DESIGN AND CHARACTERIZATION OF BUCCAL PATCHES CONTAINING METFORMIN HYDROCHLORIDE

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ABSTRACT

Buccoadhesive patches for delivery of metformin hydrochloride were prepared using carbopol (CP), hydroxypropyl methyl cellulose (HPMC), hydroxy ethyl cellulose (HEC) and plasticizer, glycerol. Physical appearance, thickness, percent swelling index, percent moisture uptake, folding endurance, tensile strength, elongation at break and bioadhesive characteristics were determined for plain buccal patches. The buccal patches prepared using 50% glycerol w/w of polymer weight was found to have good physical characteristics. The mean thickness of buccal polymeric patches increased with an increase in the amount of polymer percent, CP-HEC (1:3) containing glycerol 50% w/w of polymer weight had maximum thickness. Percent swelling index determined at 5, 10, 30 and 60 minutes increased with time and with an increase in hydrophilic polymer. HPMC buccal patches showed maximum swelling index. Maximum percent moisture uptake was found in HEC (R_6C) buccal patches. CP-HEC buccal patches showed maximum folding endurance while HEC buccal patches were observed to have better tensile strength and elongation at break was highest in CP-HEC patches. Bioadhesive strength was found to be maximum for CP-HPMC patches and minimum for HPMC buccal patches. Increase in hydrophilic polymers. HPMC and HEC increased the bioadhesion force. Increase in the amount of polymer retarded the release of metformin hydrochloride. R_7C(CP-HPMC 1:1) showed maximum and faster release (93.51%) in 12 hours and 6.11 hours for 50% release of metformin hydrochloride. The best fit model for R_7C was found to be zero order. All buccal patches studied i.e., R_1C, R_2C, R_3C, R_4C, R_5C, R_6C, R_7C, R_8C, R_9C, $R_{10}C$ except $R_{11}C$ and $R_{12}C$ showed zero order release mechanism. Whereas $R_{11}C$ showed Hixon-Crowell model and $R_{12}C$ was observed to release metformin by first order mechanism. The buccal patches of metformin hydrochloride were found to be stable at 52% and 75% RH at 29±2°C and 45°C when stored for 6 weeks.

KEY WORDS: Buccal patches, Metformin hydrochloride, Polymers, Bioadhesion, *In vitro* release.

INTRODUCTION:

New drug delivery systems impact nearly every branch of medicine and annual sales of these systems are far in excess of 10 billion dollars. One of the novel approaches in this area is mucoadhesive drug delivery system which comprises buccal delivery system as one of the major delivery system (Devarajan and Ashok, 1997). This system enables administration of drug through the buccal mucosa (Shojaei , 1998). Buccal drug delivery system having many advantages like it avoids degradation of drug which are sensitive to pH and digestive enzymes of gastrointestinal tract and avoids first pass metabolism and also provides rapid onset of action, ease of drug administration, easy termination and has no stratum corneum barrier. Drug's lipid solubility, pH, drug ionization, improved patch design and the use of prodrugs, have all been shown to be important in drug absorption and delivery.

Metformin is an antihyperglycemic agent and acts by lowering the blood glucose concentration without causing hypoglycemia (Klepser and Kelly , 1997). Metformin quite frequently causes gastrointestinal problems such as nausea, stomach pain, floating, diarrhea and malabsorption of vitamin V-12 folic acid (Goodman ,1990). It has a short duration of action, low peak plasma level and poor bioavailability. These factors necessitated formulation of buccal release drug delivery system for Metformin Hydrochloride (MH), as this route of drug administration would reduce the dosing frequency hence better patient compliance (Chowdhary and Shrinivas, 2005). Buccal patches of MH will provide ease of administration and controlled release of this drug.

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The objective of this study was to prepare and evaluate mucoadhesive polymeric buccal patches of MH. Patches were prepared by using carrier like carbopol (CP), hydroxypropyl methyl cellulose (HPMC), hydroxy ethyl cellulose (HEC) and plasticizer, glycerol. They were evaluated for physical appearance, thickness, percent swelling index, percent moisture uptake, folding endurance, tensile strength, elongation at break and bioadhesive characteristics of the prepared mucoadhesive buccal delivery systems and to study the in- vitro release of MH through the selected buccal patch.

2.MATERIALS AND METHODS

MH obtained as gift sample from Kothari Phytochemicals International, Madurai, the chemicals and reagents used were of analytical grade. The raw material analyzed as per official monograph.

Preparation of polymeric patches

Required quantity of polymer (Table 1) was mixed with water and kept aside for 24 hrs for polymer hydration. The hydrated polymeric solution was dissolved with the help of magnetic stirrer. Plasticizer glycerol (Chowdhary and Shrinivas, 2005) was added and dissolved. Air bubbles were removed by sonication. The solution was filtered and polymeric patches were prepared as per the method mentioned by (Salmat , 2005) using 10ml polymeric solution. The patches were dried in an oven for 24 hrs at 45°C. The dried polymeric patch was wrapped in an aluminium foil and stored in a dessicator for further studies.

Selection of best polymer composition

For selecting best polymer composite, polymeric patches using varied amount of plasticizer glycerol and polymers composition were prepared. Physical characteristics of these polymeric patches were studied and best polymer composite was then selected. To it MH 600 mg was added. The final composition of buccal patches containing 600mg of MH of selected polymeric patches is shown in Table 1.

Preparation of backing membrane

Backing membrane were prepared using ethyl cellulose (4% w/v), in solvent ethanol– toluene (1:4) and glycerol (10% w/w of polymer weight) as plasticizer.

Evaluation of Polymeric Patches

Physical Appearance and Surface Texture: It includes visual inspection of patches and evaluation of texture by feel or touch.

Thickness: The thickness of the patch was measured using screw gauge at five different spots (Saisivam , 2000).

Percent Swelling Index: The polymeric patches cut into 1 x 1 cm were weighed accurately and kept immersed in 50 ml of water. The patches were taken out carefully at 5, 10, 30 and 60 minutes intervals blotted with filter paper to remove the water present on their surface and weighed accurately (Ilango , 1997).

The percent swelling is calculated using formula:

$$\% \text{ swelling} = \frac{\text{Wet weight} - \text{dry weight}}{\text{Wet weight}} \times 100$$

Moisture Uptake: A modification of the American Standard for Testing Material (ASTM) method was used. Specimens were subjected to dessication over sodium hydroxide at room temperature for 48 hours. This weight was recorded as the initial weight. These samples were then exposed to 52%, 75% and 98% relative humidity (RH) using sodium chloride, sodium bisulfate and potassium dichromate respectively in their saturated solution at room temperature. These specimens were weighed periodically until no further increase in weight was recorded (ASTMD guideline, 1980). The moisture uptake was calculated at each RH as given below:

$$MU = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Folding Endurance: Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (approximately 2x2 cm) at the same place till it broke. The number of times patch could be folded at the same place, without breaking gives the value of folding endurance (Deasy and Neil, 1989).

Tensile Strength: Tensile Strength was determined with an instrument assembled in the laboratory based on the ASTM standard tests principles. The instrument used to measure the tensile strength designed in our laboratory especially for this project work. For this both the ends of the patches were enclosed between two pairs of acrylic slides with the help of clamps. One pair of acrylic slides enclosed with the upper end of the patch is fixed to a metal stand at convenient height so that the patch elongation can be conveniently observed with the traveling microscope. To the other pair of acrylic slides a pan is suspended with the help of a wire loop. Stripes of 6 cm in length and 1 cm in width were cut using a razor blade and stainless steel guide. This procedure was preferred to die cutting in order to avoid notching of the specimen. Two small markings 4 cm

apart and 1 cm of each end of specimen were made on sample with ink samples were then observed under traveling microscope to detect flaws. The specimen was held between two clamps in such a way that the marking towards the fixed clamp as just inside it, whereas marking towards the movable clamp was measured. The change in length of the specimen that occurred with increase in weight was measured. The rate of change of stress was kept constant by increasing the load on the pan at the rate of 10 g/2 min because stress strain relationship changes with rate of change of stress.

The definition of tensile strength as per ASTM standards is the maximum load during the tensile strength test divided by the original minimum cross-sectional area of the specimen. Thus, tensile strength:

$$T = \frac{M \times g}{B \times t} \text{ dynes/cm}^2$$

= force at break/ initial cross-sectional area of sample

Where,

M = mass in grams

g = acceleration due to gravity 980 cm/sec²

B = breadth of the specimen in cm

t = thickness of sample in cm.

Percent Elongation at Break:

The percent elongation at break is defined as the elongation at the moment of rupture of the specimen divided by the initial gauge length of the specimen and multiplying by 100 (Khanna , 1997).

$$\text{Percent elongation at break} = \frac{L_B - L_0}{L_0} \times 100$$

L_B = length of the specimen in cm when it breaks.

L_0 = original length of the specimen in cm.

The instrument and procedure is similar to that used for tensile strength.

Measurement of Bioadhesive Strength:

The tensile strength required to detach the polymeric patch from the mucosal surface was applied as measure of the bioadhesive performance. The apparatus was locally assembled and was a modification of the apparatus applied by Parodi. The device was mainly composed of a two-arm balance. The left arm of the balance was replaced by small stainless steel lamina vertically suspended through a wire. At the same side, a movable platform was maintained in the bottom in order to fix the model mucosal membrane. The fabricated balance described above was used for the bioadhesion studies. The bovine cheek pouch, excised and washed was fixed to the movable platform. The mucoadhesive patch was fixed of 3 cm², was fixed to the stainless steel lamina using 'fevi-quick' as adhesive. The exposed patch surface was moistened with 1 ml of isotonic phosphate buffer for 30 seconds for initial hydration and swelling. The platform was then raised upward until the hydrated patch was brought into the contact with the mucosal surface. A preload of 20 gms was placed over the stainless steel lamina for 3 minutes as initial pressure. And then weights were slowly increased on the right pan, till the patch detaches from the mucosal membrane. The weight required to detach the patch from the mucosa give the bioadhesive strength of the mucoadhesive patch. The procedure is repeated for 3 times for each patch and mean value of the 3-trials was taken for each set of formulation. After each measurement the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 5 minutes before taking reading (Ali and Raza , 2004).

Drug Content Uniformity: The patch of known weight (dimension 1cm x 1cm) was extracted with 100 ml of phosphate buffer by shaking (Raghuraman, 2001). The solution was diluted with phosphate buffer and the absorbance was measured in UV-spectrophotometer at 233 nm against the same phosphate buffer.

***In Vitro* Release Study:** A buccal strip of 1 cm² (containing 30 mg of drug) affixed with the backing membrane was held at the centre of a microscope slide by means of rubber band. The slide was placed at an angle of 45° in a 150 ml beaker containing 100 ml of pH 6.6 buffer preheated to 37°C. The beaker was kept in 37°C water bath. A non-agitated system was selected to eliminate any effect of turbulence on the release rate to assure that no disruption of strip occurred. Periodic assay of samples were obtained by removing the slide, stirring the medium and pipetting a 1 ml sample with graduated pipette, whose tip was covered with a piece of muslin cloth. The volume of the sample was immediately replaced with 1 ml of fresh buffer. The slide was quickly reinserted, making sure that the slide remained completely immersed throughout the release rate studies. The beaker was kept covered throughout the run to prevent evaporation

(Khanna , 1997). All samples were analyzed spectrophotometrically at 233 nm.

Stability Studies: Stability studies were performed as per ICH guidelines. The MH buccal patches were stored at room temperature (29±2°C), at 52% relative humidity and at 75% relative humidity and the drug content was determined spectrophotometrically. Similarly, studies were also done at 45°C. (Raghuraman, 2001).

3.RESULTS AND DISCUSSION:

MH, polymers and plasticizers were found to comply with pharmacopoeial standards. Polymeric patches R_1C to $R_{12}C$ with different polymeric composition (Table 1) were evaluated for their physical properties.

The mean film thickness of the buccal polymeric patches increases with an increase in amount of polymer. The $R_{12}C$ formulation i.e. HEC-CP (3:1) containing glycerol 50% w/w of polymer weight had maximum thickness 0.343±0.024 mm (Table 2).

The percent swelling index determined (Figure 1) at intervals of 5, 10, 30, 60 minutes increased with an increase in the hydrophilic polymer concentration. Higher the polymer content greater was the percent swelling observed. HPMC-CP, HEC-CP combination patches showed lesser percent swelling than HPMC and HEC alone. HPMC buccal patches showed greatest swelling (R_3C – 78.35% in 60 minutes) followed by HEC, CP-HEC, CP-HPMC.

The percent moisture uptake (Table 3) had 52%, 75% and 98% relative humidity (RH). It was observed that the percent moisture uptake increase with an increase in the amount of hydrophilic polymer. The percent moisture uptake was found to be in the order as HEC>CP-HEC>HPMC>CP-HPMC. R_6C buccal patches showed 62.9±2.54% moisture uptake had 98% relative humidity.

The maximum folding endurance was observed (Table 2) for $R_{12}C$ polymeric patch 254±2.56. Tensile strength, elongation at break result showed that HEC patched as better tensile strength whereas elongation at break is highest for CP-HEC patches ($R_{12}C$) showed the elongation at break 27.83±0.98.

From the results obtained as shown in Figure 2, it can be concluded that any rise in the amount of hydrophilic polymer increases mucoadhesion. These results corroborates with earlier studies of Li ,1998 ; Ayyapan and Kasture, 2006.

After incorporation of MH in the selected polymeric buccal patches, the drug content uniformity (Table 4) values were observed to be between 99.943% and 100.215% of the labeled amount.

In vitro release of MH (Table 5) from buccal patches (100 mg/cm²) showed decrease in percent cumulative drug release with an increase in amount of polymer. Patch R_1C containing HPMC-CP (1:1) showed maximum release in 12 hrs (93.511%). The patches containing HEC and HPMC in combination with CP showed faster release as compare to patches with HEC and HPMC the results were in variance with the results reported by Soliman , 2005 ; Ayyapan and Kasture, 2006.

The release mechanism of MH from various buccal patches prepared was studied. The best fit model for R_1C to $R_{10}C$ buccal patches showed zero order whereas $R_{11}C$ showed Hixson-Crowell and $R_{12}C$ showed first order release mechanism.

MH buccal patches at 52% and 75% relative humidity (29±2°C) were found to be stable. Similarly, when these patches were stored at 45°C, they were found to be stable at this temperature for six weeks (Table 6).

4.CONCLUSION:

From the study it can be finally concluded that amongst the various polymer composites HPMC, HEC, CP-HPMC, CP-HEC studied, R_7C (CP-HPMC 1:1) mucoadhesive patches using 50% glycerol w/w of dry polymeric weight demonstrated good potential as carrier systems for buccal delivery of MH.

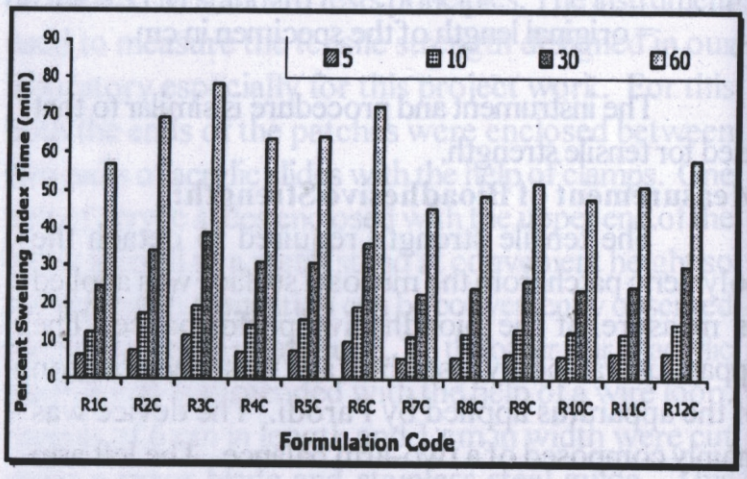

Figure 1: Percent Swelling Index of Polymeric Patches Versus time

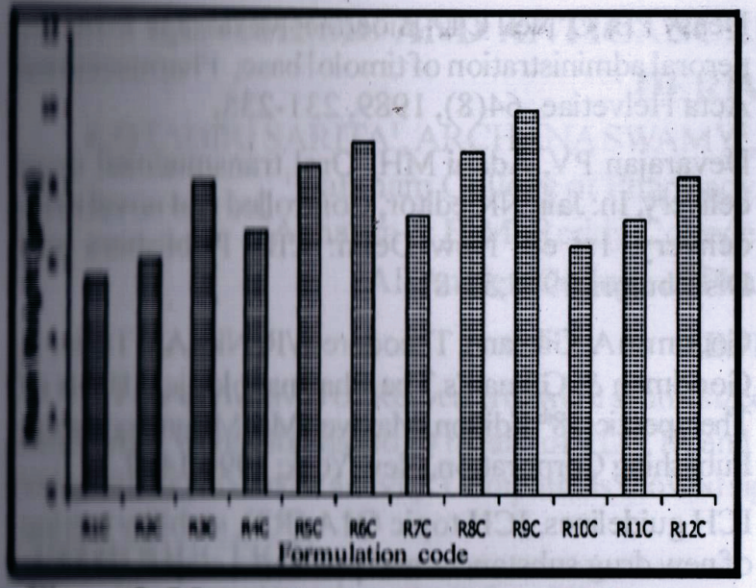

Figure 2: Mucoadhesive Strength of Polymeric Patches

Table 1: Composition of MH Buccal Patches

Ingredient	R_1C	R_2C	R_3C	R_4C	R_5C	R_6C	R_7C	R_8C	R_9C	$R_{10}C$	$R_{11}C$	$R_{12}C$
	600	600	600	600	600	600	600	600	600	600	600	600
	3%	4%	6%	"	"	"	1%	2%	3%	"	"	"
	"	"	"	3%	4%	6%	"	"	"	1%	2%	3%
	"	"	"	"	"	"	1%	1%	1%	1%	1%	1%
	50	50	50	50	50	50	50	50	50	50	50	50

Table 2 : Evaluation of Physical Parameters of Buccal Patches

Formulation code	Parameters			
	Thickness	Folding endurance	Tensile strength (dynes/ cm x 10^3)	Elongation at break
R_1C	0.16±0.02	210±5.14	61.93±1.24	17.32±2.15
R_2C	0.18±0.03	240±3.15	66.81±1.70	19.52±3.29
R_3C	0.30±0.03	244±4.10	68.54±1.83	24.33±3.29
R_4C	0.17±0.03	220±4.16	64.74±1.92	18.94±3.29
R_5C	0.21±0.04	228±4.14	67.34±1.44	21.64±2.88
R_6C	0.32±0.05	247±3.18	69.84±0.93	23.14±1.78
R_7C	0.14±0.04	225±2.44	62.34±2.22	21.39±1.22
R_8C	0.17±0.02	233±3.25	63.14±1.22	22.14±1.39
R_9C	0.33±0.03	245±2.14	66.14±2.26	24.33±1.47
$R_{10}C$	0.338±0.01	239±3.18	64.39±1.48	25.38±2.13
$R_{11}C$	0.304±0.013	245±1.23	66.77±2.18	26.34±1.47
$R_{12}C$	0.343±0.034	254±2.56	68.13±2.56	27.34±0.98

Table 3: Percent Moisture Uptake of polymeric patches

Formulation code	Percent Moisture Uptake (w/w)		
	52% Relative Humidity	75% Relative Humidity	98% Relative Humidity
R_1C	12.14±1.13	17.45±2.22	38.94±1.88
R_2C	15.33±1.40	19.74±1.88	42.39±2.19
R_3C	16.14±1.88	22.99±1.11	53.64±1.74
R_4C	14.88±1.94	20.66±1.43	44.89±1.16
R_5C	17.78±2.14	20.37±1.88	48.29±2.27
R_6C	19.94±1.33	24.34±1.27	62.90±2.54
R_7C	14.68±0.94	17.54±1.03	38.33±1.12
R_8C	15.53±1.25	19.54±1.33	40.65±1.20
R_9C	16.34±0.95	21.56±1.16	49.36±1.35
$R_{10}C$	16.32±1.88	20.43±1.25	54.45±2.29
$R_{11}C$	19.44±1.33	26.54±1.91	56.25±2.14
$R_{12}C$	19.86±1.32	28.15±1.48	60.45±1.95

Table 4: Drug content of MH containing polymeric batches

Formulation code	Mean % drug content (± SEM)
R_1C	100.078±0.0277
R_2C	100.042±0.02128
R_3C	99.943±0.05063
R_4C	100.072±0.0213
R_5C	100.044±0.05123
R_6C	100.215±0.0423
R_7C	100.035±0.06485
R_8C	99.984±0.06933
R_9C	100.143±0.4531
$R_{10}C$	100.148±0.01391
$R_{11}C$	100.072±0.05426
$R_{12}C$	100.182±0.02817

Table 5: *In- vitro* drug release studies of MH buccal patches

Time (hr)	Average % Drug Release											
	R_1C	R_2C	R_3C	R_4C	R_5C	R_6C	R_7C	R_8C	R_9C	$R_{10}C$	$R_{11}C$	$R_{12}C$
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	4.402	1.028	1.196	0.015	0.184	0.184	0.521	0.015	0.353	0.184	1.028	1.365
1	9.363	2.904	1.876	4.436	0.522	0.522	1.367	0.015	1.198	0.691	5.418	3.901
2	12.775	9.985	7.788	12.856	9.635	3.392	8.29	10.982	12.338	8.117	17.25	13.871
3	16.318	21.329	13.725	19.824	13.891	9.392	17.096	21.992	18.461	14.055	23.899	23.206
4	26.843	29.175	20.528	26.315	21.033	16.266	28.3	34.565	22.921	20.691	30.405	29.203
5	30.324	31.991	30.227	30.975	29.384	21.561	38.367	46.176	34.148	24.991	37.95	39.949
6	42.761	39.541	37.602	40.546	35.068	29.239	47.968	48.721	41.201	40.95	43.837	45.338
7	47.992	46.953	44.331	45.599	40.438	33.573	57.269	52.289	47.269	45.499	48.397	49.398
8	56.617	55.068	48.387	50.166	44.815	41.973	66.775	58.401	54.036	50.403	50.613	52.461
9	66.795	61.359	55.327	54.076	48.535	49.056	78.343	64.873	60.155	61.063	56.886	54.692
10	76	64.975	62.125	60.699	55.138	56.505	84.557	72.383	67.14	68.053	58.29	57.438
11	84.566	74.172	67.599	68.193	62.947	60.271	90.289	82.79	73.478	72.539	65.733	59.856
12	90.635	80.537	74.613	72.678	68.087	64.051	93.511	87.333	81.865	77.041	72.104	64.307

Table 6: Drug Content Estimation of stability studies

Formulation code	Stability Studies of MH Buccal Patches (% Drug Content Estimation)		
	52% Relative Humidity at 29±2°C	75% Relative Humidity at 29±2°C	At 45°C
R_1C	100.042±0.4123	100.148±0.043	99.957±0.0606
R_2C	100.036±0.0648	100.032±0.051	100.147±0.0452
R_3C	100.072±0.0253	100.082±0.053	100.190±0.0391
R_4C	100.082±0.0542	100.192±0.038	100.045±0.0511
R_5C	99.984±0.6923	100.036±0.074	100.070±0.0272
R_6C	100.182±0.0391	100.078±0.028	100.085±0.0542
R_7C	100.217±0.132	100.148±0.012	100.092±0.0263
R_8C	100.984±0.050	100.217±0.124	100.042±0.0361
R_9C	100.148±0.012	99.984±0.059	100.224±0.1238
$R_{10}C$	100.068±0.027	99.954±0.060	99.897±0.0693
$R_{11}C$	100.042±0.036	100.042±0.030	100.026±0.0748
$R_{12}C$	100.147±0.045	100.082±0.028	100.145±0.0127

REFERENCES

Ali Raza SM, Raza A, Preparation and *in vitro* assessment of various mucosa-adhesive films for buccal delivery, Iranian Journal of Pharmaceutical Sciences, 18(12), 2004, 20041-20049.

American Society for Testing of Materials, American National Standard, ASTMD 882-80a, 1980: 380-388.

Ayyapan T and Kasture PV, Development and in-vitro evaluation of buccoadhesive tablets of Ondensetron HCl, Indian Drugs, 43(2),2006.

Chowdhary KPR and Shrinivas L, Mucoadhesive drug delivery Systems: a review of Current Status, Indian Drugs, 37(9), 2000,400-406.

Deasy PB, O'Neil CT, Bioadhesive dosage form for peroral administration of timolol base, Pharmaceutica Acta Helvetiae, 64(8), 1989, 231-235.

Devarajan PV, Adani MH, Oral transmucosal drug delivery, In: Jain NK editor, Controlled and novel drug delivery, 1st ed. New Delhi: CBS Publishers and Distributors,1997,52-81.

Goodman A, Gilmann, Theodore WR, Nies AS, Taylor P, Goodman & Gilman's The Pharmacological Basis of Therapeutics, 8th Edition, Maxwell MacMillan Pergamon Publishing Corporation, New York; 1990,1487.

ICH guidelines, ICH topic Q1A (R2), stability testing of new drug substances and products, step 5, 2736.

Ilango R, Kavimani S, Mullaicharan AR, Jayakar B, *In vitro* studies on buccal strips of glibenclamide using chitosan, Indian Journal of Pharmaceutical Sciences, 59(5),1997,232-233.

Khanna R, Agrawal SP and Alka Ahuja, Preparation and evaluation of mucoadhesive buccal films of clotrimazole for oral candida infections, Indian Journal of Pharmaceutical Sciences, 59(6), 1997,299-296.

Klepser TB, Kelly MW, Metformin hydrochloride: An antihyperglycemic agent, Americal Journal of Health System Pharmacy,54(8), 1997, 893-903.

Li C, Bhatt PP, Johnston TP, Evaluation of a mucoadhesive buccal patch for delivery of peptides: in-vitro screening of bioadhesion, Drug Development and Industrial Pharmacy, 24(10),1998,919-926.

Raghuraman S, Ravichandran V, Shaffia SH, Rajasekaran T, Denito Johnson D, Sankar V, Design and evaluation of propranalol hydrochloride buccal films, Eastern Pharmacist, 2001,109-111.

Saisivam S, Muhammed Ashereff MH, Maria Gerald NS, Jayaprakash S and Nagaranjan M, Design and evaluation of diltiazem hydrochloride buccal patches. Indian Journal of Pharmaceutical Sciences, 2000,236-242

Salmat-Miller N, Chittchang M, Johnston TP, The use of mucoadhesive polymer in buccal drug delivery, advance drug delivery review, 57(11), 2005,1666-1691.

Shojaei AH, Buccal mucosa as a route for systemic drug delivery, Journal of Pharmacy and Pharmaceutical Sciences, 1(1), 1998, 15-30.

Soliman MS, Rahim BN and Golamhosein Y, Formulation and in-vitro evaluation of prednisolone buccoadhesive tablets II, Famaco, 60(4), 2005, 339-334.