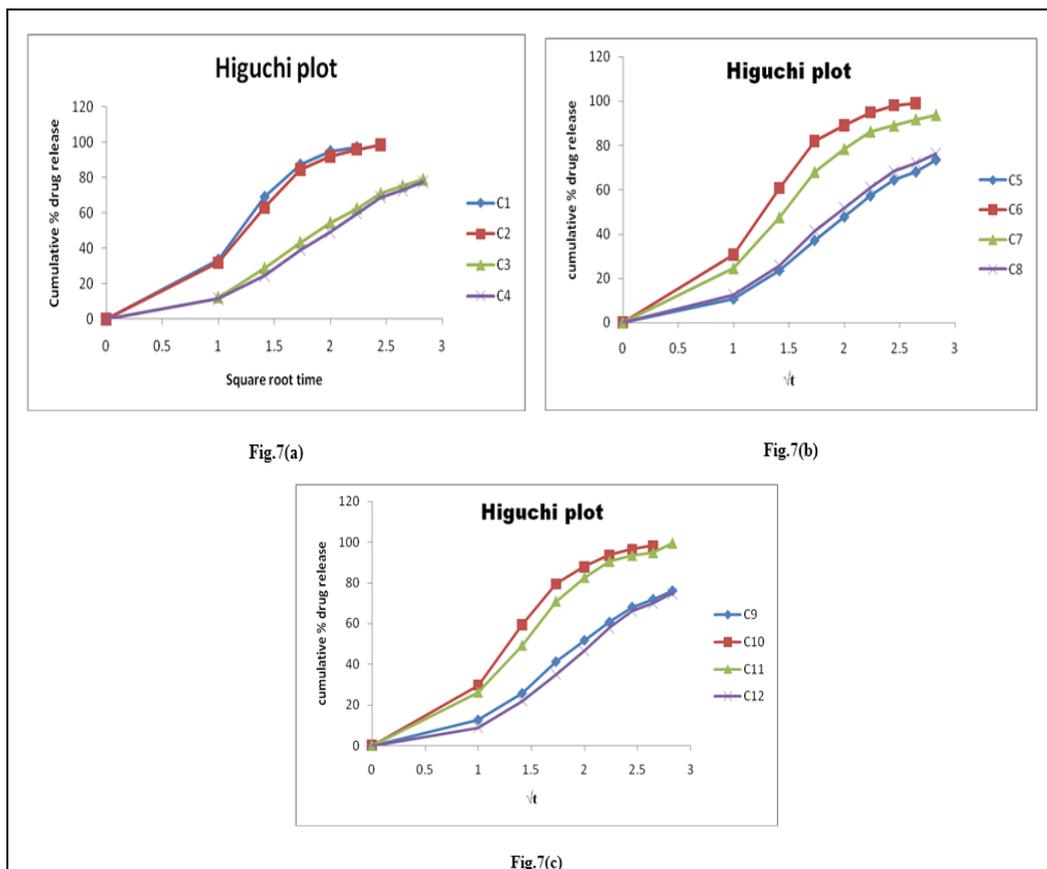


Fig. 7: Higuchi plots of Candesartan cilexetil mucoadhesive buccal film formulations.

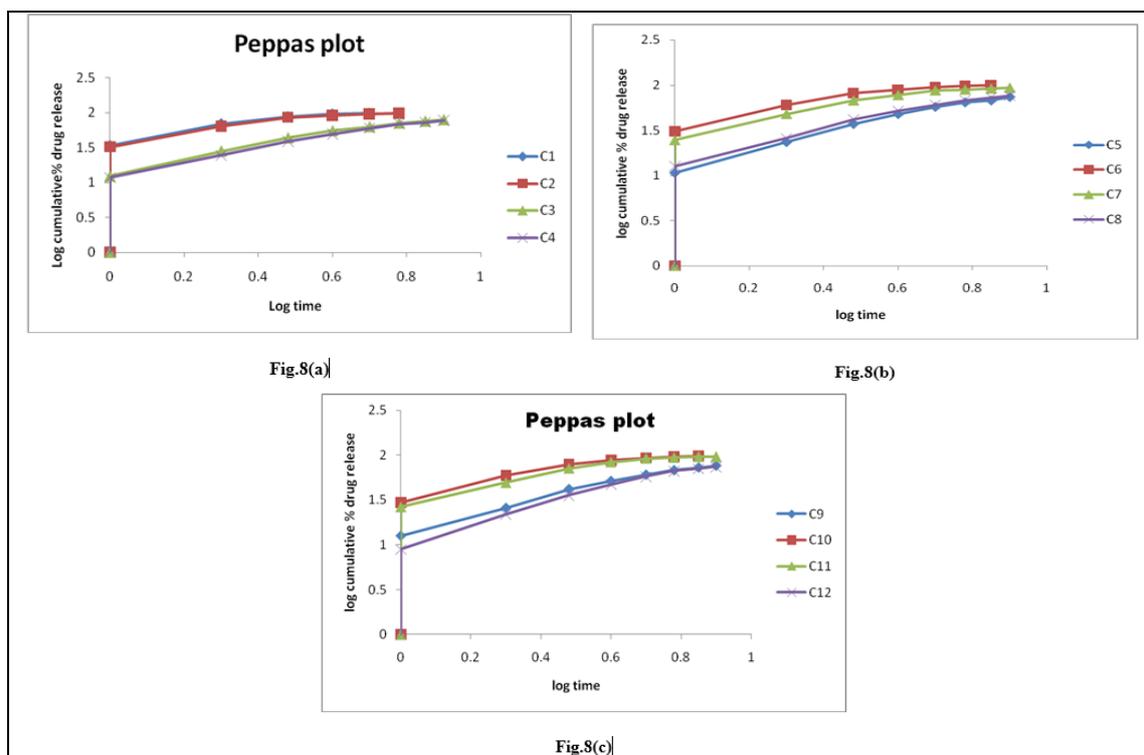


Fig. 8: Peppas plots of Candесartan cilexetil mucoadhesive buccal film formulations.

Table 3: Release kinetics of various formulations for Candесartan cilexetil 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°C 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 °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 |

CONCLUSION

Buccal films have gained relevance in pharmaceutical industry as a novel, patient-friendly convenient products. The present work is to improve the bioavailability of

candesartan cilexetil using the polyox polymer with other polymers. The results of all the physical characterization of all formulations C1-C12 were found to be satisfactory. The results of the study show that therapeutic levels of

Candesartan cilexetil can be delivered through buccal route. It was concluded that the films containing 16 mg of Candesartan cilexetil in HPMC E50LV and polyox (formulation C11) showed good swelling and promising sustained drug release. Thus, C11 buccal film can be used for effective therapeutic uses.

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