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Fexofenadine HCl Immediate Release Tablets: *In vitro* Characterization and Evaluation of Excipients

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Abstract

Fexofenadine HCl immediate release tablets were designed to increase the dissolution rate by using superdisintegrants. Different formulations of Fexofenadine HCl were prepared by direct compression method. These formulations were evaluated for hardness, thickness, friability, weight variation, disintegration time, and *in vitro* dissolution study. The drug release from the formulations were studied according to USP specification (USP paddle method at 50 rpm for 60 minutes) maintaining the temperature to 37^0C. Sodium starch glycolate, cross carmellose sodium, crospovidone (kollidon CL), ludiflash and xanthan gum were used in 3%, 6% and 8% concentrations as superdisintegrants. Thus, the ratio of superdisintegrants was changed whereas all the other excipients as well as the active drug (Fexofenadine HCl) remained same in every formulation. Here, 0.001N HCl was used as dissolution medium according to USP and absorbances were determined by using UV spectrophotometer at 217 nm. The F-3 and F-6 formulation prepared by 8% of Sodium starch glycolate and 8% of Cross carmellose sodium showed 99.99% drug release within 30 minutes and 45 minutes, respectively. The disintegration times of F-3 and F-6 formulation were within 9 seconds. The interactions between drug and excipients were characterized by FTIR spectroscopic study.

Key words: Fexofenadine HCl, Sodium starch glycolate, Cross-carmellose sodium, Kollidon CL, Ludiflash, Xanthan gum, immediate release tablet.

Introduction

isintegrants are agents added to tablet formulations to promote the breakup of the tablet into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix. In recent years, several newer agents have been developed known as "Superdisintegrants". These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength (Bhowmik *et al.*, 2010). An important variable in any tablet system is the rate at which the drug substance dissolves and for many solid dosage forms, disintegration precedes drug dissolution. Hence, the proper choice of disintegrants and its consistency of performance are of critical importance to the formulation development of such tablets (Zhao *et al.*, 2005). Superdisintegrants (Shangraw *et al.*, 1980) such as Cross carmellose sodium (CCS), Sodium starch glycolate (SSG) and Kollidon CL (KCL) are now frequently used in tablet formulations to improve the rate and extent of tablet disintegration thereby increasing the rate of drug dissolution.

Fexofenadine HCl (FFN) is a second-generation non-sedating histamine H_1 receptor antagonist widely used in seasonal allergic rhinitis (Peter *et al.*, 2003). The purpose of the present study was to compare the effect of mode of addition of different superdisintegrants (with various concentrations) and evaluate their effect on dissolution of Fexofenadine HCl (slightly soluble) in 0.001N HCl as specified in the compendia. Several attempts using different superdisintegrants with various concentrations have been made by direct compression to prepare several formulations of Fexofenadine HCl immediate release solid dosage forms with improved dissolution properties. Thus, the rationality of the ongoing study lies in meeting the challenge to increase the dissolution profile by decreasing the disintegration time.

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Materials and Methods

Materials

Fexofenadine HCl, Avicel Ph 101, Ludiflash (LD) were obtained as gift samples from Incepta Pharmaceutical Ltd., Bangladesh. Sodium starch glycolate (SSG), Cross carmellose sodium (CCS) and Kollidon CL (KCL), Aerosil, Xanthan Gum (XG), Maize Starch, Magnesium stearate were obtained as gift samples from ACI Pharmaceutical Ltd., Bangladesh and other reagents were of analytical grade.

Methods

Preparation of standard solutions: Stock solutions of Fexofenadine HCl were prepared by dissolving the drug in 0.001N HCl. These stock solutions were diluted to desired strengths by buffer solution (0.001N HCl) to get the working standard solution.

Formulation design: Orally disintegrating tablets were prepared by direct compression method using single punch tablet machine. The formulations were developed by using various ratios.

*Formulation design for orally disintegrating tablet by direct compression using superdisintegrants***:** The superdisintegrants in 3%, 6%, and 8% concentrations were used to develop the tablets. All the ingredients were passed through sieve having mesh no. 40. All the ingredients were cogrounded in a moter pestle. Finally aerosil and magnesium stearate were added and mixed for 5 minutes. The mixed blend of excipients was compressed using a single punch machine to produce convex faced tablets weighing 155, 159 and 163 mg for 3%, 6% and 8% concentrations, respectively with an average of 2.5 mm thickness. A minimum 35 tablets were prepared for each formulation. The compression force and compression time were 2 tonnes and 15 seconds, respectivly. Before compression, the surfaces of the die and punches were lubricated with Magnesium Stearate. All the preparations were stored in airtight containers at room temperature for further study. Effect of different superdisintegrants with various concentrations was used to study *in vitro* dissolution characteristics and disintegration time of the formulation (Table 1).

Table 1. Formulations (F1-F15) of different batches by using superdisintegrants-direct compression (quantity in mg).

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
FFN (drug)	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60
SSG	4.6	9.6	13.08	-	-	-	-	-	-	-	-	-	-	-	-
CCS	-	-	-	4.6	9.6	13.08	-	-	-	-	-	-	-	-	-
KCL	-	-	-	-	-	-	4.6	9.6	13.08	-	-	-	-	-	-
LD	-	-	-	-	-	-	-	-	-	4.6	9.6	13.08	-	-	-
XG	-	-	-	-	-	-	-	-	-	-	-	-	4.6	9.6	13.08
Avicel Ph101	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80
Maize Starch	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Aerosil	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mg-stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Total	155	160	163.5	155	160	163.5	155	160	163.5	155	160	163.5	155	160	163.5

Evaluation of orally disintegrating tablets

Thickness and diameter: The thickness and diameter of the prepared tablets were measured using slide calipers. These two parameters were expressed in mm.

Weight variation: Weight variation was determined by weighing 20 tablets individually. The average weight and percent variation of tablet was calculated individually.

Hardness and crushing strength: Hardness was determined by taking ten tablets from each formulation, using a Veego tablet hardness tester and the average of applied pressure (kgf) for crushing the tablet was determined.

Friability: The friability of the tablets were determined by friabilator. Initially 20 tablets (W_o) were weighed and placed in a friability tester, which was rotated for 4 minutes at 25 rpm. After dusting, the total remaining mass of tablets (Wt) was recorded and the percent friability was calculated by

$$F = 100 \times \frac{Wo - Wt}{Wo}$$

Here, W_O = Initial weight, Wt = Wight after 25 revolution

In vitro disintegration test: One tablet in each of the 6 tubes of the basket were taken and a disc to each tube were added and the temperature was maintained at 37±2^{0}C. The assemblies were raised and lowered between 30 cycles per minute. The time (in seconds) for complete disintegration of all the tablets in the apparatus were measured and recorded.

In vitro dissolution study: The dissolution rate was studied using USP type II tablet dissolution test apparatus with a paddle stirrer in 900 mL of 0.001N HCl. A speed of 50 rpm and a temperature of 37 ± 0.5^{o}C were used in each test. Aliquots were withdrawn at different time intervals, filtered and analyzed spectrophotometrically at 217 nm for Fexofenadine HCl against appropriate blank. To maintain a constant volume of dissolution medium, fresh medium equivalent to the volume of withdrawn sample was added immediately after withdrawal of the sample.

Characterization of release kinetics: In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order, Higuchi square root (Higuchi, 1963), Korsmeyer (Korsmeyer, 1983) kinetics.

MDT study: Mean dissolution time (MDT) was calculated from dissolution data using the following equation (Mockel. and Lippold., 1993):

$$MDT = \left(\frac{n}{n+1}\right) k^{-\frac{1}{n}},$$

Where, n = slope for Korsmeyer model

k = Korsmeyer constant

Results and Discussion

Physical parameter study: All the formulations showed uniform thickness. The average percentages of deviation of all tablet formulations were within the limit. In this study the percentage friability for all the formulations were below 1%, indicating that the friability was within the prescribed limits. All the tablet formulations showed (Table 2) acceptable pharmacotechnical properties and complied with the compendial specifications for weight variation, hardness and friability, disintegration time.

Table 2. Physical properties of Fexofenadine HCl tablets.

Formulation	Weight (mg)	Hardness (kgf)	Thickness (mm)	Friability (%)	Disintegration time (Sec)
F1	155.46±0.58	2.54±0.03	2.01±0.023	0.4±0.010	47
F2	159.71±0.23	2.63±0.09	2.87±0.024	0.3±0.032	17
F3	163.47±0.61	2.7±0.18	2.55±0.024	0.5±0.010	5
F4	155.70±0.51	2.26±0.11	2.85±0.023	0.2±0.012	46
F5	159.80±0.41	2.70±0.02	2.35±0.024	0.5±0.067	16
F6	163.53±0.50	2.58±0.14	2.99±0.023	0.4±0.023	9
F7	155.95±0.56	2.45±0.30	2.69±0.024	0.3±0.050	135
F8	159.35±0.54	3.23±0.10	2.96±0.023	0.4±0.025	84.6
F9	163.29±0.64	3.48±0.14	2.90±0.023	0.2±0.056	56
F10	156.67±0.50	2.47±0.14	2.46±0.024	0.4±0.014	900
F11	159.2±0.67	3.38±0.22	2.93±0.025	0.4±0.010	765
F12	164.1±0.47	3.63±0.16	2.85±0.023	0.4±0.075	840
F13	154.9±0.61	3.11±0.14	2.84±0.023	0.09±0.016	970.8
F14	163.9±0.54	3.47±0.19	2.79±0.024	0.4±0.025	1590
F15	155.50±0.47	3.93±0.42	2.69±0.024	0.07±0.032	1950

It is clearly observed from comparing tables (Table 2) that incorporating of different concentration of disintegrant in the formulation definitely decreased the disintegration time to a noticeable extent. With the increase in concentrations of superdisintegrants, disintegration times were reduced significantly except Xanthan gum, which didn't act as disintegrant rather than it acts as binder (Figure 1).

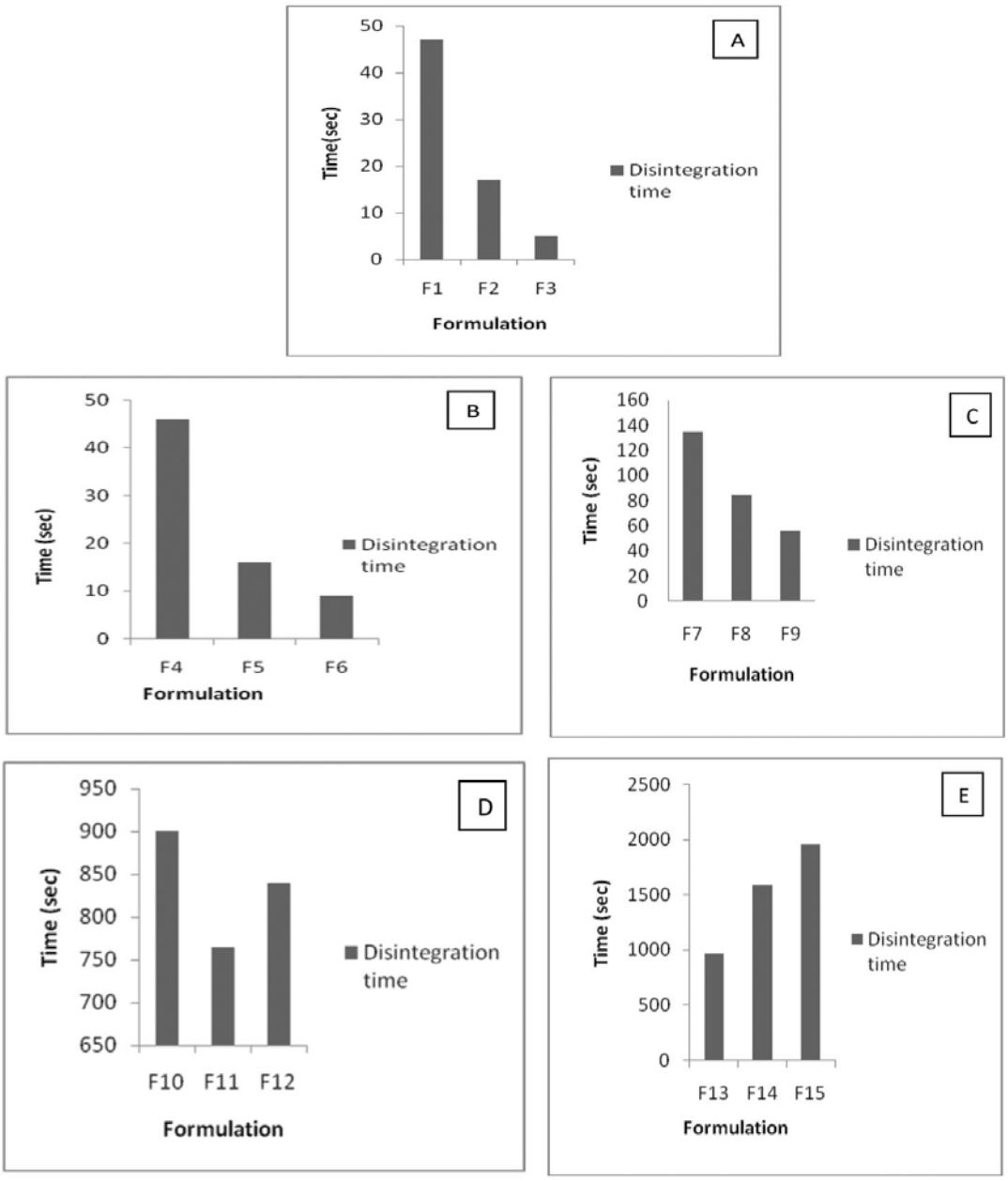

Figure 1. Bar diagram for disintegration time of various formulation. **A**=Formulations of Sodium starch glycolate, **B**=Formulations of Cross carmellose sodium, **C**=Formulations of crospovidone (kollidon CL), **D**=Formulations of ludiflash, **E**=Formulations of Xanthan gum.

Release profiles of Fexofenadine HCl

Dissolution study for tablets containing 3% disintegrants: F-1 and F-4 formulations were released almost 84% within 60 minutes, and other F-7, F-10, F-13 were released less than 60% at same time (Figure 2).

Dissolution study for tablets containing 6% disintegrants: Formulation F-5 showed rapid drug dissolution, 95% drug released within 60 minute and F-2 showed 86% drug released at the same time. On the other hand, formulation F-8 which contained Kollidon CL, showed 77% release in 60 minute (Figure 3).

Dissolution study for tablets containing 8% disintegrants: The rapid drug dissolution observed from formulation F-3 and F-6 showed 99% drug released within

30 minutes and 45 minutes, respectively (Figure 4) than the market product which released 76% of drug at the end of 60 minutes. This rapid drug dissolution may be due to easy breakdown of particles and dissolution of drug into the medium. Thus the orally disintegrating tablets, apart from fulfilling all official and other specifications, exhibited faster release rates of Fexofenadine HCl.

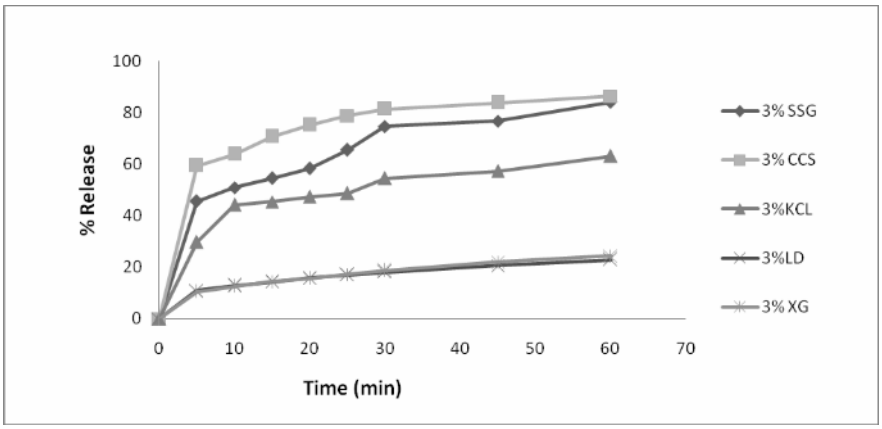

Figure 2. Zero order curve for F-1, F-4, F-7, F-10 and F-13

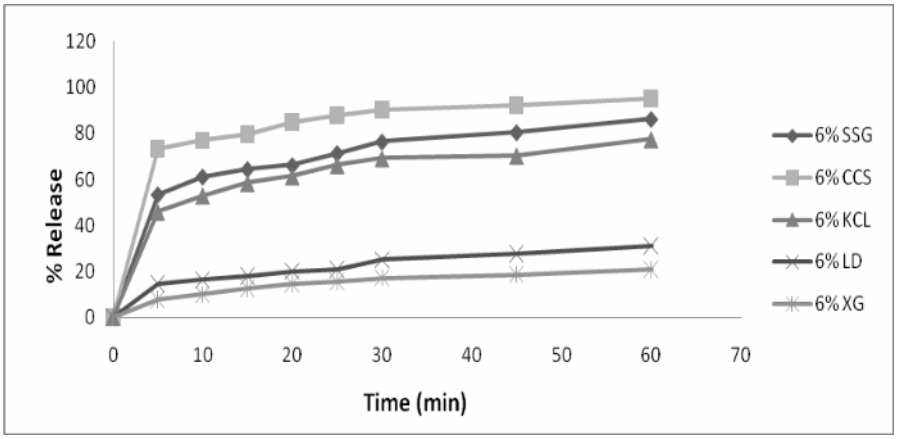

Figure 3. Zero order curve for F-2, F-5, F-8, F-11 and F-14.

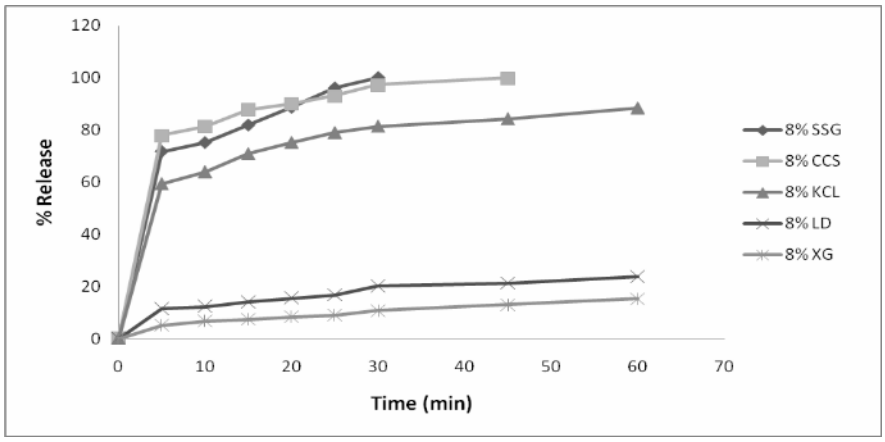

Figure 4. Zero order curve for F-3, F-6, F-9, F-12 and F-15.

Best fitted model and their release mechanism: To investigate the effect of disintegrant agents on Fexofenadine HCl release fifteen formulations were made. From table 3, F-1 best fits with Korsmeyer (R^2=0.949) then Higuchi (R^2=0.914). The values of release exponent obtain from Korsmeyer model is 0.261 which indicates that the release pattern of Fexofenadine HCl from F-1 can be characterized by Fickian diffusion. In this case, the drug release is dominated by the diffusion mechanism. F-2 to F-9 also followed Korsmeyer model (R^2= 0.982, R^2= 0.922, R^2= 0.970, R^2= 0.968, R^2= 0.972, R^2= 0.926, R^2= 0.984, R^2= 0.980), the release exponent values of these formulations were 0.192, 0.193, 0.163, 0.121, 0.113, 0.270, 0.208 and 0.169, these value indicates Fickian diffusion. Again F-10, F-11, F-12, F-13, F-14 and F-15 were found to best fit with Kosmeryer and also Higuchi model. The R^2 values of Korsmeyer model for F-10, F-11, F-12, F-13, F-14 and F-15 were 0.990, 0.955, 0.947, 0.989, 0.987 and 0.973 respectively. The R^2 value of Higuchi for F-10, F-11, F-12, F-13, F-14 and F-15 were 0.950, 0.960, 0.955, 0.975 and 0.99, respectively. The values of release exponent of Korsmeyer model for F-10, F-11, F-12, F-13, F-14 and F-15 were 0.297, 0.319, 0.318, 0.345, 0.404 and 0.430, respectively, which denoted that Fickian diffusion phenomenon dominates. For each disintegrating agent the values of diffusion exponent (n) was reduced with the increase of disintegrant load which indicated the shifting of release mechanism except F-13 , F-14 and F-15 which contained Xanthan gum.

Table 3. Kinetic parameters of different formulation of Fexofenadine HCl tablet.

Formulation	Zero order		Higuchi		Korsmeyer		MDT (min)
	k_0	R^2	k_H	R^2	R^2	n	
F1	1.063	0.687	10.14	0.914	0.949	0.261	25.81
F2	0.994	0.573	9.965	0.841	0.982	0.192	22.27
F3	2.586	0.677	17.11	0.898	0.922	0.193	5.66
F4	0.959	0.489	10.03	0.782	0.970	0.163	17.57
F5	0.975	0.415	10.55	0.710	0.968	0.113	8.98
F6	1.544	0.479	13.70	0.771	0.972	0.121	4.85
F7	0.776	0.640	7.573	0.890	0.926	0.270	67.23
F8	0.899	0.574	9.049	0.848	0.984	0.208	34.97
F9	0.985	0.508	10.20	0.796	0.980	0.169	16.79
F10	0.295	0.745	2.764	0.95	0.990	0.297	2152.19
F11	0.416	0.787	3.805	0.960	0.955	0.319	640.83
F12	0.318	0.772	2.932	0.955	0.947	0.318	1453.40
F13	0.330	0.805	3.014	0.976	0.989	0.345	994.27
F14	0.294	0.794	2.705	0.975	0.987	0.404	1067.43
F15	0.216	0.896	1.886	0.990	0.973	0.430	1677.43

Mean dissolution time (MDT) study: From the table 3, it is clear that MDT values were changed due to the change of the amount of disintegrants in the tablets. In all these formulations, the values of MDT are larger for those formulations which contain smaller quantities of disintegrating agent. For example MDT values for F-1, F-2 were 25.81 minutes and 22.27 minutes which contain 3% and 6% concentration of disintegrant, respectively but for F-3 was 5.66 minutes. So this reduction of the magnitude of MDT is most valuable observation which indicates that when the amount of sodium starch glycolate was increased, the drug release rate was increased gradually due to the disintegrating effect of the Sodium starch glycolate and the same picture was observed in case of formulations F-4 to F-9 where Cross carmellose sodium, Kollidon CL were used as disintegrants. In case of formulations F-13, F-14 and F-15 it was found that when the amount of xanthan gum were increased then the drug release rates were decreased, because xanthan gum didn't act as disintegrant in formulation at high concentration.

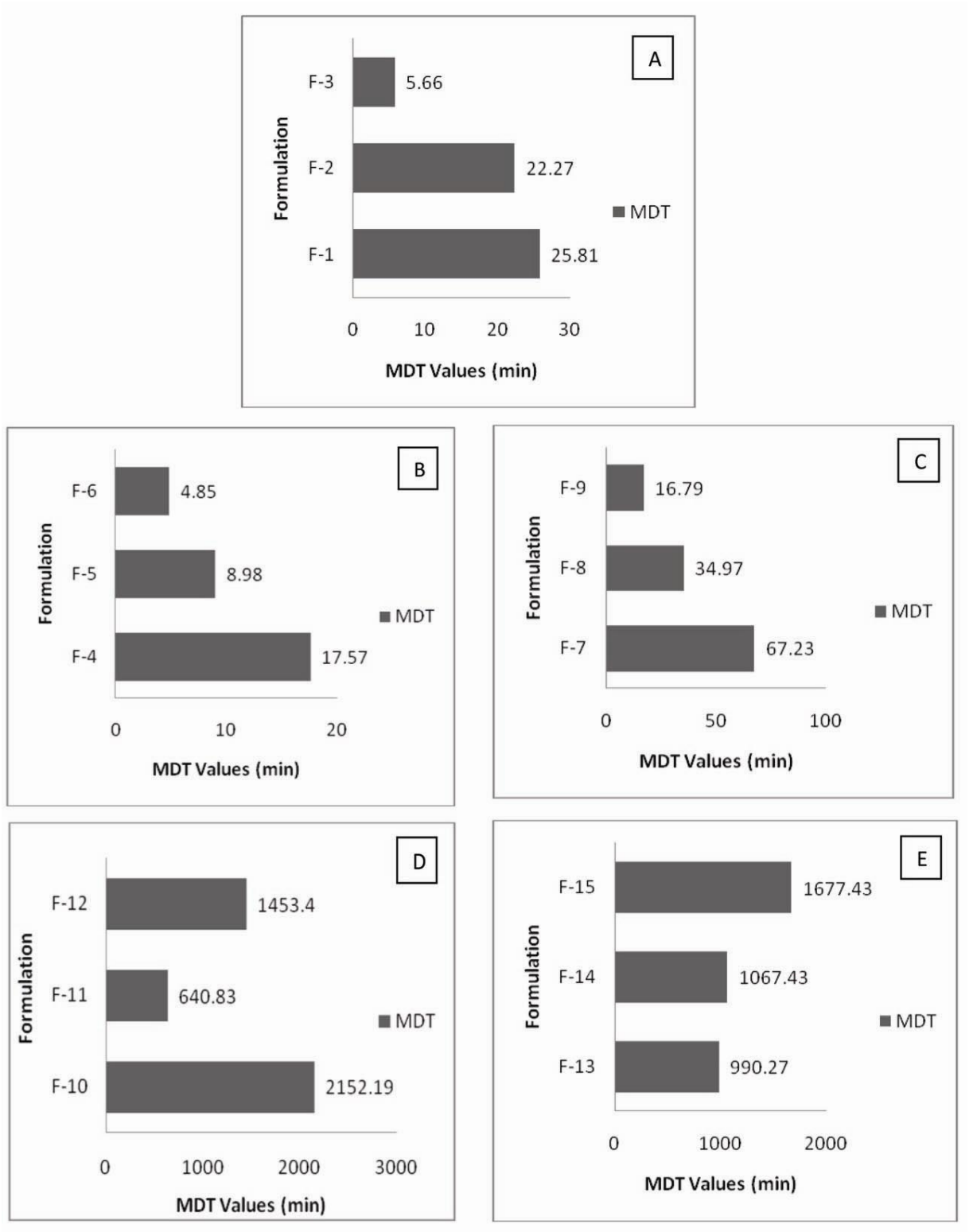

Figure 5. MDT values for various formulations. **A**=Formulations of sodium starch glycolate, **B**=Formulations of Cross carmellose sodium, **C**=Formulations of kollidon CL, **D**=Formulations of ludiflash, **E**=Formulations of Xanthan gum

Fourier transform infrared spectroscopic (FTIR) study: FTIR spectra were recorded to examine drug-polymer interactions. FTIR of pure Fexofenadine HCl is shown in figure 6. It shows –NH stretching at 3301.28 cm^{-1}, C-O stretching at 1705 cm^{-1}, C=O stretching at 1451.04 cm^{-1} and C-N stretching at 1278.68 cm^{-1}. These peaks are identical for Fexofenadine HCl. These peaks were found unchanged in F-3, F-6, F-9, F-11 and F-14 which are shown in figures 7, 8, 9, 10, 11, respectively. This proves that there was no drug-polymer interaction.

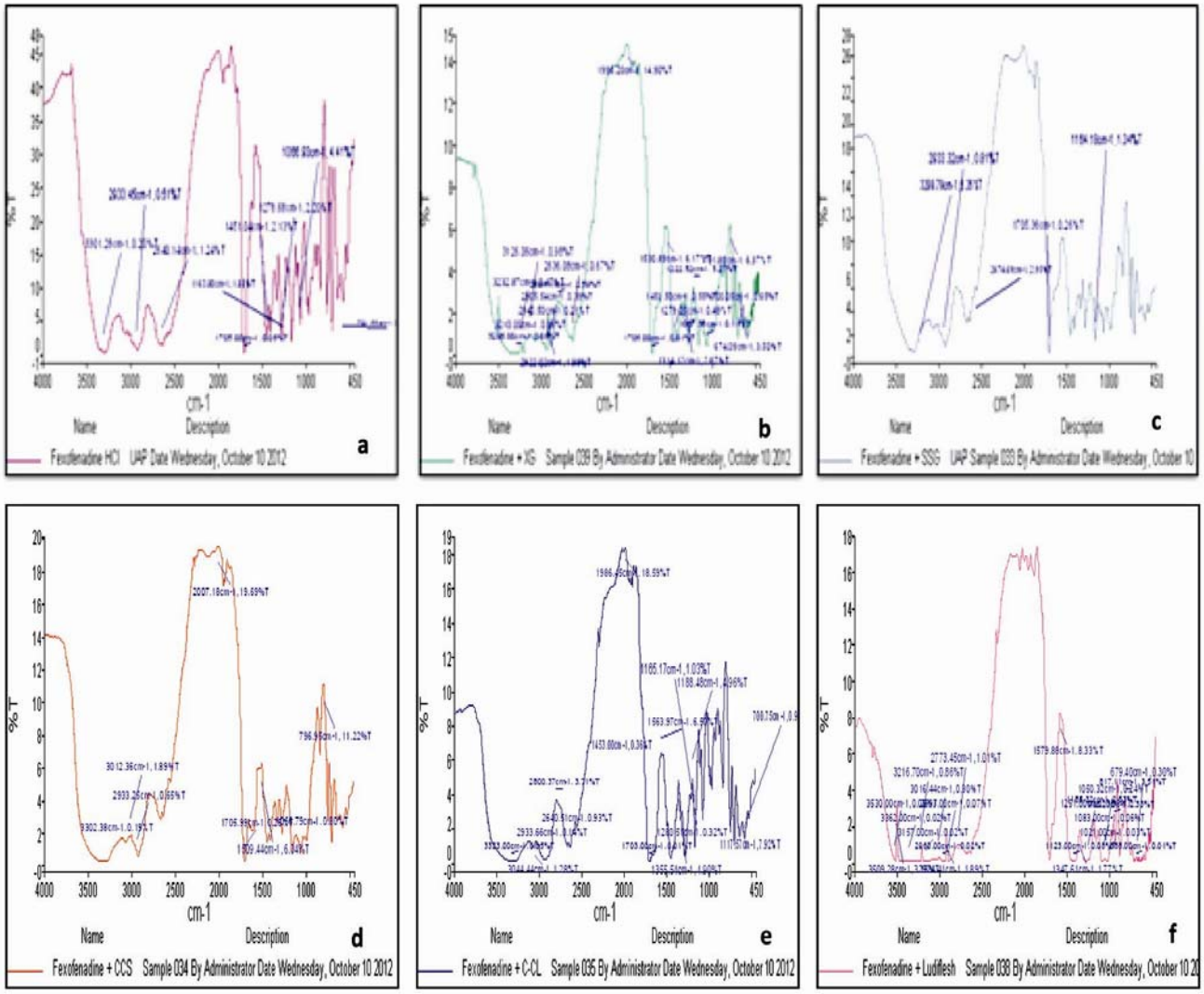

Figure 6. a, b, c, d, e and f represent IR spectra of pure FFN (Drug), FFN formulation with 8% XG, FFN formulation with 8% SSG, FFN formulation with 8% CCS, FFN formulation with 8% KCL and FFN formulation with 8% Ludiflash, respectively.

Conclusions

In this study, tablets of Fexofenadine HCl were prepared by direct compression, where SSG, CCS, KCL, Xanthan Gum and Ludiflash were used as disintegrants. The release mechanism was explored and explained with Zero order, Higuchi and Korsmeyer model. Release profiles showed a tendency to diffusion mechanism. Disintegration time of F-3, F-6 formulations were within 9 seconds because of the presence of 8% superdisintegrant of sodium starch glycolate and cross carmellose sodium, respectively, which resulted in improved rate and extent of dissolution. This was supported by the percent release of the formulations. Comparison of the release profile of the 15 formulations showed that formulation F-3 and F-6 was

superior as compared to other formulations. On the other hand, Xanthan gum did not act as a superdisintegrant rather than it acted as a binder hence decreased the release of drug from respective formulations. So, it is suggested that the studied superdisintegrants (SSG, CCS) can be incorporated (in various concentrations) in the formulation by direct compression method to obtain desired result of Fexofenadine HCl.

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