**IJPSR (2024), Volume 15, Issue 5** **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 15 March 2024; received in revised form, 16 April 2024; accepted, 29 April 2024; published 01 May 2024

# DESIGN, FABRICATION AND EVALUATION OF BIOADHESIVE BUCCAL TABLETS OF CILNIDIPINE

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**Keywords:**

Buccal Tablets, Cilnidipine, HPMC, Carbopol, Mucoadhesive polymers

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**ABSTRACT:** Buccal drug delivery is the most suited route for local as well as systemic delivery of drugs. The purpose of this study was to develop and optimize formulations of mucoadhesive tablets of Cilnidipine with an objective to enhance therapeutic efficacy, bioavailability and was developed to administer into the unconscious and less-co-operative patients. Cilnidipine buccal tablets were prepared by direct compression method using various concentrations of mucoadhesive-polymers such as Carbopol and Hydroxyl propyl methylcellulose (HPMC) the Prepared Tablets were evaluated for their weight variation, Hardness, thickness, Friability, swelling-index, drug content uniformity and *in-vitro* release studies. The infra-red (IR) spectra showed no interaction, and Physico-chemical characteristics were found within the limit. Swelling index increases with increasing concentration of polymers. The formulation F8 showed a promising Bio adhesive strength and *in-vitro* drug release of 98.29% for 8 hrs thus can be selected as an optimized formulation of mucoadhesive buccal film.

**INTRODUCTION:** The buccal region offers an attractive route for systemic drug delivery for extended periods of time. Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs. Over the last two decades mucoadhesion becomes of interest for its potential to optimize localized and systemic delivery. The buccal mucosa has an absorptive function and provides numerous advantages, including avoiding the first pass effect and increasing bioavailability through a non-invasive route. It also makes it feasible for a quick action and minimizes side effects [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.15(5).1533-38

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.15(5).1533-38

Bioadhesive polymers can sustain the effectiveness of multiple medications and have a lengthy contact period with the tissues. The controlled medication delivery products have improved bioavailability, excellent patient compliance, and cheap cost [2].

Cilinidipine, a calcium channel blocker belonging to dihydropyridines, is used as a potent peripheral vasodilator, which effectively reduces blood pressure when given at doses of 10-20 mg per day. After a single, 10 mg oral dose of Cilinidipine, peak plasma concentrations are achieved within 2.5 hrs. It was reported to be well absorbed following oral administration but undergoes extensive first pass metabolism; leading to poor bioavailability [3].

## MATERIALS AND METHODS:

**Materials:** Cilnidipine was gifted by Sun pharmaceuticals (Baroda, India). Carbopol 940, HPMC were gifted by Dr Reddys Laboratories

(Hyderabad, India). All reagents used were of analytical grade.

**Drug and Polymer Compatibility Studies [4]:**

**Drug Excipient Compatibility Studies by FTIR:** IR spectrum of Cilnidipine (drug), physical mixture with excipients was recorded and it was found in accordance with the reported peaks. **Fig. 1** shows the FTIR spectra of Cilnidipine. There are no observed significant peak shifts and no generation of a new peak, although there might be no possible interaction between drug and excipients of buccal film. FTIR spectra were found to be pure, stable and unaltered. **Fig. 2** shows the FTIR spectra of Cilnidipine and excipients.

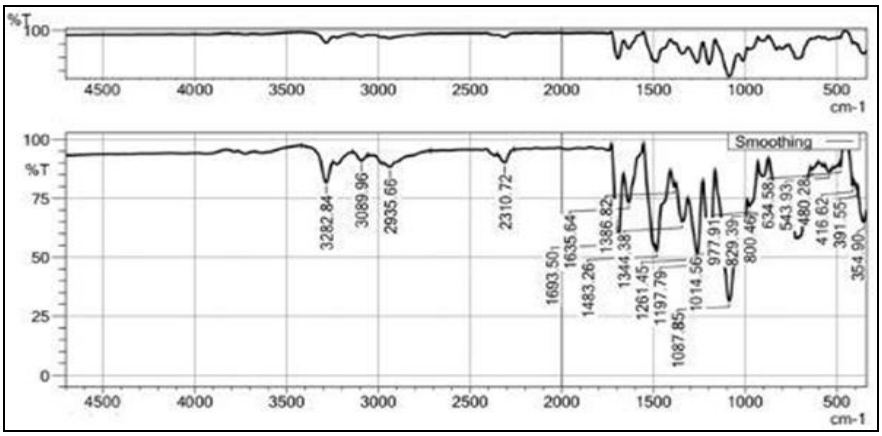


**FIG. 1: FTIR SPECTRA OF CILNIDIPINE**

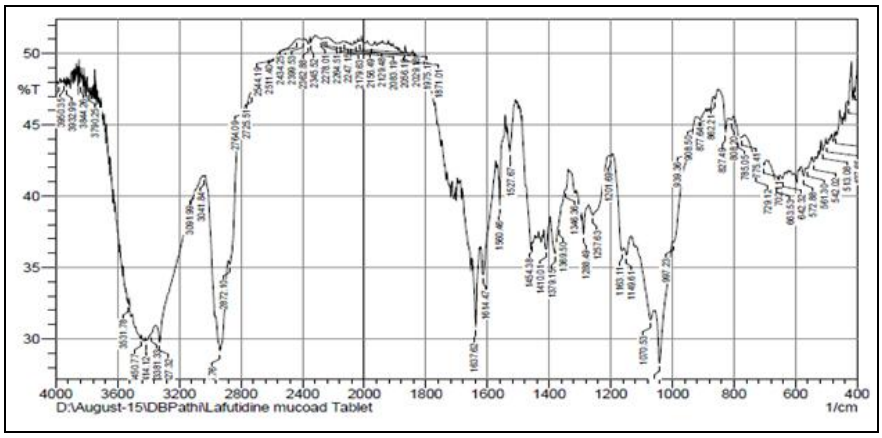


**FIG. 2: FTIR SPECTRA OF CILNIDIPINE AND EXCIPIENTS**

**TABLE 1: MICROMERITIC PROPERTIES OF THE POWDER BLEND OF CILNIDIPINE**

| Formulation Code | Angle of Repose (Degree) * | LBD (g/cm$^3$) * | TBD (g/cm$^3$) * | Compressibility Index (%) * | Hausner ratio* |
|---|---|---|---|---|---|
| CT1 | 30.38 ± 0.32 | 0.742 ± 0.15 | 0.804 ± 0.75 | 8.56 ± 0.88 | 1.06 |
| CT2 | 32.67 ± 0.43 | 0.708± 0.22 | 0.798 ± 0.32 | 10.54 ± 0.74 | 1.11 |
| CT3 | 31.78± 0.72 | 0.695 ± 0.32 | 0.784 ± 0.79 | 9.33 ± 0.65 | 1.12 |
| CT4 | 32.33 ± 0.44 | 0.706 ± 0.57 | 0.792 ± 0.52 | 10.12 ± 0.59 | 1.10 |
| CT5 | 32.77 ± 0.21 | 0.709 ± 0.51 | 0.785 ± 0.47 | 9.64 ± 0.71 | 1.13 |
| CT6 | 33.15 ± 0.75 | 0.744 ± 0.76 | 0.823 ± 0.33 | 9.26 ± 0.76 | 1.11 |
| CT7 | 32.28 ± 0.87 | 0.768 ± 0.75 | 0.842 ± 0.19 | 8.28 ± 0.47 | 1.10 |
| CT8 | 32.91± 0.86 | 0.749 ± 0.28 | 0.802± 0.28 | 10.64 ± 043 | 1.11 |

*Mean ± S.D (n=3)

**Micromeritic Properties of Powdered Blend of Cilnidipine Formulations:** The powdered blends of different formulations were evaluated for Bulk density, Tapped density, Compressibility index, Hausner's ratio and Angle of repose. The results were tabulated in Table **Table 2.** Bulk density values were in the range between 0.695-0.768gm/ml, Tapped density values were in the range between 0.784-0.842 gm/ml, Compressibility index values were in the range between 8.28–

10.64%, indicates good flow properties of powder. Hausner's ratio values were range between 1.06-1.13 Angle of repose values were in the range between 30.38º-33.15º, which indicates good flow properties of powder.

**TABLE 2: FORMULATIONS (CT1 TO CT8) OF CILNIDIPINE BUCCAL TABLETS**

| Ingredients | CT1 | CT 2 | CT 3 | CT 4 | CT 5 | CT 6 | CT 7 | CT 8 |
|---|---|---|---|---|---|---|---|---|
| Cilnidipine (mg) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Carbopol 934 | 10 | 15 | 20 | 25 | 10 | 15 | 20 | 25 |
| HPMC | 80 | 75 | 70 | 65 | 90 | 85 | 80 | 75 |
| Spray dried Lactose | 44 | 44 | 44 | 44 | 34 | 34 | 34 | 34 |
| Mannitol | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Magnesium Stearate | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Total Weight(mg) | 160 | 160 | 160 | 160 | 160 | 160 | 160 | 160 |

**Preparation of Bioadhesive Buccal Tablets:** Buccoadhesive flat-faced tablets (110 mg, 8 mm in diameter, 1.4 mm mean thickness) of combined dosage form were prepared by direct compression using a rotary tabletting machine (Cadmach, Mumbai, India). HPMC and Carbopol were used as bioadhesive polymers. Cilinidipine first mixed with the bioadhesive polymeric mixture for 10 min in a polybag. Then remaining excipients were added, and mixing continued for another 10 min. The machine was adjusted to produce tablets with a weight of 160 mg.

**Evaluation of Benidipine Buccal Tablets:**

**Average Weight and Weight Variation:** The weight variation test of the tablets was done as per the guidelines of Indian Pharmacopoeia. Ten tablets from each batch were weighed in sartorius digital balance and average weight was determined and standard deviation was calculated [5, 9]. The results are shown in **Table 3.**

**Thickness:** The thickness of ten buccal tablets in each batch was determined using a digital vernier caliper. The average thickness and standard deviation was calculated. The results are shown in **Table 3.**

**Hardness:** Hardness of the tablets was measured by using Monsanto hardness tester. It is a measuring the force required to break the tablet [5-10]. The results are shown in **Table 3.**

**Friability:** Friability is the measure of a tablet's ability to with stands both shock and abrasion without crumbling during the handling of manufacturing, packing, shipping and consumer use. The weight of 10 tablets was noted and placed them in Roche friabilator. The device subjects the tablets to the combined effect of shock and abrasion by utilizing a plastic chamber, which revolves at 25 rpm, dropping the tablets a distance of 6 inches with the revolution. The pre-weighed tablet sample is removed after 100 revolutions, dusted and reweighed. The results are shown in **Table 3.**

Friability (%) = Initial wt. of 10 tablets – final wt.of 10 tablets / Initial weight of 10 tablets x 100

**Determination of Mucoadhesive Strength [5, 11]:** Mucoadhesive strength is defined as the tensile force required breaking the adhesive bond between the model mucous membrane and the test polymer. It is important to assess its *in-vivo* buccal residence time. In the present study, the mucoadhesive strength of formulated buccoadhesive tablets was evaluated using a modified physical balance. The results are shown in **Table 3.**

**Drug Content Uniformity [5]:** The Drug content of Cilnidipine in the prepared buccoadhesive tablets was determined by UV spectrophotometry. From each batch 5 tablets were triturated to form fine powder after knowing the individual weight of each tablet. The powder equivalent to 100 mg Cilnidipine was weighed and transferred into a 100 ml volumetric flask and was dissolved in a mixture of phosphate buffer of pH 6.8. The absorbance of this solution was measured at 240nm by using UV Visible spectrophotometer. The results are shown in **Table 3.**

**Swelling Studies [5-12]:** The tablet was weighed accurately (W1) and placed in Petri dish containing 4 ml of phosphate buffer of ph 6.8.

At the end of 2 hours, the tablets were removed from the Petri dish and excess surface water was removed carefully using filter paper and swollen tablets were reweighed (W2). The swelling index was calculated according to the formula. The results are shown in **Table 3.**

Swelling index (%) = $W_2 - W_1) / W_1 \times 100$

**TABLE 3: EVALUATION OF COMPRESSED CILNIDIPINE BUCCAL TABLETS**

| S. no. | Evaluation parameter | CT1 | CT 2 | CT 3 | CT 4 | CT 5 | CT 6 | CT 7 | CT 8 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Weight variation (mg) | 158 ±0.08 | 157 ±0.01 | 158 ±0.09 | 157 ±0.06 | 156 ±0.01 | 158 ±0.07 | 157 ±0.05 | 158 ±0.06 |
| 2 | Thickness (mm) | 2.56 ±0.07 | 2.57 ±0.03 | 2.68 ±0.01 | 2.48 ±0.03 | 2.89 ±0.08 | 2.62 ±0.04 | 2.68 ±0.01 | 2.82 ±0.04 |
| 3 | Hardness (Kg/ $cm^2$) | 4.2±0.3 | 4.1±0.4 | 3.9±0.5 | 4.1±0.1 | 4.3±0.2 | 4.2±0.7 | 4.5±0.2 | 4.4±0.6 |
| 4 | Friability (%) | 0.64 ±0.02 | 0.63 ±0.01 | 0.65 ±0.02 | 0.67 ±0.03 | 0.65 ±033 | 0.64 ±0.26 | 0.62 ±0.14 | 0.64 ±0.44 |
| 5 | Mucoadhesive strength (g) | 18.76 ±0.52 | 19.95 ±0.26 | 24.99 ±0.23 | 24.65 ±0.19 | 27.90 ±0.27 | 28.65 ±0.40 | 28.70 ±0.33 | 29.45 ±0.24 |
| 6 | Drug content (%) | 97.90 ±0.61 | 96.46 ±0.33 | 95.27 ±0.72 | 93.88 ±0.15 | 94.23 ±0.48 | 95.94 ±0.21 | 96.90 ±0.70 | 98.16 ±0.86 |
| 7 | Swelling index (%) | 76.40 ±3.05 | 80.57 ±2.85 | 84.11 ±6.29 | 86.77 ±2.84 | 77.44±9. 21 | 80.11±4. 44 | 80.96±6. 21 | 88.46±6. 24 |

***In-vitro* Dissolution Study [6]:** The *in-vitro* dissolution study was carried out in the USP dissolution test apparatus – II. 900 ml of the dissolution medium i,e phosphate buffer pH 6.8 was taken in a dissolution vessel and the temperature was maintained at 37±0.5°C. The speed of the paddle was set at 50 rpm. 5 ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. Samples were collected periodically (0, 0.5, 1, 2, 3, 4, 5, 6, 7 and 8h). And the samples were analysed by UV spectrophotometer at 240nm. The results are shown in **Fig. 3.**

**TABLE 4: CUMULATIVE % DRUG RELEASE OF CILNIDIPINE BUCCAL TABLETS FORMULATIONS FROM CT1 TO CT8**

| Time (Hrs) | Cumulative % Drug release ± SD, n=6 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CT1 | CT2 | CT3 | CT4 | CT5 | CT6 | CT7 | CT8 |
| 30 minutes | 9.67 | 6.84 | 7.32 | 5.79 | 7.82 | 8.45 | 9.34 | 10.22 |
| 1 | 27.12 | 20.74 | 25.94 | 22.16 | 26.73 | 27.41 | 28.85 | 30.12 |
| 2 | 40.89 | 38.67 | 33.13 | 30.86 | 32.54 | 43.58 | 46.79 | 49.26 |
| 3 | 62.48 | 58.55 | 50.69 | 40.21 | 47.23 | 53.18 | 62.24 | 69.14 |
| 4 | 78.16 | 67.32 | 58.11 | 51.77 | 59.21 | 72.18 | 74.63 | 76.85 |
| 5 | 84.37 | 76.51 | 70.06 | 63.37 | 70.47 | 74.16 | 78.81 | 85.22 |
| 6 | 95.32 | 79.76 | 72.16 | 68.69 | 90.11 | 92.78 | 94.92 | 97.89 |
| 7 | 96.77 | 91.32 | 86.61 | 80.34 | 92.11 | 94.11 | 95.65 | 98.44 |
| 8 | 97.11 | 97.99 | 96.13 | 90.54 | 97.56 | 98.18 | 97.97 | 98.29 |

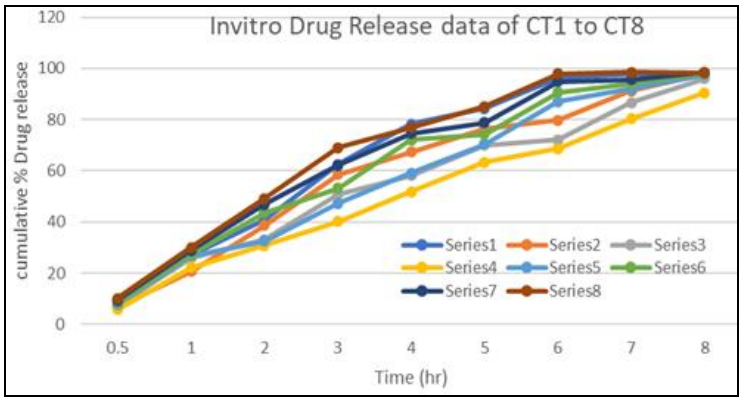


**FIG. 3: GRAPHICAL REPRESENTATION OF CUMULATIVE % DRUG RELEASE OF CILNIDIPINE BUCCAL FORMULATIONS FROM CT1 TO CT8**

**Mathematical Modelling of Cilnidipine Buccal Tablets [6]:** Mathematical modeling of the release kinetics of specific classes of release systems may be used to predict solute release rates from and solute diffusion behaviour through polymers. And elucidate physical mechanisms of solute transport by simply comparing the release data to mathematical models. The results are shown in **Fig. 4 & 5.**

**Kinetic Modeling of *In-vitro* Drug Release of Optimized Formulation (CT8):** To explore the mechanism of drug release from optimized Cilnidipine tablets, various kinetic models like zero order, first order, Higuchi and Korsmeyer-peppas equations were applied. The release kinetics was shown in **Table 4** and **Fig. 3** from the data it was concluded that the optimized formulation (CT8) followed zero order kinetics and drug release data was fitted for Higuchi equation and the korsmayer-peppas equation, "n" value is 0.865 indicating non-fickian diffusion. And the release mechanism was anamolous i.e, diffusion and erosion.

**Zero Order and First Order Release for CT8 Formulation:**

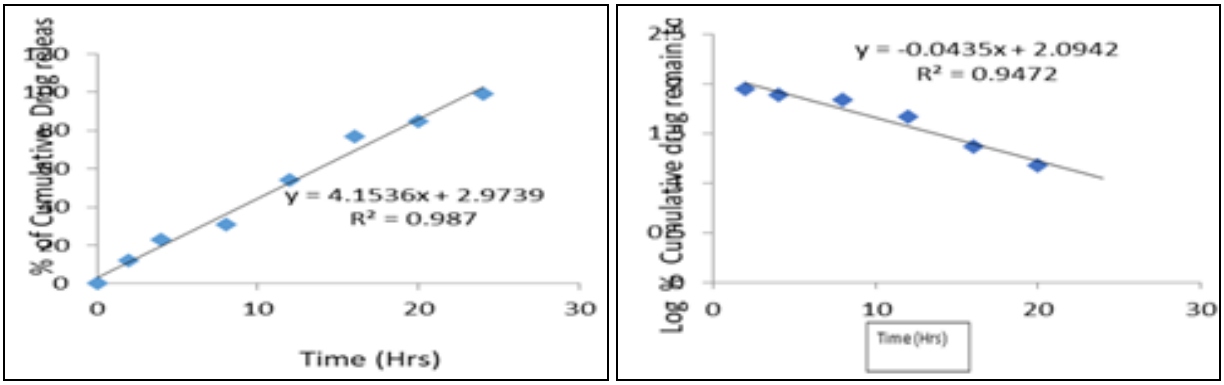


**FIG. 4: ZERO-ORDER AND FIRST-ORDER PLOT OF OPTIMIZED FORMULATION OF CILNIDIPINE (CT8)**

**Higuchi Model and Korsmeyer-Peppas for CT8 Formulation:**

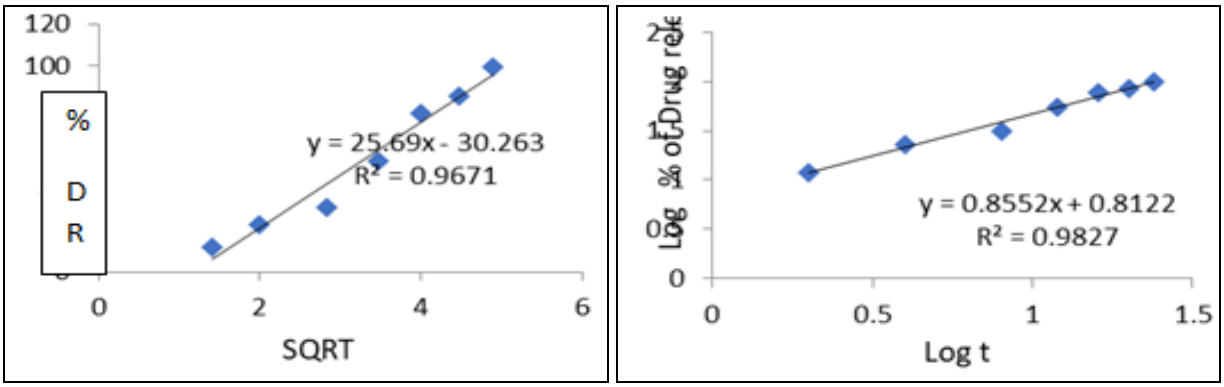


**FIG. 5: HIGUCHI MODEL PLOT AND KORSMEYER-PEPPAS PLOT OF OPTIMIZED FORMULATION OF CILNIDIPINE (CT8)**

**TABLE 5: RELEASE KINETICS OF CILNIDIPINE CONTROLLED RELEASE FORMULATION (CT8)**

| Formulation | Zero order ($r^2$) | First order ($r^2$) | Higuchi model ($r^2$) | Korsmayer-Peppas model | | Best fit model |
|---|---|---|---|---|---|---|
| | | | | $r^2$ | "n" | |
| CT8 | 0.987 | 0.947 | 0.967 | 0.982 | 0.855 | Zero order |

**CONCLUSION:** Cilnidipine buccal tablets were prepared by using carbopol 934, HPMC, (CT8) has released drug (98.29%) for 8 hrs. FT-IR studies revealed that there was no drug-excipient incompatibility. The drug release mechanism was anomalous diffusion i.e diffusion and erosion. Buccal Tablet of Cilnidipine to ensure satisfactory drug release with the help of polymers and thereby avoid first pass metabolism, enhance bioavailability. And the present optimized

Cilnidipine containing buccal tablets is considered to be potentially useful for the treatment of hypertension where improved patient compliance and convenience is expected.

**ACKNOWLEDGEMENT:** Nil

**CONFLICTS OF INTEREST:** Nil

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**How to cite this article:**
Muzib YI and Nagamani D: Design, fabrication and evaluation of bioadhesive buccal tablets of cilnidipine. Int J Pharm Sci & Res 2024; 15(5): 1533-38. doi: 10.13040/IJPSR.0975-8232.15(5).1533-38.