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FORMULATION AND EVALUATION OF MONTELUKAST SODIUM MUCOADHESIVE BUCCAL PATCHES FOR CHRONIC ASTHMA ATTACKS.

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ABSTRACT

The montelukast is a leukotrine receptor antagonist (LTRA) used for the maintenance treatment of asthma, chronic asthma attacks and to relieve symptoms of seasonal allergies. Because of poor bioavailability of montelukast sodium by oral route, there is a need to increase its bioavailability by formulating it into buccal dosage forms. Hence, montelukast sodium is a suitable drug for buccal dosage forms and may provide a better therapeutic profile than oral route. In the present research work, montelukast sodium buccal patches were prepared by using hydrophilic and hydrophobic polymers. Buccal patches were characterized for number of parameters like physical appearance and surface texture, weight uniformity, thickness, folding endurance, swelling index, surface pH, drug content uniformity, *in vitro* residence time, bursting strength, drug–excipients interaction study, and *in vitro* drug release study. All the patches were uniform and translucent, having good strength, and smooth surface. The thickness of the prepared patches was in the range of 0.266 to 0.326 mm. Folding endurance of all prepared patches was > 250. The results of swelling index between the range of 30.03 - 44.27 %, and the surface pH was in the range pH of buccal region. The results of drug content were in the prescribed range. The i*n vitro* residence time for all the patches is in between 3.20 - 5.59 hrs. The Bursting strength of patches is in the range of 4.166 to 5.733 Kg/cm^2. *In vitro* release studies were conducted for montelukast loaded patches exhibited drug release in the range of 68.83 - 92.22 % in 8 hrs. FT-IR studies revealed that, there was no interaction between drug and excipients used. Release of montelukast from all patches followed zero order and mechanism was diffusion rate limited. Finally it can be concluded that F3 and F6 are the best formulation.

KEYWORDS

Montelukast sodium, Eudragit RL-100, PVP, buccal patch, *in-vitro* release, physical properties.

INTRODUCTION

The interest in novel rout of drugs administration occurs from their ability to enhance the bioavailability of the drugs impaired by narrow absorption windows in the gastrointestinal tracts. Drugs delivery via the buccal routs using bioadhesive dosage forms offer such a novel routs of drugs administration. This route has been used successfully for the systematic delivery of number of drugs candidates[1-5]. Problems such as high first pass metabolisms and drugs degradation in the gastrointestinal tract can be circumvented by administrating the drug buccal routes[6, 7]. Moreover,

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buccal drug delivery offers safe and easy method of drugs utilization, because drug absorption can be promptly terminated in case of toxicity by removing buccal dosage form from buccal cavity. The buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and provides rapid absorption for drugs than oral route. The oral route has been preferred route of administration for many drugs. Pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because it provides the possibility of avoiding either destruction by gastrointestinal contents or hepatic first-pass inactivation of drug[8]. Various studies have been conducted on buccal delivery of drugs using mucoadhesive polymers. Attempts have been made to formulate various mucoadhesive devices including tablets[9], films[10], patches[11], strips[12], and gels[13].

The montelukast sodium is a leukotrine receptor antagonist (LTRA) used for the maintenance treatment of asthma, chronic asthma attacks and to relive symptoms of seasonal allergies[14]. The main drawback of conventional montelukast formulation is that it undergoes hepatic first pass metabolism. Thus, it shows plasma or biological half-life 2.5 to 5.5 hrs[15], there by decreasing bioavailability upto 64%[16]. The present work describes such delivery system, which will improve the biological half-life as well as bioavailability of montelukast.

The objective of the present work to develop the mucoadhesive patches of montelukast sodium (MS) using solvent casting technique. Two different film formers such as hydroxyl ethyl cellulose (HEC) and sodium carboxy methylcellulose (NaCMC) were used. The prepared patches will be evaluated for parameter related to buccal drug delivery system like weight uniformality, thickness, folding endurance, swelling index, surface pH, drug content estimation, *in vitro* residence time, bursting strength, i*n vitro* release study and drug polymer interaction. In the proposed research work, we will prepare buccal patches to improve the bioavailability by avoiding hepatic metabolism, greater therapeutic efficacy, and improve patient compliances.

MATERIALS AND METHODS

Montelukast sodium was obtained as gift sample from Morepen Pharma. Pvt. Ltd., Solan (Delhi). Eudragit RL-100 was obtained as gift sample form Evonik Pharma Pvt. Ltd., Mumbai. HEC, Na CMC, PVP K-30, and Propylene glycol (PG) were purchased from S.D. Fine Chem. Lab., Mumbai.

Preparation of mucoadhesive buccal patches

Buccal patches of MS were prepared by solvent casting technique employing mercury as substrate[17]. The mucoadhesive patches were prepared using polymers like HEC, Na CMC, Eudragit RL-1OO and PVP K-30. PG was used as plasticizer. The calculated amount of polymer was dispersed in three fourth volume of water with continuous stirring using magnetic stirrer and the final volume was adjusted with distilled water. In case of Eudragit RL-100 containing patches, a polymer was firstly dissolved in ethanol (95%) with continuous stirring[18]. The calculated amount of montelukast sodium was incorporated in the polymeric solutions after levigation with 0.1ml of PG. The solution was casted onto mercury substrate then kept in hot air oven at 40^0C. for 24 hrs. Compositions of circular cast patches of various formulations are mentioned in **Table-1**. The patches were punched into size 10 mm containing 5 mg of MS. The 10 mm MS patches are shown in **Fig 1.**

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Table 1.
Composition of mucoadhesive MS buccal patches.

Ingredients	Formulation code					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
MS (mg)	31	31	31	31	31	31
HEC (mg.)	360	360	360	---	---	---
NaCMC (mg.)	---	---	---	360	360	360
PVP-K30 (mg.)	---	60	---	---	60	---
Eudragit RL-100 (mg.)	---	---	60	---	---	60
Ethanol (95%) (ml)	---	---	4	---	---	4
PG (ml)	0.1	0.1	0.1	0.1	0.1	0.1

Each 10 mm patch contains 5 mg of montelukast sodium.

Fig 1. ***10 mm buccal patches containing Montelukast sodium.***

Evaluation of mucoadhesive buccal patches

The prepared buccal patches were evaluated for different physical properties like weight uniformity, thickness, folding endurance, swelling index, surface pH. Mechanical properties like *in-vitro* residence time, bursting strength of patches and evaluation of MS patches like drug content, *in vitro* release study.

Weight uniformity and thickness of patches

Three patches of the size 10mm diameter were weighed individually using digital balance and the average weights were calculated[19,20]. Thickness of the patches was measured using screw gauge with a least count of 0.01mm at different spots of the patches. The thickness was measured at three different spots of the patches and average was taken[21,22]. The weight uniformity and thickness of all formulations was recorded (n=3).

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Folding Endurance and percentage Swelling Index of patches

The flexibility of patches can be measured quantitatively in terms of folding endurance. Folding endurance of the patches was determined by repeatedly folding a small strip of the patches (approximately 2x2 cm) at the same place until it broke. The number of times patches could be folded at the same place, without breaking gives the value of folding endurance[23]. The swelling index of the patches was determined by immersing preweighed patch of size 2 cm^2 in 50 ml water. The strip were taken out carefully at 5, 10 upto 30 min intervals, blotted with filter paper and weighed accurately[24]. The folding endurance and percent swelling index of patches are carried out for three time and average.

The swelling index calculated by

$$\% \text{ Swelling Index} = \frac{W2 - W1}{W1} x100$$

Where,

W1 is the initial patch weight at zero time.

W2 is the weight of the swollen patch afterr time‘t’.

Surface pH of patches

For determination of surface pH three patches of each formulation were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of patches and allowing equilibrate for 1 min [25]. A mean of three reading was recorded.

***In vitro* residence time and bursting strength of patches**

The *in vitro* residence time[26] was determined using IP disintegration apparatus. The disintegration medium was 800ml of 0.5% SLS solution maintained at 37 ± 2ºC. The segments of rat intestinal mucosa, each of 3 cm length, were glued to the surface of a glass slab, which was then vertically attached to the apparatus. Three mucoadhesive patches of each formulation were hydrated on one surface using 0.5% SLS solution and the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down. The patch was completely immersed in the 0.5 % SLS solution at the lowest point and was out at the highest point. The time required for complete erosion or detachment of the patches from the mucosal surface was recorded (n=3). A test for measuring the resistance of patches to bursting and reported in kilo-Pascal or pounds per square inch or Kg/cm^2. The burst strength of all the patches was evaluated by using standard bursting strength tester.

Drug content uniformity study of patches

The patches were tested for drug content uniformity by UV-Spectrophotometric method. Patches of 10 mm diameter were cut from three different places from the casted patchs[27]. Each patch was placed in 100 ml volumetric flask and dissolved in 0.5% SLS solution and 5 ml is taken and diluted with 0.5% SLS solution upto 10 ml. The absorbance of the solution was measured at 342 nm using UV/VIS spectrophotometer (Shimadzu UV-1700). The percentage drug content was determined using the standard graph and the same procedure was repeated for three patches (n=3).

***In vitro* drug release of patches**

In vitro release studies were carried out by attaching sigma dialysis membrane to one end of the open

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cylinder, which acts as donor compartment. The prepared buccal patches containing drug was placed inside donor compartment, which is, agitated continuously using magnetic stirrer and then temperature was maintained at 37±1ºC [28]. Receptor compartment consists of 100 ml of 0.5 % SLS solution, sample of 2 ml were withdrawn at periodic intervals from receptor compartment and replaced with fresh 2 ml of 0.5 % SLS solution immediately and the drug release was analyzed spectrophotometrically at 342nm.

Characterization of montelukast films

FTIR Studies: IR spectra for drug, excipients and formulations F3, and F6 were recorded in a Fourier transform infrared (FTIR) spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

RESULT AND DISCUSSION

Mucoadhesive patches of MS were prepared using mucoadhesive polymers like HEC, NaCMC, PVP K-30 and Eudragit RL-100. The drug delivery system was designed as a matrix. All the patches were shows smooth surface and elegant texture. The physical characteristics of various patches are given in **Table 2**. The weights of 10 mm patch were in the range of 27.66 to 33.00 mg and patch thickness in the range of 0.266 to 0.326 mm. Surface pH of patch was in the range of 6.13 to 6.80 pH. The folding endurance was measured manually, patches were folded repeatedly until it broke, and it was considered as the end. Folding endurance was found to be in the range of 274 to 293. **Fig 2** shows the results of percent swelling index. The swelling behavior and *in vitro* residence time of the mucoadhesive polymers are observed as given in **Table 2 and 3**. The PVP K-30 containing patches showed high swelling values to Eudragit RL-100 containing patches because PVP K-30 is freely soluble in water, which enhanced the water uptake capacity in the finished dosage form. The incorporation of PVP K-30 induced significant reduction of *in vitro* residence time of the studied formulae, which may correlate with the increase in swelling behavior due to enhanced erosion rate. The percent swelling index and *in vitro* residence time for the patches is in between 30.03 to 44.27 %. and 3.20 to 5.59 hrs respectively.

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Table 2.
Physical Evaluation of Mucoadhesive Buccal patches of MS.

Formulation code	Weight Uniformity (mg) ± SD, (n=3)	Thickness (mm) ± SD, (n=3)	Surface pH ± SD, (n=3)	Folding Endurance ± SD, (n=3)	% Swelling Index ± SD, (n=3)
F1	30.66 ± 1.527	0.266 ± 0.015	6.80 ± 0.100	291 ± 2.000	32.28 ± 2.005
F2	33.00 ± 1.732	0.300 ± 0.010	6.33 ± 0.152	293 ± 2.645	42.30 ± 0.910
F3	32.33 ± 1.527	0.303 ± 0.011	6.30 ± 0.173	274 ± 1.732	30.03 ± 0.499
F4	27.66 ± 0.577	0.286 ± 0.020	6.63 ± 0.152	280 ± 2.645	38.39 ± 1.686
F5	29.33 ± 1.154	0.303 ± 0.011	6.53 ± 0.321	283 ± 1.732	44.27 ± 1.017
F6	31.00 ± 1.000	0.326 ± 0.015	6.13 ± 0.152	275 ± 3.000	36.34 ± 1.361

Note: values in parenthesis are standard deviation (±SD).

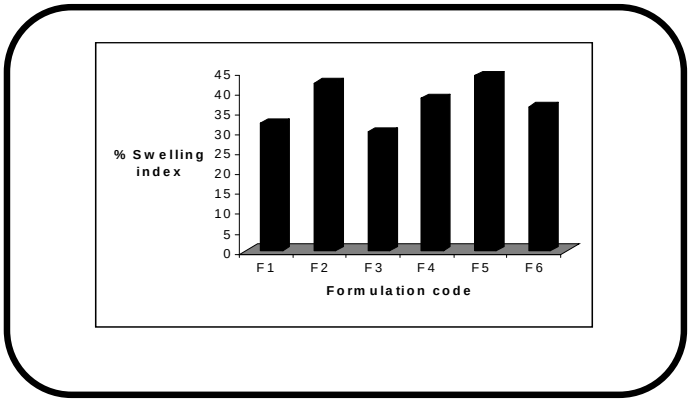

Fig 2. P*ercentage-swelling index of different formulations.*

The drug content in formulations was uniform with the range of 95.88 to 98.76 %. On the basis determination, it was considered that the drug was dispersed uniformly through out the patch. The Bursting

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strength of patches is in the range of 4.166 to 5.733 Kg/cm^2. The Bursting strength results and apparatus used to measuring the resistance of patches to burst are shown in **Table 3 and Fig 3** respectively.

Table 3.
Physical evaluation of mucoadhesive MS buccal patches.

Formulation code	*In vitro* residence time(Hrs) ± SD, (n=3)	%Drug Content ± SD, (n=3)	Bursting Strength ±SD, (n=3)	Drug released in 4 hrs. ±SD, (n=3)	Drug released in 8 hrs. ±SD, (n=3)
F1	4.11 ± 0.076	98.76 ± 0.350	5.733 ± 0.305	32.20 ± 0.266	80.90 ± 2.453
F2	3.56 ± 0.115	97.81 ± 0.902	5.166 ± 0.208	37.65 ± 0.338	83.39 ± 2.571
F3	5.43 ± 0.152	96.99 ± 1.791	5.066 ± 0.378	30.27 ± 0.325	68.83 ± 0.834
F4	3.35 ± 0.056	98.70 ± 0.540	4.733 ± 0.208	42.69 ± 0.240	90.88 ± 1.610
F5	3.20 ± 0.035	96.87 ± 1.002	4.466 ± 0.251	37.70 ± 0.228	92.22 ± 0.834
F6	5.59 ± 0.105	95.88 ± 1.963	4.166 ± 0.152	34.65 ± 0.254	73.95 ± 0.825

Note: values in parenthesis are standard deviation (±SD).

Fig 3.*Bursting strength tester.*

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The *in vitro* release studies of various formulations were performed in 0.5% SLS solution at 342 nm. Distinguishable difference was obtained in the release pattern of montelukast sodium patch containing PVP K-30 and Eudragit RL-100. The *in vitro* drug release studies in the range of 68.83 to 92.22 % in 8 hrs results were given in **Table 3** and graphical representation was shown in **Fig 4**.

Table 4.
Kinetic parameters of MS buccal patches.

Formulation code	Zero-order (r^2)	First- order (r^2)	Higuchi plot (r^2)	Peppas plot (r^2)
F1	0.9934	0.9406	0.9537	0.9814
F2	0.9937	0.9112	0.9485	0.9849
F3	0.9842	0.9154	0.9362	0.9901
F4	0.9945	0.8524	0.9545	0.9924
F5	0.9882	0.8287	0.9345	0.9884
F6	0.9909	0.9206	0.9476	0.9903

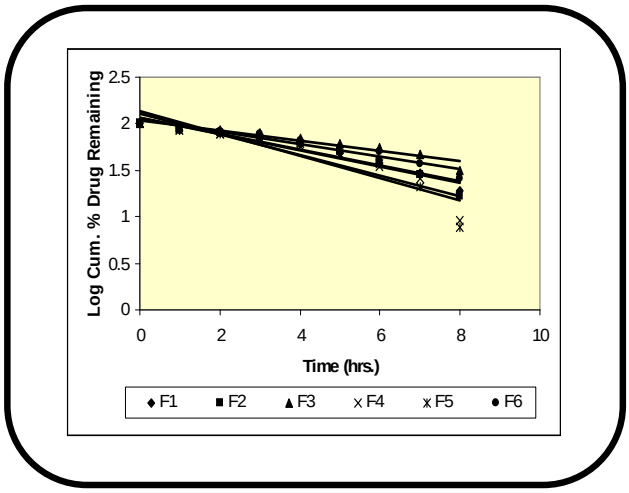

Fig 4. ***Comparative in vitro drug release profiles of formulation F1 to F6.***

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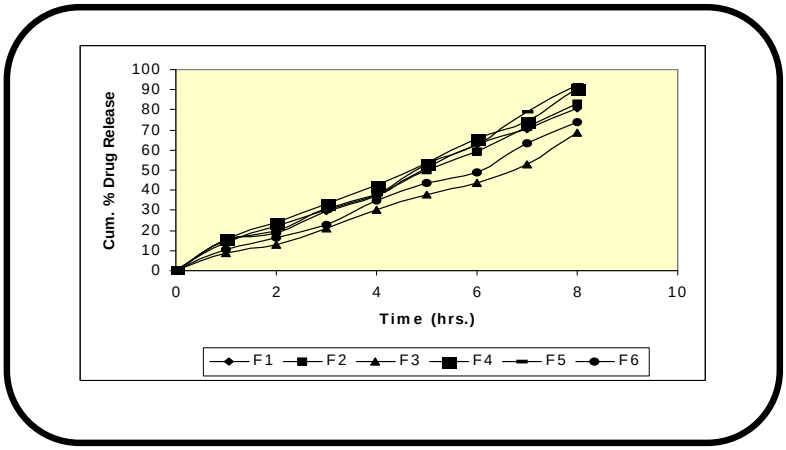

Fig 5. ***Log cumulative drug remaining of different formulations.***

Kinetics drug release results were given in **Table 4** and shown in **Fig 5-7**, correlation coefficient (r^2) values are significantly correlation (99% probability level) was found and also coefficient (r^2) values are higher than that of first-order release kinetics. It may be concluded that release kinetics followed zero order **(Fig 5)**. Mechanism of drug release pattern i.e. diffusion and swelling was confirmed by Higuchi plots**. Fig 6** shows the graphical representation of cumulative percentage drug release versus square root of time. The Higuchi plots were found to be linear with correlation coefficient values shown in **Table 4**. It was concluded that the release of drug from the patches followed the diffusion-controlled mechanism in all the formulations. The plots of log cumulative percentage drug release versus log time were found to be linear to the all formulations. The correlation coefficient values were shown in **Table 4**. From **Fig 7**, it is concluded that the release of MS from patches have obeyed Non-fickian diffusion release mechanism.

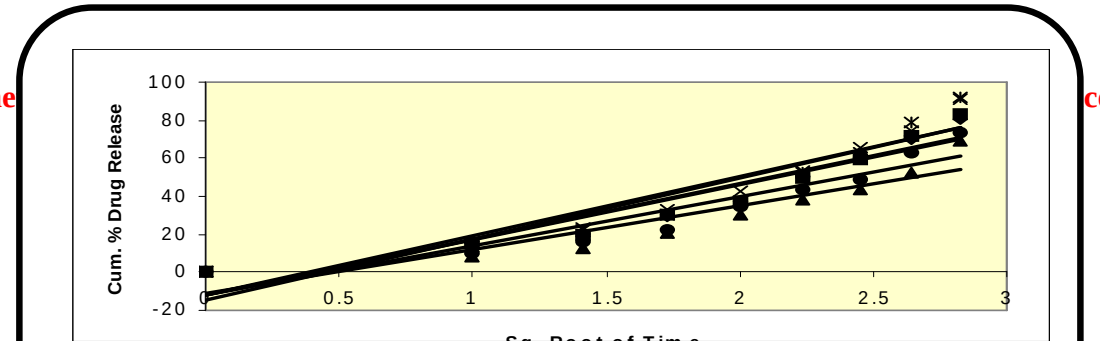

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Fig 6.*Higuchi's plots of different formulations.*

In **Fig 8** shows the IR spectrum of the pure drug Montelukast sodium has exhibited IR spectrum a broad band around 3411 cm^{-1} indicating overlapping of these peaks. The peaks due to the C-H peaks have appeared as shoulders between 2900 cm^{-1} to 3100 cm^{-1}. The C=O peak has appeared at 1636 cm^{-1} along with a merged peak at 1613 cm^{-1}.

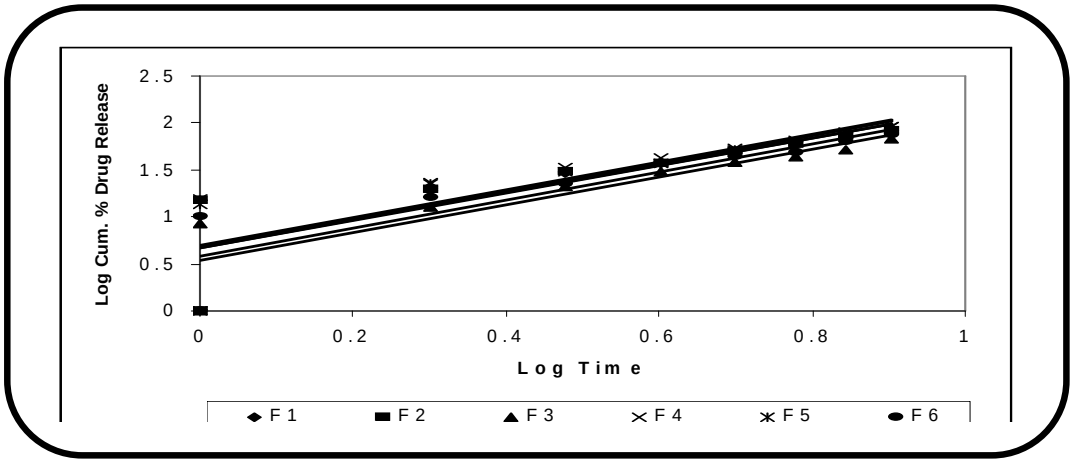

Fig 7. *Peppa's plots of different formulations.*

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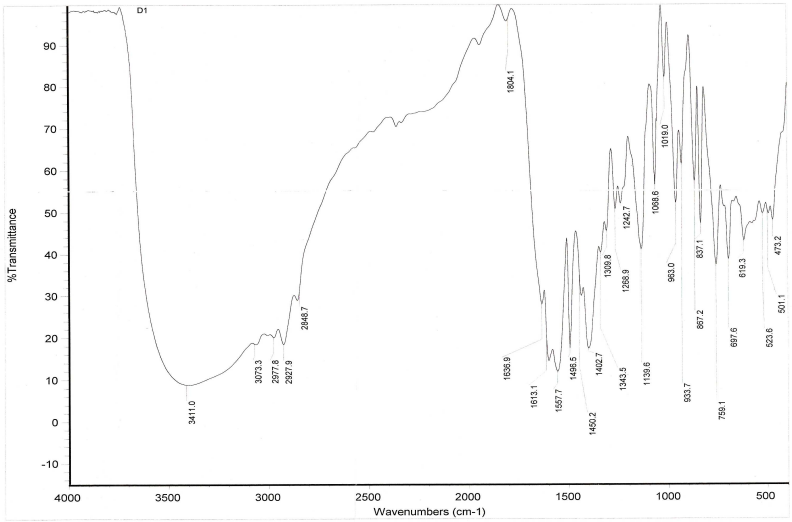

Fig 8. IR Spectrum of pure drug Montelukast sodium.

In F3 formulation **(Fig 9)** spectrum MS is taken along with polymer HEC (3%), eudragit RL-100 (0.5%) and 30% PG. when the all spectrum of this formulation is taken, it clearly indicating that chemical reaction between the any of three components in the polymer has not taken place. This fact is supported by the fact that distinct appearance of peaks due to the O-H, C-H and C=O are the place of anticipation. The broad band is appeared at 3442 cm^{-1} and also 2929 cm^{-1}. The sharp peak is noticed at 1641 cm^{-1}. These observations suggested that drug has not undergone any chemical reaction. In F6 **(Fig 10)** formulation spectrum, the formulation has been taken along with polymer NaCMC 3%, and eudragit RL-100. It is observed that, the C=O of ester present in eudragit RL-100 has predominated to exhibit is distinct observation peak 1731 cm^{-1}. Suggesting that drug, NaCMC and eudragit RL-100 remain unaffected. Suggesting that, this is just a physical mixture not chemical reaction product.

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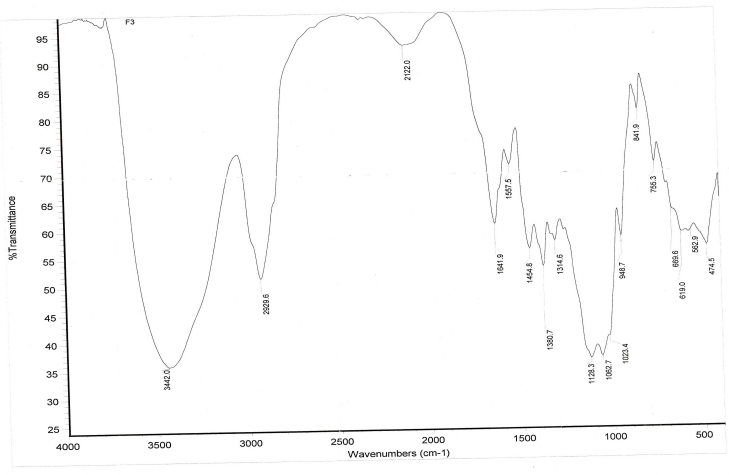

Fig 9.*IR Spectrum of Formulation F3.*

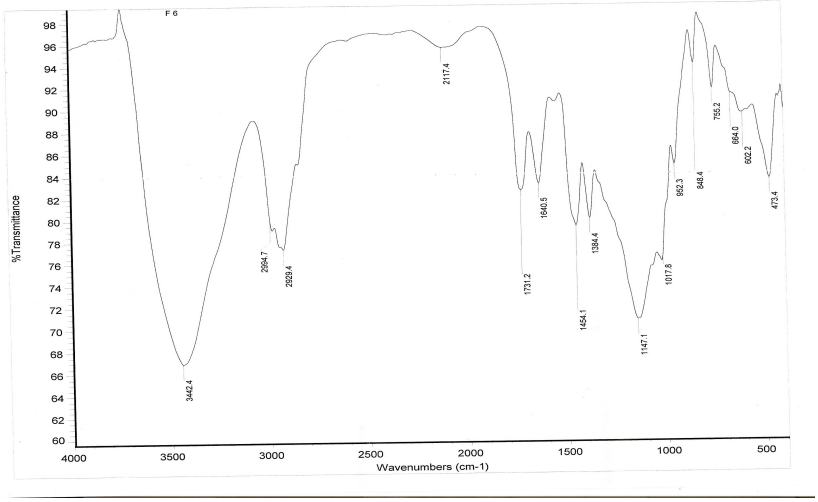

Fig10. *IR Spectrum of Formulation F6.*

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CONCLUSION

From this study it was concluded that the patch containing 5 mg of MS were prepared by using eudragit RL 100, and HEC, and Na CMC (F3, and F6 formulations) were best formulations. Hence these formulations of MS mucoadhesive buccal patches promising one as the controlled drug delivery, shows moderate swelling, convenient resident time, greater therapeutic efficacy, improve the bioavailability.

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