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Preparation and *In vitro* Evaluation of Mucoadhesive Tablets of Montelukast Sodium

Farzana Akter Bithi, Tushar Saha, Nusrat Ahmed, Ikramul Hasan and Md. Selim Reza

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh

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Abstract

Mucoadhesive tablets of montelukast sodium were prepared in order to release the drug for a prolonged period of time so as to reduce the frequency of administration. Direct compression technique was applied using the mucoadhesive polymers which were Methocel K4M CR, Methocel K15M CR, Methocel K100M CR and Eudragit RLPO. Highest percent release of drug after 8 hours was 76% for Methocel K4M CR, 72.13% for Methocel K15M CR, 65.68% for Methocel K100M CR, 65.53% for the combination of Methocel K15M CR and Eudragit RLPO. Higuchi, Krosmeyer-Peppas was the best fitted model for drug release. The Methocel K15M CR containing drug showed good mucoadhesive strength. The highest *ex-vivo* mucoadhesive strength and *ex-vivo* residence time were observed with Methocel K15M CR and Eudragit RLPO combination. Fourier transform infrared (FT-IR) spectroscopy revealed the compatibility of drug with the polymers.

Key words: Direct compression, drug release, mucoadhesive polymers, mucoadhesive strength.

Introduction

Montelukast which is a selective antagonist of leukotriene receptors can be used to lower blood pressure and to treat asthma, allergic rhinitis, heart attack as well as arthritis (Wang *et al.*, 2017; Walia *et al.*, 2006). Montelukast is used as the sodium salt, but doses are expressed in terms of the base; Montelukast Sodium 10.37 mg is equivalent to about 10 mg of Montelukast and the bioavailability of Montelukast is almost 62% (Zhao *et al.*, 1997). Metabolism occurs through liver P450 (CYP) 3A4 and 2CP microsomes, with potent inhibition of P450 2C8. Excretion happens almost exclusively in bile having a half-life from 2.7 to 5.5 hours in healthy adults. The pharmacokinetic profile is almost similar in females and males, young and adults. In patients with mild to moderate hepatic insufficiency, dosage adjustment is not required but data is insufficient regarding severe hepatic impairment. Montelukast and its metabolites are mainly excreted in bile and not urine, and it therefore has not been evaluated in patients having renal insufficiency. Hepatic first pass metabolism is the main drawback of conventional Montelukast sodium and sustained release formulation of Montelukast sodium is needed for that reason (Panchal *et al.*, 2012). Controlled or sustained release drug delivery systems have advantages as it reduces side effects, hepatic first pass effect and dosing frequency. Bioavailabilty enhancement and localized treatment can also be possible (Panchal *et al.*, 2012). Mucoadhesive drug delivery system using mucoadhesive polymers may be an effective way to sustain the drug release (Madgulkar *et al.*, 2008). Mucoadhesive polymers attach with the mucus by several process which can be explained by wetting theory, electronic theory, adsorption theory, fracture theory and diffusion theory (Boddupalli *et al.*, 2010). Different grades of Methocel which is actually hydroxylpropylmethylcellulose derivatives are widely used as mucoadhesive polymers along with Eudragit which is acrylic acid derivatives. Adsorption can be enhanced by using mucoadhesive

Correspondence to: Md. Selim Reza; Tel: 880-2-9661920-73 Ext- 8182, Fax: 880-2-9667222; E-mail: selim.du@gmail.com

polymers in formulation as they change the permeability of mucosal membrane or tissues. Furthermore, the interaction between mucoadhesive formulations and mucosal surface offers prolonged residence time of the dosage form at the site of application, thereby reducing the dosing frequency and increasing patient compliance which is the main objective of this work.

Materials and Methods

Materials

Montelukast sodium was received as gift sample from Incpeta Pharmaceuticals Ltd. Bangladesh. Merhocel K4M, Methocel K15M, Methocel K100M and Starch 1500 were obtained from Colorcon, USA. Eudragit RLPO was obtained from Evonik Industries and magnesium stearate was purchased from local market of Dhaka, Bangladesh.

Methods

Preparation of matrix tablets: Drug, polymer and other excipients were weighed separately according to proposed formulations shown in table 1. active ingredient (Montelukast sodium) and other excipients were blended for 15 minutes and then taken in the hopper and the die and punch were adjusted to get desired weight of the tablet. After compression the tablets were weighed and tablet weight was measured. Tablets were prepared by direct compression method (Thoorens *et al.*, 2014).

Table 1. Composition of mucoadhesiveMontelukast Sodium (MONT.) tablets.

Formulation Code	MONT. (mg)	Methocel K15M (mg)	Methocel K4M (mg)	Methocel K100M (mg)	Eudragit RLPO (mg)	Starch 1500 (mg)	Magnesium Stearate (mg)	Total weight (mg)
F1	10	40	-	-	-	70	0.12	120
F2	10	50	-	-	-	60	0.12	120
F3	10	60	-	-	-	50	0.12	120
F4	10	-	60	-	-	50	0.12	120
F5	10	-	70	-	-	40	0.12	120
F6	10	-	80	-	-	30	0.12	120
F7	10	-	-	50	-	60	0.12	120
F8	10	-	-	60	-	50	0.12	120
F9	10	25	-	-	15	70	0.12	120
F10	10	30	-	-	20	60	0.12	120
F11	10	35	-	-	25	50	0.12	120

*Measurement of thickness:*Thickness gauge was used to measure the thickness of tablets. Five tablets from each batch were used, and the average value is calculated.

Measurement of weight variation: To study weight variation, 20 tablets from each formulation were weighed using an electronic balance and test was performed according to official method of USP pharmacopoeia.

Preparation of calibration curve: Standard Montelukast sodium solution was prepared in concentration range of (2.5 mcg/ml to 25 mcg/ml). Then the absorbance of those standard solutions of different concentration was observed in the double beam spectrophotometer (Shimadzu UV) at 283 nm.

Measurement of drug content: Five tablets were weighed accurately and powdered equivalent to 10 mg of Monteluakst sodium was accurately weighed and extracted in 100 ml methanol by shaking for 20 min. After filtration through whatman 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 phosphate buffer.

Measurement of swelling study: The swelling properties of tablets were evaluated by determination of percent swelling. Each tablet was weighed (W_1) and immersed in simulated gastric fluid at pH 6.8 for predetermined times. After immersing the formulation for a fixed period of time, the tablets were wiped off so that excess surface water can be removed by using filter paper and weighed (W_2).

The swelling index was calculated by the following formula (Hassan *et al*., 2009).

Swelling Index = [(W2-W1) ÷ W1] × 100

In vitro dissolution study of mucoadhesive Montelukast tablets: The release rate of Montelukast sodium from mucoadhesive tablets was determined using USP dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of simulated gastric fluid containing phosphate buffer pH 6.8 at 37 ± 0.5 ºC and 75 rpm. Aliquot volume was withdrawn from the dissolution apparatus hourly for 8h and the samples were replaced with fresh dissolution medium. The amount of drug released was determined from the standard calibration curve of pure drug after completing the filtration (Costa, 2001).

Successive fractional dissolution time: $T_{25\%}$, $T_{50\%}$, $T_{80\%}$, and MDT were calculated from dissolution data in order to characterize the drug release rate in different experimental conditions (Arefin *et al.*, 2016).

Measurement of ex-vivo mucoadhesive strength: Fresh intestinal mucosa of goat was used to perform *ex vivo* mucoadhesive strength. Mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was cleaned with distilled water and then divided into pieces. A piece of intestinal mucosa was pasted to a Petri dish by the help of cyanoacrylate adhesive and the it was wetted with 2-5 drops of 6.8 phosphate buffer media and the test was carried out by using the weight.

Measurement of ex-vivo residence time: The *ex vivo* residence time was determined using a modified USP disintegration apparatus, which gave an idea about *in vivo* retention time.

For this study the time for complete erosion or detachment of the tablet from the mucosal surface was recorded as the mucoadhesion time. The total experiment was carried out for 6 hours to see the retention time and correlate this value with the sustaining property of the formulation.

Drug compatibility study with polymers: Fourier transform infrared spectroscopy (FTIR) was performed for checking any interaction between drug and polymer (Balpande, 2013). For this purpose Fourier transform infrared spectroscopic (FTIR) study was conducted for pure drug (Montelukast sodium), Methocel K15M CR, Methocel K4M CR, Methocel K100M, Eudragit RL PO, Formulation F-6 and physical mixture of drug and polymers.

Results and Discussion

Physical properties of mucoadhesive Montelukast Sodium tablets: The physical parameters of mucoadhesive Montelukast sodium tablets (Table 2) were performed and all the data were within the USP pharmacopoeia limit.

Percent hydration of mucoadhesive Montelukast Sodium tablets: Percent hydration of mucoadhesive Montelukast tablets were observed for 8 hours (Table 3) and highest percent hydration value was obtained for F-9 formulation and the lowest percent hydration was obtained for formulation F-4.

In vitro dissolution and kinetic studies of mucoadhesive Montelukast sodium tablets: Formulation F1- F11 was evaluated for dissolution pattern. Various kinetics treatments were investigated to find out their release pattern (Figure 2). All the formulations F1-F11 were checked for dissolution pattern (Table 4). The highest percent release of drug after 8 hour was 76.0% from F-4. Best fitted model for this formulation was Higuchi (R^2=0.976), Korsmeyer-Peppas (R^2 = 0.956). The release mechanism of this formulation followed Case I, QasiFickian transport Fickian transport (Table 5). On the other hand, the lowest percent release of drug after 8 hour was 58.5% which was obtained from

F-11. Best fitted model for this formulation was Higuchi (R^2 =0.963), Korsmeyer-Peppas (R^2 =0.930). The release mechanism of this formulation followed Anomalous / non- Fickian transport.

Table 2. Physical properties analysis of mucoadhesive Montelukast sodium (MONT.) tablets.

Formulation code	Average weight (mg)	Diameter	Thickness	Hardness (kg/cm^2)	Friability (%)
F-1	120 ± 0.10	7.2 ± 0.5	3.3 ± 0.01	3.23 ± 0.05	0.16
F-2	119 ± 1.06		3.2 ± 0.02	3.12 ± 0.04	0.42
F-3	119 ± 0.15		3.3 ± 0.02	3.10 ± 0.01	0.60
F-4	119 ± 0.09		3.2 ± 0.02	3.60 ± 0.01	0.82
F-5	120.38 ± 0.05		3.3 ± 0.02	5.50 ± 0.05	0.00
F-6	121.54 ± 0.15		3.3 ± 0.02	3.23 ± 0.05	0.16
F-7	121.85 ± 0.05		3.2 ± 0.03	3.10 ± 0.01	0.33
F-8	118.67 ± 1.10		3.3 ± 0.02	3.00 ± 0.00	0.08
F-9	121.70 ± 0.15		3.2 ± 0.03	4.00 ± 0.01	0.08
F-10	121.18 ± 0.05		3.3 ± 0.01	4.2 ± 0.05	0.00
F-11	120.30 ± 0.10		3.2 ± 0.02	3.12 ± 0.04	0.24

Table 3. Precent hydration of mucoadhesive tablets of Montelukast sodium.

Formulation code	Percent hydration				
	1 hr	2 hr	4 hr	6 hr	8 hr
F-1	46.2	55.7	62.1	65.4	68.2
F-2	43.9	53.9	60.3	64.3	67.3
F-3	40.8	50.2	59.5	61.4	65.8
F-4	38.3	48.6	58.6	60.1	63.9
F-5	47.6	60.5	66.1	70.2	80.3
F-6	47.9	57.3	65.2	68.3	74.7
F-7	47.8	56.2	63.7	67.2	72.4
F-8	48.9	53.7	60.2	65.4	70.3
F-9	45.6	60.3	67.52	69.23	81.20
F-10	47.2	54.7	60.5	68.9	73.1
F-11	42.7	55.9	67.2	71.4	76.3

Table 4. Release rate constants and R^2 values for different release kinetics of different formulation (F1-F11).

Formulation Code	Zero order		First order		Higuchi		Korsmeyer-Pappas	
	K_o	R^2	K_1	R^2	K_h	R^2	n	R^2
F-1	7.179	0.919	0.117	0.926	22.29	0.966	0.393	0.942
F-2	06.509	0.851	0.097	0.975	21.33	0.969	0.371	0.949
F-3	6.410	0.919	0.097	0.937	20.09	0.958	0.390	0.930
F-4	7.639	0.920	0.138	0.951	24.15	0.976	0.403	0.956
F-5	6.873	0.920	0.105	0.989	21.85	0.987	0.404	0.967
F-6	6.577	0.905	0.101	0.957	20.81	0.961	0.382	0.923
F-7	6.849	0.942	0.108	0.946	21.18	0.955	0.462	0.931
F-8	6.377	0.941	0.094	0.959	19.87	0.969	0.452	0.95
F-9	7.098	0.951	0.110	0.983	22.12	0.980	0.472	0.953
F-10	6.136	0.881	0.089	0.991	19.85	0.978	0.346	0.965
F-11	6.378	0.936	0.092	0.967	19.85	0.963	0.441	0.930

Table 5. The best fitted model and mechanism of drug release from formulations (F1-F11).

Formulation code	Best fitted model	n value (Korsmeyer-Peppas model)	Release mechanism
F-1	Higuchi, Korsmeyer-Peppas	0.393	Case I, QasiFickian transport Fickian transport
F-2	Higuchi, Korsmeyer-Peppas	0.371	Case I, QasiFickian transport Fickian transport
F-3	Higuchi, Korsmeyer-Peppas	0.390	Case I, QasiFickian transport Fickian transport
F-4	Higuchi, Korsmeyer-Peppas	0.403	Case I, QasiFickian transport Fickian transport
F-5	Higuchi, Korsmeyer-Peppas	0.404	Case I, QasiFickian transport Fickian transport
F-6	Higuchi, Korsmeyer-Peppas	0.382	Case I, QasiFickian transport Fickian transport
F-7	Higuchi, Korsmeyer-Peppas	0.462	Anomalous / non- Fickian transport
F-8	Higuchi, Korsmeyer-Peppas	0.452	Anomalous / non- Fickian transport
F-9	Higuchi, Korsmeyer-Peppas	0.472	Anomalous / non- Fickian transport
F-10	Higuchi, Korsmeyer-Peppas	0.346	Case I, QasiFickian transport
F-11	Higuchi, Korsmeyer-Peppas	0.441	Anomalous / non- Fickian transport

Table 6. Comparison of *ex-vivo* mucoadhesive strength, force of mucoadhesion and *ex-vivo* residence times of different mucoadhesive polymers.

Polymers	*Ex-vivo* mucoadhesive strength (gm)	Force of mucoadhesion[a]	Ex-vivo residence time (hr)
Methocel K15M CR	53	0.519	4.4
Methocel K4M CR	50	0.491	4.2
Methocel K100M CR	45	0.441	4
Methocel K15M CR + Eudragit RLPO	75	0.735	5

a **=** (mucoadhesive strength × 0.00981)

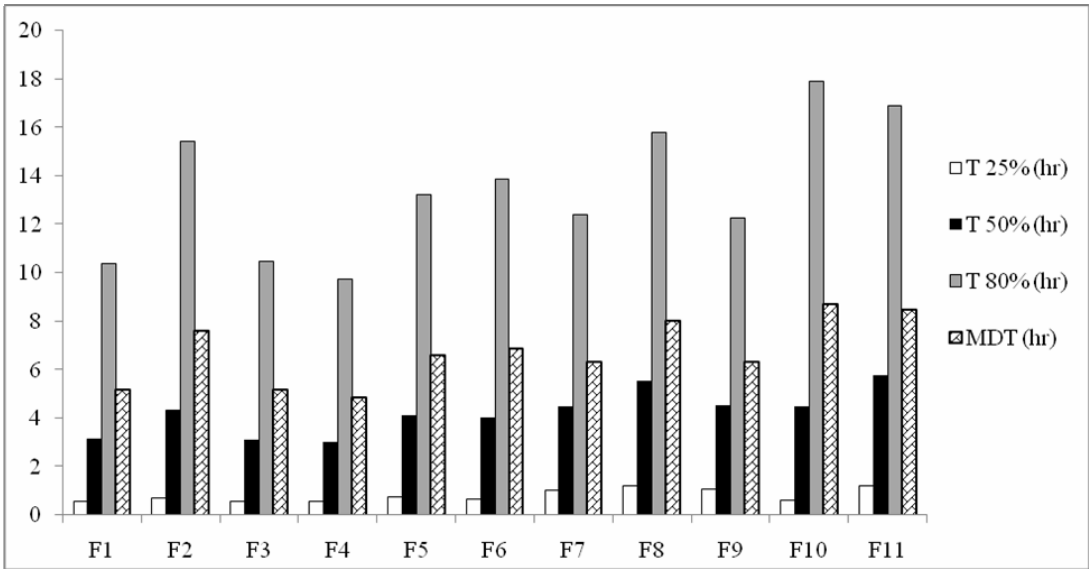


Figure 1. Successive fractional dissolution time of different formulations (F1-F11).

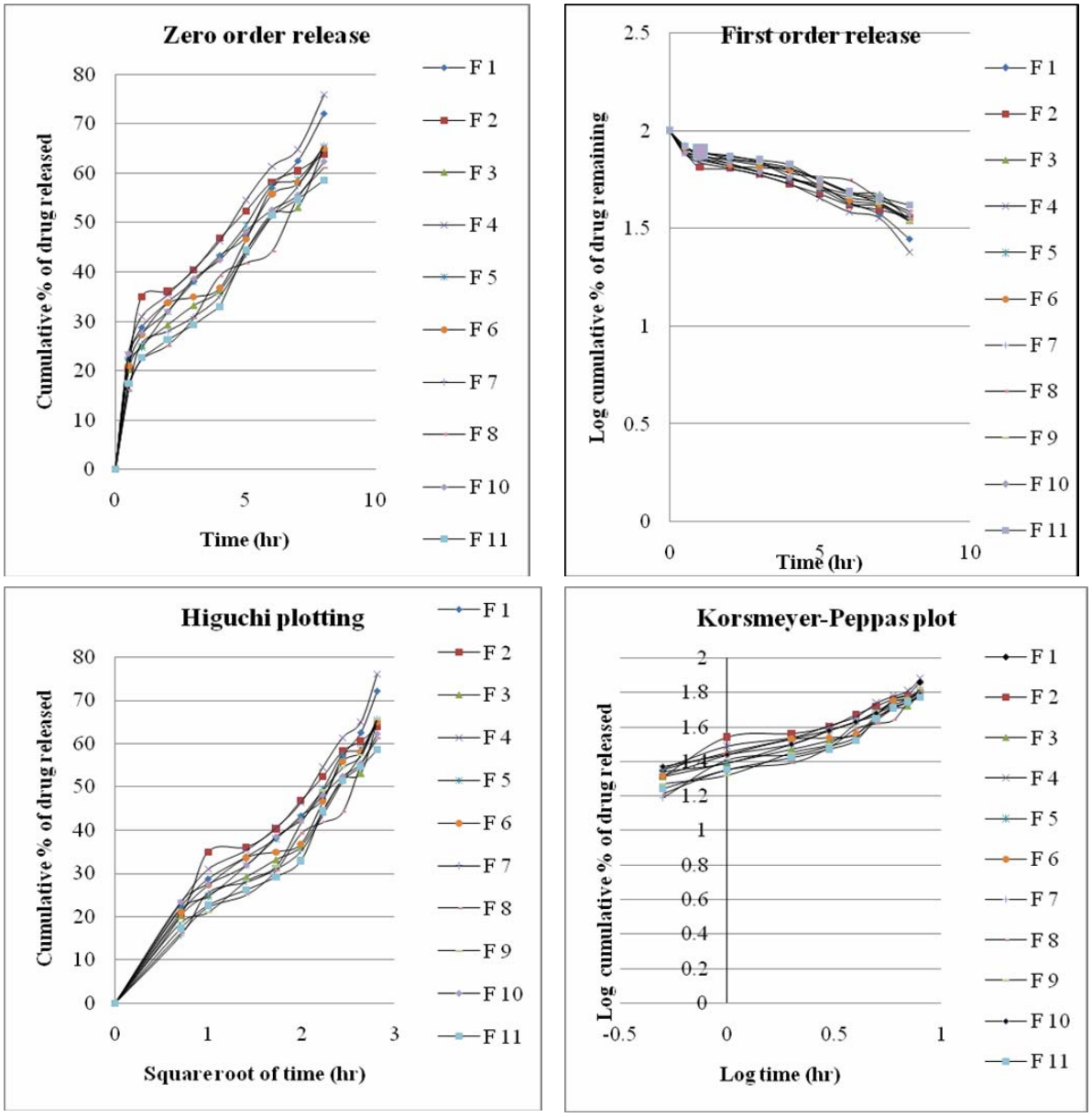
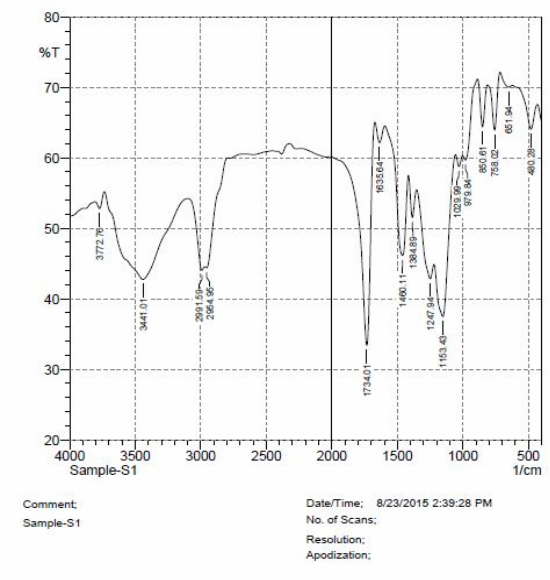


Figure 2. Release kinetics of different formulations (F1-F11) of mucoadhesive Montelukast sodium tablets.

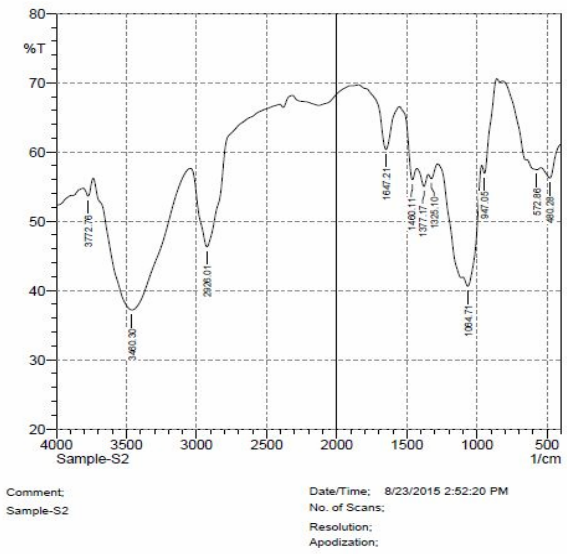
Comparison of ex-vivo mucoadhesive strength, force of mucoadhesion and ex-vivo residence times of different mucoadhesive polymers: Ex-vivo mucoadhesive strength, force of mucoadhesion and *ex-vivo* residence time were highest for mixture of polymers (Methocel K15M CR & Eudragit RLPO) and the value was lowest for Methocel K100M CR polymer (Table 6).

Successive fractional dissolution time: From figure 1, successive fractional dissolution time was observed to be highest for F-10 and the values was lowest for F-4. A higher value of MDT indicates a higher retaining ability of the polymer and vice-versa. Release retarding capability of the polymers was quite good which was indicated from the figure 1.

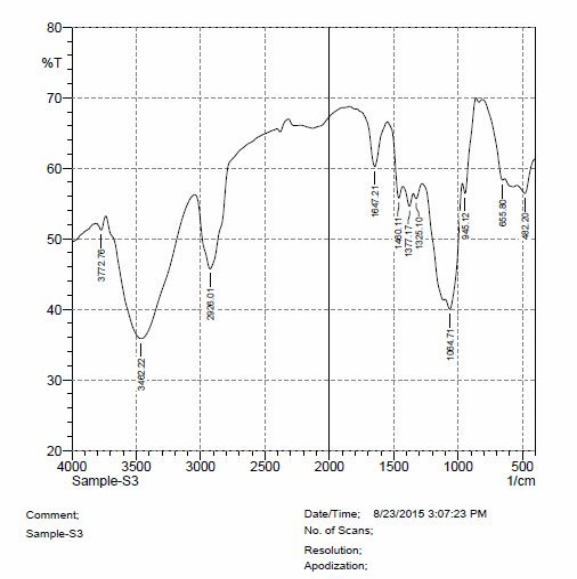
Fourier transforms infrared spectroscopy (FT-IR) for compatibility study: Figure 3(A) represents the FTIR spectra of pure Montelukast sodium. In FTIR spectra of pure Montelukast powder the characteristic bands at 3441 cm^{-1} (-OH stretching vibration), 3058 cm^{-1} (Aromatic C-H stretching vibration), 2991 cm^{-1} (Aliphatic C-H stretching vibration), 3058 cm^{-1} (Aromatic C-H stretching vibration), 1460.11 (Aliphatic C-H bending vibration)and1153.43(-C=O stretchingvibration).-OH



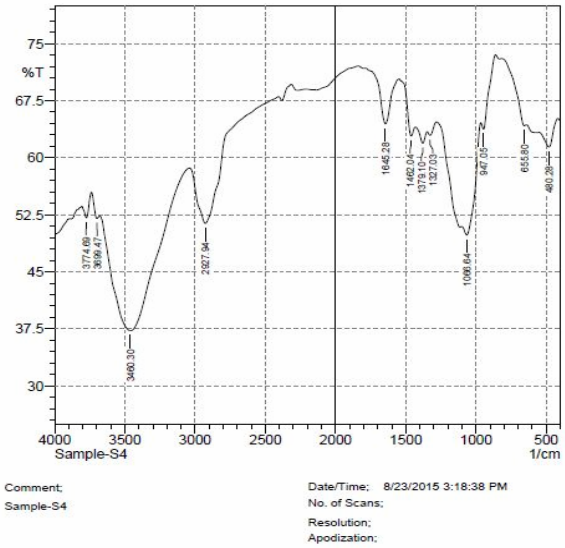
(A) FTIR spectram of Montelukast sodium



(B) FTIR spectram of Methocel K15M CR

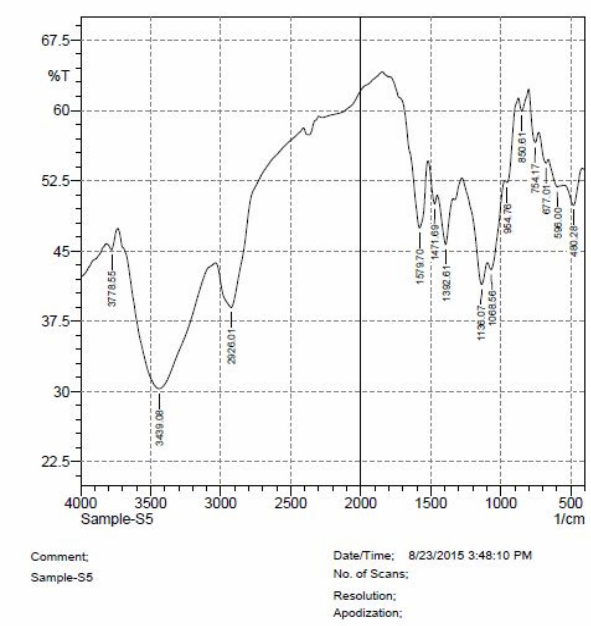


(C) FTIR spectram of Methocel K4M CR

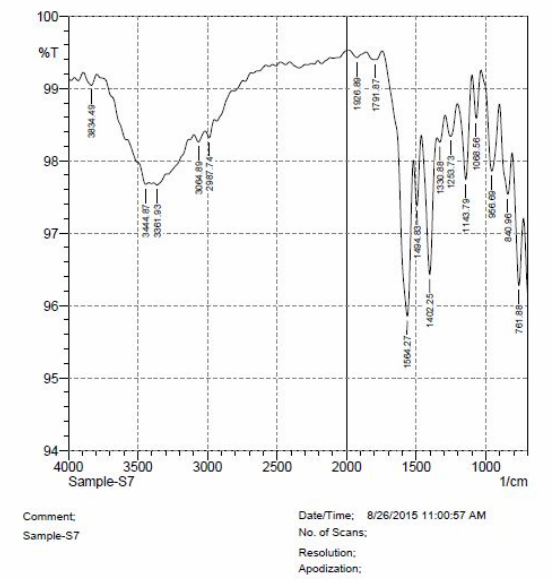


(D) FTIR spectram of Methocel K100M CR

Figure 3 (A) FTIR spectram of Montelukast sodium (B) FTIR spectram of Methocel K15M CR (C) FTIR spectram of Methocel K4M CR (D) FTIR spectram of Methocel K100M CR.



(E) FTIR spectram of Eudragit RLPO



(F) FTIR spectram of drug and polymers mixture (Methocel K4M CR, K100M CR, K15M CR and Eudragit RLPO)

Figure 4. (E) FTIR spectram of Eudragit RLPO (F)FTIR spectram of drug and polymers mixture (Methocel K4M CR, K100M CR, K15M CR and Eudragit RLPO).

stretching vibrations occur at 3392 cm^{-1}. Based on this, in the present investigation, -OH symmetric stretching vibrations are observed at 3441 cm^{-1}. Aliphatic C-H- stretching vibrations occur at 2975 cm^{-1} and 2928 cm^{-1}. In present investigation it is observed at 2991 cm^{-1}. C=O stretching vibrations occur at 1144 cm^{-1}. In present investigation it is observed at 1153.43 cm^{-1}.

Conclusion

The hydrophilic matrix of Methocel and mucoadhesion property of the polymer controls the release effectively for 8 hours. Drug release kinetics indicated that the drug release was best explained by Higuchi equation. The experiment revealed that Methocel K15M and Methocel K4M were more efficient polymer in retarding drug release. The highest mucoadhesive strength was observed with HPMC K15M and Eudragit RLPO combination. Because of its increased concentration and thus the viscosity of the polymer increases, it shows higher strength in combination with Eudragit RLPO.

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