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# FORMULATION AND INVITRO EVALUATION OF BUCCAL PATCHES OF BISOPROLOL FUMARATE

**V. T. Iswariya*, A. Hari Om Prakash Rao, T. Shyamkumar, N. Naresh, M. Suraj, M. Ramesh Yadav**

Dept of Pharmaceutics, MRR College of Pharmacy, Hyderabad.

***Corresponding Author: V. T. Iswariya**

Dept of Pharmaceutics, MRR College of Pharmacy, Hyderabad.

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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 was 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.

**KEYWORDS:** Beta-Blockers, Patches, Buccal Delivery, Bisoprolol**.**

## 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 know 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. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.

### Ideal properties of MDT

- Not require water or other liquid to swallow but it should dissolve or disintegrate in the mouth within matter of seconds[6,7]
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral

administration.

- Exhibit low sensitivity to environmental conditions as humidity and temperature more rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action[8,9]

**Advantages of MDTs[10]**

- Rapid drug therapy intervention.
- Bitter taste can be masked by use of flavour and sweetener to produce good mouth feel particularly for paediatric patients.
- Accurate dosing as compared to liquids.
- First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.

**Main ingredients used in preparation of MDT**

Important ingredients that are use should allow quick release of drug resulting in faster dissolution. This includes both the actives and the excipients. Super disintegrants: Use of disintegrants is the basic approach in development of MDTs. Disintegrants play a major role in the disintegration and dissolution of MDT.

Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, which promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution.

**Table 1: Superdisintegrants employed in MDT[11]**

| Super disintegrants | Nature | Mechanism of action | Brand names |
|---|---|---|---|
| Crosscarmellose | Modified cellulose or cross linked cellulose | Wicking due to fibrous structure swelling with minimal gelling. | Ac-Di-Sol Nymce 25X. |
| Crosspovidone | Cross linked PVP | Water wicking, swelling and possible some deformation recovery. | Kollidone Polyplasdone. |
| Aliginic Acid NF | Cross linked aliginic acid | Wicking action. | Satialgine. |
| Soy polysaccharides | Natural disintigrants | - | EMCOSOY. |
| Calcium silicate | - | Wicking action. | - |
| Sodium starch glycolate | Modified starch | Rapid and extensive swelling with minimal gelling. | Explotab Primogel. |
| Ion Exchange resin | Resin | | Amberlite(IPR88) |

**Mechanism of action of disintegrants**

1. By capillary action[12]
2. By swelling.
3. Because of heat of wetting.
4. Due to release of gases.
5. By enzymatic action.
6. Due to disintegrating particle/particle repulsive forces.
7. Due to deformation.

**Approaches for preparation of MDT[13-15]**

1. Freeze-drying or lyophilisation
2. Sublimation
3. Spray drying
4. Moulding
5. Mass extrusion
6. Direct compression
7. Cotton-candy process
8. Nanonization.
9. Fast dissolving films.
10. Melt granulation.

**Table 2: Marketed Products of MDT**

| Trade Name | Active Drug | Manufacturer |
|---|---|---|
| Nimulid-MD | Nimesulide | Panacea Biotech, New Delhi, +India. |
| Feldene Fast Melt | Piroxicam | Pfizer Inc., NY, U.S.A. |
| Zyrof Meltab | Rofecoxib | Zydus, Cadila, India. |
| Pepcid RPD | Famotidine | Merck and Co., NJ, U.S.A. |
| Romilast | Montelukast | Ranbaxy Labs Ltd., New Delhi, India. |
| Torrox MT | Rofecoxib | Torrent Pharmaceuticals, Ahmedabad, India. |
| Olanex Instab | Olanzapine | Ranbaxy Labs Ltd., New Delhi, India. |
| Zofran ODT | Ondansetron | Glaxo Wellcome, Middlesex, UK. |
| Mosid-MT | Mosapride Citrate | Torrent Pharmaceuticals Ahmedabad, India. |
| Febrectol | Paracetamol | Prographarm, Chateauneuf, France. |

**Preformulation studies**

It is the first step in rational development of dosage forms of drug substance. Pre formulation testing is defined as investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It gives information needed to define the nature of the drug substance and provide frame work for

the drug combination with pharmaceutical excipients in the dosage form.

- Bulk Density (Db).
- Tapped Density (Dt).
- Carr's index (or) % compressibility.
- Hausner ratio.
- Angle of Repose.

In vitro studies of orally disintegrating tablets.
Weight Variation, Thickness, Hardness & Friability, Wetting Time and Water Absorption Ratio.

**Oral Disintegrating Films (Odf)**

From past few decades there is a fabulous change in designing various drug delivery systems to achieve rapid onset of action in order to treat sudden surprising disorders. Travelling through various milestones from discovering a conventional tablet, capsule, modified release tablet and capsules, oral disintegrating tablets, wafers to achieve oral drug administration and now aspiring another milestone in novel era of formulating fast dissolving oral films[74].

**Table No 3: Flow Chart for the Development of Oral Solid Dosage**

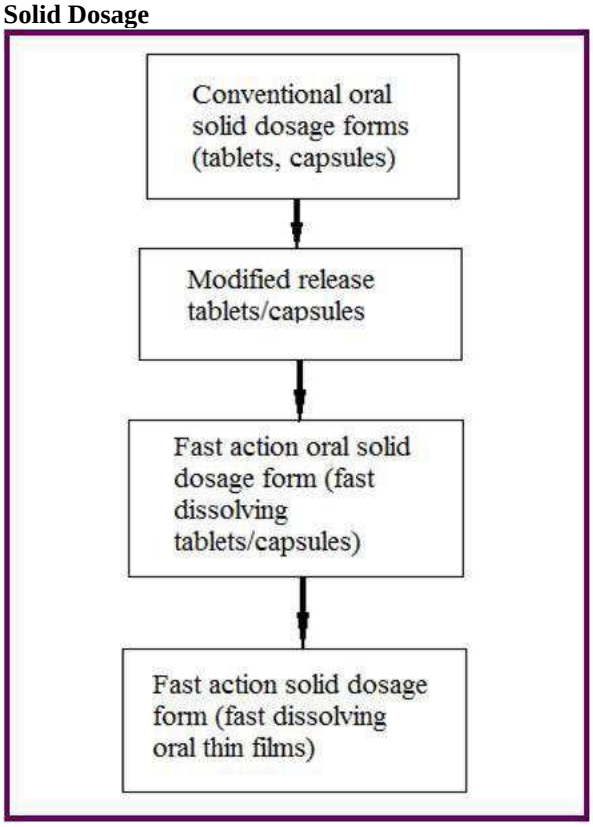
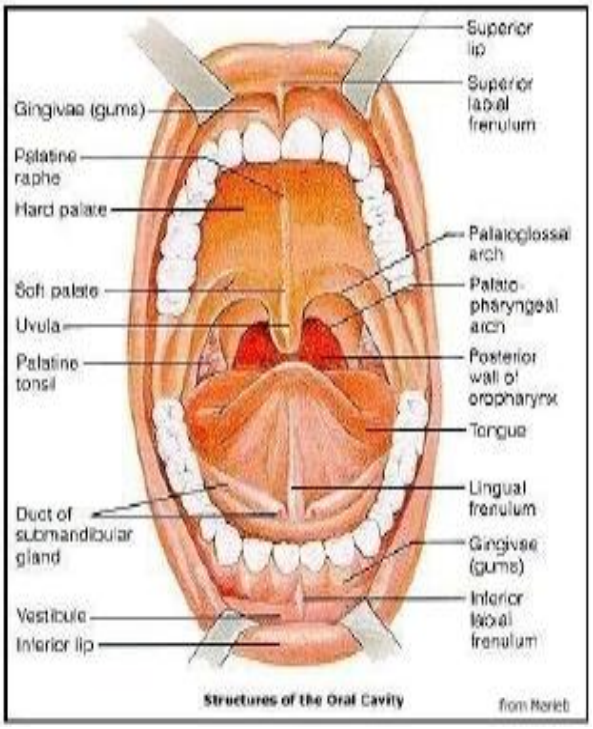



**Fig No 1: Overview of oral cavity**




Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth.The oral cavity consists of two regions:

Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingiva (gums). Oral cavity proper, which extends from teeth and gums back to the fauces (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity.

The drug administered via the oral mucosa gain access to the systemic circulation through a network of arteries and capillaries. The major artery supplying the blood to the oral cavity is the external carotid artery. The venous backflow goes through branches of capillaries and veins and finally taken up by the jugular vein.

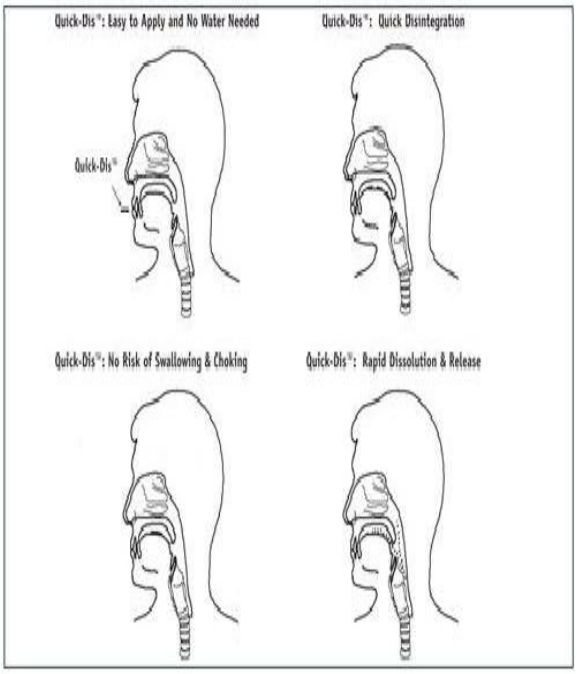
**Mechanism of Fast Dissolution in Mouth**

The delivery system is simply placed on a patient's tongue or any oromucosal tissue. Instantly wet by saliva due to presence of hydrophilic polymer and other excipients, the film rapidly hydrates and dissolves to release the medication for oromucosal absorption. The permeability of the buccal mucosa is 4-4000 times greater than that of the skin. For the better absorption of APIs in oral region permeation enhancer play important role.

The fast passage of dissolved dosage form to the stomach provides a better opportunity for the medication to be absorbed through the membrane of the buccal cavity, pharynx and esophagus for improved bioavailability and quick onset of drug action.

**Application of Oral Strip in Drug Delivery**

Oral mucosal delivery via Buccal, sublingual, and mucosal route by use of OTFs could become a preferential delivery system for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleep difficulties, and central nervous system disorders.




**Topical applications**

The use of dissolvable films may be feasible in the delivery of active agents such as analgesics or antimicrobial ingredients for wound care and other applications.

**Gastro retentive dosage systems**

Dissolvable films are being considered in dosage forms for which water-soluble and poorly soluble molecules of various molecular weights are contained in a film format. Dissolution of the films could be triggered by the pH or enzyme secretions of the gastrointestinal tract, and could potentially be used to treat gastrointestinal disorders.

**Diagnostic devices**

Dissolvable films may be loaded with sensitive device to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device.

**Method of preparation**

One or more of the following process can be used to manufacture the mouth dissolving films.

1. Solvent casting
2. Semisolid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling

**MATERIALS**

Bisoprolol, Ethanol, Eudragit L-100, HPMC, Methanol, Chloroform, PEG.

**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 258 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 258 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 258 nm.

**Selection of drug and other ingredients**

- Bisoprolol was selected as model drug based on its physico-chemical and biological properties and also based on its suitability for Buccal drug delivery system.
- Eudragit-L100 (mg), HPMC$k_4$ M (mg), HPMC$k_{15}$ M (mg) were selected as matrix forming polymers.
- Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer.

**II. Formulation**

- **Development of Buccal patches**

Buccal drug delivery patches were prepared by solvent casting method.

- **Solvent casting method**

Eudragit L100, HPMC$K_4$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 patches. After 24h, the dried patches were taken out and stored in desiccator.

**Table 4: Formulations of Bisoprolol Buccal Patch**

| S.No | Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Drug(mg) | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| 2 | Eudragit-L100(mg) | 200 | 250 | 300 | - | - | - | - | - | - |
| 3 | $HPMCk_4M$(mg) | - | - | - | 200 | 250 | 300 | - | - | - |
| 4 | $HPMCk_{15}M$(mg) | - | - | - | - | - | - | 200 | 250 | 300 |
| 5 | Dichloromethane(ml) | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| 6 | Ethanol(ml) | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| 7 | Propylene glycol(ml) | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| 8 | Tween-80(ml) | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |

**A) Evaluation of Buccal patch by physical methods**
Physical appearance, Thickness, Weight variation, Flatness, Folding endurance, Moisture uptake, Moisture content, Swelling study, Drug content determination**.**

**B) Evaluation of Buccal patch by permeation studies:**
Diffusion cell, In vitro permeation studies using dialysis membrane, Kinetic modeling of drug release, Mechanism of drug release Drug excipients interaction studies : FT-IR spectrum interpretation.

## RESULTS AND DISCUSSION

**Standard Calibration curve of Bisoprolol**

**Table 5.Concentration and absorbance obtained for calibration curve of Bisoprolol in (pH 6.8)**

| S. No. | Concentration (µg/ml) | Absorbance* (at 258 nm) |
|---|---|---|
| 1 | 2 | 0.128 |
| 2 | 4 | 0.267 |
| 3 | 6 | 0.456 |
| 4 | 8 | 0.589 |
| 5 | 10 | 0.762 |
| 6 | 12 | 0.963 |

It was found that the estimation of Bisoprolol by UV spectrophotometric method at $\lambda_{max}$ 258 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 = 0.0636x + 0.0751.

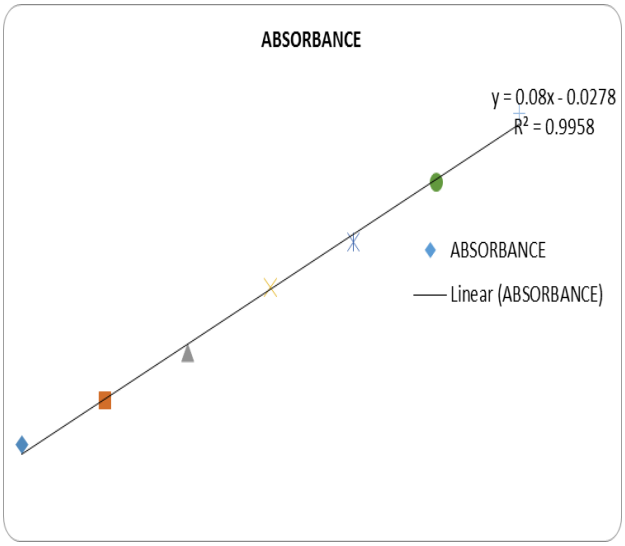



**Fig 2: Standard graph of Bisoprolol in pH 6.8 Phosphate buffer**

**EVALUATION OF BISOPROLOL BUCCAL PATCHES**

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

**Flatness**
All the Buccal patches was found to be flat with out any foams.

**Table No. 6: Evaluation of Buccal patch by physical methods**

| Formulation | Thickness (mm) | Folding endurance | Drug content (%) | Moisture uptake (%) | Moisture content (%) |
|---|---|---|---|---|---|
| F1 | 0.3569 | 20 | 45 | 7.98 | 3.77 |
| F2 | 0.3520 | 25 | 65 | 25.05 | 9.2 |
| F3 | 0.3470 | 27 | 57.5 | 13.09 | 5.16 |
| F4 | 0.3496 | 24 | 60 | 15.63 | 5.66 |
| F5 | 0.3460 | 30 | 67.5 | 11.73 | 4.87 |
| F6 | 0.3517 | 32 | 92.5 | 19.65 | 12.67 |
| F7 | 0.3478 | 40 | 101.7 | 9.42 | 3.43 |
| F8 | 0.3437 | 37 | 85 | 10.87 | 4.72 |
| F9 | 0.3503 | 34 | 55 | 16.44 | 6.62 |

The prepared Bisoprolol Buccal patches 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. 7. 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 | 9.05 | 15.1 | 10.1 | 9.49 | 10.9 | 20.2 | 17.5 | 12.0 | 11.1 |
| 2 | 13.3 | 19.8 | 12.8 | 11.3 | 19.6 | 27.8 | 21.9 | 17.5 | 13.0 |
| 4 | 14.6 | 28.3 | 21.5 | 22.6 | 24.9 | 42.8 | 33.5 | 23.4 | 23.3 |
| 6 | 21.9 | 34.1 | 25.9 | 32.3 | 31.2 | 53.5 | 40.0 | 30.9 | 33.4 |
| 8 | 32.7 | 41.1 | 33.4 | 43.9 | 38.0 | 66.3 | 46.5 | 48.1 | 52.7 |
| 10 | 40.4 | 50.1 | 44.5 | 56.3 | 50.3 | 82.0 | 64.2 | 60.0 | 66.4 |
| 12 | 54.2 | 65.8 | 56.7 | 69.4 | 65.9 | 94.7 | 91.9 | 78.7 | 79.1 |

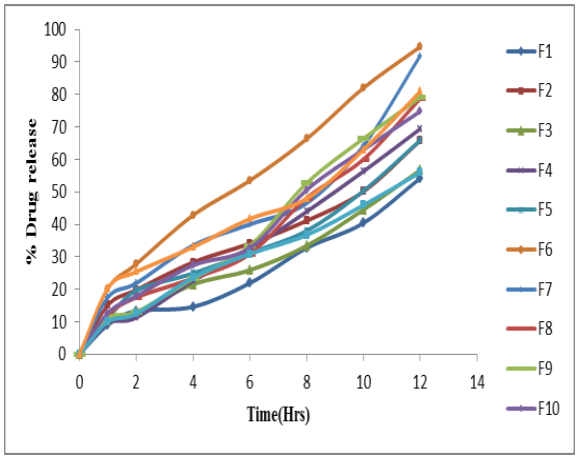



**Fig No. 3: Release profile of In-vitro permeation studies using dialysis membrane**

The prepared Bisoprolol Buccal patches were evaluated for In-vitro permeation studies 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.

**Table No 8: kinetics of In-vitro permeation studies using dialysis membrane**

| Cumulative (%) release Q | Time (T) | Root (T) | Log (%) release | Log (T) | Log (%) remain | Release rate (cumulative % release/t) | 1/cum % release | Peppas log Q/100 | % drug remain | Q01/3 | Qt1/3 | Q01/3-Qt1/3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | | | 2.000 | | | | 100 | 4.642 | 4.642 | 0.000 |
| 20.2356 | 1 | 1.000 | 1.306 | 0.000 | 1.902 | 20.236 | 0.0494 | -0.694 | 79.7644 | 4.642 | 4.305 | 0.337 |
| 27.80759 | 2 | 1.414 | 1.444 | 0.301 | 1.858 | 13.904 | 0.0360 | -0.556 | 72.19241 | 4.642 | 4.164 | 0.478 |
| 42.87958 | 4 | 2.000 | 1.632 | 0.602 | 1.757 | 10.720 | 0.0233 | -0.368 | 57.12042 | 4.642 | 3.851 | 0.790 |
| 53.59293 | 6 | 2.449 | 1.729 | 0.778 | 1.667 | 8.932 | 0.0187 | -0.258 | 46.40707 | 4.462 | 3.594 | 1.048 |
| 66.38743 | 8 | 2.828 | 1.822 | 0.903 | 1.527 | 8.270 | 0.0151 | -0.178 | 33.61257 | 4.642 | 3.227 | 1.414 |
| 82.0877 | 10 | 3.162 | 1.914 | 1.000 | 1.253 | 8.209 | 0.0122 | -0.086 | 17.9123 | 4.642 | 2.616 | 2.025 |
| 94.7055 | 12 | 3.464 | 1.976 | 1.079 | 0.724 | 7.892 | 0.0106 | -0.024 | 5.294503 | 4.642 | 1.743 | 2.899 |

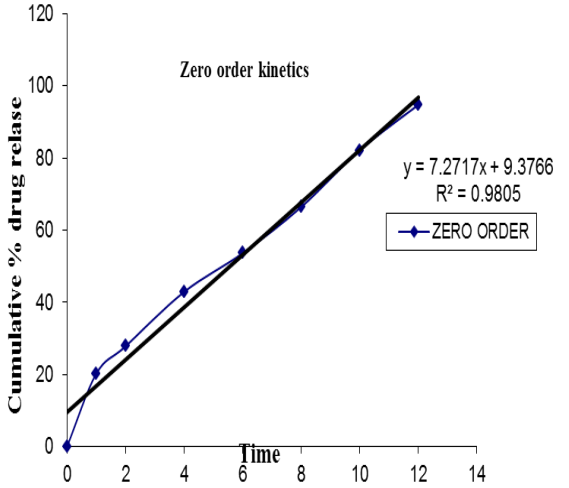



**Fig No. 4: Zero order kinetics**

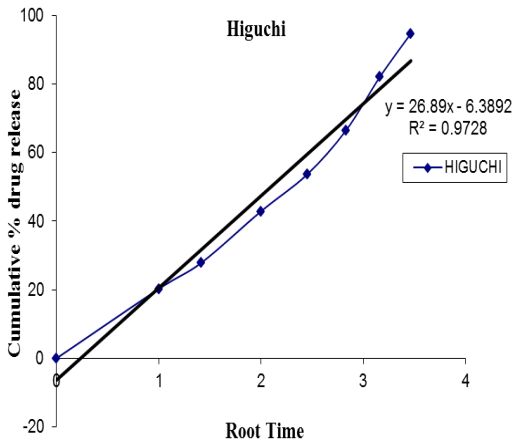



**Fig No. 5: Higuchi plot**

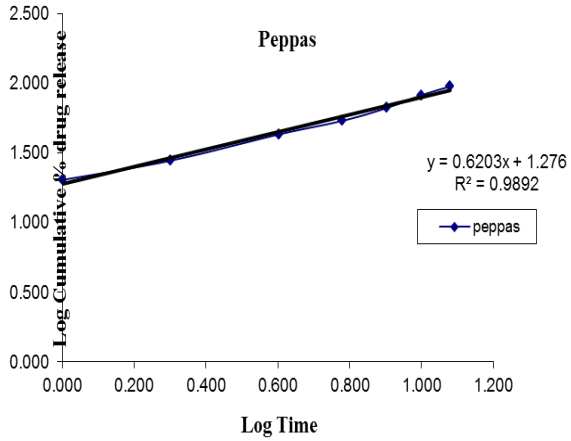



**Fig No. 6: Peppas plot**

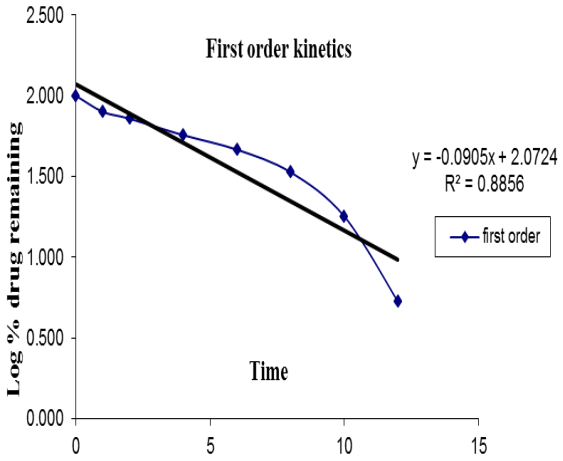



**Fig No. 7: First order kinetics**

The kinetics of In-vitro permeation studies using dialysis membrane for F6 formulation was plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.9892. And the n value was found to be 0.6203 which indicates the drug release pattern was found to be non-Fickian diffusion.

## SUMMARY AND 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, HPMCk$_4$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 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.

For F6 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.

## ACKNOWLEDGEMENT

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