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# Formulation and Evaluation of Mucoadhesive Buccal Films of Dothiepin HCl

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**Keywords:** Dothiepin HCl, HPMC K 100, HPC, HEC, Vanillin, Sodium saccharine, Polyethylene glycol, Solvent casting method

**ABSTRACT**

Buccal mucoadhesive systems among novel drug delivery systems have attracted great attention in recent years due to their ability to adhere and remain on the oral mucosa and to release their drug content gradually Buccal mucoadhesive films can improve the drug therapeutic effect by enhancement of drug absorption through oral mucosa increasing the drug bioavailability via reducing the hepatic first-pass effect The aim of the current study was to formulate the drug as buccal bioadhesive film, which releases the drug at sufficient concentration with a sustained manner reducing the frequency of the dosage form administration. One of the advantages of this formulation is better patient compliances due to the ease of administration with no water to swallow the product. Dissolution profile as studied in USP dissolution apparatus type 1 using pH 6.8 simulated saliva. The influence of variables like polymer type, concentration, of Dothiepin HCl release profile was studied. The formulation was optimized based on various evaluation parameters like drug content and in-vitro drug release. Formulation F6 successfully release of drug within 7 hrs. The IR spectra showed stable properties of Dothiepin HCl in a mixture of polymers used and revealed the absence of interaction between drug and selected polymer, stability studies were as per ICH guidelines, and results indicated that the selected formulation was stable.

## INTRODUCTION

The oral route is the most preferred route of drug delivery to the patient. However, orally administered drugs are either prone to hepatic first-pass metabolism or metabolism in gastro intestine (GI) tract or both,[1] over the last two decades mucoadhesion has become of interest for its potential to optimize localized drug delivery by retaining a dosage form at the site of administration (eg. Within gastrointestinal tract) or systemic delivery, by retaining a formulation in intimate contact with the absorption site (eg. The buccal cavity) mucoadhesion may be defined as a state in which two materials, one of which is mucus or a mucous membrane is held together for an extended period.[2] The buccal mucosa permits prolonged retention of a dosage form especially with the use of mucoadhesive polymers without much interference in activities such as speech or mastication unlike the sublingual route, Buccal film may be preferred over an adhesive tablet in terms of flexibility and comfort.[3] Dothiepin HCl is formerly known as Dosulepin is a tricyclic antidepressant drug prescribed for the treatment of depression. It is also useful in chronic pain disorder and insomnia. It acts as serotonin (SNRI) and also other activities including antihistamine, antiadrenergic, antiserotonergic, anticholinergic, and sodium channel blocking effect. The use of Dotheipin HCl is only recommended in patients who are intolerant or unresponsive to alternative depression therapies.[4-5]

**Potential advantages of mucoadhesive buccal film:[6]**

Less enzymatic activity.

Avoid the first-pass metabolism.

High permeability so more bioavailability.

No need for water during film administration.

Significant reduction in a dose.

Easily accessible for self-medication.

Improved patient compliance.

Systemic absorption is rapid.

Rich blood supply.

Enhanced stability

## MATERIALS AND METHODS

Dothiepin HCl from Yarrow chemicals, Hydroxypropyl methylcellulose (HPMC K 100), Hydroxypropyl cellulose (HPC), Hydroxyethylcellulose (HEC), from Yarrow chemicals. All other chemicals used were of analytical grade.

## METHODOLOGY

### Preparation of mucoadhesive buccal film:

The films are preferably formulated using the solvent casting method. The required quantity of polymer was added in small quantities and mixed well to dissolve in distilled water. The small quantity of drug is dissolved in the above solution. Add plasticizers to the above solution and mixed well. The solution was then cast on the Petri dish and kept in a hot air oven for drying at 40° C. After drying films were removed with the help of a sharp blade and kept in a desiccator for 24 hrs then cut into pieces of the desired shape and size.

### Standard Curve of Dothiepin HCl:

Dothiepin HCl is a white fine powder which was soluble in water. Though several methods are reported for its estimation, the UV spectrophotometric method was employed in the study. Dothiepin HCl shows maximum absorbance at 232 nm in simulated saliva H 6.8. Based on this information, a standard graph was constructed (Figure No.1).

### FTIR studies:

FT-IR spectra of pure Dothiepin HCl, and combination with HPMC K100, HEC, HPC, showed in (Figure 2). Pure Dothiepin HCl showed principle absorption peaks at 3500-3000cm$^{-1}$ (NH Stretch) and 1600-1475 cm$^{-1}$ (C=C Strech) 1350-1000 cm$^{-1}$ (C-N Strech), 900-690 cm$^{-1}$(CH bend). The same peak of NH-Stretch, C=C Stretch, N-H stretch, CH Bend, bonds were present as that of the pure drug without much shifting in the spectra of Dothiepin HCl along with the polymers. This suggested no chemical interaction between the drug and the polymer.

**DSC study:**

DSC thermogram was carried out for thermal compatibility of the drug and physical mixtures were shown in (fig 3). The melting point of the pure drug was 224.25 $^0$C whereas the melting point of drugs in the physical mixture of drugs with HPMC K100 was 219.29 $^0$C and drug with HPC 217.63 $^0$C and drug with HEC was 202.10 $^0$C. There is no change in the melting point peak of the drug in the physical mixture was retained indicating there is no interaction between the drug and polymers.

**Drug-polymer interaction study of films:**

There is always a possibility of drug-excipients interaction in any formulation due to their intimate contact. The technique employed in this study to know drug- excipients interactions is IR spectroscopy. IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. Infra-red spectra of pure drug Dothiepin HCl and formulations were scanned by using FTIR and DSC, by a thin film method.

**EVALUATION OF MUCOADHESIVE BUCCAL FILMS:**

**Physical appearance and surface texture of films:**

This parameter was checked simply with a visual inspection of films and evaluation of texture by feel or touch.

**a. Weight uniformity of films:** Three films of the size 2×2 cm were weighed individually using digital balance and the average weights were calculated.

**b. The thickness of films:** Thickness of the films was measured using a screw gauge with a least count of 0.01mm at different spots of the films. The thickness was measured at three different spots of the films and the average was taken.

**c. Folding endurance of patches:** The flexibility of films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the films was determined by repeatedly folding a small strip of the films (approximately 2x2 cm) at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance.

**d. Drug content uniformity of films:** The films were tested for drug content uniformity by UV Spectrophotometric method. Films of 2×2 cm size were cut from three different places from the casted films. Each film was placed in a 100 mL volumetric flask and dissolved in simulated saliva pH 6.8 and 5 mL is taken and diluted with water up to 10 mL. The absorbance of the solution was measured at λ max 232 nm using a UV/ visible spectrophotometer (Shimadzu). The percentage of drug content was determined.

***In-vitro* dissolution studies:**

The release rate of Dothiepin HCl dissolving Buccal films was determined by using USP dissolution testing apparatus II at 50 RPM. The film with 2×2 cm was placed in the 300 mL of 6.8 pH simulated saliva as a dissolution medium, and the temperature was maintained at 37°C.

From this dissolution medium, 2 ml of the sample solution was withdrawn at different time intervals. The samples were filtered through Whitman filter paper and absorbance was determined 232 nm using double beam UV- Visible spectrophotometer.

**Permeation study:**

The prepared mucoadhesive buccal films are placed in the diffusion cell on the upper membrane of the (donor compartment) and the receptor compartment contains simulated saliva (20 ml) it can be contacted with the dialysis membrane upper side of the donor compartment contain a film attach the film of length and width (2×2) cm it contains 20 mg of the drug. And the receptor compartment it contains simulated saliva and magnetic bead and this diffusion compartment placed in the magnetic stirrer the drug permeation start through the dialysis membrane and enter into the receptor compartment the drug to be entered in the receptor compartment and this solution took 2 ml every one hour and maintain the sink condition by replacing the 2ml of simulated saliva into the receptor compartment and this every interval taken samples analyzed by (Shimadzu) UV-visible spectrophotometer.

**Stability studies:**

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors. To assess the drug and formulation stability, stability studies were done as per ICH guidelines.

The formulated mucoadhesive buccal films were wrapped in aluminum foil and stored at 45 ± 0.5ºC for twelve weeks. After three months, films were tested for appearance, drug content, and *in-vitro* drug release.

## RESULTS AND DISCUSSION

The optimized formulation was F6 which shows maximum drug content and percentage drug release. The formulated mucoadhesive buccal films were appeared to be clear, homogeneous, some are transparent and some are partially transparent. They were found to be physically flexible and dry. The folding endurance was measured manually, by folding the mucoadhesive buccal film repeatedly at a point till it broke. The breaking time was considered as the endpoint. Folding endurance was found to be highest for F4 and lowest for F2. It was found that the folding endurance of the mucoadhesive buccal films was affected by the increase of carrier concentration. The folding endurance values of the mucoadhesive buccal films were found to be optimum and therefore, the mucoadhesive buccal films exhibited good physical and mechanical properties. The folding endurance of films was found to be in the range of 314 to 354(Table No.3). As all the formulations contain different amounts of polymers, the thickness was gradually increased with the number of polymers. All the film formulations were found to have a thickness in the range of 0.14 to 0.22 mm and were observed within the limits.

### Weight variation

The randomly selected film strips about 2 × 2 cm areas were cut at different places from the casted film and weight was measured. The weight of film strip units varies from 46.85 to 52.08 mg.

### Drug content

The prepared film formulations were studied for their drug content. The drug was dispersed in the range of 92.08 to 98.04 %. Suggesting that the drug was uniformly dispersed in all films.

### *In-vitro* drug release:

The *in-vitro* drug release profiles of the formulation in pH 6.8 simulated saliva buffer (300ml). Therefore, the difference depending on their comparison of the rate of drug release

from the HPMC K 100 films was significantly more than the films containing HPC and HEC. The formulation F6 films containing an HPMC K100 showing a high percentage of drug release (98.25%) within 7 hours compared to that of films containing HEC and HPC as a polymer.

**Table No 1: Calibration curve of Dothiepin HCl.**

| Concentration (µg/mL) | Absorbance at 232 nm |
|---|---|
| 2 | 0.13 |
| 4 | 0.27 |
| 6 | 0.39 |
| 8 | 0.52 |
| 10 | 0.69 |
| 12 | 0.82 |

**Table No. 2: Formulation details of Dothiepin HCl mucoadhesive buccal films**

| Formulation code | Drug (mg) | Polymer and its composition (mg) | | | Polyethylene glycol (mL) | Sodium saccharin (mg) | Vanillin (mg) | Distilled water (mL) |
|---|---|---|---|---|---|---|---|---|
| | | HEC | HPMC K 100 | HPC | | | | |
| F1 | 120 | 200 | | | 0.1 | 2 | 2 | 10 |
| F2 | 120 | 250 | | | 0.1 | 2 | 2 | 10 |
| F3 | 120 | 300 | | | 0.1 | 2 | 2 | 10 |
| F4 | 120 | | 200 | | 0.1 | 2 | 2 | 10 |
| F5 | 120 | | 250 | | 0.1 | 2 | 2 | 10 |
| F6 | 120 | | 300 | | 0.1 | 2 | 2 | 10 |
| F7 | 120 | | | 200 | 0.1 | 2 | 2 | 10 |
| F8 | 120 | | | 250 | 0.1 | 2 | 2 | 10 |
| F9 | 120 | | | 300 | 0.1 | 2 | 2 | 10 |

**Table No. 3: Evaluation data for mucoadhesive buccal films**

| Formulation Code | Weight variation (mg) | Thickness (mm) | Folding endurance | % drug content | Disintegration time (sec) |
|---|---|---|---|---|---|
| F1 | 46.98±0.141 | 0.20±0.0102 | 334.66±1.503 | 92.75 ± 0.82 | 50.00±0.333 |
| F2 | 50.08±0.082 | 0.16±0.0030 | 314.66±1.503 | 94.10 ± 1.71 | 36.00±0.333 |
| F3 | 52.08±0.180 | 0.22±0.0033 | 343.66±0.509 | 95.44 ± 0.47 | 45.33±1.170 |
| F4 | 46.85±0.182 | 0.18±0.0050 | 354.33±1.347 | 97.06 ± 1.22 | 34.00±0.577 |
| F5 | 49.07±0.293 | 0.14±0.0050 | 346.33±0.192 | 95.41 ± 1.67 | 34.33±0.333 |
| F6 | 50.57±0.144 | 0.21±0.0033 | 330.66±1.347 | 98.04 ± 1.25 | 45.33±0.693 |
| F7 | 50.78±0.167 | 0.18±0.0033 | 350.00±0.333 | 92.08 ± 2.07 | 50.00±0.333 |
| F8 | 50.68±0.307 | 0.19±0.0102 | 332.33±1.347 | 95.41 ± 2.04 | 40.33±0.333 |
| F9 | 46.98±0.141 | 0.20±0.0050 | 320.00±1.666 | 96.42 ± 1.67 | 44.33±0.838 |

**Table No. 4: *In-vitro* release data of various Dothiepin HCL mucoadhesive buccal films prepared using HPMC K100, HPC, HEC Cumulative % drug release from buccal films F1 to F9 prepared from HEC, HPMC K100, HPC**

| FORMULATION CODE | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| **15 mins** | 13.95 | 16.93 | 18 | 14.78 | 21.8 | 23.78 | 12.3 | 17.34 | 18.33 |
| **30 mins** | 26.06 | 24.06 | 34.11 | 29.96 | 37.01 | 42.98 | 28.46 | 30.45 | 35.43 |
| **1h** | 39.17 | 40.16 | 43.15 | 43.98 | 45.97 | 57.09 | 45.47 | 41.49 | 48.54 |
| **2h** | 48.21 | 50.2 | 53.19 | 53.03 | 59.08 | 65.06 | 54.52 | 49.54 | 59.58 |
| **3h** | 53.19 | 59.25 | 58.25 | 66.05 | 71.12 | 73.11 | 62.57 | 61.57 | 71.61 |
| **4h** | 63.23 | 70.29 | 69.29 | 74.1 | 78.17 | 81.16 | 69.62 | 74.6 | 75.6 |
| **5h** | 75.26 | 79.33 | 80.33 | 83.15 | 86.13 | 88.21 | 78.67 | 81.65 | 79.66 |
| **6h** | 79.33 | 85.31 | 90.37 | 89.21 | 91.2 | 92.19 | 84.64 | 87.71 | 88.71 |
| **7h** | 88.38 | 91.36 | 96.09 | 95.18 | 96.18 | 98.25 | 90.7 | 92.69 | 94.68 |

**Table No. 5: Permeability data of films**

| FORMULATION CODE | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **0.5** | 18.72 | 22.84 | 25.23 | 26.33 | 28.53 | 34.22 | 22.84 | 26.06 | 28.53 |
| **1** | 35.23 | 36.22 | 42.06 | 44.7 | 44.92 | 50.86 | 40.07 | 46.9 | 44.92 |
| **2** | 42.06 | 46.9 | 48.88 | 51.96 | 51.85 | 59.67 | 47.89 | 54.72 | 56.7 |
| **3** | 49.87 | 56.7 | 57.69 | 61.54 | 61.1 | 72.33 | 56.7 | 62.53 | 66.5 |
| **4** | 57.69 | 63.52 | 65.5 | 68.48 | 70.35 | 80.15 | 63.52 | 69.36 | 73.32 |
| **5** | 65.5 | 73.32 | 75.3 | 74.31 | 77.28 | 85.1 | 67.49 | 73.32 | 80.15 |
| **6** | 72.33 | 75.3 | 76.29 | 81.14 | 83.12 | 88.95 | 75.3 | 79.16 | 84.11 |
| **7** | 76.29 | 83.12 | 85.1 | 85.1 | 85.98 | 91.93 | 79.16 | 83.12 | 88.95 |
| **8** | 81.14 | 85.98 | 86.97 | 87.96 | 90.94 | 95.78 | 84.11 | 87.96 | 90.95 |

**Table No. 6: Percentage drug content of optimized formulation F6 during stability studies**

| Trial No. | 1st Day | After 4 weeks | After 6 weeks | After 12 weeks |
|---|---|---|---|---|
| I | 97.21 | 96.32 | 96.96 | 97.15 |
| II | 97.26 | 96.41 | 97.06 | 97.06 |
| III | 97.23 | 96.43 | 97.11 | 97.18 |
| Mean | 97.23 ± 0.02 | 96.39 ± 0.04 | 97.04 ± 0.06 | 97.13 ± 0.05 |

**Table No. 7: *In vitro* release data of optimized formulation F6 during stability studies.**

| Time (in hours) | % CDR | | | |
|---|---|---|---|---|
| | 1st Day | After 4 weeks | After 6 weeks | After 12 weeks |
| 15m | 23.00 | 22.21 | 21.85 | 21.85 |
| 30m | 41.91 | 42.45 | 40.13 | 41.75 |
| 1h | 55.93 | 56.04 | 55.83 | 55.87 |
| 2h | 67.88 | 67.94 | 67.97 | 67.97 |
| 3h | 76.97 | 76.86 | 76.97 | 76.82 |
| 4h | 84.27 | 83.94 | 83.89 | 83.88 |
| 5h | 91.10 | 90.53 | 90.88 | 91.51 |
| 6h | 96.69 | 96.89 | 96.72 | 97.00 |

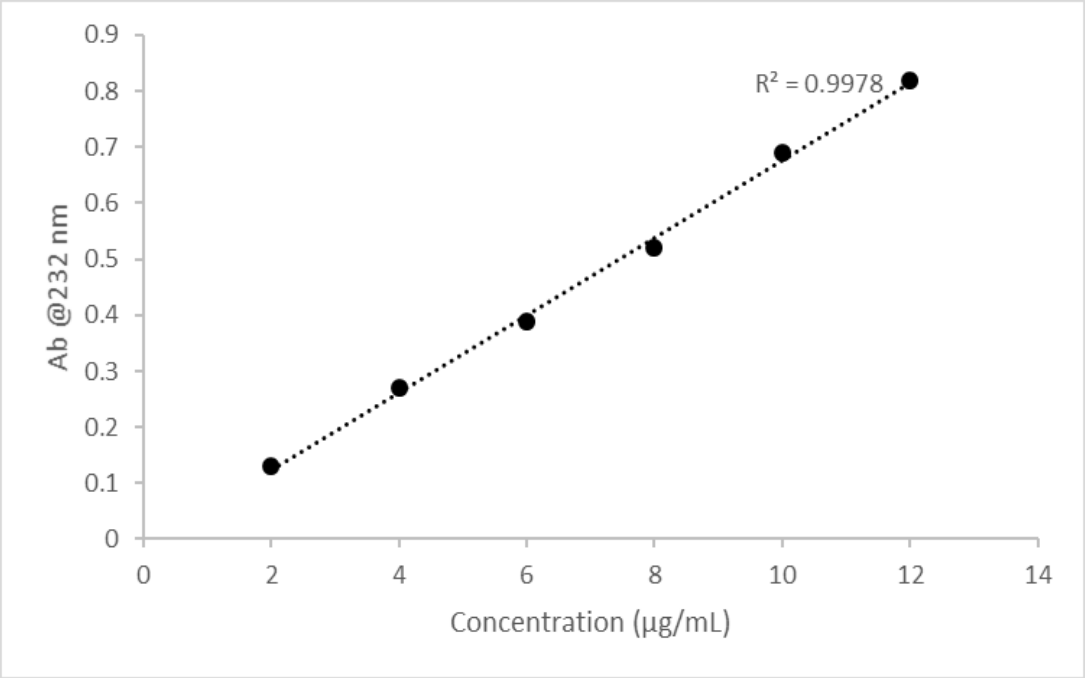


**Figure No. 1: The standard graph of Dothiepin HCL using simulated saliva buffer of pH 6.8**

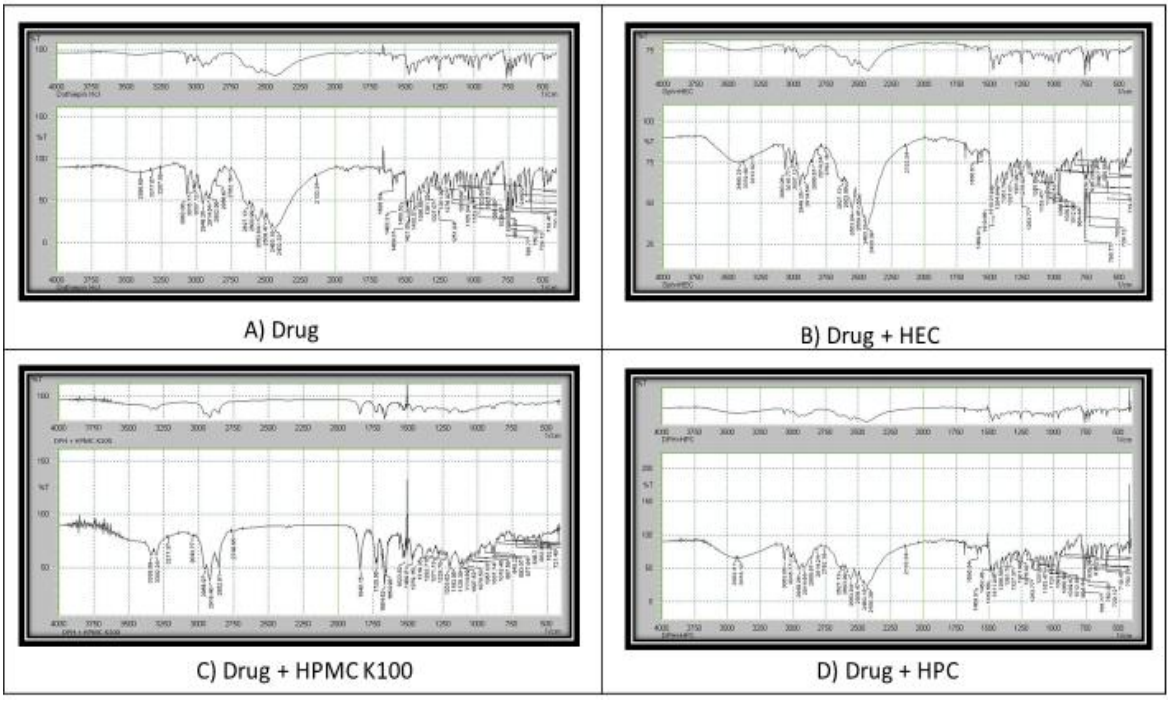


**Figure No. 2: FTIR Spectra of (A) Dothiepin HCl; (B) Physical mixture of drug and HEC; (C) Physical mixture of drug and HPMC K100; (D) Physical mixture of drug and HPC**

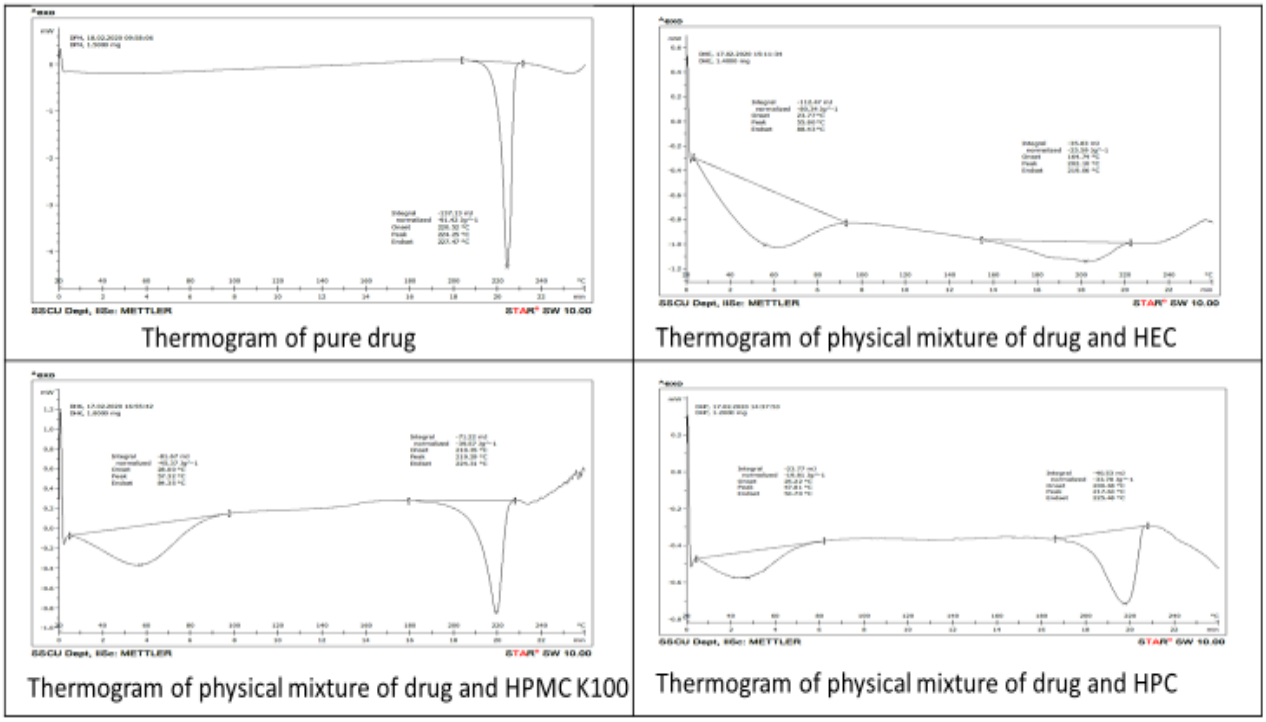


**Figure No. 3: DSC thermogram of (A) pure drug, (B) Drug + HEC, (C) Drug + HPMC K100, (D) Drug + HPC**

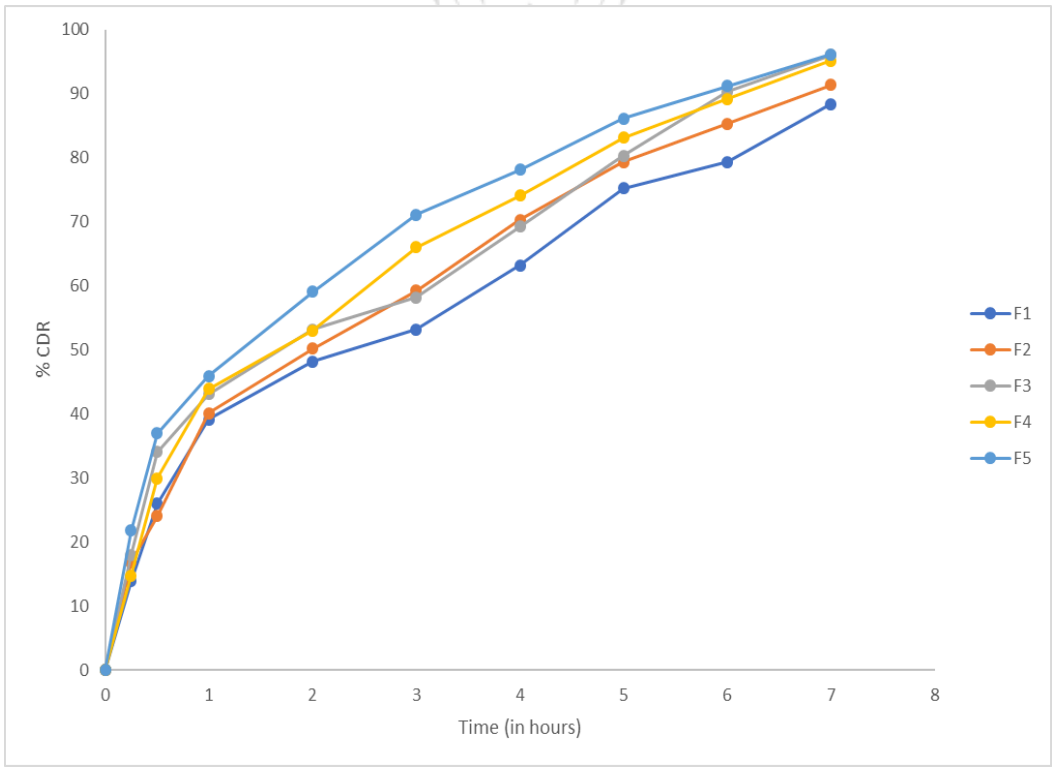


**Figure No. 4: *In-vitro* release data of various mucoadhesive buccal film of Dothiepin HCl (F1-F5)**

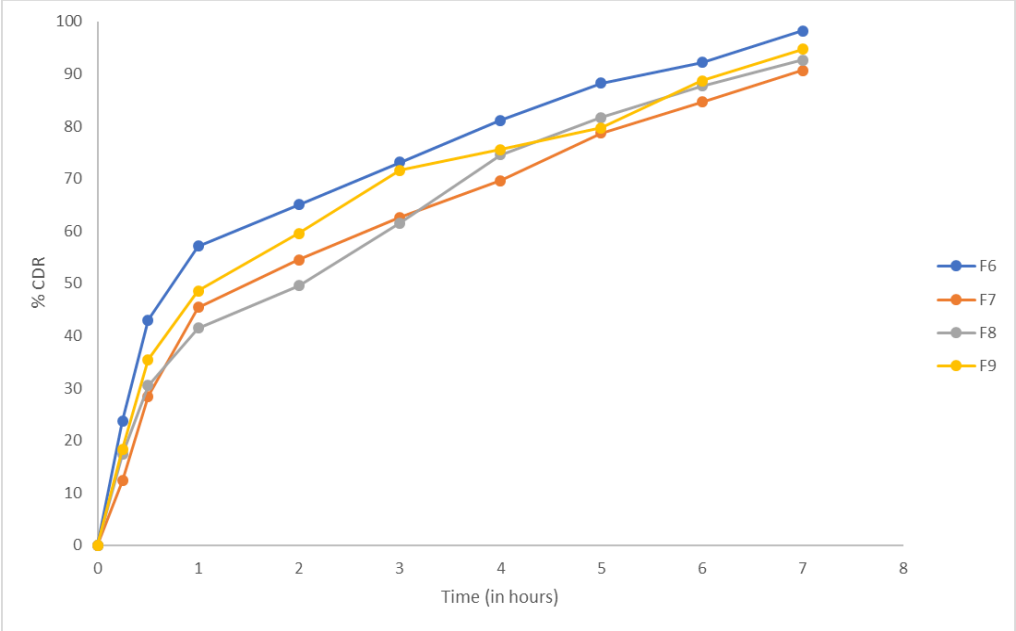


**Figure No. 5: *In-vitro* release data of various mucoadhesive buccal film of Dothiepin HCl (F6-F9)**

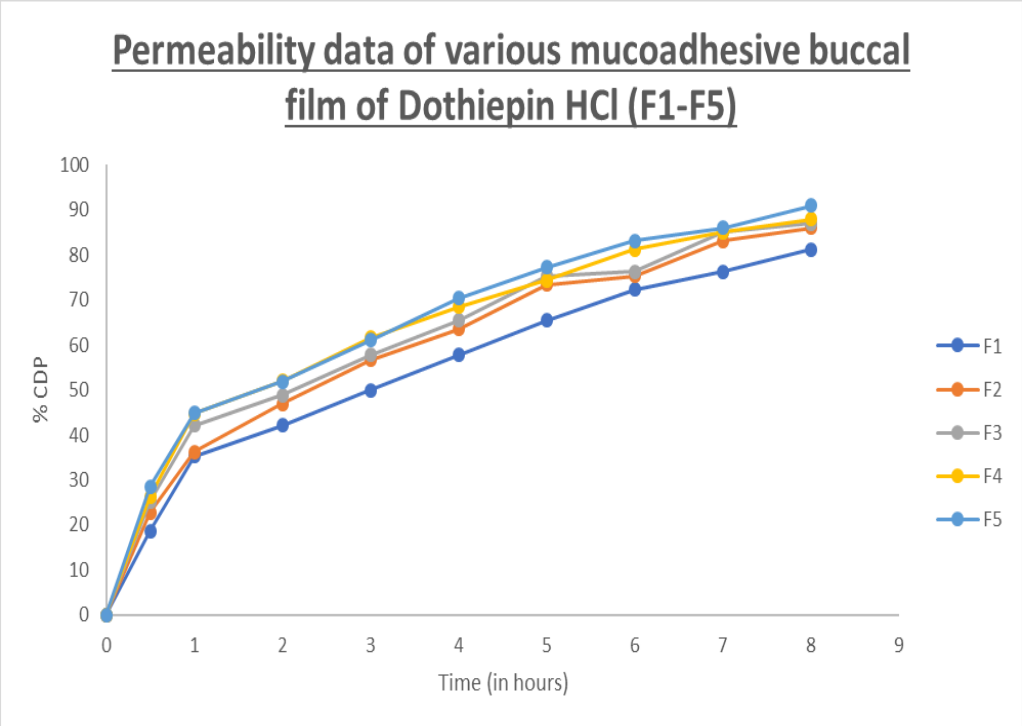


**Figure No. 6: Permeability data of various mucoadhesive buccal film of dothiepin hcl**

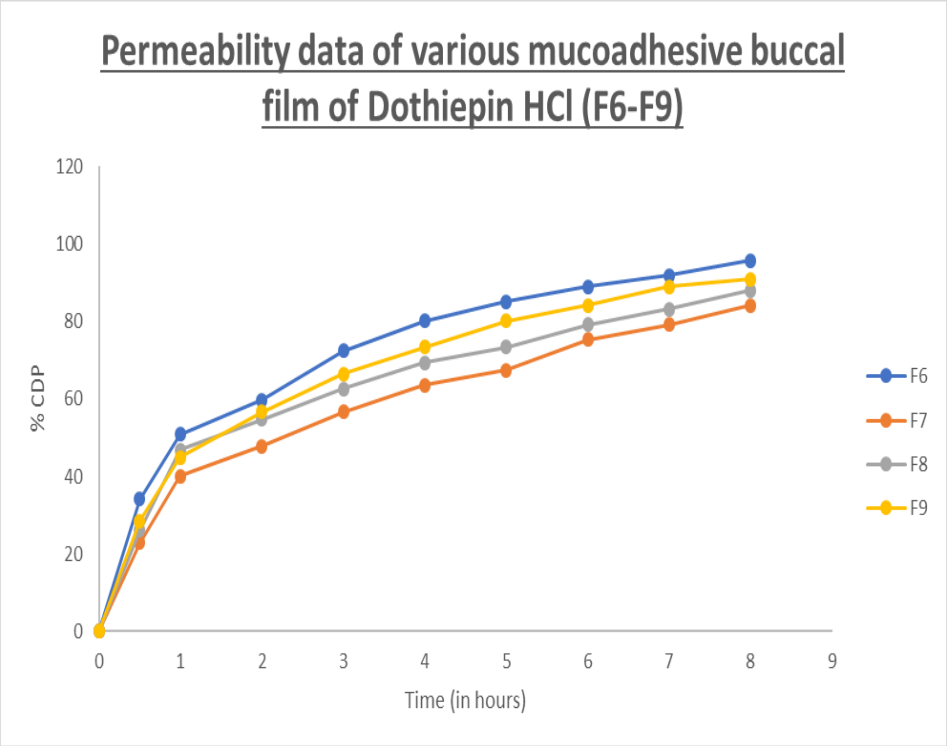


**Figure No. 7: Permeability data of various mucoadhesive buccal film of dothiepin HCl**

## CONCLUSION

All the formulation showed acceptable quality control property formulation F6 having polymer concentration HPMC K100 showed better drug release rate over 7 hours thus formulation F6 was found to be the most promising formulation based on acceptable evaluation property and the *In-vitro* drug release rate of 98.25%. Based on the FTIR studies appear to be no possibility of interaction between the Dothiepin HCl and polymers of other excipients used in the films.DSC Studies was confirmed that there is no interaction between drug and selected polymers. Stability studies were conducted for the optimized formulation as per ICH guidelines for 90 days which revealed that the formulation was stable. The result suggests that the developed mucoadhesive buccal film of Dothiepin HCl could perform better than conventional dosage form leading to improved efficacy and better patient compliance.

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