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Formulation and Evaluation of Immediate Release Tablets of Fexofenadine Hydrochloride

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ABSTRACT

The present research work is to develop immediate release tablets of Fexofenadine hydrochloride. The rate of dissolution and bioavailability of the Fexofenadine HCL has been increased by using superdisintegrants in its immediate release tablets. Direct compression method was adapted to prepare the tablets by using Sodium lauryl sulphate, microcrystalline cellulose as filler, crospovidone and sodium starch glycolate as superdisintegrant in different concentration (2-8%). Tablets were prepared and evaluated pre and post compressional parameters. *In-Vitro* Disintegration study shows that as there is increase in disintegration time with increase in concentration of sodium starch glycolate while there is decrease in disintegration time with increase in the level of crospovidone. The results indicate that the selected batch of tablet formulation containing crospovidone provides disintegration time between 3-6 minutes with sufficient crushing strength and accepted friability. It was concluded that immediate release tablet for Fexofenadine hydrochloride can be formulated for fast treatment of allergic rhinitis.

KEYWORDS: Allergic rhinitis, Crospovidone, Croscarmellose sodium.

INTRODUCTION [1,2]

In the last 15 to 20 years, there has been a huge resource in both academia and industry devoted to the development of drug delivery systems that target drugs more effectively to their therapeutic site. Much of this work has been successful and is reported within this text. In spite of this, oral solid dosage forms such as tablets and hard gelatin capsules, which have been in existence since the nineteenth century, remain the most frequently used dosage forms. This is not simply a reflection of the continued use of established products on the market, tablets and capsules still account for about half of all new medicines licensed.

There are several reasons for the continued popularity of the oral solid dosage form. The oral route of delivery is perhaps the least invasive method of delivering drugs, it is a route that the patient understands and accepts. For the manufacturer, solid oral dosage forms offer many advantages: they utilize cheap technology, are generally the most stable forms of drugs, are compact and their appearance can be modified to create brand identification. Tablets and capsules are also very versatile. It is beyond the scope of this chapter to cover all these dosage forms, instead it will review the common principles, with more specific detail being given for those most commonly used. For drugs that demonstrate good oral bioavailability and do not have adverse effects on the gastro-intestinal (GI) tract, there may be very little justification for attempting to design a specific drug delivery system. It is likely, therefore, that tablets and capsules will continue to remain one of the most used methods of delivering drugs to the patient in the future. This chapter reviews the science behind the development of solid dosage forms, particularly tablets and hard gelatin capsules. Solid dosage forms are one of the most widely.

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Immediate Release Dosage Form [2,3]

An immediate release dosage form allows a manufacturer to extend market exclusivity, while offering patients a convenient dosage form or dosage regimen. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities. Superdisintegrants are first choice of excipients which are extensively used for the formulation development of the immediate release tablets as they effectively result into the immediate disintegration, release and absorption of the drug after administration into the body.

MATERIALS AND METHODS [6,7,8,9]

Fexofenadine hydrochloride was from Glenmark Generics Limited, Gujarat, Sodium Lauryl Sulphate, Microcrystalline cellulose, Croscarmellose sodium, Crosspovidone, Sodium Saccharine, Talc, Pearlitol sd 200 received from Research-Lab Fine chem. Industry, Mumbai.

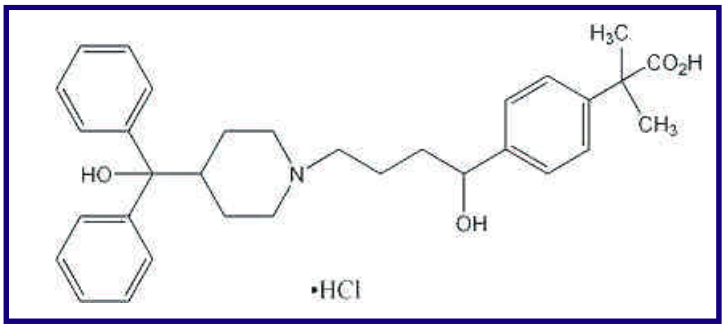

Fig. 1 - Chemical Structure of Fexofenadine Hydrochloride

Preparation of standard calibration curve of Fexofenadine HCl.

Fexofenadine HCl showed maximum absorption at wavelength 223 nm in 0.001 N HCl. Standard curve was plotted by taking absorption of diluted stock solution (2, 4, 6, 8, 10, 12) at wavelength 217 nm.

Table 1: Standard calibration curve of Fexofenadine HCl

Sr. No.	Concentration (mg/ml)	Absorbance at 217 nm
1.	2	0.126
2.	4	0.204
3.	6	0.272
4.	8	0.339
5.	10	0.411
6.	12	0.492

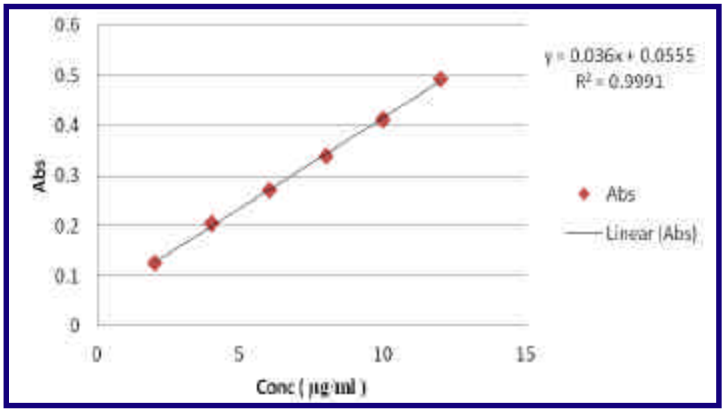

Fig 2 - Standard calibration curve of Fexofenadine in 0.001 N HCl

EXPERIMENTAL WORK:

API Characterization:

Melting Point:

Melting point of API was determined by glass capillary method.

Solubility:

The solubility of Fexofenadine HCl was checked in different solvents like water, methanol, ethanol & chloroform.

UV-Visible spectrophotometric study:

The UV spectrum of Fexofenadine HCl solution in 0.001 N HCl (pH 6.8) was scanned in the range of 400 nm to 200 nm.

Preparation of test solutions:

Preparation of 0.1N Hydrochloric acid (pH 1.2):

0.85 ml of concentrated hydrochloric acid was taken and then diluted with distilled water up to 1000 ml and remove 100 ml and diluted with distilled water up to 1000 ml. (Indian Pharmacopoeia, 1996).

Determination of λ max:

Fexofenadine (10 mg) was accurately weighed and dissolved in 100 ml of 0.00 1 N HCl to give a stock solution of concentration 100µg/ml. This was the primary stock solution of 100µg/ml. It was shaken to get the drug dissolved. UV spectrum was recorded in the wavelength range 400-200nm.

Preparation of standard curve of Fexofenadine in 0.001N HCl (pH 6.8):

Aliquots (0.2, 0.4, 0.6, 0.8, 1.0, 1.2 ml) from standard solution of Fexofenadine HCl were pipette out in 10 ml volumetric flasks and the volume was made up to 10 ml with 0.001N HCl. The absorbance was measured at 217 nm against reagent blank. The calibration curve was constructed by plotting absorbance v/s concentration (mg/ ml).

Dissolution Study:

All the ratios of Drug-PEG 4000 solid dispersions prepared were characterized by Dissolution studies. In-vitro dissolution study of the formulations prepared was performed using USP (Type-II) apparatus at a speed of 50 rpm. Dissolution study was carried out using 900 ml of 1% 0.001N HCL as dissolution medium maintained at temperature of 37°C ±5ºC. At appropriate intervals, 10 ml of the solution was taken and dissolution medium was replaced by 10 ml of fresh dissolution fluid to maintain constant volume. The samples were then analyzed at 217 nm by UV/visible spectrophotometer using 0.001N HCL as blank. The mean of three determinations was used to calculate the drug release from each of the formulations.

Precompression parameter study [10,11]

Angle of repose

Angle of repose is defined as the maximum angle possible between

the surface of pile of powder and horizontal plane. The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation (Aulton, 2003).

Tan = H / R.....Equation I

Where, H = Pile height and R = Radius of Pile

Therefore; **= tan –1 H / R**

Table 2: Relationship between angle of repose and flowability

Angle of repose (q)	Flowability
< 20 Excellent	Excellent
20-30	Good
30-34	Acceptable
> 40	Very poor

Bulk density

The sample equivalent to 25g was accurately weighed and filled in a 100 ml graduated cylinder and the powder was leveled and the unsettled volume, V_O was noted. The bulk density was calculated by the formula (Lachman *et al*, 1991)

Bulk density (?o) = M/Vo.....Equation II

Where,

M = mass of powder taken

Vo = Apparent unstirred volume

Tapped density

The tapped density was determined by mechanically tapping the measuring cylinder and the volume was noted (Lachman *et al*, 1991)

Tapped density (rt) = M / Vt.....Equation III

Where,

ρt = tapped density

M = weight of granules

Vt = tapped volume of granules in cm^3

Compressibility index

The bulk volume and tapped volume was measured and compressibility index was calculated using the formula (Aulton, 2003).

Compressibility index =100 (Vo-Vf)/Vo.....Equation IV

Where,

Vo = Bulk volume

Vf = Tapped volume

Table 3:- Relationship between % compressibility and flowability

Compressibility	Flowability
5-15	Excellent
12-16	Good
18-21	Fairly
23-35	Poor
33-38	Very pure
>40	Extremely

Hausner's ratio

Tapped volume and bulk volume were measured and the hausner's ratio was calculated using the formula

Hausner's ratio = Vo/Vf.....Equation V

Where, Vo = Bulk volume

Vf = Tapped volum

Table 4:- Hausner's ratio & Type of flow.

Hausner's ratio	Type of flow
<1.25	Good flow
1.25 - 1.5	Moderate
>1.5	Poor flow

Preparation of fast dissolving tablets by direct compression technique:

Method: Fast dissolving tablets of Fexofenadine HCl were prepared by direct compression method according to the formula.

Table 5:- Composition of formulation F1-F10

Ingredients	Batch & Quantity in mg									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Fexofenadine HCl	30	30	30	30	30	30	30	30	30	30
Crosscarmellose sodium	2.4	4.8	7.2	9.6	12	-	-	-	-	-
Crospovidone	-	-	-	-	-	2.4	4.8	7.2	9.6	12
MCC PH-102	80.6	78.2	78.8	72.6	70.2	80.6	78.2	78.8	72.6	70.2
Pearlitol sd 200	30	30	30	30	30	30	30	30	30	30
Sodium saccharin	4	4	4	4	4	4	4	4	4	4
Sodium lauryl sulphate	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2

All the ingredients were passed through 60 # sieve separately, Crospovidone & Talc through 40 #. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed with 7 mm sizes flat round punch to get tablet using Rimek Compression Machine.

Post compression parameter study [12,13,14,15]

Thickness

The thickness of the tablets was determined using a Vernier caliper. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm. (Lachman *et al*, 1991)

Hardness

The resistance of tablets to shipping, breakage, under conditions of storage, transportation and handling before usage depends on its hardness. For each formulation, the hardness of 6 tablets was determined using the Monsanto Hardness Tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted (Lachman *et al*, 1991).

Friability

Friability is the measure of tablet strength. Roche Friability or was used for testing the friability using the following procedure. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre weighed 6 tablets was placed in Roche friability or which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1 % in weight in generally considered acceptable.

Percent friability (% F) was calculated as follows (Lachman *et al*, 1991).

$$\% F = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100 \quad \text{—Equation VI}$$

Weight variation test

To find out weight variation, 20 tablets of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight. (Indian pharmacopoeia, 1996).

Table 6:- Specifications for tablets as per Pharmacopoeia of India

Sr .No.	Average Weight of Tablet	% Deviation
1	80 mg or less	10
2	More than 80 mg but less that 250 mg	7.5
3	250 or more	5

Uniformity of drug content:

Five tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 50 mg of Fexofenadine HCl was weighed and dissolved in 100 ml of 0.001N HCl (pH 6.8). This was the stock solution from which 0.2 ml sample was withdrawn and diluted to 10 ml with 0.001N HCl. The absorbance was measured at wavelength 217 nm using double beam UV-Visible spectrophotometer. Content uniformity was calculated using formula.

% Purity = 10 C (Au / As) ———Equation VII

Where, C - Concentration,
Au and As - Absorbance's obtained from unknown preparation and standard Preparation respectively.

Wetting time

The method was applied to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small Petri dish (i.d. = 6.5 cm) containing 10 ml of water, a tablet was placed on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined.

In vitro disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. I.P. Specifications: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using distilled water maintained at 37° ± 2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the 0.001 N HCL maintained at 37° ± 2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

In vitro dissolution studies

Dissolution rate was studied by using USP type-II apparatus (50 rpm) using 900 ml 1% SLS of 0.001 N HCL as dissolution medium. Temperature of the dissolution medium was maintained at 37 ± 0.5°C, aliquot of dissolution medium was withdrawn at every 5 min interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 217 nm and concentration of the drug was determined from standard calibration curve.

In vitro drug release studies details

- Apparatus used : Electrolab USP PADDLE II
- Dissolution medium : 0.001 N HCL of 1% SLS
- Dissolution medium volume : 900 ml

- Temperature : 37 ± 0.5°C
- Speed of basket paddle : 50 rpm
- Sampling intervals : 5 min
- Sample withdraw : 10 ml
- Absorbance measured : 217 nm

RESULTS AND DISCUSSION

A) l max Determination of Fexofenadine

The UV spectrum of Fexofenadine in 0.001 N HCl scanned in the range of 400-200 nm. The spectrum indicated that the observed λ_{max} of Fexofenadine is 217 nm which is matched with pharmacopoeial value.

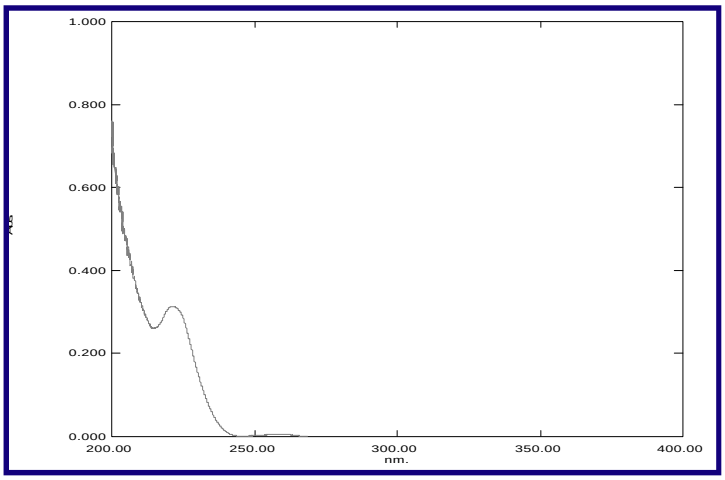

Fig No. 2 : UV Spectra Of Fexofenadine HCl

Infrared Spectroscopy:

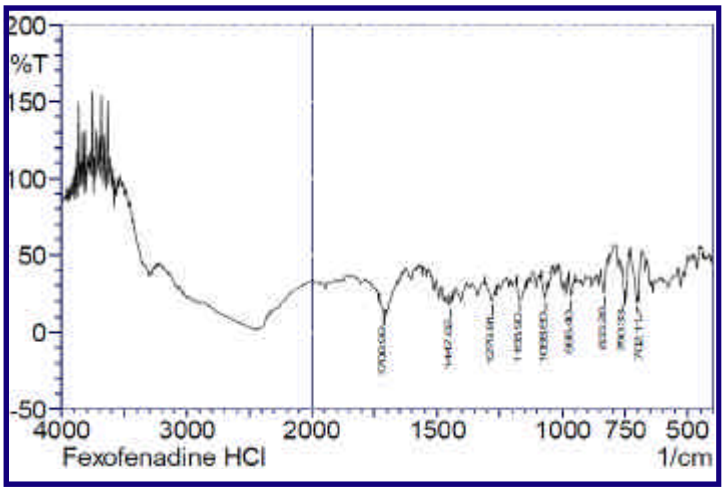

Fig 4- FT-IR Spectrum of Fexofenadine HCl

Table 7:- Interpretation of FT-IR of Fexofenadine

Peak (cm-1)	Chemical group
1709	C-O stretching of Carboxylic
1279	C-N stretching of Tertiary amine
3301	N-H stretching of Amine

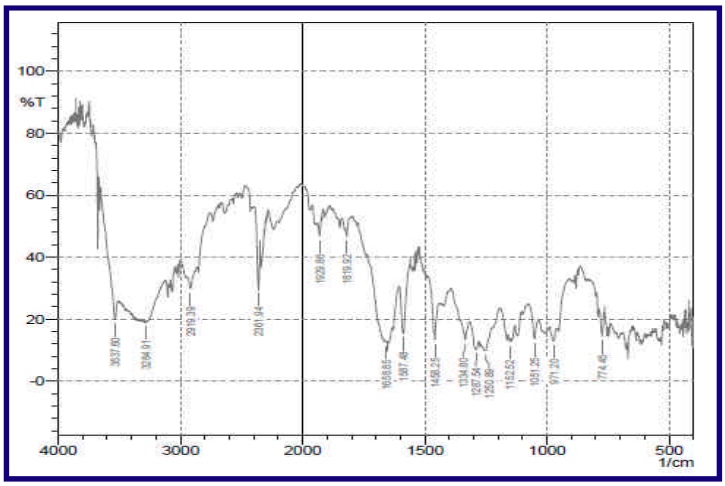

Fig 5- FT-IR Spectrum of Mixture

Infrared Spectroscopy Result:

The result revealed that there was no significant interaction between the drug and the excipients used. The IR spectrum did not show presence of any additional peaks for new functional groups indicating no chemical interaction between Fexofenadine HCl and the used excipients. The observed peaks along with assignment of functional groups to the peak are in table 7.

Evaluation Parameters of Immediate Release Tablets of Fexofenadine

Table 8 : Results of pre-compression parameters

Batch code	Angle of Repose ($_q$) ± SD	Bulk density (g/cc) ± SD	Tapped density (g/cc) ± SD
F1	18.26±0.27	0.961±0.010	1.041±0.0069
F2	21.80±0.17	0.988±0.0057	1.146±0.0080
F3	13.49±0.17	0.968±0.0051	1.136±0.0075
F4	10.59±0.18	0.925±0.005	1.086±0.0075
F5	15.21±0.17	0.925±0.0051	1.041±0.008
F6	21.40±0.18	0.9430±0.004	1.063±0.0069
F7	9.64±0.21	0.961±0.0051	1.077±0.0075
F8	10.21±0.12	0.925±0.0046	1.028±0.0046
F9	10.28±0.15	0.976±0.0043	1.030±0.0040
F10	14.24±0.19	0.987±0.0049	1.090±0.0089

Batch code	Carr's index (%) ± SD	Hausner's Ratio ± SD
F1	7.684±0.6870	1.083±0.0098
F2	13.78±0.2078	1.159±0.0028
F3	14.78±0.2251	1.173±0.0028
F4	14.82±0.1501	1.175±0.0023
F5	11.14±0.2771	1.125±0.0034
F6	11.28±0.1443	1.127±0.0023
F7	10.77±0.1962	1.120±0.0028
F8	10.01±0.230	1.111±0.008
F9	12.05±0.241	1.123±0.005
F10	13.64±0.453	1.187±0.060

values are mean ± SD, n=3

Evaluation of Post-Compression parameters of Fexofenadine Immediate Release Tablets

Table 9: Results of Post-Compression parameters of Fexofenadine Immediate Release Tablets

Batch code	Weiht variation (mg) ±SD	Thickness (mm) ±SD	Hardness (kg^2cm) ±SD	Friability (%)
F1	103±0.65	2.8±0.06	2.4±0.57	0.829
F2	101±0.58	2.64±0.05	3.0±0.115	1.157
F3	101±0.45	2.81±0.17	2.60±0.1	0.985
F4	102±0.78	2.61±0.03	2.3±0.115	1.151
F5	100±0.86	2.76±0.05	2.1±0.1	0.819
F6	106±0.67	2.6±0.03	2.5±0.057	0.993
F7	103±0.65	2.95±0.10	2.2±0.057	0.988
F8	105±0.96	2.81±0.19	2.6±0.11	0.980
F9	104±0.97	2.71±0.17	2.5±0.9	0.894
F10	102±0.89	2.85±0.26	2.8±0.75	0.945

Batch code	Wetting time (sec) ±SD	In-vitro dispersion time(sec) ±SD	Water absorption ratio±SD	Drug content (%)±SD
F1	32±1.123	45±1.165	6.79±5.12	96.±0.09
F2	42±0.167	30±0.132	10.20±6.52	98.00±0.19
F3	39±0.383	53±0.07	4.90±8.937	93.01±0.19
F4	46±1	50±0.362	2.85±3.44	95.02±0.19
F5	39±0.664	40±0.09	8±3.925	96.25±0.1
F6	48±0.260	43±0.0642	3.84±3.92	97.45±0.19
F7	360.664	56±0.170	2.80±8.03	93.27±0.19
F8	450.664	58±0.723	8.57±8.93	95.60±0.09
F9	438.365	59±0.452	8.45±8.87	98.00±0.25
F10	448.153	58±0.568	10.28±6.75	99.00±0.35

In-Vitro Dissolution Studies of Fexofenadine HCl

Table 10: Result of In-Vitro Dissolution Studies Of Fexofenadine HCl

Time (mins)	% Drug Release F1	F2	F3	F4	F5
0	0	0	0	0	0
5	21.72	19.22	22.85	24.56	25.47
10	31.87	30.01	40.47	42.67	44.58
20	45.06	45.84	62.01	65.52	68.98
30	54.63	55.59	71.61	71.87	81.78
45	56.48	69.45	80.89	84.32	90.98

Time (mins)	% Drug Release F6	F7	F8	F9	F10
0	0	0	0	0	0
5	22.13	23.05	35.88	44.55	47.13
10	36.45	40.58	48.65	56.37	70.49
20	61.89	64.84	70.55	79.66	96.51
30	79.68	83.09	85.47	88.20	99.40
45	91.92	91.19	91.99	99.909	99.985

FINAL FORMULATION BATCH:

The finalized batch follows 1st order

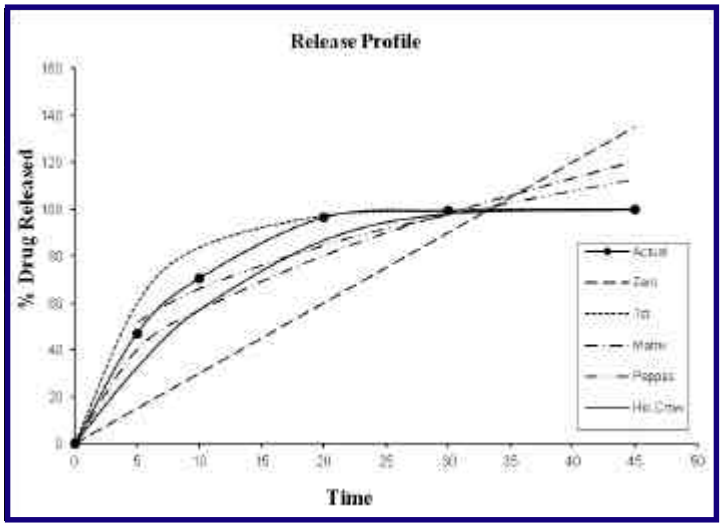

Fig 6 - First order release profile of Fexofenadine of Formulation F10

SUMMARY AND CONCLUSION

Pre-Compression Parameters

Powder ready for compression containing drug and various excipients were subjected for pre-compression parameters (Micromeritic properties) to study the flow properties of powder, to achieve uniformity of tablet weight. The results of all the pre formulation parameters are given no 8.

For each formulation blend of drug and excipients were prepared and evaluated for various parameters as explained 0.961, 0.988, 0.968, 0.925, 0.925, 0.943, 0.961, 0.925 g/cc earlier. Bulk density was found in the range of 0.9 and tapped density 1.041, 1.146, 1.136, 1.086, 1.041, 1.063, 1.077, 1.028 g/cc shown in table no 6.3. Using these two densities data compressibility index and hausner's ratio was calculated. Carr's index for all the formulations had compressibility index 7.684, 13.78, 14.78, 14.82, 11.14, 11.28, 10.77, 10.01 which indicating good flow ability of the powder blend are shown in table no-6.3. Hausner's ratio for all the formulation fall in the range of 0.083, 1.159, 1.173, 1.174, 1.125, 1.127, 1.120, 1.111, indicated good flow ability these results are shown in table no-8. The compressibility flow ability correlation data indicated an excellent flow ability of all powder blends, the good flow ability of the blend was also evidenced with angle of repose which is 18.26, 21.80, 13.49, 10.59, 15.21, 21.40, 9.64, 10.20. The results are shown in table no- 8.

Post-compression parameters:

The hardness was found to be in the range of 2.1 to 3 kg/cm^2 for all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while han-

dling. The results showed that the Thickness of the tablets was in range of 2.6 to 2.95 mm. Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately 100 mg; so the permissible limit is ± 7.5%. The results of the test showed that, the tablet weights were within pharmacopial limit. Tablets of each batch were evaluated for percentage friability and the data's were shown in Table-9. The average friability of all the formulations lies in the range of 0.829 to 1.157% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Tablets of each batch were evaluated for percentage friability and the data's were shown in Table-9. The average friability of all the formulations lies in the range of 0.829 to 1.157% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets. Wetting time is closely related to the inner structure of the tablet. The results of wetting time are shown in table no-9. The wetting time of Fexofenadine HCl tablets prepared by wet granulation method were found to be 32 to 48 sec. Tablets of each batch were evaluated for Water Absorption ratio and the data's were shown in the table no-9. The results showed that the Water Absorption ratio of prepared tablets were in the range of 6.79 to 10.20. Drug content uniformity study was carried out on the tablets of every batch and the data's were shown in the Table no-9. The content uniformity of all the formulations was found to be in the range of 93.01 to 98.00 which showed that there was uniform distribution of the drug throughout the batch. Finally, the tablets were evaluated for in vitro dissolution studies in simulated gastric fluid and the results were shown in the Table no-10. Final optimized formulation F10 showed 99.983% drug release. Formulation F10 which contain Crospovidone, the drug release at 30 mins was found to be 99.983% respectively. The formulation with Crospovidone shows more release than the tablets with MCC, Cross carmellose sodium. The experiment proves that the disintegration is also a release rate-limiting step for the drug release. The disintegrant Crospovidone shows the faster disintegration than other. So release of drug and release rate was higher from these tablets.

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