Available online on www.jadd.in

Journal of Advanced Drug Delivery 2014; 1(1); 45-57

ISSN: 2348-3792

Research Article

Formulation and Evaluation ofa Bioadhesive Patch for Buccal Delivery of Bisoprolol Fumarate

Raksha Laxman Mhetre*, GhanshyamSakhare, Vishal BhanudasHol,MirzaWajidBaig, Dr. Prabhakar

*RJSPM's College of Pharmacy,Alandi, Pune, Maharashtra, India.
Trinity College of Pharmacy, Karimnagar, Andhra Pradesh, India.

Available online: April, 2014

Abstract:
Buccal delivery of drugs provides an attractive alternate to other conventional methods of systemic drug administration, since buccal mucosa is relatively permeable with rich blood supply and acts as an excellent site for the absorption of drugs. BisoprololFumarate is acid labile drug and its half-life 10hrs.Hence In the present work, the main aim was to develop unidirectional buccal patches of Bisoprololfumarateto avoid degradation of drug in GIT and there by improve the patient compliance and also to reduce the frequency of administration. The patches were prepared bysolvent casting method using hydroxylpropyl methyl cellulose (HPMC K15), glycerine as plasicizer, propylene glycol (PG) & polyethylene glycol (PEG) as permeation enhancer. From preformulation studies, therewas no chemical interaction between Bisoprolol fumarate and excipients.PG 6% shows the maximum drug released as compared to PEG. The patches were evaluated for thickness,uniformity of weight of films, percentage moisture absorption, percentage moisture loss, mucoadhesion time. Thickness was found to be 0.46±.006 to 0.56±0.0026mm. Mucoadhesion time was 4hrs. – 6hrs 45min. From the kinetic study, the formulation follows First order kinetics and the release mechanism is diffusion.

Keywords: Bisoprolol Fumarate, Buccal patch

INTRODUCTION:

The buccal route as an alternative to other traditional method of systemic drug administration, is a subject of growing interest because of numerous advantages. It is well known that absorption of therapeutic compound from the oral mucosa provide a direct entry of the drug into the systemic circulation, therefore avoiding the first pass hepatic metabolism and gastrointestinal drug degradation which is associated with oral administration.[1,2] The oral cavity is easily accessible for self-medication and hence it is well accepted by patient.Safe since the device can be easily administered and even removed from the site of application, stopping the input of drug whenever desired.[3]

Bisoprolol fumarate is belonging to the class of beta blocker drugs which used primarily in cardiovascular diseases. More specifically, it is a selective type β1 adrenergic receptor blocker. The bisoprolol fumarate has 9-12 hours

elimination half-life. Initial dose is 5 mg orally once a day and maintenance dose is 5 to 20 mg orally once a day. The absolute bioavailability after a 10 mg oral dose of Bisoprolol fumarate is about 80%. Binding to serum proteins is approximately 30%. Bisoprolol fumarate is acid labile.[4]

Therefore, in the present study an attempt was made to formulate mucoadhesive buccal dosage form of Bisoprolol fumarate in order to avoid degradation of drug in GIT and to treat cardiac diseases.The influence of various proportions and combinations of permeation enhancer used in the study (PG and PEG) on physic mechanical properties, mucoadhesive characteristics, *in vitro* drug release, and *ex vivo* drug permeation were investigated.

MATERIALS AND METHODS:

MATERIALS:

Bisoprolol fumarate received as gift sample from Aurobindo Labs, (Hyderabad, India).Methocel E15 was obtained from Fenosalab. All other chemicals and solvents used were of analytical reagent.

METHOD:

1. Preparation of mucoadhesive film:

The mucoadhesive films were prepared by Solvent Casting Method. The polymeric solution ofHPMC was prepared using distilled water under occasional stirring for 4 hrs. The resulting viscous HPMC solution was filtered through nylon gauze to remove debris and suspended particles. Propylene glycol and polyethylene glycol was added as permeation enhancer under constantstirring. The resultant solution was leftovernight at room temperature to ensure aclear, bubble-free solution. The solution waspoured into a glass petri dish. It was kept for drying to form films. Dried films were slowly removed from the petri plate and cut into appropriate size. Prepared film stored in a dessicator.

A. Characterization and evaluation of Mucoadhesive film

1. Measurement of Weight Variation andThickness: The thickness of the patches was assessed at six different points of the patch using thickness gauze (Mitutoyo, Japan). For each formulation, three randomly selected patches were used. Six films from each batchwere weighed individually, and the average weights were calculated.

2. Measurement of Folding Endurance: The folding endurance was determined manually for the prepared films by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking or cracking gave the value of folding endurance [5].

3. ***Ex Vivo* Mucoadhesion Study:** The mucoadhesiontime was determined using a locally modified USP disintegrationapparatus (Electrolab ED-2L), the disintegration medium was composed of 500 mL simulatedsaliva pH 6.2 maintained at 37ºC. A segment of pig buccal mucosa (3 cm long), was glued to thesurface of a glass slide, vertically attached to the apparatus and allowed to move up and down sothat the patch was completely immersed in and out buffer solution.The time taken by the patchto detach from the mucosal surface was recorded and the averages of three readings wererecorded[6].

4. Percentage Moisture Absorption (PMA): The percentage moisture absorption test was carried out to check the physical stability of the buccal films at high humid conditions. In the present study the moisture absorption capacity of the films were determined as follows. Three 1cm diameter films were cut out and weighed accurately. The films were placed in desiccator containing saturated solution of aluminium chloride, keeping the humidity inside the desiccator at 79.5 %. After 3 days the films were removed, weighed and

percentage moisture absorption was calculated. Average percentage moisture absorption of three films was calculated.

$$\text{Moisture absorption (\%)} = \frac{\text{Final weight} - \text{Initial weigl}}{\text{Initial weight}}$$

5. Percentage Moisture Loss (PML): Percentage moisture loss was also carried to check the integrity of films at dry condition. Three 1cm diameter films was cut out and weighed accurately. Films kept in desiccator containing fused anhydrous calcium chloride. After 72 hours the films were removed, weighed. Average percentage moisture loss of three films was calculated.

$$\text{Moisture content (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

6. Content Uniformity: To determine content uniformity, films were taken at different locations of the prepared film and these films were dissolved in 100mL of pH 6.8 phosphate buffer solution. The solution was centrifuged at 3000rpm for 15min. The supernatant was taken and absorbance was noted spectrophotometrically at 222nm.

7. Percent Drug content: Prepared buccal patch was dissolved in 100ml of Phosphate buffer solution (PBS) of pH 6.8 using a magnetic stirrer for 12 hours and then sonicated for 30 minutes. The solution was centrifuged and filtered. The drug content was determined by validated UV spectroscopy at 222 nm.

8. **Surface pH:**

The patches was allowed to swell in contact with 0.5 ml of distilled water (pH 6.5±0.5) for one hour at room temperature and pH was noted down by bringing electrode in contact of surface, allowing it equilibrate for 1 minute.

***9. In-vitro* diffusion studis:** The commercially available dialysis membrane (obtained from Sigma Chemicals) was employed for the study, and the *in vitro* drug release study was carried outusing a Franz diffusion cell. The receptor compartment (40 ml) was filled with phosphate buffer saline (PBS), pH 6.8. The patches were applied under occlusion on the dialysis membrane fitted between the donor and receptor compartments of the diffusion cell. The drug release was performed at 37 ± 0.5°C, at a stirring speed of 50 rpm using a magnetic stirrer. Five milliliters of the sample from receptor medium was withdrawn at regular intervals and replaced immediately with an equal volume of phosphate buffer saline, pH 6.8. The amount of Bisoprololfumarate released into the receptor medium was quantified by using UV–visible spectrophotometer at 222 nm against a blank.

***10.In vitro* permeation**

The *in vitro* buccal permeation study of Bisoprololfumarate buccal patches through the pig buccal mucosa was performed using Franz diffusion cell at 37ºC ± 0.2ºC. Pig buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. Freshly obtained pig buccal mucosa was mounted between the donor and receptor compartments. The patch was placed on the mucosa so the smooth surface of the mucosa placed towards receptor compartment and the compartments were clamped together. The donor compartment was wetted phosphate buffer (pH 6.2). The receptor compartment was filled with isotonic phosphate buffer (pH 7.4) stirred with a magnetic bead at 50 rpm. sample(1 mL)was withdrawn at predetermined intervals and replaced with fresh buffer solution and assayed by UV spectrophotometer (Shimadzu 1800,Japan) at 222nm.

11.Scanning electron microscopy

Film morphology was characterized by scanning electron microscopy. Samples were mounted on round brass stubs (12mm diameter) using double-backed adhesive

tape and then sputter coated for 8 min at 1.1 LV under argon atmosphere with gold palladium before examination under the scanning electron microscope (JEOL JSM-6100 Scanning Electron Microscope, Japan). The images were captured on an Ilfrd PANF 50 black and white 35mm film. The Scanning Electron Microscopy (SEM) study of optimized batch was found at different set. The SEM photograph of optimized batch F9 were shown in figure.

RESULTS AND DISCUSSION:

A) PREFORMULATION STUDIES

The following preformulation studies were performed on Bisoprolol fumarate and excipients.

1. Partition Coefficient:

The Partition Coefficientof Bisoprolol fumarate was found to be: $K_{O/W} = 0.5162$

2. Fourier Transform Infrared Spectroscopy (FTIR) Studies:

As described in the methodology section the FT-IR studies were carried out for pure drug alone and in combination with polymers. The results are summarized as follows.

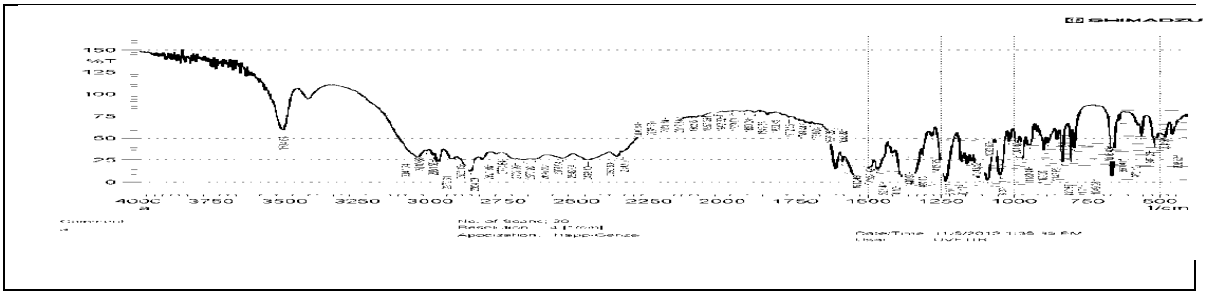

Figure 1: FTIR spectra of Pure Bisoprolol Fumarate(TIF)

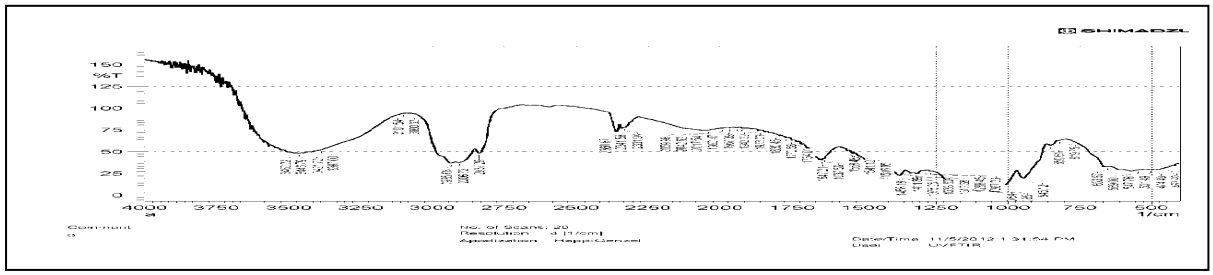

Figure2 : FTIR spectra of HPMC (TIF)

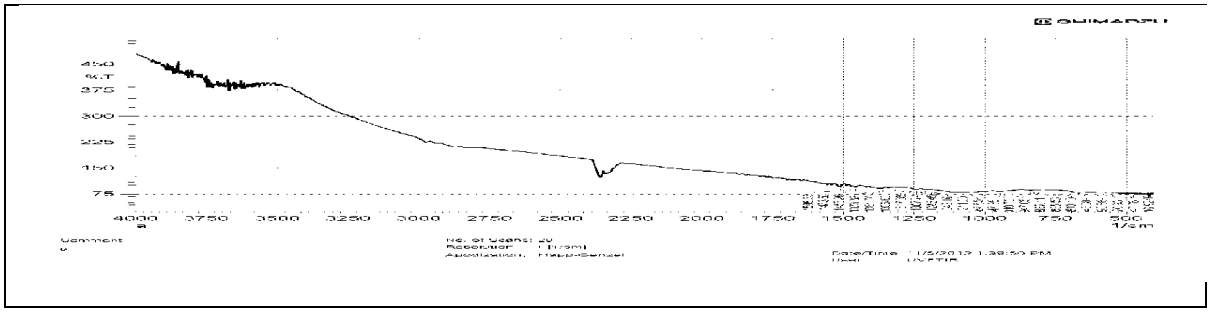

Figure 3: FTIR spectra of F10 formulation (TIF)

From the above FTIR Drug-Excipient compatibility studies data, significant changes in peak positions were not observed between pure drugs, mixture of drug and excipients thus indicating no chemical interaction between drug and excipients. So it is clear that Bisoprolol fumarate is compatible with all the excipients tested above.

1. Differential Scanning Calorimetry (DSC) Studies:

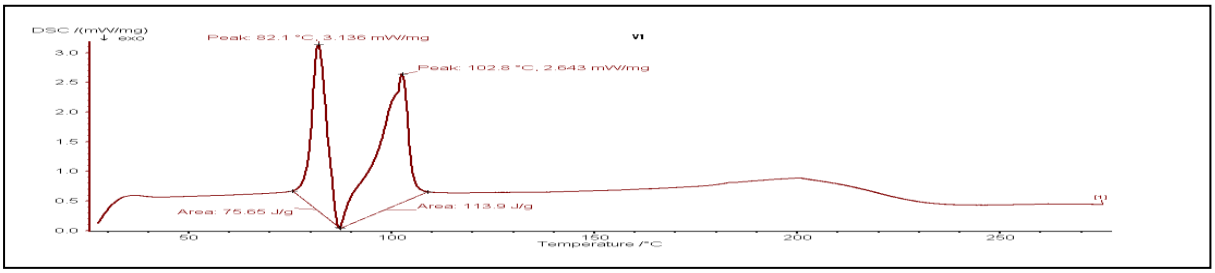

Figure 4: DSC Studies of Bisoprolol fumarate

Observation: From the DSC studies, the melting point of Bisoprolol fumarate was found to be 102.8º C.

B) FORMULATION STUDIES

Bisoprolol patches in polymers were prepared by solvent casting method. Formulated patches were subjected to the preliminary evaluation tests. Patches with any imperfections or differing in thickness, weight (or) content uniformity were excluded from further studies.

The thickness of formulated patches was ranges from 0.46±.006 to 0.56±0.0026mm; while the average weight of patch from each batch ranges from 0.23±0.04to 0.39±0.023.Surface pH of patches was ranges from 5.93 to 6.78 were found around neutral pH. Films did not show any cracks even after folding for more than 200 for all batches. The drug content of films was quite uniform. The average drug content of the films was found to bewithin the range of 95.18– 97.52 percent and the low values of standard deviation and coefficient of variation indicateuniform distribution of the drug within the prepared films.The data of the Thickness,Uniformity of weight of films, Percentage Moisture Absorption, Percentage Moisture Loss given in the following table :

Table 1: Evaluation parameters of Bisoprolol fumarate buccal films

Film code	Thickness (mm)	Uniformity of weight(mg)	% Moisture absorption	%Moisture Loss	Surface pH
F1	0.47±0.0057	0.25±0.11	10.2±2.2	4.2±2.2	6.16
F2	0.50±0.0015	0.30±0.09	11.2±2.3	4.0±2.3	6.06
F3	0.52±0.0023	0.34±0.087	14.0±1.8	4.5±1.8	5.93
F4	0.56±0.0026	0.39±0.023	14.3±2.2	4.8±2.2	7.2
F5	0.46±0.0005	0.23±0.034	12.2±1.8	4.1±1.8	6.73
F6	0.46±0.0005	0.23±0.021	14.2±2.6	4.3±2.6	6.7
F7	0.45±0.0123	0.23±0.04	15.7±2.9	4.9±2.9	6.19
F8	0.45±0.003	0.23±0.076	16.0±2.0	5.3±2.0	6.72
F9	0.46±0.012	0.23±0.012	10.1±1.8	3.8±1.8	6.78

F10	0.46±.006	0.23±0.033	9.6±1.2	3.6±1.2	6.12
F11	0.47±0.023	0.24±0.013	9.2±1.5	3.2±1.5	6.42
F12	0.47±.0111	0.24±0.032	8.7±1.3	2.9±1.3	6.48

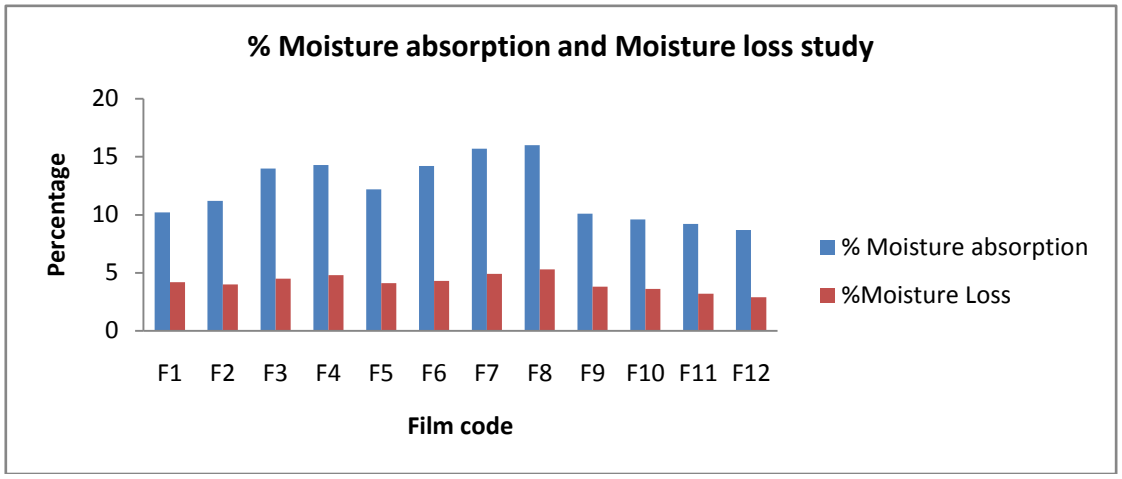

Figure 5: Chart representing Percentage moisture absorption and Percentage moisture loss

Mucoadhesiontime:

The Mucoadhesion time of the testedpatches ranged between 4hrs.and6.hrs 45 residence time of all thepatches was sufficient to retain on the buccal mucosa.

***IN -VITRO*AND EX VIVO DIFFUSION STUDIES:**

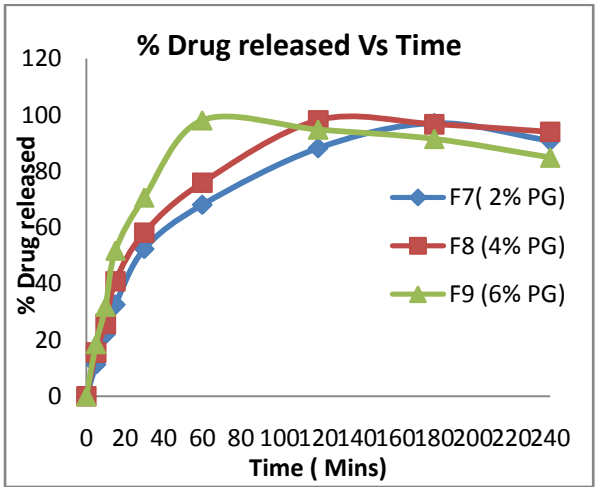

Figure 7*: In vitro*diffusion study

min. All the selected patches retained on the pigbuccal mucosa over the study period and which is indicated that the

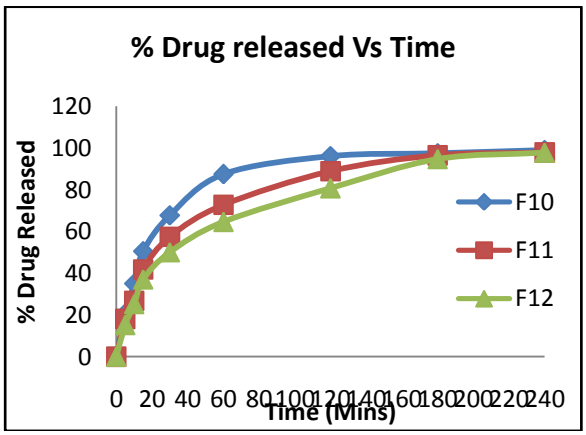

Figure 8: Exvivo study

Drug release of formulations F1 to F4 shows that F1 has obtained the maximum release at 4th hour than the other F2, F3, F4 formulations because from the known fact that drug release decrease as the polymer concentration increases**.**

PG has attained maximum release at 4thhr than PEG. So we take PG for further studies on different concentrations of polymer.PG 6% has given the maximum release when compared to other 2% and 4% of PG.Formulation F10 has given the maximum release with 6% of PG, compared with other formulations F11&F12.Thus the release rates of all the formulations has shown more faster release on mucus membrane than compared with the percentage drug release of all the formulations on soaked/activated dialysis membrane.Different kinetic models applied to F9 optimized formulation.Kinetics drug release results reveal that all formulations followfirst-order kinetics as correlationcoefficient (r2) values are higher than that of zero-order release kinetics. Mechanism of drug release pattern i.e.diffusion and swelling was confirmed by Higuchi plots. The Higuchi plots represent of cumulative percentage drugrelease versus square root of time. It was concluded that the release of drug from the patches followed the diffusion controlled.

SCANNING ELECTRON MICROSCOPY:

The SEM photograph indicates the uniform dispersion of polymeric solution with drug molecule and HPMC patch shown porous surface, which may be suitable for the matrix system.

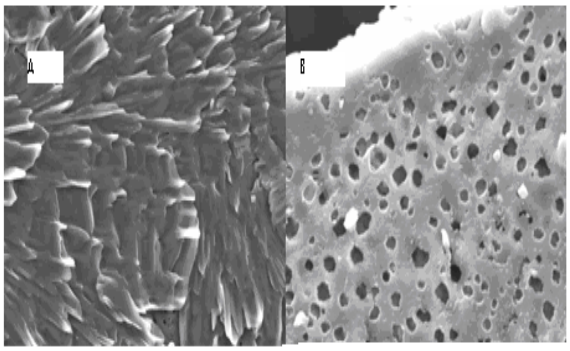

Figure 9: Optical microscopy of formulated patch

SUMMARY& CONCLUSION:

The aim of the invention was to develop a novel unit dosage form of Bisoprolol fumarate; a satisfactory attempt was made to develop mucoadhesive buccal films of Bisoprolol with HPMC polymer &further evaluated its release rate.Bisoprolol fumarate drug & polymer HPMC is used to formulate mucoadhesive films with an aim of work to select the polymer ratio and optimize the concentration of the polymer for the release of drug from the formulation. From preformulation studies, there was no chemical interaction between Bisoprolol fumarate and excipients. The patches were evaluated for tthickness,uniformity of weight of films, percentage moisture absorption, percentage moisture loss, mucoadhesion time. Thickness was found to be 0.47 mm-0.52 mm. Mucoadhesion time was 4 hrs. – 6 hrs 45min. PG has attained maximum release at 4thhr than PEG. So we take PG for further studies on different concentrations of polymer.PG 6% has given the maximum release when compared to other 2% and 4% of PG.From the kinetic study, the formulation follows First order kinetics and the release mechanism is diffusion.

References:

1. Shojaei A, Buccal mucosa as a route for systemic drug delivery: a review, J Pharm Pharm Sci. 1998 Jan-Apr;1(1):15-30.
2. Harris D, Robinson JR, Drug delivery via the mucous membranes of the oral cavity, J Pharm Sci. 1992 Jan;81(1):1-10.
3. Santosh K., Navneet G and Ranjit S., "Development and evaluation of mucoadhesive buccal patches of flurbiprofen" Actapoloniaepharmaceutica and drug research, 2011,vol. 68, 6 pp. 955- 964,

4. Rathi B. Jadhav V., Karwa M., " Bioequivalence Study of Two Formulations of Bisoprolol Fumarate Tablets in Healthy Subjects"Medical Services, SAVA Healthcare Ltd., Pune 2.Auriga Research Ltd., New Delhi
5. Nafee NA, Ahemed F, Borale A. Preparation and evaluation of mucoadhesive patches for delivery of cetylpyridinium chloride (CPC). ActaPharma.2003; 199–212
6. Prasanth V. et al. "Formulation and Evaluation of Mucoadhesive Buccal Patches ofAceclofenac" Der Pharmacia Lettre, 2012, 4 (1):297-306.
7. Attama A, Akpa PA, Onugwu LE, Igwilo G. Novel buccoadhesive delivery system of hydrochlorothiazide formulated with ethyl cellulose hydroxypropyl methylcellulose interpolymer complex. Scientific Res Essay. 2008;3(6):26–33.
8. Neelam R. et.al, Formulation and evaluation of buccal patches of pantaprozole, Int. J. Pharm & Ind. Res.2012**,** 2(1).37-40.
9. U. S. Pharmacopoeia 23/National Formulary 18, USP Convention, Roockwile (MD) 1995.
10. F. Nakamura, R. Ohta, Y. Machida and T. Nagai, In vitro and in vivo nasal mucoadhesion of some water-soluble polymers, *Int. J. Pharm.* 1996, 134, 173–181.
11. M Vishnu; G Patel Bhupendra; Prajapati; Madhabhai M Patel, Formulation, evaluation and comparison of bilayer and multilayer mucoadhesive buccal devices of propranolol hydrochloride, *AAPS PharmSciTech*, **2007,**8 (2), E1-E8.
12. Panigrahi L., Pattanaik S., Ghosal. S.K., Design andcharacterization of Mucoadhesive Buccal Patches ofDiclofenac Sodium, *Indian J .Pharm.Sci*.,2005, 67 (3):319-326
13. Patel V.M, Prajapati B.G, Patel M.M, Design and characterization of chitosan containing mucoadhesive buccal patches of propranolol hydrochloride. ActaPharm. 2007, 57: 61–72
14. Doijad R. C., Manvi F. V., Malleswararao V.S.N., Patel P.S., Buccoadhesive drug delivery system of isosorbidedinitrate: formulation and evaluation. Indian J. Pharm. Sci. 2006, 68(6)744-748.
15. Singh S, Jain S, Muthu M. S, Tiwari S, Tilak R., Preparation and Evaluation of Buccal Bioadhesive Films Containing Clotrimazole. AAPS PharmSciTech, 2008, Vol. 9, No. 2, 660-667.
16. Junginger H. E, Hoogstraate J. A, Verhoef J. C, Recent advances in buccal drug delivery and absorption — in vitro and in vivo studies. J. Controlled Release 1999, 62: 149–159.
17. Parikh Bhavik, Design and evaluation of buccal patches of valsartan, IJPI's Journal of Pharmaceutics and Cosmetology, Vol 1: 2 (2011), 50-55.
18. Santosh kumar, Development and Evaluation of mucoadhesive buccal Patches of flurbiprofen, Actapoloniaepharmaceutica- drug research, vol. 68 no. 6, 2011 pp. 955-964