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Formulation and Evaluation of Flurbiprofen Buccal Patches for Ostioarthritis

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ABSTRACTS:
The main objective of the present study was to improve the bioavailability of Flurbiprofen and decrease the frequency of dosage form administration by mucoadhesive drug delivery system. Flurbiprofen is an NSAIDS belonging to the class non selective cox-2 inhibitor, well known to cause gastrointestinal disorders and renal effects when given orally. A buccal patch for systemic administration of Flurbiprofen in oral cavity were developed using polymers chitosan, sodium alginate, Gelatin, in order to deliver the drug to the particular region of the body for extended period of time, maximizing the drug availability, minimize the adverse effects, avoiding the first pass metabolism and thereby improving patient compliance. The formulated patches were evaluated for Mass uniformity and thickness uniformity, folding endurance, Drug content uniformity, Measurement of surface pH, Swelling index, Tensile strength, bioadhesion test, In vitro residence time, In vitro membrane permeation studies. Drug polymer compatibility studies were carried out by FTIR. & shows drug is compatible with polymers. The in vitro drug releases and in-vitro drug permeation studies showed that drug was released from the patches and permeated through the porcine buccal mucosa and hence the formulated buccal patches possibly permeate through the human buccal membrane also.

Keywords: Flurbiprofen, Gelatin, sodium alginate, Chitosan, gum patches, Mucoadhesive drug delivery.

I. INTRODUCTION:

Flurbiprofen is a NSAIDs belonging to the class of non selective cox-2 inhibitors, shown to possess marked anti-inflammatory, analgesic and antipyretic activity. NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. It is used to relieve the pain which is associated with the headache, muscle aches, tendonitis, dental pain, menstrual cramps, metastatic bone pain, and post operative pain. [(1)] It is also used to reduce the pain, swelling, joint stiffness, caused by gout and arthritis attacks. NSAIDS are well known to cause the gastrointestinal disorders and renal effects when administered by oral route. However these effects are dose-dependent and in many cases sever enough to cause the risk of ulcer proliferation, upper gastrointestinal bleeding and death. [(2)] It is highly (99%) bound to plasma protein. Its absorption from upper gastrointestinal tract is interfered with food and alkali such as magnesium oxide and aluminum hydroxide. Flurbiprofen half life is 10 to 13 hours. About 95% of a given dose of Flurbiprofen is excreted in the urine as such or as the conjugated product. The main reason behind the administration of $NSAID_s$ by oral route was poor bioavailability due to first pass metabolism and enzymatic degradation in the gut wall; also they cause the gastrointestinal disorders and renal effects. Intravenous administration is very painful and difficult to administer in geriatric and unconscious patient. [(2,3,4)]

The work on mucoadhesive gum patch containing Flurbiprofen using Chitosan, gelatin, sodium alginate a non-toxic, biocompatible and biodegradable polymer yet not found. The NDDS is the only areas in which necessary changes and improvements are have been made. Oral mucosal drug delivery is an alternative method of drug delivery system that offers the advantages as compared to oral as well as Parenterals. Alternative to oral route, administration of drug through mucosal route offer many benefits like non invasive administration, enhanced bioavailability, avoiding first pass effect, reduce the amount of dose and lower the dose dependent side effects and having quick onset of action as compared to oral route. [(4)] Oral cavity is a target to deliver the drug at a predetermined rate for an extended period of time.

II. MATERIALS AND METHODS:

Flurbiprofen was purchased from Divi's lab Pvt. Ltd. Hyderabad. Gelatin and sodium

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alginate were purchased from S.D. Fine Chemicals Ltd; Mumbai. Chitosan was purchased from Indian sea foods, Cochin; Glycerin was purchased from Ranbaxy Laboratories Ltd. Punjab. Formaldehyde was purchased from Loba Chemicals Mumbai. All other chemicals used were of analytical grade.

Methods of Formulation of Flurbiprofen mucoadhesive buccal patches:

Mucoadhesive buccal patches containing Flurbiprofen were prepared by using following method.

Weighed quantity of gelatin & sodium alginate were sprinkled on the surface of the water in a beaker and stirred well to avoid formation of lumps and allowed to hydrate for 15 minutes. Rehydrated Chitosan was added to above gelatin solution stirred it well, Now Glycerin as plasticizing agent was added and heated over a water bath at 60^0C until gelatin dissolves [5,6]. In other beaker Flurbiprofen was dissolved in the little quantity of methanol and this solution is dissolved in the above gelatin solution, sodium saccharin was added to the above solution, prepared mixture of drug & polymer was poured in to a glass Petri dishes (10cmx10cm) to a 1mm height and allowed to gel for 30 minutes by placing the Petri dishes in ice cooled water and dried at room temperature for 72 hours [7]. After drying the patches were cut into 20mm size. (Table no.1)

Evaluation of patches:

Appearance: The formulated mucoadhesive buccal patches were noted visually for flexibility and its sticky nature. (9)

Mass uniformity: For evaluation of weight of the formulated patches, randomly three patches of each formulation were individually weighed on a digital balance, then the mean weight is calculated for each formulation. (10)

Thickness uniformity: Three patches of each formulation where selected for measurement of thickness using a micrometer screw gauge at three different places. (11)

Folding endurance:

The folding endurance of randomly selected patches (without backing membrane) was determined by repeatedly folding one patch at the same place till it break or folded maximum 250 times. [18]

Drug content uniformity:

Flurbiprofen buccal patches are allowed dissolve in 100 mL of simulated saliva pH (6.2), under occasional shaking for 3 hrs, solution was filtered, and suitably diluted. The amount of patch was determined by using UV spectrometer (Shimadzu 1800, Japan) at 272nm. [19]

Measurement of surface pH:

Buccal patches were placed on the surface of agar plate (the agar plate is prepared by dissolving agar 2% w / v in warmed phosphate buffer pH 6.2 under stirring then poured to Petri dish to solidify at room temperature) allow to swell for some time. The surface pH is measured bringing a pH paper in contact with surface of the patch and allow to equilibrate for 1 min as per the reported method. Averages of three readings are recorded. [20]

Swelling studies:

The weight of the patch, without backing membrane was determined by digital electronic weighing balance. Patches are placed on the surface of an agar plate and allowed to swell by keeping it an incubator at 37 ºC and the diameter is measured at predetermined time intervals for 90 minutes. Swelling index was calculated from following equation. Swelling index = (W2- W1 / W1) ×100 Where SI (%) is percent swelling, W2 is the swollen patch weight, W1 is the initial weight of the patch. [21]

Tensile strength:

A tensile strength means the resistance of a material to a force which tends to tear it apart and it is the maximum stress in stress strain curve. The tensile strength study was done by using a rectangular frame with two plates made up of Plexiglas's [22,23]. The one plate is in front and is movable part of device and can be pulled by loading weights on the string, which is connected to movable part. The formulated 1x1 cm2 buccal patch equivalent to 50 mg drug from each batch was fixed between the two plate i.e. one is movable and other is stationary plate. The force required to rupture the film was determined by measuring the total weight loaded in the string and the equation as: Tensile strength (TS). TS (g/cm^2) = Force at break (g) / Initial cross sectional area of patch. The weight corresponds to break the patches were taken as tensile strength and the values were shown in table3. [3,23,]

Determination of In vitro residence time:

The in vitro residence time of buccal patch were evaluated by accessing the time required for the buccal patch to detach from buccal mucosa in a stirred beaker which is filled with 500 ml phosphate buffer pH 6.8 at 37^0c. The buccal

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mucosal membrane was fixed on the side of beaker with the help of adhesive cynoacrylate glue. The buccal patch attached to the membrane by applying a force by the finger tip for 60sec. the beaker then stirred at an 150 rpm to stimulate the movement of buccal and saliva. The time which is required for complete separation of the buccal patch from mucosal membrane was taken as an indication of in vivo adhesion time. [2,3,24,]

Measurement of mucoadhesive strength:

In vitro mucoadhesion of formulated buccal patch to detach from goat buccal mucosa in a stirred beaker filled with 500 ml phosphate buffer pH 6.8 at 37°c. the buccal mucosal membrane was fixed on the side of the beaker with the adhesive cyanoa crylate glue. The buccal patch attached to membrane by applying force by the finger tip for 60s. the beaker then stirred at an 150 rpm to stimulate buccal and saliva movement. The time which is required for complete separation of the buccal patch from mucosal membrane was taken as an indication of in vitro adhesion time.[3,25,]

In vitro release study:

For the determination of in- vitro residence time modified USP disintegration apparatus (Electrolab ED-2L) were used. The medium was composed of 500 ml simulated saliva pH 6.2 at 37±5°c stirred at 50 rpm. The buccal patch of appropriate size was fixed to the square shaped glass disk by using the cyanoacrylate and placed in a beaker containing dissolution medium. 2 ML of samples are withdrawn at predetermined intervals of 240 min and same volume replaced with fresh solution. The collected samples are filtered through 0.45 um filter paper and suitable dilution was made and the amount of drug release was made and the amount of drug release is assayed by UV spectrophotometer. (shimadzu, 1800 Japan) [4,26,]

Ex vivo buccal permeation study:

The buccal permeation test was performed for optimized batch only. For this study porcine buccal mucosa was selected because the non - keratinized buccal mucosa similar to the human and it is inexpensive. The removed buccal epithelium was used within two hour after removal. [27] The glass modified two chambered diffusion cell was used to permeation studies, it consists of two compartments, one is donor compartment and another is receptor compartment of 25 ml capacity.[28] the upper compartments lower side was closely tied membrane of goat was kept at 34°c. The buccal mucosa was placed in saline solution in order to prevent the damage to the cells. The appropriate size of patch was cut down and fixed in between and lower surface of the diffusion cells. The mouth of receptor compartment was fixed with donor compartment having 1 ml capacity. the lower chamber of apparatus had small volume compartment i.e about 60 ml and the liquid was stirring with the help of needle (steel coated) at 100rpm. The 1 ml of sample was withdrawn at predetermined intervals and replaced with fresh buffer solution and assayed by using UV spectrophotometer. (Shimadzu 1800 Japan).[27,]

Free formaldehyde test:

Test for Free Formaldehyde to ascertain the absence of free formaldehyde, the buccal patches were subjected to pharmacopoeia test for free formaldehyde. During the test the color of 1ml of 1 in 10 dilutions of patches were compared with the color of 1ml of standard formaldehyde solution. (IP, 1985) [29]

To 1ml of 1 in 10 dilution preparation to be examined in a test-tube, 4ml of water and 5ml of acetyl acetone solution were added. The tube was placed in a water bath at 400 C for 40 minutes. The solution was not intensely colored than a reference solution prepared at the same time and in the same manner using 1ml of standard formaldehyde solution in place of the dilution of the preparation being examined. The comparison should be made by examining the tubes down their vertical axis.[30]

Stability study:

The stability study of mucoadhesive patches for all five Formulations were performed at 40 °C 37 ±5°C & 75±5% RH for three months. The value of all parameter after three months remain same as their values and minor changes occur in value of volume entrapment efficiency,% elongation & %drug release after 8 hour which was considerable.[30]

III. RESULT AND DISCUSSIONS:

The thickness of formulated batches was ranges from0.29± 0.002 to 0.42± 0.002mm. While the average weight of patch from each batch ranges from 96± 4.8 to 100 ± 8.9. The surface pH of patch as per the reported was ranges from 5.9 to 6.3 were found at neutral pH. Physical

Appearance and flexibility were noted visually. Weight uniformity for each formulations F1,F2,F3, F4, F4 &F5 is 100±5.1, 100±8.9, 98±5.0, 96±4.8, 97±9.3 respectively. Folding indurance time for each formulations F1,F2,F3,F4,F4 & F5 is130, 180, 197, 192, 125 respectively. Drug

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content , for each formulations F1,F2,F3,F4,F4 & F5 is100.4±0.3, 99.8±0.1, 98.7±0.6, 99.9±0.8, 100.3±0.9 respectively. Appearance is quit same, for all formulations is opaque, non sticky & flexible. Swelling index of selected Flurbiprofen buccal patches from all formulations for 30 min that is for F1, ,F2 , F3, F4, F4 & F5 is 120±8, 115±5, 105±3, 110±2, 103±6 , respectively. In-Vitro release studies of buccal patches for F1 shows up to 180min. released up to 99.36 %, F2 shows up to 160min. released up to 98.21 %, F3shows up to 390 min. released up to 93.96 %., F4 shows up to 180min. released up to 99.11 %,. F5 shows up to 360min. released up to 99.85 %, overall Formulation F3 shows better prolongation of drug release up to 390 min. which contains 90 % of Gelatin & 10% of Chitosan. Formaldehyde vapours are passed for different time intervals like 1 min, 2 min,& 3 min which helps in prolongation of drug release , free formaldehyde test is performed by air drying buccal patches for 72 hrs & avoiding corrosive effect patches are compared with std formaldehyde solution. Stability test is performed at 40^{o}C 37 ±5^{0}C & 75±5% RH for three months that indicates minor changes in drug release. Ex vivo buccal permeation study is performed by using porcine buccal mucosa and assayed by using UV spectrophotometer.

IV. CONCLUSION:

A new mucoadhesive patches for improvements of bioavailability of Flurbiprofen was developed by Chitosan and gelatin in appropriate ratio used for various chronic diseases. Long term oral administration of such an NSAIDS for chronic diseases causes tissue localization which is very dangerous to a particular organ. A film forming and bioadhesion property of Chitosan with drug plays an important role in mucoadhesive patches. From overall study we can conclude that Chitosan with gelatin and sodium alginate meet the ideal requirements for buccal patches which is a good way to prevent first pass hepatic metabolism and improved bioavailability as compared to oral dosage form with no any adverse effects.

Prepared buccal patches are essential in future aspects for post operative surgical care as well in Rheumatic disorders.

Table no.1

Formula for preparation of Flurbiprofen buccal patches:

Formulation	Drug mgs	Chitosan Pectin Ratio	Chitosan gms	Pectin gms	PVP K-30 mg	Sodium alginate gms	Propylene Glycol
F_1	100	1:1	50	50	0.5	0.5	1 ml
F_2	100	1:2	50	100	0.5	0.5	1ml
F_3	100	2:1	100	50	0.5	1	1 ml
F_4	100	3:1	150	50	0.5	1.5	1ml
F_5	100	2:2	100	100	0.5	1.5	1 ml

Table no.2

Cross liking with formaldehyde:

Formulation	Time in min.		
F_1	1	2	3
F_2	1	2	3
F_3	1	2	3
F_4	1	2	3
F_5	1	2	3

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Table no.3

Evaluation of buccal patches containing Flurbiprofen:

formulation codes	Weight Uniformity	Film Thickness mm	Folding endurance Times	Surface pH	Drug Content	Appearance
F_1	100±5.1	0.39±0.008	130	5.9	100.4±0.3	Opaque, non sticky & flexible.
F_2	100±8.9	0.35±0.002	180	6.1	99.8±0.1	Opaque, non sticky & flexible
F_3	98±5.0	0.42±0.002	197	6.3	98.7±0.6	Opaque, non sticky & flexible.
F_4	96±4.8	0.31±0.006	192	6.0	99.9±0.8	Opaque, non sticky & flexible.
F_5	97±9.3	0.29±0.002	125	6.1	100.3±0.9	Opaque, non sticky & flexible.

Table no.4

Swelling index of selected Flurbiprofen buccal patches:

Time in min.	Swelling Index				
	F_1	F_2	F_3	F_4	F_5
5	63±6	60±3	69±4	66±8	61±1
10	81±6	80±3	79±4	76±8	81±8
15	81±6	80±3	79±4	76±8	81±8
20	100±8	99±5	96±3	93±2	98±6
30	120±8	115±5	105±3	110±2	103±6

Table no.5

Time in min	F_1	F_2	F_3	F_4	F_5
0.5	7.99	8.38	5.13	4.61	6.49
1	18.12	20.31	17.17	16.04	18.41
1.5	36.31	33.26	33.01	63.36	32.63
2	41.06	42.69	48.34	71.28	54.63
2.5	53.77	62.36	67.46	82.18	64.38
3	62.01	69.12	68.14	84.54	76.1
3.5	76.96	79.32	70.17	87.39	84.07
4	89.31	84.21	79.96	96.48	88.19
4.5	93.36	92.33	81.31	99.11	90.61
5		96.61	84.06		94.19

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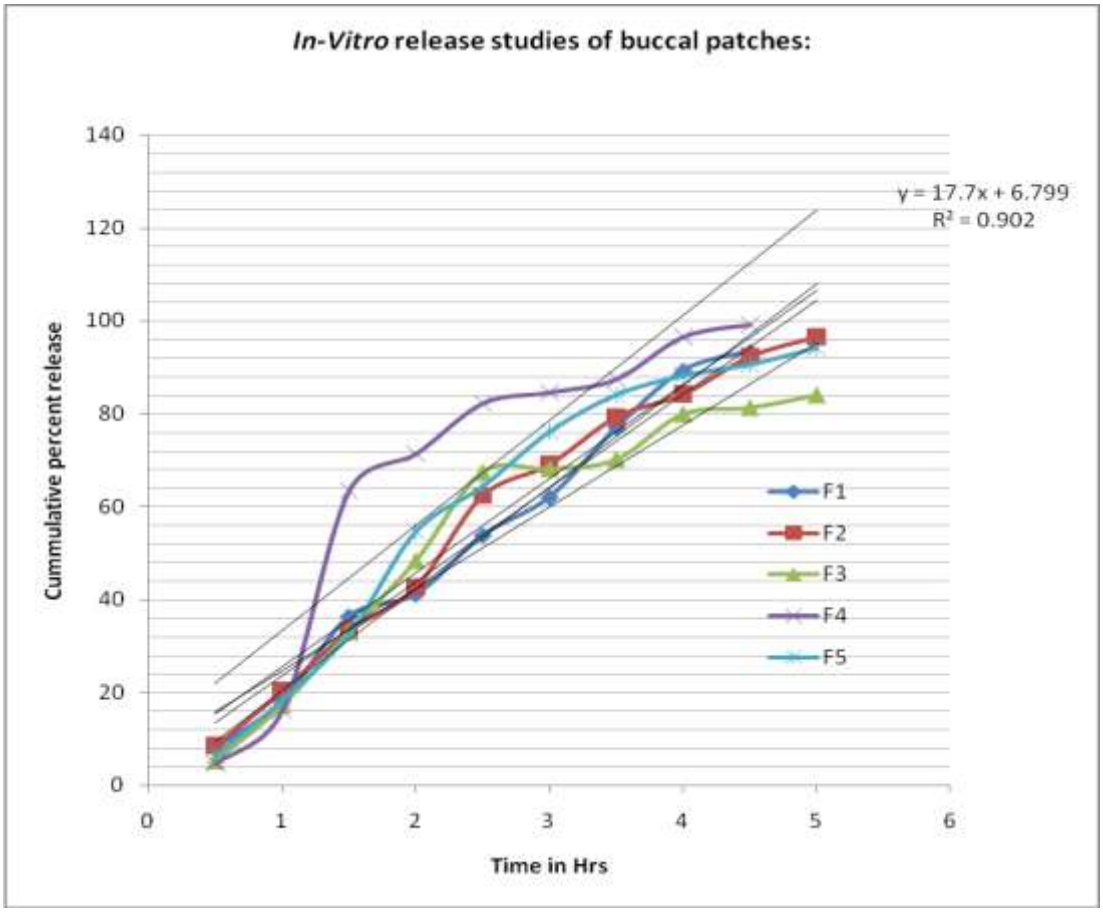

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