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# FORMULATION AND *INVITRO* EVALUATION OF BUCCAL FILMS OF BISOPROLOL FUMARATE

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**Abstract:**

*Bisoprolol is a drug belonging to the group of beta-blockers, a class of medicines used primarily in cardiovascular diseases. More specifically, it is a selective type β1 adrenergic receptor blocker. The U.S. Food and Drug Administration (FDA) approved an application by Duramed Pharmaceutical for Zebeta Oral Tablets (bisoprolol fumarate) as a new molecular entity on July 31, 1992. In current work buccal drug delivery of Bisoprolol was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. buccal patches were prepared by using polymers Eudragit-L100, HPMCk$_4$M and HPMCk15M. by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. all the formulations prepare (F1-F9)were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be were found to be with in the pharmacopeial limits, invitro drug release studies by using dialysis membrane. Among all the 9 formulations F6 formulation which contain HPMC K4M 300mg and Eudragit L-100 60mg had shown 94% cumulative drug release with in 12 hours. And compared to HPMC K15M, HPMC K4M showed better drug release profile. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions.*

***Key words: Beta-blockers, Patches, Buccal delivery, Bisoprolol.***

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## INTRODUCTION:

**ORAL DISINTEGRATING TABLETS (ODT):**

The tablet is the most widely used dosage form existing today because of its convenience in terms of self-administration, compactness and ease in manufacturing. However, geriatric, paediatric and mentally ill patients' experiences difficulty in swallowing conventional tablets, which is common among all age groups, especially in elderly and dysphasic patients[1] which leads to poor patient compliance. To overcome these problems, scientists have developed innovative drug delivery system known as mouth dissolving/disintegrating tablets (MDTs)[2].

This dosage form dissolves and disintegrates in the oral cavity within minutes without need of water or chewing. This formulation is useful in administration of drug in paediatrics, geriatric patients[3]. Mouth dissolving tablets are also known as Fast-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet. Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, anti allergics and drugs for erectile dysfunction[4]. It has been shown in Table 1. Most Mouth dissolving tablets contain substances to mask the bitter taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients [4,5]. MDTs are formulated mainly by two techniques first the use of superdisintegrants like Cross linked carboxymethyl cellulose (Croscar - meliose), Sodium starch glycolate (Primogel, Explotab), Polyvinylpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. Another method is maximizing pore structure of the tablets by freeze drying and vacuum-drying. Mouth dissolving drug delivery system emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and gelatin capsules. Hence, they do not comply with prescription, which results in noncompliance and ineffective therapy. In some cases, such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Paediatric and geriatric patients experience particularly this difficulty. Such problems can be resolved by means of mouth dissolving tablet. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form

## METHODOLOGY:

**Determination OF UV Absorption maxima:**

Bisoprolol solution was prepared in 0.1 N HCL and diluted suitably. The UV spectrum of the solution was taken on Lab India 3200 UV/Vis double beam Spectrophotometer. The Solution exhibited UV maxima at 241 nm. The procedure was repeated with pH 6.8 phosphate buffer.

**Preparation of Standard Calibration Curve of Bisoprolol:**

100 mg of Bisoprolol was accurately weighed and dissolved in little amount of Methanol and make up the final volume up to 100 ml with 0.1 N HCl (pH 1.2) to prepare stock solution. The 10 ml of stock solution was further diluted with 0.1 N HCl (pH 1.2) in 100ml to get 100µg/ml (working standard). Then 0.2,0.4,0.6.0.8, and 1 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 0.1N HCl to prepare 2µg,4µg,6µg,8µg, and 10µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 241 nm against 0.1 N HCl (pH 1.2) as blank. The procedure was repeated with pH 6.8 phosphate buffer and absorbance's were measured at 241 nm.

**Formulation:**

- **Development of Buccal films:**
- Buccal drug delivery films were prepared by solvent casting method.
- **Solvent casting method:** Eudragit L100, HPMCK$_4$M and HPMCK15M were weighed in requisite ratios and they were then dissolved in dichloromethane and ethanol as solvent using magnetic stirrer.

Bisoprolol (36mg) propylene glycol and tween 80 was added to the above dispersion under continuous stirring.

The uniform dispersion was poured in the petri plate. The rate of evaporation of solvent was controlled by inverting cut funnel over the filmes. After 24h, the dried films were taken out and stored in desiccator.

**Table 1: Formulations of Bisoprolol Buccal Film**

| S.No | Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Drug(mg) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 2 | Eudragit-RSPO(mg) | 100 | 150 | 200 | - | - | - | - | - | - |
| 3 | HPMC E 5 LV (mg) | - | - | - | 100 | 150 | 200 | - | - | - |
| 4 | $HPMCK_{15}M$(mg) | - | - | - | - | - | - | 100 | 150 | 200 |
| 5 | Dichloromethane(ml) | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| 6 | Ethanol(ml) | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| 7 | Propylene glycol(ml) | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| 8 | Tween-40(ml) | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |

## RESULTS & DISCUSSION:

**Standard Calibration curve of Bisoprolol:**

**Table 2:** Concentration and absorbance obtained for calibration curve of Bisoprolol in (pH 6.8**)**

| S. No. | Concentration (µg/ml) | Absorbance* (at 241 nm) |
|---|---|---|
| 1 | 2 | 0.156 |
| 2 | 4 | 0.284 |
| 3 | 6 | 0.46 |
| 4 | 8 | 0.601 |
| 5 | 10 | 0.785 |
| 6 | 12 | 0.925 |

It was found that the estimation of Bisoprolol by UV spectrophotometric method at $\lambda_{max}$ 241 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10µg/ml. The regression equation generated was y = 0.077x + 0.007.

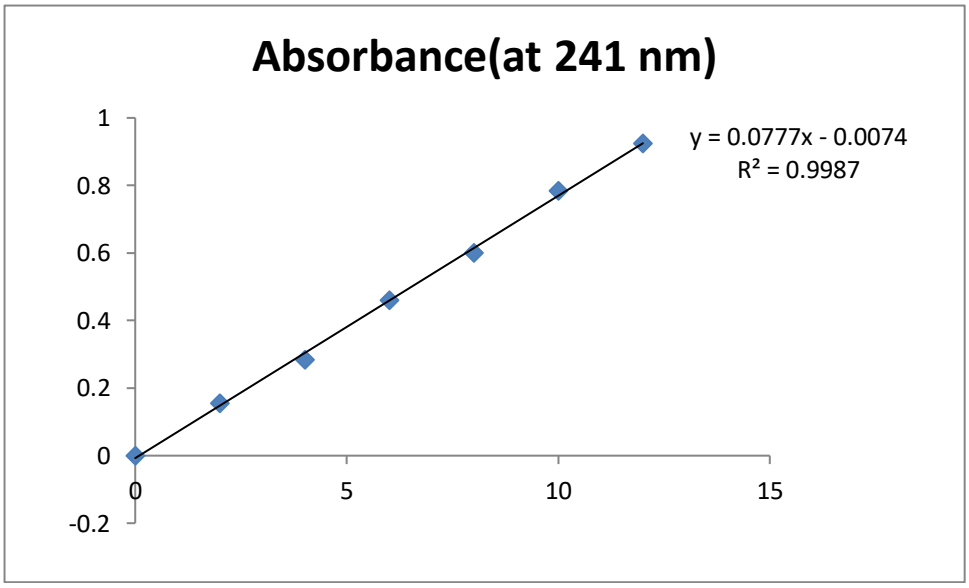



**Fig 1: Standard graph of Bisoprolol in pH 6.8 Phosphate buffer**

**Evaluation of Bisoprolol Buccal films:**

**Compatibility studies :**

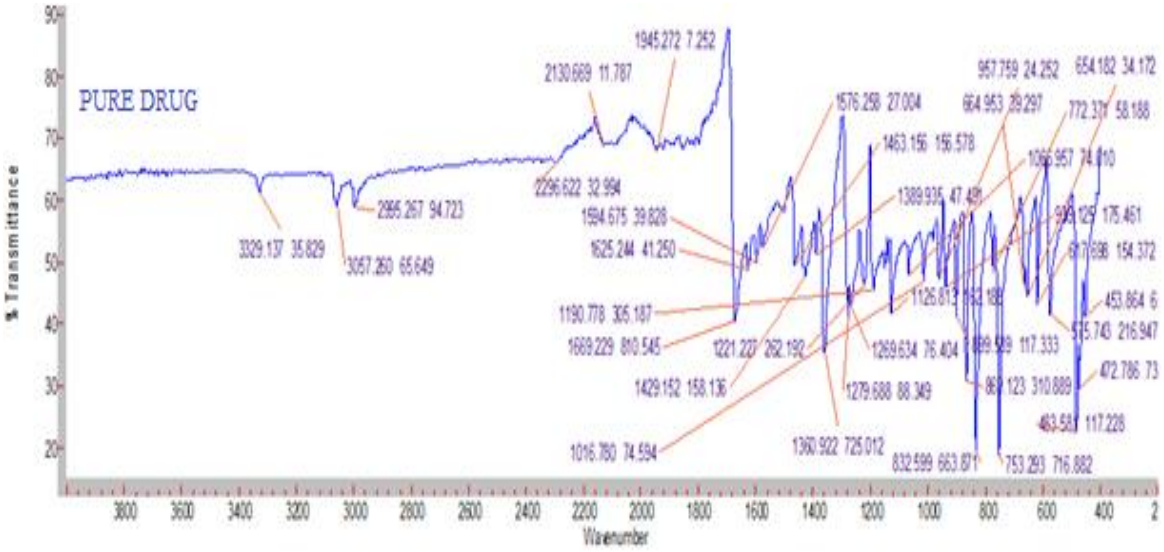



**Fig:2 FTIR spectrum of pure drug**

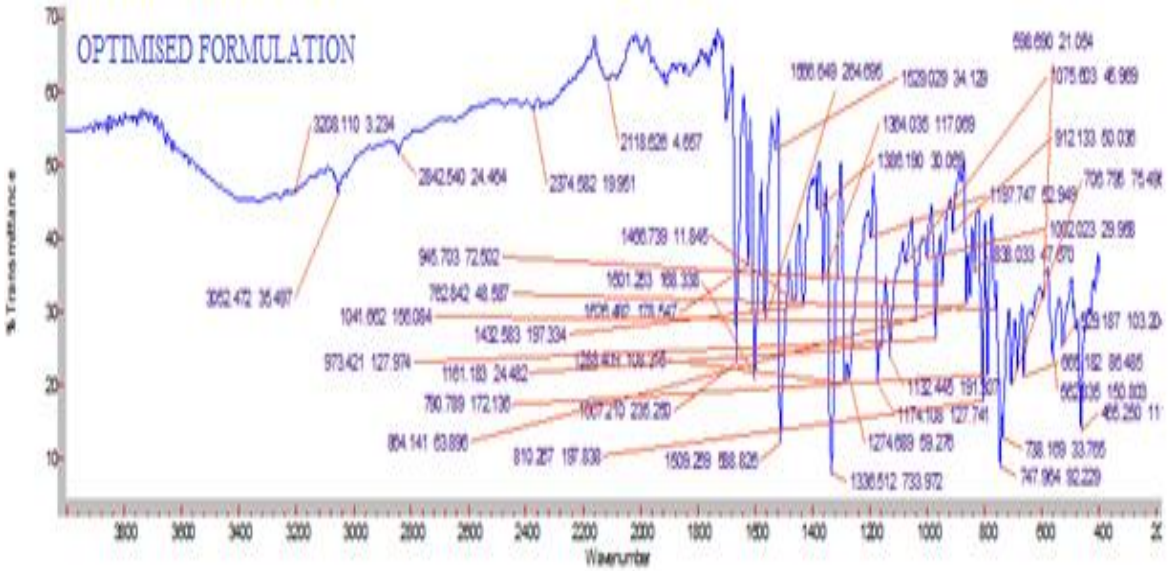



**Fig 3 FTIR spectrum of optimized formulation**

**Physical appearance:** All the Buccal films were visually inspected for colour, clarity, flexibility.

**Flatness:** All the Buccal films was found to be flat without any foams.

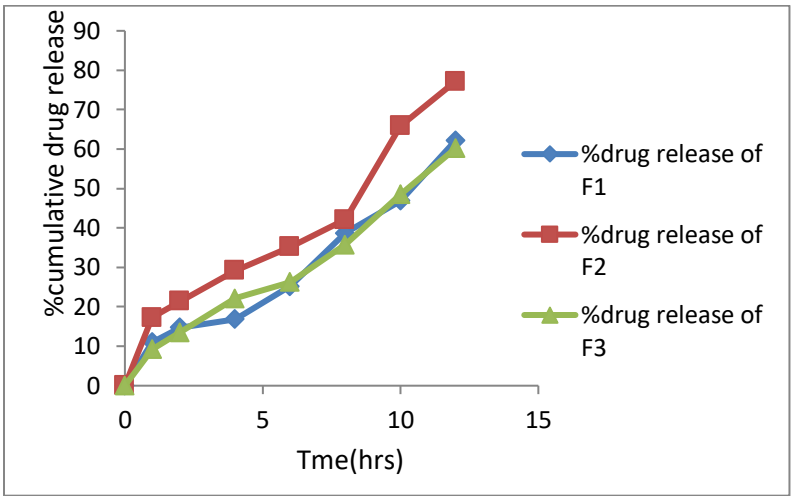
**Table No. 3: Evaluation of Buccal patch by physical methods**

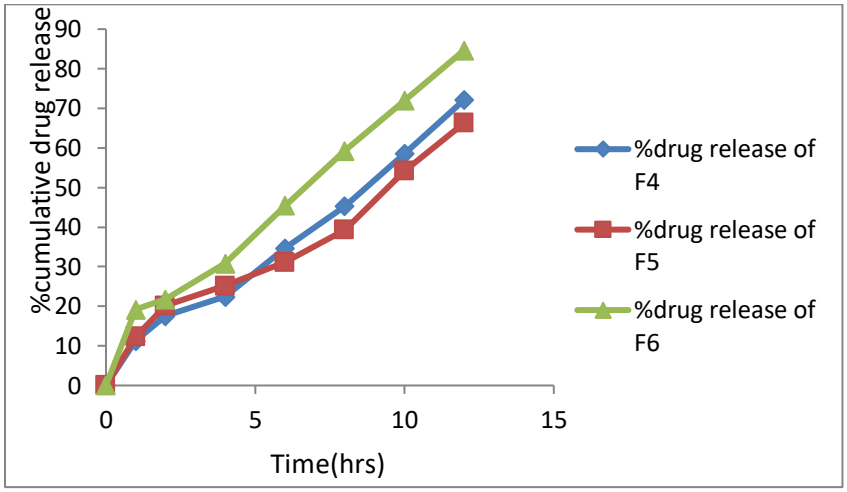
| Formulation | Thickness (mm) | Folding endurance | Drug content (%) | Moisture uptake (%) | Moisture content (%) |
|---|---|---|---|---|---|
| F1 | 0.3545 | 21 | 49 | 8.31 | 4.78 |
| F2 | 0.3519 | 23 | 59 | 24.25 | 8.5 |
| F3 | 0.3542 | 25 | 58.5 | 12.54 | 4.21 |
| F4 | 0.3489 | 22 | 59 | 14.32 | 6.17 |
| F5 | 0.3454 | 29 | 69.5 | 18.21 | 5.81 |
| F6 | 0.3575 | 30 | 93 | 19.54 | 13.64 |
| F7 | 0.3485 | 41 | 100.2 | 10.24 | 4.45 |
| F8 | 0.3432 | 35 | 79 | 11.24 | 5.01 |
| F9 | 0.3507 | 32 | 57 | 17.54 | 7.01 |

The prepared Bisoprolol Buccal films were evaluated by physical methods such as Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake and Moisture content and all the results were found to be with in the pharmacopeial limits.

**Table No. 4 : Evaluation of Buccal patch by In-vitro permeation studies using dialysis membrane**

| Time (hrs) | % Drug release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 1 | 11.05 | 17.24 | 9.21 | 11.25 | 12.31 | 19.2 | 18.51 | 13.0 | 11.1 |
| 2 | 14.8 | 21.45 | 13.54 | 17.54 | 20.15 | 21.8 | 22.15 | 17.5 | 15.0 |
| 4 | 16.9 | 29.24 | 22.14 | 22.45 | 25.14 | 30.8 | 35.23 | 23.4 | 23.3 |
| 6 | 25.21 | 35.24 | 26.32 | 34.75 | 31.12 | 45.5 | 42.76 | 30.9 | 33.41 |
| 8 | 38.71 | 42.15 | 35.79 | 45.31 | 39.32 | 59.3 | 62.94 | 50.17 | 52.74 |
| 10 | 46.88 | 65.89 | 48.51 | 58.54 | 54.21 | 72.0 | 79.21 | 60.0 | 68.47 |
| 12 | 62.21 | 77.21 | 60.21 | 72.15 | 66.31 | 84.7 | 95.31 | 79.64 | 81.24 |



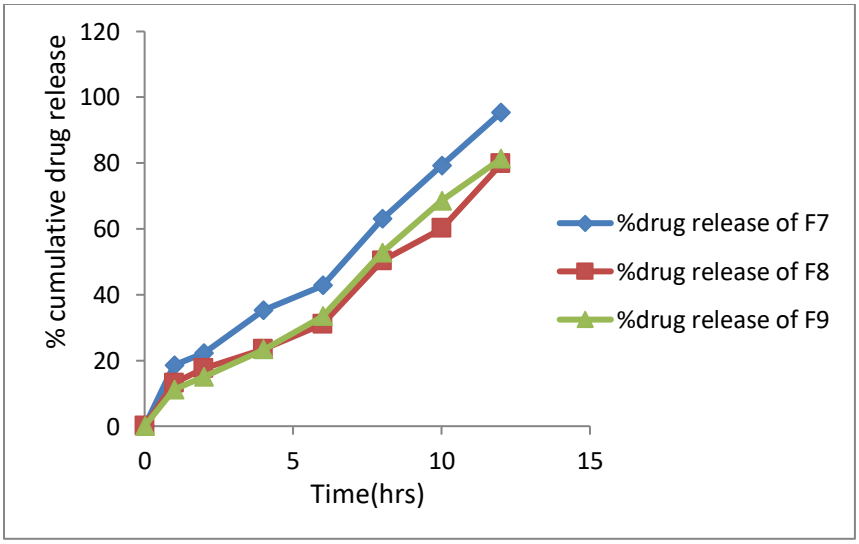




**Fig No. 4 : Release profile of In-vitro permeation studies using dialysis membrane**

The prepared Bisoprolol Buccal films were evaluated for In-vitro permeation studies using dialysis membrane, Among all the 9 formulations F7 formulation which contain HPMC K4M 300mg and Eudragit L-100 60mg had shown 94% cumulative drug release with in 12 hours. And compared to HPMC K15M, HPMC K4M showed better drug release profile.

**Table No 5 : kinetics of In-vitro permeation studies using dialysis membrane**

| CUMULATIVE (%) RELEASE Q | TIME ( T ) | ROOT ( T) | LOG( %) RELEASE | LOG ( T ) | LOG (%) REMAIN |
|---|---|---|---|---|---|
| 0 | 0 | 0 | | | 2.000 |
| 18.51 | 60 | 7.746 | 1.267 | 1.778 | 1.911 |
| 22.15 | 120 | 10.954 | 1.345 | 2.079 | 1.891 |
| 35.23 | 240 | 15.492 | 1.547 | 2.380 | 1.811 |
| 42.76 | 360 | 18.974 | 1.631 | 2.556 | 1.758 |
| 62.94 | 480 | 21.909 | 1.799 | 2.681 | 1.569 |
| 79.21 | 600 | 24.495 | 1.899 | 2.778 | 1.318 |
| 95.31 | 720 | 26.833 | 1.979 | 2.857 | 0.671 |

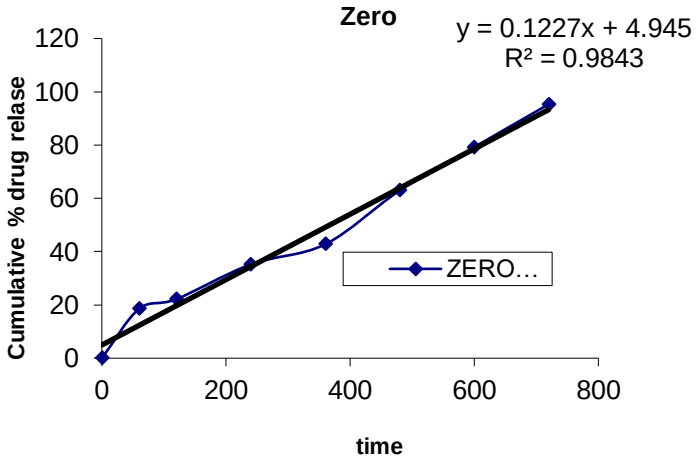



**Fig No.5 : Zero order kinetics**

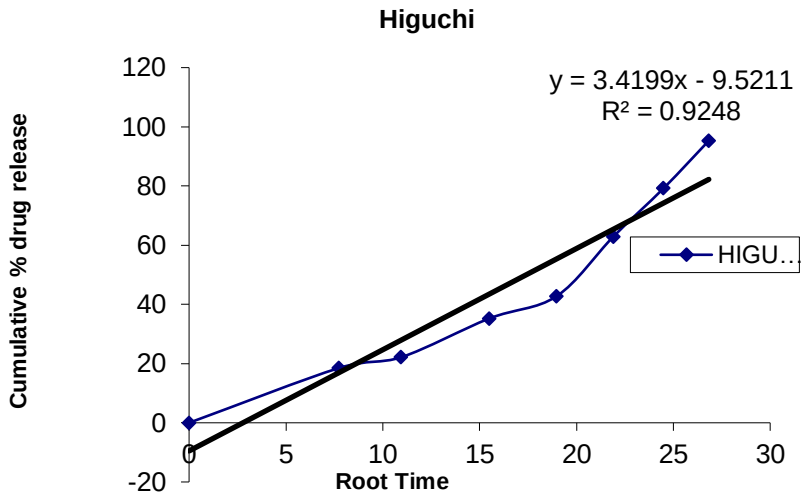



**Fig No. 6 : Higuchi plot**

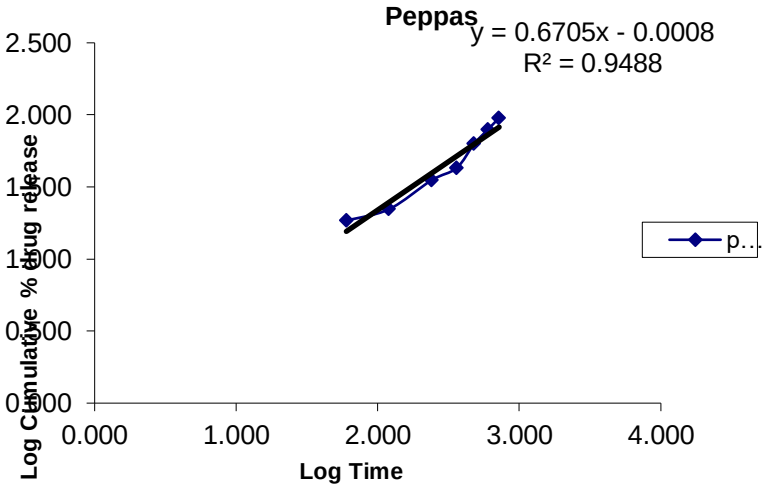



**Fig No. 7 : Peppas plot**

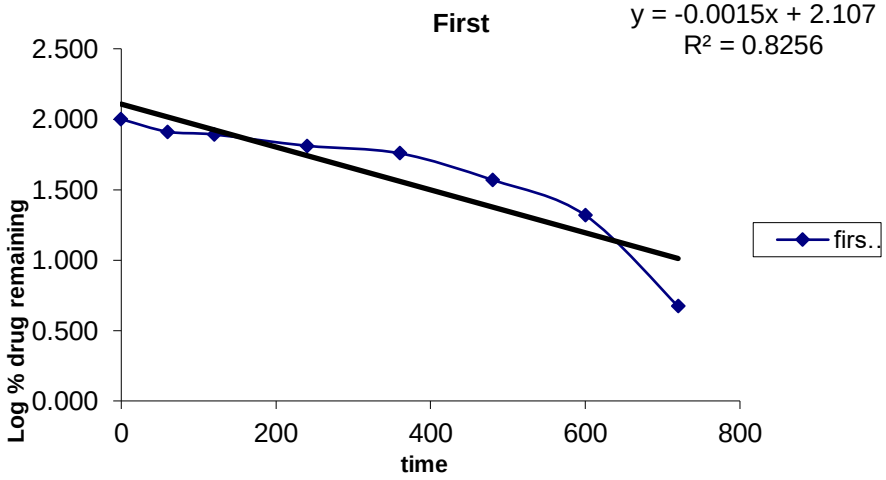



**Fig No. 8 : First order kinetics**

The kinetics of In-vitro permeation studies using dialysis membrane for F7 formulation was plotted and the Regression coefficient value was found to be high for Zero order release model i.e., 0.984. And the n value was found to be 0.6203 which indicates the drug release pattern was found to be non-Fickian diffusion.

## SUMMARY & CONCLUSION:

In present study buccal drug delivery of Bisoprolol was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route.

Matrix type of buccal patches was developed by using polymers Eudragit-L100, HPMC$k_4$M and HPMCK15M.

Buccal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer.

Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions.

Formulations were prepared with the varying concentrations polymers ranging from F1-F9, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be were found to be with in the pharmacopeial limits, invitro drug release studies by using dialysis membrane. Among all the 9 formulations F7 formulation which contain HPMC K4M 300mg and Eudragit L-100 60mg had shown 94% cumulative drug release within 12 hours. And compared to HPMC K15M, HPMC K4M showed better drug release profile.

For F7 formulation release kinetics were plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.9892.
The n value was found to be 0.6203 which indicates the drug release pattern was found to be non-Fickian diffusion.

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