

FAST DISSOLVING FILMS: A NOVEL APPROACH FOR THE DELIVERY OF MONTELUKAST SODIUM

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ABSTRACT

Montelukast sodium fast dissolving films were prepared by solvent casting method using HPMC as film base with different concentrations of superdisintegrants like crospovidone and croscarmellose sodium using glycerin as plasticizer. The physicochemical parameters of the fast dissolving films were evaluated. The compatibility of the drug in the formulation was confirmed by IR and DSC studies. Scanning electron microscopy revealed the morphology of the films. *In vitro* dissolution studies and mechanism of drug release was identified. The formulation F₂ and F₅ with 4% of crospovidone and 4% croscarmellose sodium respectively shows a maximum cumulative percentage drug release of 97.42% and 99.27% at the end of 30 min respectively. The release of drug from the films has followed first-order kinetics. No significant change in the physical parameters, *in vitro* disintegration time and drug content of F₂ was observed during storage at 40±2°C/75±5% RH for 3 months. The data demonstrated that 4% crospovidone and 4% croscarmellose sodium with 4% HPMC as a film base was suitable for developing fast dissolving films of Montelukast sodium.

Keywords: Fast dissolving films, Montelukast sodium, HPMC, Crospovidone, Croscarmellose sodium.

INTRODUCTION

Recently fast dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. These delivery systems either dissolve or disintegrate in the mouth rapidly, without requiring any water to aid in swallowing¹. They also impart unique product differentiation, thus enabling use as line extensions for existing commercial products. This novel drug delivery system can also be beneficial for meeting the current needs of the industry are improved solubility/stability, biological half life and bioavailability enhancement of drugs^{2,15}. Although oral disintegrating tablets have an advantage of administration without choking and fast disintegration; the disintegrated materials contained in them are insoluble and remain until swallowing. In such cases formulation of fast dissolving film will be advantageous^{3,4}. Montelukast sodium^{5,6} is a leukotriene receptor antagonist (LTRA) used in maintenance treatment of asthma and to relieve symptoms of seasonal allergies. It is usually administered orally. Montelukast blocks the action of leukotriene D₄ on the cysteinyl leukotriene receptor CysLT₁ in lungs and bronchial tubes by binding to it. This reduces the bronchoconstriction otherwise caused by the leukotriene, and results in less inflammation⁴. Montelukast sodium is freely soluble in ethanol, methanol and water and practically insoluble in acetonitrile and its bioavailability is 63%⁷. Present study is undertaken to prepare fast dissolving films of montelukast sodium with an aim to overcome the drawbacks of fast dissolving tablets.

MATERIALS AND METHODS

Montelukast sodium was obtained as a gift sample from Matrix India (P) Ltd., Hyderabad. HPMC was obtained from Hi Media lab (P) Ltd., Mumbai. Glycerin, Citric acid and Sucrose were obtained from S.D. Fine Chemicals (P) Ltd., Mumbai. Crospovidone and croscarmellose sodium were obtained from Signet Chemical Corporation., Mumbai. Trusil mixed flavor RSV obtained from International flavors of fragrance India Ltd. All other chemicals and solvents used were of analytical grade.

Preparation of fast dissolving films

HPMC is known for its good film forming properties and has an excellent acceptability. Glycerin as a plasticizer. Crospovidone and croscarmellose sodium were used as a superdisintegrants. Citric acid as saliva stimulating agent, sucrose as a sweetening agent⁸ and Trusil mixed fruit RSV as a flavoring agent. The fast dissolving films of montelukast sodium were prepared by solvent casting technique⁹ using HPMC as a film forming polymer. Glycerin is used as plasticizer. The calculated amount of polymer was dispersed in 3/4th volume of water with continuous stirring using magnetic stirrer and the final volume was adjusted up to 10 ml with distilled water. The calculated amount of montelukast sodium was incorporated in the polymeric solutions after levigation with required volume of glycerin. The solution was casted on to Petri dish (Anumbra®, area of 66.31cm²) then kept in hot air oven at 40°C for 24 h. Films of various formulations are mentioned in Table-1. The films were punched in to size of 2 cm diameter (an area of 6.28 cm²) containing 5 mg of montelukast sodium.

Table 1: Formulation of Fast Dissolving Films of Montelukast sodium

Ingredients*	F _h	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆
Montelukast Sodium (mg)	52.79	52.79	52.79	52.79	52.79	52.79	52.79
HPMC (% w/v)	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Crospovidone	--	2.0	4.0	6.0	--	--	--
Croscarmellose sodium	--	--	--	--	2.0	4.0	6.0
Sucrose	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Citric acid	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Trusil flavor	8.0	8.0	8.0	8.0	8.0	8.0	8.0
Glycerin	30	30	30	30	30	30	30
Water (ml)	10	10	10	10	10	10	10

*Quantities are expressed in %w/w of polymer

Evaluation of fast dissolving films

The fast dissolving films were evaluated for physical appearance, surface texture, thickness, weight uniformity, folding endurance, surface pH and drug content uniformity of films. The physical

appearance was checked with visual inspection of films and texture by feel or touch, thickness was measured by micrometer screw gauge (Mitutoyo, Japan) at different points and the mean values were calculated. The film weights were determined by using electronic balance⁹. Disintegration test was performed in the USP

disintegration time testing apparatus (Electro lab Mumbai)¹⁰. To check the uniformity of the drug in the cast film, films were cut at different places in cast film and each film was placed in 100 ml of 0.5% SLS to extract drug, the resulting solution was filtered and further dilution was made with 0.5% SLS and the absorbance at 342 nm was measured spectrophotometrically. The concentration of the drug was determined from the standard curve. Same procedure was adopted for other formulations of cast films in the triplicates and mean drug content and standard deviation were calculated⁹.

In vitro Dissolution Study

In vitro dissolution of montelukast sodium fast dissolving film was studied in USP XXIV dissolution test apparatus (Electro lab, Mumbai) using 900 ml of 0.5% SLS solution at 50 rpm¹¹⁻¹³. The temperature was maintained at $37 \pm 0.5^\circ\text{C}$ throughout the experiment. 5 ml Sample was withdrawn by means of syringe fitted with pre-filter at 5 min intervals and the same quantity was replaced with 0.5% SLS solution. The cumulative percentage of drug released was determined using Shimadzu spectrophotometer at 342 nm. The experiment was carried out in triplicate and average values were reported.

Compatibility studies by FTIR:

The compatibility of drug in the formulation was confirmed by IR spectra of pure drug and formulations were determined using Shimadzu FTIR-8400S Spectrophotometer by KBr Disc method.

Differential scanning calorimetry (DSC)¹⁴:

The DSC measurements were performed using a mettler equipped with an intracooler 2P cooling accessory. Samples of 4 mg were

placed in standard aluminum pans and sealed with a lid. Heating scans by $10^\circ\text{C}/\text{min}$ were applied with a nitrogen purge of 20 ml/min, over a temperature range of 35°C to 380°C . An empty aluminum pan was used as reference.

Scanning Electron Microscopy (SEM)¹⁵:

The surface morphology of the fast dissolving film was observed with scanning electron microscope, Model QUANTA-200 FEI Netherlands. The samples were attached to the slab surfaces with double-sided adhesive tapes and the scanning electron photomicrograph was taken at 2000X magnification.

Accelerated Stability studies

The optimized formulation in its final pack was stored at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$ for 3 months in Stability chamber (Thermo lab). The sample was withdrawn at every 10 day time intervals and analyzed for physical parameters, *in vitro* dispersion time and drug content.

RESULTS AND DISCUSSION

Physical appearance and surface texture of films were found to have smooth surface and they are elegant enough to see. The physicochemical evaluation data presented in Table 2 indicating thickness of the films varies from 0.130 to 0.155 mm. The weight of films varies from 64.01 to 67.89 mg. The folding endurance of the films varies from 275 to 283, as the plasticizer concentration increases the flexibility of the film increases thus folding endurance. Since the surface pH of films was found to be around neutral pH, there will not be any kind irritation to the mucosal lining of the oral cavity.

Table 2: Evaluation of Fast Dissolving Films of Montelukast sodium

Formulations	Weight (mg)	Thickness (mm)	Folding endurance	Drug content uniformity (%)	<i>In Vitro</i> disintegration Time (sec)
F _h	64.01±0.08	0.130 ± 0.010	279 ± 1.466	98.34 ± 1.657	75.57 ± 0.102
F ₁	65.21±0.54	0.140 ± 0.010	274 ± 2.545	97.44 ± 0.540	15.11 ± 0.045
F ₂	66.09±0.22	0.145 ± 0.015	288 ± 1.665	96.34 ± 1.002	9.74 ± 0.085
F ₃	66.97±0.10	0.150 ± 0.005	275 ± 3.343	96.98 ± 1.963	11.09 ± 0.099
F ₄	65.05±0.24	0.145 ± 0.020	287 ± 2.994	95.23 ± 0.355	13.21 ± 0.034
F ₅	66.90±0.33	0.150 ± 0.025	283 ± 2.633	96.67 ± 0.880	7.25 ± 0.111
F ₆	67.89±0.26	0.155 ± 0.015	282 ± 3.121	97.98 ± 2.403	9.98 ± 0.087

*All values are Mean ± SD, (n=3)

All the formulations found to contain almost uniform quantity of drug as per content uniformity studies indicating reproducibility of the technique. IR spectra analytical reports shown in fig. 1 and 2 indicating that there was no interaction between drug and excipients used. DSC thermo grams of montelukast sodium with

excipient does not show profound shift in peaks which indicates compatibility as shown in fig 3 and 4 and SEM of the film at 2000X magnification showed smooth surface with some little pores and without any scratches or transverse striations as shown in fig 5

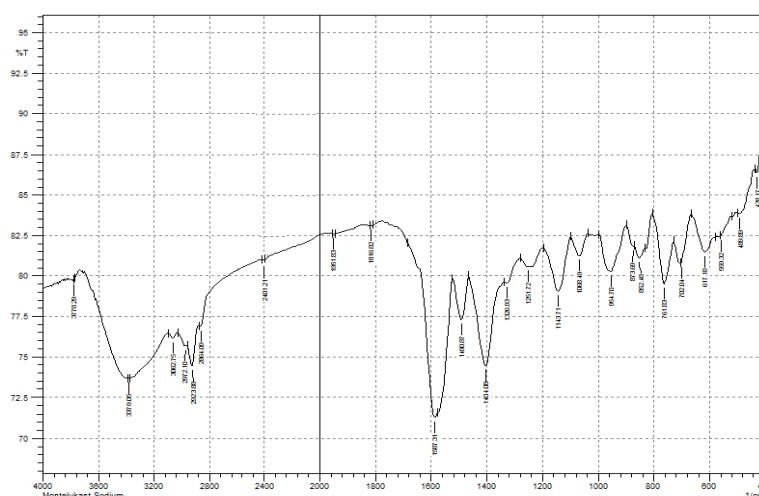


Fig. 1: FTIR spectra of Montelukast sodium

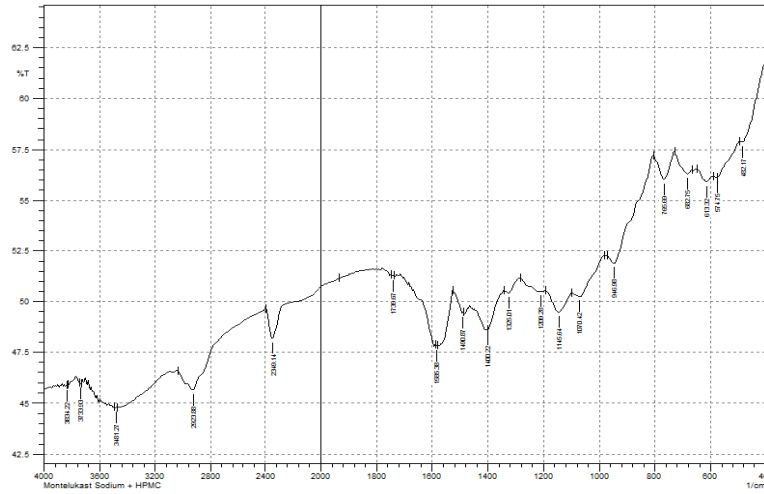


Fig. 2: FTIR spectra of Montelukast sodium + HPMC

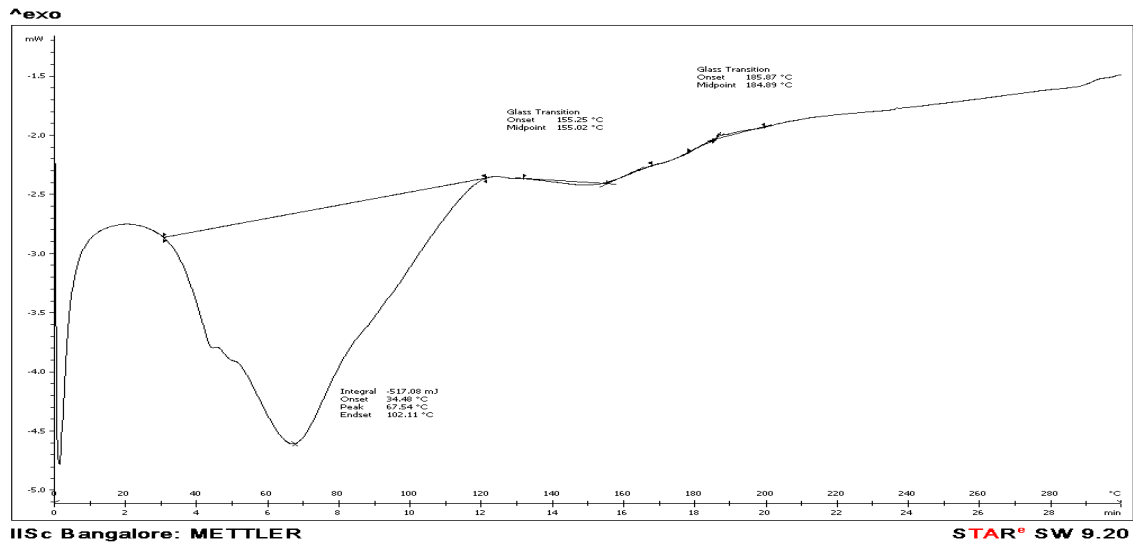


Fig. 3: DSC of Montelukast sodium

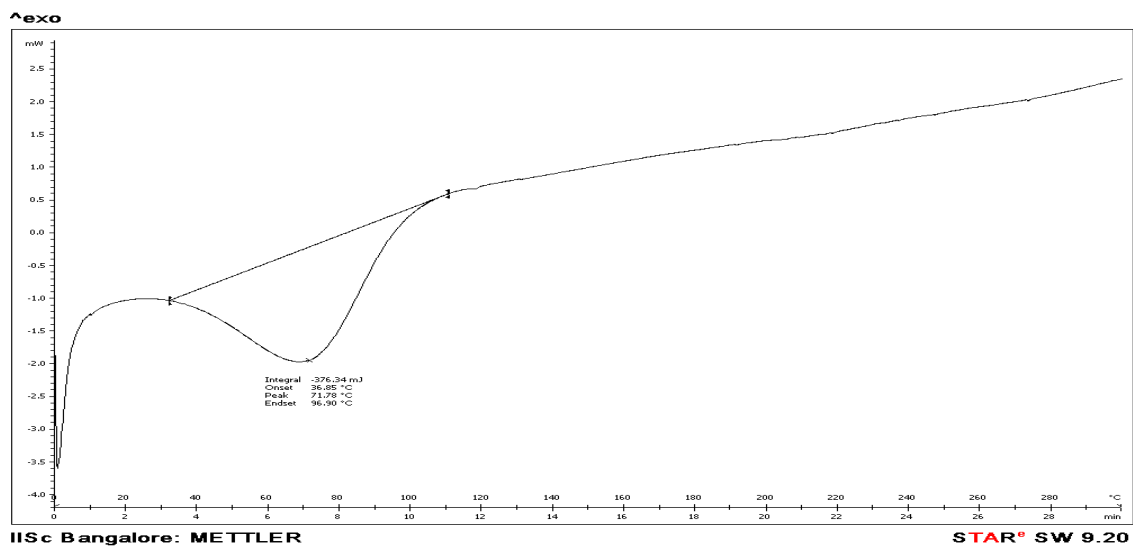


Fig. 4: DSC of Montelukast sodium + HPMC

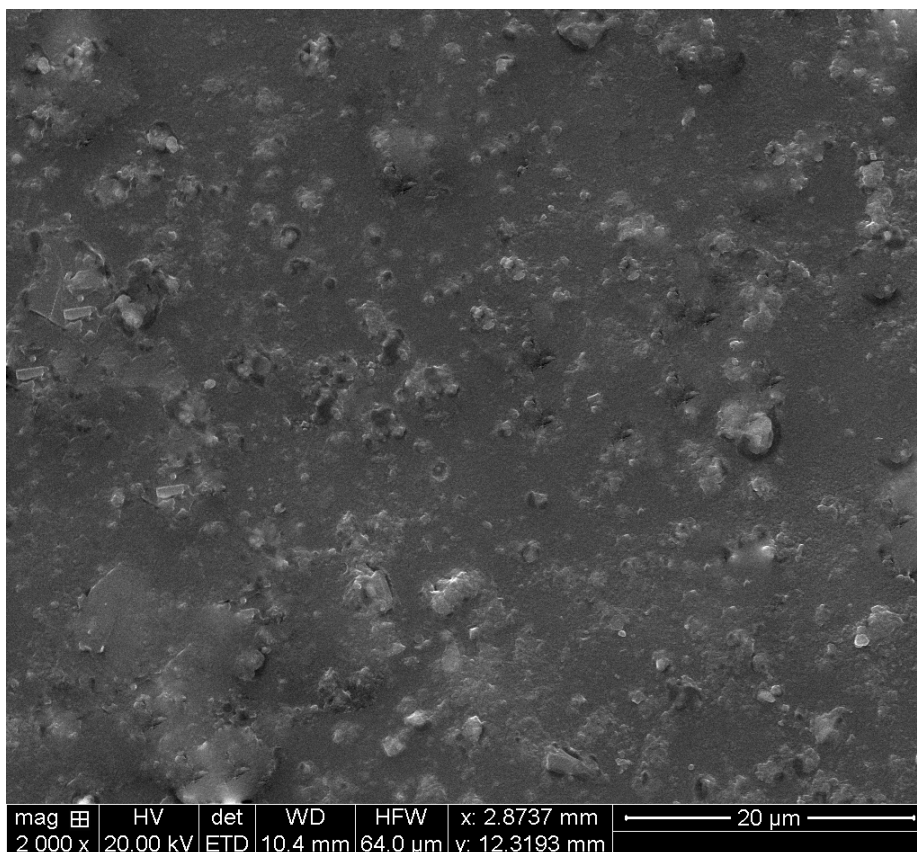


Fig. 5: SEM of Montelukast sodium Fast Dissolving Films

All the formulations of fast dissolving films were found to disintegrate in less than 30 sec. *In vitro* disintegration time was found to decrease with increase in concentration of superdisintegrants used in formulations. It is observed that disintegration time of the film decreased from 15.11 to 9.74 sec and 13.21 to 7.25 sec with increase in the concentration of crospovidone and croscarmellose sodium from 2 to 4% respectively, further increase in the concentration of crospovidone and croscarmellose sodium, increased the disintegration time due to blockage of capillary pores which prevents the entry of fluid in to the film.

The cumulative percentage drug release of all the formulations is shown in fig 6 and 7. Based on the trial basis it has been found that 10 ml of 4% w/v of HPMC solution in water shown as optimized film forming base. The fast dissolving film prepared with HPMC as a film base with crospovidone as a superdisintegrant in the concentration of 2, 4 and 6% shown 89.07, 97.42 and 93.71% respectively of drug release in 30 min and with croscarmellose sodium as a superdisintegrant in the concentration of 2, 4 and 6% shown 92.78, 99.27 and 96.49% of drug release in 30 min.

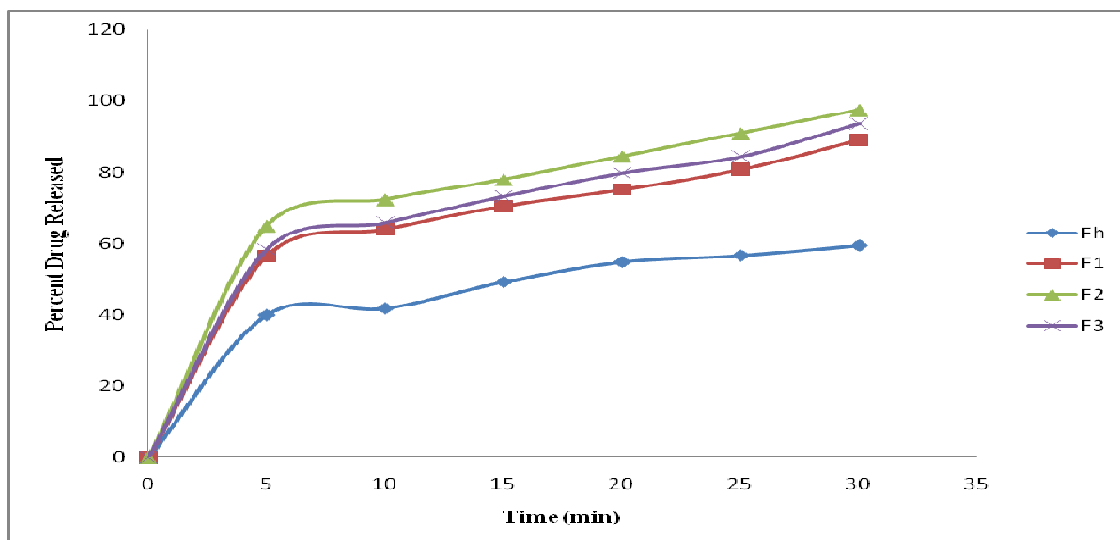


Fig. 6: *In Vitro* drug release of Fast Dissolving Films containing Crospovidone

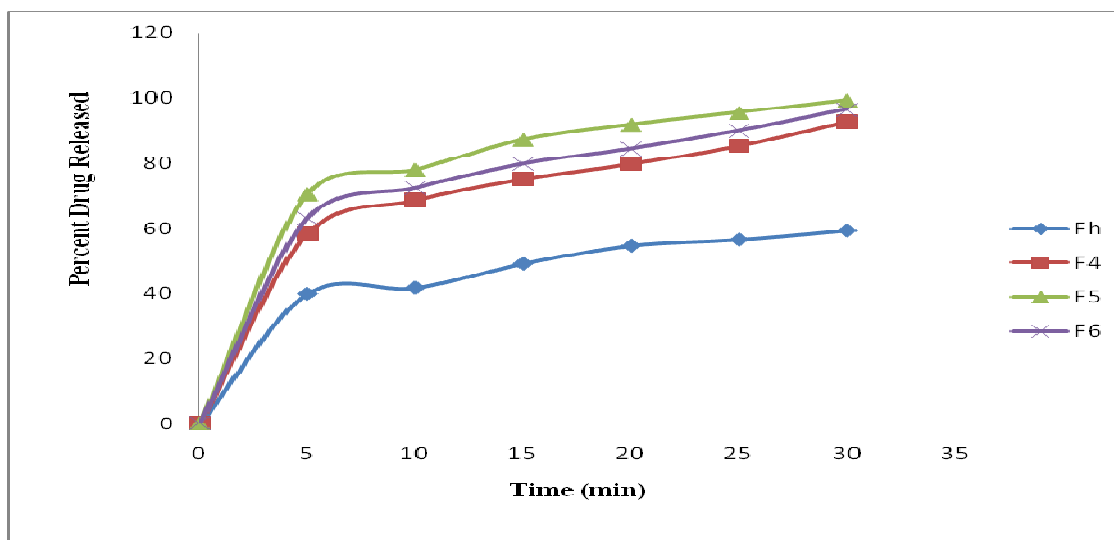


Fig. 7: *In vitro* drug release of Fast Dissolving Films containing Croscarmellose sodium

It is observed that drug release from the film increased from 89.07 to 97.42% and 92.74 to 99.27% with increase in the concentration of crospovidone and croscarmellose sodium from 2 to 4% respectively, further increase in the concentration of crospovidone and croscarmellose sodium, decreased the drug release due to increase in the disintegration time. The release of the drug from the films follows first-order.

Among all the formulations, the best formulation was found to be F₂ containing 4% crospovidone and F₅ containing 4% croscarmellose sodium, because it has shown lesser disintegration time and faster release of drug. These formulations were subjected to stability studies; from the results of accelerated studies it was found that the formulations were stable.

CONCLUSION

Finally, it can be concluded that, fast dissolving films of montelukast sodium can be prepared by solvent casting technique using HPMC as film base, and with different concentrations of Crospovidone and Croscarmellose sodium as superdisintegrants.

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