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DELIVERY OF DRUG VIA BUCCAL DRUG DELIVERY SYSTEM IN THE FORM OF PATCH FOR THE ANTI-HYPERTENSION DISEASE

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ABSTRACT

Losartan Potassium, drug used to prepare buccal patches by solvent casting method. Buccal delivery, is a favourable route compare to the parenteral and injectable adds a several advantages over other routes. paroral route possess some inconvenience to patients, hence for the immediate release of medication and for instant release at desire location in which the drug is absorbed distributer and easily metabolized. Buccal mucosa has absorptive function and offers many benefits like avoidance of first pass effect, which is a non-invasive route, increase in bioavailability, a rapid action is possible and reduce side effects. The permeability of oral mucosa denotes the physical nature of the tissues. The permeable part is sublingual mucosa and buccal mucosa is thinner part and in which there is a high blood flow and surface area; it is a feasible site when a rapid onset of action is desired. For the treatment of acute disorders sublingual route is a preferred one; however, its surface washed with saliva which makes formulations in the oral cavity hard in nature. Drug content was found highest in F9 98.42 %. F 8 shows highest in vitro drug release 98.08 % in 8 hours but ex vivo drug releases is best in F9 (525 min). Ex vivo permeation study shows best in F 9 (79.98 % in 480 minutes).

KEY WORDS

Buccal, Drug release, In vitro, Losartan Potassium, Mucosa, paroral route.

INTRODUCTION

Mucoadhesive drug delivery systems are delivery system which utilized the property of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time. Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological nature are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as adhesion between a polymer and a biological membrane. Oral route is the most commonly employed route of a drug administration for the drugs which are susceptible to gut and for hepatic metabolism and also for drug which cause G.I.T. side effects. To avoid disadvantages, various mucoadhesive dosage forms are given by different route other than oral route. eg. buccal, nasal, vaginal. Various newer researches are carried out in these sections. Like antihypertensive, anti-anginal, analgesic, anti-inflammatory, anti-asthmetic, anti-infective, anti-neoplastic, hormonal and ophthalmic drugs. [1]

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. Buccal delivery of drugs provides an attractive alternate to other conventional methods of systemic drug administration, since buccal mucosa is relatively permeable with rich blood supply and acts as an excellent site for the absorption of drugs. 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 harsh gastrointestinal environment, which are often associated with oral administration. The buccal cavity is easily accessible for self-medication, and hence it is safe and well accepted by patients, since buccal patches can be very easily administered and even removed from the application site, terminating the input of drug whenever desired. Moreover, buccal patches provide more flexibility than other drug deliveries. [2]

Losartan potassium is an angiotensin II receptor antagonist and is widely used in the management of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction following myocardial infarction, and in the management of heart failure. Although it is completely absorbed from the gastrointestinal tract, the systemic availability is approximately 25–35% because of high first-pass metabolism. Higher bioavailability of losartan potassium has been observed after absorption from the buccal mucosa. This suggests that the oral availability of losartan potassium could be improved by formulating a buccoadhesive dosage form. Hence, buccoadhesive patches can be envisaged to ensure both enhanced oral availability as well as maintenance of effective plasma concentration over prolonged duration by extending the release of losartan potassium. This in turn is expected to reduce the frequency of administration by maintaining effective plasma concentration over longer duration, providing better control of hypertension and thereby, improving patient compliance. In the present study, buccal patches of losartan potassium using chitosan and polyvinyl alcohol have been developed and evaluated. [3]

2. MATERIAL AND METHODS

2.1.1 Material- Losartan potassium, Polyvinyl alcohol, Chitosan, Ethyl cellulose, Isopropyl alcohol, Acetone, Dibutyl phthalate, Glycerine.

2.1.2 Equipment required- FTIR (Shimadzu NF), Dissolution (PLC), Melting point apparatus (Jyoti scientific Laboratories), Electronic balance (Citizen CX 220), Homogenizer (Remi), Magnetic stirrer (omega).

2.2 Methods

Pre-formulation study by IR spectroscopy- Physical mixture of Losartan potassium found NO interaction in the formulation and pure IR spectra of Losartan potassium is shown in Figure 1.

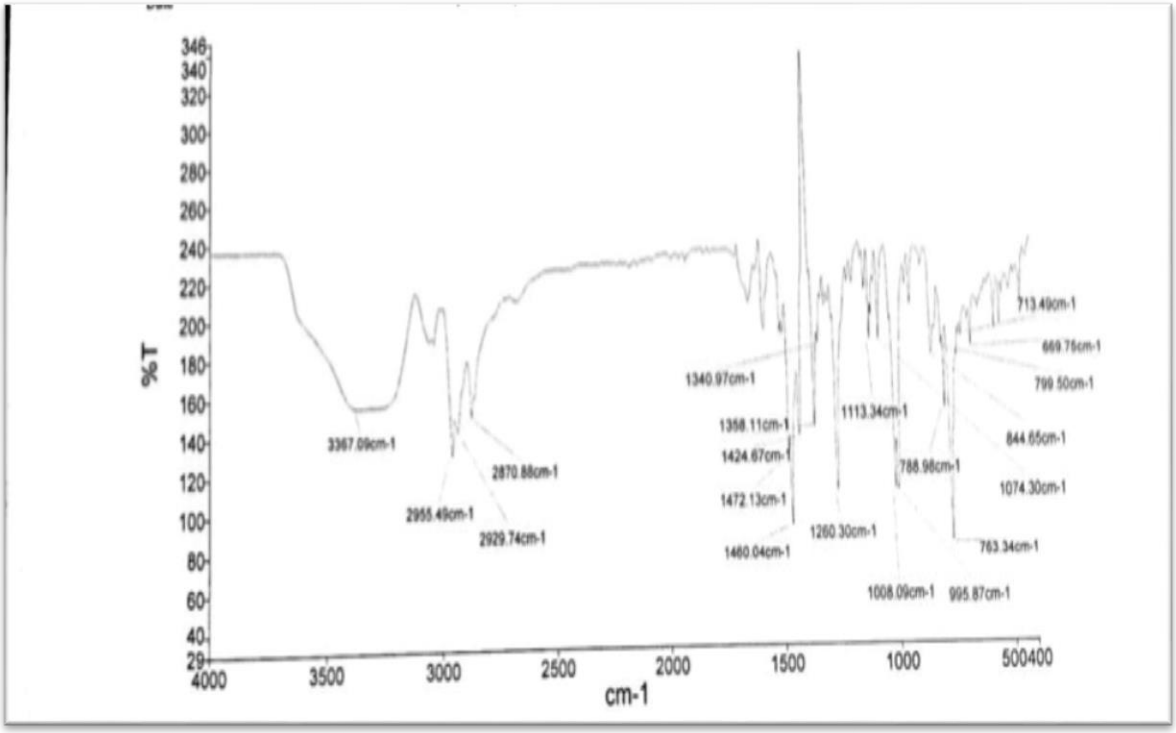

Figure 1- IR spectra of Losartan potassium

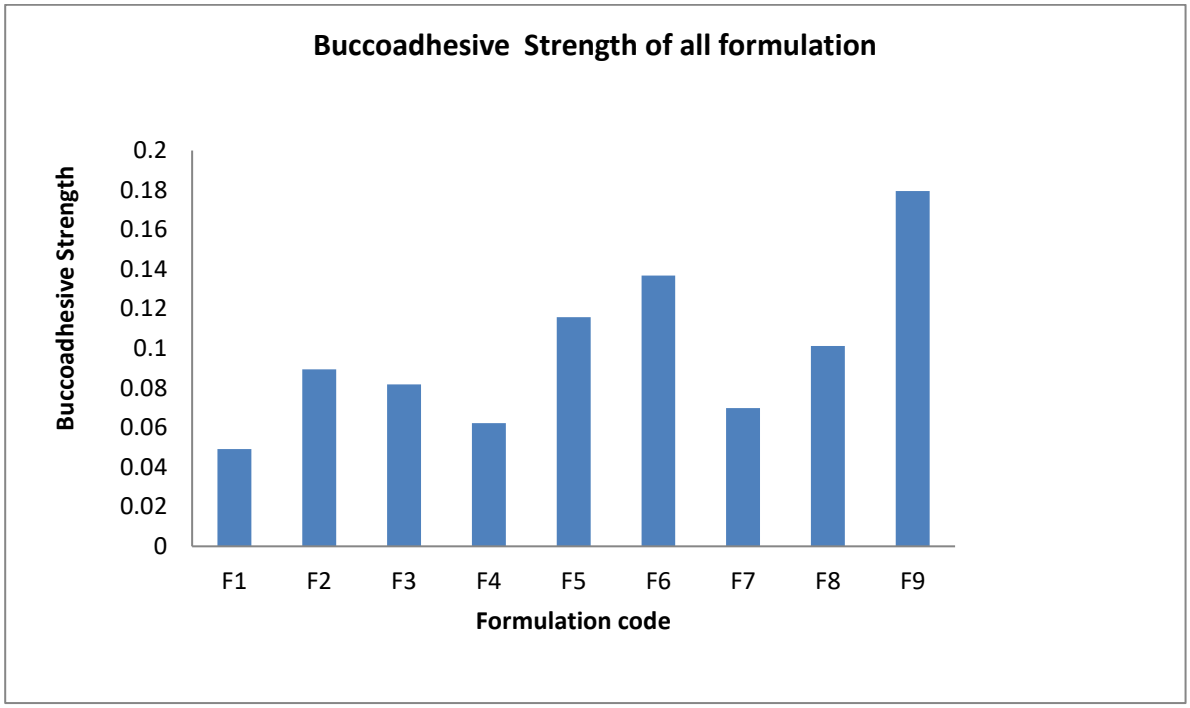

Figure 2- Buccoadhesion strength of all formulations

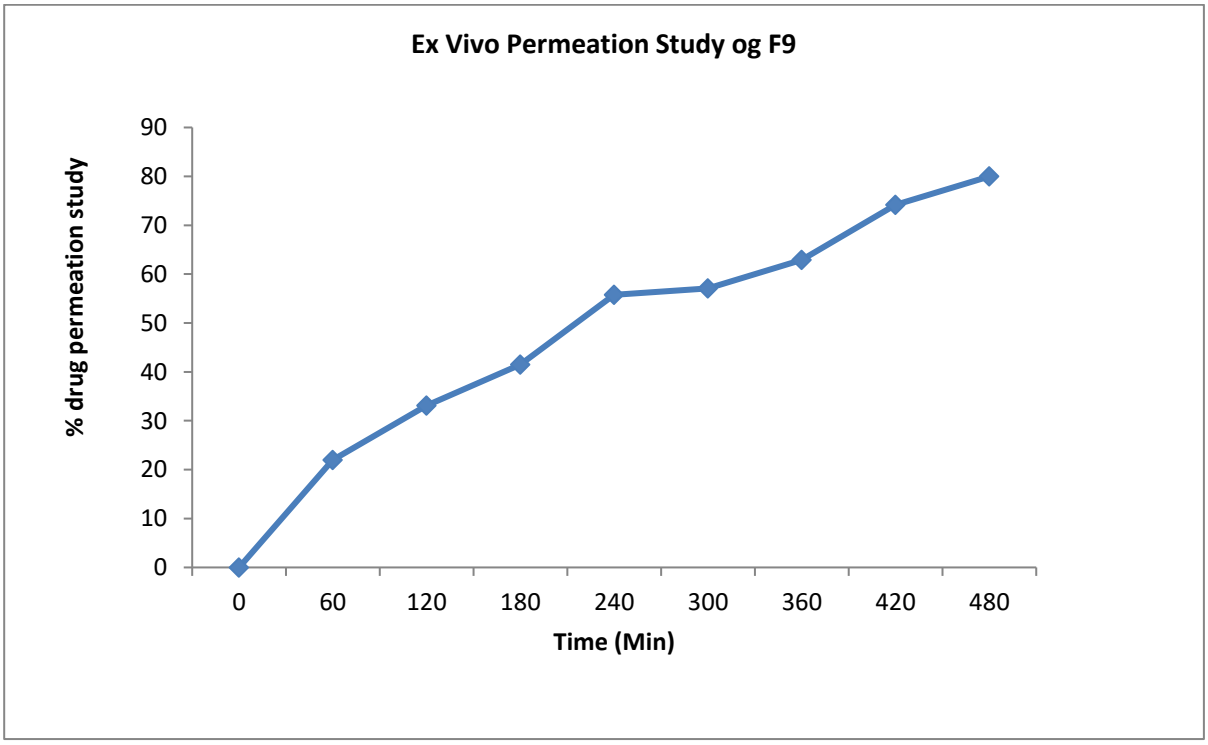

Figure 3 – Ex-vivo permeation study

Formulation	Weight (mg)	Thickness (mm)

F1	266.33±0.71	0.60±1.44
F2	281.33±2.88	0.67±1.51
F3	301.33±1.51	0.74±2.51
F4	287.33±0.42	0.70±1.15
F5	307.33±0.49	0.75±2.3
F6	323.66±0.57	0.77±1.52
F7	304.66±1.03	0.76±3.75
F8	320.66±2.55	0.77±2.10
F9	359.33±0.08	0.79±0.177

Table 1. Thickness and Weight of all patches

Formulation	Folding Endurance
F1	>300
F2	>300
F3	>300
F4	>300
F5	>300
F6	>300
F7	>300
F8	>300
F9	>300

Table 2. Folding Endurance of all patches

Formulation	Drug content (%)
F1	91.82±0.55
F2	88.16±0.51
F3	91.22±0.42
F4	90.43±0.53
F5	90.44±0.66
F6	93.27±0.62
F7	91.48±0.5
F8	92.78±0.59
F9	98.42±0.66

Table 3. Drug content of all patches

Formulation	Surface pH study	Swelling index (%)
F1	6.65±0.12	50.90±0.80
F2	6.28±0.25	54.35±0.58
F3	6.72±0.21	57.32±0.82
F4	6.72±0.18	45.37±0.65
F5	6.45±0.3	50.47±0.67
F6	6.58±0.16	63.52±0.59
F7	6.54±0.25	49.37±0.57
F8	6.71±0.14	57.97±0.88
F9	6.71±0.18	66.60±0.68

Table 4. Surface pH of all patches

Time (min.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
60	30.83	33.03	33.46	37.33	37.81	38.80	38.12	41.80	44.90
120	38.59	41.09	39.39	40.14	42.72	45.66	43.52	46.82	50.83
180	47.56	45.52	50.82	45.47	46.27	53.14	48.36	51.21	59.28
240	52.75	52.58	51.93	50.55	52.78	59.90	54.19	66.18	68.19
300	59.75	62.67	58.98	58.57	56.82	65.22	62.22	71.80	75.86
360	66.54	69.91	65.75	73.34	75.81	73.75	71.29	85.30	86.37
420	73.00	77.46	76.27	88.33	84.09	81.14	76.29	96.08	54.07
480	85.09	88.10	83.54	90.82	93.06	89.28	84.44	94.10	95.06

Table 5. *In vitro* drug releases of all patch

2.2.1 Preparation of Backing Layer

The ethyl cellulose (1.5 gm) backing membrane was prepared by solvent casting technique. Ethyl cellulose was dissolved in 30 ml mixture of acetone (19 ml) and isopropyl alcohol (11 ml) and kept for 1 hour in magnetic stirrer for continuous stirring. Dibutyl phthalate (2 ml) was added in above solution as plasticizer. This solution was poured in a petridish and kept overnight for drying at the room temperature to obtain the backing membrane.

2.2.2 Preparation of Buccoadhesive Patches-Buccal patches of losartan potassium were prepared by solvent casting technique, using combination of two polymers chitosan and polyvinyl alcohol (150-250 mg each patch). PVA was dissolved in hot water and chitosan was dissolved in 1 % acetic acid solution. Then both solutions were mixed together with slow stirring to get a clear viscous solution. Propylene glycol was used as plasticizer. The solution was poured in a petridish and allowed to dry over night at room temperature to remove the bubbles. Then solution was dried in an oven maintained at 40ºC till a flexible patch was formed. The dried patch was carefully removed from the petridish and cut into squares of 2 cm^2. [3]

3. RESULT AND DISCUSSION

3.1.1 Thickness - Thickness of the formulated patches were measured on three different places to ensure the uniformity of patches. Average and standard deviation of all three readings were calculated and recorded in table 1. Thickness was found to be in the range of 0.60 ± 1.44 mm to 0.79 ± 0.177 mm. From the results obtained it was confirmed that all the patches were uniform and did not have any significant differences in the thickness at different points. F1 batch showed the minimum thickness while F9 batch showed the maximum. Thickness of the patch was increasing with increase in concentration of polymers. The thickness of the all prepared patches was measured by using digital vernier calliper. The measurement was done at three different corners. [4]

3.1.2 Weight Uniformity - Drug loaded patches (2 cm^2) were tested for uniformity of weight. The average weight of the patch was found in the range of (266.33±0.71) to (359.33±0.08) mg. Weight uniformity of the mucoadhesive patches are observed as given in Table 1.

Patches of size 2 × 2 cm^2 were cut. The uniformity of weight for prepared buccal patches was analysed by weighing the patches on the electronic balance and the weight variation was calculated. [5]

3.2 Folding endurance - The average folding enduranse of the patch was found good folding endurance exceeding 300, indicating that they are tough and flexible. Folding endurance did not vary when the comparison was made between plain patches and drug loaded patches. The folding endurance results are observed as given in Table 2.

The test is performed by repeated folding of the film at the same place until film failure. A maximum of 300 times is sometimes reported as a limit to the test, and the value is reported as the number of times the film can be folded prior to rupture. This is considered satisfactory to reveal good patch properties. The number of times a patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on all the patches three times. [6]

3.3 Drug content- The results of content uniformity indicated that the drug was uniformly dispersed. Drug content of all the formulations was determined using UV-Visible spectrophotometer and result showed that

the drug was uniformly distributed throughout the patches and standard deviation of all the batches is very less and within the limits as recorded in table 3. Drug content was found to be in range of 91.82 ± 0.55 % to 98.42 ± 0.66 %.

Drug content uniformity was determined by dissolving the patch by homogenization in 50 ml of an isotonic phosphate buffer pH 6.8 for 2 hr with occasional shaking. Aliquot 1 ml was withdrawn and diluted with isotonic phosphate buffer pH 6.8 up to 10 ml and the resulting solution was filtered through a 0.45 mm Whatman filter paper.

3.4 Surface pH of the buccal patches- Surface pH of all patches were determined by using pH meter and recorded in table 4. Surface pH ranged from 6.65 ± 0.12 to 6.71 ± 018. Surface pH of all formulations was near to neutral pH hence, should not cause any irritation in the buccal cavity. The surface pH of the patches was determined in order to investigate the possibility of any side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the buccal mucosa. The patch to be tested was placed in petri dish and was moistened with 1 drop of distilled water and kept for 1-2 h. The pH was noted after bringing the electrode of pH meter in contact with the surface of the formulation and allowing equilibrating for 1 min. The average of 10 determinations for each of the formulation was taken.

3.5 Swelling Index studies- Appropriate swelling behavior of a buccal adhesive system was an essential property for uniform and prolonged release of drug and effective mucoadhesion. Swelling studies of prepared patches were performed using 6.8 pH phosphate buffer for 8 hr and the results are shown in table 4. Maximum swelling was observed in batch F9 (66.6 %) while batch F4 showed minimum swelling (45.37 %). Maximum swelling percentage was observed for F9 batch because of more concentration of hydrophilic polymers. Weak aqueous solubility of Chitosan which is a cationic polymer, limited the swelling of the patches.

The patch sample of 1.5 cm diameter was weighed and placed in a pre-weighed stainless-steel wire sieve of approximately 800 µm mesh. The mesh containing the sample was then submerged into 15 ml of simulated salivary fluid of pH 6.8 contained in a porcelain dish. At definite time intervals, the stainless-steel mesh was removed; excess moisture was removed by carefully wiping with absorbent tissue and reweighed. Increase in weight of the film was determined at each time interval until a constant weight was observed. The degree of swelling was calculated using the formula, [8]

Swelling index (S.I.) = Wt– Wo / Wo

Where, Wt is weight of the patch at time t and Wo is weight of the patch at time zero.

3.6 In vitro drug release studies - The in vitro release studies of various formulations were performed in isotonic phosphate buffer (pH 6.8) at 50 rpm. The data obtained from in-vitrom drug release study performed up to 8 hr gives a clear indication that prepared patches showed necessary controlled release profile. Release of Losartan potassium from patches was also increased with increased swelling index of patches. Maximum in vitro release was found to be 96.08 % over a period of 8 hours in batch F8 while minimum in vitro release was found to be 41.09 % in batch F2 and the results for release studies are shown in table 5.

In vitro release studies were carried out by slight modification of the method. A buccal patch was attached to the wall of the dissolution vessel such as a 250 ml beaker midway from the bottom with instant adhesive. After 2 min the vessel was filled with 200 ml of simulated saliva of pH 6.8 and placed on a magnetic stirrer. The temperature of the dissolution medium was maintained at 37ºC and stirred at 50 rpm. Samples of 3 ml were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were diluted appropriately with simulated saliva and assayed spectrophotometrically at 269 nm and 217 nm by simultaneous estimation method. Three patches of each formulation were subjected to drug release studies in the same manner and the average cumulative percentage drug was determined. [9]

3.7 Ex vivo drug release studies- Buccoadhesion is a very important aspect for maintaining high drug levels at the site of administration and prevents expulsion of formulation All the batches showed good mucoadhesive strength. Maximum buccoadhesion time was shown by formulation F9 which was 525 min and minimum bioadhesion time was 389 min. Formulation F1 has minimum amount of PVA and Chitosan and formulation F9 has maximum amount of PVA and Chitosan. The decrease in the polymer concentration resulted in a decrease in buccoadhesion time.

Ex vivo mucoadhesion was performed by application of the patch on freshly cut porcine buccal mucosa. The porcine tissues were fixed on the internal side of a beaker with cyanoacrylate glue. The patch was wetted

with 50 µl of simulated salivary fluid and was attached to the porcine buccal tissue by applying light force with fingertip for 20 seconds. The beaker was filled with 200 ml of simulated salivary fluid and kept at 37ºC. After 2 min, stirring at 50 rpm was maintained to simulate the buccal cavity environment. The time taken for the patch to completely erode or detach from the mucosa was observed as the ex vivo mucoadhesion time. [10, 11]

3.8 *Ex vivo* permeation studies- The ex-vivo drug permeation studies were performed using porcine buccal mucosa as a model membrane using franz diffusion cell. The study was conducted at 37±2°C for 8 hr. The result of ex-vivo drug permeation study is shown in figure 3. From the results, it was observed that after 8 hr the drug permeation from buccal mucosa was found best in F9 patch formulation among all the patch F1-F8 (79.98 %). In this study, porcine buccal mucosa was used as a barrier membrane. Diffusion studies were carried out, to evaluate the permeability of drug across the porcine buccal mucosal membrane, by using glass surface Franz diffusion cell. Porcine buccal mucosa was obtained from local slaughter house and used within 2 hrs of slaughter. The tissue was stored in phosphate buffer pH 6.8 solution upon collection. .[12, 13] The epithelium was separated from underlying connective tissues with surgical scissors clamped between donor and receiver chamber of diffusion cells form permeation studies. The smooth surface of the mucosal membrane faced the donor chamber and receiver chamber was filled with phosphate buffer of pH6.8. Whole assembly was placed on a magnetic stirrer maintained at 37±10°C. Buccal epithelium was allowed to stabilize for 1hr and receiver chamber was maintained by stirring with magnetic bead at 50 rpm. After the stabilization of buccal epithelium, the patch was kept on buccal epithelium and 3ml of phosphate buffer pH 6.8 was added in donor chamber. Then samples of 0.1 ml were withdrawn at time intervals of 1 hr up to 8 hrs and replaced with equal volume of fresh dissolution medium.

4. CONCLUSION

The results of stability studies of buccal patches showed no significant change with respect to physical appearance, surface pH, swelling index and *in vitro* drug release Stability of the product may be defined as the capability of a particular formulation to remain with the physical, chemical, therapeutic and toxicological specification. Study of storage stability is an important concern in the development of pharmaceutically acceptable product. In present work stability studies of prepared formulation were carried out at 40±2ºC for 1 month. The formulations were evaluated and F9 was found maximum folding endurance more than 300, drug content (98.42 %). Surface pH and swelling index 6.71, 66.6%, respectively. Buccoadhesive time maximum for F9 was found 525 min. The initial drug content was considered as 100%, this was probably due to loss of moisture and plasticizer from the patches when stored at this temperature. Aging did not alter the drug release profiles of any of the films significantly at the end of the storage period. [14]

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REFERENCES

[1] Surya N., Adhikari R., Nayak B.S., Formulation and Evaluation of Buccal Patches for Delivery of Atenolol Patches. AAPS PharmSciTech, 11: 1-8, (2010)

[2] Semalty M., Nautiyal U., Formulation and Evaluation of Mucoadhesive Buccal Film of Enalapril Maleates. Indian J. Pharm. Sci., 5: 571-575, (2010)

[3] Bansal S., Bansal M., Garg G., Preparation and Evaluation of Buccoadhesive Patches of an Antihypertensive Drug. American Journal of Phytomedicine and Clinical Therapeutics, 2: 2321-2748, (2013)

[4] Gupta S.K., Singhvil J., Shirsat M., Karwani, Agarwal A., Agarwal A., Buccal Adhesive Drug Delivery System. Asian Journal of Biochemical and Pharmaceutical Research, 1: 105-114, (2011)

[5] Roychowdhury S., Gupta R., Saha S., A Review on Buccal Mucoadhesive Drug Delivery Systems. Indo-Global Journal of Pharmaceutical Sciences. 1: 223-233, (2011).

[6] Reddy P.C., Chaitanya K.S.C., Rao M.Y., A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. DARU Journal of Pharmaceutical Sciences, 6: 385–403, (2011)

[7] Murali K.K., Nagaraju T., Gowthami R., Rajashekar M., Sandeep S., Himabindu S., Shravan Y. K., Comprehensive Review on Buccal Delivery. International Journal of Pharmacy, 2: 205-217, (2012).

[8] Bobade N.N., Atram S.C., Wankhade V.P., Pande S.D., Tapar K.K., A Review on Buccal Drug Delivery System. International Journal of Pharmacy and Pharmaceutical Science Research, 1: 35-40, (2013).

[9] Fiza F., Bharadwaj S., Jat R.C, Arjariya P., Sharma G., Ratnakar D., Khan I., Tiwari R., Rathore A., Buccal Patches. Indo American Journal of Pharmaceutical Research, 3: 3324-3335, (2013).

[10] Sravanthi R.R., Rajalakshmi R., Krishnamoorthy S.B., Rupangada V., Ramya S., Mucoadhesive Buccal Films: An Innovativ, Drug Delivery System. International Journal of PharmTech Research, 6: 1665-1678, (2014)

[11] Muhammad H., Muhammad Z., Chaurasiya V., Polymers used in buccal film Designed Monomers and Polymers. Journal Information, 18: 105-111, (2014)

[12] Mohamed M I., Mohamed R.A., Kamal G. M., Formulation and evaluation of anti-asthmatic drug montelukast in mucoadhesive buccal patches. Journal of Coastal Life Medicine, 1: 907-914, (2014)

[13] Vyas K., Garg S. K., Buccal Patches: Novel Advancement in Mucoadhesive Drug Delivery System. Indo American Journal of Pharmaceutical Research, 5: 727-740, (2015)

[14] Prasad N., Kakar S., Singh R., A Review on Buccal Patches. International Journal of Sciences, 3: 4-8, (2016)

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