World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Original Article

Formulation and Development of Fast dissolving tablets of Montelukast Sodium and Fexofenadine Hydrochloride

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Received: 06-07-2020 / Revised Accepted: 19-08-2020 / Published: 30-08-2020

ABSTRACT

The study was aimed to formulate and evaluate fast dissolving tablets of Fexofenadine HCl and Montelukast Sodium using superdisintegrants. Fexofenadine HCl and Montelukast Sodium fast disintegrating tablets were prepared by direct compression method and characterized for pre-compression and post-compression parameters. FT-IR spectroscopy studies indicated no interaction between the drug-excipient used in the formulation. In the direct compression method, crospovidone, croscarmellose sodium and sodium starch glycolate were used along with directly compressible diluents, microcrystalline cellulose to enhance palatability. The prepared FDT tablets were evaluated for hardness, friability, drug content uniformity, wetting time, water absorption ratio and disintegration time. Based on disintegration time best formulation was chosen. The disintegration time for optimized formulation (F6) has shown better drug release (96 %) in 12 minutes. Short-term stability studies indicated that there were no significant changes in drug content and disintegration time.

Keywords: Fexofenadine Hydrochloride, Montelukast Sodium, Fast dissolving tablet, Croscarmellose sodium and *In-vitro* drug release

INTRODUCTION

Oral route of drug administration has been one of the most convenient and accepted route of drug delivery among the intraoral route. It is the most preferred due to its convenience and rapid onset of action. Intraoral dosage forms have evolved as an alternative to conventional tablets, capsules.[1]

FDTs are novel drug delivery system that dissolves, disintegrate or disperse the drugs in saliva within few seconds with or without intake of water. The faster the dissolution of drug into the solution, quicker is the absorption and onset of clinical effect. Natural and synthetic Superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose) and sodium starch glycolate (primogel), poly vinyl pyrrolidone etc; provide immediate disintegration of tablets and facilitate the design of delivery system with desirable characteristics.[2]Stability for longer duration of time, since the drug remains in solid

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How to Cite this Article: Priyanka Bharat Gaikwad and V. Felix Joe. Formulation and development of fast dissolving tablets of montelukast sodium and fexofenadine hydrochloride. World J Pharm Sci 2020; 8(9): 146-155.

dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.[3]

Fexofenadine Hydrochloride (FH) a second-generation, long lasting H_1-receptor antagonist (antihistamine) which has a selective and peripheral H_1-antagonist action. It belongs to BCS-II and it possesses low solubility and high permeability, it is non-sedating anti- histamine drug specified for the symptomatic relief of symptoms associated with rhinitis, urticarial and allergic skin conditions.[4]

Montelukast is absorbed rapidly, with 60–70 % bioavailability. The $t_{1/2}$ of Montelukast is 3–6 hours, with volume of distribution of 8 to 11 lit.[5] Montelukast (MS) is a leukotriene receptor antagonist used in treatment of asthma. The leukotriene-modifying drugs are administered orally. It has extensive first-pass metabolism and has poor dissolution rate;it has low bioavailability due to first pass metabolism.[6] Cysteinyl leukotriene receptor is the most potent broncho constrictor agents yet discovered, about 100-1000 times more potent than histamine.[7]

Hence the study was aimed to formulate and evaluate fast dissolving tablets containing drug Fexofenadine HCl and Montelukast Sodium by using superdisintegrants to improve patient compliance.

MATERIALS AND METHODS

Fexofenadine Hydrochloride and Montelukast Sodium, Croscarmellose Sodium, Crospovidone and Sodium Starch Glycolate were procured from Glenmark Pharmaceuticals pvtLtd, Nasik. All the other chemicals and reagents were used of analytical grade.

METHODS:

Preformulation studies: Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The following Preformulation studies were performed for FH and MS and superdisintegrants.[8]

Formulation of FH and MS FDTs: Formulations of orally disintegrating tablets containing FH and MS are prepared by direct compression method. All the ingredients were passed through # 60 mesh sieves separately. The drug and micro crystalline cellulose were mixed by adding small quantities followed by blending. Then super disintegrants like crospovidone, croscarmellose sodium, sodium starch glycolate were mixed in geometrical order and passed through coarse sieve (#44 mesh) and the tablets were compressed using Rotary punching machine. Compression force of the machine was adjusted to obtain the hardness in the range of 4-5 kg/cm^2 for all batches. Six batches of formulations were prepared fromF1 to F6.The composition of ingredients were given in Table No 1.

Evaluation of FH and MS FDTs

A) Drug–Superdisintegrant compatibility studies

FTIR spectroscopy was employed to ascertain the compatibility between FH and MS and the selected superdisintegrants.FTIR spectrum of pure drug were taken and subsequently IR spectrum of formulations with highest percentage of superdisintegrants was taken. The spectra of FH and MS were compared with FTIR spectra formulations with superdisintegrants.

B) Precompression studies:[8]

a) Angle of repose (θ): The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$$\tan(\theta) = h / r$$

$$\theta = \tan^{-1}(h / r)$$

The powder mixture was allowed to flow through the funnel to a fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

b) Determination of bulk density: Weighed accurately about 25 g of drug, which was previously passed through 20 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in g/ml by the following formula

Bulk density = Weight of powder / Bulk volume

c) Determination of Tapped bulk density: Weigh accurately about 25 g of drug, which was previously passed through 20 # sieve and transferred in 100 ml graduated cylinder.Then mechanically tapped the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. Tapped the cylinder for 500 times initially and measure the tapped volume to the nearest

graduated units, repeat the tapping an additional 750 times and measure the tapped volume to the nearest graduated units. If the difference between the two volume is less than 2 % then make the volume as final.

Tapped density = Weight of powder / Tapped volume of packing

d) Carr's Compressibility index & Hausner's Ratio: The compressibility index and Hausner ratio measures the propensity of powder to be compressed. Carr's compressibility index and Hausner's ratio can be calculated as follows

Carr's index = Tapped density - Bulk density / Tapped density X 100
Hausner's ratio = Tapped density / Bulk density

Post Compression Parameters: The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e., shape of the tablets, thickness and diameter of the tablets, weight uniformity test, hardness, friability, disintegration time, and *in vitro* drug release studies.

Physical Properties

a) Shape of tablets: Directly compressed tablets were examined under the magnifying lens for the shape of the tablet.

b) Thickness: Thickness and diameter were measured using a calibrated Vernier Caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

c) Hardness: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

d) Uniformity of weight: Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. The percentage deviation was calculated and evaluated for weight variation.[9]

Friability of tablet: Friability of the tablet was determined using Roche friabilator (Electrolab USP friabilator). This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at l height of 6- inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de-dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula

F = W initial- W final /W initial× 100

a) ***In vitro* Disintegration Test:** The disintegration time for ODT needs to be modified as disintegration is required to take place without much water, thus the test should mimic disintegration in salivary contents. For this purpose, a beaker (100 ml) was filled with10 ml of water. The tablet was carefully put in the center of the beaker and the time for the tablet to completely disintegrate into fine particles was noted.[10]

b) Water absorption ratio: Water absorption ratio is a measure of quantity of water absorbed by the tablet. A petridish containing 6 ml of distilled water was taken. The tablet containing small quantity of amaranth color was placed on it. Time required for the upper surface of the tablet to become red was noted. It is done by calculating the weight difference of the tablets before and after wetting.[11]

c) *In vitro* drug release: *In vitro* drug release was determined by estimating the dissolution profile.USP type II Paddle apparatus at 50 rpm, 6.8 pH phosphate buffer was used as dissolution medium. The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment. One tablet was used in each test. Aliquots were withdrawn from the dissolution apparatus and the samples were replaced with fresh dissolution medium. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug by measuring the absorbance at 285 nm and 241 nm. Cumulative percent of FH and MS released was calculated and plotted against time.[12]

Stability Study: The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Selected formulations were subjected to stability studies the following conditions were used for stability studies 30 °C/65 % RH analyzed at a time interval of 30 days till a period of 60 days.[13]

RESULTS AND DISCUSSION

Preformulation studies of FH and MS:

Organoleptic characteristics: FH drug was found to be white to off-white crystalline powder, bitter in taste and odorless.

MS drug was found to be white to off-white powder, bitter in taste and odorless.

Evaluation of FH and MS FDTs

Drug–superdisintegrant compatibility studies: The presence of any drug excipients interaction in the formulation was studied by performing the FTIR of the mixture of drug and superdisintegrants. The FTIR peaks of the drug; superdisintegrant mixture was compared with the principle peaks of the drug in the literature to observe any change. The principle peaks of the drug FH were observed at 2938.02 cm^{-1} (C-H stretching), 1708.62 cm^{-1} (C=O stretching), 3304.43 cm^{-1} (O-H stretching). The principle peaks of MS were observed at 1409.71 cm^{-1}(O-H bending) of alcohol and 837.91 cm^{-1} (C-Cl Bending). The peaks at 1145.51 cm^{-1} represented the (C-O stretching) for tertiary alcohol.

The characteristics peaks of FH and MS were observed in formulations as well with no significant peak shift and hence it was concluded that there was no interaction between the drug and the superdisintegrants used in the formulation of the FDT.

Bulk Density: The values obtained for bulk density for all (F1-F6) formulations are tabulated in Table No.2.The values were found to be in range of 0.473 to 0.533 gm/cm^3.

Tapped Density: The values obtained for bulk density for all (F1-F6) formulations are tabulated in Table No.2.Tapped density ranges from 0.531 to 0.620 gm/cm^3.

Angle of Repose (θ): The values were found to be in the range from 26º.05′ to 28º.05′, tabulated in Table No.2.This indicates good flow property of the powder blend.

Compressibility Index (Carr's index): Compressibility index value ranges between 9.174 % to 16.721 %, tabulated in Table No.2, indicating that the powder blends have the required flow property for direct compression.

Hausner's Ratio: The values were found to be in the range from 1.101 to 1.200, tabulated in Table No.2. Angle of repose, Carr's index values etc. indicated satisfactory to good flow of powder mix, which is suitable for direct compression technique.

Post compression parameters

A. Physical properties

a) Shape of the tablet: Microscopic examination of tablets from each batch of formulation showed circular shape with no cracks and pinholes.

b) Tablet dimensions (Thickness and Diameter): Tablets mean thicknesses were almost uniform in all the formulations and were found to be in the range of 3.28 mm to 3.30 mm. The diameter of the tablet ranges between 6.00 mm to 6.02 mm**.** All the tablets produced were of near uniform thickness. There was no significant variation in thickness of tablets of same batch. The results are tabulated in Table No.3.

c) Crushing Strength/Hardness test: The measured hardness of tablets of each batch ranged between 3.2 kg/cm^2 to 3.6 kg/cm^2.F6 formulations showed better hardness while, all formulations containing CCS, SSG showed lower hardness. The results are tabulated in Table No.3.

d) Friability Test: The % friability of formulations F1 – F6 ranges from 0.199% to 0.634% ensuring that the tablets were mechanically stable. All the batches exhibited a friability loss which was less than 1 % w/w, and thus comply with standards. The results are tabulated in Table No.3.

e) Weight Variation Test: The % weight variation of formulations from F1 to F6 was found to be in the range of 100.1±1.49 to100.8±2.09. The weights of all the tablets were found to be uniform with low standard deviation values. Weight of the tablets was set to 100 mg. All the formulations indicated a deviation which was within the official limits. The results are tabulated in Table No.3.

f) Disintegration test: The tablets prepared by using different superdisintegrants like sodium starch glycolate, croscarmellose sodium are shown *in vitro* dispersion time between 28.01 to 24.66 sec, 92.66 to 93.00 sec respectively. All the formulations had dispersion time of less than 32 sec. Formulations containing CCS, SSG, CP (F6) showed the least dispersion time of 17.33 sec. *In vitro* dispersion time varied from 17.33 sec to 92.66 sec for formulations compressed with superdisintegrants. *In vitro* dispersion time was the least for F6 formulations. The results are tabulated in Table No.4.

g) Water absorption ratio: The water absorption ratio or water uptake of superdisintegrants follows the order CCS, CP, SSG>CP, SSG>CP, CCS. There was a linear increase in water uptake with increase in concentration of superdisintegrants. This was in contrast to dissolution rate, which decreases with increase in concentration. Formulation prepared with Crospovidone, Croscarmellose sodium showed the least water absorption ratio, while for F6 formulations it is greater. The results are tabulated in Table No.4.

h) Drug content: The % drug content found to be in between 75.25 to 96.89 % for FH and 80.33 to 98.32 % for MS. The results are tabulated in Table No.4.

***i) In vitro* Drug release:** Drug release study was carried out using USP type II Paddle apparatus in 6.8 pH phosphate buffer as the dissolution medium at 37 °C at 50 rpm. The % CDR of FH and MS was given in Table No.5.

Stability Studies: Stability studies were carried out on optimized formulation F6 at 30 ± 2 °C/65 ± 5 % RH and 40 ± 2 °C/75 ± 5 % RH for two months to assess their long term stability as per ICH guidelines. The samples were evaluated for different time intervals of 30 and 60 days after stability studies. There was no significant change in physicochemical parameters like hardness, drug content, *in vitro* dispersion time and *in vitro* drug release indifferent sampling points. There was no significant difference between the initial values and the results obtained during stability studies.

CONCLUSION

The orally-disintegrating tablets of FH and MS was prepared by direct compression method using superdisintegrants SSG, CCS, CP. Based on *in vitro* disintegration time, formulation F6, was found to be likely and exhibited a dispersion time of approximately 17 seconds. Formulation (F6) have displayed good water absorption ratio of about 66 % which indicate better and faster swelling ability of the disintegration in presence of little amount of water. FH and MS is soluble in water but its bioavailability is limited and hence this method is useful for improving the solubility for poorly soluble drugs. Hence the formulated fast dissolving tablets of FH and MS is suitable for immediate release with improved dissolution rate, which can improve the patient compliance leading to better therapeutic efficacy.

Table No 1. Formulation of orally disintegrating tablets of FH and MS

Formulation code	F1	F2	F3	F4	F5	F6
Ingredients						
Montelukast sodium	10	10	10	10	10	10
Fexofenadine HCl	30	30	30	30	30	30
Sodium starch glycolate	-	-	3	6	3	6
Croscarmellose sodium	5	10	-	-	5	10
Crospovidone	6	6	6	6	6	6
Microcrystalline cellulose	30	30	30	30	30	30
Magnesium stearate	5	5	5	5	5	5
Sodium saccharin	2	2	2	2	2	2
Talc	3	3	3	3	3	3
Vanillin	1	1	1	1	1	1

Table No.2: Micromeritic properties of all the formulations of FH and MS

Formulation Code	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Angle of Repose (θ)	Compressibility Index (%)	Hausner's ratio
F1	0.495	0.545	27.01	9.174	1.101
F2	0.473	0.531	26.05	12.262	1.122
F3	0.519	0.589	28.05	13.487	1.134
F4	0.508	0.610	27.88	16.721	1.200
F5	0.501	0.580	27.69	13.620	1.157
F6	0.533	0.620	26.70	14.032	1.163

Table No.3: Post compression parameters of prepared tablets

Formulation Code	Diameter (mm)	Thickness (mm)	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (%)
F1	6.02±0.052	3.30±0.007	100.8±2.09	3.32±0.2	0.265
F2	6.01±0.036	3.30±0.011	100.1±1.49	3.48±0.3	0.332
F3	6.01±0.043	3.28±0.010	100.8±1.22	3.36±0.5	0.265
F4	6.00±0.024	3.29±0.008	100.7±1.25	3.25±0.3	0.634
F5	6.01±0.041	3.29±0.007	100.4±2.16	3.61±0.2	0.199
F6	6.01±0.043	3.30±0.059	100.8±1.13	3.52±0.1	0.395

Table No.4: Post Compression parameters of tablets

Formulation Code	Water absorption ratio	Disintegration Time (Sec)	% Drug Content	
			FH	MS
F1	56.4±0.529	92.66	75.25	80.33
F2	57.9±0.080	93.00	76.91	83.10
F3	60.05±1.95	28.01	81.56	89.50
F4	62.98±0.2	24.66	85.51	90.95
F5	66.77±1.09	18.27	93.55	95.50
F6	66±0.556	17.33	96.89	98.32

Table No.5: % CDR profiles of FH & MS from FDT formulations

Time in mins	% CDR of FH						% CDR of MS					
	F1	F2	F3	F4	F5	F6	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0	0	0	0	0	0
2	40.33	50.12	75.54	73.11	76.59	77.55	50.12	53.21	60.81	62.13	70.55	73.22
4	44.23	77.33	80.21	79.18	80.54	79.21	56.55	55.89	69.55	70.12	78.98	79.86
6	50.32	80.25	82.66	80.96	84.98	85.41	68.99	69.80	78.33	76.52	86.58	88.23
8	56.65	83.96	88.58	85.22	87.56	89.98	79.55	76.55	79.98	88.20	90.10	91.20
10	58.6	89.56	90.96	88.36	92.22	95.22	89.22	87.86	89.33	90.01	92.12	93.08
12	60.23	91.64	93.54	92.52	95.63	98.11	91.00	91.58	93.05	94.98	95.20	96.98

Table No.6: Stability studies of FH and MS FDT

Evaluation parameters	Stored at 30±2 ^{o}C, 60±5 % RH		Stored at 40±2 ^{o}C, 75±5 % RH	
	After 30 days	After 60 days	After 30 days	After 60 days
Disintegration time (sec)	16	15	17	18
Hardness(kg/cm^2)	3.50	3.51	3.49	3.45

Table No.7: Drug Release profile of F6 formulations during stability studies

Time in minutes	% Cumulative drug release of FH			
	Stored at 30±2 ^{o}C, 60±5 % RH		Stored at 40±2 ^{o}C, 75±5 % RH	
	After 30 days	After 60 days	After 30 days	After 60 days
0	0	0	0	0
2	76.98	76.96	76.97	76.94
4	79.05	79.00	79.06	79.06
6	85.38	85.30	85.38	85.37
8	89.10	89.09	89.10	89.08
10	95.20	95.17	95.10	95.10
12	98.01	98.00	98.02	98.00

Table No.8: Drug Release profile of F6 formulations during stability studies

Time in min	% Cumulative drug release of MS			
	Stored at 30±2 °C, 60±5 %RH		Stored at 40±2 °C, 75±5%RH	
	After 30 days	After 60 days	After 30 days	After 60 days
0	0	0	0	0
2	73.33	73.32	73.30	73.28
4	79.23	79.20	79.22	79.21
6	88.50	88.48	88.49	88.49
8	91.38	91.30	91.37	91.38
10	93.56	93.55	93.55	93.54
12	96.03	96.01	96.00	95.98

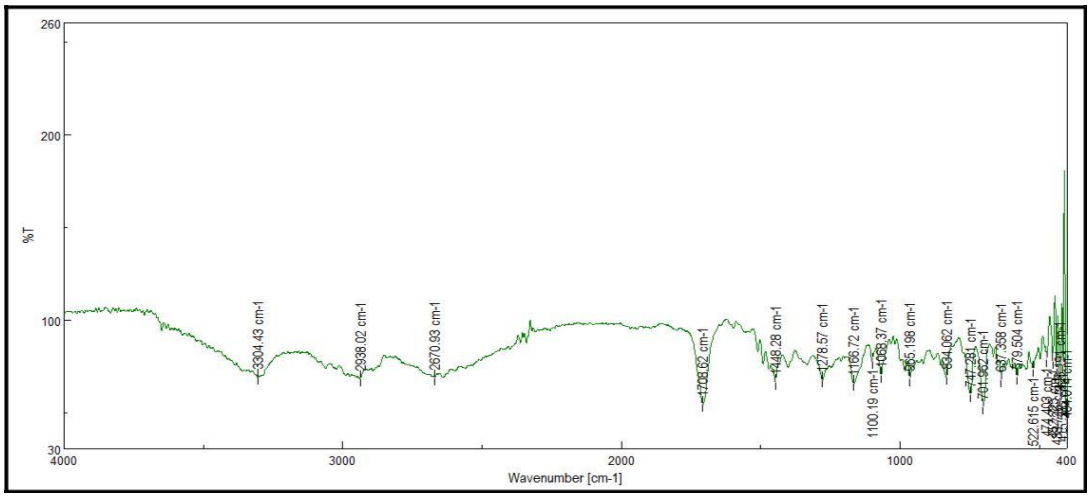

Fig No.1: FTIR spectra for Fexofenadine Hydrochloride

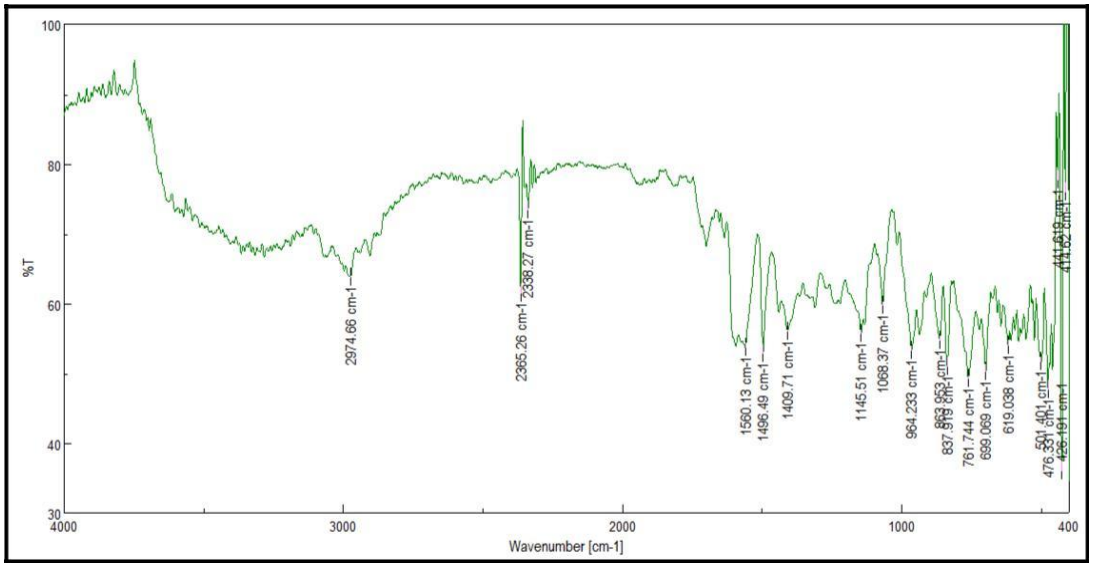

Fig No.2: FTIR spectra for Montelukast Sodium

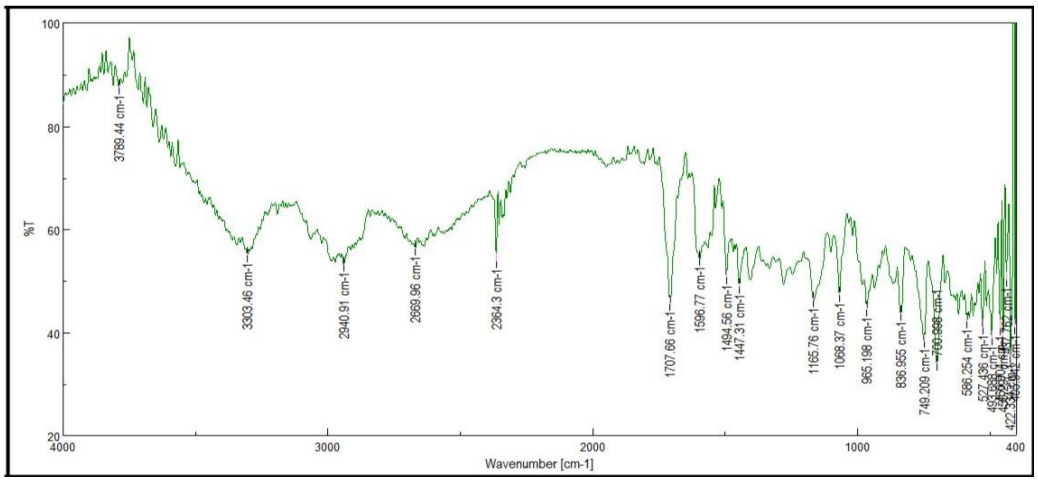

Fig No.3: FTIR spectra for Fexofenadine Hydrochloride and Montelukast Sodium

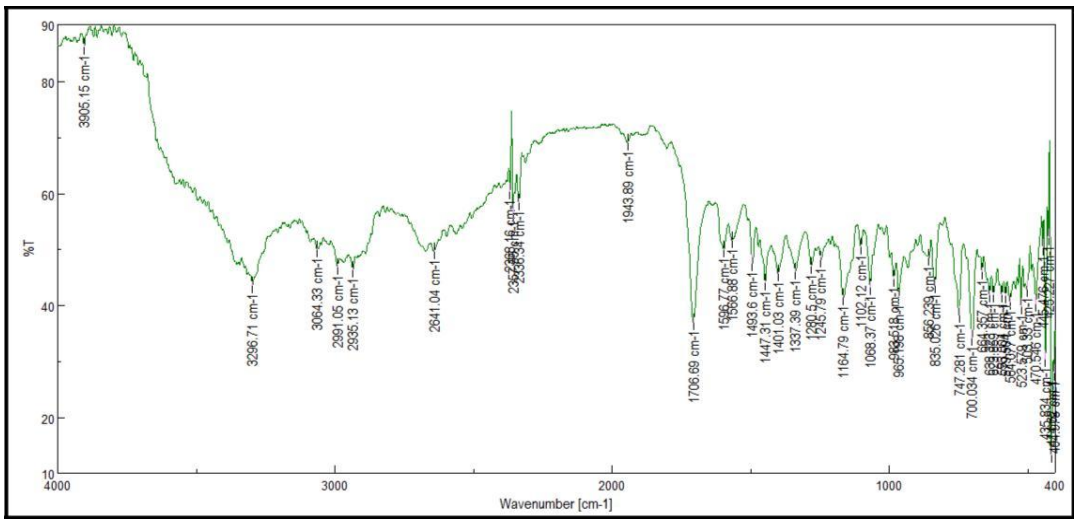

Fig No.4: FTIR spectra for Fexofenadine Hydrochloride, Montelukast Sodium and Croscarmellose Sodium

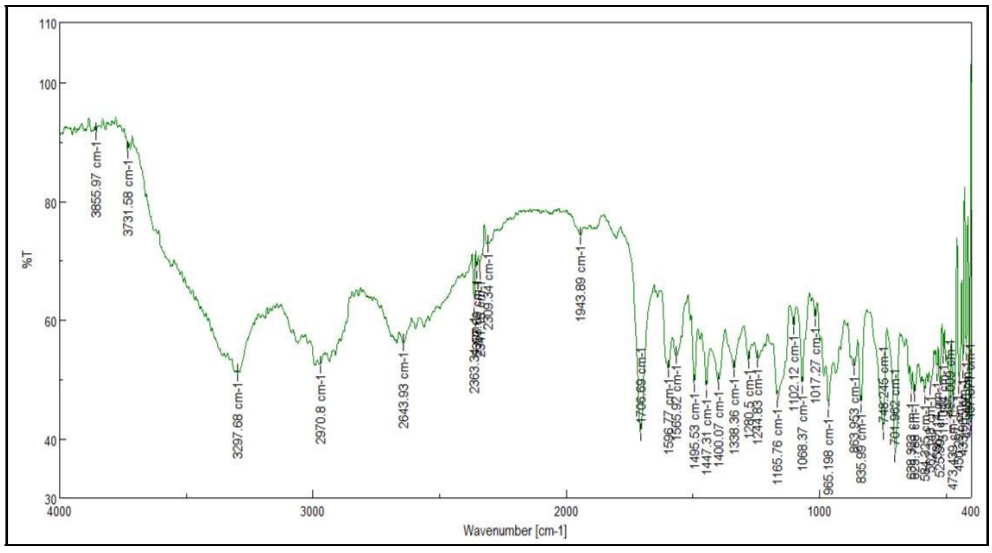

Fig No.5: FTIR spectra for Fexofenadine Hydrochloride, Montelukast Sodium and Sodium Starch Glycolate

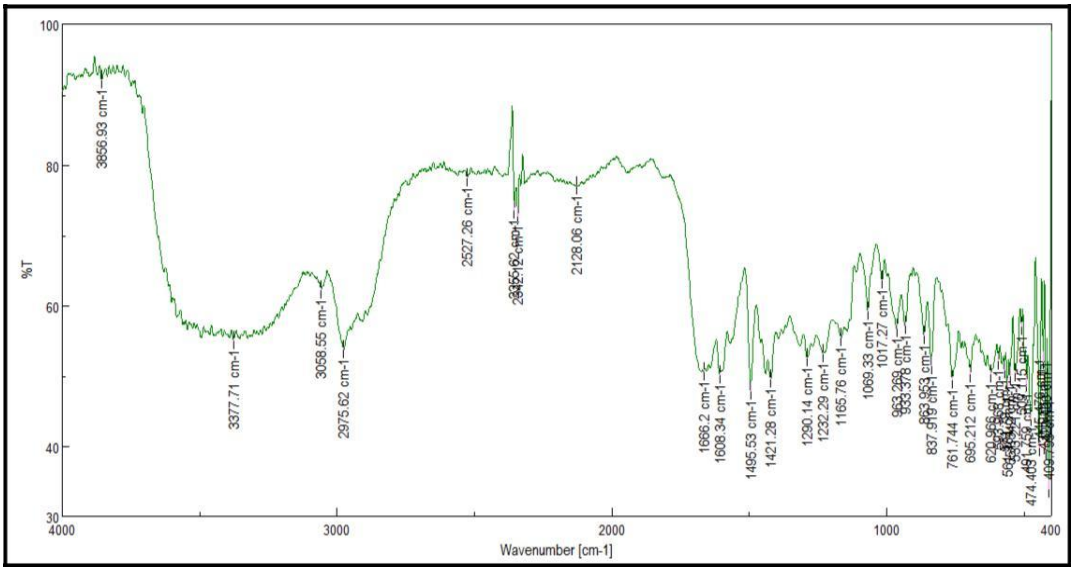

Fig No.6: FTIR spectra for Fexofenadine Hydrochloride, Montelukast Sodium and Crospovidone

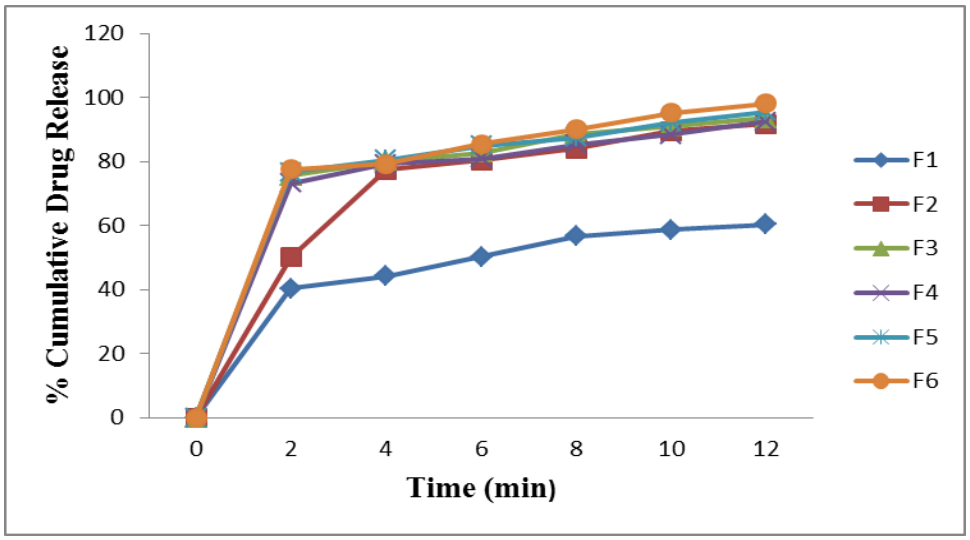

Fig no 7: % CDR profiles of FH from FDT formulations

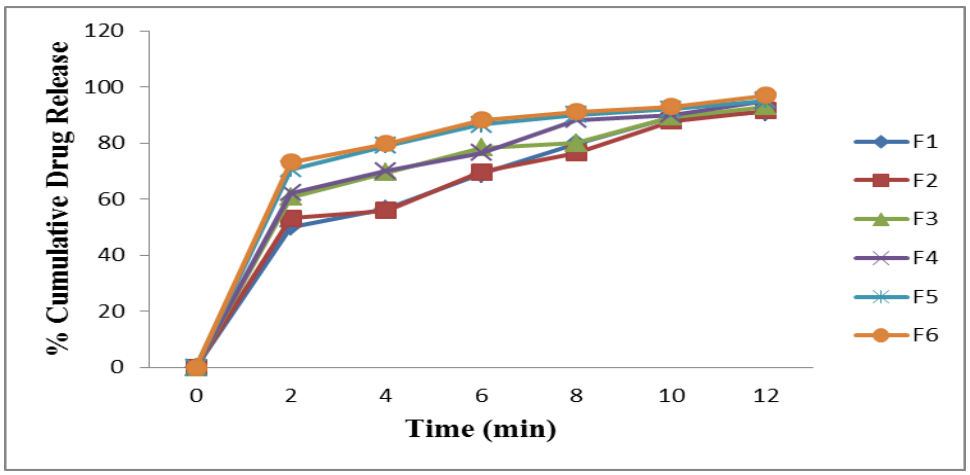

Fig 8: % CDR profiles of MS from FDT formulations

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