Mucoadhesive buccal film containing candesartan cilexetil loaded nanosuspension: Formulation, characterization and ex vivo permeation

Harshitha Gona[1], Saritha Chukka[1*]

[1]Department of Pharmacy, Chaitanya (Deemed to be University), Himayathnagar, Moinabad, Hyderabad, Telangana, India

Corresponding Author: Dr. Saritha Chukka, M. Pharm., Ph.D., Associate Professor, Chaitanya (Deemed to be University) Pharmacy, Himayathnagar, Moinabad, Hyderabad, Telangana, India
Email: sarithapuligilla28@gmail.com

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ABSTRACT

Introduction: Candesartan cilexetil (CC) is an antihypertensive drug and is also used for the management of many coronary heart diseases. It is a selective, reversible and competitive angiotensin II type-1 (AT1) receptor blocker. It belongs to class II drug and is characterized by low solubility and high permeability. It has limited bioavailability due to poor aqueous solubility and first pass metabolism.

Aim & Objective: The main objective of this research work was to develop and evaluate nanosuspension incorporated Candesartan cilexetil mucoadhesive buccal films for bioavailability enhancement by avoiding first-pass metabolism.

Materials & methods: Candesartan cilexetil-loaded nanosuspension was prepared by a precipitation-ultrasonication method with varying concentrations of the polymer and was analyzed for size, size distribution, surface charge and morphology. Optimized nanosuspension was incorporated into drug gel layer which was sandwiched between a mucoadhesive layer and a backing layer to form tri-layered buccal films. They were evaluated for their physical, mechanical and bioadhesive parameters followed by *in vitro* studies and stability studies.

Results & Discussion: The optimized nanosuspension incorporated Candesartan cilexetil mucoadhesive buccal films showing good physical and mechanical properties. The developed formulation was found to be stable for 3 months period.

Conclusion: Using precipitation-ultrasonication method, Candesartan cilexetil-loaded nanosuspension containing mucoadhesive buccal films were developed successfully and the particle size of the formulation was reduced to nano-size, which was further responsible for the improvement in dissolution and bioavailability of the drug. The drug delivery system has been designed as a novel platform for potential buccal delivery of drugs having high first-pass metabolism.

Keywords: Nanosuspension, Candesartan cilexetil, particle size, Buccal film

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INTRODUCTION

Oral route is considered as the most traditional and effective method of administering drugs[1]. The oral cavity is more permeable to low molecular medicines than any other route due to its high blood capillary enrichment[2]. This approach can be applied to both localized and systemic impacts[3]. Conventional oral medicines, such pills, are easy, but a convenient alternate route is much needed for some medications that have bioavailability issues for various reasons[4]. Due to the buccal mucosa's robust blood supply, relative permeability, and excellent drug absorption location, buccal delivery of pharmaceuticals offers an appealing alternative to other traditional methods of systemic drug administration[5]. By avoiding the first-pass metabolism and drug degradation in the harsh gastrointestinal environment that are frequently associated with oral administration, the buccal route of drug delivery allows drug molecules to enter the systemic circulation directly[6]. Nanosuspensions have become one of the most promising dosage forms in recent years for the production of medications that are sparingly soluble and water insoluble[7]. Hydrophobic drug particles in the nanoscale (100–1000 nm) that are disseminated in a hydrophilic

media (often water) and stabilized by polymers, surfactants, or a combination of the two make up nanosuspension[8]. Low soluble but highly permeable medicines may be absorbed more readily due to the improved rate of dissolution caused by the low particle radius and increased surface area of nanosuspension[9]. The low hold duration of any liquid formulation, including nanosuspension, must be overcome by suitable delivery methods in order to take advantage of this potential benefit for buccal distribution[10]. A little portion of the dose is left for systemic absorption after traditional buccal devices, such as chewing gums, release a significant portion of the dose into buccal fluid that is ingested. In order to minimize medication loss into the buccal cavity, a triple layer buccal patch with a drug layer sandwiched between a mucoadhesive layer with an absorption promoter and a backing membrane would be optimal[11]. Nevertheless, the medication is distributed throughout the polymeric matrix in the majority of the buccal patches, which could lead to an increase in particle size[12]. This work suggests a micronized drug reservoir-based buccal patch with Candesartan cilexetil nanosuspension suspended in a polymeric gel matrix to address this issue[13].

In addition to being an antihypertensive medication, Candesartan cilexetil (CC) is used to treat a variety of coronary heart conditions[14]. It is a competitive, reversible and specific blocker of the angiotensin II type-1 (AT1) receptor[15]. It is a class II medication with high permeability and limited solubility[16]. Candesartan cilexetil has an absolute bioavailability of between 14-40% [17]. Additionally, when given as an oral convenient dosage form, it experiences considerable first-pass metabolism in the liver, which also results in a decrease in its bioavailability[18].

MATERIALS AND METHODS

Materials

Candesartan cilexetil was received as gift sample from Natco pharma Ltd, Hyderabad. Acetone, polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP)-K 90, Hydroxyl propyl methyl cellulose (HPMC) (15 cps), Sodium carboxy methyl cellulose (Na CMC), Methanol, PEG 400, Tween 80 and EC purchased from S.D fine chem. HPLC grade methanol was obtained from Merck. All other chemicals used were of pharmaceutical grade. Triple distilled water was obtained from Milli-Q water purification system (Millipore).

Methods

Preparation of Candesartan cilexetil nanosuspension

The anti-solvent precipitation-ultrasonication approach was used to develop Candesartan cilexetil nanosuspension. Since acetone and water are miscible, they were chosen as the solvent and anti-solvent, respectively, with a fixed ratio of 1:20. To create solutions with 20, 30, 40, 50, and 60 mg/ml of the medication, Candesartan cilexetil was dissolved in acetone. To create anti-solvent solutions with different PVA concentrations (0.1%, 0.15%, 0.2, 0.5 and 1% w/v), PVA was dissolved in water. Before being used, the anti-solvent was chilled down below 3ºC in an ice water bath. A magnetic stirrer was used to continuously mix the organic drug solution (2 ml) into a beaker containing 20 ml of aqueous PVA solution. Because the drug was insoluble in water, it precipitated out right away, creating submicron particles. A probe sonicator was used to further reduce the size of this precipitated drug suspension. Probe sonication was applied to a drug suspension in an ice bath at 90% amplitude for varying durations (4, 8, 12, 16 and 20 minutes). Centrifugation at 16000 rpm for 40 minutes in an ultracentrifuge was used to concentrate the resulting nanosuspension. Following centrifugation, 2 ml of 0.2% PVA solution were added to the supernatant. A bath sonicator was used to redisperse solid residue[19-22].

Optimization of concentrations of drug and surfactant

Different formulations were created utilizing varying doses of Candesartan cilexetil (20, 30, 40, 50 and 60 mg/ml) while maintaining a constant surfactant content and ultrasonication time in order to maximize the drug's concentration. Similar to this, other formulations were made with different PVA concentrations i.e., 0.1%, 0.15%, 0.2%, 0.5% and 1% w/v, while maintaining the same drug concentration and ultrasonication duration. Size was used to evaluate the formulations[23-25].

Characterization of Candesartan cilexetil Nanosuspension

Particle size, size distribution and zeta potential

The fundamental and crucial metric for characterizing nanoparticles is their size. It establishes the particle size and dispersion. Photon correlation spectroscopy (PCS) is used to characterize the particle size at room temperature using a Zetasizer (Nano ZS 90, Malvern Instruments, Malvern, UK). To obtain the ideal kilo counts per second (Kcps) of 50–200 for measurements, 100 µl of the created NS formulation was diluted to 5 ml with double-distilled water. The sample was taken straight from the device and used for size measurement. Zeta potential testing was also done using the same equipment[26-30].

Entrapment Efficiency

By centrifuging the nanosuspension at 20,000 rpm, decanting the supernatant, and twice washing the sediment with distilled deionizer water, the amount of Candesartan cilexetil entrapped in the

nanosuspension was calculated. The amount of medication unentrapped in the supernatant was measured using a UV spectrophotometer set to 254 nm. The amount of drug that was entrapped was determined by deducting the amount of drug that was not entrapped from the total amount of drug that was added to formulate the nanosuspension. The study was conducted in triplicate, and the average results were presented[31].

Preparation of Candesartan cilexetil nanosuspension incorporated mucoadhesive buccal film

Nanosuspension incorporated buccal film contains three distinct layers, namely, mucoadhesive layer, nanosuspension containing layer and backing membrane. All three layers were prepared by a solvent casting method[32-33].

Preparation of Mucoadhesive Layer

A magnetic stirrer was used to continuously mix the weighed amount of polymer in 15 ml of distilled water until the final volume was 20 ml. Following levigation with glycerine (15% of dry polymer weight), one drop of Tween 80 was added to the resultant polymeric solution. After being left overnight to create a bubble-free solution, the mixture was cast onto glass Petri plates with a diameter of 10 cm and heated to 40ºC for 24 hours in a hot air oven. To preserve their integrity and flexibility, the developed films were wrapped in aluminum foil and kept in an airtight glass container[34-36].

For consistent and uniform film formation, the choice of mucoadhesive polymer and its concentration are crucial. Polymer formulations were made using varying percentages of HPMC, Na CMC, PVA, sodium alginate and PVP-K90 (2%, 3% and 4% w/v) while maintaining the constant concentrations of plasticizer and permeation enhancer (i.e., Tween 80) and shown in Table-1.

Table 1: Optimization of mucoadhesive layer

Polymer	**Formulation code**	**Polymer conc (%v/v)**	**Permeation enhancer (Tween 80)**	**Optimized Concentration & Batch**
HPMC	**M1-F3**	**-4%**	**1 drop**	**3 (M2)**
Na CMC	M4-M6	2-4%	1 drop	3 **(M5)**
PVA	M7-M9	2-4%	1 drop	4 **(M9)**
Sodium alginate	M10-M12	2-4%	1 drop	2 **(M10)**
PVP-K90	M13-M15	2-4%	1 drop	3 **(M14)**

Preparation of nanosuspension containing layer

In order to create a gel, a weighed quantity of HPMC (15 cps) and carbopol 934P were distributed as film-forming polymers in a 20 ml Candesartan cilexetil nanosuspension while being continuously stirred with a magnetic stirrer. After adding 15% PEG 400 w/v as a plasticizer to the resultant gel, it was cast onto glass petri dishes with a diameter of 10 cm and allowed to dry for up to 24 hours in vacuum desiccators. To preserve their integrity and flexibility, the developed films were wrapped in aluminum foil and kept in an airtight glass container[37-38].

To optimize the right concentration of polymer and gelling agent, formulations were prepared employing different concentrations of HPMC (2%, 3%, 4%, 5% and 6% & carbopol 934P (20, 40, 60, 80 and 100 mg) keeping the permeation enhancer, plasticizer concentrations constant as seen in Table 2[39-40].

Table 2: Optimization of nanosuspension containing layer

Formulation Code	**HPMC (15CPS) (%w/v)**	**Carbopol 934P (mg)**	**Permeation enhancer (Tween 80)**
NS1	2	20	1 drop
NS2	**3**	**40**	**1 drop**
NS3	4	60	1 drop
NS4	5	80	1 drop
NS5	6	100	1 drop

Preparation of Ethyl Cellulose Backing Layer

A magnetic stirrer was used to continuously mix a weighed quantity of ethyl cellulose in 15 milliliters of chloroform. To create a clear, bubble-free solution, 30% PEG 400 w/v was added to the resulting polymeric solution and set aside. To completely remove the chloroform, this solution was cast onto glass Petri dishes and allowed to dry for up to 24 hours in vacuum desiccators. To preserve their integrity and flexibility, the produced films were wrapped in aluminum foil and kept in an airtight glass container to prevent moisture loss[41-42].

To optimize the right concentration of ethyl cellulose, various formulations were prepared employing different concentrations of ethyl cellulose (1%, 2%, 3%, 4% and 5% w/v), keeping the plasticizer concentration constant as shown in Table 3[43-44].

Table 3: Optimization of ethyl cellulose baking layer

Formulation code	**Ethyl cellulose (% w/v)**	**Chloroform (ml)**	**PEG 400 (% w/v)**

BL1	1	15	1
BL2	**2**	**15**	**1**
BL3	3	15	1
BL4	4	15	1
BL5	5	15	1

Final mucoadhesive buccal formulation:

The three layers listed above are combined to develop the final buccal formulation. The nanosuspension-containing layer was affixed to the backing membrane on one side and the mucoadhesive layer on the other by spraying chloroform. The composite was sliced to a size of 2 cm^2 and placed between two stainless steel stabs in vacuum desiccators for 24 hours after the mucoadhesive side was covered with a peelable polyethylene film. To preserve their integrity and flexibility, the produced films were wrapped in aluminum foil and kept in an airtight glass container to prevent moisture loss[45].

Characterization of buccal films

The buccal films were evaluated for their physical, mechanical and bioadhesive parameters followed by *in vitro* drug release studies[46-48].

Physical appearance

The films were observed visually for their physical appearance such as color, transparency and texture[49-51].

Weight variation

Four films of each batch of formulation were weighed individually and then together by using a digital weighing balance and average weight and weight variation of the films were calculated[52].

Thickness

Four films of each combined layer formulation were taken and the thickness of the film was measured using a screw gauge at different points of the plane surface. The average film thickness was calculated[53].

Folding Endurance

The folding endurance was measured by hand. For each formulation, a 2 cm^2 strip of film was taken and folded in the same spot until it broke. The value of folding endurance was determined by how many times a film could be folded in the same location. Three determinations were averaged[54].

Surface pH

The film's surface pH was measured by letting it swell in a glass Petri dish with 1 milliliter of phosphate buffer (pH 6.8 for one hour. Using a pH meter, the surface pH was measured by bringing a combination glass electrode close to the film's surface for one minute. The average of three measurements was computed once the pH was noted[55].

Drug Content Uniformity

The three-layered film was dissolved in 100 ml of an isotonic phosphate buffer (pH 6.8) and homogenized for two hours with sporadic shaking to test the uniformity of drug content. A 0.45mm Whatman filter paper was used to filter the resultant solution after an aliquot (5 ml) was removed and diluted with isotonic phosphate buffer pH 6.8 up to 20 ml. After that, the drug content was measured using spectrophotometry at 254 nm[56].

Swelling Studies

The 1.5 cm diameter patch sample was weighed before being placed in a porcelain dish with 15 ml of simulated saliva fluid. The patch was gently wiped with absorbent tissue to eliminate any extra moisture at predetermined intervals and it was then weighed again. The film's weight increased at each interval until it reached a constant weight. The following formula was used to determine the degree of swelling[57].

Swelling index = W_t **-** W_0/W_0

***In Vitro* Mucoadhesion Test**

A modified balance method was used to assess the buccal film's mucoadhesive strength. The bioadhesive performance was evaluated using the strength needed to separate the polymeric film from the mucosal surface. The model membrane was sheep buccal mucosa, and the moistening fluid was Kreb's buffer solution (pH 7.4). After being collected, the fresh sheep buccal mucosa from a slaughterhouse was kept at 4ºC in Kreb's buffer pH 7.4. Using appropriate glue, a 1 cm^2 piece of cleansed sheep buccal mucosa was adhered to the beaker's bottom flat surface with the mucosal aspect facing up. The test films were adhered to the left arm of the balance, which was previously balanced by maintaining a 5 g weight on each side of the lower flat side of the hanging glass assembly. After blotting the mucosa's surface with Whatman filter paper, 25 ml of Kreb's pH 7.4 buffer solution were added. From the right pan, five grams of weight were taken out. As a result, the glass assembly and film with a weight of 5 g were lowered over the membrane. This was left undisturbed for three minutes before a five-gram weight was placed on the right side to restore equilibrium. Then the weights were slowly added till the film just separated from the membrane surface. The weight added to separate the stuck film from the mucosa was taken as bioadhesive strength. Three films of each formulation were tested and the average of three determinations was used to calculate the mucoadhesive force using the following equation[54, 58].

Mucoadhesive force (N) = Bioadhesive strength (g)/1000 * 9.81

***In Vitro* Drug Release Studies**

A shaking incubator rotating at 100 rpm was used to conduct *in vitro* drug release tests utilizing a dialysis bag approach. The dissolving medium was methanolic phosphate buffer (pH 6.8), which is a

90:10 ratio of phosphate buffer 6.8 to methanol. Each dialysis bag contained eight milligrams of medication in the form of buccal film. The dissolving media had a volume of 200 ml and a temperature of 37.0±0.2ºC. Samples (2 ml) were taken out at prearranged intervals, replaced with the same volume of fresh medium, filtered and tested for drug content at 254 nm against a blank using a UV-visible spectrophotometer[59].

***Ex Vivo* Drug Permeation Studies**

The Franz diffusion cell was used to conduct ex vivo drug permeation experiments of buccal films of Candesartan cilexetil through an excised layer of sheep buccal mucosa (washed in isotonic phosphate buffer, pH 6.8 after excising and trimming from the sides). The topside of the removed sheep buccal mucosa was in close proximity to a 1 cm diameter film of each formulation under investigation. Throughout the experiment, the temperature was kept at 37±5ºC while 50 ml of pH 6.8 phosphate buffer (with a Teflon bead within) was added to the receptor compartment and swirled with a magnetic stirrer. The samples were withdrawn at regular intervals, filtered, diluted suitably and then analyzed spectrophotometrically at 254 nm[60].

Mechanism of Release Kinetics

The mechanism of release was determined by fitting the release data to the various kinetic equations such as zero order, first-order, Higuchi and Korsmeyer and peppas model R^2 values were determined by regression formed by the index of linearity[61-62].

Stability Studies

Accelerated stability testing was performed on the optimized formulation. To determine the impact of temperature on the drug content in formulation, the investigation was carried out at 37°C and 45°C. Films were placed in glass Petri plates covered with aluminum foil and stored for a month at 37±0.5°C and 45±0.5°C in an incubator. After 7, 14, 21 and 28 days, changes in the bioadhesive patch appearance and medication content were examined[63-64].

RESULTS AND DISCUSSION

Formulation and Optimization of Candesartan cilexetil Nanosuspension

Candesartan cilexetil nanosuspension was prepared according to the procedure mentioned and further, it was optimized on the basis of particle size of the nanocrystals [65-66].

Table 4: Optimization of nanosuspension based on particle size and drug entrapment efficiency

Formulation code	Drug concentration	Stabilizer concentration (%w/v)	Particle size (nm)	Zeta potential (mV)	Drug entrapment (%)
NS1	20	0.2	311.1 ±2.13	-21.56 ±0.03	74.2± 0.32
NS2	30	0.4	298.2 ±1.34	-28.12 ±0.02	97.3± 0.24
NS3	40	0.6	325.3 ±1.18	-20.46 ±0.04	81.5± 0.63
NS4	50	0.8	342.7 ±0.12	-22.31 ±0.01	85.7± 0.18
NS5	60	1	338.1 ±1.93	0.25.24±0.05	88.34 ±0.53

Characterization of Mucoadhesive Buccal Film Formulation

Physical Characterization

The mucoadhesive buccal firm formulations are included in Table 5 after being assessed for a number of physical attributes. The mucoadhesive buccal film formulations had a smooth surface structure and were opaque. The optimum batch of films weighed between 28.12±0.24 mg and 36.37±0.31 mg[67-69].

Folding endurance test

Even after 300 folds, it showed no cracks, demonstrating the film's adequate flexibility. The film's surface pH varied from 6.6±0.1 to 6.8±0.4 (Table 5). These values were determined to be within the saliva pH range of 6.2 to 7.6, indicating that the films are compatible with the buccal mucosa and that there is no risk of mucosal irritation or damage during use.

Drug Content Uniformity

Mucoadhesive buccal films were found to have an average of 8.12 mg of Candesartan cilexetil per centimeter. Table 5 shows that the drug content uniformity values ranged from 87.56% to 95.02% of the theoretical values. The drug was evenly dispersed throughout the film, according to the content uniformity results.

Swelling Studies

In a pH 6.8 phosphate buffer solution, the films were seen to swell. The order of comparative swelling in several formulations was F2>F1>F4>F3>F5. Because Na CMC molecules have more hydroxyl groups, swelling was more noticeable in films F2 and F1 that include HPMC and Na CMC. PVP K-90 significantly decreased the percentage swelling of F3.

***In vitro* mucoadhesion strength**

The modified balancing method was used to determine the mucoadhesive strength for each formulation. As demonstrated, the bioadhesive

strength of formulations F1 and F2, which included Na CMC and HPMC, was greater than that of PVP K-90 (F3). Additionally, as Table 6 illustrates, an increase in polymer concentration was found to result in an increase in bioadhesive strength.

***In Vitro* Release Studies**

For all formulations, the *in vitro* drug release of the nanosuspension-incorporated buccal film was conducted for 540 minutes in methanolic PBS pH 6.8. Figure 1 illustrates that after 540 minutes, the percentage of drug released from all formulations from F1 to F5 was 99.46%, 91.41%, and 92.17.6%, 87.05±1.11 and 84.05±1.32. Only after 240 minutes did all formulations show between 55% and 69% of the medication release. Out of all the formulations, F1 delivered the most medication in 540 minutes. The retardation times for the several films were in the following order: F1>F3>F2>F5>F4. The water permeability properties of the film made of various polymers, such as HPMC (F1), PVP-K90 (F3), and Na CMC (F2), may be the cause. Lower the water permeability coefficient the greater the sustained drug release characteristics observed. Swelling of polymers may be an additional factor which controlled the release rate.

***Ex Vivo* Permeation Studies**

Excised sheep buccal mucosa was used for the ex vivo permeation analysis of the chosen buccal formulation (F1). As illustrated in Figure 2, the total amount of Candesartan cilexetil that penetrated the buccal epithelium in 5 hours was a maximum of 62.6%. The findings showed that Candesartan cilexetil could quickly pass through the mucosal barrier, most likely as a result of the medication's high lipophilicity. The total amount of Candesartan cilexetil that passed through the membrane increased quickly during the first hour and then steadily over the next five. Overall penetration was about 60% in 6 h indicating that the performance of the formulation was quite convincing.

Mechanism of drug Release Kinetics

To determine the drug release and permeation mechanism of the chosen formulation, the in vitro release and ex vivo permeation profiles of the formulation F1 were subjected to a kinetic analysis for fitting into different models, such as zero-order, first-order, and Higuchi equation. The Higuchi and Korsmeyer and Peppas model release kinetics plots were found to be linear in both situations, with r^2 values closer to 1 (r^2 = 0.992 and 0.987, respectively). Exponent values (n) in the ex vivo permeation profile indicated that the drug was released and penetrated by the diffusion mechanism after super case-II transport.

Stability Studies

The optimized formulation when subjected to accelerated stability testing. It was observed that no changes in the appearance, drug content and surface pH of the stored bioadhesive patches even after 28 days. Results were given in Table 7.

Table 5: Characterization of buccal films

Formulation code	Weight variation (mg)	Thickness (mm)	Swelling (%)	Content uniformity (%)	Surface pH	Folding endurance
F1	28.12±0.24	0.41±0.01	37.2±0.21	95.02±0.12	6.8±0.3	**>300**
F2	**31**.41±0.16	**0.**32±0.52	39.3±0.13	90.34±0.34	6.6±0.1	**>300**
F3	**32.05**±1.51	0.52±0.08	32.4±0.62	92.97±0.51	6.8±0.2	**>300**
F4	**29.53**±0.96	0.47±0.06	35.6±0.38	87.56±0.23	6.7±0.3	**>300**
F5	**36.37**±0.31	0.61±0.32	31.5±0.17	89.86±0.67	6.8±0.4	**>300**

Table 6: *In-vitro* mucoadhesion strength

Formulation code	Mucoadhesive strength (gm)	Force of adhesion
F1	14.2±0.12	0.14±0.02
F2	12.6±0.23	**0.11**±0.03
F3	11.7±0.04	0.12±0.01
F4	13.8±0.13	**0.13**±0.04
F5	12.5±0.18	0.10±0.02

Table 7: Stability study

Days	Drug content	Surface pH	Appearance
7	95.02±0.12	**6.8**±0.3	Opaque & smooth
14	**95.14**±0.15	**6.8**±0.1	Opaque & smooth
21	**95.23**±0.37	**6.8**±0.1	Opaque & smooth
28	**95.04**±0.29	**6.8**±0.2	Opaque & smooth

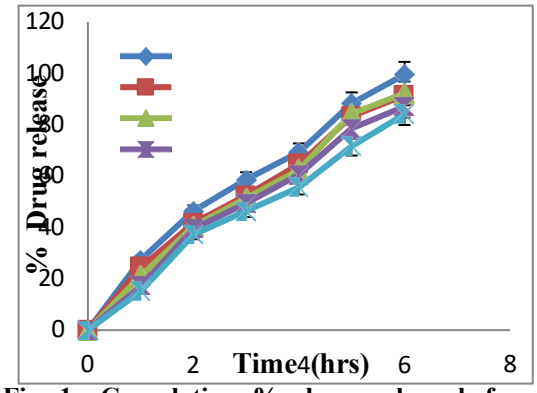

Fig 1: Cumulative % drug released from Candesartan cilexetil mucoadhesive buccal films (F1-F5)

CONCLUSION

The present study designed to incorporate Candesartan cilexetil nanosuspension into hydrophilic mucoadhesive polymers to develop a suitable formulation for buccal drug delivery. Candesartan cilexetil formed a stable nanosuspension in the presence of PVA having uniform size, size distribution and surface charge. The developed mucoadhesive films containing nanosuspension showed increased release rate due to increased drug surface area.

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CONFLIT OF INTEREST

There is no conflict of interest.

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