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# FORMULATION AND *INVITRO* EVALUATION OF MUCOADHESIVE BUCCAL FILMS OF DILTIAZEM HYDROCHLORIDE

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**ABSTRACT**

The aim of this work was the design and evaluation of Buccal mucoadhesive patches consisting basically of bioadhesive polymeric layer and impermeable backing layer to provide unidirectional flow of Diltiazem Hydrochloride across buccal mucosa. Mucoadhesive patches of about five formulations containing 20 mg Diltiazem hydrochloride are designed and evaluated for their Drug content, physical characteristics such as Appearance, Surface Texture, Folding Endurance, Thickness, Area, Swelling Studies and in-vitro release. The invitro release studies are carried out using fabricated diffusion cell and dialysis sac was used as a membrane. The patches were prepared with good bio-adhesive polymer like HPMC and copolymers like PVP K-30 and Eudragit L-100-55 .Convenient bioadhesion, acceptable elasticity, swelling and surface pH were obtained. Patches exhibited sustained release over more than 6 h and the addition of polyvinyl pyrrolidone (PVP) generally enhanced the release rate. Optimum release behaviour was shown with patches containing300mg HPMC (5cps) and 25mg Eudragit L-100-55.Storage of these patches for 6 months did not affect the elastic properties, however, enhanced release rates were observed.

**Key words:** Mucoadhesive polymers, Patches, Diltiazem hydrochloride, In vitro release, Buccal delivery.

## INTRODUCTION

Buccal drug delivery system has become an popular route of drug administration. Buccal drug delivery system improves the bio- availability of drug undergoing systemic hepatic first pass metabolism. Though oral route is the commonly employed route of drug administration, it is not suitable for drugs which are susceptible to gut/hepatic metabolism and also for drugs which cause gastro intestinal side effects. Despite various disadvantages, the oral mucosal route might be the potential option for drug delivery and for macro and micromolecular deliveries.The buccal cavity surface comprises of stratified squamous epithelium which was separated from the under lying tissue of lamina propria and submucosa by an undulating basement membrane [1]. An interesting thing to note that the permeability of buccalmucosa is higher than that of the skin, but less than that of the intestine [2–4]. It has been reported that the permeability of the buccal mucosa is approximately 4–4000 times greater than that of the skin [5]. Hence the buccal delivery serves as an excellent basement for absorption of drug molecules that have poor dermal penetration. However, the primary barrier to permeability in the oral mucosa is due to intercellular material derived from the so-called 'membrane coating granules'present at the topmost 200 micron layer [6,7]. Negatively charged mucin have sulfhydryl groups and sialic acid residues that

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are responsible for the process of mucoadhesion [8]. Saliva and salivary mucin attributes barrier properties to oral mucosa [9]. Major salivary glands consist of lobules of cells that secrete saliva, the minor salivary glands are located in the lips, buccal mucosa, and in linings of the mouth and throat [10]. Total turnover rate of the total saliva at normal physiological conditions having a flow rate of 1–2 ml/min [11]. Drug absorption through the buccal cavity can take place either by the transcellular route or paracellular pathway. The mucosa in sublingual region is more permeable leading to rapid absorption with improved bioavailability [12]. One of the reasons is that buccal mucosa is less permeable and is thus not able to produce a rapid onset of absorption and hence better suited for formulations that are intended for sustained release action. The primary disadvantage of buccal delivery route is the low flux that in turn results in low drug bioavailability. To overcome this drawback, various buccal penetration nenhancers have been studied which improve the absorption of the molecules. The constant salivary secretion with in the buccal cavity makes it quite hard for dosage forms to be retained for long periods of time. It is documented that the maximum duration of buccal delivery is 4–6h [13]. An ideal buccoadhesive system is the one that adhere to the site of attachment for a few hours, releases the drug in a controlled fashion, facilitates the rate and extent of drug absorption, does not produce any irritation to the patient. In spite of these challenges the buccal route is still the preferred route for delivery of active pharmaceutical ingredients (API) that are prone to high level of degradation in the gastrointestinal tract. Different buccal delivery products have been marketed or are proposed for certain diseases like trigeminal neuralgia, Meniere's disease, diabetes, addiction etc [14-21]. Various bioadhesive mucosal dosage forms have been developed, which includes gels, adhesive tablets, ointments, patches and more recently the use of polymeric films for buccal delivery [22]. Diltiazem hydrochloride is a calcium channel antagonist, block calcium entry by preventing opening of voltage gated L-type calcium channels. Mainly affect heart and smooth muscle; inhibiting the calcium entry caused by depolarization in these tissues. Diltiazem decreases peripheral vascular resistance and arterial blood pressure and produces vasodilation in coronary vessels, effect on heart, anti dysrhthmic action (mainly arterial tachycardia), because of impaired arterioventricular conduction and reduced contractility. Diltiazem is well absorbed after oral administration but its bioavailability is reduced because of first pass hepatic metabolism. Peak plasma concentration occurs about 3 to 4 hrs after a dose by mouth. Bio-availability is reported to be about 40%.

## MATERIALS AND METHODS

Diltiazem hydrochloride was obtained as gift sample from Aurabindo pharma Pvt Ltd, Hyderabad, Hydroxy propyl methyl cellulose, Eudragit L-100-55, and PVP K-30 was obtained as gift sample from Nicholas Piramal Pharmaceuticals Pvt Ltd, and all other chemicals used in formulations are analytical grade.

### Preparation of Phosphate buffer of pH 6.2

To 250ml of 0.2M potassium dihydrogen orthophosphate solution, 40.5ml of 0.2M sodium hydroxide solution was added and the volume was made up to 1000ml with distilled water.

### Preparation of standard stock solution

Accurately weight 100mg of diltiazem hydrochloride was dissolved in 100ml of phosphate buffer pH 6.2 to give 1000mcg/ml.

### Determination of Lambda Max

The stock solution of diltiazem hydrochloride was scanned in shimadzu spectrophotometer in U.V range of 200-300nm. Wave length of 240nm was selected and utilized for further studies in this work.

### Standard plot of Diltiazem hydrochloride

From the stock solution, 1ml was pipetted out and diluted to 100ml. From this solution, 2,4,6,8 and 10ml were pipetted out in different 10ml volumetric flasks and the volume was made up to the mark (10ml). The absorbance of the solutions was measured at 240nm. The data for the standard curve is given in the following table. A graph was plotted by taking the concentration on X –axis and absorbance on Y-axis.

### Method of Preparation of Buccal Films

The films were prepared by using 300mg of HPMC in case of formula F1. 300mg of HPMC and 25mg and 50mg of respective copolymers were used in case of formulae F2, F3, F4 and F5. While preparing F2, F3, F4 and F5, PVP and Eudragit were dissolved in 2ml of ethanol each. All the four formulations were added to alcoholic HPMC solutions.

In all the five formulations, glycerin was added as plasticizer (40%w/w of polymer). 20mg of drug was added to each formulation. The prepared polymeric drug solution was poured on glass rings placed on mercury substrate. Drying was carried out under low temperatures. The drying rate was controlled by placing an inverted glass funnel to control the drying rate. After complete drying, the films were removed from petridishes containing mercury. The films were having a diameter of 5.2cms. These films were used throughout the work. The films were found to be smooth, flexible and could be cut to any desired size and shape. The formula given above is to produce a film of area 21.22 sq.cm.

### Evaluation of buccal films of Diltiazem hydrochloride

The films were evaluated for the following parameters.

**Physical appearance**: Includes visual inspection of films.
**Surface texture**: It can be evaluated by touching the films.

**Folding endurance**: Folding endurance was determined by repeatedly folding a small strip of film at the same place till it broke. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance.

**Thickness and size:** The thickness of the film is measured using screw gauge micrometer with a least count of 0.01 mm. The maximum probable size for buccal films is 15 $cm^2$ but usual range of comfortable size is 1 to 3 $cm^2$. The thickness of the films must be limited to a few mm. The shapes comfortable to be used by the patient are either ellipsoidal or circular.

**Drug Content:** A film of area 1$cm^2$ was placed in a volumetric flask containing 50 ml of phosphate buffer of pH 6.2 and kept aside for some time to release the total drug present in the film and the volume was made up to 100 ml with the same buffer. Then the absorbance was measured after suitable dilution at 240 nm against drug devoid polymer blank solution in phosphate buffer of pH 6.2. The content of diltiazem hydrochloride was calculated using standard graph.

**Swelling studies**: 1$cm^2$ film of each formulation was accurately weighed placed in a petridish containing 20ml of water. The weight of each film was determined at 5 and 10 minutes by pressing the film with a tissue paper to remove the excess fluid. The swelling index was calculated by the formula

$$\textbf{Swelling index} = (w_2 - w_1)/ w_1$$

Where $w_1$ is initial weight of the film and $w_2$ is weight of the films after particular swelling time interval.

**In-vitro evaluation**: In-vitro release studies were carried out by using sigma dialysis membrane attached to one end of fabricated open cylinder which acted as donor compartment. Films of 2$cm^2$ area were used for each formulation. The sigma dialysis membrane was previously hydrated by soaking it in distilled water for 30 minutes after which it was fixed to the donor compartment. The film was placed over the dialysis membrane in the donor compartment. The receptor compartment was filled with 100 ml of phosphate buffer of pH 6.2. Teflon coated magnetic bead was placed in receptor compartment and the whole assembly was placed on the magnetic stirrer and the temperature maintained at 37±0.5ºC. Buffer was stirred at 50 rpm for all formulations. Samples of 5 ml were withdrawn at regular intervals, suitably diluted and absorbance was measured at 240 nm. The volume of receptor compartment was maintained constant by replacing equal volume of buffer. The results were tabulated and similarly, drug devoid film of same composition was taken and diffusion was carried out in a separate cell.

**Table 1. Formulation Chart**

| S.No. | Ingredients(mg) | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|---|
| **1** | Diltiazem Hydrochloride | 20 | 20 | 20 | 20 | 20 |
| **2** | HPMC (5cps) | 300 | 300 | 300 | 300 | 300 |
| **3** | Poly vinyl Pyrrolidone | --- | 25 | 50 | --- | _ |
| **4** | Eudragit L-100-55 | --- | --- | --- | 25 | 50 |
| **5** | Ethanol (ml) | 8 | 8 | 8 | 8 | 8 |
| **6** | Glycerine ( ml) | 0.09 | 0.1 | 0.11 | 0.1 | 0.11 |

## RESULTS AND DISCUSSION

**Figure1. Standard plot of Diltiazem hydrochloride**

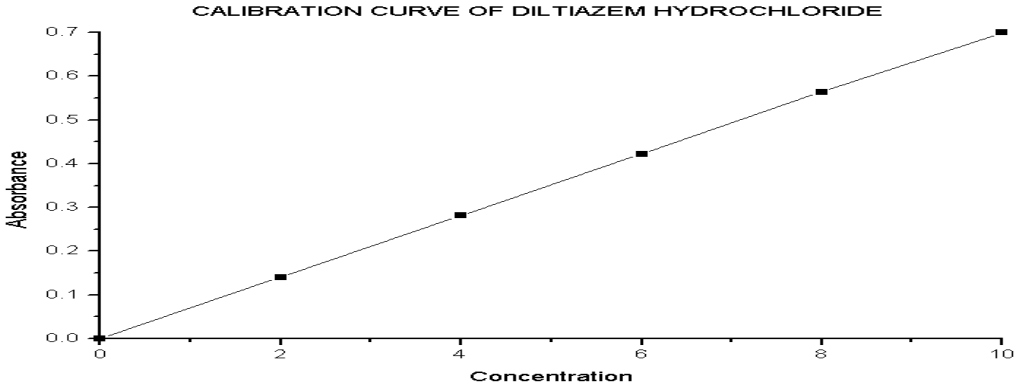


**Table 2. Standard plot of Diltiazem hydrochloride**

| S.NO | Concentration(mcg/ml) | Absorbance |
|---|---|---|
| 1. | 0 | 0 |
| 2. | 2 | 0.140 |
| 3. | 4 | 0.281 |
| 4. | 6 | 0.422 |
| 5. | 8 | 0.564 |
| 6. | 10 | 0.700 |

**Figure 2. FTIR spectra of Diltiazem hydrochloride**

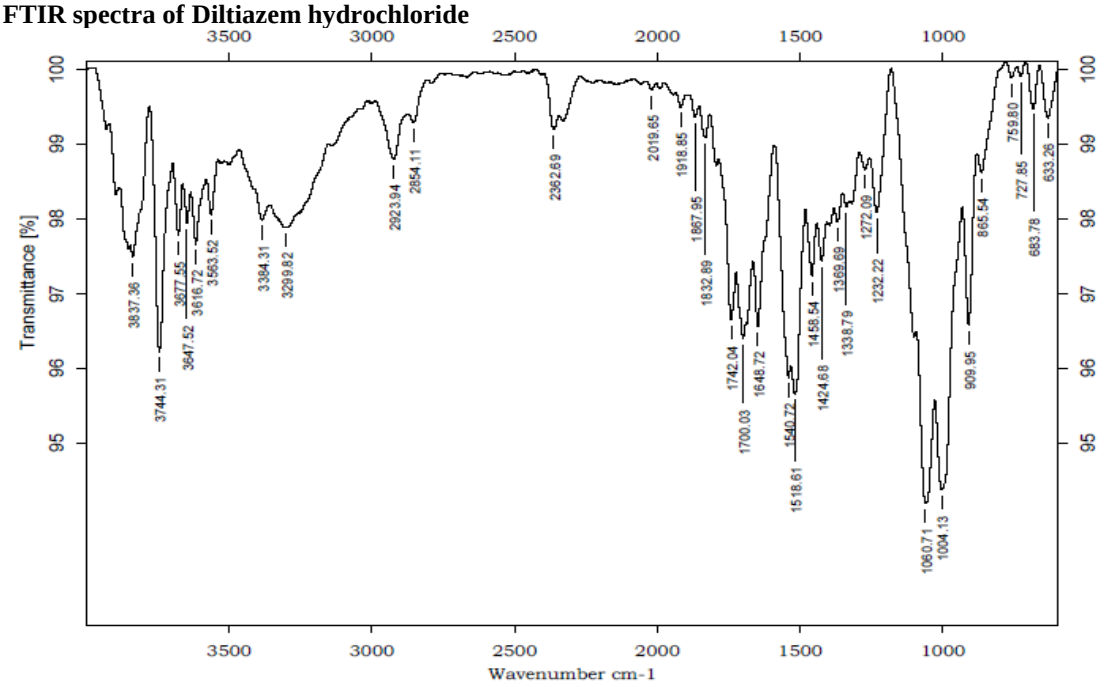



**Figure 3. FTIR spectra of HPMC**

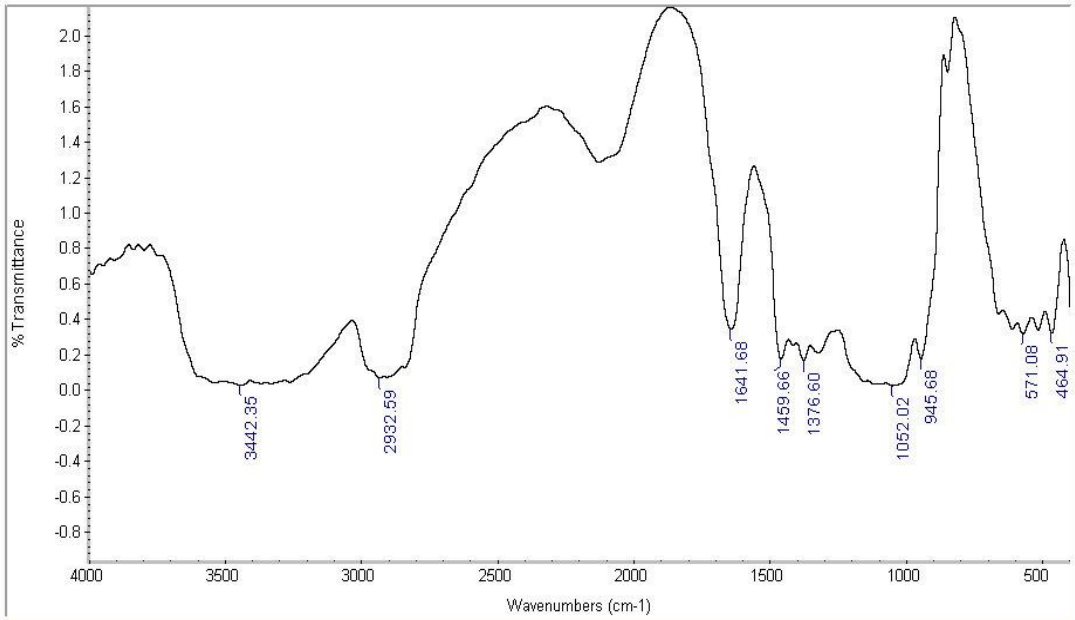


**Figure 4. FTIR spectra of Diltiazem hydrochloride+ HPMC**

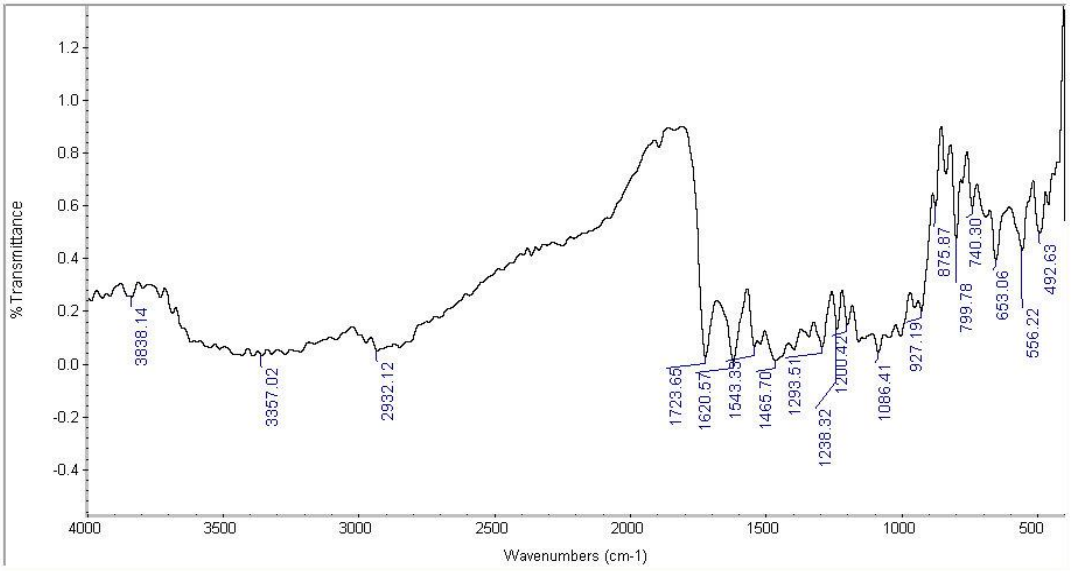



**Figure 5. FTIR spectra of Physical mixture (Formulation)**

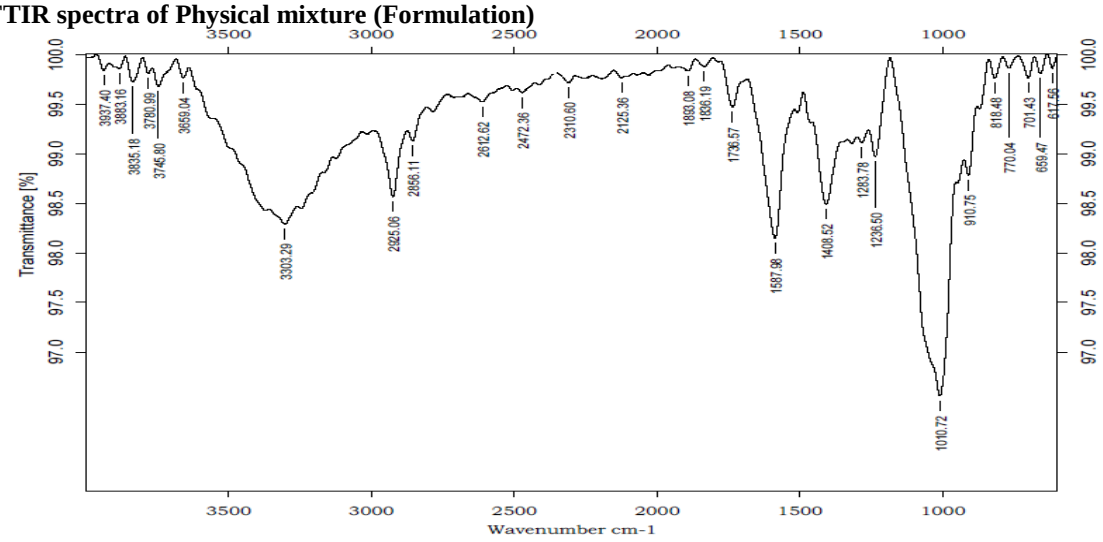



**Figure 6. DSC of HPMC (50 cps)**

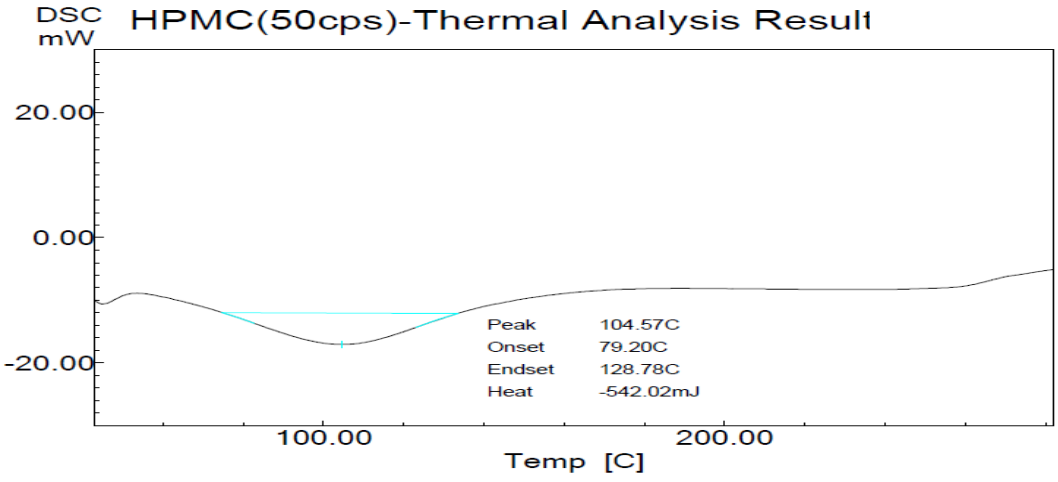


**Figure 7. DSC thermogram of Physical mixture**

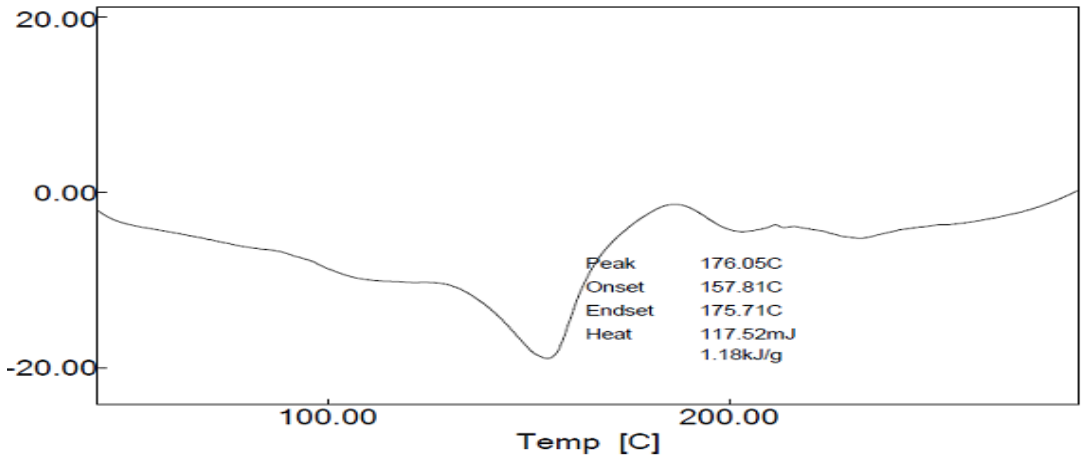



**Table 3. Physical Evaluation of Buccal Films**

| S.No | Formulation Code | Color | Surface Texture | Folding Endurance | Area($cm^2$) | Thickness (mm) | Drug content |
|---|---|---|---|---|---|---|---|
| | | | | | | Mean | |
| 1 | F1 | White | Very Smooth | ++ | 21.22 | 0.66 | 98.47 |
| 2 | F2 | White | Smooth | ++ | 21.22 | 0.71 | 98.15 |
| 3 | F3 | White | Smooth | +++ | 21.22 | 0.74 | 97.85 |
| 4 | F4 | White | Smooth | ++ | 21.22 | 0.73 | 97.42 |
| 5 | F5 | White | Smooth | +++ | 21.22 | 0.77 | 97.25 |

+++: very flexible , ++: flexible

**Table 4. Swelling studies of films**

| Formulation Code | Initial weight of film (w2) in mg | Final weight of film (w1) in mg | Swelling Index (w1-w2)/w2 |
|---|---|---|---|
| F1 | 22 | 25 | 0.136 |
| F2 | 27 | 31 | 0.148 |
| F3 | 28 | 33 | 0.178 |
| F4 | 30 | 36 | 0.2 |
| F5 | 32 | 39 | 0.218 |

**Table 5. In-vitro release studies of F1 using Phosphate buffer pH 6.2**

| Time (mins.) | Abs | Conc. | Cum% released | Log cum% released | Cum% retained | Log cum% retained | $(T)^{1/2}$ | Log $(T)^{1/2}$ |
|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 | 0.023 | 0.326 | 17.34 | 1.23 | 82.66 | 1.91 | 5.47 | 0.73 |
| 60 | 0.036 | 0.511 | 27.18 | 1.43 | 72.82 | 1.86 | 7.74 | 0.88 |
| 90 | 0.045 | 0.639 | 33.98 | 1.53 | 66.02 | 1.81 | 9.48 | 0.97 |
| 120 | 0.060 | 0.852 | 45.31 | 1.65 | 54.69 | 1.73 | 10.95 | 1.03 |
| 180 | 0.086 | 1.222 | 65 | 1.81 | 35 | 1.54 | 13.41 | 1.12 |
| 240 | 0.109 | 1.548 | 82.34 | 1.91 | 17.66 | 1.24 | 15.49 | 1.19 |
| 300 | 0.125 | 1.776 | 94.46 | 1.97 | 5.54 | 0.74 | 17.32 | 1.23 |

**Table 6. In-vitro release studies of F2 using Phosphate buffer pH 6.2**

| Time (mins.) | Abs | Conc. | Cum% released | Log cum% released | Cum% retained | Log cum% retained | $(T)^{1/2}$ | Log $(T)^{1/2}$ |
|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 | 0.021 | 0.298 | 15.85 | 1.20 | 84.15 | 1.92 | 5.47 | 0.73 |
| 60 | 0.032 | 0.454 | 24.14 | 1.38 | 75.86 | 1.88 | 7.74 | 0.88 |
| 90 | 0.040 | 0.568 | 30.21 | 1.48 | 69.79 | 1.84 | 9.48 | 0.97 |
| 120 | 0.052 | 0.738 | 39.25 | 1.59 | 60.75 | 1.78 | 10.95 | 1.03 |
| 180 | 0.079 | 1.122 | 59.68 | 1.77 | 40.32 | 1.60 | 13.41 | 1.12 |
| 240 | 0.100 | 1.421 | 75.58 | 1.87 | 24.42 | 1.38 | 15.49 | 1.19 |
| 300 | 0.120 | 1.705 | 90.69 | 1.95 | 9.31 | 0.96 | 17.32 | 1.23 |

**Table 7. In-vitro release studies of F3 using Phosphate buffer pH 6.2**

| Time (mins.) | Abs | Conc. | Cum% released | Log cum% released | Cum% retained | Log cum% retained | $(T)^{1/2}$ | Log $(T)^{1/2}$ |
|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 | 0.020 | 0.284 | 15.10 | 1.17 | 84.9 | 1.92 | 5.47 | 0.73 |
| 60 | 0.031 | 0.440 | 23.40 | 1.36 | 76.6 | 1.88 | 7.74 | 0.88 |
| 90 | 0.039 | 0.554 | 29.46 | 1.46 | 70.54 | 1.84 | 9.48 | 0.97 |
| 120 | 0.050 | 0.710 | 37.76 | 1.57 | 62.24 | 1.79 | 10.95 | 1.03 |
| 180 | 0.076 | 1.079 | 57.39 | 1.75 | 42.61 | 1.62 | 13.41 | 1.12 |
| 240 | 0.098 | 1.392 | 74.04 | 1.86 | 25.96 | 1.41 | 15.49 | 1.19 |
| 300 | 0.116 | 1.648 | 87.65 | 1.94 | 12.35 | 1.09 | 17.32 | 1.23 |

**Table 8. In-vitro release studies of F4 using Phosphate buffer pH 6.2**

| Time (mins.) | Abs | Conc. | Cum% released | Log cum% released | Cum% retained | Log cum% retained | $(T)^{1/2}$ | Log $(T)^{1/2}$ |
|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 | 0.019 | 0.269 | 14.30 | 1.1.5 | 85.7 | 1.93 | 5.47 | 0.73 |
| 60 | 0.027 | 0.383 | 20.37 | 1.30 | 79.63 | 1.90 | 7.74 | 0.88 |
| 90 | 0.038 | 0.539 | 28.67 | 1.45 | 71.33 | 1.85 | 9.48 | 0.97 |
| 120 | 0.047 | 0.667 | 35.47 | 1.54 | 64.53 | 1.80 | 10.95 | 1.03 |
| 180 | 0.073 | 1.037 | 55.15 | 1.74 | 44.85 | 1.65 | 13.41 | 1.12 |
| 240 | 0.095 | 1.349 | 71.15 | 1.85 | 28.25 | 1.45 | 15.49 | 1.19 |
| 300 | 0.111 | 1.577 | 83.88 | 1.92 | 16.12 | 1.20 | 17.32 | 1.23 |

**Table 9. In-vitro release studies of F5 using Phosphate buffer pH 6.4**

| Time (mins.) | Abs | Conc. | Cum% released | Log cum% released | Cum% retained | Log cum% retained | $(T)^{1/2}$ | Log $(T)^{1/2}$ |
|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 | 0.018 | 0.255 | 13.56 | 1.13 | 86.44 | 1.93 | 5.47 | 0.73 |
| 60 | 0.026 | 0.369 | 19.62 | 1.29 | 80.38 | 1.90 | 7.74 | 0.88 |
| 90 | 0.036 | 0.511 | 27.18 | 1.43 | 72.82 | 1.86 | 9.48 | 0.97 |
| 120 | 0.045 | 0.639 | 33.98 | 1.53 | 66.02 | 1.81 | 10.95 | 1.03 |
| 180 | 0.070 | 0.994 | 52.8 | 1.72 | 47.2 | 1.67 | 13.41 | 1.12 |
| 240 | 0.091 | 1.293 | 68.77 | 1.83 | 31.23 | 1.49 | 15.49 | 1.19 |
| 300 | 0.103 | 1.463 | 77.81 | 1.89 | 22.19 | 1.34 | 17.32 | 1.23 |

**Table 10. Kinetic values for formulations f1-f5**

| S.No. | Formulation | First order equation | | | Higuchi Equation | |
|---|---|---|---|---|---|---|
| | | Slope (n) | First order rate constant (K) | Regression co-efficient (R) | Slope (n) | Regression co-efficient (R) |
| 1 | **F1** | 0.00414 | 0.0095 | 0.9643 | 5.6580 | 0.9760 |
| 2 | **F2** | 0.0034 | 0.0078 | 0.9648 | 5.3269 | 0.9682 |
| 3 | **F3** | 0.003 | 0.0069 | 0.9746 | 5.1709 | 0.9679 |
| 4 | **F4** | 0.00269 | 0.0061 | 0.9822 | 4.9937 | 0.9653 |
| 5 | **F5** | 0.00226 | 0.0052 | 0.9903 | 4.7026 | 0.9673 |

**Figure 8. In-vitro release studies of F1**

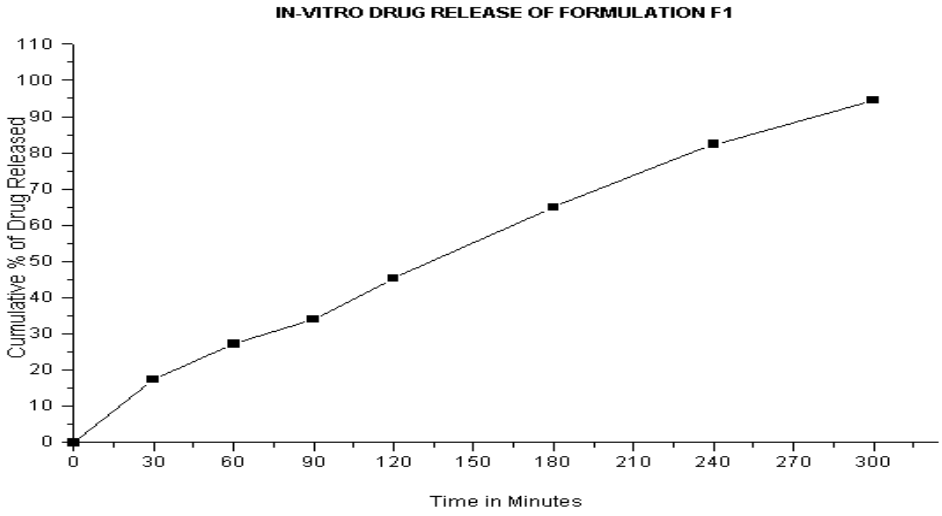



**Figure 9. *In*-vitro release studies of F2**

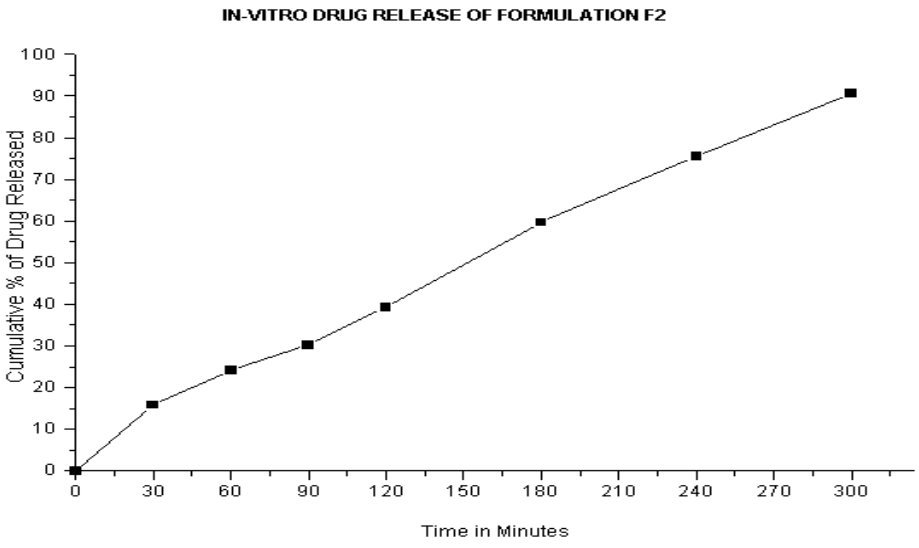


**Figure 10. In-vitro release studies of F3**

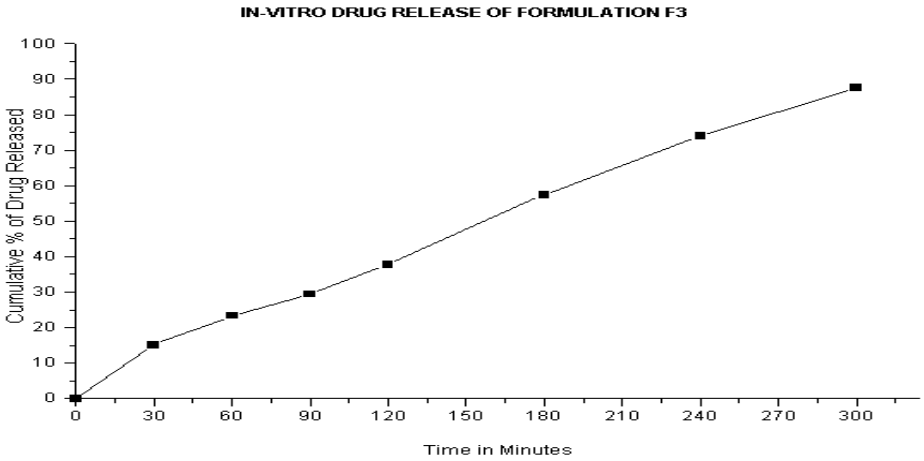



**Figure 11. In-vitro release studies of F4**

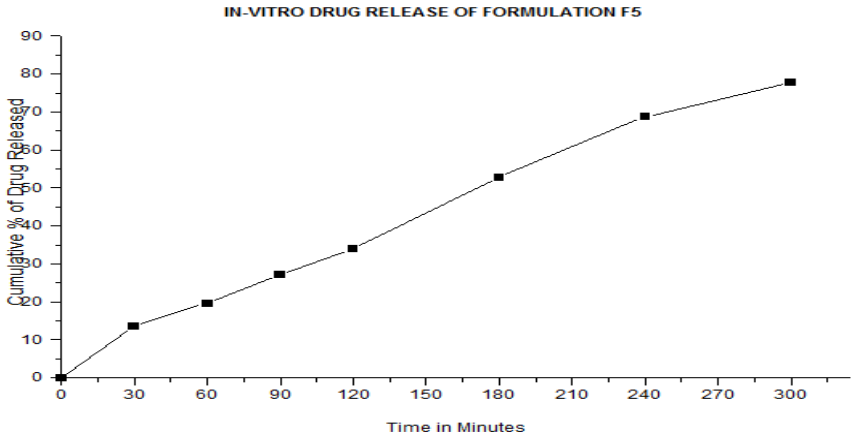



**Figure 12. In-vitro release studies of formulations F1-F5**

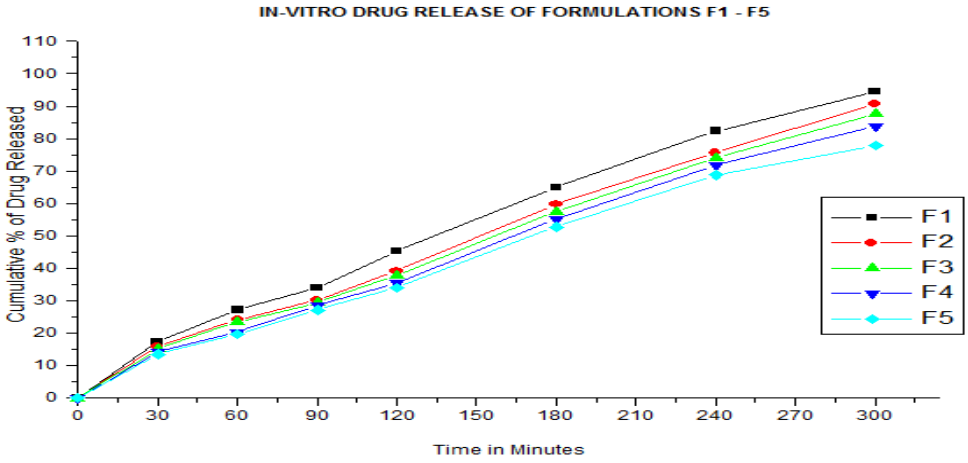


**Figure 13. Log cumulative % release studies of formulations F1-F5**

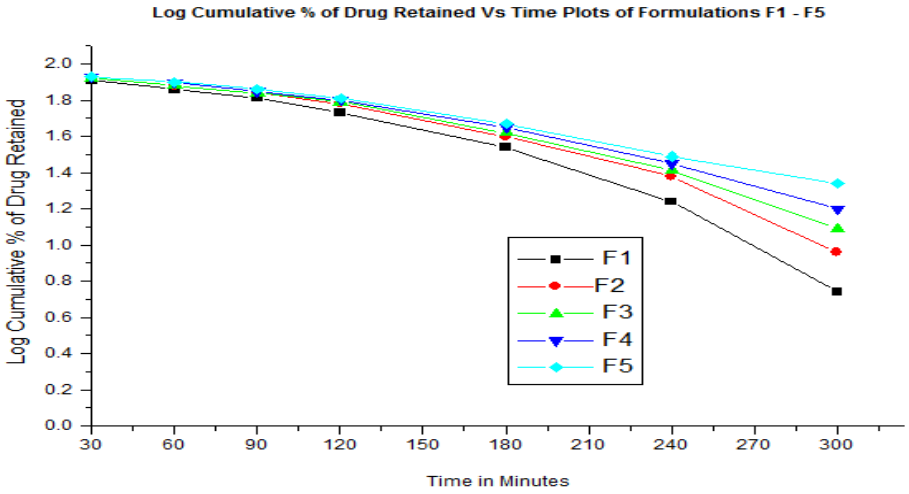
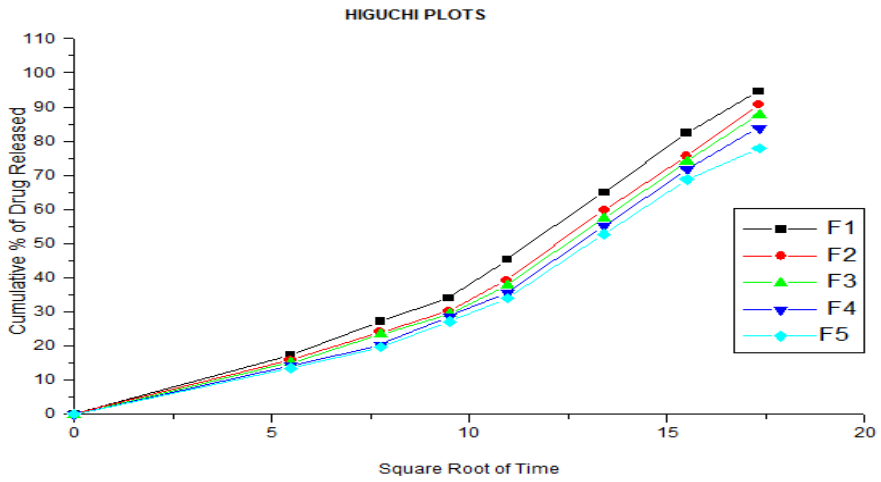



**Figure 14. Huguchi Plots**




**DISCUSSION AND CONCLUSION**

The prepared films are characterized for FTIR, DSC, and various parameters have been evaluated. The FTIR reports had concluded that the prepared Diltiazem hydrochloride buccal films showed no interactions between drug and the film forming polymers. The DSC data revealed HPMC melting point and melting point of Physical mixture which corresponds to melting point of pure forms of HPMC, and there no exhibition of polymorphism.

The drug content of the films was found to be in the range of 97.25% to 98.47%. Thickness of the films was found to be in the range of 0.66mm to 0.77mm. The order of swelling index were found to be as follows:F5>F4 > F3> F2 > F1. In-vitro release profiles for formulations were found to be in the order of :F1 > F2 > F3 > F4>F5. The mechanism of drug release was diffusion process. Best fit model for formulations was found to be first order kinetics.

Highest % drug release was shown by F1 and lowest% drug release was shown by F5, diffusion exponent was found to be less than 0.5 indicating that mechanism of drug release was found to be Non ficknian diffusion process . From the above investigations, buccal films was found to be a promising alternative approach to obtain a sustained release effect for more than 8 hrs by increasing the polymer concentration for the drug having extensive first pass effect.

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