INTRODUCTION:

In the past three decades, there is a splendid interest in researching buccal drug transport systems. The oral cavity is effortlessly acceptable for self-medication of drugs and is nicely popular among patients. The oral cavity space is the most appealing path for drug transport due to its ease of management. This path may administer each locally performing and appearing systemic drugs. The mucosa drug’s site-precise release is accomplished while used for local activity, and systemic action expects for drug absorption through the mucosal barrier to reach systemic flow. The oral route is the maximum favored and widely relevant direction for delivering the majority of the medicine.

However, problems such as less residence time, poor aqueous solubility, and chemical instability in the gastrointestinal tract minimize orally administered medicines’ bioavailability. Further, metabolism through diverse obstacles or enzymes also degrades the drug earlier than attaining the site of action. The buccal mucosa has been investigated for therapeutic agents subjected to first bypass metabolism and risky inside the rest of the gastrointestinal tract. The mucosal lining of the oral cavity and nasal cavity gives a few excellent benefits. It has primarily vascularized, and buccal drug transport has high patient acceptability. Hence, diverse alternative drug delivery systems are evolved to enhance the oral bioavailability of those medicines.

Oral mucosal drug delivery is one of the alternative systemic drug absorption strategies that offer decorate drug bioavailability. The bioavailability of such medicines can be considerably progressed if added through a buccal pathway. Recently much attention has been focused on the design, development, and evaluation of buccal drug transport systems preserving in view their potential for the future market. Candesartan cilexetil (CC) is selective angiotensin (AT) type-1 receptor antagonist used in the treatment of high blood pressure and congestive heart failure. It selectively blocks the binding of angiotensin II to AT1 in the majority of the wall of blood vessels tissues like vascular smooth muscle and the adrenal glands. It inhibits the AT 1-mediated vasoconstrictive and aldosterone-secreting consequences of angiotensin II and consequences in an overall decrease in blood pressure. However, its broad first-pass metabolism results in poor bioavailability i.e. ≈15%. It has a plasma half-life of nine hours and peak plasma concentration reaches within three to four hours. It can be given once or twice day...
by day with a complete everyday dose ranging from 8 mg to 32 mg for the treatment of high blood pressure and heart failure\textsuperscript{13,14}. It was selected as a model drug for this research due to its appropriate properties.

The present research’s main objective was to design, develop the formulation, and evaluate mucoadhesive buccal tablets of CC (CC-BT) to improve oral bioavailability. Accordingly, CC-BT was developed and evaluated for an optimized system based on various parameters it includes in vitro dissolution and permeation studies through the porcine membrane.

**MATERIALS AND METHODS:**

Candesartan cilexetil was obtained as a gift sample from Dr. Reddy’s labs, Hyderabad India. Carbopol 934P was obtained from S.D. Fine Chemicals, Mumbai. Hydroxy propyl methyl cellulose (HPMC K4M), Eudragit RLPO and sodium carboxy methyl cellulose (Na-CMC) was obtained from Loba chemicals, Mumbai. All other ingredients used in formulations were of analytical grade.

**Preparation of mucoadhesive buccal tablets:**

Buccal muco-adhesive tablets were prepared by direct compression technique using a variable concentration of carbopol 934P, HPMC K4M, Eudragit RLPO, and sodium carboxy methyl cellulose (Na-CMC)\textsuperscript{15,16}. The drug, respective polymer, and MCC have weighed accurately and then passed thru sieve no. 80 to get uniform particle size. Then all of the substances besides lubricants and glidants have been combined with the aid of triturating for 10 to 15 min in a mortar with a pestle to achieve a uniform mixture. Subsequently, magnesium stearate and t alc have been added. The combined powder turned compressed into tablets weighing 150mg the usage of a flat-faced punch and die set of 8 mm diameter (Rimek Minipress Karnavati Engg. Ltd, Ahmadabad, India). The compositions of the tablets were shown in Table 1.

| Ingredients (mg)       | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|------------------------|----|----|----|----|----|----|----|----|----|
| Candesartan cilexetil (CC) | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 |
| Carbopol 934P          | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| HPMC K4M               | 30 | 45 | 60 | -  | -  | -  | -  | -  | -  |
| Eudragit RLPO          | -  | -  | -  | 30 | 45 | 60 | -  | -  | -  |
| Na CMC                 | -  | -  | -  | -  | -  | -  | 30 | 45 | 60 |
| MCC                    | 84 | 69 | 54 | 84 | 69 | 54 | 84 | 69 | 54 |
| Talc                   | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  |
| Mg Stearate            | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  |
| Aspartame              | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| Total weight (mg)      | 150| 150| 150| 150| 150| 150| 150| 150| 150|

**Evaluation of muco-adhesive buccal tablets**

**Hardness and thickness:**

Hardness is an essential quality control check to be indicated for measuring the capacity of a tablet to withstand mechanical shocks while managing. The test was carried out for three tablets from each formulation using the Monsanto hardness tester; the expected mean and standard deviation values were calculated\textsuperscript{17}.

The thickness of randomly selected three mucoadhesive buccal tablets turned into determined with the assist of vernier calipers. Individual tablets from every formulation have been chosen, and the mean results were noted\textsuperscript{18}.

**Weight variation and friability:**

Weight variation was performed for randomly selected 20 tablets from each batch using an electronic balance, and mean values were calculated. The percentage difference in the weight variation should be within the permissible limits and shown in the below Table 2 as per the USP\textsuperscript{19,20}.

Friability is a measure of the mechanical strength of tablets. By using Roche friabilator, a sample of pre-weighed tablets were placed in the plastic chamber then operated for 100 revolutions (4 min and 25 rpm), every rotation tablet was dropped 6 inches distance, tablets have been reweighed; loss within the weight of the tablet is the measure of friability\textsuperscript{21} and is expressed in percent as:

\[
F (%) = \left(\frac{1 - W_f}{W_o}\right) \times 100
\]

Where, \(W_o\) is the weight of the tablets before the test and \(W_f\) is the weight of the tablets after test.

| S.No | Average Weight of the tablets in milligram | Maximum percentage difference allowed |
|------|------------------------------------------|--------------------------------------|
| 1    | 130 or less                              | ±10                                  |
| 2    | 130-324                                   | ±7.5                                 |
| 3    | More than 324                             | ±5                                   |

**Drug content:**

Randomly selected ten tablets from each formulation were crushed and get a fine powder from the mixture, one tablet equivalent of the mixture dissolved in pH 6.8 phosphate buffer\textsuperscript{22,24}. The amount of drug present in the mixture was analyzed using UV-Visible spectrophotometer at 256 nm.
**Swelling studies of buccal tablets:**

A mucoadhesive buccal adhesive system’s swelling behavior is an important property for uniform and prolonged release of drug and bio-adhesiveness. The swelling properties and the tablets’ erosion characteristics were determined by the percentage of hydration and matrix erosion or dissolution. The percentage values were calculated according to the following equations:

Swelling Index = [(W2 - W1) + W1] × 100

Where, W1 = initial weight of the tablet
      W2 = final weight of the swollen tablet

**In-vitro drug release studies:**

A cyanoacrylate adhesive impermeable backing membrane was placed on one side of the tablet, and a piece of glass slide was fixed as support of the tablet to prevent the dosage form from floating. Then it was placed in USP type II (Electro lab, Mumbai, India) dissolution apparatus containing 500 mL of pH 6.8 phosphate buffer, maintained a temperature of 37 ± 0.5°C, and the apparatus run at a speed of 50 rpm. Samples were collected at preset time points and analyzed using a UV-Visible spectrophotometer at 256 nm.

**Ex-vivo mucoadhesive residence time:**

The ex-vivo residence time is one of the significant parameters of the buccal mucoadhesive tablet. It was determined using a USP dissolution apparatus, and the medium was composed of 500 mL of pH 6.8 phosphate buffer maintained at 37°C ± 0.5°C. The porcine buccal tissue was glued to a glass slab’s surface, vertically attached to the apparatus. The mucoadhesive tablet was pressed over excised, glued pig mucosa for 30 seconds, and immersed in a basket. The paddle apparatus rotated at 25 rpm, and the time required for complete erosion or detachment from the mucosa was recorded.

**Ex vivo permeation of buccal tablets:**

The porcine buccal mucosa was collected from the local slaughterhouse, and a drug permeation study was performed using a Franz diffusion cell at 37°C ± 0.5°C. The buccal mucosa was fixed between the donor and receptor compartments, pH 6.8 phosphate buffer filled in the receptor chamber, and the tablet was placed in the donor chamber with a few ml of the same buffer added for wetting of tablet. The receiving compartment’s hydrodynamics was maintained by continuous stirring with a magnetic bead at a speed of 30 rpm. Samples were collected at preset time points and analyzed using a UV spectrophotometer at 256 nm.

**Dissolution data kinetic analysis:**

Inside the order of describing the kinetics of drug release the process of drug release in specific type formulations, models have been fitting to the dissolution data of all formulations for linear regression analysis.

**Zero order release kinetics:**

\[ Q_t = Q_0 - K_0 t \]

Where, Qt = amount of drug dissolved in time t
      Q0 = initial amount of drug
      K0 = is zero order release rate constant

**First order release kinetics:**

This model’s application to drug dissolution studies used to choose to describe absorption elimination of the drugs. To study 1st order release rate kinetics, the release rate data were fitted to the below equation.

\[ \log(Q_t) = \log(Q_0) + K_1t/2.303 \]

Where, K1 = is the first-order release rate constant

**Higuchi model:**

Theoretical models of Higuchi developed for the study of drug release of water soluble and slow soluble drugs incorporated in semi-solid and/or solid matrices. Mathematical expressions obtained for drug release particles were dispersed in the uniform matrix system behaving as diffusion media. The equation is

\[ Q_t = K_{H} t^{1/2} \]

Where, K_H = Higuchi dissolution constant

Higuchi model explains the release as the diffusion process based on the Fick’s law, square root time dependent.

**Korsmeyer and Peppas model:**

This model can be generally used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when > one type of release phenomenon could be involved.

\[ M_t/M = K_t n \]

Where, n is the diffusion exponent for the release and it depends on that shape of the matrix dosage form. If n < 0.45, Fickian diffusion mediated drug release occurs. Non-Fickian release occurs if 0.45< n<0.89 and erosion (i.e. complete matrix relaxation) mediated release occurs in n<0.89.

**FTIR compatibility studies:**

FT-IR spectrophotometer was used to find the possible chemical interaction of CC with polymers and other excipients. The samples were prepared for FTIR test, as pure drug and as a drug with those polymers in 1:1 ratios.
RESULTS AND DISCUSSION

CC has poor oral bioavailability due to poor aqueous solubility and first-pass metabolism. Hence, there is a need to develop alternative delivery system for enhanced oral delivery either through enhanced water solubility or avoiding first-pass metabolism. Previously, various nano delivery systems of CC has been reported to enhance oral bioavailability[33-35]. But, in the present investigation buccal delivery system has been developed for enhancement of oral bioavailability.

Various alternative drug delivery systems are developed to enhance the oral bioavailability of poorly soluble drugs. The delivery systems include: enhancement of solubility through solid dispersion[36,37], liquefied compact[38], increase the stability and prolonged residence time by floating systems[39], lipid-based delivery systems for by passing metabolism with solid lipid nanoparticles[40-44], SMEDDS[45], transfersomes[46], nanostructured lipid carriers[47] and micronization for reducing particle size using nanosuspensions[48,49].

Physical parameters muco-adhesive buccal tablets:
The physicochemical properties of all the formulations prepared with different were described in earlier sections and evaluated to various tests. The tests viz., hardness, thickness, weight variation, and drug content were found to be within the pharmacopeia limits and are given in the Table 3. The hardness of the tablets ranged 3.95±1.25 to 4.65±1.63 kg/cm² and the thickness of the tablets ranged from 2.58±0.13 to 2.65±0.66 mm. The uniformity of weight as their weights varied between 148.6±0.41 and 2.59±0.16 mg and the friability values were less than 1 %. All the formulations were satisfied with the content of the drug as they contained 2.59±0.16 to 100.12±2.55 %. Thus all the physical properties of the prepared tablets were found to be pragmatically within the pharmacopeia limits.

| Formulation | Hardness (Kg/cm²) | Thickness (mm) | Weight Variation (mg) | Friability (%) | Drug content (%) |
|-------------|------------------|---------------|----------------------|----------------|-----------------|
| F1          | 3.98±1.53        | 2.58±0.13     | 151±1.95             | 0.65±0.12      | 99.68±2.33      |
| F2          | 4.12±1.25        | 2.59±0.15     | 149±1.63             | 0.53±0.13      | 99.46±2.69      |
| F3          | 4.25±1.66        | 2.58±0.13     | 152±1.69             | 0.56±0.15      | 98.63±1.96      |
| F4          | 4.18±1.26        | 2.59±0.15     | 151±1.93             | 0.49±0.15      | 100.12±2.55     |
| F5          | 4.29±1.45        | 2.58±0.13     | 149±1.33             | 0.53±0.16      | 98.47±1.75      |
| F6          | 4.65±1.63        | 2.59±0.16     | 152±1.48             | 0.46±0.15      | 99.66±1.66      |
| F7          | 3.95±1.25        | 2.58±0.16     | 150±1.36             | 0.63±0.15      | 99.66±2.33      |
| F8          | 4.33±1.75        | 2.59±0.15     | 151±1.45             | 0.49±0.16      | 99.63±1.83      |
| F9          | 4.45±1.59        | 2.59±0.14     | 150±1.63             | 0.47±0.15      | 99.75±1.63      |

Ex-vivo mucoadhesive residence time:
The ex vivo mucoadhesive properties of the tablets were determined using porcine buccal mucosa. As the concentration of polymer increased, the retention time increased. This test reflects the adhesive capacity of polymers used in formulations. The results revealed that combination of Carbopol, with HPMCK, Eudragit and Na CMC containing formulations showed more than six hours bioadhesion time. Optimized formulation i.e., F8 showed maximum retention time than other formulations (Table 4).

Swelling studies:
The swelling index examination indicated that the rate of swelling becomes directly proportional to the used polymer content. The swelling index was calculated concerning time. The swelling index demonstrates the relative moisture absorption capacities of polymers and whether or not the formulations maintain their integrity after moisture absorption. The swelling values of the tablets showed growth in swelling value with an increase in polymer content material. The results of the present formulation were tabulated in Table 5. Formulation F8 given maximum swelling and was found to be 76.88±1.46 % within 8 h. These results were correlated with earlier reported studies[50].

| Formulation | Mucoadhesion time |
|-------------|-------------------|
| F1          | 6h 10min          |
| F2          | 7h 10min          |
| F3          | ≥8 hr             |
| F4          | 7h 20min          |
| F5          | 7h 50min          |
| F6          | ≥8 hr             |
| F7          | 6h 35min          |
| F8          | ≥8 hr             |
| F9          | 7h 40min          |
Table 5: Percent swelling index of CC buccal tablets (mean ± SD, n=3).

| Formulation | F1     | F2     | F3     | F4     | F5     | F6     | F7     | F8     | F9     |
|-------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| 1 hr        | 19.63±1.33 | 19.36±1.50 | 20.33±1.90 | 20.79±1.90 | 15.33±1.80 | 18.69±1.90 | 23.54±1.90 | 20.65±1.70 | 16.33±1.60 |
| 2 hr        | 36.55±1.09  | 36.58±1.66 | 38.33±1.60 | 34.93±1.54 | 25.66±1.90 | 28.94±1.70 | 38.58±1.54 | 36.26±1.60 | 32.55±1.54 |
| 3 hr        | 42.63±1.66  | 44.66±1.50 | 46.62±1.40 | 42.65±1.80 | 33.45±1.50 | 36.58±1.80 | 48.26±1.50 | 45.58±1.20 | 40.69±1.80 |
| 4 hr        | 47.95±1.25  | 52.25±1.50 | 55.55±1.50 | 51.47±1.14 | 42.66±1.50 | 46.59±1.90 | 60.36±1.60 | 55.69±1.30 | 51.25±1.50 |
| 6 hr        | 58.25±1.66  | 61.96±1.60 | 64.56±1.60 | 60.77±1.60 | 56.33±1.30 | 59.89±1.90 | 66.58±1.50 | 63.59±1.50 | 60.89±1.60 |
| 8 hr        | 63.25±1.45  | 69.54±1.50 | 73.56±1.60 | 64.86±1.50 | 62.55±1.60 | 68.99±1.50 | 75.69±1.80 | 76.88±1.40 | 71.78±1.50 |

**In-vitro drug release studies:**

The In-vitro drug release study has been done for various formulations (F1-F9) in phosphate buffer pH 6.8. The different ratios of polymers were used in the prepared buccal tablets. Among the nine batches, formulation F1 - F3 was developed carbopol with HPMC K4M polymer in the ratio of 1:2 to 1:4. Carbopol used as primary polymer in all formulations based on the excellent swelling and adherent characteristics to the mucosal surface. As the concentration of secondary polymer increased, the drug release was retarded. The F1-F3 formulation released 100.55±3.33%, 97.46±2.91%, and 93.66±3.63% drug release during 8 h, respectively. This might be due to the swelling of the polymer and diffusion takes place. The results are presented in Figures 1, 2, and 3.

Similarly, in the case of F4–F6 formulations, developed with carbopol and Eudragit RLPO showed 100.45±3.12%, 96.65±4.16%, and 86.59±3.33% release respectively during 8h. From F7-F9 formulations showed 99.45±3.93%, 102.37±3.81%, and 94.95±3.25% release respectively, the formulations F3, F6, and F9 prolonged the drug release could be appeared up to 8h with a controlled manner. Among all F8 denoted optimized based on controlled drug release and highest drug released at 8 h. These results were in accordance with earlier studies⁵¹. The swelling study, bioadhesion time, and ex-vivo drug permeation studies also appeared good results hence, F8 was considered as the best formulation.
Drug release kinetic mechanism:
The release mechanism and kinetics of CC formulations were to fit into mathematical models and the higher R² values for Zero-order and Higuchi suggest that the drug release follows zero-order kinetics with diffusion mechanism. Similarly, previously reported formulations followed this type of trend in release 52.

Ex vivo permeation studies:
Ex vivo permeation of F8 formulation was conducted through porcine buccal mucosa by using Franz diffusion apparatus. The cumulative amount of drug permeated was found to be 82.98 ± 2.63% in 8 h. Before the study, the permeation of pure CC drug solution was also studied and was found to be 65.66% in 8 h 53-55.

FTIR compatibility studies:
The FTIR spectra of significant peaks detected in the spectrum of pure drug optimized F8 formulation (Figure 4) and were described as follows: The spectrum of pure CC presented characteristic peaks at 3651.63 cm⁻¹. The pure drug peaks were unchanged in the spectrum of drug with polymers, which proves that there is no interaction between drug and excipients. So the drug is compatible with excipients 56,13.
CONCLUSION:

The present investigation was designed to develop the mucoadhesive buccal tablets of CC with a controlled effect that avoids the first-pass metabolism and improves oral bioavailability. All the prepared tablets were within the acceptable Pharmacopoeial limits for evaluation parameters. The optimized formulation F8 was best in terms of drug release, mucoadhesive permeation across the mucosal membrane. Hence, it can be concluded that the formulations of CC mucoadhesive buccal tablets are promising as they controlled drug delivery, improve bioavailability, and maybe a good candidate for buccal delivery. Further, in-vivo research in animal fascia is required to prove the bioavailability performance of the formulation.

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