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# DEVELOPMENT OF MUCOADHESIVE FILMS FOR BUCCAL ADMINISTRATION OF MONTELUKAST

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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. Montelukast biological half life is 2.5 to 5.5 hrs there by decreasing bioavailability upto 64%. So, in order to improve the bioavailability and efficacy, we have prepared buccal films of montelukast. In the present research work, buccal films were prepared using mucoadhesive polymers like HPMC (K4M), HPMC (50cps), HPMC (5 cps), Eudragit RL-100 and PVP K-30 by Solvent Casting technique. Buccal films 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 prepared films were smooth surface and elegant texture. All the prepared films are weighing in between 26.33 to 37.66 mg. The thickness of the films was in the range of 0.246 to 0.373 mm. Folding endurance was in the range of 259 to 289. Swelling index in the range of 29.81 to 43.48 %. Surface pH was in the range of 6.00 to 6.83 pH. Drug content uniformity study showed uniform dispersion of the drug throughout the formulation in the range of 94.33 to 98.33 %. The i*n vitro* residence time for all the films is in between 3.13 to 5.50 hrs. The bursting strength of films is in the range of 6.533 to 4.366 Kg/cm$^2$. FT-IR studies revealed that,

there was no incompatibility of the drug with the excipients used. *In vitro* drug release studies in the range of 67.35 to 93.62 at the end of 8th hrs.

**Keywords:** Montelukast, Buccal films, Polymers, Mucoadhesion / Bioadhesion, *In vitro* drug release.

**INTRODUCTION**:

For decades, peroral drug delivery has been most widely utilized route of administration for the systemic delivery of drug. The lack of efficacy of certain drug due to decrease bioavailability, Gastrointestinal intolerance, unpredictable and erratic absorption and presystemic elimination of other potential route for administration. The recent development in the drug delivery has intensified investigation of mucosal delivery of drug such route includes oral, buccal, ocular, nasal and pulmonary routes etc.[1] Mucoadhesive drug delivery systems are delivery systems which become adhesive on hydration and hence can be used for targeting of drug to particular region of the body.[2]

The montelukast is a leukotrine receptor antagonist (LTRA) used for the maintenance treatment of asthma, chronic asthma attacks and to relive symptoms of seasonal allergies. 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. There by decreasing bioavailability up to 64% [3, 4].

The objective of the present work to develop the mucoadhesive films of montelukast using solvent casting technique were prepared and evaluated for different 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, Drug polymer interaction. In the proposed research work, we will prepare buccal patches with the aim to achieve:

Greater therapeutic efficacy, avoidance of gastrointestinal disturbances and abdominal or stomach pain, improve the bioavailability of montelukast by avoiding hepatic metabolism, and improve patient compliances.

**MATERIALS AND METHODS**:

Montelukast sodium was obtained as gift sample from Morepen pharma. Pvt. Ltd., Solan (Delhi). HPMC (K4M), HPMC (50 cps) and eudragit RL-100 were obtained as gift sample from Astrazeneca pharma. Pvt. Ltd., Bangalore, Cipla pharma. Pvt. Ltd., Goa. and Evonik pharma Pvt. Ltd., Mumbai respectively. HPMC (5cps) and PVP K-30 were purchased from S.D. fine chem. Lab., Mumbai and Himedia chem. lab. respectively.

**Preparation of the films [5]:**

Buccal films of montelukast were prepared by solvent casting technique employing mercury as substrate[5]. Composition of circular cast films of various formulations are mentioned in **Table-1.** The mucoadhesive films were prepared using polymers like different grades of HPMC (K4M), HPMC (50 cps), HPMC (5cps), Eudragit RL-1OO and PVP K-30. Propylene glycol 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 films, a polymer was dissolved in ethanol (95%) with continuous stirring.[6] The calculated amount of montelukast was incorporated in the polymeric solutions after levigation with 30% propylene glycol of polymer weight. The solution was casted onto mercury substrate then kept in hot air oven at $40^0$ C. for 24 hrs.The film was punched into size 10 mm films containing 5 mg. of montelukast.

**Evaluation of Mucoadhesive Buccal Films:**

The prepared buccal films were evaluated for following properties like weight uniformity, thickness, folding endurance, swelling index, surface pH, *in-vitro* residence time, bursting strength, drug content, *in-vitro* release study.

For evaluation of film weight [6] **t**hree films of the size 10mm diameter were weighed individually using digital balance and the average weights were calculated. Thickness [7] of the films was measured using screw gauge with a least count of 0.01mm at different spots of the films. The thickness was measured at three different spots of the films and average was taken. The flexibility of films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance [8] of the films was determined by repeatedly folding a small strip of the films (approximately 2x2 cm) at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance. The swelling index [9] of the films determined by immersing preweighed film of size 2 $cm^2$ in 50 ml water. The strip were taken out carefully at 5,10 up to 30 min. intervals, blotted with filter paper & weighed accurately.

The swelling index calculated by

$$\% \text{ Swelling Index} = \frac{\text{Wet weight - Dry weight}}{\text{Dry weight}} x100$$

Surface pH [10] was determined by the films 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 films and allowing equilibrate for 1 min.

The *in vitro* residence time [11] 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 films 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 film 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 film from the mucosal surface was recorded. A test for measuring the resistance of a film to bursting and reported in kilo-Pascal or pounds per square inch or $Kg/cm^2$. The burst strength of all the films was evaluated by using standard bursting strength tester.

The films were tested for drug content [12] uniformity. Films of 10 mm diameter were cut from three different places from the casted films. Each film 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/visible spectrophotometer (Shimadzu UV-1700). The percentage drug content was determined using the standard graph and the same procedure was repeated for three films.

*In vitro* release [13] studies were carried out by attaching sigma dialysis membrane to one end of the open cylinder which acts as donor compartment. The prepared buccal films containing drug was placed inside donor compartment which is agitated continuously using magnetic stirrer and then temperature was maintained at 37±1ºC. Receptor compartment consists of 100 ml of 0.5 % SLS solution, sample of 2 ml were withdrawn at periodic intervals from receptor compartment & 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, F6 and F9 were recorded in a Fourier transform infrared (FTIR) spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

**RESULTS AND DISCUSTION:**

Mucoadhesive films of montelukast sodium were prepared using mucoadhesive polymers HPMC (K4M), HPMC (50cps), HPMC (5cps), PVP K-30 and Eudragit RL-100. The drug delivery system was designed as a matrix. All the films were shows smooth surface and elegant texture. The physical characteristics of various films are given in **Table 2.** The weight of 10 mm film were in the range of 26.33 ± 1.527 to 37.66 ± 0.576 mg and film thickness in the range of 0.246 ± 0.020 to 0.373 ± 0.015 mm. Surface pH of film was in the range of 6.00 ± 0.100 to 6.83 ± 0.057 pH. The folding endurance was measured manually, films were folded repeatedly till it broke, and it was considered as the end point. Folding endurance was found to be in the range of 259 ± 3.310 to 289 ± 2.640. 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 films showed high swelling values to Eudragit RL-100 containing films 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 swelling behaviors of polymer in film were shown in Figure 5. The percent swelling index and *in vitro* residence time for the films is in between 29.81 ± 3.444 to 43.48 ± 0.606 %. and 3.13 ± 0.151 to 5.50 ± 0.591 hrs respectively.

The drug content results were shown in **Table 3** in all the formulations drug was uniformly dispersed through out the film in the range of 94.33 ± 1.175 to 98.33 ± 0.369 %. The Bursting strength of films is in the range of 6.533 ± 0.351 to 4.366 ± 0.267 Kg/cm$^2$.

[Figures 1 to 4] shows 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 film containing PVP K-30 and Eudragit RL-100. The *in-vitro* drug release studies in the range of 67.35 ± 2.466 to 93.62 ± 4.574.The results were shown in **Table 3**.

Kinetics drug release result shown in **Table 4** reveals that all formulations follows zero-order kinetics as correlation coefficient ($r^2$) values are higher than that of first-order release kinetics. Mechanism of drug release pattern i.e. diffusion and swelling was confirmed by Higuchi plots. The Higuchi plots represent 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 films 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. On the basis of plots it is concluded that the release of montelukast from films have obeyed Super Case- II transport. The correlation coefficient values were shown in **Table 4.**

In [Figure 6] shows the IR spectrum of the pure drug and formulations. 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$^{-1}$. The IR spectrum of the formulation F3 shows all spectrum of this formulation is taken it clearly indicating that chemical reaction between the any of two 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 $cm^{-1}$. The IR spectrum of the formulation F6 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 no chemical reaction takes place. In the last formulation F9, it is supervised to notice that in this case also no change has been observed in IR spectra. Suggesting that characteristic peaks have remained unaffected in this formulation also.

**Table 1: Composition of montelukast mucoadhesive buccal films.**

| Formulation code | Polymer conc. (% w/v ) | | | | | Plasticizer* conc.(%W/V) PROPYLENE GLYCOL |
|---|---|---|---|---|---|---|
| | HPMC (K4M) | HPMC (50 cps) | HPMC (5 cps) | PVP K-30 | EUDRAGIT RL-100 | |
| **F1** | 3 | -- | -- | -- | -- | 30 |
| **F2** | 3 | -- | -- | 0.5 | -- | 30 |
| **F3** | 3 | -- | -- | -- | 0.5 | 30 |
| **F4** | -- | 5 | -- | -- | -- | 30 |
| **F5** | -- | 5 | -- | 0.5 | -- | 30 |
| **F6** | -- | 5 | -- | -- | 0.5 | 30 |
| **F7** | -- | -- | 8 | -- | -- | 30 |
| **F8** | -- | -- | 8 | 0.5 | -- | 30 |
| **F9** | -- | -- | 8 | -- | 0.5 | 30 |

*** Percentage of polymer weight.**

**Each 10 mm film contains 5 mg. of montelukast.**

**Table 2: Physical evalution of mucoadhesive buccal films of Montelukast.**

| 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** | 26.33±1.527 | 0.323±0.005 | 6.76±0.153 | 287±2.340 | 36.43±2.426 |
| **F2** | 30.66±0.576 | 0.373±0.015 | 6.23±0.152 | 289±2.640 | 43.48±0.606 |
| **F3** | 28.66±0.576 | 0.360±0.010 | 6.00±0.100 | 267±1.580 | 32.33±3.095 |
| **F4** | 30.00±1.732 | 0.263±0.005 | 6.66±0.152 | 271±1.730 | 34.33±1.999 |
| **F5** | 33.00±1.000 | 0.266±0.230 | 6.46±0.115 | 274±1.000 | 39.33±2.851 |
| **F6** | 34.33±1.154 | 0.246±0.020 | 6.06±0.153 | 259±3.310 | 30.68±3.332 |
| **F7** | 34.66±1.526 | 0.253±0.016 | 6.83±0.057 | 266±2.000 | 33.79±1.070 |
| **F8** | 37.33±1.154 | 0.263±0.005 | 6.76±0.152 | 277±3.460 | 35.23±1.157 |
| **F9** | 37.66±0.576 | 0.253±0.016 | 6.06±0.152 | 260±1.580 | 29.81±3.444 |

**Note: Values in parenthesis are standard deviation (±SD)**

**Table 3: Physical Evalution of Mucoadhesive Buccal films of Montelukast.**

| 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** | 4.33±0.171 | 96.66±0.925 | 6.533±0.351 | 34.77±0.580 | 80.82±3.263 |
| **F2** | 4.10±0.435 | 97.33±1.539 | 6.333±0.321 | 37.43±1.040 | 83.10±4.108 |
| **F3** | 5.50±0.591 | 98.33±0.369 | 5.766±0.230 | 28.35±0.956 | 67.35±2.466 |
| **F4** | 3.36±0.151 | 95.00±1.056 | 5.266±0.305 | 36.54±0.330 | 88.03±0.317 |
| **F5** | 3.36±0.151 | 96.66±1.623 | 5.000±0.300 | 42.88±0.751 | 89.20±4.667 |
| **F6** | 5.40±0.479 | 96.66±1.396 | 4.466±0.305 | 30.95±1.811 | 72.52±4.131 |
| **F7** | 3.40±0.100 | 94.66±1.545 | 5.233±0.251 | 37.18±0.296 | 91.71±0.740 |
| **F8** | 3.13±0.151 | 94.33±1.175 | 5.033±0.378 | 44.33±0.595 | 93.62±4.574 |
| **F9** | 5.43±0.057 | 96.33±1.001 | 4.366±0.267 | 32.79±1.333 | 74.24±3.024 |

**Note: Values in parenthesis are standard deviation (±SD)**

**Table 4: Kinetic parameters of montelukast buccal films.**

| Formulation code | Zero-order ($r^2$) | First- order ($r^2$) | Highuchi plot ($r^2$) | Peppas plot ($r^2$) |
|---|---|---|---|---|
| **F1** | 0.9788 | 0.8615 | 0.8794 | 0.7333 |
| **F2** | 0.9866 | 0.8913 | 0.9001 | 0.7049 |
| **F3** | 0.9854 | 0.9275 | 0.8573 | 0.8402 |
| **F4** | 0.9847 | 0.8611 | 0.8747 | 0.7507 |
| **F5** | 0.9932 | 0.8729 | 0.9205 | 0.6932 |
| **F6** | 0.9600 | 0.8605 | 0.8411 | 0.7944 |
| **F7** | 0.9755 | 0.8143 | 0.8478 | 0.7398 |
| **F8** | 0.9909 | 0.8271 | 0.9024 | 0.7041 |
| **F9** | 0.9674 | 0.8707 | 0.8706 | 0.7641 |

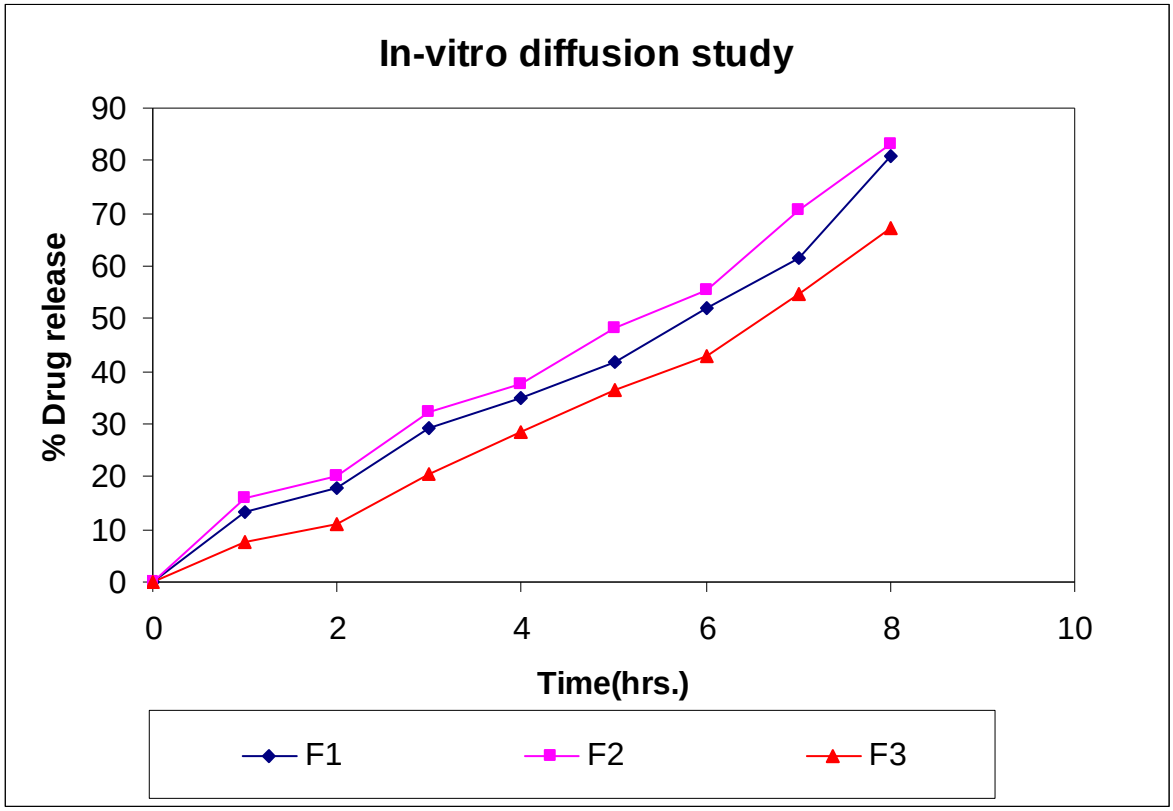


**Fig 1: Comparative release profile of formulation F1 to F3.**

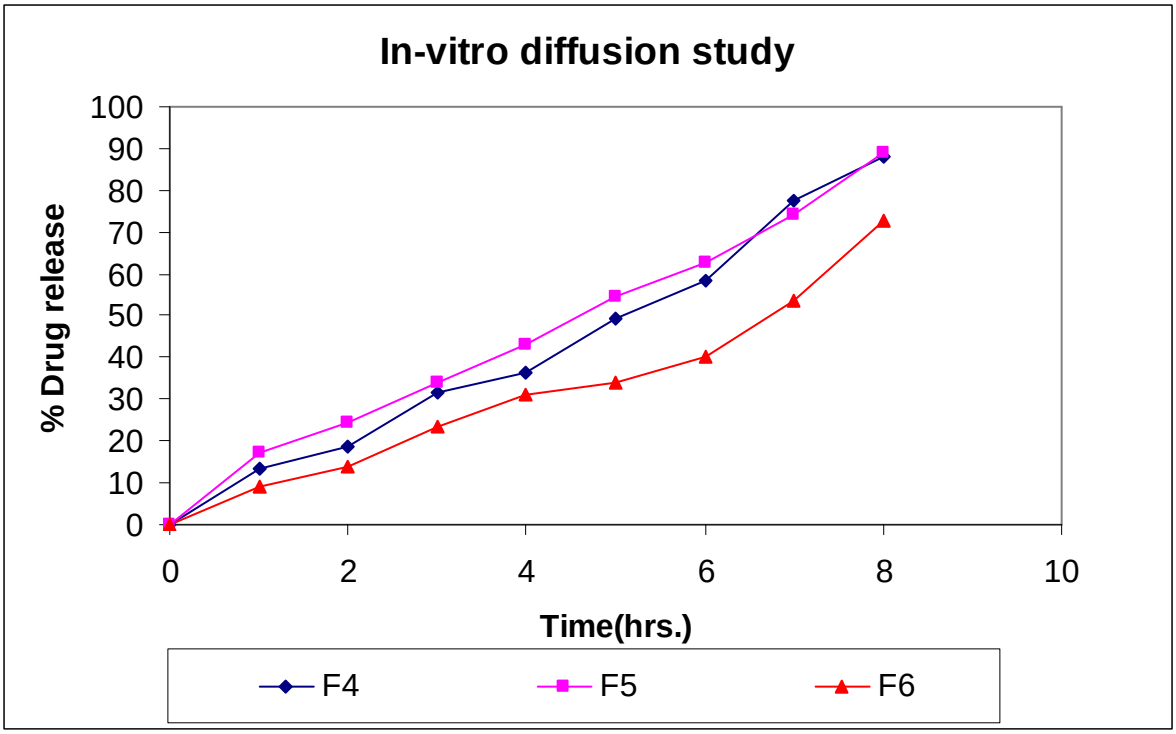


**Fig 2: Comparative release profile of formulation F4 to F6**

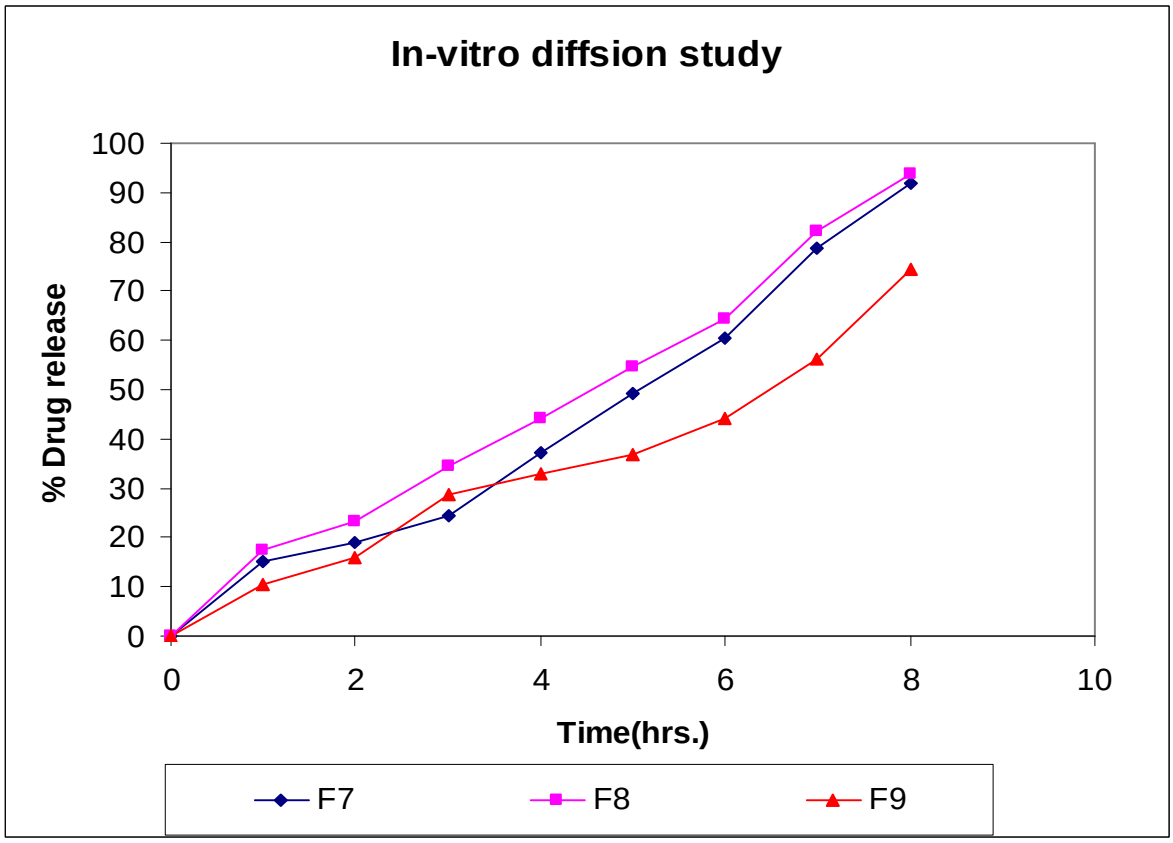


**Fig 3: Comparative release profile of formulation F7 to F9**

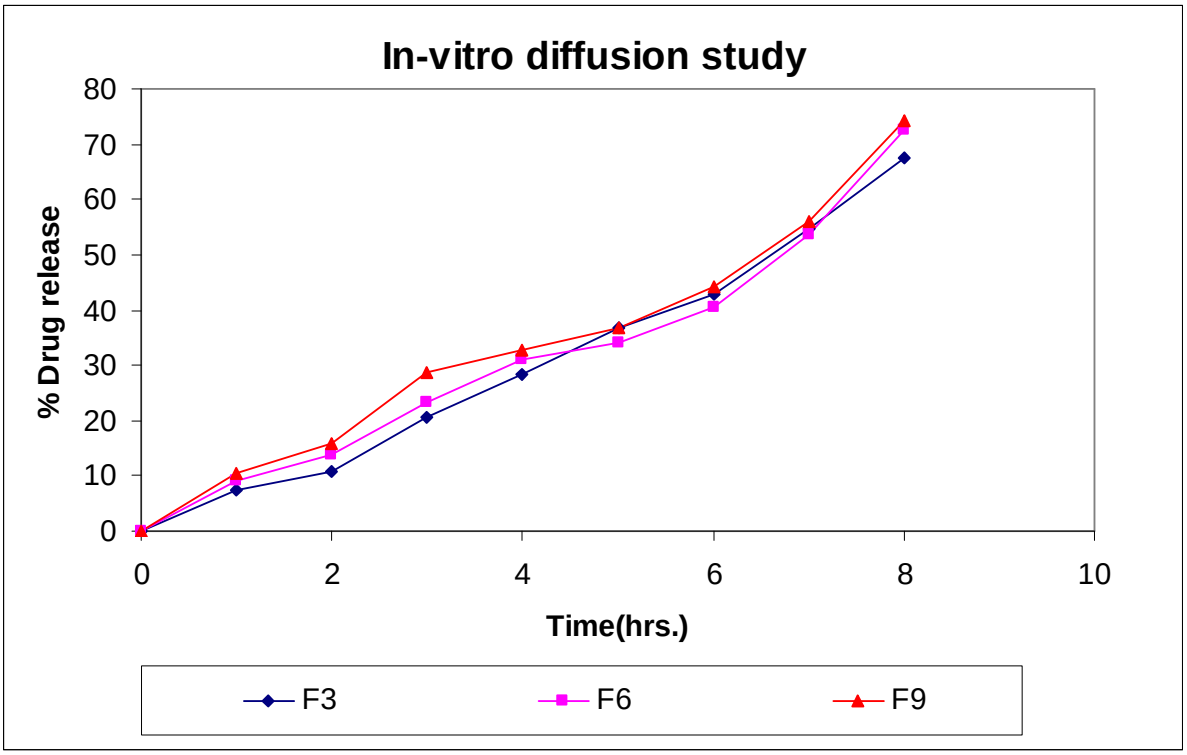


**Fig 4: Comparative release profile of formulation F3, F6 & F9**

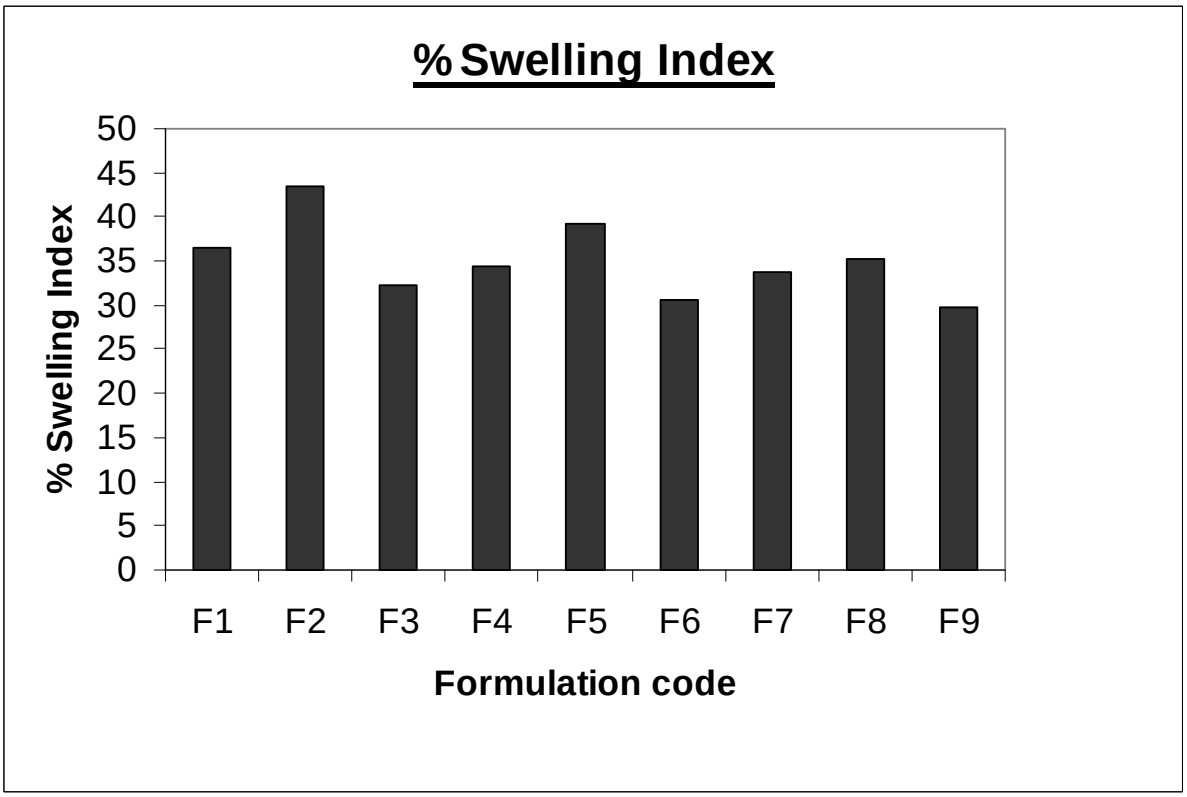


**Fig 5: Comparative Swelling index of formulation F1 to F9.**

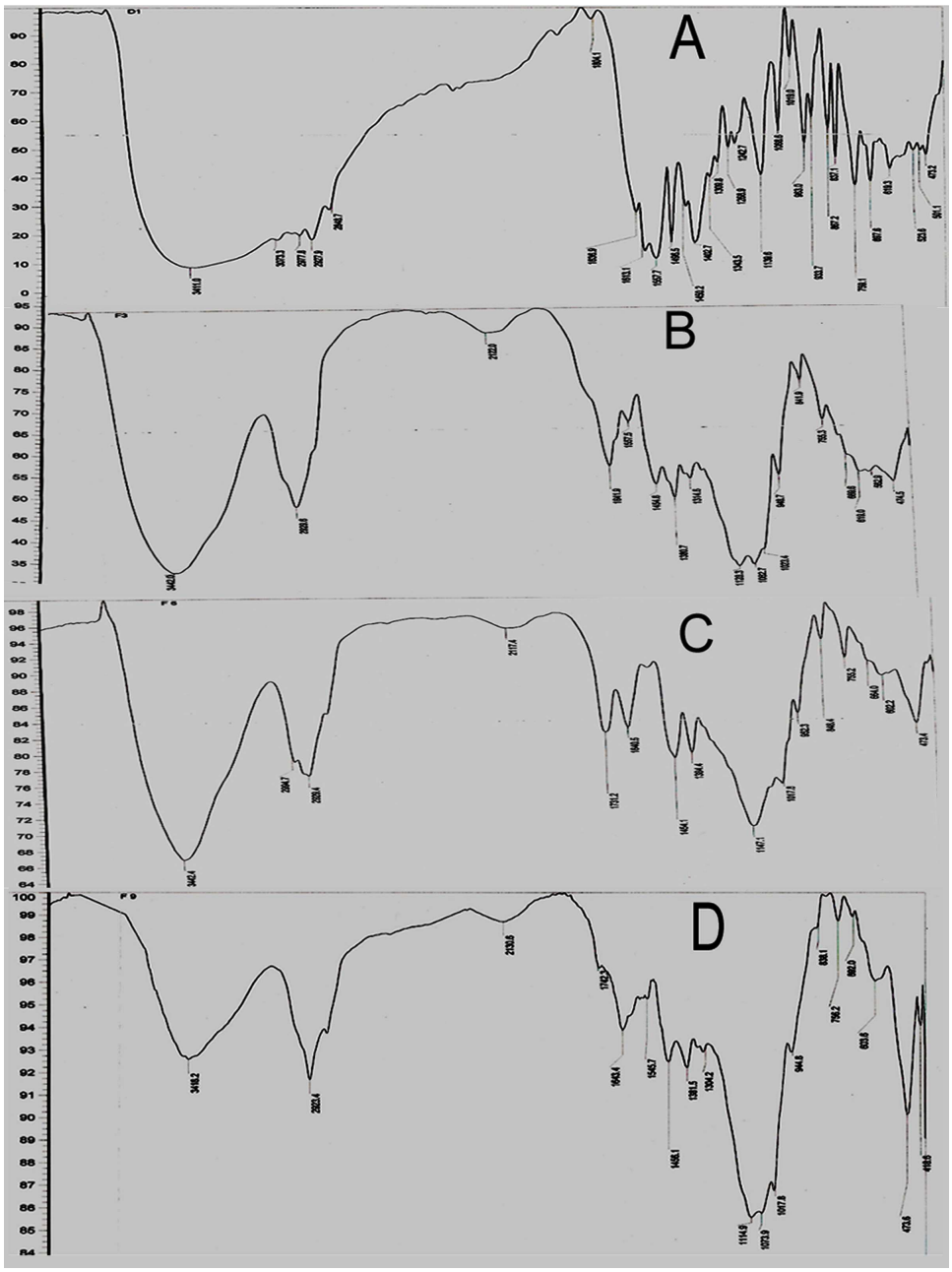


**Fig 6: A - FTIR spectra of Montelukast sodium, B - FTIR spectra of formulation F3, C- FTIRspectra of formulation F6, D - FTIR spectra of formulation F9.**

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