Research Article CODEN: IJPRNK IMPACT FACTOR: 1.862 ISSN: 2277-8713
Prabhu SC, IJPRBS, 2014; Volume 3(3): 268-281 IJPRBS

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

DESIGN AND CHARACTERISATION OF FAST DISSOLVING SUBLINGUAL FILMS OF MONTELUKAST SODIUM

PRABHU SC, PARSEKAR S, SHETTY A, MONTEIRO SS, AZHARUDDIN M, SHABARAYA AR
Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka, India

Accepted Date: 21/05/2014; Published Date: 27/06/2014

Abstract: Sublingual drug delivery systems have acquired great importance recently due to their rapid onset of action, accurate dosing, no first pass metabolism, highly vascularised area, etc. Montelukast sodium is a leukotriene receptor antagonist (LTRA) used in maintenance treatment of asthma and to relieve symptoms of seasonal allergies. Fast dissolving sublingual films of Montelukast sodium were prepared by solvent casting method using different concentrations of polymers Pullulan and HPMC E15. The FT-IR studies showed no interaction between the drug and the polymer. The prepared films were evaluated for physico-chemical parameters such as weight uniformity, thickness uniformity, folding endurance, drug content, surface pH, tensile strength, percentage moisture uptake, folding endurance, *In-vitro* disintegration time, *In-vitro* dissolution studies and *Ex- vivo* permeation studies. Formulations F1 and F4 showed maximum release of 98.61% and 99.09% at the end of 180sec respectively. Short term stability revealed that there were no significant changes in the appearance and drug release from the films.

Keywords: Fast Dissolving Sublingual Film, *In-vitro*, *Ex-vivo*

Corresponding Author: MS. SHRUTI C PRABHU

Access Online On:

www.ijprbs.com

How to Cite This Article:

Prabhu SC, Parsekar S, Shetty A, Monteiro SS, Azharuddin M, Shabaraya AR; IJPRBS, 2014; Volume 3(3): 268-281

PAPER-QR CODE

INTRODUCTION

The fast dissolving drug delivery systems came into existence in the early 1970's. Fast dissolving drug delivery systems have a major advantage over conventional dosage forms since the drug rapidly disintegrates and dissolves without the use of water1.

Many patients have difficulty in swallowing tablets and capsules specially in cases of dysphagia, coughing, sudden allergic attacks or unavailability of water. Thus, to eliminate the drawbacks of tablets, fast dissolving films can be developed2.

Fast dissolving films are meant to be placed on the patients tongue or any other oromucosal tissue. The film rapidly hydrates and disintegrates to release the medication for therapeutic absorption3. However per-oral administration of drugs gives rise to some problems such as hepatic first pass metabolism and degradation within the GI tract. These problems can be overcome by administration through the sublingual mucosa. The sublingual route can produce a rapid onset of action within a short period of time due to high permeability and vascularisation of the sublingual mucosa3.

The present work investigated the effect of various polymers on the release of Montelukast sodium from fast dissolving sublingual films. The beast formulations were then evaluated for Ex- vivo permeation studies. Montelukast is a leukotriene receptor antagonist (LTRA) used for the maintenance treatment of asthma and to relieve symptoms of seasonal allergies.

MATERIALS AND METHODS

Montelukast sodium was obtained as a gift sample from Dr. Reddy's Laboratories Ltd., Hyderabad. Pullulan was obtained from DKSH India private limited, Mumbai, India and HPMC E15 was procured from Yarrow chem. Products, Mumbai, India. PEG 400 was obtained from Loba Chemie private limited, Mumbai, India. The porcine oral mucosa was procured from a local slaughter house in Mangalore.

Preparation of fast dissolving sublingual films of Montelukast sodium4

The fast dissolving films of Montelukast sodium were prepared by solvent casting technique using film forming polymer HPMC E15, Pullulan and Sodium Carboxymethyl Cellulose.

The calculated amount of polymer was dispersed in three forth volume of water with continuous stirring. CMC polymer was weighed accurately and it was soaked in half quantity of water for 8hours to get uniform dispersion. The calculated amount of Montelukast sodium was incorporated in the polymeric solutions. Sodium starch glycolate and Sucrose were then added to polymeric solution. Then citric acid, PEG400 were added and the final volume was adjusted up to 10ml with distilled water. The resulting bubble free viscous solution was casted on to

Petri dish (area of 63.58cm2) then kept in hot air oven at 40ºC for 24 h. The films were cut in to size of 2×2 cm2 containing 5 mg of Montelukast sodium.

Table no 1: Composition of fast dissolving sublingual films of Montelukast sodium

Formulation code	Drug (mg)	HPMC E15 (mg)	Pullulan (mg)	SSG (mg)	Citric acid (mg)	PEG 400 (ml)	Sucrose (mg)	Water (ml)
F1	79.45	300	-	20	20	0.5	20	10
F2	79.45	400	-	20	20	0.5	20	10
F3	79.45	500	-	20	20	0.5	20	10
F4	79.45	-	500	20	20	0.5	20	10
F5	79.45	-	600	20	20	0.5	20	10
F6	79.45	-	700	20	20	0.5	20	10

Spectrum measurement

The standard stock solution of Montelukast sodium having concentration of 16 µg/ml in buffer 0.5% SLS was scanned between 200-400nm in UV-Visible Spectrometer. The maximum absorption (λmax) of Montelukast sodium peak was obtained at 345nm.

Drug and excipient interaction studies (FT-IR) 5

FT-IR was used to predict any chemical interaction between the drug and the excipients used. A physical mixture of drug and polymers were prepared and this was mixed with suitable quantity of Potassium bromide. This mixture was then scanned from 4000 to 400 cm-1 in an FTIR spectrophotometer (Jasco FT/IR 4100). Interpretation of IR spectrum of physical mixture was compared with those of pure drug to detect any chemical changes.

EVALUATION OF FAST DISSOLVING SUBLINGUAL FILMS

Physical appearance and surface texture

Physical appearance was checked by visual inspection and surface texture was evaluated by touch or feel of the film.

Weight uniformity[6]

The cast film was cut at different places and the weight of each film was checked with the help of an electronic balance and the average weight was calculated.

Thickness measurement[6]

The thickness of three films of each formulation was determined by a micrometer screw gauge and average thickness was calculated.

Surface pH[6]

The film was placed in a petri dish and was moistened with 0.5ml of distilled water and kept for 30sec. The pH was noted by bringing the electrode of the pH meter in contact with the surface of the formulation.

Folding endurance[6]

Folding endurance was determined by repeatedly folding the film at the same position until it breaks. The number of times the films can be folded without breaking is termed as the folding endurance value.

Drug content[5]

Drug content of the film was determined by dissolving a 4cm2 film in 100ml of 0.5% SLS using magnetic stirrer for 1 hr. The drug concentration was then evaluated spectrophotometrically at λmax of 345 nm. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded.

Percentage moisture absorption[5]

The films were weighed and placed in a dessicator containing 100ml of saturated solution of Aluminium chloride and 75 ± 5% RH was maintained. After three days the films were taken out and reweighed. The percentage moisture absorption was calculated using the following formula.

%Moisture absorption = Final weight -Initial weight x 100/ Initial weight

Tensile strength[7]

Tensile strength was determined using "ASIAN" Tensile Testing Machine. The apparatus has two clamps, the upper one is fixed and the lower is movable. The film sample was clamped between the two clamps. The force at tearing and elongation were determined.

Tensile strength = Break force/ Cross sectional area of the sample (mm2)

In- vitro disintegration time[5]

In- vitro disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

In- vitro dissolution studies[8]

Dissolution studies of the films was carried out by using USP type I (basket apparatus) with 300 ml of 0.5% Sodium lauryl sulphate as dissolution medium maintained at 37 ± 0.50C. Medium was stirred at 50 rpm. Samples were withdrawn at every 30 sec interval, replacing the same amount with the fresh medium. Amount of drug in the withdrawn samples was determined by UV spectrophotometer at 345 nm.

Ex- vivo permeation studies[8]

Permeation studies were carried using the Franz diffusion cell of internal diameter of 2.5 cm. Porcine oral mucosa was used as the model membrane. The buccal pouch of the freshly sacrificed pig was procured from the local slaughter house. The buccal mucosa was excised and trimmed evenly from the sides and then washed in isotonic phosphate buffer of pH 6.6 and used immediately. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with 100mL of buffer which was maintained at 37 ± 0.2ºC and 50 rpm. One film of dimensions 4cm2, previously weighed, was placed in intimate contact with the mucosal surface of the membrane. Samples were withdrawn at suitable intervals, replacing the same amount with the fresh medium. The percentage of drug permeated was determined by measuring the absorbance in UV Visible Spectrophotometer at 345nm.

Stability studies[9]

Best formulations were stored in an amber coloured bottle with aluminum cap as a closure. It was tightly sealed and kept in the incubator maintained at 40 ± 2 °C and 75 ± 5% RH. The stability studies were carried out for 2 months. Samples were collected at 1month interval, it was observed for physical appearance, in vitro disintegration time, drug content and in-vitro drug release.

RESULTS AND DISCUSSIONS

DRUG AND EXCIPIENT INTERACTION STUDIES

The peaks obtained in the spectra of each physical mixture correlates with the peaks of drug spectrum. The FT-IR of pure drug is characterized by C-Cl stretch at 761.744cm^{-}1 indicating the presence of Cl atoms, C=C aromatic alkene at 1558.2 cm^{-}1, C-O alcohol at 1140.69 cm^{-}1.

The characteristics peaks found in Montelukast sodium were also found in physical mixture of drug and polymers, hence it appears there was no chemical interaction between Montelukast sodium and polymers.

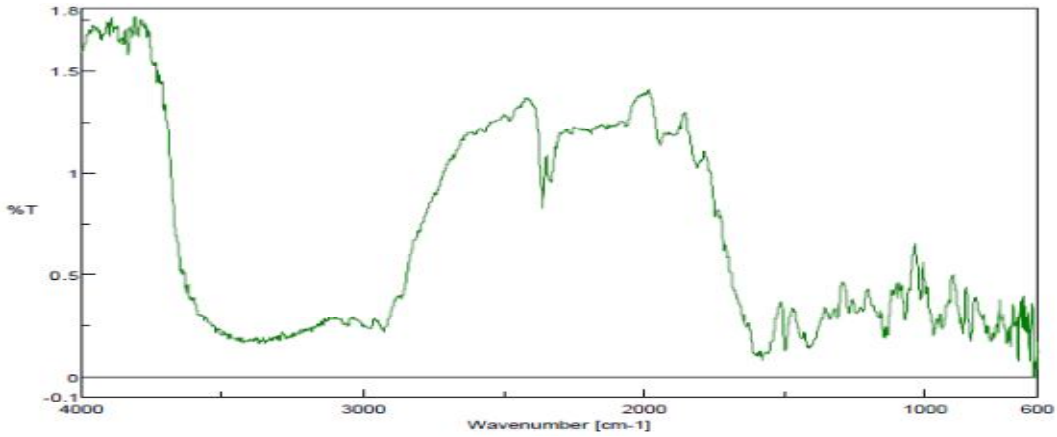

Fig no 1: IR spectra of Montelukast sodium

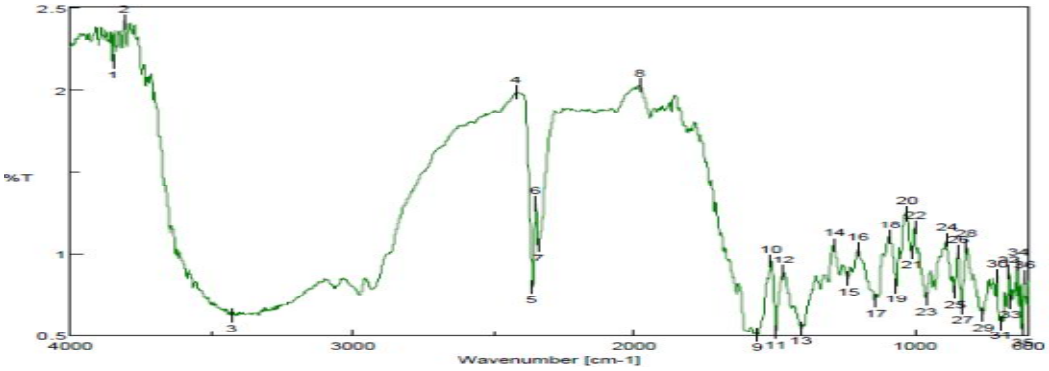

Fig no 2: IR spectra of Montelukast sodium and Pullulan

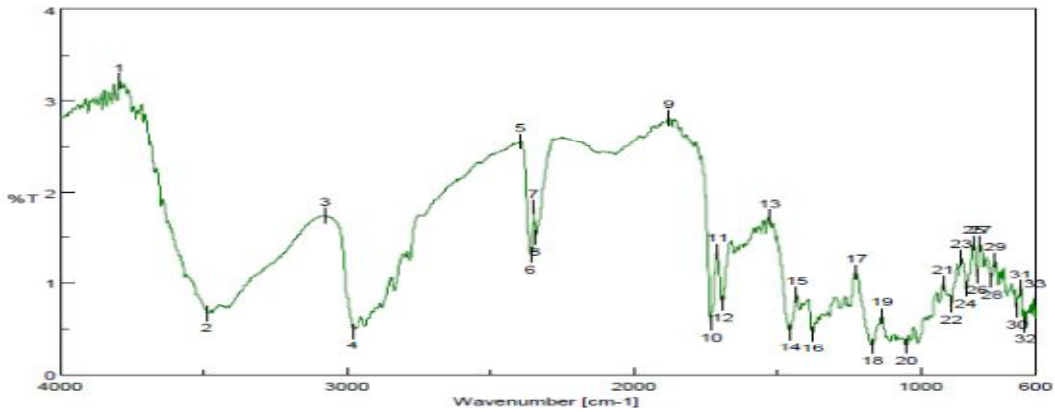

Fig no 3: IR spectra of Montelukast sodium and HPMC E15

Table no 2: Various physical properties of fast dissolving sublingual films of Montelukast sodium

Formulation code	Physical appearance	Surface texture	Thickness (mm±SD*)	Surface pH	Weight uniformity (mg±SD*)
F1	Transparent	Smooth	0.033±0.005	6.59±0.015	39.1±0.55
F2	Transparent	Smooth	0.083±0.005	6.71±0.03	43.86±0.65
F3	Transparent	Smooth	0.096±0.005	6.65±0.02	48.4±0.41
F4	Transparent	Smooth	0.056±0.01	6.76±0.02	42.7±0.35
F5	Transparent	Smooth	0.113±0.02	6.55±0.04	46.5±0.45
F6	Transparent	Smooth	0.15±0.01	6.70±0.03	52.9±0.3

*All values represented are mean of 3 readings (n = 3)

Physical appearance and surface texture of film

All the films appeared uniform. All the films were found to be transparent and the surfaces of the films were smooth in nature. Thus it was concluded that the films were elegant and aesthetically appealing.

Thickness

The thickness of the fast dissolving films F1 to F6 varies from 0.033±0.005 mm to 0.15±0.01 with low standard deviation values. Formulation F1 showed the lowest thickness maybe due to low concentration of the polymer and F6 showed highest thickness due high polymer concentration. The result of thickness measurement showed that as the concentration of polymer increases, thickness of mouth dissolving film increases. The results are shown in table no 2.

Surface pH

The surface pH of the films F1 to F6 was ranging from 6.55±0.04 to 6.76 ±0.02 as shown in table no 2. The surface pH of all the films were uniform and within the range. Acidic or alkaline pH causes irritation to the oral mucosa and influences the degree of hydration of the polymer, the surface pH of the films determine the drug permeation. Therefore it was important to keep the surface pH as close to the salivary pH as possible.

Weight uniformity

High concentration of polymer in F6 (700mg of Pullulan) may be the reason for highest weight. Hence we can say that as the concentration of polymer increases weight of the film also

increases. Films containing Sodium CMC were found to show lowest weight as compared to the other two polymers since the molecular weight of Sodium CMC was 262.18g/mol as compared to the molecular weights of HPMC E15 and pullulan that had molecular weights of 324g/mol and 904g/mol respectively. The results are depicted in table no 2.

Table no 3: Mechanical properties of fast dissolving sublingual films of Montelukast sodium

Formulation code	Folding endurance	Tensile strength (N/mm^2±SD*)
F1	>200	1.31± 0.03
F2	>200	1.57± 0.06
F3	>200	1.93± 0.01
F4	>200	1.79± 0.03
F5	>200	2.08± 0.02
F6	>200	2.46± 0.04

All values represented are mean of 3 readings (n = 3)

Folding endurance

Folding endurance measures the ability of patch to withstand rupture, higher the folding endurance lower will be chances of film to rupture easily. Folding endurance value was more than 200 which indicated good elasticity of the films. The presence of plasticizer was the reason for this good elasticity.

Tensile strength

Tensile strength is the ability of the film to withstand rupture. Tensile strength of the films was found to be between 1.31± 0.03 to 2.46± 0.04. It was seen that tensile strength was found to increase with increase in polymer concentration. Polymers contain large number of chains of molecules that are held together by different types of bonds. According to the bonds formed force required to rupture the patch will differ. Highest force required to break Pullulan films followed by HPMC E15. The tensile strength values are shown in table no 3.

Table no 4: Drug content, moisture absorption and in- vitro disintegration time of fast dissolving sublingual films of Montelukast sodium

Formulation code	Drug content (%±SD*)	Moisture absorption (%±SD*)	In-vitro disintegration (Secs ±SD*)
F1	98.2±0.7	1.51±.0.040	20± 0.5

F2	99.40±0.3	2.78±.0.035	27±0.7
F3	99.61±0.4	3.48±.0.030	36±1.5
F4	98.6±0.7	3.00±.0.035	19±0.5
F5	99±0.4	3.73±.0.020	25±1.5
F6	97.31±0.3	4.58±.0.030	33±0.5

***All values represented are mean of 3 readings (n = 3)**

Drug content

The content uniformity for all the formulations was found to be in the range 97.31±0.3% to 99.61±0.4% which showed that there was uniform distribution of the drug in films of all formulations and complied within the limits. The values are shown in table no 4.

Moisture absorption

The study of percentage moisture uptake gives the idea about the stability of the film in different environmental conditions and also about the hydrophilicity of the polymers used. More the moisture absorption property of the film less stable it will be. However it was found that the % moisture absorption increased with increase in hydrophilic polymers like Pullulan followed by HPMC E15. Percentage moisture absorption was found to be between 1.51±0.040 to 4.58±0.025. The moisture absorption values are depicted in table no 4.

In-vitro disintegration time

The disintegration time of F1 to F3 was found to be 20, 27, 36secs respectively. The disintegration time of F4 to F6 was found to be 19, 25, 33secs respectively. Study showed that disintegration time was increased with increase in the polymer concentration. This may be due increased time required by the medium for wetting the film due to high concentration of polymers. The time in secs is depicted in table no 4.

In- vitro drug release studies

Table no 5: In- vitro drug release studies of formulations F1- F6

Time (Sec)	% cumulative drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
30	31.46	30.72	29.92	33.04	32.74	30.85
60	45.55	44.95	43.70	47.02	45.92	44.95
90	66.71	63.92	61.83	68.97	69.91	68.84
120	85.45	83.84	79.99	84.11	83.01	79.85

150	90.64	89.69	88.20	91.67	89.96	85.48
180	98.61	97.06	94.83	99.09	95.87	91.68

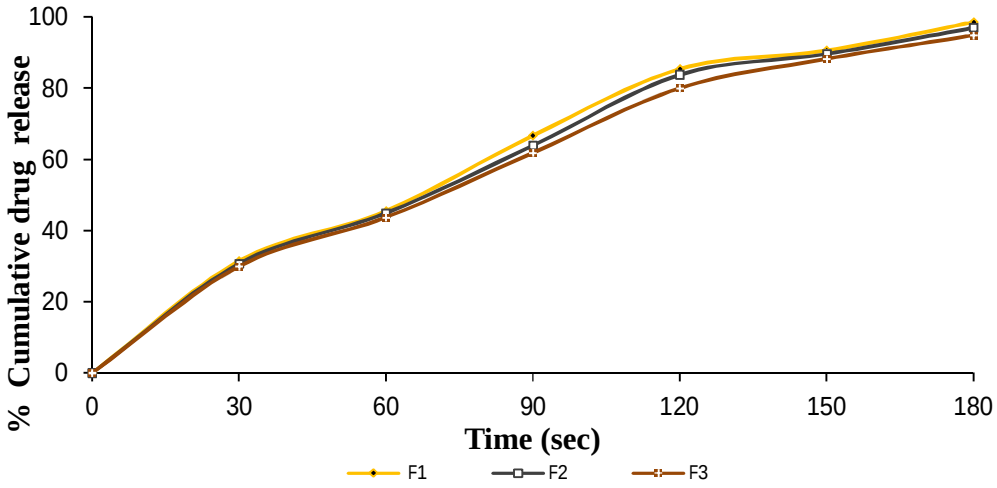

Fig no 4: % CDR v/s time graph of formulations F1, F2 & F3

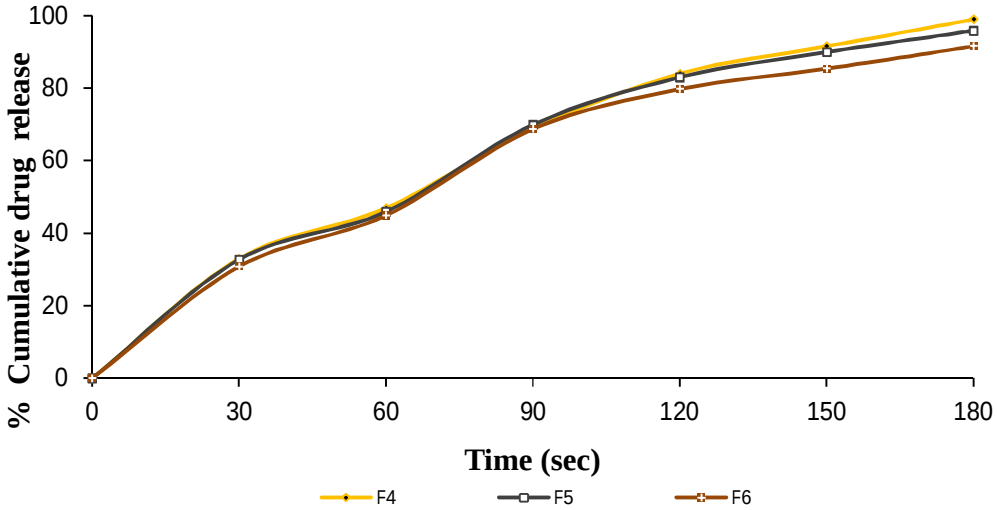

Fig no 5: % CDR v/s time graph of formulations F4, F5 & F6

In vitro drug release studies indicate the rate of release of the drug from the fast dissolving film. Dissolution studies of formulation F1 to F3 showed that the films containing HPMC E15 has release of 98.61%, 97.06%, 94.83% of drug at the end of 180seconds respectively. The studies indicated that the rate of drug release decreases with increase in molecular weight of the polymer. Dissolution studies of formulation F4 to F6 showed that the films containing Pullulan

has release of 99.09%, 95.87%, 91.68% of drug at the end of 180seconds respectively. Higher polymer concentration results in viscous environment of the system, thus inhibiting the movement of water through the polymer matrix for the diffusion of drug.

Ex- vivo permeation studies

Table no 6: Ex- vivo permeation data of formulations F1 and F4

Time (Sec)	Percentage drug permeation	
	F1	F4
0	0	0
30	9.24	11.80
60	18.16	21.63
90	26.74	29.28
120	33.10	37.41
150	39.34	44.23
180	46.22	48.71
210	51.86	53.45
240	57.62	61.20
270	66.23	70.47
300	74.21	79.63
330	82.34	87.22
360	88.35	93.79

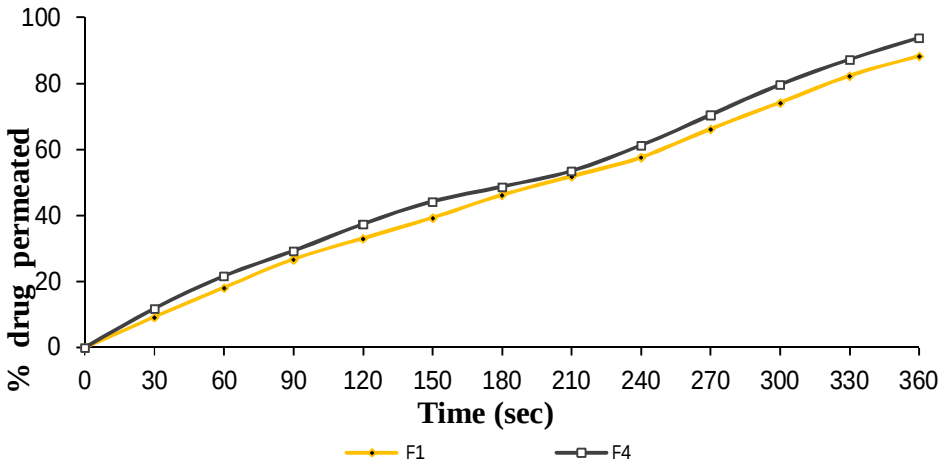

Fig no 6: % drug permeated v/s time of formulations F1 & F4

Fig no 7: *Ex- vivo* permeation studies with porcine oral mucosa

Ex vivo permeation study was performed on two formulations i.e. F1 and F4 since they give the maximum drug release among all the formulations. Porcine oral mucosa was used to study the drug permeation since the porcine oral mucosa resembles the oral mucosa of humans. Permeation studies of formulation F1 and F4 showed permeation of 88.35% and 93.79% of drug at the end of 360seconds respectively. These results showed that the drug was absorbed rapidly through the oral mucosa making it available for systemic circulation. Rapid penetration was seen through the oral mucosa because Montelukast sodium is a highly lipophillic drug with a partition coefficient value of 8.98.

Stability studies

Table no 7: Drug content, Disintegration time, Moisture uptake of formulation F1 after stability studies

Time (months)	Appearance	Drug content (%)	Disintegration time (sec)	Moisture absorption (%)
	*	*	*	*
Zero	Transparent	98.2	20	1.51
First	Transparent	97.73	22	1.68
Second	Transparent	97.35	23	1.80

*** 40±2°C and 75±5% RH**

Table no 8: *In- vitro* drug release under stability study of formulation F1

Time (sec)	%CDR 40±1°C and 75 % RH		
	0 day	30 days	60 days
30	31.46	31.01	30.75
60	45.55	45.12	44.85
90	66.71	66.27	65.93
120	85.45	85.11	84.84
150	90.64	90.28	89.90
180	98.61	98.33	98.07

Table no 9: Drug content, Disintegration time, Moisture uptake of formulation F4 after stability studies

Time (months)	Appearance	Drug content (%)	Disintegration time (sec)	Moisture uptake (%)
	*	*	*	*
Zero	Transparent	98.6	19	3.00
First	Transparent	97.86	20	3.22
Second	Transparent	97.40	22	3.48

Table no 10: Drug release under stability study of formulation F9

Time (sec)	%CDR 40±1°C and 75 % RH		
	0 day	30 days	60 days
30	33.04	32.76	32.43
60	47.02	46.82	46.61
90	68.97	68.63	68.48
120	84.11	83.90	83.79
150	91.67	91.41	91.20
180	99.09	98.87	98.70

The stability studies were carried out for two months on formulations F1 & F4 at 40±2°C and 75±5% RH and the films were observed for appearance, drug content, in- vitro disintegration time, in-vitro drug release studies. It was studied that no significant change was observed in the

drug content, in- vitro disintegration time, in-vitro drug release studies. The films were found to be stable as no characteristic changes were observed.

CONCLUSION

It can be concluded that fast dissolving sublingual films of Montelukast sodium can be formulated using Pullulan and HPMC E15 as polymers. The results of all the studies were found to be within limits and the bioavailability of Montelukast sodium was foud to be increased. The studies can be further extended to in- vivo evaluation using different animal models.

REFERENCES

1. Chowdary YA, Soumya M, Madhu BM, Aparna K, Himabindu P. A review of fast dissolving drug delivery systems- A pioneering drug delivery technology. Bull Env Pharmacol Life Scien 2012; 1(12): 08-20.

2. Patil SL, Mahaparale PR, Shivnikar MA, Tiwari SS, Pawar KV, Sane PN. Fast dissolving oral films: An innovative drug delivery system. Int J Res & Reviews Pharm & Applied Sci 2(3): 482-496.

3. Sarkhejiya NA, Patel VP, Pandya DJ. Sublingual delivery: A promising approach to improve bioavailability. Pharm Sci Monitor 2013; 4(2): 3870-3889.

4. Ali RK, Shabaraya AR, Azharuddin M. Design and evaluation of fast dissolving oral films of Granisetron Hydrochloride. Am J PharmTech Res 2012; 2(6): 591-609.

5. K. Vijaya sri, Rohini P, Reddy GK. Montelukast sodium oral thin films: Formulation and in vitro evaluation. Asian J Pharma & Clinical Res 2012; 5(4): 266-270.

6. Kapadia YD, Trambadiya DA, Patel AV, Patel VP. Formulation and evaluation of fast dissolving sublingual film of Metoprolol succinate. An Int J Pharma Sci 2013; 4(3): 140-154.

7. Qadir KA, Charyulu RN, Prabhu P, Bhatt P, Shastry CS. Formulation and evaluation of fast dissolving films of Loratidine for sublingual use. Int Res J Pharm 2012; 3(7): 157-161.

8. Koland M, Sandeep VP, Charyulu RN, Subrahmanyam EVS. The design and Characterisation of sublingual films of Ondansetron hydrochloride. Int J Chem Sci 2009; 7(4): 2927-2938.

9. Bhupinder B, Jangra S. Formulation and evaluation of fast dissolving sublingual films of Rizatriptan Benzoate. Int J Drug Dev & Res 2012; 4(1): 133-143.