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Research Article

FORMULATION, DEVELOPMENT AND *IN-VITRO* EVALUATION OF MUCOADHESIVE BILAYERED BUCCAL PATCHES OF MONTELUKAST SODIUM

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ABSTRACT

The present study was an attempt to develop and evaluate mucoadhesive bilayered buccal patches to ensure satisfactory unidirectional release of montelukast sodium (MS). The patches were designed to release the drug for a prolonged period of time so as to reduce the frequency of administration of the available conventional dosage forms of MS. Experimental design was built to investigate the effect of two factors sodium carboxymethylcellulose (NaCMC) and Carbopol 974P (CP 974P), each at three levels, as independent variables on mucoadhesion strength and in-vitro residence time as dependent variables. The Design Expert software has given the optimized formulation as desired patches with mucoadhesion strength in the range 41–48 g and in-vitro residence time in the range 243–268 minutes could be obtained by using NaCMC amount in the range 2.1%w/v to 2.7% w/v and CP 974P amount in the range 0.6%w/v to 0.9% w/v. The patches were prepared by solvent casting method and also evaluated for key test parameter such as in vitro drug release. The impermeable backing layer prepared was of ethyl cellulose based to ensure unidirectional drug release. Efficiency of impermeable backing membrane found suitable for mucoadhesive dosage form was also evaluated. After 8 hours the drug lost from ethyl cellulose based backing membrane was <9% of the total amount. The drug release kinetics and mechanism was found to be function of suitable combination of polymers NaCMC and CP 974P. The drug release mechanism was found to follow non-fickian diffusion as release mechanism. Stability study was conducted at accelerated storage condition and prepared mucoadhesive bilayered buccal patches were found to be suitable with respect to morphological characteristics and with in-vitro drug release mechanism unaffected after three months.

Keywords: Montelukast sodium; Mucoadhesive buccal patch; Sodium carboxymethylcellulose, Carbopol 974P; Impermeable backing membrane.

INTRODUCTION

Asthma is one of the most common diseases affecting human for the period of 6–8 hours (hr) also during which most individuals are asleep. A limiting factor is the relatively short duration of bronchodilator activity of β2-adrenergic agonists. MS is a leukotriene receptor antagonist (LTRA) prescribed in maintenance treatment of asthma, chronic asthma attacks and to relieve symptoms of seasonal allergies [1].

Administration of montelukast through mouth dissolving tablet has been addressed in recently reported work [2]. But the known drawback of per oral delivery of montelukast is that it undergoes hepatic first pass metabolism. Thus it shows plasma or biological half-life of 2.5 to 5.5 hr, thereby limiting bioavailability up to nearly 64%. Also the repeated administration of MS through conventional mode of delivery leads to tolerance to its bronchodilator effect [3]. Hence, there is a need to develop controlled drug delivery system which can overcome the first pass effect, reduce the frequency of dosing and improve bioavailability. To control the delivery rate and as well as to increase the bioavailability, attempts have been made to deliver montelukast through buccal mucosa [4]. But not enough potential pharmaceutical work has been reported pertaining to mucoadhesive buccal bilayered patches of MS. The present work therefore describes such stable delivery system of MS, which will expectedly improve the biological half-life as well as bioavailability of montelukast.

The interest in novel route of drug administration occurs from their ability to enhance the bioavailability of the drugs impaired by narrow absorption windows in the gastrointestinal tract. Buccal drug delivery has lately become an important route of drug administration. Attempts have been made to formulate various mucoadhesive devices including tablets [5], films [6], patches [7,8] disks [9,10] strips [11] ointments [12] and gels [13]. Buccal patch may be preferred over adhesive tablet in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which is easily washed away and removed by saliva.

A wide range of polymers of synthetic, semi synthetic and natural origin like carbopol, polycarbophil, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, eudragit RL-100, polyvinylpyrrolidone k30, chitosan and xanthan gum have been described for the formulation of bioadhesive systems, but none of these polymer possess all the characteristics of an ideal polymer (nontoxic, nonirritant, strong non covalent adhesion, sustained release, stable and cheap) for a bioadhesive drug delivery system. Carbopols, which are widely explored industrially for commercial applications, are excellent bioadhesives but with potential mucosal irritating character. Irritant properties of carbopols can be reduced by combining it with other non-irritant bioadhesive polymers like NaCMC, while still retaining relevant bioadhesiveness at targeted concentration range of polymeric combinations[14].

Therefore, the present study was aimed to design and characterize mucoadhesive buccal bilayered patches of MS prepared using a combination of NaCMC and CP 974P, backed with ethylcellulose based membrane which would improve the biological half-life as well as bioavailability of montelukast therefore expectedly also prolonging and improving the leukotriene receptor antagonism activity of MS.

MATERIALS AND METHODS

Montelukast sodium reference standard (Montelukast Purity: 99.93%) and Montelukast Sodium drug was kindly supplied by Ranbaxy Research Laboratories, Gurgaon and was used as received. Sodium carboxymethylcellulose, Ethyl cellullose (S.D. Fine Chemicals, Mumbai, India), Carbopol 974P (Loba Chemicals Private Limited, Mumbai, India), propylene glycol (Qualigens Fine Chemicals, Mumbai, India) were used. All other chemicals and reagents were of analytical grade.

Preformulation studies

Solubility studies

Solubility studies were performed according to the Higuchi and Connoras method [15]. A saturated solution of MS was prepared by shaking an excess amount in 2 ml phosphate buffer pH 6.8/distilled water at 25 ± 10°C room temperature for 24 h. The saturated solution was withdrawn, filtered and analyzed at 282 nm using UV visible spectrophotometer (Shimadzu 1601, Japan)

Partition coefficient

A major criterion in evaluating the ability of a drug to penetrate the lipid membranes is its apparent oil/water partition coeffi cient [16]. Mutually saturated 1-octanol and phosphate buffer solution (pH 6.8) at 37°C were used containing Montelukast Sodium (100 µg/ml). The two phases were then allowed to equilibrate at 37°C for 24 h on a magnetic stirrer. The aqueous phosphate buffer phase was assayed using UV-spectrophotometer at 282 nm to get partition coefficient.

Solid state characterization

In order to ascertain whether or not any interaction occurred of drug substance into required formulation compositon, solid state characterization of drug and physical mixtures representative of optimized formulation were carried using differential scanning calorimetry (DSC) and fourier transform infrared spectroscopy (FTIR).

DSC study was carried out [17]on Mettler TA3000, Mettler DSC20 equipment. Calorimetric measurements were made with an empty cell (high purity alpha alumina discs) as the reference. The instrument was calibrated using high purity indium metal as a standard. The scans were recorded in a nitrogen atmosphere at a heating rate of 10°C/min.

The sample was dispersed in KBr powder and analyzed. Spectra were obtained by powder diffuse reflectance on a FT-IR spectrophotometer type FT-IR 1600 Perkin Elmer Co. Yokohama, Japan [18].

Formulation of mucoadhesive bilayered buccal patch [19]

Backing Layer

For preparing a formulation a borosilicate glass mould (10 cm x 10 cm x 1.5 cm) was used as a casting surface. Initially, backing membrane of ethyl cellulose was fabricated by slowly pouring a solution containing 500 mg of ethyl cellulose and 2% dibutyl phthalate in 10 ml acetone to the clean dry borosilicate glass mould and air drying for 1 hr.

Mucoadhesive layer containing drug

Doubled distilled water (DDW), used in the preparation of polymeric gel, was degassed under vacuum to avoid the formation of air bubbles. The mucoadhesive films were prepared by using polymers like CP 974P and NaCMC. Propylene glycol (PG) was used as plasticizer. The weighed amount of CP 974P was added to one-third portion of the required DDW and stirred for at least 30 minutes until clear polymeric solution was obtained. The weighed amount of NaCMC was added to minimum portion of the required DDW and stirred for at least 30 minutes until clear polymeric solution was obtained. The calculated amount of Monetukast Sodium 5.2 mg equivalent to Montelukast 5.0 mg was incorporated under continuous stirring in NaCMC polymeric solution after levigation with 1.5 % v/v of PG. The CP 974P was added to the dispersion of NaCMC under continuous stirring. Final volume adjusted with DDW and stirring continued for 3 hr. The resultant clear solution thus obtained was then poured on the preformed backing layer of ethyl cellulose in a dust free atmosphere and allowed to dry undisturbed for 4 hr- 6 hr at 60°C in the oven till a flexible patch was formed. The dry bilayered films (patch) obtained were peeled off, cut into smaller pieces of 1 cm x1 cm sizes, packed in aluminum foil and stored in a well closed glass containers at room temperature until evaluation.

Table 1: Formulae for different experimental runs

Batch code	Experimental run	MS (mg/ Patch)	Polymer Combination with coded factor levels		PG (%v/v)	DDW
			NaCMC (%w/v)X1	CP 974P (%w/v)X2		
F1	1	5.2	2.1	0.9	1.5	q.s.
F2	2	5.2	2.4	0.9	1.5	q.s.
F3	3	5.2	2.7	0.9	1.5	q.s.
F4	4	5.2	2.1	0.6	1.5	q.s.
F5	5	5.2	2.4	0.6	1.5	q.s.
F6	6	5.2	2.7	0.6	1.5	q.s.
F7	7	5.2	2.1	0.3	1.5	q.s.
F8	8	5.2	2.4	0.3	1.5	q.s.
F9	9	5.2	2.7	0.3	1.5	q.s.

Optimization of using 3^2 full factorial designs [20]

A 3^2 randomized full factorial design was used in this study. Two factors were evaluated, each at three levels, and experimental trials were performed on all nine possible combinations (Table 1). The amount of NaCMC (X1) and the amount of CP974P (X2) were selected as independent variables. The mucoadhesion strength and in-vitro residence time were selected as dependent variables.

Regression polynomials for the individual dependant variables (mucoadhesion strength and in-vitro residence time) were calculated with the help of Design Expert 8.0 software and applied to approximate the response surface and contour plots. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

$$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X1^2 + b22X2^2$$

Where, Y is the dependent variables, b0 is the arithmetic mean response of the nine runs, and b1 is the estimated coefficient for the factor X1. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1X2) show how the response changes when two factors are simultaneously changed.

The polynomial terms ($X1^2$ and $X2^2$) are included to investigate non-linearity. Formulation of desired characteristics can be obtained by factorial design application

Evaluation of formulated mucoadhesive bilayered buccal patch

Thickness Testing

The thickness of ten randomly selected patches from every formulation batch was determined using a standard screw gauge with least count of 0.01mm. The thickness was measured at three different spots of the patch and average was taken [21].

Weight Uniformity

For the evaluation of weight ten patches of 1 cm x1 cm sizes from every formulation were taken and weighed individually on electronic balance. The average weights were calculated [21].

Folding Endurance

Folding endurance of the patch was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance [21].

Swelling Study

Increase in weight due to the swelling was measured. Patch of 1 cmx1 cm size was weighed on a pre-weighed cover slip and patch initial weight was recorded (W0). It was kept in a petridish of diameter 4cm and 5ml of phosphate buffer pH 6.8 was added. At

time interval of 1, 2, 4, 6 and 8 hr the cover slip was removed and excess of water was carefully removed and swollen patch was weighed (Wt) [22]. The difference in the weights provided the weight increase due to absorption of water and swelling of patch. The experiment was repeated three times. The % swelling (S) was calculated by following formula

$$\% S = \frac{Wt - Wo}{Wo} \times 100 \quad \ldots\ldots 1$$

Drug Content Uniformity

The patches were evaluated for drug content by referring reversed phase (RP) HPLC method of Ahmed B. Eldin et. al [23] and Ibrahim A. Alsarra [24]. Chromatographic data was acquired using Winchrome software. The reversed phase (RP) HPLC method was hence explored using Shimadzu model HPLC system to suitably proceed as follows:

Chromatographic conditions

The separation of compound was made on an Kromasil® C18 column, (5µm, 250mm×4.6mm), with column oven temperature 30°C. The mobile phase pumped at a flow-rate of 1.5 mL/min. Detection was set at a wavelength of 282nm. The injection volume was 20 µl & run time 15 minutes.

Preparation of buffer (pH 3.5)

Dissolved about 3.85 g of ammonium acetate in 1 L of water (HPLC grade). Adjusted pH to 3.5 ± 0.05 with glacial acetic acid (AR grade). Filtered the solution through 0.45µm porosity nylon filter.

Preparation of mobile phase

Prepared a suitable quantity of a mixture of buffer (pH 3.5) and methanol (HPLC grade) in the ratio of 15:85, mixed and degassed.

Preparation of diluents

Prepared a suitable quantity of a mixture of water and methanol in the ratio of 30:70, mixed and degassed.

Preparation of standard solution

Accurately weighed and transferred about 52 mg of Montelukast Sodium primary reference standard into a 50 mL volumetric flask, added about 30 mL of diluents and dissolved, sonicated if necessary and made up the volume with diluents. Diluted 5 mL of this solution to 100 mL with diluents. Filtered the solution through 0.45µm nylon filter and discarded first few mL of the filtrate.

Preparation of sample solution

Transferred one intact patch into a 200 mL volumetric flask. Added about 120 mL of diluents and sonicated for about 20 minutes with intermittent shaking. Made up the volume with diluents and mixed. Filtered through 0.45µm nylon filter and discarded first few ml of the filtrate.

All the volumetric flasks containing montelukast were wrapped with aluminum foil and stored in the dark until used. Repeated the operation on eight other patches.

Evaluation of system suitability parameters:

Injected the standard solution into the chromatograph and monitored the chromatograms. The system was suitable for analysis if and only if; the symmetry factor for montelukast was not more than 1.5, the column efficiency determined from the montelukast peak should not be less than 2500 theoretical plates, the relative standard deviation for five replicate injections of standard solution was not more than 1.5%.

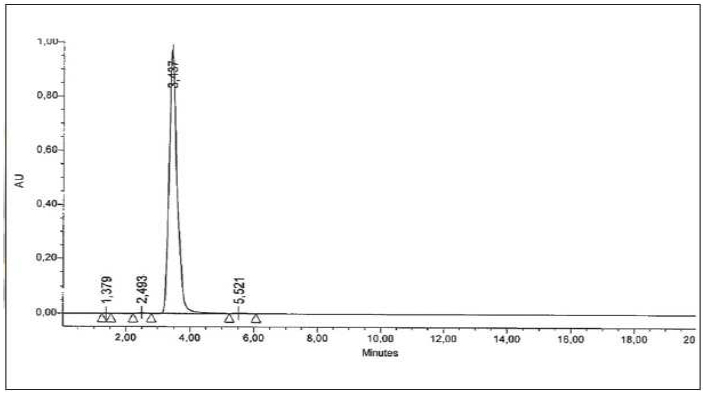

Fig. 1: A typical chromatogram of montelukast sodium standard (10µg/ ml).

Showing retention time at 3.4 min

Procedure

Injected sample solution (single injection) into the chromatograph and recorded the chromatograms. The retention time of sample, montelukast peak is about 3.4 minutes.

Calculations

Individual content of montelukast was calculated by the equation;

$$\frac{AT}{AS} \times \frac{DS}{DT} \times \frac{P}{C} \times \frac{586.2}{608.2} \quad \ldots\ldots 2$$

Where;

AT = Area counts of montelukast peak in the chromatograms of the sample solution.

AS = Average area counts of montelukast peak in the chromatograms of the standard solution as obtained under system suitability.

DS = Dilution factor of the standard solution.

DT = Dilution factor of the sample solution.

P = Percent potency of montelukast sodium working standard, on as is basis.

C = Label claim of montelukast in mg

586.2 = Molecular weight of montelukast.

608.2 = Molecular weight of montelukast sodium.

Corrected percent potency was calculated using the following formula;

$$P\ (\%w/w) = \frac{(100 - W_t)}{(100 - W)} \times P_1 \quad \ldots\ldots 3$$

Where

P_1 = Percent potency of Montelukast sodium working standard, on as is basis

W = Percent water content of Montelukast sodium working standard

W_t = Percent water content of Montelukast sodium working standard on the day of use using water by Karl Fischer (Kf) method.

Similarly the individual content of montelukast for eight other patches was also calculated.

Microenvironment pH [25]

The patch was left to swell in 5 ml of phosphate buffer pH 6.8 in small beakers, and the pH was measured after 8 hr by placing the electrode in contact with the microenvironment of the swollen patch. The average pH of five determinations was reported.

Mechanical characterization

Mechanical parameters, tensile strength and elongation at break were calculated from the load time profiles of the patches using INSTRON® tensile tester. Upper and lower grips of the sample with a gauge length of 5×1 cm, were attached to the crosshead and the base plate respectively in such a way that the former was located exactly 5 cm above the latter. The crosshead was moved upwards at a speed of 1 cm/s. The force and elongation were measured when the film broke [26]. Results were reported as the mean (±SD) of five replicates.

The following equations were used:

$$\text{Tensile strength (Kg.mm}^{-2}) = \frac{\text{Force at break (Kg)}}{\text{Initial cross sectional area of sample (mm}^2)} \quad \ldots\ldots\ldots\ldots\ldots 4$$

$$\text{Elongation at break (\%mm}^{-2}) = \frac{\text{Increase in length (mm) x 100}}{\text{Original length (mm) x Cross sectional area (mm}^2)} \quad \ldots 5$$

Measurement of mucoadhesion strength

The strength of bond formed between the formulation and mucosa membrane excised from porcine buccal mucosa was determined using two-arm balance method [27]. Fresh porcine buccal mucosa was obtained from a local slaughterhouse and used within 2 hr of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water and then with isotonic phosphate buffer pH 6.8 (IPB) as moistening fluid. Briefly, buccal mucosa section (2.4 mm thick, 3×5 cm) was fixed on the plane surface of glass slide (3×5 cm) attached (with adhesive tape) to bottom of smaller beaker, kept inverted in 500 ml beaker attached to the bigger beaker. IPB was added to the beaker up to the upper surface inverted beaker with buccal mucosa. The buccal patch of size 1 cmx1 cm was stuck to the lower side of the upper clamp with cyanoacrylate adhesive. The exposed drug loaded surface of patch was moistened with 15 µl of IPB and left for 30 seconds (s) for initial hydration and swelling. Then the platform was slowly raised until the drug loaded surface came in contact with mucosa. Two sides of the balance were made equal before study. After a preload (50 g) time of 2 minutes, water was added to the polypropylene bottle present in another arm, until the film was detached from the buccal mucosa. The water collected in the bottle was measured and expressed as weight (g) required for the detachment as indicative of mucoadhesion strength of the formulated patches (Table 7).

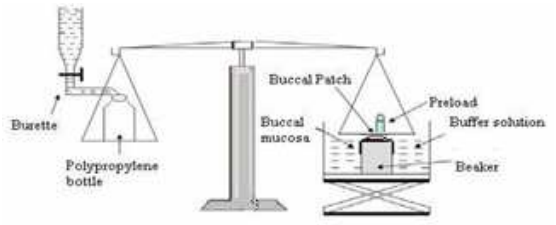

Fig. 2: Schematic diagram of apparatus used for determination of mucoadhesive strength

Determination of In vitro residence time

The in vitro residence time was determined using a locally modified USP disintegration apparatus, based on the apparatus applied by Nakamura et al [28]. The disintegration medium was composed of 500 ml phosphate buffer pH 6.8 maintained at 37 ± 0.5 °C. A porcine buccal mucosa section (2.4 mm thick, 3×5 cm) was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive patch was hydrated from drug loaded surface using 15µl phosphate buffer and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the patch of each batch from the mucosal surface was recorded in Table7.

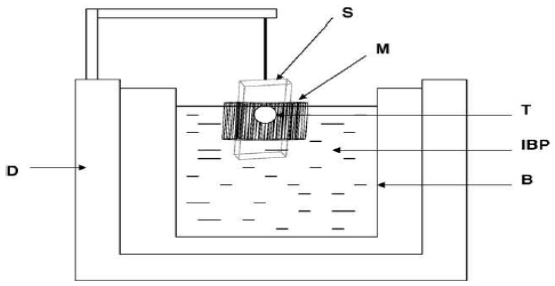

Fig. 3: Schematic diagram of apparatus used for determination of residence time.

S-Glass slab;

D-Disintegration apparatus;

B- Glass beaker;

M- Porcine mucosal membrane

T- Mucoadhesive buccal patch;

IBP- Isotonic phosphate buffer pH 6.8

Moisture Absorption

Moisture absorption (MA) study was performed by a modified method of Kanig and Goodman [29]. Accurately weighed preconditioned patches (W_0) were placed in a constant humidity chamber (containing a saturated solution of ammonium chloride which gives a relative humidity of 79.5%) set at room temperature. Patches were weighed (Wt) at an interval of 1, 3 and 7 days.

Percent MA was calculated using the following equation:

$$\% \text{ MA} = \frac{(W_t - W_0)}{W_0} \times 100 \quad \ldots\ldots\ldots\ldots\ldots 6$$

Vapor Transmission

A modification of the method used by Kanig and Goodman [29] was employed for the determination of vapor transmission from the patches. Glass-bottle (length=3.7 cm, internal diameter=1.3 cm) filled with 2 g anhydrous calcium chloride and an adhesive (Quickfix®) spread across its rim, was used in the study. The patch was fixed over the adhesive and the assembly was placed in a constant humidity chamber maintained at 37±2 °C. The difference in weight after day 1, day 3 and then day 7 was calculated. Vapor transmission rate (VTR) was obtained as follows:

$$\text{VTR} = \frac{\text{(Amount of moisture transmitted)}}{\text{(Area} \times \text{Time)}} \quad \ldots\ldots\ldots\ldots\ldots 7$$

In Vitro Drug Release Studies

Different methods have been reported for in vitro drug release using different dissolution media [30]. The method described by Varsha Agarwal et al. was further explored in which a modified dissolution apparatus was used for in vitro release studies [22]. The USP dissolution apparatus (Paddle method) was thermostated at the temperature of 37 ± 0.5 °C and stirred at rate of 50 rpm. Each patch was fixed on a glass slide with the help of cyanoacrylate adhesive so

that the drug could be released only from upper face. Then the slide was immersed in the vessel containing 500 ml of phosphate buffer solution pH 6.8. The aliquots of 3 ml were withdrawn at predetermined time intervals of over 8 hr and replaced with equal volumes of the dissolution medium equilibrated at the same temperature. Drug concentration of the withdrawn samples was analyzed after filtration (0.45 µm Millipore filter) by UV-Visible Spectrophotometer at 282 nm using 10 mm quartz cells with a slit width of 1 nm and a scan speed of 60 nm/min (a computer controlled double-beam Jasco 7800, UV-Visible Spectrophotometer, Tokyo, Japan). All experiments were carried out in triplicate. Sink conditions were maintained throughout the study. All the volumetric flasks containing montelukast were wrapped with aluminum foil and stored in the dark.

Calibration curve of montelukast sodium in phosphate buffer solutions pH 6.8 were obtained at λmax 282 nm with a UV-Visible Spectrophotometer. Beer's law obeyed to construct the calibration curve was in the concentration range of 0-30 µg/ml. Analyses were done in triplicate.

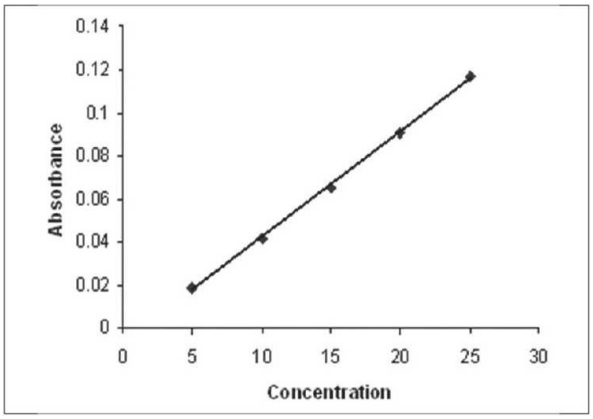

Fig. 4: A typical calibration curve for montelukast sodium at 282 nm.

Percent drug released was calculated by the equation;

$$\frac{AT}{AS} \times \frac{DS}{DT} \times \frac{P}{100} \times \frac{586.2}{C\ 608.2} \quad \ldots\ldots 8$$

Where;

AT = Absorbance of sample solution of montelukast.

AS = Absorbance of standard solution of montelukast.

DS = Dilution factor of the standard solution.

DT = Dilution factor of the sample solution.

P = Percent potency of montelukast sodium working standard, on as is basis.

C = Label claim of montelukast in mg

586.2 = Molecular weight of montelukast.

608.2 = Molecular weight of montelukast sodium.

Corrected percent potency was calculated using equation 3 described above.

Drug Release Kinetics

To examine the release mechanism of MS from the prepared mucoadhesive buccal bilayered patches, the results were analyzed according to the following equation [31, 32].

$$M_t / M_\infty = Kt^n \quad \ldots\ldots 9$$

where M_t / M_∞ is the fractional drug released at time t, k is a kinetic constant incorporating structural and geometrical characteristics of the drug/polymer system (device), and n is the diffusional exponent that characterizes the mechanism of drug release. For non-Fickian release, the n value falls between 0.5 and 1.0 (0.5< n <1.0), whereas in the case of Fickian diffusion, n < 0.45; for zero-order release (case II transport), n =1, and for super case II transport, n > 1 [27, 33, 34].

Table 2: Drug release behaviors

n value	Mechanism
n≤0.5	Quasi-fickian diffusion
0.5	fickian diffusion
0.5≤n≤1.0	Anomalous(non-fickian) diffusion
n≥1.0	Non –fickian super case II
1	Non –fickian case

Drug loss from Backing Layer [35]

Drug loss from the backing layer was determined by introducing single patch into Franz diffusion cell {(External diameter 3.0 cm, internal diameter 2.8 cm, total height of the apparatus 8.0 cm, height of the receptor compartment 5.0 cm with a hat shaped stainless steel wire mesh basket for placing the patch (2.6 cm diameter and 1 cm height)} having 30 mL of phosphate buffer solution pH 6.8 in receptor compartment (Fig. 5). The receptor compartment maintained at 37±1 °C was continuously stirred at 100 rpm. Samples of 3 mL were withdrawn at predetermined time intervals of over 8 hr and replaced with equal volumes of the drug release medium equilibrated at the same temperature. Drug concentration of the withdrawn samples was analyzed after filtration (0.45 µm Millipore filter) by UV-Visible Spectrophotometer at 282 nm using 10 mm quartz cells with a slit width of 1 nm and a scan speed of 60 nm/min (a computer controlled double-beam Jasco 7800, UV-Visible Spectrophotometer, Tokyo, Japan). All experiments were carried out in triplicate. Sink conditions were maintained throughout the study. All the volumetric flasks containing montelukast were wrapped with aluminum foil and stored in the dark. Percent drug loss was calculated according to equations described above for in-vitro drug release study.

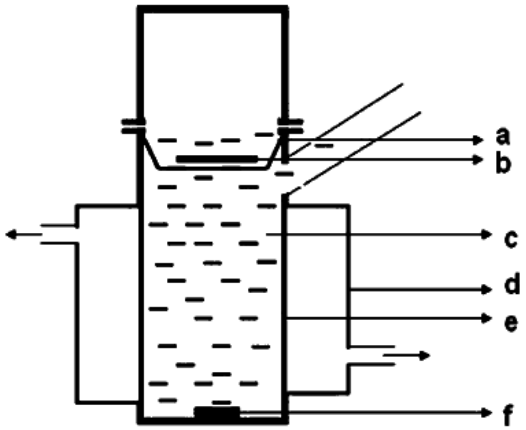

Fig. 5: a. Wire mesh, b. buccal patch, c. phosphate buffer pH 6.8, d. water bath, e. Franz diffusion cell, f. small magnetic bead.

Scanning electron microscopy

Buccal patch morphology was characterized by scanning electron microscopy. Samples were mounted on round brass stubs (12mm diameter) using double-backed adhesive tape and then sputter coated for 8 min at 1.1 LV under argon atmosphere with gold palladium before examination under the scanning electron microscope (JEOL JSM-6100 Scanning Electron Microscope, Japan). The images were captured on an Ilford PANF 50, film.

Stability study

Stability study was determined on optimized batch to check any morphological or physicochemical changes. The buccal patch was wrapped in aluminum foil and stored at condition 40°C±2°C/ 75%RH±5%RH for period of three months. Patch morphology and drug release characteristics were also evaluated after the period of three months.

RESULTS AND DISCUSSION

Preformulation studies

The solubility of MS in water and phosphate buffer pH 6.8 was found to be 100 ± 0.16 g/l and 95 ± 0.275 g/l, respectively. The apparent partition coefficient of montelukast sodium in an octanol/ phosphate buffer (pH 6.8) system was found to be 0.023 ± 0.63.

DSC studies were carried out with drug and also with physical mixture representative of actual qualitative composition which comprised of drug and polymers. To study the thermal stability of the drug it was subjected for DSC studies in the range of 20°C to 280°C. During the process of study it was observed that the drug had a DSC as follows: exotherm starts at >60°C (broad peak), followed by endotherm with onset: 155.25°C. The DSC thermogram of physical mixture showed sharp distinct endothermic peaks for MS and likely polymer which corresponds to individual drug without exhibiting any distinguished modification, which indicates that MS presented into the physical mixture is compatible with the polymers (Fig. 6, Fig. 7).

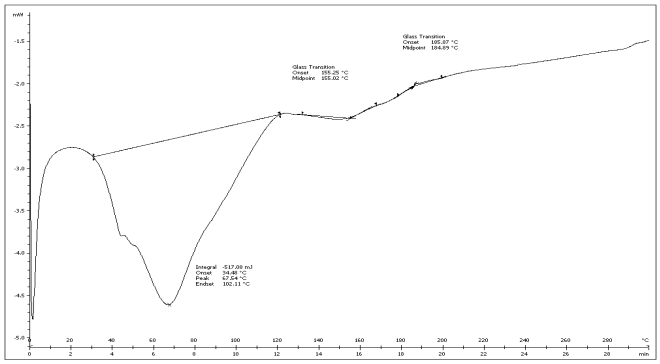

Fig. 6: DSC of pure montelukast sodium.

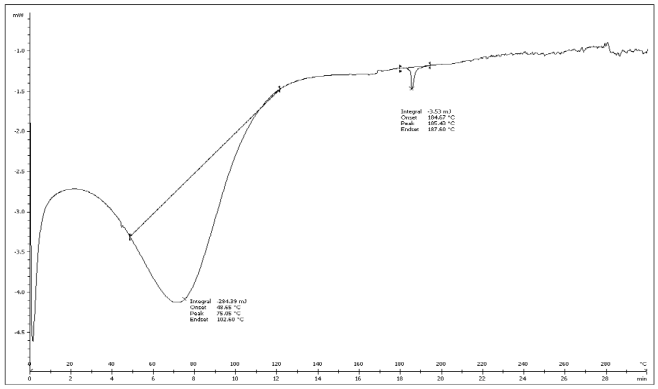

Fig. 7: DSC of physical mixture: optimized formulation.

From the FTIR studies, characteristic bands for important functional groups of drug and physical mixture of drug: polymers were identified. MS has got tertiary hydroxyl groups which have exhibited a broad peak around 3300 cm-1 and a carboxylic acid peak which is in the form of a salt has exhibited a strong peak near 1700 cm-1. Numbers of aromatic C-H peaks are also observed between 2900 cm-1 to 3000 cm-1. These are the characteristic absorption peak of MS. IR spectra indicating that there was no disappearance or shift in the bands of MS when combined with polymers. MS and polymers were compatible in the formulation (Fig. 8, Fig.9).

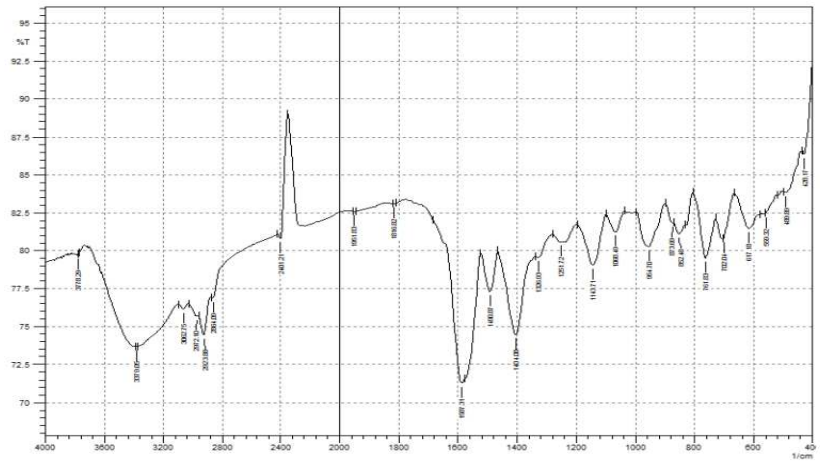

Fig. 8: FTIR spectra of Montelukast sodium.

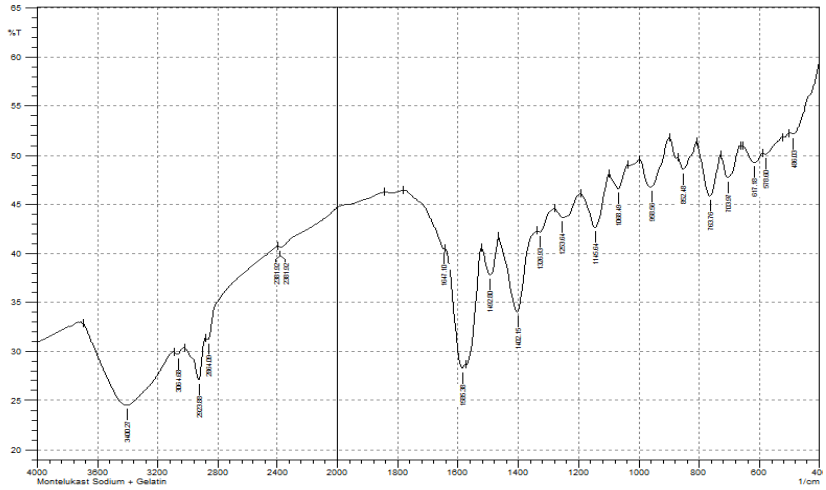

Fig. 9: FTIR spectra of physical mixture: optimized formulation.

Optimization of formulation using response surface quadratic model

The model F-value of 58.96 implied that the model was significant. There was only a 4.52% chance that a "Model F-value" this large could occur due to noise. Values of "Prob>F" less than 0.0500 indicate model terms were significant. In this case X1, X2, X12, X22 were significant model terms. Values greater than 0.1000 indicate the model terms were not significant (Table 3). (R2=0.9418), as seen from Fig. 10, the surface response plot revealed that a corresponding increase in the mucoadhesion strength of patches was observed with increase in concentration of CP 974P. This may be due to contact of the polymers with glycoprotein rich mucus wound fluid. Carbopol and NaCMC, the polyanionic polymers bearing carboxylic groups are responsible for hydrogen bonding with buccal mucosa. Therefore, the mucoadhesive preparations with the desired mucoadhesion strength could be designed by controlling the percentage of charged groups by adjusting to known pH range 35. The results also laid down predictive indications that the effect of concentration of CP 974P was more pronounced than the effect of concentration of NaCMC; that is, as the concentration of NaCMC increased the mucoadhesion strength decreased.

As seen from Table 4, the Model F-value of 18.54 implied the model was significant. Values of "Prob>F"indicated that X1, X2, X12, X22 were significant model terms. (R2=0.9686), the in-vitro residence time with porcine buccal mucosa in simulated saliva (pH 6.8) varied from 166 to 268 minutes. The results also indicated that the effect of concentration of CP 974P was more pronounced than the effect of concentration of NaCMC (Fig. 11). Patches containing low proportion of CP 974P, formed gel very fast and got eroded rapidly. Moreover, NaCMC had comparatively diminished effect on in-vitro residence time; that is, as the concentration of NaCMC increased in-vitro residence time decreased.

It was concluded that the desired patches with mucoadhesion strength in the range 41–48 g and in-vitro residence time in the range 243–268 minutes could be obtained by using CP 974P amount in the range 0.6%w/v to 0.9% w/v and NaCMC amount in the range 2.1%w/v to 2.7% w/v. Therefore batches F3 to F7 could be predicted as optimized formulations.

Table 3: Response 1- Mucoadhesive Strength: Analysis of variance (ANOVA) for Response Surface Quadratic Model

Source	Sum of Squares	Df	Mean square	F value	P value Prob > F	
Model	55.67	5	11.13	58.96	0.0034	Significant
X1-NaCMC	3.05	1	3.05	16.17	0.0276	
X2-Carbopol 974P	48.56	1	48.56	257.16	0.0005	
X1X2	0.66	1	0.66	3.52	0.1574	
$X1^2$	0.056	1	0.056	0.29	0.6253	
$X2^2$	3.34	1	3.34	17.67	0.0246	
Residual	0.57	3	0.19			
Cor total	56.24	8				

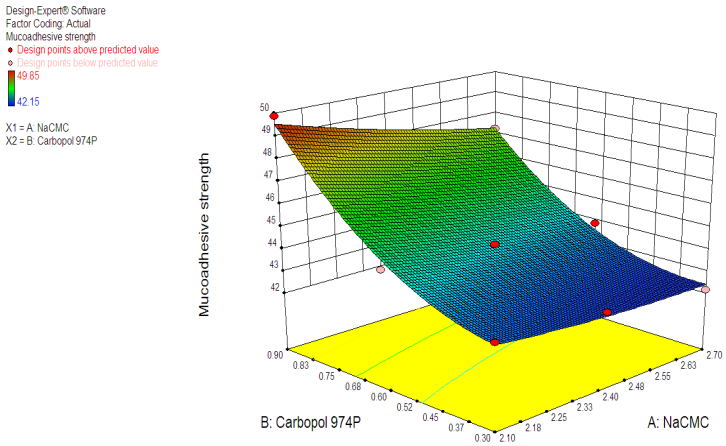

Fig. 10: Surface response plot for mucoadhesion strength.

Table 4: Response 2 – In-vitro Residence Time: Analysis of variance (ANOVA) for Response Surface Quadratic Model

Source	Sum of Squares	Df	Mean square	F value	P value Prob > F	
Model	8601.58	5	1720.32	18.54	0.0183	Significant
X1-NaCMC	2320.67	1	2320.67	25.01	0.0154	
X2-Carbopol 974P	4648.17	1	4648.17	50.09	0.0058	
X1X2	6.25	1	6.25	0.067	0.8120	
$X1^2$	2.00	1	2.00	0.022	0.8926	
$X2^2$	1624.50	1	1624.50	17.50	0.0249	
Residual	278.42	3	92.81			
Cor total	8880.00	8				

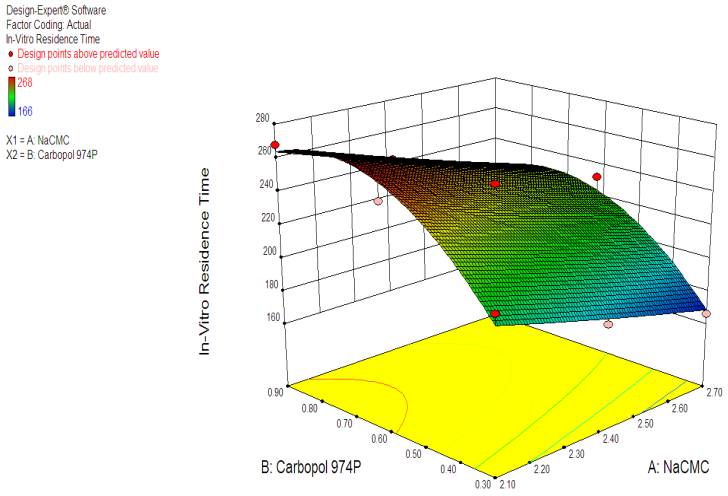

Fig. 11: Surface response plot for in-vitro residence time.

Physicochemical Characteristics of the patches

Physicochemical characteristics of the patches are summarized in the Table 5. The prepared patches were smooth, devoid of any imperfections (Fig. 17), uniform in thickness, mass, and drug content.

The average weight of patch is reported in Table 5 and calculated by using ten patches of sizes 1 cmx1 cm for standard deviation. The weight of buccal patch ranged from 75.7 ± 1.7 mg to 82.9 ± 1.3mg. The patch thickness ranged from 650 ± 0.33µm to 725 ± 0.46µm. The higher CP 9474P ratio in the buccal patch showed a thickness variation when compared with the thickness of batches prepared with lower ratios of CP 974P. The drug content in the buccal patches was found to be well within the range of 98.0% to 103.0%, indicating favorable drug loading and uniformity of patches in terms of drug content. Surface (microenvironment) pH decreased with the increasing concentration of CP 974P due to its acidic nature. The surface pH of the drug loaded mucoadhesive films was found well within the range of 5.5 to 6.3 which indicates no risk of mucosal damage or irritation [36]. Moreover no statistically significant difference was found in surface pH among F1 to F9 ($p>0.05$, one way ANOVA).

The folding endurance of the buccal patch was measured manually and it did not show any cracks even after folding at one place for more than 300 times for batch F1 – F9. Folding endurance was found to more than 300 for each case, indicative of reasonable flexibility of the films. It can be concluded that sodium carboxymethylcellulose at defined concentration range[37] is responsible for the inducing flexibility in film because it is best film forming agent.

Table 5: Physicochemical characteristics of the prepared buccal mucoadhesive patches of MS

Batch Code	Thickness (µm) (mean ± S.D. [a])	Weight (mg) (mean ± S.D. [a])	Drug content (mg) (mean ± S.D. [a])	Microenvi-ronment pH (mean ± S.D. [b])	Folding endurance (mean ± S.D. [a])
F1	725 ± 0.46	79.0 ± 1.6	4.93 ± 0.18	5.5 ± 0.09	> 300
F2	713 ± 0.32	76.4 ± 1.7	4.96 ± 0.13	5.8 ± 0.15	> 300
F3	709 ± 0.39	75.7 ± 1.7	5.05 ± 0.09	5.9 ± 0.11	> 300
F4	688 ± 0.48	80.2 ± 1.1	5.02 ± 0.14	6.1 ± 0.12	> 300
F5	682 ± 0.11	79.4 ± 1.7	4.98 ± 0.12	6.3 ± 0.08	> 300
F6	681 ± 0.09	82.9 ± 1.3	4.96 ± 0.18	6.0 ± 0.18	> 300
F7	650 ± 0.12	80.2 ± 1.9	5.05 ± 0.06	6.0 ± 0.16	> 300
F8	653 ± 0.15	78.5 ± 1.4	5.02 ± 0.09	6.2 ± 0.15	> 300
F9	652 ± 0.14	79.7 ± 1.8	5.02 ± 0.11	6.2 ± 0.10	> 300

a) n=10; S.D.: standard deviation for ten determinations. b) n=5; S.D.: standard deviation for five determinations.

Swelling study

The swelling state of the polymer (in the formulation) was reported to be crucial for its bioadhesive behaviour. Hydration is required for a mucodhesive polymer to expand and create a proper "macromolecular mesh" of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. Adhesion occurs shortly after the beginning of swelling but the bond formed between mucosal layer and polymer is not very strong. The adhesion will increase

with the degree of hydration until a point where over hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface [26].

The swelling profiles of different batches are shown in Table 6. These profiles indicate the uptake of water into the patch, producing an increase in weight. The swelling index of the prepared patches showed swelling rates in the order: highest with batch F9 and lowest with batch F1, indicating that as the concentration of CP 974P was decreased, the swelling index increased. Increased NaCMC containing patches showed higher percent swelling due to presence of more hydroxyl group in the NaCMC molecules. The maximum swelling was attained found to be more within 4 hours, then slowly up to 8 hours for all the 9 batches. The water soluble hydrophilic additive dissolves rapidly resulting in high porosity. The void volume is thus expected to be occupied by the external solvent diffusing into the film and thereby accelerating dissolution of the gel.

Mechanical properties and mucoadhesion strength

Table 7 shows the mechanical properties of the prepared buccal patches. The results shows that decrease in CP 974P content reduced both the tensile strength and elongation break significantly, indicative of a weaker and less elastic, less flexible patches. The formulations with high concentration of CP 974P resulting into the formation of hard and brittle patches [26].

Mucoadhesion strength of the prepared patches on porcine buccal mucosa as a function of CP 974P and NaCMC ratio have been shown in Table 7. The force required to detach patches from the mucosal membrane was found to be highest with the batch F1 while lowest with F9 which again leads to confirmation of the fact that as the concentration of carbopol decreases mucoadhesion strength decreases [37, 38, 39]. But no statistically significant difference was found in mucoadhesion strengths among F1 to F9 ($p>0.05$, one way ANOVA).

Table 6: Swelling Index of drug loaded buccal mucoadhesive films at different time intervals.

Swelling Index (mean ± S.D.)					
Batch Code	**Time (hr)**				
	1	**2**	**4**	**6**	**8**
F1	0.950 ± 0.230	1.330 ± 0.160	1.690 ± 0.200	2.940 ± 0.090	3.650 ± 0.150
F2	1.120 ± 0.180	1.500 ± 0.150	1.900 ± 0.180	3.550 ± 0.130	4.230 ± 0.185
F3	1.150 ± 0.170	1.830 ± 0.140	2.335 ± 0.110	3.995 ± 0.210	4.880 ± 0.130
F4	1.183 ± 0.135	2.343 ± 0.185	2.850 ± 0.175	4.225 ± 0.170	5.225 ± 0.158
F5	2.115 ± 0.150	2.650 ± 0.200	3.090 ± 0.127	4.774 ± 0.090	5.990 ± 0.115
F6	2.130 ± 0.190	3.225 ± 0.215	3.555 ± 0.130	5.335 ± 0.145	6.225 ± 0.163
F7	2.520 ± 0.125	3.770 ± 0.178	4.335 ± 0.200	5.995 ± 0.180	6.856 ± 0.180
F8	3.245 ± 0.130	3.990 ± 0.105	5.228 ± 0.235	6.353 ± 0.110	7.240 ± 0.145
F9	3.402 ± 0.090	4.172 ± 0.170	5.985 ± 0.230	6.980 ± 0.120	7.920 ± 0.110

a) n=3; S.D.: standard deviation for 3 determinations.

Table 7: Mechanical Properties, mucoadhesion strength and in-vitro residence time of the prepared buccal mucoadhesive patches of MS.

Batch Code	Tensile strength (Kg mm^{-2}) (mean ± S.D. [a])	Elongation at break (%mm^{-2}) (mean ± S.D. [a])	Mucoadhesion strength (g) (mean ± S.D. [b])	In-Vitro residence time (minutes)
F1	9.25 ± 0.15	42.13 ± 3.25	49.85 ± 1.53	268
F2	8.75 ± 0.15	35.15 ± 2.85	47.96 ± 1.65	243
F3	7.21 ± 0.26	32.86 ± 1.68	47.25 ± 1.24	217
F4	5.90 ± 0.22	25.23 ± 2.90	44.57 ± 0.95	253
F5	5.34 ± 0.10	24.23 ± 3.54	44.22 ± 1.10	245
F6	4.72 ± 0.38	19.65 ± 1.98	43.86 ± 1.86	232
F7	3.85 ± 0.27	14.86 ± 3.32	43.12 ± 2.85	212
F8	3.14 ± 0.15	10.15 ± 1.17	42.72 ± 1.10	183
F9	2.74 ± 0.32	10.05 ± 2.20	42.15 ± 2.15	166

a) n=10; S.D.: standard deviation for ten determinations. b) n=5; S.D.: standard deviation for five determinations.

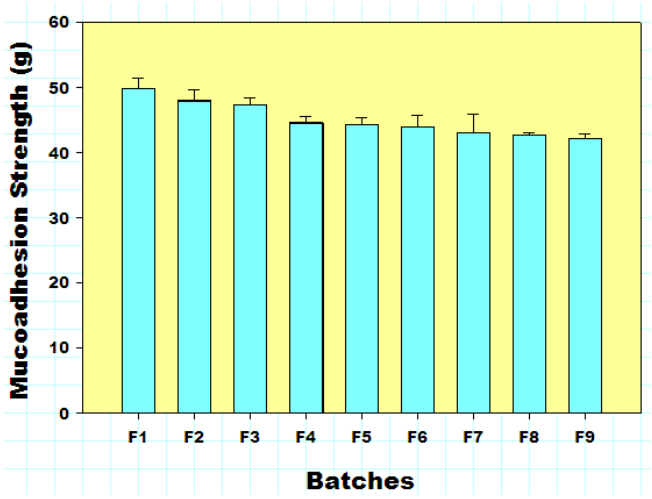

Fig. 12: Mucoadhesion strength of different batches F1-F9 (*n*=5)

In-Vitro residence time

The in vitro residence of patches showed that none of the polymer combinations became detached from the porcine buccal mucosa during the experiments for at least 2 hours (Table 7). The in-vitro residence time of different formulation was in the order; highest with F1 while lowest with F9 which correlates with mucoadhesve strength of the batches F1 to F9 indicating that as the concentration of NaCMC increased in-vitro residence time decreased. The water-soluble hydrophilic polymers like NaCMC dissolve rapidly and introduce porosity. The void volume is thus expected to be occupied by the external solvent which diffuses into the dosage form and thereby accelerate the dissolution of the gel.

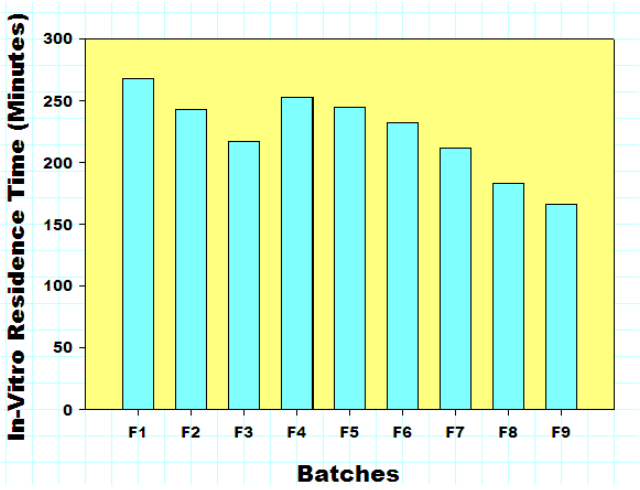

Fig. 13: In-vitro residence time of different batches F1-F9.

Moisture absorption and vapor transmission study

Tables 8 and 9 show the percentage of moisture absorbed and moisture vapor transmission rate from the prepared batches at different time intervals. The percent moisture absorbed decreased while vapor transmission rate increased with decreasing concentration of NaCMC. There was no significant difference between the batches F1 to F9 ($p>0.05$, one way ANOVA). Percent moisture absorbed increased as the period of exposure to the humidity condition was increased up to 3 days. From the day 3 to 7, there was no significant ($p>0.05$, one way ANOVA) absorption of moisture by the films, which might be due to saturation of vapour in polymeric structure of dosage form and / or in calcium chloride present in bottle.

Table 8: Percent moisture absorbed by the prepared buccal mucoadhesive patches of MS

Percent moisture absorbed (mean ± S.D. [a])			
Batch Code	**Day 1**	**Day 3**	**Day 7**
F1	19.35 ± 2.56	25.32 ± 1.24	26.11 ± 1.21
F2	19.98 ± 2.13	24.51 ± 2.10	24.98 ± 1.56
F3	19.82 ± 2.10	24.21 ± 2.87	24.45 ± 2.22
F4	18.11 ± 1.25	22.85 ± 1.54	23.33 ± 2.47
F5	18.73 ± 1.85	23.13 ± 0.96	23.88 ± 1.10
F6	19.11 ± 1.93	23.14 ± 1.12	23.25 ± 0.86
F7	17.87 ± 1.35	21.87 ± 1.86	22.11 ± 1.14
F8	17.85 ± 1.52	20.23 ± 1.12	21.17 ± 1.05
F9	16.98 ± 1.87	20.45 ± 1.47	22.45 ± 1.86

[a]n=3; standard deviation for three determinations

Table 9: Vapour transmission through the patches at different time intervals.

Moisture vapour transmission, g cm^{-2} h^{-1} (mean ± S.D. [a])			
Batch Code	**Day 1**	**Day 3**	**Day 7**
F1	$2.12 \times 10^{-3} \pm 0.95 \times 10^{-3}$	$3.35 \times 10^{-3} \pm 1.23 \times 10^{-3}$	26.11 ± 1.21
F2	$2.55 \times 10^{-3} \pm 1.12 \times 10^{-3}$	$3.42 \times 10^{-3} \pm 1.23 \times 10^{-3}$	24.98 ± 1.56
F3	$2.45 \times 10^{-3} \pm 1.89 \times 10^{-3}$	$3.34 \times 10^{-3} \pm 1.72 \times 10^{-3}$	24.45 ± 2.22
F4	$3.23 \times 10^{-3} \pm 1.12 \times 10^{-3}$	$4.96 \times 10^{-3} \pm 1.83 \times 10^{-3}$	23.33 ± 2.47
F5	$3.66 \times 10^{-3} \pm 1.52 \times 10^{-3}$	$4.93 \times 10^{-3} \pm 1.10 \times 10^{-3}$	$4.90 \times 10^{-3} \pm 1.12 \times 10^{-3}$
F6	$3.85 \times 10^{-3} \pm 1.05 \times 10^{-3}$	$5.23 \times 10^{-3} \pm 1.15 \times 10^{-3}$	$5.25 \times 10^{-3} \pm 1.10 \times 10^{-3}$
F7	$4.34 \times 10^{-3} \pm 1.12 \times 10^{-3}$	$5.86 \times 10^{-3} \pm 1.45 \times 10^{-3}$	$5.95 \times 10^{-3} \pm 1.52 \times 10^{-3}$
F8	$4.55 \times 10^{-3} \pm 1.58 \times 10^{-3}$	$5.95 \times 10^{-3} \pm 1.22 \times 10^{-3}$	$5.86 \times 10^{-3} \pm 1.43 \times 10^{-3}$
F9	$4.86 \times 10^{-3} \pm 1.53 \times 10^{-3}$	$6.13 \times 10^{-3} \pm 1.31 \times 10^{-3}$	$6.11 \times 10^{-3} \pm 1.30 \times 10^{-3}$

[a]n=3; standard deviation for three determinations

In vitro drug release studies

Based on the predictions drawn out of response surface plots and evaluated parameters like optimum mucoadhesion strength, in-vitro residence time and swelling index characteristics, the patches obtained from the formulation F3, F5 and F7 were randomly selected and used for in-vitro drug release studies.

Fig. 14 shows release profiles of the buccal patches of MS. The rate and extent of drug release increased in the order F3>F5>F7 as the concentration of CP974P decreased in NaCMC based patches. Sustained release behavior was observed in all the case which may be attributed to the highly coiled network of CP974P [43]. The difference in cumulative percent drug release of formulations F3 and F5 was found significant ($p<0.05$, one way ANOVA).

F7 batch showed the highest cumulative percent release (101.06±1.9 after 8 h) which may be attributed to the higher swelling ability of NaCMC (Table 7). Pronounced swelling along with erosion of NaCMC matrix allowed the drug to diffuse at a faster rate. No significant difference was found in cumulative percent drug release of formulations F5 and F7. F3 batch showed cumulative percent release of 53.10±0.92 after 8 h which is significantly ($p<0.05$, one way ANOVA) less than F7 batch. Based on the slope and intercept values of in vitro release curves, cumulative percent drug releases were expected to reach 100% for batches F3 and F5 at 13, 10 respectively.

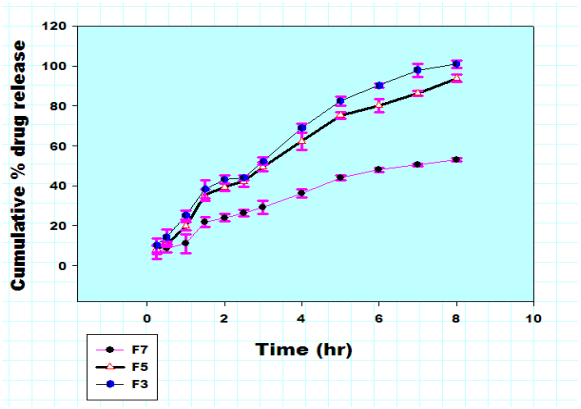

Fig. 14: Release profiles of MS from different fresh buccal mucoadhesive patches in phosphate buffer (pH 6.8) (*n*=3)

Drug release kinetics and mechanisms

Based on empirical calculations, the n values were found between 0.5 and 1.0 for the release of MS from all the formulations, indicating non-fickian release kinetics, which is indicative of drug release mechanisms involving a combination of both diffusion and chain relaxation mechanisms [40, 41, 42].

It was concluded that mucoadhesive bilayered buccal patches containing NaCMC (% w/v) and CP974P (% w/v) in the ratio 2.4:0.6 (Batch F5) was characterized by moderate swelling rate, maximum mucoadhesion strength as well as slower rate of in-vitro drug release which are favorable for sustained release buccal mucoadhesive patch. Therefore, only batch F5 was selected for investigation of further in-vitro studies.

Drug release (loss) from backing layer

To evaluate the performance of backing membrane in avoiding release of montelukast sodium, a study was conducted using Franz diffusion cell. Results of study showed that no drug was released in 120 min in the receptor compartment of diffusion cell and this modification lowered the loss of the drug up to 7 hours. After 8 hours the drug lost was <9% of the total amount. This modification practically stopped the loss of drug from backing layer. This indicated that ethyl cellulose membrane was impermeable to montelukast sodium and the swelling of mucoadhesive layer did not change integrity of backing layer. Hence patch was found to be efficient for unidirectional release of montelukast sodium through buccal mucosa.

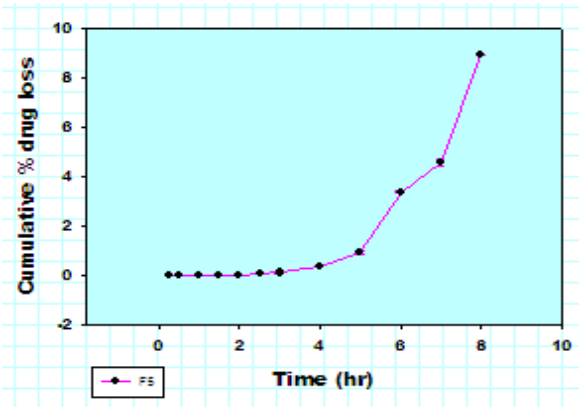

Fig. 15: Drug loss profile of MS from optimized buccal mucoadhesive patch, F5, in phosphate buffer (pH 6.8).

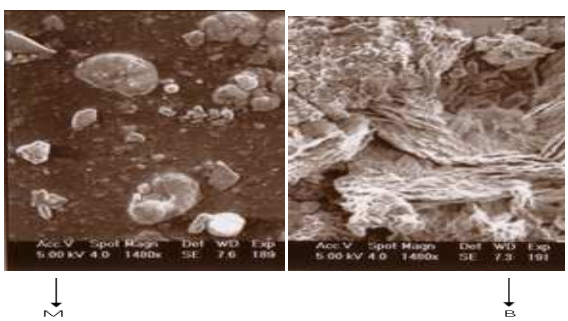

Fig. 16: Scanning electron micrographs showing backing (B) and drug loaded mucoadhesive (M) portions respectively of fresh patch (magnification 1480x)

Scanning electron microscopy

The SEM photograph (Fig. 16) indicates the uniform dispersion of polymeric solution with drug molecule (drug loaded mucoadhesive portion) and the hydrophobic ethylcellulose based film (backing membrane) shows closed polymeric network, which may be suitable as impermeable backing membrane

Stability study

The percent MS released versus time of stored patches demonstrates a decrease in the amount of drug release with time. Freshly prepared optimized buccal patches (F5) released nearly 93.8 % MS after 8 hours, whereas patches (F5) after storage at 40°C±2°C/ 75%RH±5%RH for period of three months released nearly 87.3 % drug at the same time point (Fig. 18), however, the decrease in extent of drug release was found to be insignificant (One Way ANOVA, P > 0.05). Also the values of n are between 0.5 and 1.0, indicating no change in release mechanism after three months storage at the specified condition. It can, therefore, be concluded that the prepared patch is stable at 40°C±2°C/ 75%RH±5%RH for period of three months. Scanning electron microscopy was also carried out to substantiate any change in the patches after storage (Fig. 19).

Fresh patches appeared as a smooth surface of a supersaturated solution of the drug in the polymer matrix. After storage at 40°C±2°C/ 75%RH±5%RH for period of three months, some crystallization of drug was observed. It is, therefore, apparent that the crystallization of MS during storage, as evidenced by the electron micrographs, may be responsible for the insignificant decrease in its release rate after storage.

Backing layer likely distended which might be due to pressure from inside due to hydration at high relative humidity. These findings suggest that prepared buccal mucoadhesive bilayered patch can be stored at stability 40°C±2°C/ 75%RH±5%RH for period of three months without any significant impact on in-vitro functional behavior.

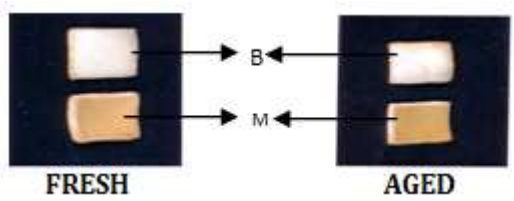

Fig. 17: Photographs showing backing (B) and drug loaded mucoadhesive (M) films of fresh and aged patches respectively.

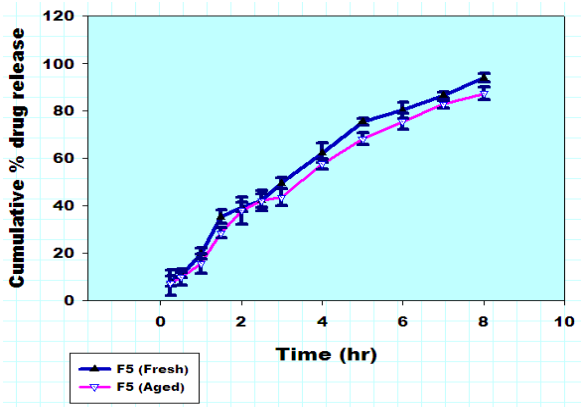

Fig. 18: Comparative drug release profiles of MS from fresh & aged buccal mucoadhesive patches in phosphate buffer (pH 6.8) (*n*=3).

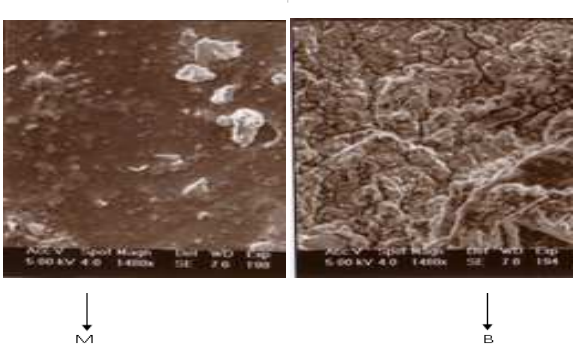

Fig. 19: Scanning electron micrographs showing backing (B) and drug loaded mucoadhesive (M) portions respectively of aged patch (magnification 1480x)

CONCLUSION

The main advantage of this drug delivery system is that it contains a lower drug dose, sufficient for therapeutic effect for prolonged time as it bypass first pass metabolism. All the prepared MS buccal mucoadhesive patches gave a reasonable mucoadhesion strength and in-vitro residence time, which is important for prolonging the contact time of the drug with the buccal mucosa, thus improving the overall therapy of asthma. Increasing CP 974P concentration resulted in decreasing the swelling index and microenvironment pH. Percent moisture absorbed decreased while vapor transmission rate increased with decreasing the concentration of CP 974P. Also, decrease in CP 974P content reduced both the tensile strength and elongation at break. The prepared buccal mucoadhesive patches of

MS provided a controlled and prolonged in vitro release of MS. This would be important for better patient compliance because of the decrease in the frequency of administration. Additionally, it may avoid the tolerance formation of MS. The prepared dosage form was found to stable with respect to morphological characteristics and drug release kinetics at accelerated storage condition after 3 months also. It may be concluded that buccal route is one of the alternatives available for administration of montelukast sodium. However use of impermeable backing membrane is necessary to ensure practically insignificant drug loss throughout the period of mucoadhesion and hence to achieve close to unidirectional delivery of drug through buccal mucosa.

Further work is recommended to support its efficacy claims by pharmacodynamic studies using guinea pigs in line with published research article of author [37].

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