ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation and evaluation of Montelukast sodium fast dissolving films by using Gelatin as a film base

Vijaykumar Ghorwade, Ajaykumar Patil*, Sudheer Patil, Krishnakanth Ikkurthi, Krishna Sujan Inuganti, Vishal Porandla.

Department of Pharmaceutics, Karnataka College of Pharmacy, Bidar – 585403, Karnataka, India.

ABSTRACT

Montelukast sodium fast dissolving films were prepared by solvent casting method using gelatin as film base with different concentrations of superdisintegrants like microcrystalline cellulose and crospovidone using PEG 400 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 F_2 and F_5 with 4% of crospovidone and 10% MCC respectively shows a maximum cumulative percentage drug release of 98.35% and 95.57% 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 F_2 was observed during storage at 40±2^{0}C/75±5% RH for 3 months. The data demonstrated that 4% crospovidone and 10% MCC with 4% Gelatin as a film base was suitable for developing fast dissolving films of Montelukast sodium.

Keywords: Fast dissolving films, Montelukast sodium, Gelatin, Crospovidone, MCC.

Corresponding author

ISSN: 0975-8585

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 swallowing [1]. 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 $CysLT_1$ in lungs and bronchial tubes by binding to it. This reduces the bronchoconstriction otherwise caused by the leukotriene, and results in less inflammation [4]. 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 draw backs of fast dissolving tablets.

MATERIALS AND METHODS

Materials

Montelukast sodium was obtained as a gift sample from Matrix India (P) Ltd., Hyderabad. Gelatin, PEG 400, Citric acid, Sucrose were obtained from S.D. Fine Chemicals (P) Ltd., Mumbai. Crospovidone and MCC 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.

Methods

Preparation of fast dissolving films

Gelatin is known for its good film forming properties and has an excellent acceptability. PEG 400 as a plasticizer. Crospovidone and microcrystalline cellulose were used as a superdisintegrants. Citric acid as saliva stimulating agent, sucrose as a sweetening agent [8] and Trusil mixed fruit RSV as a flavoring agent. The fast dissolving films of montelukast sodium were prepared by solvent casting technique [9] using film forming polymer gelatin. PEG is used as plasticizer. The calculated amount of polymer was dispersed in three forth 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

ISSN: 0975-8585

polymeric solutions after levigation with required volume of PEG. The solution was casted on to Petri dish (Anumbra®, area of 66.31cm^2) then kept in hot air oven at 40^{0}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 cm^2) containing 5 mg of montelukast sodium.

Table 1: Formulation of fast dissolving films of montelukast sodium

Ingredients*	F_g	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
Gelatin (% w/v)	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Crospovidone	--	2.0	4.0	6.0	--	--	--
MCC	--	--	--	--	5	10	15
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
PEG 400	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 balance [9]. Disintegration test was performed in the USP disintegration time testing apparatus (Electrolab 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 calculated [9].

In vitro Dissolution Study

In vitro dissolution of montelukast sodium fast dissolving film was studied in USP XXIV dissolution test apparatus (Electrolab, Mumbai) using 900 ml of 0.5% SLS solution at 50 rpm [11, 12, 13]. The temperature was maintained at 37± 0.5º 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.

ISSN: 0975-8585

Compatibility studies by FTIR:

The compatibility of drug in the formulation was confirmed by IR spectra of pure drug and formulations were determined using Simadzu 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^{o}C/min were applied with a nitrogen purge of 20 ml/min, over a temperature range of 35^{o}C to 380^{o}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 1000X magnification.

Accelerated Stability studies

The optimized formulation in its final pack was stored at 40 ± 2^{0}C/75±5% RH for 3 months in Stability chamber (Thermolab). 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

Table 2: Evaluation of fast dissolving films of montelukast sodium

Formulations	Weight (mg)	Thickness (mm)	Folding Endurance	Drug Content Uniformity (%)	In Vitro Disintegration time(sec)
F_g	63.92 ± 0.12	0.135 ± 0.010	272 ± 1.674	95.54 ± 0.342	72.21 ± 0.342
F_1	65.2 ± 0.28	0.140 ± 0.005	287 ± 2.340	96.66 ± 0.925	14.33 ± 0.171
F_2	65.90 ± 0.31	0.145 ± 0.010	289 ± 2.640	98.04 ± 1.539	9.10 ± 0.435
F_3	67.04 ± 0.21	0.150 ± 0.010	267 ± 1.000	97.33 ± 0.369	11.50 ± 0.591
F_4	66.84 ± 0.38	0.160 ± 0.015	271 ± 1.730	95.00 ± 1.056	18.76 ± 0.151
F_5	68.21 ± 0.41	0.165 ± 0.005	274 ± 1.000	97.66 ± 1.396	12.86 ± 0.151
F_6	72.12 ± 0.11	0.170 ± 0.010	259 ± 3.310	96.66 ± 1.396	14.10 ± 0.479

*All values are Mean ± SD, (n=3)

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 0.135 to 0.170 mm. The weight of films varies from

ISSN: 0975-8585

63.92 to 72.12 mg. The folding endurance of the films varies from 259 to 289, 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.

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 1000X magnification showed smooth surface with some little pores and without any scratches or transverse striations as shown in fig 5

Figure 1: FTIR spectra of Montelukast sodium

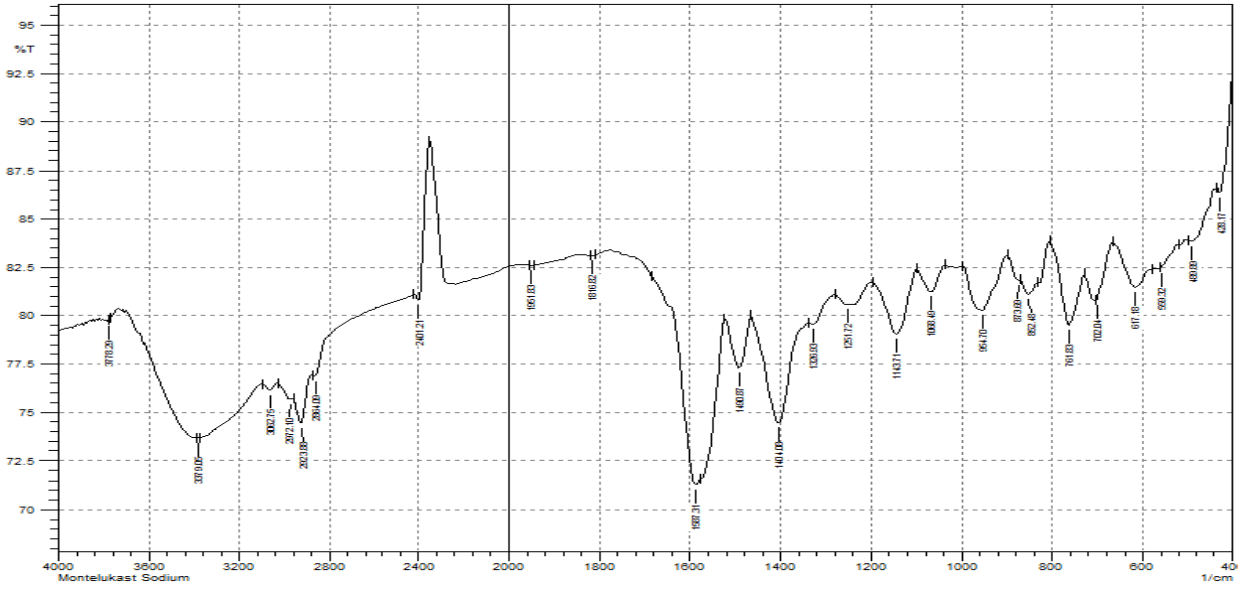


Figure 2: FTIR spectra of Montelukast sodium + Gelatin

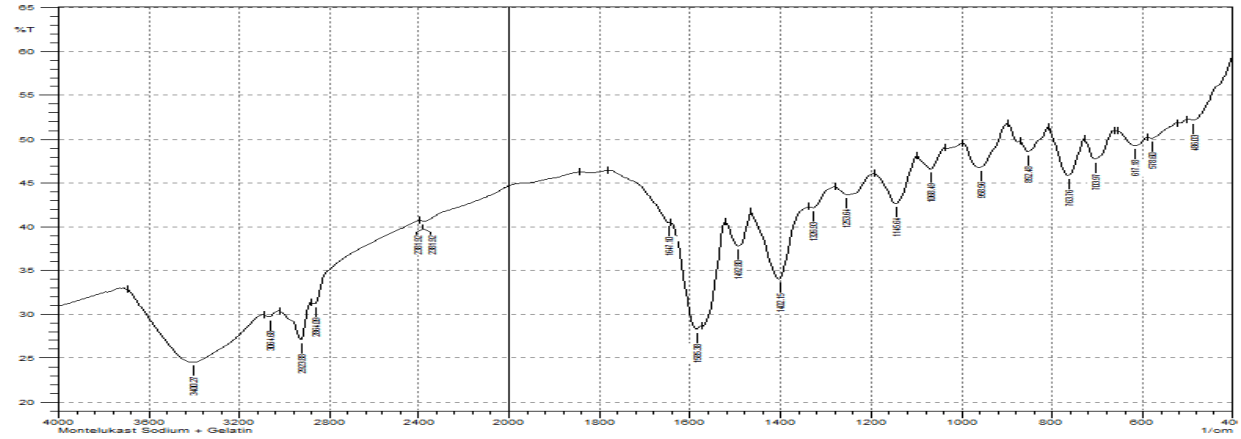


Figure 3. DSC of Montelukast sodium

ISSN: 0975-8585

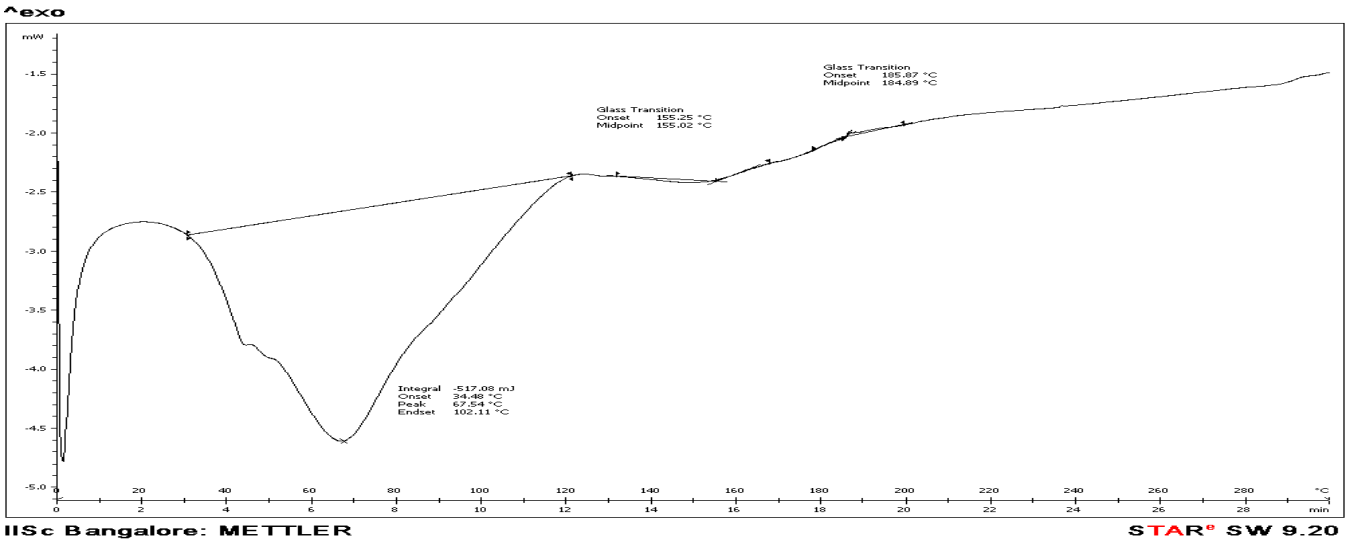


Figure 4. DSC of Montelukast sodium + Gelatin

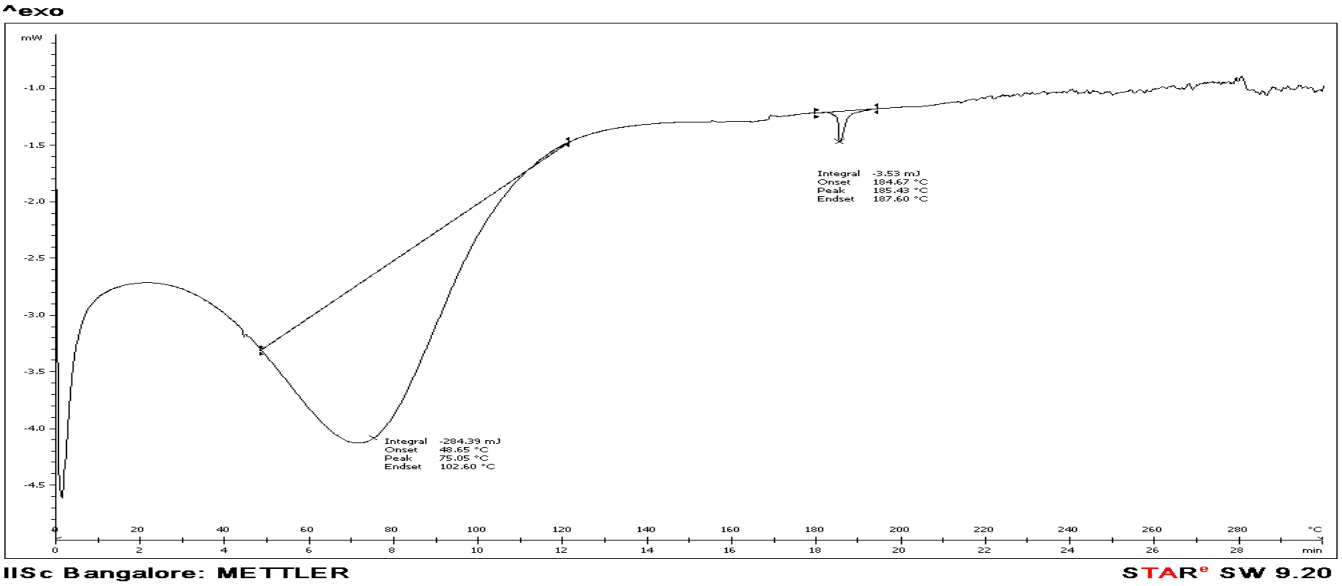
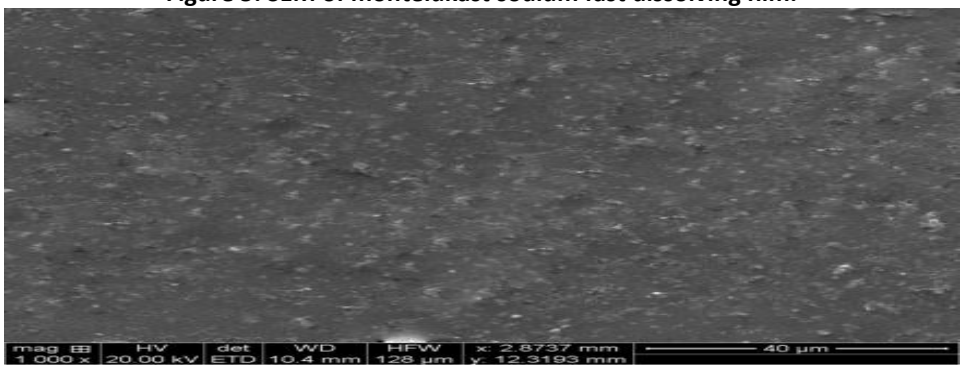


Figure 5: SEM of montelukast sodium fast dissolving film.



ISSN: 0975-8585

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 14.33 to 9.10 sec and 18.76 to 12.86 sec with increase in the concentration of crospovidone from 2 to 4% and MCC from 5 to 10% respectively, further increase in the concentration of crospovidone and MCC, increased the disintegration time due to blockade of capillary pores which prevents the entry of fluid in to the film.

Figure 6: In vitro drug release of fast dissolving films containing crosspovidone

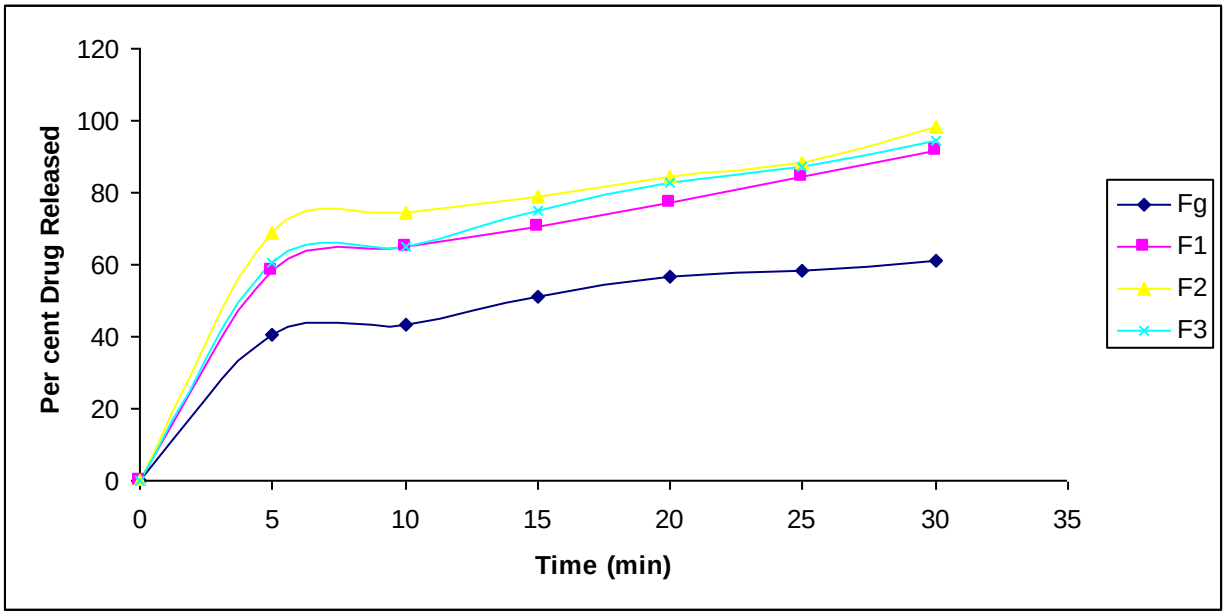
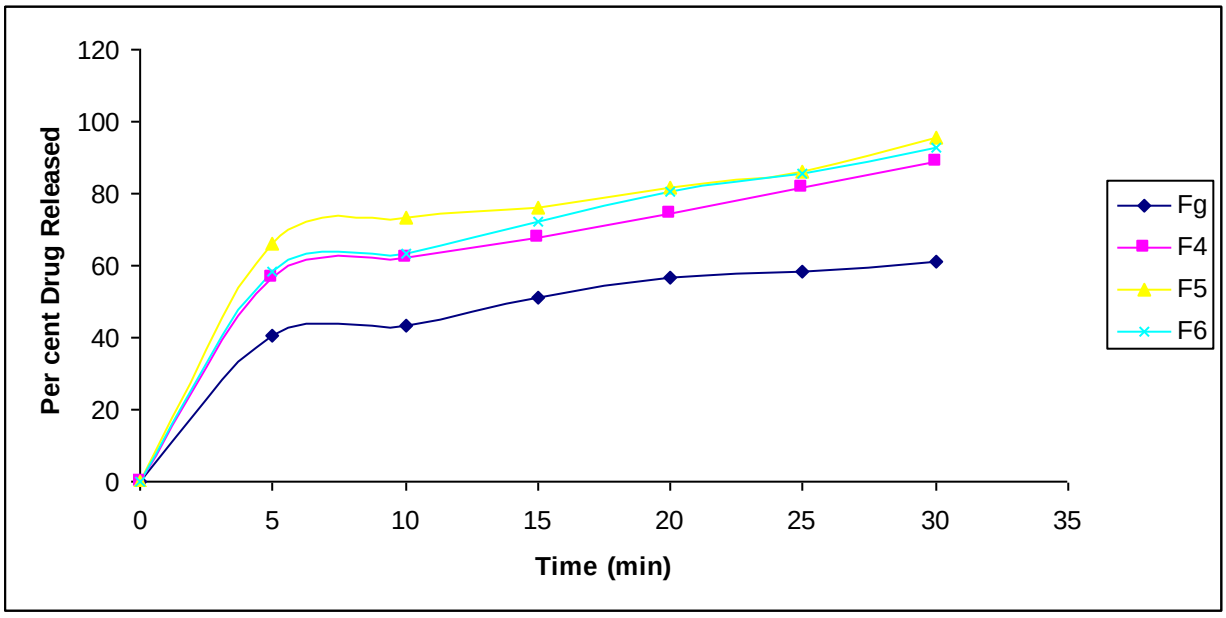


Figure 7: In vitro drug release of fast dissolving films containing microcrystalline cellulose



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 gelatin solution in water shown as optimized film forming base. The fast dissolving film prepared with gelatin as a film base with crospovidone as a superdisintegrant in the concentration of 2, 4 and 6% shown 91.86, 98.35 and 94.64% respectively of drug release in 30 min and with MCC as a superdisintegrant in the concentration of 5, 10 and 15% shown 89.07, 95.57 and 92.78% of drug release in 30 min.

It is observed that drug release from the film increased from 91.86 to 98.35% and 89.07 to 95.57% with increase in the concentration of crospovidone from 2 to 4% and MCC from 5 to 10% respectively, further increase in the concentration of crospovidone and MCC, 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 F_2 containing 4% crospovidone and F_5 containing 10% MCC. Because it has showed 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 gelatin as film base, and crospovidone and MCC as superdisintegrants.

ACKNOWLEDGEMENT

The authors are thankful to Management, Principal and Staff members of KRES's Karnataka College of Pharmacy, Bidar for providing necessary facilities.

REFERENCES

[1] Dixit R and Puthil S. J Control Release 2009; 139: 94-107.
[2] Arya A, Chandra A, Sharma V, and Pathak K. Int J ChemTech Res 2010; 2: 576-583.
[3] Nishimura M, Matsuura K, Tsukioka T, Yamashita H, Inagaki N and Sugiyama T. Int J Pharm 2009; 368:98-102.
[4] Shimoda H, Taniguchi K, Nishimura M, Matsuura K, Tsukioka T and Yamashita H. Eur J Pharm Biopharm 2009;73:361-365.
[5] http://www.rxlist.com/singulair_drug.html
[6] http://www.drugs.com/pdr/montelukastsodium.html.
[7] http://singulair.msd.jo/secure/downlands/resources/pi/singulair5mg.pdf
[8] Rowe RC, Sheskey PJ, and Owen SC, Hand book of Pharmaceutical Excipients, 2006; 5.
[9] Raghavendra Rao NG, and Suryakar VB. International Journal of Pharma and Bio Sciences 2010; 1(2): 1-14.
[10] Kunte S, and Tandale P. J Pharm Bilall Sci 2010; 4: 325-328.

[11] Siewert M, Dressman J, Brown CK, and Shah VP. AAPS PharmSciTech 2003; 4: E7.
[12] Patel R, Naik S, Patel J, and Baria A. Arch Pharm Sci Res 2009; 1: 212-217.
[13] Mohammad A, Harish N, Charyulu R, and Prabhu P. Trop J Pharm Res 2009; 8:33-41.
[14] Patil A, Shaik M and Gulam I. Int J PharmTech Res 2011; 3(2):619-625.
[15] Mashru C, Sutariya V, Sankali M, and Parikh P. Drug Dev Ind Pharm 2005; 31: 25-34.
[16] USP30-NF25, the United States Pharmacopoeia-National Formulary and its supplements, 2007.