RESEARCH ARTICLE

# Formulation and Evaluation of Buccoadhesive Tablets of Diltiazem Hydrochloride

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**ABSTRACT**

Calcium channel blocker diltiazem hydrochloride is used to treat hypertension and angina. The study aimed to develop and evaluate bioadhesive buccal tablets that would bypass hepatic metabolism and boost bioavailability. With the use of bioadhesive polymers like kondagogu gum and guar gum in various concentrations, the direct compression method was used to manufacture buccal tablets. Fourier-transform spectroscopy (FT-IR) spectroscopy analysis of the physicochemical compatibility of the active ingredient and excipients demonstrates that the excipients are compatible with the active component. Permeation across porcine buccal mucosa, moisture absorbance, *in-vitro* drug release, surface pH, and swelling index were all tested on the developed tablets. The best formulation, which contained a combination of kondagogu gum and guar gum (F8), was the most effective, showing a flux of 208.46 µg $hr^{-1}$ $cm^{-2}$.

**Keywords:** Buccal tablets, Diltiazem hydrochloride, Guar gum, Kondagogu gum.

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## INTRODUCTION

Buccal tablets placed in the buccal pouch for a buccal route may disintegrate or wear away slowly.[1] To achieve one-way release, spray coating techniques or compression methods were used to coat every side of the dosage form except the one in contact with the buccal mucosa with hydrophilic impermeable materials such ethylcellulose hydrogenated castor oil, and so on.[1] This route's main benefit is circumvent the first-pass metabolism of drug clearance. In mucoadhesive systems, polymers (natural or synthetic) are utilized to interact with the mucus membrane[2] and make the treatment more effective and safer. Absorption of remedial agents from these routes overcomes premature drug degradation within the GIT and loss due to liver metabolism associated with oral administration. Diltiazem HCl was selected due to its high hepatic metabolism and shorter half-life (3–5 hours).[3]

## MATERIALS AND METHODS

### Materials

Diltiazem hydrochloride was obtained from Hetero drug Pvt. Ltd, Kondagogu gum and Guar gum from Universal laboratories, Lactose, Potassium dihydrogen orthophosphate and agar from Finar chemicals, Magnesium Stearate, and sodium hydroxide Talc from Nice Chemicals Ltd, and all other solvents used are of pharmaceutical grade.

## Methods

Buccal tablets were developed using the direct compression approach. Diltiazem HCl (DH) was mixed with various ratios of kondagogu gum (KG) and guar gum (GG) as natural mucoadhesive polymers, talc as a glidant, magnesium stearate as a lubricant, and lactose as a binder, all of which were well mixed before being compressed with 7 mm flat-faced punches. The composition of the prepared tablets is shown in Table 1.

### Evaluation of Buccal Tablets

### Physico-chemical Characterization of Tablets

The developed Diltiazem HCl tablets were assessed for weight variation, hardness, thickness, friability, and drug content.[4] The tablets were weighed and checked for weight variation at random, which is an appropriate way of determining homogeneity.[5,6] Because thickness varies with changes in weight due to variations in the mix's density and the speed of the compression machine, the thickness parameter is required for uniformity and packing.

The strength required to fracture a tablet in a diametric compression test using a Monsanto hardness tester and

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**Table 1:** Composition of diltiazem hydrochloride buccal tablets

| *F. code* | *Ingredients* | | | | | |
|---|---|---|---|---|---|---|
| | *DH* | *Guar gum* | *Kondagogu gum* | *Lactose* | *Magnesium stearate* | *Talc* |
| F1 | 30 | - | 30 | 86 | 2 | 2 |
| F2 | 30 | - | 60 | 56 | 2 | 2 |
| F3 | 30 | - | 90 | 26 | 2 | 2 |
| F4 | 30 | 30 | - | 86 | 2 | 2 |
| F5 | 30 | 60 | - | 56 | 2 | 2 |
| F6 | 30 | 90 | - | 26 | 2 | 2 |
| F7 | 30 | 30 | 30 | 26 | 2 | 2 |
| F8 | 30 | 30 | 60 | 26 | 2 | 2 |
| F9 | 30 | 60 | 30 | 26 | 2 | 2 |

determine if it can endure mechanical shocks during handling and transportation is known as tablet hardness. Because some of the tablets were compressed into extremely hard tablets, it is not a perfect indicator. As a result, the Roche friabilator is frequently used to determine the tablet strength.

### Assay

Randomly twenty tablets selected from each formulation were taken, and powder corresponding to one dose was added in 100 mL of phosphate buffer followed by shaking for 24 hours using a rotary shaker. The filtered sample was measured for absorbance by UV-visible spectrophotometer using against blank at 237 nm.[7]

### Drug Release

The drug release was determined using USP type V dissolution equipment mounted on a glass slide, as the drug was only expected to release from one surface. At 50 rpm and 37 ± 0.5°C, the dissolution was carried out in 900 mL (pH 6.8) buffer. Samples were drawn, and drug content was tested on a regular basis[8]. Kinetic models were examined to explain the release kinetics *in-vitro* to appraise the data.[9,10]

### Swelling Studies

Individually weighed ($W_1$) buccal tablets were positioned discretely in petri dishes holding a phosphate buffer solution of 5 mL. The tablets were removed, and excess surface water was removed carefully and weighed again ($W_2$) and calculated.

### Surface pH

The bioadhesive dosage forms were permitted to swell for 2 hours by placing them in distilled water. After that, surface pH was recorded at preset intervals with the support of a digital pH meter.[11]

### Moisture Absorption

Three tablets from each batch were placed in a vacuum oven to remove moisture before being placed on the outside of the agar and incubated at 37°C. They were weighed, and moisture absorption was calculated after 1-hour.[12]

### *Ex vivo* Permeation Studies Through Porcine Buccal Mucosa

The Krebs buffer solution was used to store buccal tissue taken within 10 minutes of the slaughter. It was immediately taken to the lab and extensively cleaned with saline to remove the adhering material. Using a Franz-type diffusion cell containing a pH 6.8 buffer solution, the *ex-vivo* penetration of Diltiazem hydrochloride throughout the porcine buccal mucosa was investigated. The tablet was placed and wetted in the donor chamber with a small amount of buffer solution. The amount of medication that infiltrated the membrane was measured[13,14] and the flux (J) and permeability coefficient were computed (P).

## RESULTS AND DISCUSSION

The formulation of bioadhesive Diltiazem hydrochloride is one of the other routes to circumvent liver metabolism and prolong the drug's release. Diltiazem hydrochloride buccal tablets were compressed using various bioadhesive rate-limiting membranes like Kondagogu gum and Guar gum alone and combined at different concentrations. The developed buccal tablets were evaluated for excipient compatibility studies, physicochemical properties, pre-compression, and post-compression parameters, swelling studies, residence time, absorption studies, and permeation through buccal mucosa of the pig.

FT-IR spectra of pure active pharmaceutical ingredients and other excipients were recorded. The spectra of the drug, polymer and the physical mixture were recorded and compared with the principal peaks and found to be no interaction between the ingredients, and they are compatible with each other (Table 2). FT-IR study revealed that all the excipients used were compatible since there is no sign of lack of interaction between the active and other ingredients used in the formulation. The physicochemical properties were observed for the prepared

**Table 2:** FT-IR studies of drug and polymer mixture

| *Interpretation* | *IR absorbance bands ($cm^{-1}$)* | |
|---|---|---|
| | *Diltiazem HCl* | *Optimized (F8)* |
| C-H Stretching (Aromatic) | 3056 | 3194.24 |
| C-H Stretching (Aliphatic) | 2966 | 2920 |
| N-H Stretching (Amine) | 2389 | 2384 |
| C=O Stretching (Ketones) | 1743 | 1738.86 |
| C-O-C | 1475 | 1470 |
| C-O-C Alkyl Aryl Ether | 1255 and 1026 | 1258 and 1021 |

**Table 3:** Post compression parameters of diltiazem hydrochloride buccal tablets

| *F* | *Wt. var(mg)* | *Thickness (mm)* | *Hardness (kg/cm$^{2)}$* | *Friability (%)* | *Assay (%)* |
|---|---|---|---|---|---|
| F1 | 149.66 ± 0.37 | 3.00 ± 0.03 | 5.97 ± 0.15 | 0.35 | 99.65 ± 0.24 |
| F2 | 149.48 ± 0.20 | 3.11 ± 0.02 | 5.90 ± 0.05 | 0.53 | 99.93 ± 0.35 |
| F3 | 150.08 ± 0.31 | 3.00 ± 0.03 | 6 ± 0.11 | 0.26 | 99.28 ± 0.12 |
| F4 | 148.45 ± 0.24 | 3.00 ± 0.02 | 5.96 ± 0.1 | 0.28 | 100.77 ± 0.30 |
| F5 | 149.91 ± 1.41 | 3.00 ± 0.02 | 6.01 ± 0.1 | 0.34 | 99.96 ± 0.34 |
| F6 | 148.98 ± 0.40 | 3.11 ± 0.01 | 5.93 ± 0.2 | 0.27 | 100.81 ± 0.22 |
| F7 | 149.38 ± 0.27 | 3.00 ± 0.02 | 6.1 ± 0.11 | 0.16 | 98.47 ± 0.32 |
| F8 | 150.04 ± 0.30 | 2.95 ± 0.03 | 6.1 ± 0.11 | 0.25 | 100.27 ± 0.14 |
| F9 | 149.94 ± 0.26 | 3.00 ± 0.02 | 6.0 ± 0.19 | 0.43 | 99.85 ± 0.41 |

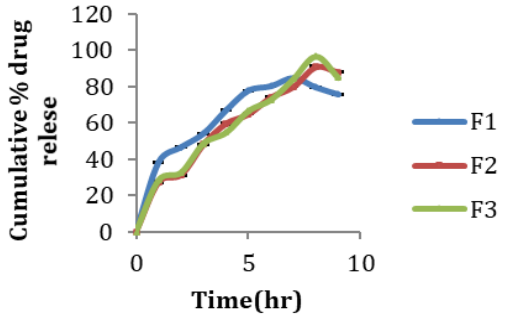


**Figure 1:** *In-vitro* %drug release of diltiazem HCl made of kondagogu gum

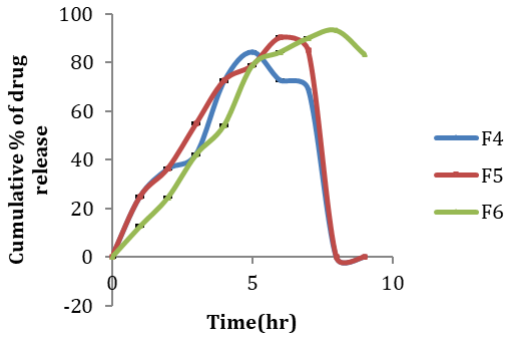


**Figure 2:** *In-vitro* %drug release of diltiazem HCl buccal tablets made of guar gum

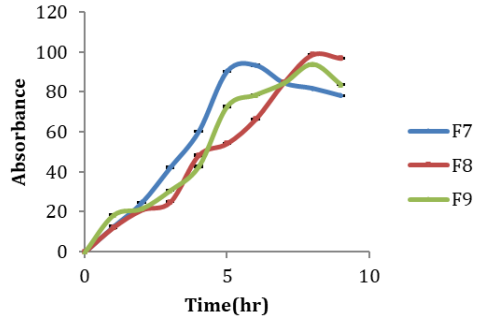


**Figure 3:** *In-vitro* %drug release of diltiazem HCl buccal tablets with kondagogu gum and guar gum

**Table 4:** Data of moisture absorption and surface pH

| *F. code* | *Moisture absorption* | *Surface pH* |
|---|---|---|
| F1 | 12.76 ± 0.25 | 6.96 ± 0.16 |
| F2 | 14.66 ± 0.25 | 6.86 ± 0.43 |
| F3 | 13.45 ± 0.25 | 6.9 ± 0.35 |
| F4 | 21.50 ± 0.30 | 6.71 ± 0.12 |
| F5 | 23.61 ± 0.25 | 6.86 ± 0.23 |
| F6 | 24.93 ± 0.25 | 7.43 ± 0.15 |
| F7 | 13.18 ± 0.25 | 6.67 ± 0.43 |
| F8 | 11.43 ± 0.30 | 6.79 ± 0.24 |
| F9 | 13.16 ± 0.30 | 6.67 ± 0.13 |

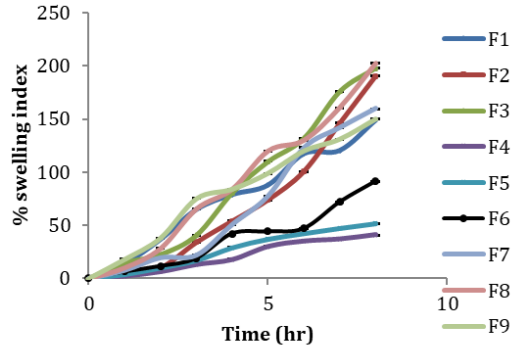


**Figure 4:** Swelling studies of diltiazem HCl selected buccal tablets

tablets, and the weight variations were within limits as per USP. The thickness of buccal tablets varied from 2.95–3.11 mm; all the batches showed uniform thickness. Acceptable physicochemical properties were observed for the prepared buccal tablets. The hardness of the tablets was found to be good depending upon the compression force applied (5.2–6.0 kg/cm²). Friability was obtained between the ranges of 0.16–0.53%, which was below 1%, indicating sufficient mechanical integrity of the tablets. The drug content show values in the range of 98.47 ± 0.32 to 100.27 ± 0.14, which reveals good uniformity in drug among all the formulations (Table 3).

*In-vitro* drug release was carried in pH 6.8 PB and the study exposed that the tablets formulated using kondagogu gum, in the ratio of 1:3 showed maximum drug release of

96.6% in 8 hours. Tablets formulated using guar gum, in the ratio of 1:3 shows maximum drug release of 93.4% in 8 hours. Tablets formulated using the combination of kondagogu gum and guar gum, in the ratio of 2:1 (kondagogu gum: guar gum) shows maximum drug release of 98.7% in 8 hours.

Finally, *in-vitro* drug release studies confirmed that Diltiazem hydrochloride release varied according to the nature and concentrations of different polymers (Figure 1–3). The surface pH was measured to examine the chance of any side effects. The surface pH of the dosage forms containing kondagogu gum and guar gum was 6.7 ± 0.43 to 7.3 ± 0.25, and the pH was almost neutral. The results recommended that the polymeric mix was appropriate for the oral route and was not irritant to the buccal mucosa (Table 4).

The moisture absorption studies of all the formulations reveal that the formulation containing guar gum F5 shows maximum moisture absorption capacity than the formulation containing kondagogu gum. The formulation containing the combination of guar gum and kondagog gum (F8) showed higher water uptake than other preparations containing guar gum and kondagogu gum alone. The absorption studies provide a hint regarding the capability of polymers and whether they can sustain their integrity following moisture absorption and was in the order of Guar gum > Kondagogu gum.

The Swelling behavior of tablets was shown in Figure 4. The %swelling index was found to be in the range of 149, 190.3, 198 at $8^{th}$ hour for the formulations containing kondagogu gum F1, F2 and F3, respectively, within the formulations containing guar gum F4, F5 and F6 showed %swelling index values 41, 51.7 and 91.2, respectively at $8^{th}$ hours and the formulations containing the combination of guar gum and kondagogu gum F7, F8 and F9 showed %swelling index of 160, 202.4 and 150 at $8^{th}$ hours. Therefore, a formulation containing the combination of guar gum and kondagogu gum (F8) shows higher water uptake values.

The *ex-vivo* permeation studies were carried out for optimized formulation. The values of flux were noted. It indicates that the formulation containing the combination of kondagogu gum a guar gum (F8) showed maximum flux, *i.e.,* 208.46 µg $hr^{-1}cm^{-2}$. The optimized formulations were appropriate for buccal delivery based on the results of *in-vitro* drug release, surface pH, and swelling *in-vitro* and *ex-vivo* studies.

## CONCLUSION

The formulation of bioadhesive diltiazem hydrochloride is one of the other routes to circumvent liver metabolism and prolong the drug's release. Diltiazem hydrochloride buccal tablets were compressed using various bioadhesive rate-limiting membranes like kondagogu gum and guar gum alone and combined at different concentrations. All the formulations prepared with kondagogu gum and guar gum sole and in combination were shown to be within limits. *In-vitro* drug release established the appropriateness of developed formulations for the release of diltiazem hydrochloride. The results recommended that the polymeric mix known be suitable for application as an oral route without causing any irritation to the buccal mucosa.

The optimized formulations such as F8 (kondagogu gum and guar gum) follow the first and Higuchi order of release kinetics governed by the Fickian diffusion mechanism. The study concludes that buccal drug delivery of diltiazem hydrochloride formulated with the natural polymers (kondagogu gum and guar gum) be able to be an effective way to circumvent the hepatic metabolism and prolongs the action by reducing the dosing frequency.

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