International Journal of Pharmacy and Pharmaceutical Sciences
ISSN- 0975-1491 Vol 2, Suppl 3, 2010

Research Article

DESIGN AND *IN VITRO* EVALUATION OF MUCOADHESIVE BUCCAL FILMS CONTAINING FAMOTIDINE

MANISH KUMAR*, GARIMA GARG, PUSHPENDRA KUMAR, G.T. KULKARNI, ARUN KUMAR

NKBR College of Pharmacy and research centre, Meerut, U.P. Email:manish_singh17@rediffmail.com

Received: 30 March 2010, Revised and Accepted: 20 April 2010

ABSTRACT

The buccal region offers an attractive route of administration for systemic drug delivery. A buccal patch for systemic administration of famotidine in the oral cavity has been developed using hydroxypropylmethylcellulose, sodium carboxymethylcellulose (SCMC) and polyvinyl alcohol by solvent casting method. The physicochemical interactions between and polymers were investigated by Fourier transform infrared (FTIR) Spectroscopy. According to FTIR the drug did not show any evidence of an interaction with the polymers used and was present in an unchanged state. The patches were evaluated for their physical characteristics like weight variation, thickness, drug content uniformity, surface pH, folding endurance, tensile strength, mucoadhesion strength, *In vitro* release studies were conducted for famotidine patches in phosphate buffer (pH, 6.6) solution. Patches exhibited drug release in the range of 72.58 to 91.91% in 20 min.

Keywords: Famotidine, Buccal patches, *In vitro* release, Evaluation.

INTRODUCTION

Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs. The mucosa is relatively permeable with a rich blood supply. The oral transmucosal drug delivery bypasses liver and avoids pre-systemic elimination in the GI tract and liver (Edith *et al.,* 1999). These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery. A few drugs, such as buprenorphine (Guo, 1994), propranolol (Coutel, 1992), salbutamol sulphate (Pavankumar *et al.,* 2005), diclofenac sodium (Patil and Rao, 2003), flurbiprofen (Barsuhn *et al.,* 1988), and fexofenadine (Thimmasetty *et al.,* 2007) have been successfully administered via the buccal route.

Famotine is a histamine H_2-receptor antagonist (also called H_2-blocker) which decreases the amount of acid produced by the stomach and is used to treat gastric and duodenal ulcers by blocking the H2 subtype of histamine receptors. The prescribed dose of the drug[26] should be low. Any drug with a daily requirement of 40g or less would be a candidate suitable for buccal delivery. Though the prescribed dose of famotidine is 20 mg twice daily, selected dose for film formulation is 10 mg. Therefore, it is possible for the drug to get absorbed in a short time. It is available in the form of tablets and parenteral. The bioavailability of the drug should be low or variable The F value of famotidine is about 40-45 %. Therefore, this drug is suitable for buccal absorption. The pK_a of the drug should be greater than 2 for an acid and less than 10 for a base. From the above points, it is clear that famotidine is suitable drug for buccal absorption and may provide a better therapeutic profile than that of the oral route.

MATERIALS AND METHODS

Famotidine was a gift sample (Dr. Reddy's Labs, Hyderabad, India), Hydroxypropylmethylcellulose (47 centipoise) (HPMC), sodium carboxy methyl cellulose (NaCMC) and polyvinyl alcohol were obtained from Cadila Health Care Ltd., (Ahmedabad, India) and other chemicals used were of analytical grade and procured from S.D. Fine Chemicals (Mumbai, India). Concentrations of famotidine were measured with a UV VIS spectrometer (UV-1700, Shimadzu Corporation, Tokyo, Japan). Interaction between Famotidine and polymers was verified using FTIR and UV-VIS spectrometric methods.

Preparation of buccal mucoadhesive films[2, 23]

The solvent evaporation method was followed in this study for preparation of films. About 10 films of different composition of polymer were prepared. The films were observed for dispersion of drug, flexibility, and glossy structure. Based on these observations, four formulations were selected and used for further analysis. The composition of four films was given in Table 1.

Buccal mucoadhesive films were prepared using polymer or polymer blends along with the drug and a suitable solvent.

For preparing film 1, The buccal mucoadhesive films of Famotidine were prepared using hydroxypropylmethylcellulose (HPMC 15 cps) polymer by solvent evaporation method. 500 mg of HPMC polymer was weighed accurately and dissolved in 15 ml of ethanol. The beaker-containing polymer was kept aside for 5 min for swelling of polymer. 10 mg of famotidine was weighed and dissolved in 5 ml of ethanol. Further 10 ml of ethanol was added to the above polymer solution and stirred the dispersion. Then one drop of (0.0294 g) glycerin was added to the polymer solution. The drug solution was added to the polymer solution. The whole solution was mixed thoroughly with the help of a magnetic stirrer. The glass mould of size 9×9 cm^2 was placed over a flat surface. The whole solution was poured into the glass mould. The mould was kept for 24 h at room temperature for drying. After this period, the film was removed from the mould and preserved in butter paper and in a desicator. Similarly films 2, 3, and film 4 were prepared.

For preparing film 2 and 3, SCMC was dissolved in 15 ml water and HPMC was dissolved in 10 ml alcohol separately, and kept for drying 24 h. The two polymeric solutions were mixed.

For preparing film 4 polyvinyl alcohol was placed in 25 ml of water, and stirred for 20 min. The moulds were kept 24 hours for drying of films for formulations 1, 2, 3, and 4.

Table 1: Preliminary batches of blank films and with drug

Ingredient	Film 1	Film 2	Film 3	Film 4
Famotidine	10 mg	10 mg	10 mg	10 mg
HPMC	500 mg	250 mg	500 mg	-
SCMC	-	250 mg	250 mg	-
PVA	-	-	-	500 mg
Glycerin	0.213 mg	0.213 mg	0.213 mg	0.213 mg
Ethanol	15 ml	15 ml	15 ml	-
Water	15 ml	15 ml	15 ml	30 ml

Table 2: Characteristics of buccal mucoadhesive patches containing famotidine

Film code	TN (mg)	WU (mg)	Swelling	TS (kg)		C U	FE
			% weight increase after 30 min	Dummy patches	Drug loaded patches		
F1	0.181	21.03	159.66	4.645	5.011	93.80	>300
F2	0.116	17.10	132.13	2.235	2.578	92.10	>300
F3	0.144	19.33	131.66	6.983	7.813	94.00	>300
F4	0.181	15.46	128.83	8.143	8.527	88.00	>300

EVALUATION OF PRELIMINARY BATCHES

Physical Characteristics Study: Films were evaluated for the physical characteristics of dosage forms.

Film weight and thickness[20]

The weight of each film (1x1 cm^2) was measured using digital balance from different positions of the film and the average was calculated. Similarly the thickness of each film was measured using thickness tester at different positions of the film and the average was calculated.

Swelling behavior[12]

The prepared films were placed in a petri dish and 0.1 ml of the artificial saliva (2.38 g Na_2HPO_4 $2H_2O$, 0.19 g KH_2PO_4, and 8.0 g NaCl per liter pH6.2) was added to the surface of the polymeric film at a specific time interval (5, 10, 15, 30, 60 min.) using a micropipette. Samples were incubated in a decicator at room temperature. The wetted films were removed at each observation point at time interval of 5, 10, 15, 30, 60 min., when the films surface was gently dried using blotting paper and reweighed again. For each observation pointed. The test was repeated three times. The hydration percentages of the wet polymeric films were calculated according following equation.

$$\text{Hydration \%} = \frac{(WH - WD)}{WD \times 100}$$

Where,

WH = Weighed of the hydrated

WD = Dried polymeric films.

Surface pH of the Famotidine films[20]

The buccal patches were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2% (m/v) agar in warmed isotonic phosphate buffer of pH 6.2 under stirring and then pouring the solution into a petri dish till gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen patch. The mean of two observations was calculated.

Folding endurance[9]

The folding endurance of the films was determined by repeatedly folding one film at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. The mean value of three observations and standard deviation was calculated.

Tensile strength of the films[2, 42]

Tensile strength of the film is total weight, which is necessary to break or rupture the films and this was done by a device has rectangular frame with two plates made up of Plexiglas .The one plate is in the front and is the movable part of the device and can be pulled by loading weights on the string, which is connected to the movable part. The testing procedure was performed; the 1x1cm^2 films were fixed between the stationary and movable plate. The force needed to fracture the films was determined by measuring the total weight loaded in the string.

TS=breaking load (N) /cross sectional area of the film

Drug Content Uniformity of Films[2]

A film of size 1 × 1 cm was cut and placed in a beaker. 10 ml of phosphate buffer solution (pH 6.2) was placed. The contents were stirred in magnetic stirrer to dissolve the film. The contents were transferred to a volumetric flask (10 ml). The absorbance of the solution was measured against the corresponding blank solution at 268.5 nm. A blank solution was prepared in a similar manner by using a blank polymer film. The experiments were carried out in triplicate and average value was calculated.

***In Vitro* Release Studies of Famotidine Films in Phosphate Buffer (pH 6.2)**[14, 36]

A film of 1 x 1 cm^2 size was cut and attached to a glass slide with a few drops of phosphate buffer (pH 6.2). This slide was kept at an angle of 45° in a 250 ml beaker containing 100 ml of phosphate buffer pH 6.2 solutions. The beaker was kept in circulating water bath in which the temperature was maintained at 37°C. A non-agitated system was selected to eliminate any effect of turbulence on the release rate. Samples were withdrawn periodically after removing the slide from the beaker. The solution was stirred with a glass rod and 5 ml of sample was withdrawn using a graduated pipette, whose tip was attached to a tube with glass wool (as a filter). The slide was quickly reintroduced into the beaker. 5 ml of the buffer was replaced immediately and the beaker was kept covered with a Petri dish to prevent evaporation of the fluid. The samples were taken at 2, 4, 8, 12, 16, 20 min predetermined intervals and analyzed for drug content at 268.5 nm. The release studies were conducted for three times and average was determined.

***In Vivo* of Famotidine Film Test on Human Volunteers**[12]

All the films were subjected for *in vivo* patch test on three human volunteer. A film of 1 x 1 cm^2 containing 10 mg of famotidine was cut and before application of the patch the human volunteers were asked to rinse their mouth thoroughly with water. The patches were applied to the buccal mucosa of human volunteers for 20 min. After that, the films were taken out and added to a beaker containing 10 ml of solution. The subjects were directed to rinse their mouth with 10 ml of distilled water. The washing was added to the previous solution. This solution was completely transferred in to a 100 ml volumetric flask and volume was made up with solution. After appropriate dilution, solutions were analyzed for drug content at 268.5 nm. Time of mucoadhesive, possible irritation, loss of fragmentation, bad taste, dry mouth were evaluated in order to study the drug influence on the *in vivo* film behavior. The results represent the amount of drug remaining unabsorbed.

***In Vitro* Bioadhesive Test**[17]

In vitro bioadhesive test of the prepared films was examined using chicken pouch as a model mucosal membrane. The tissue was obtained from chicken after slaughter, removed from its contents and surface fats and stored frozen in simulated artificial saliva solution. It has thawed to room temperature before study. A rectangular piece of the tissue was cut and glued with adhesive on the ground surface of the two tissue holders made of Plexiglas. One centimeter of the buccal film was placed between the two tissue surfaces and put in contacts with each other with uniform and constant light pressure between fingers for one minute to facilitate adhesive bonding. The upper tissue holder was allowed to hang on an iron stand with the help of an aluminum wire fastened with a hook provided on the back of the holder. A pre-weighed light weight

polyethylene bag was attached to the hook on the back of the lower tissue holder with aluminum wire. After pre-load time of one minute, water was added to the polyethylene bag through an intravenous infusion set at a rate of 2.0 drops per seconds until the lower tissue detached due to the heavy weight of the water infused. The water collected in the bag was measured and expressed as weight (gram force) required for the detachment, using the following equation:

Detachment stress (dyne/ cm^2) = (m*g/A)

Where m is the weight of the water infused at detachment, g the acceleration due to gravity considered as 980 cm/s^2 , and A the area of tissue exposed (cm^2).

Fig. 1: Modified balance method

RESULTS AND DISCUSSION

Drug estimation

Calibration curves of famotidine in phosphate buffer (pH 6.6) solutions were obtained at λ_{max} 268.5 nm with a UV-VIS spectrometer (UV-1700, Shimadzu Corporation, Tokyo, Japan). Beer's law obeyed to construct the calibration curve was in the concentration range of 5-50 µg/ml. Analyses were done in triplicate.

Drug-polymer compatibility

IR spectra of famotidine alone and its combination with polymers are shown in figure 1. An IR spectrum of pure famotidine showed the peaks 3400 cm–1 (N-H, str), 1540 cm–1 (C-CH_2, str,), These peaks can be considered as characteristic peaks of famotidine and were not affected and prominently observed in IR spectra of famotidine along with polymers as shown in the figure 1, indicated no interaction between famotidine and polymers. Further, the interference was also verified using UV spectrometric method.

Preparation of the patches

The patches of HPMC (15 cps) were prepared. Further different copolymers like Sodium carboxy methyl cellulose was added to HPMC. Addition of the plasticizer produced a patch of good strength. Maximum drug (%) was released from HPMC patches in 90 min. Sodium carboxy methyl cellulose was found to possess less bioadhesion compared to HPMC. By trial methods 1g of HPMC (film I) and was considered to be a right candidate. The patches were translucent and visually smooth surfaced.

Folding endurance: Films did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point. Folding endurance did not vary when the comparision was made between plain films and drug loaded films.

Weight uniformity: Drug loaded patches (1 x 1 cm2) were tested for uniformity of weight. The patches were found uniform. The average weight of the patch found was about 18.23 mg.

Content uniformity: The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 88.00 to 94.00 %.

Swelling studies: The swelling of the patches were observed in phosphate buffer solution (pH 6.6) and shown in table 2. Swelling was more pronounced in film 1 and 3 which contains HPMC: SCMC (2:1) respectively. The Famotidine film was containing HPMC showed higher percent swelling because of its higher swelling index. The addition of water–insoluble famotidine increased the water uptake of the films. This was possible due to micronized famotidine particles which exist between the HPMC chain allowing each chain to hydrate freely, resulting in weak hydrogen bonding area around the famotidine molecules. These results were in agreement with the increase in area due to swelling.

Tensile strength: The tensile strengths of drug-loaded patches were higher than dummy patches (table 2). This is justified because dissolved famotidine strengthened the bonding of polymer chains. The tensile strengths of patches were in the order of I > VI > III > II. This indicates among all the films studied film I showed highest tensile strength and patch film II showed lowest tensile strength. This must be due to the hydrogen bonding between alcohol groups of drug and polymer.

Surface pH: The surface pH of all formulations was within + 0.5 units of the neutral pH and hence no mucosal irritation was expected and ultimately achieve patient compliance.

***In vitro* release:** The release data of famotidine from all the patches are given in figure 2. The release of Famotidine may follow the mechanisms such as diffusion controlled, dissolution controlled or a combination *In vitro* of both. The release data of famotidine was given in Tables19, respectively for films 1, 2, 3 and 4. A perusal to Table 19 and Figure 20 indicated that the drug release was higher in HPMC (film 1) and HPMC: SCMC (2:1) (film 3). The increased HPMC concentration in the film would enhance hydration and channel formation leading the enhanced release of Famotidine from the films. During the dissolution HPMC containing film swelled forming a gel layer on the exposed films surfaces. The loosely bound HPMC molecules in these films were readily eroded, allowing the easy release of Famotidine as compared to SCMC and PVA. The concluded that the HPMC along combination (HPMC: SCMC) (2:1) showed good swelling, as well as uniform drug release pattern.

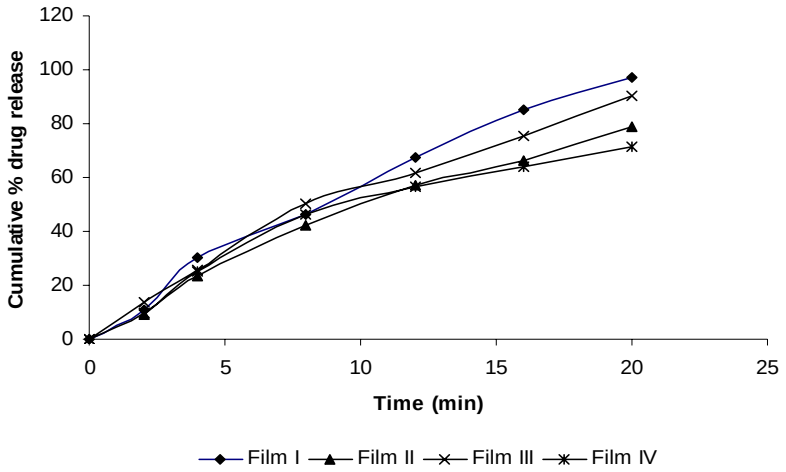

Fig. 2: *In vitro* release of famotidine from buccal mucoadhesive patches I to IV

Buccal absorption test on human volunteers

The buccal absorption test was suggested as an *in vivo* model for passive drug transfer through a lipid membrane. The absorption of drugs increases linearly with the time of contact of the drug solution with the buccal membrane. It was found that a rapid absorption of drug takes place upto 5 min. buccal absorption test revealed the satisfactory amount (35.23 + 2.311 %) of drug absorption. Higher absorption could be possible, with the increased contact time. Absorption of drugs is dependent on the concentration gradient (Michael, 1996) and therefore, it may be possible to increase the amount of absorption by increasing the dose of the drug administered. These results encouraged the designing of buccal adhesive patches of famotidine.

***In Vitro* Bioadhesive Test of the Famotidine Films:** The bioadhesive property of prepared films was measured with the help of modified balance method. The results were given in Table 21. The bioadhesive properties of film III and IV is slightly high. The mucoadhesive force follows: F3> F1> F2> F4.

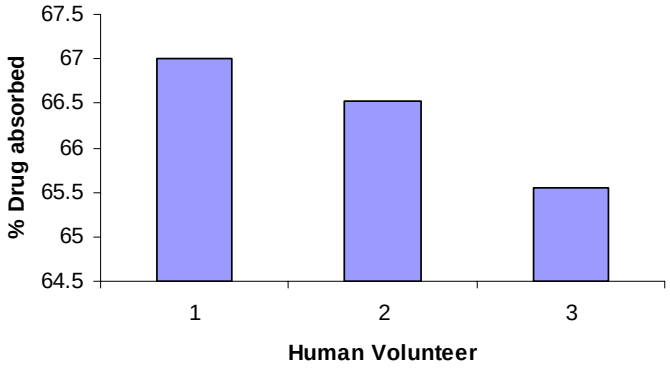

Fig. 3: Buccal absorption test in human volunteers

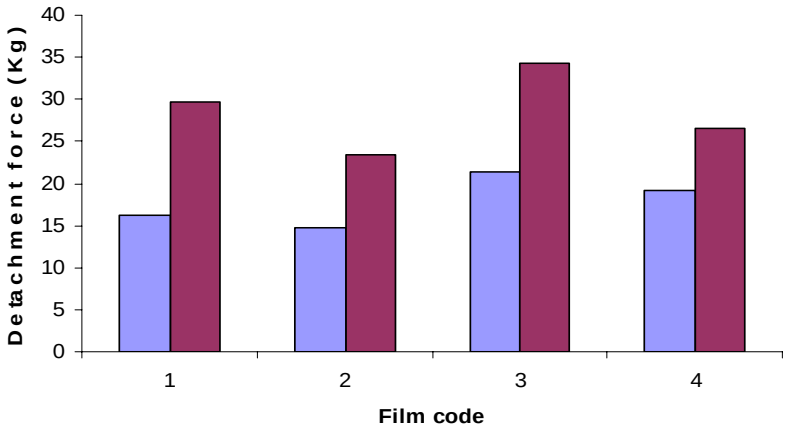

Fig. 4: Detachment force of film determined using modified balance method for the blank and drug loaded films

The use of HPMC and SCMC was found to increase the bioadhesive property of buccal films. As a result mucoadhesive was enhanced since the films contained higher amount of HPMC and SCMC. The HPMC and SCMC were showed to produce membrane with higher modulus of elasticity and Mucoadhesive interaction may results from hydrogen bonding or other types of bonding made possible by the hydrophilic nature of both polymers. It was observed that in comparision of Famotidine in the film increases the bioadhesive of the film as compared to blank film.

CONCLUSION

Good results were obtained both *in vitro* and *in vivo* conditions for famotidine films. The buccal release of famotidine 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 famotidine may be a promising one as the dose of famotidine may be decreased and hence side effects may be reduced.

REFERENCES

1. Anders R and Merkle HP (1989). Evaluation of laminated mucoadhesive patches for buccal drug delivery. *Int. J. Pharm.,* 34: 498-502.
2. Balamurugan K, Pandit JK, Choudary PK and Balasubramaniam J (2001). Systemic absorption of propranolol hydrochloride from buccoadhesive films. *Ind. J. Pharm. Sci*., 63: 473-480.
3. Barsuhn CL, Planoff LS, Gleason DD, Adkins EL and Ho NFH (1988). Human buccal absorption of flurbiprofen. *Clin. Pharmacol. Ther.*, 44: 225-231.
4. Beckett AH and Triggs EJ (1967). Buccal absorption of basic drugs and its application as an *in vivo* model of passive drug transfer through lipid membranes. *J. Pharm. Pharmacol.*, 19: 31s-41s.
5. Borodkin S and Tucker FE (1974). Drug release from hydroxy propyl cellulose-polyvinyl acetate films. *J.Pharm. Sci.*, 9: 1359-1364.
6. Choy FW, Kah HY and Kok KP (1999) Formulation and evaluation of controlled release eudragit buccal patches. *Int. J. Pharm.,* 178: 11-22.
7. Coutel-Ergos A, Maitani Y, Veillard M, Machida Y and Nagai T (1992). Combined effects of pH, cosolvent and penetration enhancers on the *in vitro* buccalabsorption of propranolol through excised Hamster cheek pouch. *Int. J. Pharm.*, 84: 117-128.
8. Edith M, Donald EC and Claus ML (1999). Bioadhesive Drug Delivery Systems. Marcel Dekker Inc., New York, pp. 541-562.
9. Gua JH and Cooklock KM (1995). Bioadhesive Polymer buccal patches for buprenorphine controlled delivery: Solubility Consideration. *Drug Devel. Ind. Pharm.*,21: 2013-2019.
10. Guo JH (1994). Bioadhesive polymer buccal patches for buprenorphine controlled delivery: Formulation *in vitro* adhesion and release properties. *Drug Dev. Ind.Pharm.*, 20: 2809-2821.
11. Khanna R, Agrawal SP and Ahuja A (1997). Preparation and evaluation of buccal films of clotrimazole for oral Candida infections. *Ind. J.Pharm. Sci*., 59: 299-305.
12. Michael JR, Gilles P and Firoz AG (1996). Oral Mucosal Drug Delivery. Marcel Dekker Inc., New York,74: 233-234.
13. Michael V (1998). Famotidine, a new agent for chronic heart failure. *J. Pharm. Soc. Wisconsin*, 2: 31-36.
14. Mollendorff EV, Reiff K and Neugebauer G (1987). Pharmacokinetics and bioavailability of famotidine, a vasodilating beta-blocker. *Eur. J. Clin. Pharmacol.,* 33(5): 511-513.
15. Noha AN, Nabila AB, Fatima A, Ismail and Lobna MM (2003). Design and characterization of mucoadhesive buccal patches containing cetylpyridium chloride. *Pharm. Acta Helvetiae*., 53: 199-212.
16. Patil JS and Rao KP (2003). Design and evaluation of mucoadhesive buccal patches of diclofenac sodium. *Ind. J. Pharm. Sci*., 4: 420-422.
17. Pavankumar GV, Ramakrishna V, William J and Konde A (2005). Formulation and evaluation of buccal films of salbutamol sulphate. *Ind. J. Pharm. Sci*., 2: 160- 164.
18. Siegel IA, Izutsu KT and Watson E (1981). Mechanisms of non-electrolyte penetration across dog and rabbit oral mucosa *in vitro*. *Arch. OralBiol*., 26: 357-361.
19. Thimmasetty J, subrahmanyam CVS, Manish kumar DS, Manjunath K and Shivanand K (2007). Designand evaluation of fexofenadine HCl buccl mucoadhesive patches. Biomed, 2: 73-83.