6. DISCUSSION OF RESULTS

6.1 Development of Analytical Methods:

Linear regression of absorbance on concentration gave the equation \( Y=0.038x-0.002 \), where ‘\( x \)’ is the concentration in \( \mu g/ml \) of Montelukast sodium and \( Y \) is the absorbance at 350 nm with correlation coefficient \( r^2 = 0.999 \). This indicates a good linear relationship. The selected method is found to be sensitive, accurate, precise and reproducible.

From the linear regression equation, \( y=0.037x+0.003 \), where \( x \) is the concentration \( \mu g/ml \) of Levoceterizine dihydrochloride and \( y \) is the absorbance (231nm), with the correlation coefficient \( r^2 = 0.998 \). Linear relationship was found. The selected method is found to be sensitive, accurate, precise and reproducible.

Linear regression of absorbance on concentration gave the equation \( Y=0.0799x-0.0002 \), where ‘\( x \)’ is the concentration in \( \mu g/ml \) and \( Y \) is the absorbance at 238nm with correlation coefficient \( r^2 = 1 \). This indicates a good linear relationship. The selected method was found to be sensitive, accurate, precise and reproducible and could be used for routine estimation of Zafirlukast in bulk and pharmaceutical formulation. The in-vitro analytical method data were given in Tables 5.1 - 5.3 and shown in Figures 5.1 - 5.3 respectively.
6.2 Solubility Studies

The solubility of the pure drug (Montelukast sodium) was found to be more in water with 0.5% sodium lauryl sulphate that is 0.96mg/ml and form this it is inferred that Dissolution medium 900ml of water with 0.5% sodium lauryl sulphate can easily maintain Sink condition.

The solubility of the pure drug (Levo cetrizine Di hydrochloride) was found to be more in water with 0.5% sodium lauryl sulphate that is 0.99mg/ml and form this it is inferred that Dissolution medium 900ml of water with 0.5% sodium lauryl sulphate with can easily maintain Sink condition. The solubility data were given in Tables 5.4 to 5.6 respectively.

6.3 Preformulation studies

The flow ability of the Montelukast sodium, Levocetrizine Di hydrochloride and Zafirlukast were found to be fair. The Sieve analysis and physico -chemical properties data of Montelukast Sodium, Levocetirizine Dihydrochloride and Zafirlukast were given in Tables 5.7 to 5.12 respectively.
6.4. Drug – Excipient Compatibility study

The drugs and all excipients used for study were compatible with respect from initial to final description and also there is no fall in percent of drug content with respect from initial to 30 days. The compatibility study data were given in Tables 5.13 and 5.14.

FTIR, DSC and XRD studies were performed to detect the possible molecular interaction between Montelukast sodium and beta cyclodextrin.

The IR spectrum of Montelukast exhibited peak at 3366.88 cm\(^{-1}\) due to N-H stretching and at 2923.68 cm\(^{-1}\) due to alkane saturated peak. The IR spectrum of β-CD showed peaks at 3394 cm\(^{-1}\) and 2925.57 cm\(^{-1}\). The IR spectrum of Montelukast: β-CD (1:1) inclusion complex prepared by kneading method has shown peaks at 3388.15 cm\(^{-1}\) and 2925.06 cm\(^{-1}\). The shift in peaks indicates interaction between Montelukast and β-CD.

The DSC thermogram of Montelukast exhibited an endothermic peak at 69.81°C corresponding to its melting point. The DSC thermograms of Montelukast: β-CD (1:1) inclusion complex prepared by Kneading method showed slight shift in peaks which indicates interaction between Montelukast and β-CD. The DSC thermograms of Montelukast sodium and β-cyclodextrin individual samples as well as kneaded system in 1:1 ratio.
X-ray diffraction patterns were recorded on a Powder X-ray diffractometer (Braker AXS, D8 Advance) using Ni –K beta filter, CuKα1 radiation, a voltage of 40 kV, and a 30-mA current. The scanning rate employed was 0.2 seconds using start angle 3.00°, stop angle 50.00° and step size of 0.02° with a divergent slit of 0.300° and anti scattering slit of 3mm. The sample rotation speed was 30 rpm and the detector used was Lynxeye. The X-ray diffraction of Montelukast sodium and β-cyclodextrin individual samples as well as kneaded system in 1:1 ratio.

The FTIR, DSC and XRD spectrums of Montelukast sodium and β-cyclodextrin individual samples as well as kneaded system in 1:1 ratio and results were shown in Figures 5.4 -5.6.

6.5 Determination of drug content in the complexes of Montelukast sodium with β-CD

Almost all the complexes have shown satisfactory drug content values and the percentage of drug content for all the ratios considered. 1:1 complex has shown 100% where as 1:0.5,1:0.75, 1:2 and 1:3 have shown between 97- 99% of drug content and results were given in Table 5.16.

6.6 In-vitro drug release

When kneaded system was dispersed in a dissolution medium, a very rapid dissolution was observed. Dissolution studies were based on the observation in order to characterize the inclusion complexation between
the β-cyclodextrin and Montelukast sodium (drug). The dissolution profiles of pure drug and kneaded system of all ratios (1:0.5, 1:0.75, 1:1) in the official medium of the drug that is distilled water with 0.5% sodium lauryl sulphate. The dissolution studies were conducted in triplicate. Among the three ratios 1:1 has shown better release of the of Montelukast sodium (drug). The results were given in Table 5.17 and were shown in Figure 5.7.

6.7 Taste evaluation of Montelukast sodium and β-CD complexes

The tastes of the complexes were evaluated. 1:1 inclusion complex was confirmed to have better taste masked property by taking in to consideration the average of the opinion of all the volunteers. 1:1 complex was found to have good palatability and the results were given in Tables 5.18 – 5.19.

6.8 Preparation and Evaluation of Taste Masked complexes of Levocetirizine Di Hydrochloride – Resin (Kyron - T114)

Preparation of Levocetirizine-resin complexes:

6.8.1 Selection of Resin: It is observed that Kyron T - 114 shown maximum adsorption for Levocetirizine which may be attributed to difference of cross linking ion exchange capacity and form of resin. The percentage drug loading obtained with the Kyron T 114 is found to be
more than the Kyron T 104. Hence Kyron T 114 was selected to obtain better drug loading efficiency. The results were given in Table 5.20.

6.8.2 Effect of Resin Activation: The percentage drug loading obtained without activation form of resin is found to be more than alkali activation and acid activated form of resin. Hence resin without activation was selected for preparing the complexes to obtain better drug loading efficiency. The results were given in Table 5.21.

6.8.3 Effect of Levocetirizine - Kyron T - 114 ratio on loading: The drug loading efficiency for a drug-resin ratio 1:1, 1:1.5, 1:2, 1:2.5 and 1:3 of batch process was found to be 65.71%, 73.33%, 78.62%, 80.12%, and 82.51% respectively. The maximum drug loading was achieved in 1:3 ratio and hence selected for optimum ratio for the preparation of drug-resin complex. The results were given in Table 5.22.

6.8.4 Effect of volume of Distilled water on drug loading: The percentage drug loading obtained with the 25 ml water is found to be more compared to mixtures prepared from 10, 40, 60 and 75 ml distilled water. Hence 25 ml distilled water was selected to prepare the complexes to obtain optimum drug loading efficiency. The results were given in Table 5.23.

6.8.5 Effect of Kyron T-114 pH on Drug loading: Levocetirizine - Kyron T - 114 complexation involves the exchange of ionizable drug and hydrogen ions in resin, which in turn depends on the pKa of drug and
resin. The complexation was enhanced with increasing pH from 4 to 5.5. A maximum of 96.90% wt/wt drug loading was obtained at pH 5.5. The pH of the solution affects both solubility and the degree of ionization of drug and resin. The percentage drug loading obtained with the pH 5.5 is found to be more compared to pH 2, 3, 4, 5, 6, 7.5 and 8. Hence pH 5.5 was selected to prepare the complexes to obtain optimum drug loading efficiency. The results were given in Table 5.24 and were shown in Figure 5.8.

6.8.6 Effect of Temperature on Drug loading: Efficient drug loading on kyron T-114 occurred uniformly in the experimental temperature range of 27°C to 80°C. The results were given in Table 5.25 and were shown in Figure 5.9.

6.8.7 Effect of soaking time of Resin on drug loading: The results reveal that a 30 minute swelling time of Kyron T 114 in distilled water gave the maximum Levocetirizine loading of 91.3% wt/wt. The swelling and hydrating properties of Kyron T 114 affect the rate of ion exchange, which in turn affects the percentage drug loading. The results were given in Table 5.26 and were shown in Figure 5.10.

6.8.8 Effect of Stirring time on drug loading: The equilibrium ion exchange in solution occurs stoichiometrically and hence is affected by stirring time. This may indicate the significant involvement of van-der-waals forces or chemisorptions taking place along with drug exchange
during complexation. Increasing the stirring time above 4hrs did not further increase the complexation values. Hence, 4 hrs contact time between drug and resin could be optimized to equilibrate the ion exchange process to achieve maximum drug loading. This study indicated that the optimum ion exchange could be completed in a period of 4 hrs. The results were given in Table 5.27. and were shown in Figure 5.11.

6.8.9 Molecular properties of drug resin complex: The complexation was confirmed by carrying out FTIR studies which evaluated possible solid-solid interactions between the drug and resin. The FTIR spectra of complex showed that there was no interaction between drug and resin. Peaks of both drug as well as resin were observed and interpreted. The results were shown in Figures 5.12.

6.8.10 Estimation of drug content and invitro release from DRC in 0.1N HCl: The batch process of complexing Levocetirizine with Kyron T-114 produced efficient drug loading. The study also suggests that an ion exchange resin system is a useful alternate for masking taste of drugs like Levocetirizine. The results of this study can be extrapolated to other intensely bitter drugs by suitable selection of ion exchange resins. The results were given in Table 5.28 – 5.29 and were shown in Figure 5.13.

6.8.11 Taste evaluation: Bitterness evaluation results made by the consensus of trained persons. It is confirmed that the taste of
Levocetirizine was masked by complexing with Kyron T-114. Levocetirizine release from the DRC was studied in gastric pH of 1.2, which showed that the drug release was more than 95% within 30 minutes. The results were given in Table 5.30.

6.9 Preparation and Evaluation Inclusion Complexes of Zafirlukast with γ- cyclodextrin

6.9.1 Phase solubility studies: The aqueous solubility of the drug increased linearly as function of γ -cyclodextrin concentration. At all the concentrations of γ –CD used for the preparation of the inclusion complexes showed significant increase in the solubility of Zafirlukast. As the concentration of the γ –CD increased, the solubility of the drug was found to be increased. The results were given in Table 5.31 and were shown in Figure 5.14.

6.9.2 Preparation of Inclusion complex of Zafirlukast with γ – Cyclodextrin and Drug content analysis: The zafirlukast Inclusion complexes were tested for drug content and it was found that the drug was within the compendial limits 95-101% w/w. All the Inclusion complexes were uniform in drug content. The results were given in Table 5.32.

6.9.3 In vitro dissolution studies: Zafirlukast release from the inclusion complexes and alone was studied up to 60 minutes. The average percentage release of the pure drug was found to be 18.8% in 60
minutes. In the inclusion complexes, γ-cyclodextrin was used as carrier and the dissolution rate increased with increased amount of γ-CD. The best results among inclusion complexes with γ–CD were obtained for the complex KM1:1. Dissolution rates of zafirlukast and its cyclodextrin complexes prepared by three methods in different ratios and comparative study by ANOVA. The results were given in Table 5.33(a), (b) and were shown in Figure 5.15.

6.9.4 Compatibility analysis: The FTIR spectrum of Zafirlukast, γ-CD, and Zafirlukast: γ-CD (1:1) complex were shown in Fig. 5.16. The FTIR spectrum of Zafirlukast exhibited peak at 3370 cm\(^{-1}\) due to N-H stretching, while peak at 1338 cm\(^{-1}\) indicate SO\(_2\) stretching. The FTIR spectrum of γ-CD showed peak at 3394 cm\(^{-1}\). The FTIR spectrum of Zafirlukast: γ–CD (1:1) inclusion complex prepared by Kneading method has shown peaks at 3374 cm\(^{-1}\) and 1340 cm\(^{-1}\). The shift in peaks indicates interaction between Zafirlukast and γ-CD. The results were shown in Figure 5.16.

Differential scanning calorimetry was used to characterize the Zafirlukast: γ–CD complex. The DSC thermogram of Zafirlukast exhibited an endothermic peak at 105.72\(^{\circ}\)C corresponding to its melting point. DSC thermograms of Zafirlukast: γ-CD(1:1) inclusion complex prepared by Kneading method showed slight shift in peaks which indicates interaction between Zafirlukast and γ-CD. The results were shown in Figure 5.17.
6.10. Development of Orally Disintegrating Tablets of Montelukast sodium

6.10.1. Optimization of Diluents: The flow property of the prepared powder blends was good and the low disintegrating time, wetting time, mechanical properties uniformity of dispersion and mouth feel was shown by the D2 that contains Mannitol (pearlitol 200) as the diluent. So, I selected it as diluent for the preparation of Orally Disintegrating Tablets Montelukast sodium formulations. The results were given in Tables 5.34 -5.35.

6.10.2. Optimization of Super disintegrants: nine sets of tablet formulations (M1 – M9) were prepared and evaluated accordingly. Different concentrations of superdisintegrants (5,7.5 and 10%) were investigated. The final blend of drug and excipients of all the formulations were evaluated for flow properties and was found to be good. The results were given in Tables 5.36. After the preparation of tablets all the formulations were evaluated for tablet characteristics and were found to exhibit satisfactory results. The disintegration time for each tablet batch was found to be less than one minute and results are shown in Table 5.37. The tablets containing Polyplasdone XL10 (M7, M8 and M9) showed lowest disintegration time and among polyplasdone XL10 formulations particularly M8 showed the lowest disintegration time of 11sec. The wetting time of all the formulations was within the range (15-22sec) the lowest (15sec) was obtained with formulation M8. All the
tablets release almost 70% of the drug with in 10min providing their fast dissolving friend. Among all the formulated tablets M8 which was based on Montelukast sodium with 7.5% with polyplasdone XL10 gave the highest dissolution (99%) in 15min. based on dissolution rate, the disintigants were ranked as polyplasdone XL10 greater than Ac-di-sol > primojel hence polyplasdone XL10 was recommended as suitable superdisintegrant for the preparation of directly compressible oral disintegrating tablets of Montelukast sodium as this tablets are a good alternative drug delivery to geriatric and pediatric patients.

6.10.3. Evaluation of Orally Disintegrating Tablets of Montelukast sodium: All the prepared Orally Disintegrating Tablets of Montelukast sodium exhibits satisfactory tablet characteristics. The drug content of all the formulations was found to be existed between 90 - 100% and formulation M8 was found to be within the USP limits as per the drug content. The invitro disintegration time and wetting time were found to be very less for M8 formulation that is 11 Sec. and 15 Sec. respectively. The results were given in Tables 5.37.

6.10.4. Dissolution profile of Orally Disintegrating Tablets of Montelukast sodium: M8 batch tablets have shown better dissolution profile when compared to remaining formulations. The results were given in Table 5.38 and were shown in Figure 5.18.
6.10.5. **In-vitro Dissolution kinetic parameters for all Orally Disintegrating Tablet formulations of Montelukast sodium:** From the Correlation Coefficient\( (r^2) \) Values of all formulations (M1-M9) it was found that the orally Disintegrating Tablets of Montelukast sodium have followed the first order kinetics. \( T_{90}, \) \( D_{P15} \) and \( D_{E15} \) were found to be 10mins, 99% and 75.59% respectively for the formulation M8 (Final). For the remaining formulations it was found that the \( T_{90} \) values were high and \( D_{P15} \) and \( D_{E15} \) values were low when compared to the optimized formula that is **M8(Final)**. The results were given in **Table 5.39 - 5.41** and were shown in **Figure 5.19 – 5.21**.

6.10.6 **Comparative study of Final formulation with market product:**
Comparative study of Final formulation with market product was done and the results given in **Table 5.42 - 5.47** and were shown in **Figure 5.22 – 5.24**.

6.10.6.1 **ANOVA:** Calculated F value is more than F table value. So Null-hypothesis \( (H_0) \) rejected. Therefore it is concluded that there is extremely significant difference in disintegration time among the three formulations. The results were given in **Table 5.42 - 5.43**

6.10.6.2 **Fit factor test \( (f_1 \ and \ f_2) \):** Based on the dissolution results it was found to be Final (M8) formulation is comparable with Marketed (Romilast) product. The results were shown in **Figure 5.24**.
6.10.7 Stability study: Stability studies for finalized orally Disintegrating formulations of Montelukast sodium were done and the results were given in Table 5.48 and disintegration of final tablet (M8) shown in Figure 5.25.

6.11 Development of Orally Disintegrating Tablets of Montelukast plus Levocetrizine

6.11.1 Evaluation of Orally Disintegrating Tablets of Montelukast plus Levocetrizine: All the prepared Orally Disintegrating Tablets of Montelukast sodium with Levocetrizine exhibits satisfactory tablet characteristics. The drug content of all the formulations was found to be existed between 90 - 100% within the USP limits as per the drug content. The invitro disintegration time and wetting time were found to be 16Sec. and 27 Sec. respectively for final formulation. The results were given in Table 5.49.

6.11.2. Dissolution profile of Orally Disintegrating Tablets of Montelukast sodium with Levocetrizine: Final formulation of Montelukast sodium with Levocetrizine has shown better dissolution profile when compared to marketed formulation. The results were given in Tables 5.50 – 5.51 and were shown in Figures 5.26 – 5.27.
6.11.3. In-vitro Dissolution kinetic parameters for all Orally Disintegrating Tablet formulations of Montelukast sodium with Levocetrizine: From the Correlation Coefficient($r^2$) Values of formulations, it was found that the orally Disintegrating Tablets of Montelukast sodium with Levocetrizine has followed the first order kinetics. $T_{90}$, $DP_{15}$ and $DE_{15}$ were found to be 10min, 99%, 73.56% and 10mins, 99%, 75.58% for the final formulation of Montelukast sodium with Levocetrizine respectively. For the marketed formulation it was found that the $T_{90}$ values were high and $DP_{15}$ and $DE_{15}$ values were low when compared to the final formulation. The results were given Tables 5.52 – 5.57 and were shown in Figures 5.28 – 5.29.

6.11.4 Comparative study of Final formulation with market product.

6.11.4.1 Student t-test: Student t- test was done for final and marketed formulations and results were given in Tables 5.58 – 5.59.

6.11.4.2 Fit factor test ($f_1$ and $f_2$): Based on the dissolution results it was found to be Final product is comparable with Marketed (Montair lc) product. The results were shown in Figures 5.30 – 5.31.

6.11.5 Stability study: Stability studies for finalized orally Disintegrating formulations of Montelukast sodium with Levocetrizine were done and the results were given in Table 5.60.
6.12 Formulation and Evaluation of Montelukast sodium Chewable Tablets by Different Techniques

6.12.1 Evaluation of Tablets: All the prepared chewable Tablets of Montelukast sodium exhibits satisfactory tablet characteristics. The drug content of all the formulations were found to be existed between 90 - 100% and formulation C3 was found to be best among all the formulations. The results were given in Table 5.61.

6.12.2 Dissolution test: C3 batch tablets have shown better dissolution profile when compared to remaining formulations. The results were given Tables 5.62 and were shown in Figures 5.32.

6.12.3 Taste Evaluation: All the tablets showed good hardness. Batch‘C2’ had minimum hardness while ‘C3’ had maximum hardness. The friability was carried out for all the batches of tablets. The friability was less than 0.2% for all the blends and are said to be satisfactory. From the data obtained it was found that 99% of drug was released for the trial ‘C3’ at 30 min other trials ‘C1’& ‘C2’ had shown 98% & 96% drug release at 45 min respectively. The variation in the dissolution of Montelukast sodium tablets was in the following order C1<C2<C3.The dissolution profile of batches of tablets prepared by direct compression method has shown better results compared to the tablets prepared by other methods as well as marketed product. The sweetness intensity was
found to be good in tablets prepared by direct compression technique. The results were given in Table 5.63.

6.12.4 Comparison of Dissolution Profiles of Montelukast chewable tablet Final with Marketed formulation: Final (C3) formulation have shown better dissolution profile when compared to Marketed (emulcast) product. And the results were given in Table 5.64 and shown in Fig 5.33.

6.12.5. In–vitro Dissolution kinetic parameters of Montelukast chewable tablets: From the Correlation Coefficient($r^2$) Values of all formulations, it was found that the chewable Tablets of Montelukast sodium have followed the first order kinetics. $T_{90}$, $DP_{30}$ and $DE_{30}$ were found to be 15 mins, 99% and 78.58 % respectively for the final (C3) formulation. For the remaining formulations it was found that the $T_{90}$ values were high and $DP_{30}$ and $DE_{30}$ values were low when compared to the optimized formula that is final (C3) formulation. The results were given Tables 5.65 – 5.67 and were shown in Figure 5.34.

6.12.6. Fit factor test ($f_1$ and $f_2$): Based on the dissolution results it was found to be final (C3) formulation is comparable with Marketed (emlucaast). The results were shown in Fig 5.35.

6.12.7. Stability study: Stability studies for finalized chewable formulations of Montelukast sodium were done and the results were given in Tables 5.68.
6.13 Formulation and Evaluation of Orally Disintegrating Tablets of Zafirlukast

6.13.1 Selection and optimization of direct compressible diluents:
Three direct compressible fillers were tried to prepare Zafirlukast of direct compressible tablets (100mg), such as Microcrystalline cellulose (Avicel 102), Pearlitol 200 and Lactose Anhydrous (SuperTab 21AN). These prepared tablets were evaluated for hardness, friability, thickness, weight-variation and drug content. The formulation A-2 exhibited good hardness, faster disintegration and wetting time when compared to the other formulations. Formulation A-2 was mechanically stable and fulfilled all the requirements of the compressible tablets. Based on the disintegration time and wetting time, mechanical properties, Pearlitol 200 was found to be suitable direct compressible diluent for the preparation ODT of Zafirlukast. Pearlitol 200 was used as direct compressible diluent for further studies. Based on the evaluation tests of the prepared tablets A-2 Formulation containing Mannitol (Pearlitol 200) as diluent was selected and the results were given in Tables 5.69 and 5.70.

6.13.2. Selection and optimization of superdisintegrants: In the preparation of tablets, 1:1 Zafirlukast: γ –CD inclusion complex prepared by kneading method was used. The drug content was estimated in the complex and it was found that the drug was within the compendial
limits. ODT of Zafirlukast were prepared by direct compression method employing Super–disintegrants such as Croscarmellose Sodium, Sodium Starch Gylcolate(SSG) and Polacrilin Potassium at different concentration levels.

The final blend was evaluated for flow properties and was found that the flow property of prepared blend was good. The tablets containing Polacrilin Potassium (S8) showed the low disintegration time (32Sec). All the obtained formulations exhibited satisfactory tablet characteristics. The wetting time for all the formulations was calculated. The lowest (42sec) was obtained with formulation S8. The results were given Tables 5.71.

6.13.3. Dissolution profile of Orally Disintegrating Tablets of Zafirlukast: 10% Polacrilin Potassium(Kyron T-314) showed better dissolution efficiency among the superdisintegrants studied at three levels (2.5%, 5% and 7.5%). Hence Polacrilin Potassium (Kyron T-314) was recommended as suitable superdisintegrant and the study shows that the dissolution rate of Zafirlukast can be enhanced to a great extent by Direct- compression technique with the addition of super disintegrants, which gives quick release. The results were given Tables 5.72 and were shown in Fig 5.36. Based on the data obtained on the dissolution rate, the superdisintegrants can be ranked as Polacrilin
Potassium (Kyron T-314) > Sodium starch glycolate > Croscarmellose Sodium.

6.13.4. In – vitro Dissolution kinetic parameters for all Orally Disintegrating Tablet formulations of Zafirlukast:

In-vitro dissolution studies for S8 tablet which is based on 5% Polacrilin Potassium showed good dissolution efficiency. The cumulative percent drug released data was shown in the Table 5.72. Various dissolution parameters values viz., Dissolution efficiency at 30 min (DE<sub>30</sub>%), Percent drug dissolved in 30 min (DP<sub>30</sub>), Time taken to dissolve the 90% drug (t<sub>90</sub>) were given in the Table 5.73.

6.13.5 Selection and optimization of Effervescent agents: Effect of Effervescent agents on weight, Hardness, Thickness, Friability, Percent drug content and In-vitro dispersion time of Orally Disintegrating formulations of Zafirlukast was studied. The results were given in Table 5.74.

6.13.6. Effect of effervescent agents on dissolution profile of Orally Disintegrating Tablets of Zafirlukast: Effect of Effervescent agents on dissolution of Orally Disintegrating formulations of Zafirlukast was studied. The results were given in Table 5.75. and shown in Fig 5.37.

6.13.7. Effect of effervescent agents on In–vitro Dissolution kinetic parameters for all Orally Disintegrating formulations of Zafirlukast:
From the Correlation Coefficient ($r^2$) Values of formulations, it was found that the orally Disintegrating Tablets of Zafirlukast has followed the first order kinetics. $T_{90}, DP_{20}$ and $DE_{20}$ were found to be 12min, 100%, 77.2%. For the marketed formulation it was found that the $T_{90}$ values were high and $DP_{15}$ and $DE_{15}$ values were low when compared to the final formulation. The results were given Tables 5.76 – 5.79 and were shown in Figures 5.38 – 5.40.

6.13.8. Comparative study of Final formulation with market product: The dissolution data was given in Table 5.80 and shown in Fig. 5.41.

6.13.8.1 Student t – test: Student t - test (Unpaired) was performed for the disintegration times of final and marketed formulations. The results were given in Tables 5.81 – 5.82.

6.13.8.2 Fit factor test ($f_1$ and $f_2$): Fit factor test was performed for the dissolution profiles of final and marketed formulations. The results were shown in Fig. 5.42.

6.13.9. Stability studies for finalized Orally Disintegrating Tablets of Zafirlukast: Stability studies for finalized Orally Disintegrating Tablets of Zafirlukast given in Table 5.83 were done. No considerable differences in the parameters were observed for tablet in the conducted accelerated stability studies after one month and the test will be continued for 6 months. The results were given in Table 5.84.
6.14 Development and Optimization of core and press coated tablets of Zafirlukast for pulsatile drug delivery

6.14.1. Evaluation of directly compressible blends of barrier layer and press coated tablets of Zafirlukast: The blends of all the press coated formulations showed good flow property and all the sets of tablets exhibited satisfactory tablet characteristics. The water uptake was optimum and the rupturing property was good for the optimized formulae of all the polymers i.e., for X12 and H3. The results were given in Table 5.85. Viscosity of the selected polymers was determined and the results were given in Table 5.86.

6.14.2. Dissolution profiles of press coated tablets: Among the I set formulations X12 was found to maintain the predetermined lag time that is 5 hrs where as remaining formulations show more or less lag time. The dissolution data was given in Table 5.87 and shown in Figure 5.43.

When the dissolution was conducted at different RPM, this formulation X12 was found to resist the RPM pressure and has shown the 5hrs lag time. The dissolution data was given in Table 5.88 and shown in Figure 5.44.

When the dissolution was conducted in different dissolution media, the formulation X12 was found to resist the changes in different media. The dissolution data was given in Table 5.88 and shown in Figure 5.45.
When the dissolution was conducted in Simulated GI fluids, the formulation X12 was also failed in maintaining lag time and this may be due to the enzymatic degradation. The dissolution data was given in Table 5.88 and shown in Figure 5.46.

Dissolution of Formulations of II set of Press coated tablets was carried out. Among the II set H3 were found to maintain the predetermined lag time that is 5 hrs where as remaining formulations haven’t shown expected lag time. The dissolution data was given in Table 5.89 and shown in Figure 5.47.

Dissolution of H3 Formulation different rpm and media was done. When the dissolution was conducted at different RPM, H3 was found to resist the RPM pressure and have shown the 5hrs lag time. The dissolution data was given in Table 5.90 and shown in Figure 5.48.

When the dissolution was conducted in Simulated GI fluids, the formulation H3 was stable at various pH ranges. The dissolution data was given in Table 5.90 and shown in Figure 5.49.

H3 is the optimized formula as it resists all RPM pressures and pH ranges and even did not undergo enzymatic degradation.

6.14.3. In-vitro release kinetic parameters for press coated tablets: From the (r²) values it was found that the drug release was following the
first order kinetics after their maintained corresponding lag times. The results were given in Table 5.91 and shown in Fig. 5.51 – 5.52.

6.14.4 Physical and kinetic parameters of Optimized Formulation (H3): All the physical parameters observed for optimized press coated tablet are found to be satisfactory and it has maintained Lag time of 5hrs and shown the drug release following first order. Final formulation of press coated Zafirlukast tablet was given in Table 5.92 and the results were given in Table 5.93.

6.14.5 Stability studies for finalized Core and press coated tablets of Zafirlukast: No considerable differences in the parameters observed for both core tablet and press coated tablet in the conducted accelerated stability studies after 6months. The results were given in Table 5.94.

6.15 IN – VIVO STUDIES

Pharmacokinetic evaluation of Montelukast sodium: Pharmacokinetic evaluation was done on (i) Orally disintegrating tablets of Montelukast sodium(M8) and (ii) mouth dissolving tablets of Marketed product (Romilast) containing Montelukast sodium in Newzeland white male rabbits weighing 1.7Kg and 15 months age as per a cross-over block design (n=6). From the time Vs plasma concentration data $C_{\text{max}}$, $T_{\text{max}}$, $(\text{AUC})_{0-\infty}$ and residual concentrations at various times were calculated. The results of Pharmacokinetic evaluation were given in Tables 5.95 - 5.99 and shown in Figs. 5.53 – 5.55.
The results of pharmacokinetic studies indicated a low absorption of Montelukast sodium from Marketed formulation (Romilast) than final formulation (M8) containing Montelukast. A peak plasma concentration ($C_{\text{max}}$) of 600.3±35 ng/ml was reached in 1.5 hr and the concentrations at all time points were low. Where as in the case of Final formulation (M8) the mean plasma concentrations were found to be higher than those observed with marketed formulation (Romilast). The higher peak plasma concentrations observed with Final formulation (M8) were due to faster absorption.

The absorption rate constants ($K_a$) of both Marketed formulation (Romilast) and Final formulation (M8) were calculated by applying the method of residuals. Residual concentrations were calculated at various time points. The absorption rate constant ($K_a$) of Final formulation (M8) was 3.658±0.173 and of Marketed formulation (Romilast) was 3.263±0.123, because of this greater absorption rate constant Final formulation (M8) reaches peak plasma concentration ($C_{\text{max}}$) of 720±39.2 ng/ml with in 1 hr only. The (AUC)$_{0-\infty}$ was found to be 4261.544 and 4237.692 ng.h/ml respectively with the Final formulation (M8) and Marketed formulation (Romilast).

**Pharmacokinetic evaluation of Zafirlukast:** Pharmacokinetic evaluation was done on (i) Zafirlukast orally disintegrating tablets formulated employing Zk–γ CD (1:1) complex – (E9)Zafirlukast and (ii) Marketed product (Zuvair) containing zafirlukast in Newzeland white
male rabbits weighing 1.7Kg and 15 months age as per a cross-over block design (n=6). From the time Vs plasma concentration data \( C_{max} \), \( T_{max} \), \( (AUC)_{0-\infty} \) and residual concentrations at various times were calculated. The results of Pharmacokinetic evaluation were given in Tables 5.100 - 5.104 and shown in Figs. 5.56 – 5.58.

The results of pharmacokinetic studies indicated a low absorption of Zafirlukast from Marketed formulation (Zuvair) than final formulation (E9) containing Zafirlukast. A peak plasma concentration \( (C_{max}) \) of 340±18.5 ng/ml was reached in 3 hr and the concentrations at all time points were low. Where as in the case of Final formulation (E9) the mean plasma concentrations were found to be higher than those observed with marketed formulation (Zuvair). The higher peak plasma concentrations observed with Final formulation (E9) were due to faster absorption.

The absorption rate constants \( (K_a) \) of both Marketed formulation (Zuvair) and Final formulation (E9) were calculated by applying the method of residuals. Residual concentrations were calculated at various time points. The absorption rate constant \( (K_a) \) of Final formulation (E9) was 1.537±0.070 and of Marketed formulation (Zuvair) was 0.887±0.067. Because of this greater absorption rate constant Final formulation (E9) reaches peak plasma concentration \( (C_{max}) \) of 358.3±29.1 ng/ml with in 1.5 hr only. The \( (AUC)_{0-\infty} \) was found to be1711.365 and1557.822 ng.h/ml respectively with the Final formulation (E9) and Marketed formulation (Zuvair).