Vijay Kumar D. *et al.* / *International Journal of Pharmacy & Therapeutics*, 4(2), 2013, 76-81.

e- ISSN 0976-0342
Print ISSN 2229-7456

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

IJPT

DEVELOPMENT AND EVALUATION OF CELECOXIB BUCCAL MUCO ADHESIVE PATCHES

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ABSTRACT

Mucoadhesive buccal patch of Celecoxib were prepared using polymer like Gelatin, Poly Sodium CMC and Poly Vinyl Alcohol. Eight formulations were prepared with varying the concentration of Poly Sodium CMC and evaluated for various parameters like weight variation, patch thickness, volume entrapment efficiency %, and measurement of % elongation at break, folding endurance, in-vitro mucoadhesive time, in-vitro mucoadhesive strength, *invitro* and *invivo* study. The formulations showed a sustained release. The F4 formulation containing Celecoxib 7%, Gelatin 4.5%, Poly Sodium CMC 5.5%, Propylene Glycol 5%, Poly vinyl Alcohol 2.5% and Distilled Water up to 100%, showed a release of 88.4% after 8 hours. The Celecoxib stability studies were performed at 40 ± 20C / 75 ± 5% RH. Among the eight formulation, F4 formulation showed maximum desired properties release.

Key Words:- Celecoxib, Buccal patch, Mucoadhesion, Gelatin.

INTRODUCTION

The buccal mucosa provides a readily accessible route for transmucosal delivery. The oral cavity is being increasingly used for the administration of drugs, which are mainly designed for the contained medicaments through the oral mucosa into the systemic circulation (Anders R and Merkle HP, 1989). Buccal mucosa consists of stratified squamous epithelium supported by a connective tissue lamina propia was investigated as a site for drug delivery several decades ago, and the interest in this area for the transmucosal drug administration is still growing. Delivery of drug through buccal mucosa overcomes premature drug degradation within the GI tract, as well as active drug loss due to the first pass metabolism, and inconvenience of parenteral administration. In addition, there is excellent acceptability and the drug can be applied localized, and may be removed easily at any time during the treatment period. A few drugs, such as metaprolol tartarate, ibuprofen, salbutamol sulphate, diclofenac sodium, diltiazem hydrochloride, isosorbide dinitrate and pyridinium chloride have been successfully administered via the buccal route (Baichwal MR, 1984).

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms (Ali J *et al*., 2007). The mechanism of action of Celecoxib is believed to be due to inhibition of prostaglandin synthesis. Unlike most NSAIDs, which inhibit both types of cyclooxygenases (COX-1 and COX-2), Celecoxib is a selective noncompetitive inhibitor of cyclooxygenase-2 (COX-2) enzyme. It binds with its polar sulfonamide side chain to a hydrophilic side pocket region close to the active COX-2 binding site. Both COX-1 and COX-2 catalyze the conversion of arachidonic acid to prostaglandin (PG) H2, the precursor of PGs and

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thromboxane. Though it is rapidly absorbed after oral administration, the bioavailability of Celecoxib is 40-50% as it undergoes significant first pass metabolism and will be eliminated from body through urine and feces. Celecoxib is a weak base and its pKa value is approximately 8.32, which satisfies the criterion for the selection of the drug. The log P (partition coefficient) value for Celecoxib is about 5.2. It indicates that Celecoxib has sufficient lipophilicity to pass through the buccal membranes. The minimum dose of Celecoxib is 1 mg/day. By observing the above points, it is inferred that Celecoxib has a need to formulate into buccal patches and the drug is suitable for it.

MATERIALS AND METHODS

Materials

Celecoxib was gifted by Alkem Laboratories Limited, Mumbai. Gelatin, Poly-Sodium CMC and Polyvinyl Alcohol was purchased from Loba Chemicals. All chemicals used were of analytical grade.

Methods

Preparation of Mucoadhesive Patches

Mucoadhesive patch were prepared by solvent casting method. All ingredients were accurately weighed and mixed by trituration in glass pestle and mortar (Beckett AH and Triggs EJ, 1967). The mixture was then added gradually to magnetically stir solvent system containing the plasticizer. Stirring was continued until a clear solution was obtained. The solution was then transferred quantitatively to petri-dish (glass) diameter 6cm .The petri-dishes were covered with inverted funnels to allow controlled evaporation of the solvents. These were lefts undisturbed upon temperature (20-25^{0}C) for one to two days depending upon the solvent system used. Small patches of size 15 mm and 20mm diameter, 0.2 to 0.3 mm thick were carefully pull out from the petri-dishes.

EVALUATION OF MUCOADHESIVE PATCHES

Weigh variation

Weigh variation was tested by comparing the averages weighed of 10 different randomly selected patches from each batch with individual patch (Hanna R *et al.*, 1998)

Patch thickness

Patch thickness was measured at 5 different randomly selected spots using a screw gauge.

Volume entrapment efficiency %

Volume entrapment efficiency % is volume uptake by capacity by buccal capacity of fluid (saliva) by buccal patches after adhesion into the buccal cavity. Mucoadhesive patch were weighed individually (X0) and placed separately in 2% agar gel plates and incubated at 37^0C±1^0C. after 90 min. the final weight of the patch (XT) were noted and the volume entrapment efficiency was using the following formula.

Volume entrapment efficiency % = (XT– X0) 100/X0

Where X0= initial weight of patch, XT= final weight of patch (after 90min).

Measurement of the % elongation at break

The initial length of the patch was measured on scale and applying the force the patch unit the patch was broken and calculated the % elongation of patch by using the following formula

% Elongation at break = Increase in length x 100/Initial length

Surface pH

The patches was allowed to swell then 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 electron in contact the surface the pH , allowing it equilibrate for 1 minute.

Folding endurance

Folding endurance of the patches was determined by repeatedly folding one patch at 180^0 angle of plane at same plane till it broke or folded to 200 time without breaking.

Swelling Index

Swelling index was determined by placing the pre-weighed patches (2×2 cm^2) from each formulation in a beaker (containing 20 mL of water). After particular interval of time patches was removed and wiped with tissue paper and weighed. The swelling index can be computed by using the formula:

Swelling Index = W2-W1/ W1 x100

Where, W1is the weight of buccal patches before dipping into beaker and W2is the weight of buccal patch after dipping in beaker and wiped.

Mucoadhesive Strength

The strength of bond between the patch and mucosal membrane (excised from sheep buccal mucosa) was determined using tensile experiments on a specially fabricated. The sheep buccal mucosa was used as model membrane and isotonic phosphate buffer pH 7.4 was used as the moistening fluid. The sheep buccal mucosa was stuck onto inner surface of the petri dish using suitable glue such that a mucosal surface faces upwards. Then the

phosphate buffer pH 7.4 was added into petri dish such that the buffer was contacted with the mucosal membrane. Two sides of balance were made equal before study, by keeping a 5g weight on the left side.

A petri dish containing mucosal membrane was kept below the right-hand setup of the balance. The test dummy films were stuck on to lower flat side of hanging glass assembly. The surface of mucosa was blotted with Whatmann filter paper no. 42. Two mL of phosphate buffer pH 7.4 was added to the mucosal surface and 5 g weight from the left pan was removed. This lowered the glass assembly along with film over the membrane with weight of 5g. This was kept undisturbed for 3 min. Then the weights on the left hand side were slowly added till the patch just separated from the membrane surface. The excess weight on the left pan that is total weight minus 5g was taken as adhesive strength.

Mucoadhesive time

The in- vitro mucoadhesive time was determined using disintegration apparatus. The disintegration medium was 800 mL of phosphate buffer (pH 7.4) maintained at 37±2°C. The segment of buccal mucosa of sheep was glued to the surface of glass slab, which was then vertically attached to the apparatus. Three mucoadhesive films of each formulation were hydrated on one surface with Phosphate buffer (pH 7.4) and the hydrated surface was brought into contact with the mucosal membrane and allowed the apparatus to move up and down. The time required for complete detachment of the film from surface was recorded. The results were analyzed for mean and standard deviation.

Drug Content

Three films (2×2 cm^2) from each film were taken in separate 10 mL volumetric flask. Ten mL of phosphate buffer (pH 7.4) was added and continuously stirred for 24 h. The solutions were filtered, diluted suitably and analyzed at 303 nm in an U.V Spectrophotometer. The average values were determined. The results were analyzed for mean and standard deviation.

In-vitro release studies

For in vitro release study, cellophane membrane was used as a barrier membrane with Phosphate buffer (pH 7.4) as a medium. The cellophane membrane was soaked for 24 h in Phosphate buffer. The patches were evaluated for drug release using Keshary-Chain type diffusion cells.

Cellophane membrane was mounted between the donor and receptors compartments. The patch was placed on the cellophane membrane. The diffusion cell was placed in a water bath maintained at 37±2°C.The receptor compartment was filled with 50 mL phosphate buffer (pH 7.4) and hydrodynamics was maintained by stirring with a magnetic bead at 100 rpm. Five mL sample was withdrawn and replaced with 5 mL fresh medium to maintain the sink condition. The samples were analyzed in U.V spectrophotometer at 303 nm (Paulson SK *et al*., 2000).

Ex-vivo release studies

The sheep buccal mucosa was used as a barrier membrane instead of cellophane membrane and the same procedure as above was followed. The samples were analyzed in UV spectrophotometer at 303 nm.

In vivo studies

Buccal absorption test of Celecoxib in human volunteers

Buccal absorption test carried out on three healthy male volunteers aged between 23 to 25 years. Since this test indicates the prima facei evidence of buccal absorption of Celecoxib, only three human volunteers selected. Before the test, the volunteers asked to moisten their mouth with a few ml of buffer solution. Twenty -five ml of phosphate buffer, pH 6.6, solution containing 5 mg of the drug placed in the volunteer's mouth. The volunteers asked to swirl the solution approximately at 60 swirlings per min for 5 min. Then the solution expelled and the mouth rinsed further. The expelled solutions combined, suitably diluted and analyzed at 320 nm using UV-Vis spectrometer (Khurana R *et al*., 2000).

In vivo patch test in human volunteers

Among 18 male human volunteers selected for this test, 16 research scholars and 2 authors. All of the age between 23 to 35 years. The details of the test and drug informed to the volunteers and consent taken from them before the commencement of the work. Permission obtained from Institutional Ethics Committee to carry out the work. A film (1 cm^2) containing 5 mg of Celecoxib cut and fixed on a cellophane paper, which acted as a backing layer so that the drug release will be unidirectional. Before application of the patch, the human volunteers asked to rinse their mouth thoroughly with water. The patches applied to the buccal mucosa of human volunteers. After 90 min, the patches taken out and added to a beaker containing 10 ml of phosphate buffer, pH 6.6, solution. The volunteers directed to rinse their mouth with 10 ml of phosphate buffer, pH 6.6, solution. The rinsed solution added to the previous solution. After appropriate dilution, solutions analyzed for drug content at 320 nm. The results represent the amount of drug remaining unabsorbed.

In vivo patch test in rabbits

In vivo absorption studies conducted on rabbits. Three male rabbits weighing about 5.0, 5.5 and 6.0 kg of either sex used for the release study of Celecoxib. The animals fasted for overnight with ad-libitum storing them in individual cages before the experiment carried out. The approval to carry out the work on animals and human volunteers given by Institutional Ethics Committee. The rabbits anaesthetized with phenobarbital sodium IP (1 ml containing 200 mg) and diazepam 0.5 ml (1 ml containing 100 mg) by intra peritoneal route. Films (1 cm^2) cut and fixed on a cellophane paper which acts as a backing layer so that the drug release will be unidirectional and threads tied to it, so that the films can be easily removed from the buccal cavity. After 10 min of anesthetic injection, the films placed (separately) in the buccal cavity one at time. After a gap of 2 min, further films attached. The films taken out at 15, 30, 45 and 60 min. The process repeated for two more times. The films dissolved in 10 ml of phosphate buffer, pH 6.6, solution, then diluted suitably and the drug remained unabsorbed analyzed at 320 nm [5].

Ageing

The optimized medicated patches subjected to stability testing. Patches placed in a glass beaker lined with aluminium foil and kept in a humidity chamber maintained at 40+2^oC and 75+5% relative humidity for 1 month. Changes in the appearance and drug content of the stored patches investigated at the end of every week. The data presented the mean of three determinations.

RESULT AND DISSSION

All formulation showed more than 75% of drug release after 8hrs. Among them, F4 formulation shows maximum %release i.e. 94% as compared to other.

The various formulation of mucoadhesive patches prepared by varying the concentration of one or more ingredients (Table -1) and evaluated for various parameter .All the eight mucoadhesive patch formulation comply with referred values excepts F1 &F2 for %elongation parameter (Table-2). The folding endurance, mucoadhesive time, %drug release (after 8hrs) were maximum i.e. 204, 224, 94% respectively in F4 formulation. Based on this parameter F4 formulation was as optimized formulation. The surface pH of all mucoadhesive patch formulation within the range 6.01 to 6.7 but F1, F2, F3, F4 formulation does not comply with referred values i.e. 6.2 to 7.2. The F4 formulation had pH 6.78 that was almost near to pH (7.0) & hence expected to be non-irritant to buccal mucosa (Table -2).

The in-vitro drug release a study was performed using cellophane membrane. The release rate from different formulations through cellophane membrane showed that, release of drug from these patches exhibited two phases. There is a initial burst effect is followed by the completion of a stable gel layer which in turn, controls the release of drug from the delivery system. The kinetics of different formulations was also studied and the R^2 values are shown in Table 3. The formulation F3 showed the Higuchi release kinetics because the R^2 value of Higuchi was closer to 1 (0.976). In this context, the formulation F4 was selected as the best formulation for further ex-vivo release study. The drug release pattern of selected formulation F4 through sheep buccal mucosa was studied and the results are provided in Table 3. The release kinetics of Celecoxib through buccal mucosa was studied. The ex-vivo drug release data of formulation F4 was fitted to first order, zero order and Higuchi release kinetics, where it shows zero order release kinetics because the R^2 value of zero order was the highest among other kinetics and closer to 1(0.971).

Ageing

The prepared patches subjected to ageing studies. The Patches placed in humidity chamber at 37+2^oC and 75+5% RH. The patches are withdrawn for every week and analysed for their drug content. Percentage drug present in the patches determined spectrometrically. Drug content retained in the patches after 30 days, is to the extent of 86.32 to 89.2%. It found that the drug loss is less though the patches stored for one month. The patches also observed for their appearance and texture. These properties did not change in patches during the period of study.

Table 1. Various Formulation for Mucoadhesive Buccal Patches

Sl.No	Ingredient (W/V)	Formulation code							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Celecoxib	7%	7%	7%	7%	7%	7%	7%	7%
2	Gelatin	4.5%	4.5%	4.5%	4.5%	4.5%	4.8%	5%	5.5%
3	Poly Sodium CMC	3%	3.5%	4%	4.5%	5.5%	6%	6.5%	7%
4	PEG	5%	5%	5%	5%	5%	5%	5%	5%
5	PVA	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
6	Distilled water	78%	77.5%	77%	76.5%	76%	75.2%	75%	74%

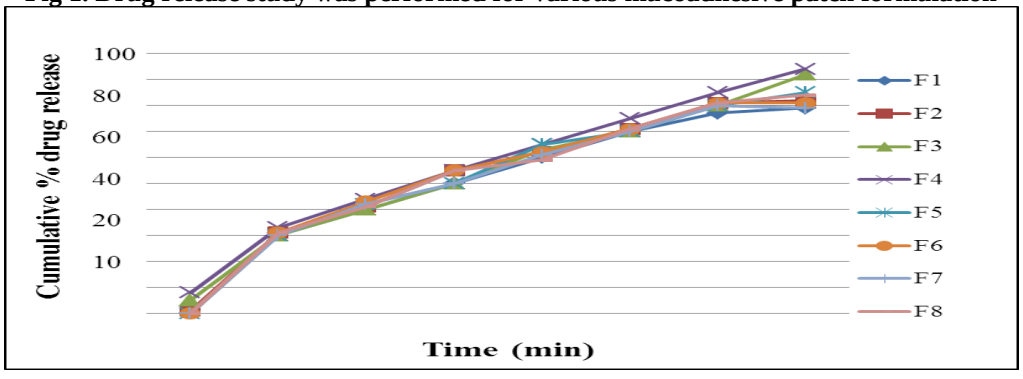
Table 2. Optimization of Mucoadhesive Patch formulation (*Optimized formulation)

Sr.No	Parameter	Referred value	F1	F2	F3	F4*	F5	F6	F7	F8
1	Weight variation	Average ± 25mg	201	204	206	208	206	209	203	200
2	Patch thickness(mm)	Uniform	0.90	0.91	0.92	0.92	0.93	0.91	0.92	0.93
3	Volume entrapment efficiency (%)	Not less than 1.5%	2.9	2.8	2.6	2.9	3.3	3.2	3.0	2.9
4	%Elongation at break	Not less than 25%	28	29	31	34	29	30	31	30
5	Surface pH	6.2 - 7.0	6.01	6.14	6.12	6.78	6.42	6.23	7.71	6.5
6	Folding endurance	Not less than 250	186	190	195	204	212	201	204	205
7	Swelling Index	% weight increase (60 min)	182	185	188	191	184	183	187	186
		% area increase (90 min)	61	72	69	75	79	82	85	73
8	Mucoadhesive Strength	30-50	39.25 ±0.23	37.42 ±0.41	37.23 ±0.24	34.67 ±0.71	41.21 ±0.62	37.36 ±0.52	39.34 ±0.38	35.27 ±0.21
9	Mucoadhesive time	Above 180 min	231±1 5.21	222±2 9.32	210±1 4.11	224±3 2.39	239±2 6.67	228±1 9.21	238±2 5.21	218±1 1.42
11	Drug Content	Above 75%	79%	82%	92%	94%	85%	81%	79%	84%

Table 3. In-vitro drug release kinetics of various formulations through cellophane membrane

Formulations	R^2 values					
	Cellophane Membrane			Sheep Buccal Mucosa		
	Zero order	First order	Higuchi	Zero order	First order	Higuchi
F1	0.922	0.945	0.952	0.948	0.935	0.945
F2	0.935	0.921	0.945	0.952	0.945	0.921
F3	0.945	0.915	0.921	0.958	0.967	0.951
F4*	0.976	0.971	0.961	0.968	0.971	0.971
F5	0.928	0.951	0.924	0.945	0.952	0.945
F6	0.953	0.932	0.912	0.954	0.915	0.942
F7	0.915	0.921	0.951	0.947	0.941	0.915
F8	0.921	0.955	0.923	0.942	0.961	0.935

Fig 1. Drug release study was performed for various mucoadhesive patch formulation



CONCLUSION

On the basis of above studies patch formulation F4 comprises of gelatin 4.5 %, poly sodium CMC 5.5%, Propylene glycol 5%, Poly vinyl Alcohol for stability drug release, folding endurance and mucoadhesive time. Good results obtained for both in vitro and in vivo studies for Celecoxib patches. The buccal release of Celecoxib from patches in healthy human beings and rabbits showed a significant improvement. The results can be extrapolated to the human beings as the structure and permeability of buccal membrane of rabbits is similar to that of human beings. Hence, the development of bioadhesive buccal formulations for Celecoxib may be a promising one as the dose of Celecoxib may be decreased and hence side effects may be reduced.

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