WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 6.647
Volume 6, Issue 11, 628-648 Research Article ISSN 2278 – 4357

DESIGN AND EVALUATION OF BUCCAL PATCHES OF NSAID'S FOR GINGIVITIS

***Chandrika Y. and Dr. Sathish C. S.**

Department of Pharmaceutics, PES College of Pharmacy, Bangalore, Karnataka, India, 560050.

Article Received on
24 August 2017,
Revised on 14 Sept. 2017,
Accepted on 04 October 2017
DOI: 10.20959/wjpps201711-9660

***Corresponding Author**
Chandrika Y.
Department of Pharmaceutics, PES College of Pharmacy, Bangalore, Karnataka, India, 560050.

ABSTRACT

Objective: The aim of the present work is to design and evaluate the buccal patches of NSAID's for gingivitis using different mucoadhesive polymers such as hpmc 5cps, carbopol 934p, eudragit rl 100 in various combination. **Method:** The buccal patches were prepared by solvent casting method. The formulation of buccal patch, dose is released immediately due to presence of polymer in different concentration. All the buccal formulation were subjected to pre-formulation and physical evaluation studies, jn-vitro drug release and ex-vivo permeation studies. In-vitro drug release from the formulation was studied using buffer pH 6.8. **Results:** From in vitro studies formulation F6 and F7 were selected for mucoadhesive studies and ex vivo permeation studies using buffer Ph 6.8. After all studies formulation F7 containing hpmc 5cps and eudragit rl 100 in the ratio (400 mg: 200 mg) was selected as optimized formulation and its muccoadhesive strength and exhibited optimum drug release. FTIR results showed no evidence of interaction between the drug and polymers. **Conclusion:** It was concluded that the assay of the formulations revealed that the drug content was within the limits. The results indicated that delivery of aceclofenac to the local drug delivery via the buccal route improve its bioavailability and also was found to be stable during stability studies conducted for 3 months as per ICH guidelines.

KEYWORDS: Aceclofenac; buccal patches; mucoadhesive polymers; physicochemical parameters; In vitro drug release; Mucoadhesive studies; Ex vivo permeation studies; stability studies.

INTRODUCTION

Extensive research efforts have recently been focused on placing a drug delivery system in a particular region of the body for maximizing biological drug availability and minimizing dose-dependent side effects. Hence buccal drug delivery is a highly effective way to improve bioavailability. Buccal delivery of drugs provides an attractive alternate to other conventional methods of systemic drug administration this is because the buccal mucosa has a rich blood supply which facilitates direct entry of drug molecules into the systemic circulation.

Since buccal mucosa is relatively permeable with rich blood supply and acts as an excellent site for the absorption of drugs.[1,2] Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity.

The administration of drugs via buccal route facilitates a direct entry of drug molecules into the systemic circulation, avoiding the first-pass metabolism and drug degradation in the gastrointestinal environment, which are often associated with oral administration.[3–5]

So for various route of administrated tried in the novel drug delivery systems. localized drug delivery to tissues of the oral cavity has been investigated for the treatment of periodontal disease, bacterial and fungal infection, therefore localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site (e.g. buccal cavity).[6]

Buccal drug delivery is well accepted by patients as the buccal cavity is easily accessible for self-medication. In addition, buccal dosage forms allow drug absorption to be rapidly terminated in case of an adverse reaction. The use of mucoadhesive polymers in buccal drug delivery which includes adhesive tablets[7] gels and patches of which patches are preferable in terms of flexibility and comfort.[8,9]

In the recent years the interest in developing a drug delivery system with the use of a mucoadhesive polymer that will attach to related tissue or to the surface coating of the tissue for targeting various absorptive mucosa such as ocular, nasal, pulmonary, buccal, vaginal, etc. This system of drug delivery is called mucoadhesive drug delivery system.[10]

Other advantages includes excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or

pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action.[11]

ORAL MUCOSA

Anatomy of the oral mucosa: Light microscopy reveals several distinct patterns of maturation in the epithelium of the human oral mucosa based on various regions of the oral cavity. Three distinctive layers of the oral mucosa are the epithelium, basement membrane, and connective tissues.[13-14]

The oral cavity is lined with the epithelium, below which lies the supporting basement membrane. The basement membrane is, in turn, supported by connective tissues ie lamina propria followed by the sub mucosa as the innermost layer (Fig. 1).

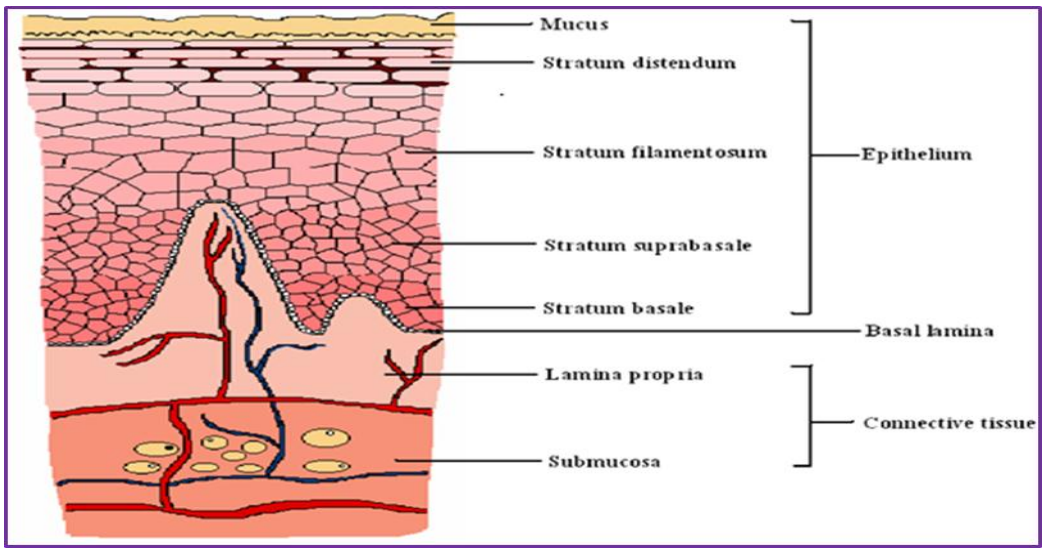

Fig 1 Anatomy of Oral skin.

MUCOADHESIVE POLYMERS

Mucoadhesive polymers are the important component in the development of buccal delivery systems. The first step in the development of buccoadhesive dosage forms is the selection and characterization of appropriate bioadhesive polymers in the formulation. Bioadhesive polymers play a major role in buccoadhesive drug delivery systems of drugs. Bioadhesive polymers have properties to get adhered to the biological membrane and hence capable of prolonging the contact time of the drug with a body tissue. The use of bioadhesive polymers can significantly improve the performance of many drugs. This improvement ranges from better treatment of local pathologies to improved bioavailability and controlled release to enhance patient compliance.

GINGIVITIS

Gingivitis describes inflammation of the gingivae, which is a reversible form of periodontal disease characterized by inflammation of the gingivae in response to a mature dental plaque biofilm. Which includes swelling, redness, influx of inflammatory cells, edema in the tissue, change of normal contours and bleeding. Gingival pockets from tissue swelling and loss of attachment not involving bone are usually present.[14,15]

The most common type of gingivitis involves the marginal gingiva and is brought on by the accumulation of microbial plaques in persons with inadequate oral hygiene.

Gingivitis proceeds through an initial stage to produce early lesions, which then progress to advanced disease.

The initial stage of an acute exudative inflammatory response begins within 4 or 5 days of plaque accumulation. Both gingival fluid and transmigration of neutrophils increase. Deposition of fibrin and destruction of collagen can be noted in the initial stage.[15,16]

Gingivitis is a bacterial infection of the gums. The exact reason why gingivitis develops has not been known, but several theories exist.

This disease occurs when a bacterium from dental plaque invades surrounding tissues and accumulation of plaque at the gingival margin induces inflammatory response. The result is the formation of pockets between gingiva and tooth that causes gingival margin retraction and the development of an ideal environment for anaerobic bacterial growth responsible for the disease. This, in turn, can lead to destruction of the gingival tissues, which may progress to destruction of the periodontal attachment apparatus.[17]

NSAID is preferable in local formulations such as mouth wash, gels, to treat oral inflammatory conditions e.g. gingivitis. A relatively large number of studies have been carried out to formulate different dosage forms of aceclofenac, such as tablets, soft capsules, particulate systems and topical systems. aceclofenac is the example of biopharmaceutical classification system (BCS) Class II compound.

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID'S) belongs to class phenyl acetic acid and possess good anti-inflammatory, analgesics and anti-pyretic and it is widely used for treating condition like osteoarthritis, rheumatoid arthritis, management of dental pain

and post-operative pain.[18] It directly blocks the prostaglandin synthesis and has less gastrointestinal complications since it is highly protein bound and possess short biological half-life of 4-5 hours, volume of distribution 25l, 99% of protein binding and 60-70% of bioavailability after oral administration.[19]

The aim of this work is to design and evaluation of buccal patches for gingivitis using non-steroidal anti-inflammatory drugs using various combination of hydrophilic and hydrophobic polymer in different ratio.

MATERIALS AND METHODS

Drugs and chemicals

Aceclofenac was obtained from (Mahalaxmi Chemi Pharm, Mumbai), HPMC (5cps) was obtained from (CDH Laboratory Reagent), eudragit rl 100 Complimentary sample from (Zydus Recon, Bangalore), Carbopol 934 P, peg 400, glycerine, sodium hydroxide pellet, potassium dihydrogen phosphate, menthol, dichloromethane, was obtained from (S.D.Fine Chemical Limited, Mumbai), ethanol (Changshu yangyuan chemical, china), calcium chloride (Priya Fine Chem Ltd, Bangalore).

Instruments

Electronic weighing balance (Shimadzu, Japan), UV Visible spectrophotometer (Shimadzu (UV-1800), Japan.), Digital Vernier Caliper (R. K Industries, Mumbai), Hot air oven (Analytical Technologies, Bangalore, India), pH meter (Elico, Bangalore, India), Fourier Transform IR Spetroscopy (Aglient Carry 630FTIR), Magnetic Stirrer (Remi Equipment Pvt.Ltd), Stability Chamber (Analytical Technologies, Bangalore), Dissolution apparatus (Electrolab TDT-08L) Franz Diffusion Cell (Neutron Scientific, Kolkata).

METHOD

Analytical Method Used in the Determination of Aceclofenac

The UV spectrophotometry method was developed for the analysis of drug using double beam spectrophotometer 1601 spectrophotometer.

Determination of λmax

Aceclofenac (20mg) was dissolved in 25ml of distilled water and 10ml of the resulting solution was diluted to 100ml and 1ml was withdrawn from that and diluted to 10ml i.e. 10µg/ml solution. The drug solution was scanned for maximum absorbance in UV

double beam spectrophotometer (Shimadzu 1601) in the range from 200 to 400 nm. The λmax of the drug was found to be 274nm.

Standard plot of Aceclofenac by UV-Spectroscopic Method

Preparation of Phosphate buffer (pH 6.8)- sodium hydroxide (100mg) and Potassium Di hydrogen phosphate(13.6g) are dissolved and make up to 1000ml with distilled water.[20]

Preparation of Stock-I Solution of Aceclofenac

Standard stock solution were prepared by weighing out 50 mg of drug in 50 ml volumetric flask which was dissolved and made up to the mark using phosphate buffer (pH 6.8) to get 1000 µg/ml solution and was used as a standard solution (SS).

Preparation of Stock-II Solution of Aceclofenac

Take 5mL of Stock-I solution and made up to 50mL with Phosphate buffer (pH 6.8) to give 100 µg/mL solution.

Preparation of working standard

From Stock-II solution 0.5, 1, 1.5, 2, 2.5, 3 ml were taken in different 10 ml volumetric flask and were diluted up to the mark with phosphate buffer (pH 6.8) to get a concentration of 5, 10, 15, 20, 25, 30µg/ml respectively. These solutions were scanned and the absorbance was measured at 274nm against blank. The absorbance values thus obtained were plotted in graph of concentration on X-axis versus absorbance on Y-axis.

Drug – Excipients Interaction Study

FT-Infrared spectroscopy to find out the compatibility of drug with polymer.

This was carried out to find out the compatibility between the drug Aceclofenac and the polymers such as HPMC 5cps, Eudragit RL 100 and Carbopol 934P. 10 mg of the sample and 400 mg of potassium bromide (KBr) were taken in a mortar and triturated. A small amount of the triturated sample was taken into a pellet maker and was compressed at 10 kg/cm2 using a hydraulic press. The pellet was kept onto the sample holder and scanned from 4000 cm-1 to 400 cm-1 in Perkin Elmer FT-IR spectrophotometer. The spectra obtained were compared and interpreted for the functional group peaks.

Formulation of buccal patches of aceclofenac.

The patches were prepared by the solvent casting method by using hydrophilic and hydrophobic polymers for the patches mentioned in table 4.3. Predetermined amount of

Carbopol 934 P and Eudragit RL100 were dispersed in required quantity of ethanol under stirring and HPMC 5cps were dispersed in required quantity of ethanol and dichloromethane (1:1) ratio. For the different batches of formulation the polymer solution in the different proportions were mixed in the magnetic stirrer continuously until the homogenous clear solution was obtained, The beaker containing polymer was kept aside for 5 minutes for swelling of polymer. The drug was dissolved in ethanol in such an amount to load 10mg of Aceclofenac per $2\times2cm^2$ of the final patch. Then one drop of (0.0294 g) glycerine and followed by Specified quantity of PEG 400 was added to the polymeric solution. The drug solution was added to the polymer solution and the whole solution was mixed thoroughly with the help of magnetic stirrer for 30min. The solution was then transferred quantitatively to petri-dish (glass) of size 63.64cm2. The petri-dish covered with inverted funnels to allow controlled evaporation of the solvents. These were lefts undisturbed upon temperature (20-25^0C) for one to two days depending upon the solvent system used. Small patches of size 0.2 to 0.3 mm thick were carefully pull out from the petri-dishes.[21-23]

FORMULATION CHART

FORMULATION CODE		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
POLYMERS	HPMC 5cps (mg)	450	400	350	300	250	450	400	350	300	250
	CARBOPOL 934 P (mg)	150	200	250	300	350	-	-	-	-	-
	EUDRAGIT RL 100 (mg)	-	-	-	-	-	150	200	250	300	350
Plasticizer (PEG 400) % of polymer wt.		46%	46%	46%	46%	46%	46%	46%	46%	46%	46%
Drug (mg)		160	160	160	160	160	160	160	160	160	160
Glycerine (% of polymer wt)		12%	12%	12%	12%	12%	12%	12%	12%	12%	12%
Menthol (%)		0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Solvent		E:D	E:D	E:D	E:D	E:D	E:D	E:D	E:D	E:D	E:D

E:D (ethanol: dichloromethane), area of patch = 4 cm2, weight of polymers = 600 mg.

Evaluation of Buccal Patches

Thickness

The patches are selected from each formulation and thickness of the patches was determined using digital vernier caliper and was measured at three different places on the patch. The average of the three value i.e., Mean thickness, standard deviation were calculated.[24]

Weight Variation

Five films from each batch having an area of 2×2cm were weighed individually in a digital balance and average weight and standard deviation was calculated.[24]

Folding Endurance

The folding endurance of patches was determined by repeatedly folding 1 patch at the same place till it broke or was folded up to 200 times without breaking. The experiments were performed in triplicate and average values and standard deviation were reported.[25]

Drug content uniformity

Drug content uniformity was determined by dissolving the patch by homogenization in 100 mL of IPB, (pH 6.8) for 10 h under occasional shaking and the resulting solution was filtered through a 0.45 µm whatman filter paper. The drug content was then determined after proper dilution at 274 nm using a UV spectrophotometer. The experiments were performed in triplicate and average values were reported.[25]

Swelling study

The initial weight of the patch (without backing membrane) was determined using a digital balance (Wo). Then the patches were allowed to swell on the surface of an agar plate (described under measurement of surface pH) and kept in an incubator maintained at 37°C. Weight of the swollen patch was determined (Wt) at predetermined time intervals for 60 min. The percentage of swelling (% S) was calculated using the following equation.[26]

$$\%S=\frac{(Wt-Wo)}{Wo}\times 100$$

Where Wt is the weight of swollen patch after time t, Wo is the initial weight of patch at t=0.

Surface pH Study

Each patch was allowed to swell by keeping it in contact with 5 mL of distilled water for 2 hours at room temperature and the pH was noted by bringing the electrode into contact with the surface of the patch and allowing it to equilibrate for 1 minute. The experiments were performed in triplicate and average values and standard deviation was calculated.[25]

In-vitro Drug Release

The USP Dissolution test apparatus (type 2) with slight modification (paddle over disc) method was used to study the In-vitro drug release from buccal patches. The dissolution

medium consisted of 300 mL of IPB, pH 6.8. The release was performed at 37ºC, at a paddle rotation speed of 50 rpm. One side of the buccal patch was attached to the glass disk with instant adhesive (cyanoacrylate). The disk was put in the bottom of the dissolution vessel so that the patch remained on the upper side of the disk. Samples 5 mL were withdrawn at predetermined time intervals and fresh medium was used to replace sample volume. The samples were filtered through 0.45 µm whatman filter paper with appropriate dilutions with phosphate buffer pH 6.8 and analysed using a UV spectrophotometer (Shimadzu (UV-1800), Japan) at 274 nm.[27]

Mucoadhesive Strength

Mucoadhesion strength of the patch was carried out on a modified physical balance employing the method using sheep buccal mucosa as model mucosal membrane. A piece of sheep buccal mucosa was washed in distilled water and was tied to the mouth of a glass vial filled completely with PBS pH 6.8. The buccal mucosa was tied tightly with mucosal side upward using thread over the base of inverted 50 ml glass beaker which was placed in a 500 ml beaker filled with phosphate buffer pH 6.8 kept at 37oC such that the buffer reaches the surface of mucosal membrane and keeps it moist. Patches were stuck to the lower side of rubber stoppers with glue. The balance was kept in this position for 3 min. Then, the weights were increased on the right pan until patch just separated from mucosal membrane. The excess weight on the right pan i.e. total weight minus 5 g was taken as a measure of the mucoadhesive strength and the mass(g) required to detach the patches from the mucosal surface was taken as the mucoadhesive strength (shear stress).[2,23]

Ex - vivo drug permeation

The ex-vivo permeation study of aceclofenac released from patch through the sheep buccal mucosa was performed using Franz type glass diffusion cell at 37 ± 0.5 C. Fresh goat buccal mucosa was mounted between the donor and receptor compartments. The patch was placed with the core facing the mucosa and the compartments clamped together. The donor compartment was filled with 1 mL of phosphate buffer pH 6.8. The receptor compartment (40mL capacity) was filled with phosphate buffer pH 6.8, and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm. 1 mL sample was withdrawn at predetermined time intervals and replaced immediately with equal volume of PBS (pH 6.8) and analysed for drug content at 274 nm using a UV-spectrophotometer.[22]

Stability Studies

Stability of a drug has been defined as the stability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications throughout its shelf life. The purpose of the stability testing is to provide evidence on the quality of a drug substance or its product, which varies with time under the influence of environmental factors such as temperature, humidity and light. Recommended storage conditions, re-test periods and shelf lives are to be established.

Method

Stability studies were carried out on the films of most satisfactory formulation as per ICH Guidelines. The most satisfactory was formulation stored and sealed in aluminium foil. These were stored at $25^0C \pm 2^0C$ / 30% ± 5% and $40^0C \pm 2^0C$ for 3 months. Films were evaluated for physical characteristics, drug content permeation and in-vivo studies.[28]

RESULTS

The purpose of the present work was to develop a buccal patches for gingivitis using Aceclofenac as a model drug candidate. The buccal patches were prepared by solvent casting method using various combination of hpmc 5cps, carbopol 934p, eudrgit rl 100 in different ration.

A. Evaluation of preformulation study

Preformulation study such as melting point and solubility studies was carried out and compared with actual melting point ie 152-153°C and reported melting point was found to be $151\text{-}155^0C$ and in the present study, an attempt was made to learn whether the media phosphate buffer pH 6.8, was able to maintain sink conditions in dissolution studies. From the solubility studies, the drug concentration was found to be 1538.7 ± 1.215 mg/ml. Thus, phosphate buffer pH 6.8 was chosen as the dissolution media because sufficient amount of drug dissolved in it, which is necessary to maintain sink condition.

Table No 2: STANDARD CURVE OF ACECLOFENAC.

SL NO	CONCENTRATION (µg/ml)	ABSORBANCE
1	5	0.146
2	10	0.282
3	15	0.403
4	20	0.528
5	25	0.691
6	30	0.811

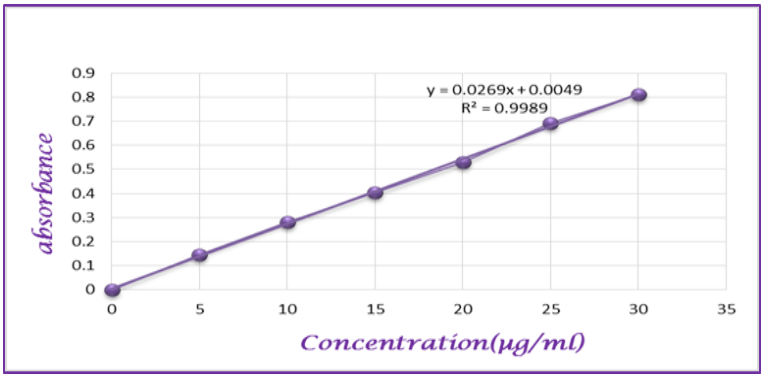

Fig 2: STANDARD CURVE OF ACECLOFENAC.

B. FT-IR Studies: IR spectrum of pure drug and drugs-polymer mixture revealed no chemical interaction between drug and polymers.

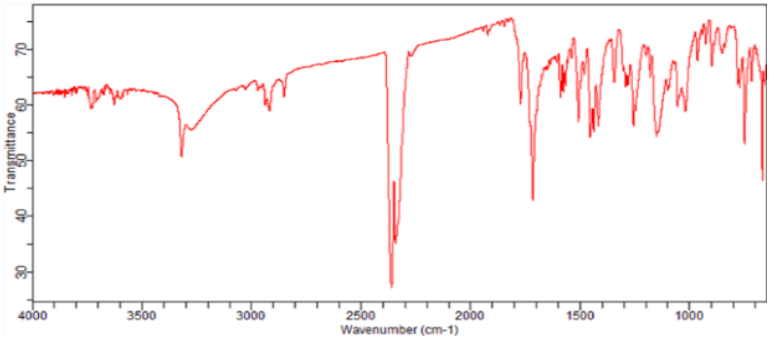

Fig 3: FTIR spectra of pure aceclofenac.

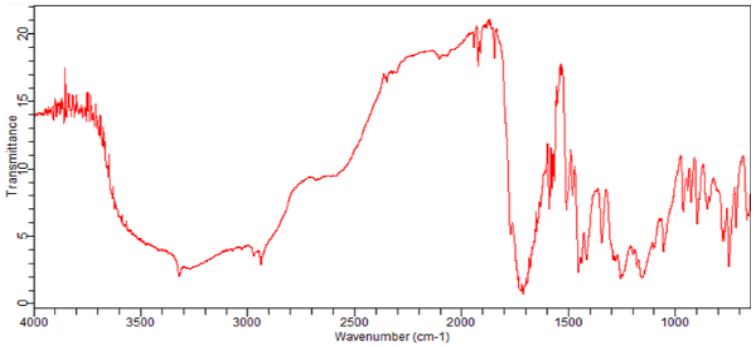

Fig.4: FTIR spectra of API +carbopol+HPMC 5cps.

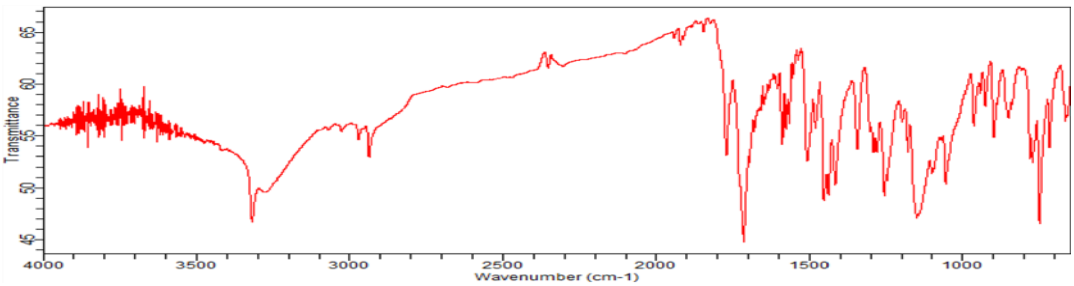

Fig. 5: FTIR spectra of API +HPMC 5cps + EUDRAGIT RL 100.

C. Thickness and Weight Variation

Table 3: Thickness and Weight Variation of F1 to F10.

SL NO	Formulation code	Thickness (mm) ± SD[a]	Weight Variation (mg) ± SD[b]
1	**F1**	0.1933 ± 0.015	72.51 ± 0.215
2	**F2**	0.22 ± 0.020	68.73 ± 1.00
3	**F3**	0.243 ± 0.068	80.75 ± 0.35
4	**F4**	0.25 ± 0.02	82.38 ± 0.45
5	**F5**	0.234 ± 0.015	78.76 ± 0.62
6	**F6**	0.211 ± 0016	70.47 ± 0.15
7	**F7**	0.240 ± 0.026	82.33 ± 0.16
8	**F8**	0216 ± 0.005	82.92 ± 0.52
9	**F9**	0.23 ± 0.02	79.16 ± 0.16
10	**F10**	0.2 ± 0.02	81.24 ± 0.40

a: mean of 3 observation **b:** mean of 5 observation.

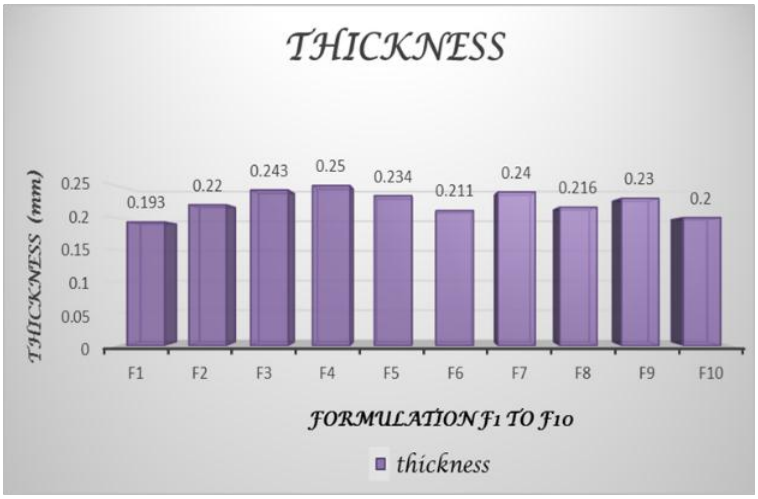

Fig 6: Thickness of the Formulation F1-F10.

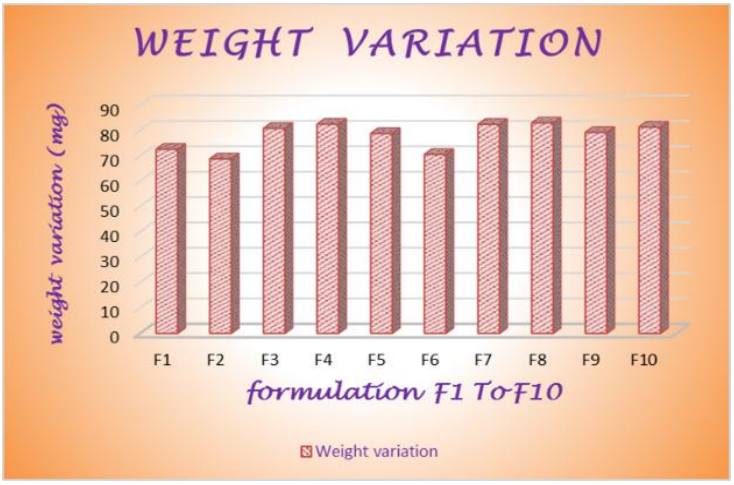

Fig 7: Weight Variation of Formulation F1-F10.

D. Swelling Index and Folding Endurance

Table 4: Swelling Index at predetermined time intervals for 60 min and Folding Endurance for F1 to F10.

SL NO	Formulation code	Swelling index ± SD[a]	Folding Endurance
1	**F1**	43.334 ± 0.06	>200
2	**F2**	39.33 ± 0.95	>200
3	**F3**	34.33 ± 0.191	>200
4	**F4**	33.79 ± 0.070	>200
5	**F5**	32.33 ± 2.81	>200
6	**F6**	35.79 ± 1.134	>200
7	**F7**	44.414 ± 0.06	>200
8	**F8**	30.68 ± 3.332	>200
9	**F9**	36.43 ± 1.24	>200
10	**F10**	29.81 ± 3.44	>200

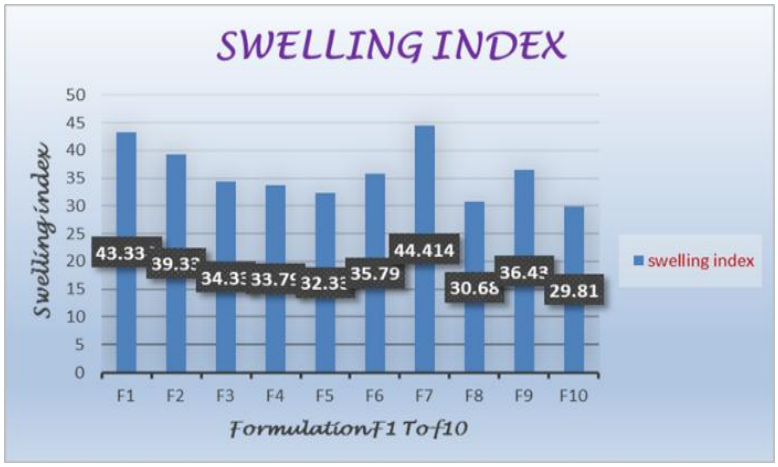

Fig 8: Percentage Swelling of Formulation F1 - F10.

E. Percentage drug content and Surface pH

Table 5: Percentage drug content and Surface pH of F1 to F10.

SL NO	Formulation code	% drug content ± SD[a]	Surface pH ± SD[b]
1	**F1**	93.368 ± 0.065	6.203 ± 0.2112
2	**F2**	88.24 ± 0.0655	6.346 ± 0.0092
3	**F3**	94.668 ± 0.339	6.470 ± 0.0201
4	**F4**	90.8566 ± 0.0550	6.336 ± 0.2059
5	**F5**	87.936 ± 0.0550	6.516 ± 0.2650
6	**F6**	95.916 ± 0.339	6.723 ± 0.049
7	**F7**	96.054 ± 0.196	6.833 ± 0.1457
8	**F8**	89.546 ± 0.0550	6.21 ± 0.2389
9	**F9**	93.974 ± 0.1961	6.450 ± 0.016
10	**F10**	89.261 ± 0.201	6.453 ± 0.0152

a: mean of 3 observation **b:** mean of 3 observation.

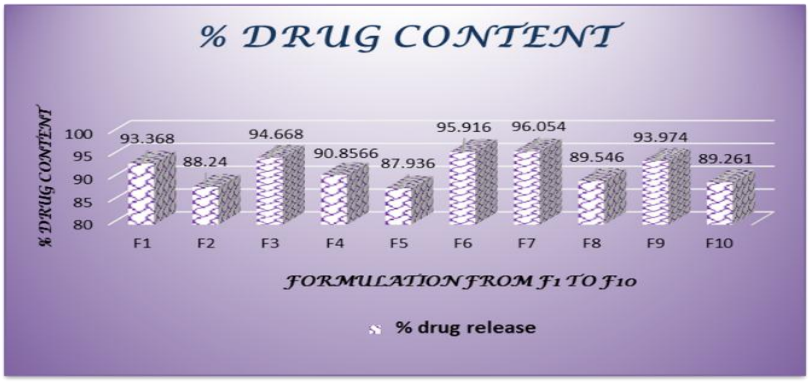

Fig 9: % Drug Content of Formulation F1- F10.

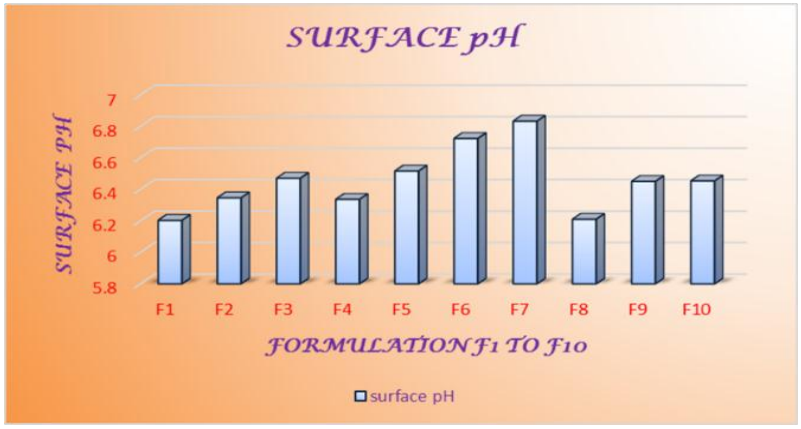

Fig 10: Surface PH of Formulation F1 - F10.

F. In Vitro Drug Release Studies of Formulations

Dissolution studies were carried out for 60 min in Phosphate buffer pH 6.8. The samples were analysed using UV spectrophotometer at 274nm and results are shown.

Table 6: In vitro drug release of formulation F1 –F10.

SL. NO.	Time (Min)	In vitro drug release studies									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0	0
1	5	11.346	9.987	8.052	7.26	6.359	17.81	19.569	14.1	11.217	10.30
2	10	21.868	15.098	12.810	11.349	9.647	34.404	35.837	34.04	22.336	12.81
3	15	30.184	27.562	22.660	15.646	14.060	43.188	44.603	37.71	32.042	28.35
4	20	44.560	36.066	24.941	21.438	17.583	48.739	49.682	46.81	40.711	33.79
5	25	52.490	43.889	37.887	29.475	25.067	54.869	59.932	51.69	48.983	39.34
6	30	63.501	52.155	39.467	36.508	35.932	57.828	61.213	52.62	50.118	50.69
7	35	66.215	55.550	53.527	43.889	42.730	66.673	69.115	65.97	57.894	54.65
8	40	69.052	66.215	64.629	52.155	45.869	75.731	77.451	69.69	62.001	56.24
9	45	72.346	69.052	66.429	59.745	49.654	79.361	81.373	71.09	67.113	64.05
10	50	78.542	75.731	71.327	64.507	57.584	85.369	88.018	78.56	75.021	71.30
11	55	84.119	80.032	78.583	76.402	66.551	89.334	92.779	80.03	79.711	77.75
12	60	86.162	85.501	82.533	81.404	73.596	92.060	96.341	87.70	84.317	78.95

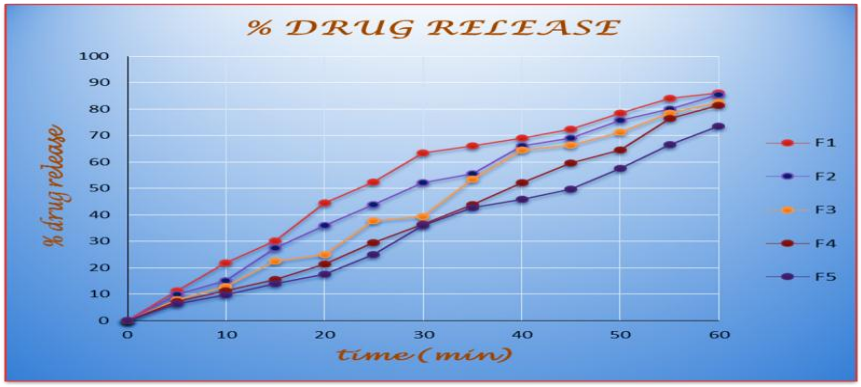

Fig 11: Percentage Drug Release of Formulation F1 – F5.

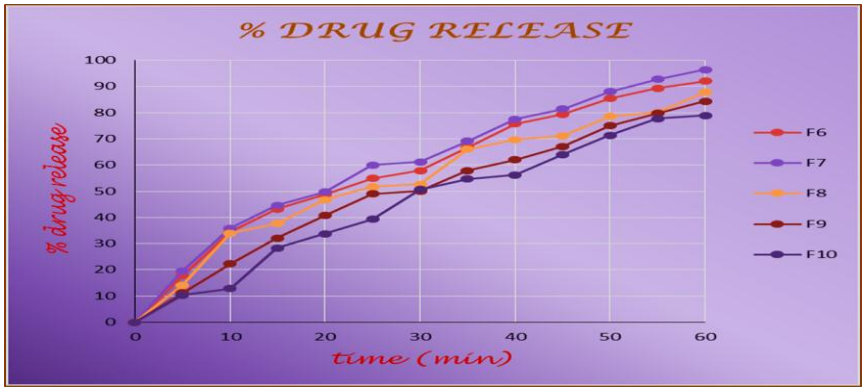

Fig 12: Percentage Drug Release of Formulation F6 – F10.

G. Ex-Vivo Studies. Ex vivo permeation study were carried out for 60 min in Phosphate buffer pH 6.8. The samples were analysed using UV spectrophotometer at 274nm and results are shown below:

Table 7: Ex-vivo Permeation study for selected formulation F6 and F7.

Sl no	Time In min	Ex vivo permeation studies	
		F6	F7
0	0	0	0
1	05	14.753	17.261
2	10	20.946	21.439
3	15	26.316	30.183
4	20	31.635	35.508
5	25	37.845	41.737
6	30	42.485	48.818
7	35	51.237	56.217
8	40	59.219	63.216
9	45	66.564	71.451
10	50	73.221	79.161
11	55	81.240	85.409
12	60	87.021	93.661

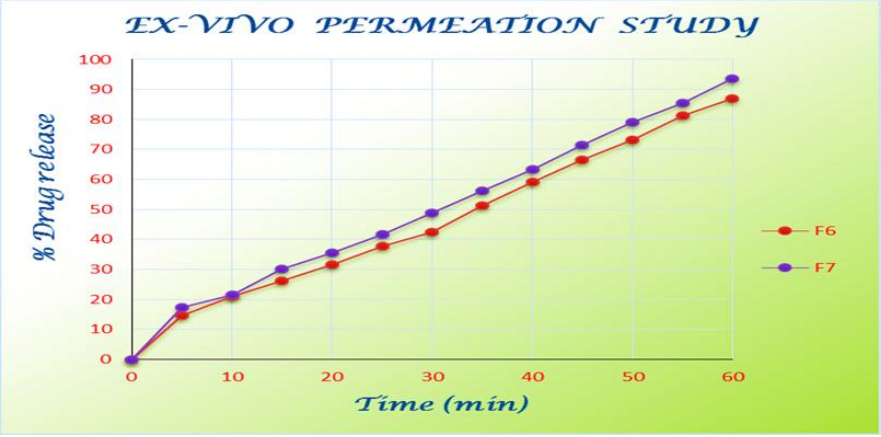

Fig 13: Ex-vivo release Study of Formulation F6 and F7.

H. In-vitro Mucoadhesion study

Table 8: In-vitro Mucoadhesion study.

Formulation	Mucoadhesive strength (g)	Force of adhesion (N)
F6	28.71 ± 1.05	0.28 ± 0.01
F7	30.12 ± 1.14	0.30 0.02

I. Stability Study

Table 9: Percentage Drug Content of F7 during Stability Study.

Time in Days	% Drug Content		
	25 ˚C/ 60% RH	30 ˚C/ 65% RH	40 ˚C/ 75% RH
0	96.054	96.054	96.054
30	96.043	96.041	96.040
60	96.037	96.036	96.035
90	96.033	96.031	96,030

Table 10: Percentage Drug Permeation of F7 during Stability Study.

Time in Days	% Drug Permeation		
	25 ˚C/ 60% RH	30 ˚C/ 65% RH	40 ˚C/ 75% RH
0	93.661	93.661	93.661
30	93.559	93.557	93.556
60	93.557	93.554	93.553
90	93.555	93.551	83.490

DISCUSSION

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID'S) belongs to class phenyl acetic acid and possess good anti-inflammatory, analgesics and anti-pyretic and it is widely used for treating condition like osteoarthritis, management of dental pain and post-operative pain. It directly blocks the prostaglandin synthesis and has less gastrointestinal complications since it is highly protein bound and possess short biological half-life of 4-5 hours. Hence we

formulated buccal patches using aceclofenac with small minimizing the dose of the drug which can overcome the first pass effect, reduce the frequency of dosing and improve bioavailability. Polymers such as hpmc 5cps, carbopol 934 p and eudragit rl 1oo selected on the basis of their adhering property and non-toxicity, the result of the finding showed excellent adhering property and immediate release. Plasticizer like PEG 400 and glycerine were added and the patch were prepared by solvent casting method.

In present study the solubility of aceclofenac in ethanol and phosphate buffer (6.8) as a receptor fluid was found to be 250mg ± 0.2 mg/ml and 1538.7 ± 1.225 mg/ml, respectively. The standard curve for aceclofenac was determined λmax 274nm and the regression was found to be 0.9989 with slope of 0.0269 and Y intercept of 0.0049. Fourier transform infrared spectroscopy (FTIR) was done to study compatibility of Aceclofenac with formulation excipients. The results indicated that the characteristic absorption peaks of pure drug with other excipient shown no significant changes. Hence, it was confirmed that there was no incompatibility between drug and various polymers used.

The prepared patches were subjected to thickness, weight variation, folding endurance, drug content uniformity, surface pH, swelling index, and stability studies at different temperature. The patches showed thickness over the range of 0.193 to 0.243 mm and a showed that no significant differences in the weight of individual formulations from the average value and the variations were all within limits. The surface pH of the patch which is close to neutral ph, which shows they have no irritancy to the buccal mucosa and therefore it is comfortable to the patient. Good uniformity of drug content was observed in all the patches. The swelling index of the formulation is an important factor for assessment of mucoadhesion. The swelling index of the buccal patches are shown in Table 4. Incorporation of HPMC 5cps with Carbopol 934 P increases the swelling index in (F1) and HPMC 5cps with Eudragit RL 100 increase the swelling index in (F7), therefore patches which have high value due to the presence of large number of hydroxylic groups in HPMC that can absorb and retain water and thus increasing weight and swelling index. It was also found that the swelling index was regulated by the addition of HPMC. Formulations F1, F2, F7, F9 exhibited a higher swelling rate than other formulations, which was attributed to the property of HPMC to retain water and become a thick swollen mass. The polymer materials become adhesive with hydration and excessive swelling.

The percentage cumulative release for F1 TO F10 range from 73.59 to 96.34%. Formulation F5 shown minimum drug release (73.59%) and formulation F7 showed the maximum drug release (96.34) for period of 60 min. hpmc is compared with carbopol 934p and eudragit rl 100, here plasticizer were maintained constant for all the formulations. since eudragit rl 100 with hpmc 5cps shows highest released than carbopol 934 p, from the above results F7 found to be optimize formulation and optimized formula F 7 shown good mucoadhesive strength. The selected formulation F6 and F7 were subjected to ex-vivo permeation studies through the sheep buccal mucosa was performed using Franz type glass diffusion cell at 37 ± 0.5C for 60 min therefore F7 showed the highest drug release and permeation it can be attributed to more permeable nature of hpmc and eudragit and also led to formation of pores in the matrix patches and hence high permeability.

Therefore Among the all the formulations F1 to F10, the formulations F7 was selected as the best formulation after considering its surface PH, Swelling index, good drug content, maximum drug release and maximum permeation through the sheep buccal mucosa.

The best formulation (F7) was subjected to accelerated stability studies for 90 days at 250C/60% RH, 300C/65% RH & 400C/75% RH for % drug content and permeation profile performed every 30 days and showed negligible change in % drug content permeation profile.

CONCLUSION

The buccal mucosa is a promising delivery route for drugs that need to avoid the gastrointestinal tract due to degradation by the gastric pH, intestinal enzymes, or due to a substantial hepatic first pass effect. It can also be an alternative to skin, pulmonary, or nasal delivery. The physiology of the buccal mucosa allows for the penetration of active substances. The present work involves the formulation development, optimization and in-vitro evaluation of buccal Patches of Aceclofenac, for the treatment of gingivitis.

Under the preformulation studies API (Active Pharmaceutical Ingredient) characterization, and drug-excipient compatibility studies were carried out. The API characterization showed compliance with the drug characteristics.

Aceclofenac buccal patches were prepared by solvent casting technique. It was shown that with the developed formulations, the release and mucoadhesion properties of buccal patches can be controlled by changing the polymer type and concentration. The formulation F7

consisting of Aceclofenac (160mg), HPMC 5cps (400mg), Eudragit RL 100 (20mg), PEG 400 (45%), Aspartame (15mg), Glycerine (12%) and Menthol (0.05%) was selected as the optimized formulation with sufficient mucoadhesive strength and in-vitro, ex-vivo correlation. Various physicochemical parameters tested for this formulation have shown good results. Mucoadhesion of the optimized formulation provided a minimum loss of drug by swallowing, which resulted in higher bio-availability.

It was concluded that development of mucoadhesive buccal drug delivery of aceclofenac as buccal patches was one of the alternative routes of administration for local effect by immediate drug release and to improve the bioavailability.

REFERENCE

1. Patel VM, Prajapati BG, Patel MM. Design and characterization of chitosan containing mucoadhesive buccal patches of propranolol hydrochloride. Acta Pharm., 2007; 57: 61–72.
2. Mohamed S. Pendekaln, Pramod K, Tegginamat. Formulation and evaluation of a bioadhesive patch for buccal delivery of tizanidine. Acta Pharmaceutica Sinica B., 2012; 2(3): 318–324.
3. Vashmi Vishnu Y, Chandrasekhar K, Ramesh G, Madhusudan Rao Y. Development of mucoadhesive patches for buccal administration of carvedilol. Curr Drug Deliv., 2007; 4: 27–39.
4. Khairnar A, Jain P, Baviskar D, Jain D. Development of mucoadhesive buccal patch containing aceclofenac: in-vitro evaluation. Int J Pharm Sci., 2009; 1(1): 91–5.
5. Hao J, Heng PWS. Buccal delivery systems. Drug Dev Ind Pharm. 2003; 29(8): 821–32.
6. Shalini Mishra, Kumar G, Kothiyal P. A Review Article: Recent Approaches in Buccal Patches., 2012; 1(7): 78-86.
7. Owens TS, Dansereau RJ, Sakr A. Development and evaluation of extended release bioadhesive sodium fluoride tablets, Int J Pharm., 2005; 288: 109–22.
8. Shah Viral A, Shah Jimish, Upadhyay UM. Formulation development and evaluation of buccal bilyer patch using thiocolchicoside and diclofenac sodium, Int. J. Inv. Pharm. Sci., 2013; 1(3): 190-211.
9. Anders R, Merkle HP. Evaluation of laminated mucoadhesive patches for buccal drug delivery, Int J Pharm., 1989; 49: 231–40.

10. Lee VHL, Lee VHK, Robinson JR. Controlled drug delivery New York: Marcel Dekker Inc., 1987; 29(2): 4.
11. Shidhaye S S, saindane NS, Sutar S, Kadam V. Mucoadhesive bilayered patches for administration of sumatriptan, AAPS Pharm Sci Tech., 2008; 9(3): 909-916.
12. Amir Shojaei H. Buccal mucosa as a route for systemic drug delivery. J Pharm Pharm Sci., 1998; 1(1): 15-30.
13. Harris D, Robinson J.R. Drug delivery via the mucous membranes of the oral cavity, J Pharm Sci., 1992; 18: 1-10.
14. Schatzle M, Loe H, Burgin W, Anerud A, Boysen H, et al. Clinical course of chronic periodontitis. I. Role of gingivitis. J Clin Periodontol., 2003; 30: 887–901.
15. http://emedicine.medscape.com/article/763801-overview.
16. Rathbone M J, Drummond B K, Tucker I G. The oral cavity as a site for systemic delivery. Adv Drug Deliv Rev., 1994; 13: 1-23.
17. Humes, H. David, et al., Kelley's Textbook of Internal Medicine. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins., 2000.
18. K Balamurugan, J K Pandit, P K Choudary, J Balasubramaniam. Ind. J. Pharm. Sci., 2001; 63: 473-480.
19. Faiyaz Shakeel, Mohammed S Faisal, Sheikh Shafiq. Comparative Pharmacokinetic Profile of Aceclofenac from Oral and Transdermal Application Journal of Bioequivalence & Bioavailability(JBB)., 2009; 1.
20. Gowthamarajan, Sachin Kumar Singh, Dev Prakash, Somashekhar. Dissolution Enhancement of Poorly Soluble Aceclofenac by Solid Dispersion Technique and Its Comparison with Marketed Formulations, International Journal of Pharm Tech Research (IJPRI)., 2010; 2(4): 2347-2356.
21. Shivhare U D, Suruse P S, Varvandkar S S. Formulation and evaluation of buccal patch containing aceclofenac. J App Pharm., 2014: 6(1): 65-76.
22. Cristina Cavallari, Adamo F B, Francesca O C. Mucoadhesive multiparticulate patch for the intrabuccal controlled delivery of lidocaine. European Journal of Pharmaceutics and Bio pharmaceutics, 2013; 83: 405–414.
23. Claudia Juliano, Massimo Cossu, Paola Pigozzi, Giovanna Rassu. Preparation, In Vitro Characterization and Preliminary In Vivo Evaluation of Buccal Polymeric Films Containing Chlorhexidine. AAPS Pharm Sci Tech., 2008; 9(4): 1155-1158.
24. Pendekaln M S, Tegginamat P K. Formulation and evaluation of a bioadhesive patch for buccal delivery of tizanidine. Acta Pharmaceutica Sinica B., 2(3): 318–24.

25. Tej Pratap Singh, Rakesh Kumar Singh, et al. Mucoadhesive bilayer buccal patches of verapamil hydrochloride: formulation development and characterization. Int J Pharm Pharm Sci., 2014; 6(4): 234;241.
26. Parthasarathy G, Bhaskar R Kesavan, Jayaveera K Narasimha, Formulation of unidirectional release buccal patches of carbamazepine and study of permeation through porcine buccal mucosa. Asian Pac J Trop Biomed, 2013; 3(12): 995-1002.
27. Burgalassi S A, Panichi L A et al. Development and in vitro/in vivo testing of mucoadhesive buccal patches releasing benzydamine and lidocaine, Int. J. Pharm., 1996; 133: 1-7.
28. Dhagla Ram Choudhary, Vishnu A Patel, Usmangani K Chhalotiya, Harsha V Patel, Aliasgar J Kundawala. Natural Polysaccharides As Film Former: A Feasibility Study For Development Of Rapid Dissolving Films of Ondansetron Hydrochloride, Int J Pharm Pharm Sci., 2001; 3: 78-85.