Academic Sciences

Asian Journal of Pharmaceutical and Clinical Research

Vol. 4, Issue 4, 2011 ISSN - 0974-2441

Research Article

FORMULATION AND EVALUATION OF BUCCOADHESIVE TABLET OF MONTELUKAST SODIUM

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Received: 6 Aug 2011, Revised and Accepted: 28 Aug 2011

ABSTRACT

The buccal route is of particular interest with regard to the systemic delivery of small molecules that are subjected to first pass metabolism or for the administration of proteins and peptides. Drug absorption through a mucosal surface is efficient because mucosal surfaces are usually rich in blood supply, providing rapid drug transport to the systemic circulation and avoiding degradation by gastrointestinal enzymes and first pass hepatic metabolism, when placed at specific location. Mucoadhesive buccal tablets of Montelukast Sodium were prepared using Hydroxy Propyl Methyl Cellulose (HPMC), Sodium Carboxy Methyl Cellulose (NaCMC) as a mucoadhesive polymers. Nine formulations were developed with varying concentrations of polymers and excepients. Tablets were prepared by direct compression method and were subjected for evaluation of various physicochemical properties such as weight variation, tablet thickness, content uniformity, surface pH, bioadhesive strength and swelling index. In vitro bioadhesive strength showed that tablets containing intermediate concentration of HPMC & Na-CMC were excellent in bioadhesive nature. The, in vitro drug release study was studied in Phosphate buffer (pH 6.8). On basis of optimization studies, formulation F 8 was found to be bearing excellent bioadhesive strength of (31.33 ±1.52 g) and exhibited sustained in vitro drug release pattern of (99.69 % for 8 h).

Keywords: Mucoadhesion, Bioadhesive Polymer, Montelukast Sodium, HPMC and NaCMC

INTRODUCTION

Asthma is a respiratory condition characterized by recurrent attacks of dyspnea (difficulty breathing) and wheezing caused by spasmodic constriction of the bronchi. Montelukast Sodium widely used as a selective and orally active leukotrine receptor antagonist, that inhibits Cysteinyl leukotriene (CycLT 1 receptor). Montelukast inhibits physiologic actions of LTD at the CysLT receptor without any agonist activity. The oral bioavailability of drug is 64% and half-life is 2.7 to 5.5 hr[1]. Buccal mucosa is an attractive route for systemic delivery of many drugs since it is relatively permeable with a rich blood supply[2].The mucoadhesive buccal drug delivery system offers several advantages as compare to traditional methods of systemic drug administrations[3]. Moreover, buccal drug absorption can be terminated promptly in case of toxicity by removing the dosage form from the buccal cavity. A suitable buccal drug delivery system should possess good bioadhesive properties so, that it can retain in oral cavity for desired duration and localize the dosage form in a specific region and control the release rate of drug[4]. The aim of the present study was to design and develop buccoadhesive controlled release tablets of Montelukast Sodium that could be applied to the buccal mucosa to release the drug unidirectionally in buccal cavity in order to decrease gastric irritation and avoid first pass effect for improvement in bioavailability, to reduce the dosing frequency and to improve patient compliance. [5, 6, 7]

MATERIALS AND METHODS

Monteluakast Sodium was obtained as a gift sample from AJANTA Mumbai, Hydroxypropylmethylcellulose, Carboxymethylcellulose sodium were procured from SD fine Chem Lim. and Lactose monohydrate from MERCK. All the reagents used for the study were of analytical grade.

Drug – polymer - excipients compatibility study

This can be confirmed by carrying out by infrared light absorption scanning spectroscopy (IR) studies. Infra red spectra of pure drug and mixture of formulations were recorded by dispersion of drug and mixture of formulations in suitable solvent (KBr) using Fourier Transform Infrared Spectrophotometer (FTIR).

Formulation of muccoadhesive buccal tablets of Montelukast Sodium

Buccoadhesive tablet containing Montelukast Sodium were prepared by the Direct Compression Method All the ingredients in formulations were weighed and mixed with definite conc. of API, forming different batches. Finally each batch was mixed in a mortar with a pestle to obtain uniform mixing and passed with sieve #30. Powder were taken in compression machine and tablets were formed, using punch size of 5.5mm diameter. The tablets were packed in aluminum foil, wrapped with brown paper. Formulation chart is given in Table 1.

Evaluation of Physiochemical parameters of Tablets

Weight uniformity

Weigh 20 tablets individually. Calculate the average weight of tablets = Total weight of tablets Number of tablets. Not more than two of the individual weights deviate from the average weight (X) by more than the % deviation shown in the table below and none deviates by more than twice that %:

Pharmaceutical form	Average tablet Weight (X)	Percentage deviation
Tablets	80 mg or less	10
	> 80- < 250 mg	7.5
	250 mg or more	5

Hardness Test

The test measures crushing strength property defined as the compressional force applied diametrically to a tablet which just fracture (break) it.A force of about 4 Kg (may be measured in Kg) is considered the minimum requirement for a satisfactory tablet. Hardness was measured by Monsanto Hardness Tester.

Friability Test

Weight 20 tablet and placed in friability chamber. (25rpm/4min). Remove the tablet, reweigh tablet.

$$\% \text{ loss} = \text{Initial} - \text{Final} / \text{Initial} \times 100$$

Drug content

Five tablets were accurately weighed and powdered equivalent to 10mg of Monteluakst Sodium was weighed accurately and extracted in 100ml methanol by shaking for 20 min. After filtration through whatmann filter paper no.1 and sufficient dilution with methanol, samples were analyzed spectrophotometrically at 283 nm. This procedure was repeated thrice. Amount of drug present was determined from the standard curve of Montelukast Sodium in methanol.

Swelling study [5]

The tablets of each formulation were weighed individually (designated as W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37 ± 1°C. At regular intervals (0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hr), the tablets were removed from the petri dishes and excess water was removed carefully by using filter paper. The swollen tablets were reweighed (W2); the swelling index of each formulation was calculated using the formula-

$$\text{Swelling Index} = [(W2-W1) \div W1] \times 100$$

Where, W1 = initial weight of the tablet

W2 = final weight of the tablet

Matrix erosion [6]

After swelling study, the swollen tablets were dried at 60°c for 24 h in an oven and kept in desiccators for 48 h and reweighed (W3). Matrix erosion was calculated using following formula (Ramana MV et. al., 2007)

$$\% \text{ Matrix erosion} = [(W1-W3) \div W3] \times 100$$

Bioadhesion strength [6]

Bioadhesive strength of the buccal tablets was measured on the "Modified Physical Balance method". The sheep buccal membrane was used as the model mucosal membrane. The fresh sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of mucosa was tied to the glass slide which was moistened with phosphate buffer pH 6.8. The tablet was stuck to the lower side of another glass slide with glue. The both pans were balanced by adding an appropriate weight on the left- hand pan. The glass slide with mucosa was placed with appropriate support, so that the tablet touches the mucosa. Previously weighed beaker was placed on the right hand pan and water (equivalent to weight) was added slowly to it until the tablet detach from the mucosal surface. The weight required to detach the tablet from the mucosal surface gave the bioadhesive strength. The experiment was performed in triplicate and average value was calculated (Ramana et. al., 2007).

***In-vitro* dissolution studies** [7]

The USP dissolution test apparatus (apparatus II paddle type) was used to study the drug release from the tablets. The dissolution medium was 500 ml of phosphate buffer pH 6.8. The release was performed at 37 ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the glass slide with instant adhesive buccal mucosa of sheep. The slide was allocated to the bottom of the dissolution vessel. 10 ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through whatmann filter paper and analyzed after appropriate dilution by UV spectrophotometer at 283 nm.

Stability studies

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. One formulation was selected for stability studies on the basis of the *in-vitro* drug release profile. The formulation was subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines. The most satisfactory formulations were sealed in an aluminum foil and stored at 40 ± 2ºC, 75 ± 5 % RH for 1 months. Tablets were periodically removed and evaluated for physical characteristics, mucoadhesive properties, *in-vitro* drug release and *in-vitro* diffusion studies.

Table 1: Formulation Batches of Buccoadhesive Tablets of Montelukast Sodium

Ingredients (mg)	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
Montelukast Sodium	10	10	10	10	10	10	10	10	10
HPMC K -15	40	50	60	-	-	-	25	30	35
Na- CMC	-	-	-	30	40	50	15	20	25
Lactose	70	60	50	80	70	60	70	60	50
Magnesium Stearate	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12

Formulation Design: Study was carried out by using polymers HPMC K-15 and Na-CMC alone or in combination with different concentration along with API, diluent and lubricant in all batches.

Table 2: Physiochemical Parameters of Developed Buccoadhesive tablets of Monteluakast Sodium

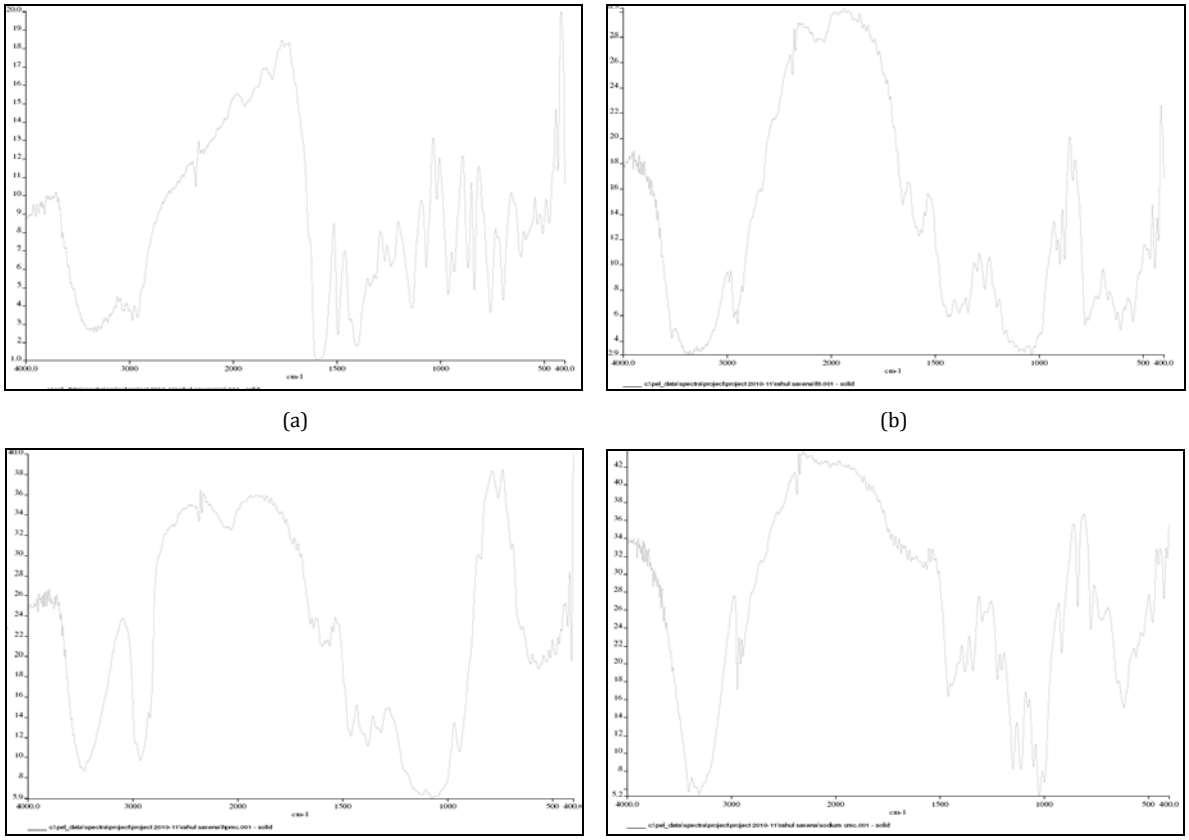
Code	Hardness (kg/cm^2)	Weight uniformity (mg)	Friability (% loss)	% Drug content
F 1	4.9 ± 0.34	120.12+1.67	0.42	82.14
F 2	5.5±0.45	120.57+1.59	0.43	82.85
F 3	4.9±0.68	120.12+1.79	0.43	85.71
F 4	5.8±0.76	120.21+1.32	0.45	89.28
F 5	5.8±0.20	120.15+1.82	0.42	82.85
F 6	5.7±0.23	120.06+ 1.64	0.45	87.14
F 7	5.8±0.66	120.23+1.72	0.42	92.14
F 8	6.0±0.87	120.15+1.36	0.41	99.28
F 9	5.1±0.24	120.22+1.72	0.42	93.57

Results were expressed in mean ± S.D

Table 3: Bioadhesive Properties of Buccoadhesive Tablets

Code	Bioadhesion strength (gm)
F 5	27.66 ± 2.08
F 6	28.16± 0.76
F 7	30.33± 2.51
F 8	31.33± 1.52
F 9	31.02± 1.01

Results were expressed in mean ± S.D, where n=3



(a) (b)

(c) (d)

Fig. 1: (a) FTIR Spectra of pure drug, (b) FTIR Spectra of blend drug with excipients, (c) FTIR Spectra of hpmc K-15, (d) FTIR Spectra of Na CMC

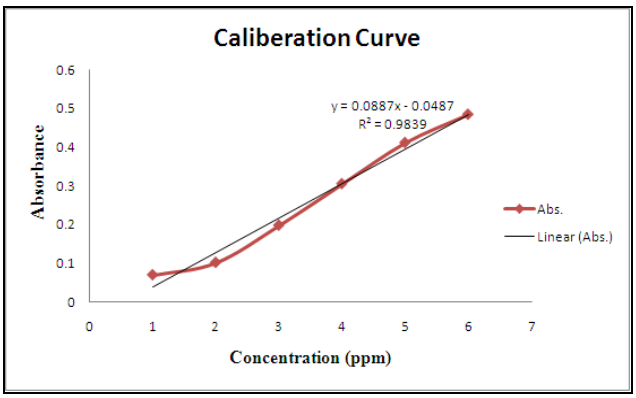


Fig. 2: Caliberation curve of montelukast sodium

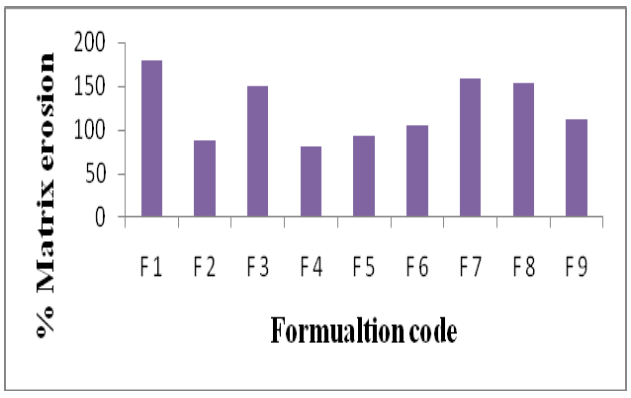


Fig. 3: Matrix Erosion of developed buccal tablets

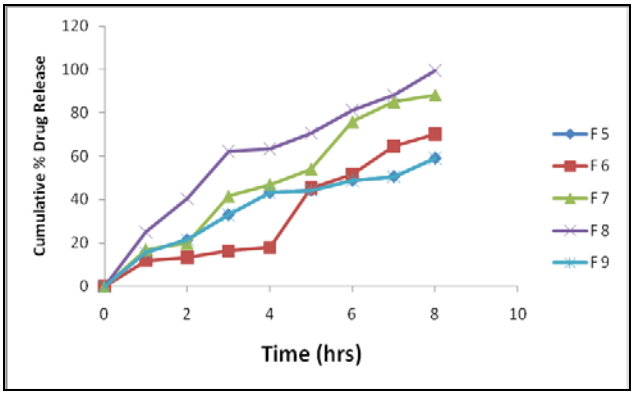


Fig. 4: Release profile of Montelukast Sodium from batches containing different concentration of excipients

RESULTS AND DISCUSSIONS

Main objective of present work was to develop Muccoadhesive tablet of Montelukast Sodium. Study was performed using HPMC K-15 and NaCMC as buccoadhesive polymers on the basis of their matrix forming properties and mucoadhesiveness while lactose is used as diluent and Magnesium stearate as lubricant. In Preformulation study, drug & excipients were kept in stability chamber and observed for 28days for any interaction , no change was observed. Further, drug polymer compatibility was done by FTIR, which gave conformation about their purity and showed no interaction between drug and selected polymers.

All the formulations were found to be satisfactory when evaluated for weight uniformity (120.12mg), hardness (6.0 kg/cm2) and friability (0.45%).Thus all tablets comply with the IP standards. Swelling index increased as the weight gain by the tablets increased proportionally with the rate of hydration. In swelling study, it was found that initially 04 batches showed higher swelling study together with higher matrix erosion. Due to these reasons in later study we considered only F 5, F 6, F 7, F 8 and F 9 batches for further evaluation.

Formulation F8, was found to be bearing excellent bioadhesive strength and the maximum cumulative percent of drug release, having intermediate concentrations of HPMC & Na-CMC. Thus , from all formulation batches F 8 was found to be optimized.

CONCLUSION

The prepared mucoadhesive buccal tablets of Montelukast sodium can help in surpass extensive hepatic first-pass metabolism and improve bioavailability. The buccal tablets showed a bioadhesive strength of more than 31gm. Similarly, *in-vitro* dissolution studies showed 99.69% drug release of the controlled dosage form. Batches containing combination of polymers showed good mucoadhesion and good release profile. It can be concluded that, F- 8 batch containing intermediate concentration HPMC (25%) & Na-CMC (16.6%) was found to be optimized. Drug will remain in buccal cavity, so first pass metabolism can be avoided.

ACKNOWLEDGEMENT

The authors are thankful to the *SVKM'S NMIMS SPTM SHIRPUR (M.S.)* College, for providing necessary facilities to carry out this work.

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