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Formulation and in vitro evaluation of fast melting tablets of Fexofenadine

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Abstract

Fexofenadine Hydrochloride is an antihistamine drug used in the treatment of hay fever and similar allergy symptoms. It does not readily pass through the blood-brain barrier and causes less drowsiness than first generation histamine-receptor antagonists. Fourteen batches of rapid dispersible tablets of Fexofenadine Hydrochloride were prepared using Cross Povidone, Cross carmellose Sodium and Sodium Starch Glycolate as Superdisintegrants in different concentrations and in different combinations by Direct Compression method. Preformulation studies of Fexofenadine Hydrochloride were performed, from the FT-IR; the interference was verified and found that Fexofenadine Hydrochloride did not interfere with the polymers used. Fexofenadine Hydrochloride formulated as Rapid Dispersible Tablets gives best results. Also negligible side effects makes it superior and effective candidate for pediatric, geriatric, bedridden and psychotic patients.

Keywords: Fexofenadine hydrochloride, Super-disintegrants, Formulation and Evaluation.

INTRODUCTION

Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure [1]. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking. Hence orally dissolving tablets have come into existence [2, 3].

To fulfill these medical needs, formulators have devoted considerable efforts for developing a novel type of dosage form for oral administration known as Rapid Dispersible Tablets (RDT). This is an innovative technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient. Fexofenadine is a second-generation, long lasting H1-receptor antagonist (antihistamine) which has a selective and peripheral H1-antagonist action. Fexofenadine Hydrochloride is a white to off-white crystalline powder. Dose is 30mg. Its chemical name is 4-[1-hydroxy-4-[4(hydroxydiphenylmethyl)-1 piperidinyl] butyl]-(alpha). Its Molecular weight is 538.13 and Emperical formula is $C_{32}H_{39}NO_4$ .HCL. Freely soluble in methanol and ethanol, slightly soluble in chloroform and water, insoluble in hexane. Bioavailability and Protein binding are 30-41% and 60-70% respectively. Half-life is 14.4hours. 80% Excretion is through feces. Unlike most other antihistamines, it does not enter the brain from the blood and therefore, does not cause drowsiness. Fexofenadine lacks the cardiotoxic potential of terfenadine, since it does not block the potassium channel involved in repolarization of cardiac cells [4].

MATERIALS AND METHODS

All the chemicals obtained and used are of analytical grade. Fexofenadine Hydrochloride, Magnesium stearate, Talc, Microcrystalline Cellulose, Cross Povidone, Sodium Starch Glycolate, Cross Carmellose Sodium, Aerosil, Mannitol, Hydroxyl propyl methyl cellulose E15 LV and Hydroxyl propyl methyl cellulose 5cps were obtained from Baris Pharmaceuticals, Hyderabad and Bright Pharmaceuticals [5].

Methods

Preparation of Oral disintegrating tablets

In the present study, the oral disintegrating tablets of Fexofenadine Hydrochloride are prepared by Direct compression method, using different polymer and concentrations.

Preparation of tablets by the direct compression technique

The steps followed in the formulation of ODT's by direct compression technique includes: Dry screening, weighing, mixing, mixing of Super Disintegrants, lubricant and glidant then compressing [6].

Procedure

All the required ingredients were passed through 40 mesh size to get uniform size particles and weighed accurately. Measured amount of drug, superdisintegrants, Avicel, sweetner and flavor except glidant and lubricant are mixed in increasing order of their weights in a mortar. To this mixture talc and magnesium stearate were added. The final mixture is manually shaken for 10mins in plastic bag. Final blend was compressed into tablets using 8mm s/c round, flat punches using Karnavathi, Rimek Compression Tablet Punching Machine [7].

Development of the formulation in the present study was mainly based on the type and concentration of polymers and properties of the drug. Various polymers in different concentrations were used so as to get tablets with good physical properties.

In the following formulations cross povidone, sodium starch glycolate and cross carmellose sodium were used in 4%, 8% and 12% concentrations each then another set of formulations were done using combinations of two superdisintegrants in different concentrations [8].

Table 1: Formulation design of Fexofenadine Hydrochloride Rapid dispersible tablets

Ingredients	T1	T2	T3	T4	T5	T6	T7	T8	T9
Fexofenadine Hyrochloride	30	30	30	30	30	30	30	30	30
Cross povidone	8	16	24	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	8	16	24			
Cross carmellose sodium	-	-	-	-	-	-	8	16	24
Magnesium stearate	2	2	2	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2	2	2	2
Microcrystalline cellulose	155	147	139	154	146	138	153	145	137
Talc	2	2	2	2	2	2	2	2	2
Mannitol	1	1	1	2	2	2	3	3	3

Evaluation

Weight variation test

Method

20 tablets were randomly selected from each formulation and their average weight was calculated using digital balance (Denver, Germany). Then individual tablets were weighed and the individual weight was compared with an average weight, the variation in the tablet was expressed in terms of %deviation.

Table 2: Limits of weight variation

Average weight of tablet	% Weight variation
130mg or less	10
More than 130mg, less than 324mg	7.5
More than 324mg	5

Thickness measurement

Method

Randomly 10 tablets were taken from each formulation and their thickness was measured using a digital screw guage, (Digimatic outside micrometer, Mitutoyo, Japan). The individual tablet was paced between two anvils of screw guage and sliding knob was rotated until the tablet was tightly fitted. The digital reading displayed was noted [9].

Hardness and Friability

Method (Hardness)

The tablet hardness of different formulations was measured using a Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet and a zero was taken [10].

The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a guage in the barrel to indicate the force. The force of fracture is recorded, and the zero force reading is deducted from it. Generally, a minimum hardness of 4 kg is considered acceptable for uncoated tablets. The hardness for ODTs should be preferably 1-3 kg.

Method (friability)

This test is performed using a laboratory friability tester known as Roche Friabilator. 10 tablets were weighed and placed in a plastic chambered friabilator attached to a motor, which revolves at a speed of 25 rpm, dropping the tablets from a distance of 6 inches with each revolution. The tablets were subjected to 100 revolutions for 4 mins. After the process, these tablets were dedusted and reweighed. Percentage loss of tablet weight was calculated [11].

Drug content uniformity

Five tablets were weighed individually and powdered. The powder equivalent to 30mg of fexofenadine hydrochloride was weighed and extracted in phosphate buffer 6.8pH and the concentration of drug was determined by measuring absorbance at 224nm by UV-Visible spectrophotometer [12].

Wetting time and water absorption ratio (R)

Method

Five circular tissue papers were placed in a Petri dish with a 10-cm diameter. Ten millimeters of water containing Eosin, a water-soluble dye, was added to the Petri dish. The dye solution is used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of tissue paper in the Petri dish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in replicated (n=6). The wetting time was recorded using a stopwatch [13].

The weight of the tablet before keeping in the Petri dish was noted (Wь) using Shimadzu digital balance. The wetted tablet from the Petri dish was taken and reweighed (W_a) using the same. The water absorption ratio, R, was determined according to the following equation:

$$\mathbf{R = 100 (W_a - W_b) / W_b}$$

Where,

W_b and W_a are the weight before and after water absorption respectively.

Disintegration Time

Disintegration time is considered to be one of the important criteria in selecting the best formulation. To achieve correlation between disintegration time In vitro and In vivo (in oral cavity) several methods were proposed, developed and followed at their convenience. One of the simple methods followed is described below [14].

Method

Disintegration time was also measured using a modified disintegration method. For this purpose, a Petri dish (10 cm diameter) was filled with 10ml of water.

Tablet was carefully put in the centre of the Petri dish and the time for the tablet to completely disintegrate into find particles was moved using a pump watch [15].

Dissolution test

Method

Drug release from RDTs was studied by using USP type-II dissolution rate test apparatus at 50rpm (USP XXIII Dissolution Test Apparatus) using 900ml of phosphate buffer pH6.8 as dissolution medium. RDTs of desired formulation were taken and placed in the vessels of dissolution apparatus. Samples were collected from the vessels at different time intervals, replenished with same volume of the blank solution and analyzed using UV-Visible spectrophotometer. Drug concentration was calculated from the standard graph and expressed as % of drug dissolved or released. The release studies were performed in replicates and means values were taken [16].

Table 3: Details of *in vitro* drug release study

Apparatus used	**USP XXIII dissolution test apparatus**
Dissolution Medium	6.8 pH Phosphate buffer
Dissolution Medium Volume	900ml
Temperature	37±0.5ºC
Speed Of Paddle	50rpm
Time Intervals	2,5,10,15,30,45,60mins
Sample Withdrawn	5ml
Absorbance Maximum λ_{max}	224nm

Stability Studies

Stability of a drug is defined as the ability of a particular formulation, in a specific container, to maintain its physical, chemical, therapeutic and toxicological specifications.

The purpose of stability testing is to provide evidence on how the quality of a drug substance varies with time under the influence of variety of environmental conditions and enables recommended storage conditions, re-test periods and shelf lives to be established.

RESULTS AND DISCUSSIONS

Preformulation studies

Determination of solubility

It was observed that it is sparingly soluble in water and chloroform, completely soluble in ethanol and methanol and insoluble in hexane.

Determination of drug polymer compatibility studies using FTIR

Drug excipient interactions play a crucial role with respect to the stability and potency of the drug. FTIR techniques have been used to study the physical and chemical interaction between the drug and excipients used.

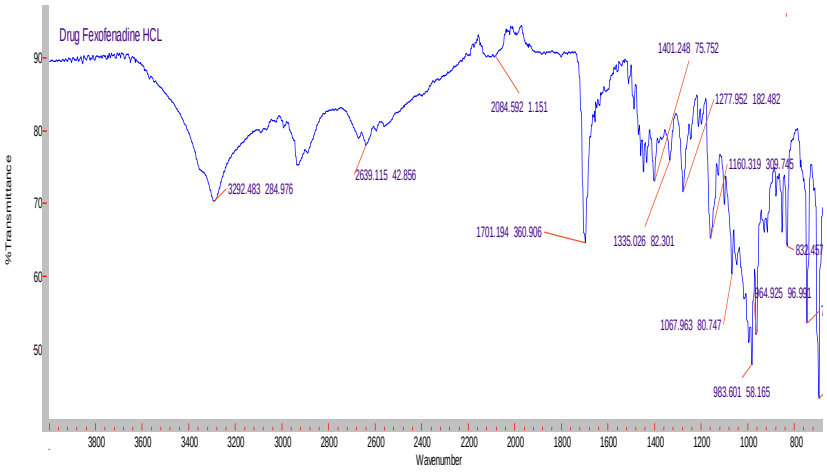

Fig 1: FT-IR spectra of Fexofenadine Hydrochloride

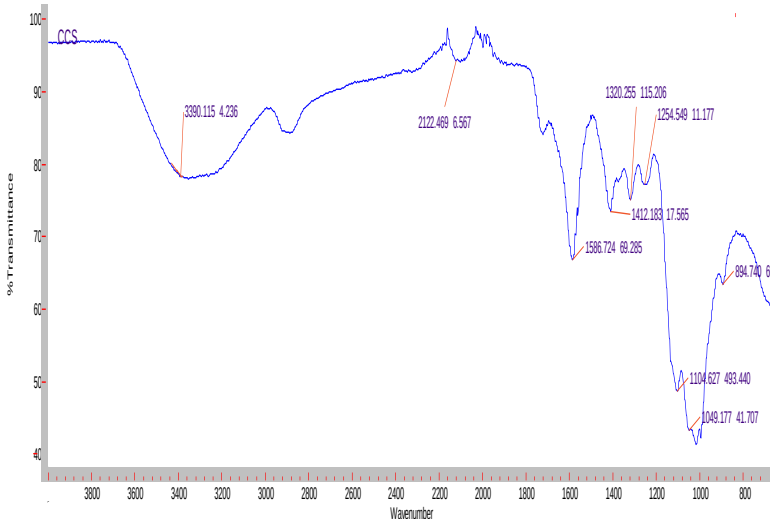

Fig 2: FT-IR spectra of Cross carmellose Sodium

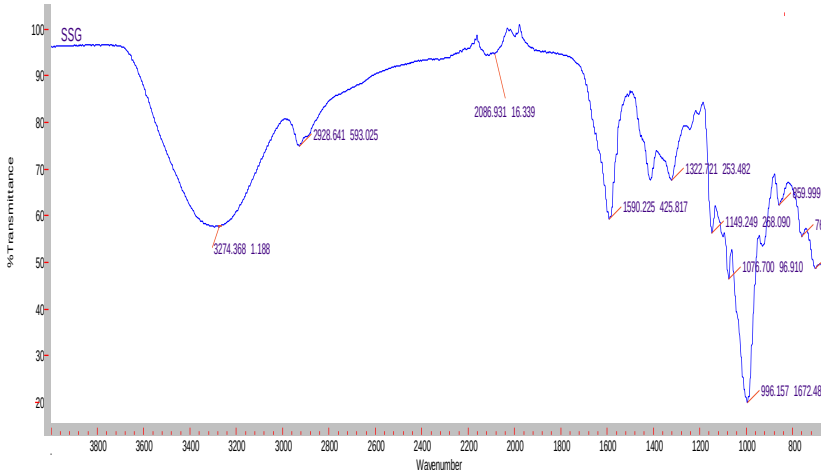

Fig 3: FT-IR spectra of Sodium Starch Glycolat

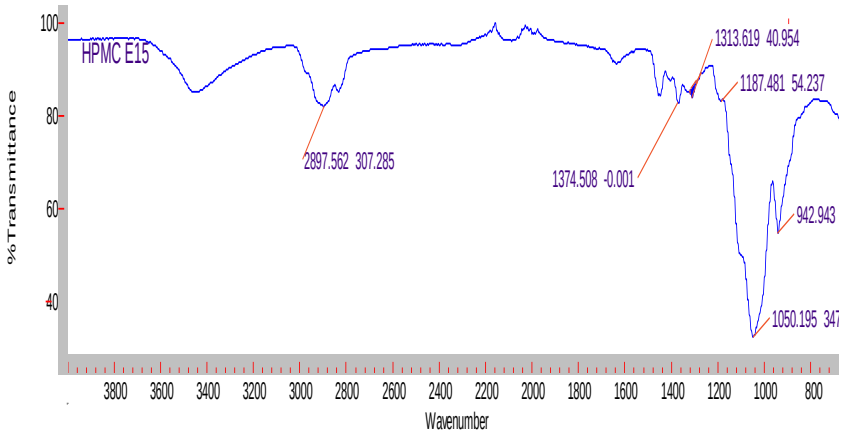

Fig 4: FT-IR spectra of HPMC K 15

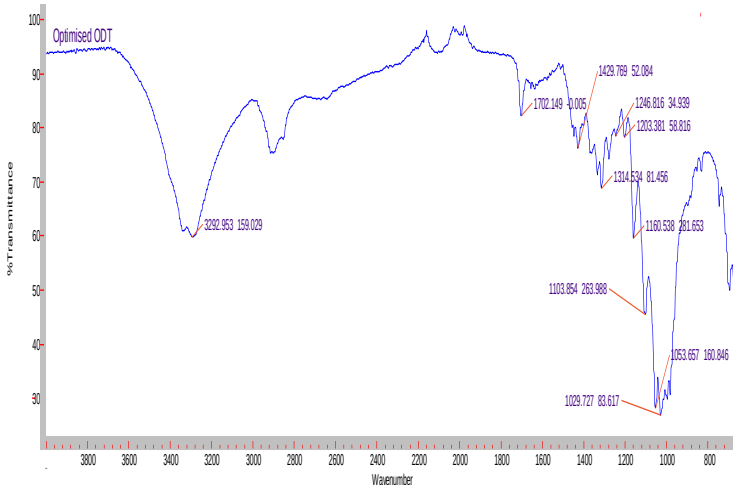

Fig 5: FT-IR spectra of optimized RDTof Fexofenadine Hydrochloride

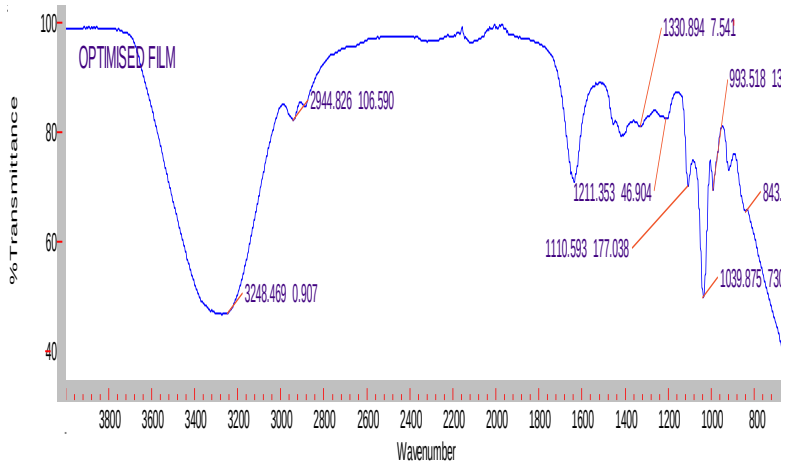

Fig 6: FT-IR spectra of optimized RDF of Fexofenadine Hydrochloride

Determination of absorption maximum λ_{max}

In the preformulation study, it was found that the λ_{max} of Fexofenadine hydrochloride by spectrophotometric method in 6.8pH phosphate buffer was found to be 224nm.

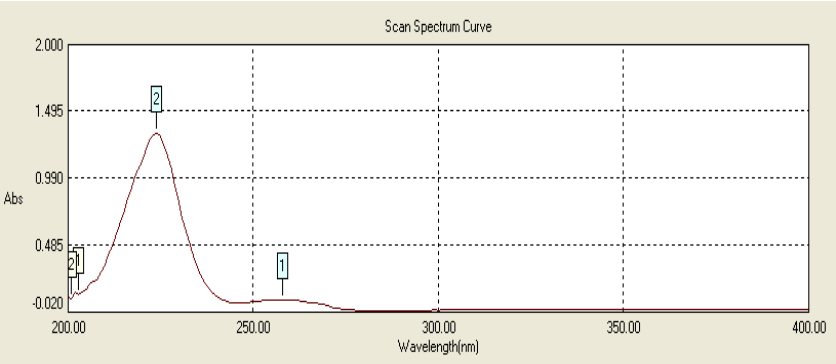

Fig 7: λ_{max} of Fexofenadine Hydrochodride in 6.8pH phosphate buffer

Pre-compression parameters

Table 4: Evaluation of the flow properties of powder blend for formulations T-1 to T-9

S. No	Formulations	Angle of repose (θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio
1	T1	21.43	0.65	0.72	10.22	1.11
2	T2	20.55	0.69	0.79	12.65	1.14
3	T3	21.45	0.69	0.81	14.81	1.17
4	T4	20.67	0.70	0.82	14.63	1.17
5	T5	20.84	0.64	0.72	11.11	1.12
6	T6	20.82	0.64	0.73	12.32	1.14
7	T7	22.29	0.65	0.74	12.16	1.13
8	T8	22.32	0.71	0.83	14.45	1.16
9	T9	21.27	0.70	0.80	12.50	1.14

Post compression studies

Table 5: Evaluation of tablets for weight variation, thickness, hardness and friability

S. No	Formulations	*Weight variation (mg)	*Thickness (mm)	*Hardness (kg/cm^2)	Friability (%)
1	T1	199.10±0.20	2.38±0.03	2.56±0.13	0.45
2	T2	201.09±0.33	2.47±0.01	2.52±0.11	0.53
3	T3	198.80±0.34	2.5±0.02	3.46±0.25	0.49
4	T4	200.33±0.76	2.46±0.04	3.32±0.21	0.57
5	T5	200.34±0.48	2.38±0.12	2.91±0.15	0.68
6	T6	201.67±0.27	2.5±0.02	2.96±0.17	0.62
7	T7	200.43±0.71	2.33±0.14	3.46±0.25	0.51
8	T8	200.19±0.21	2.5±0.02	3.05±0.21	0.63
9	T9	199.26±0.20	2.4±0.02	3.04±0.21	0.65

*Values expressed as mean±SD, n=3

Table 6: Evaluation of the disintegration time, wetting time and water absorption ratios

S. No	Formulations	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio
1	T1	22	20	109
2	T2	20	18	100
3	T3	18	16	96
4	T4	38	36	97
5	T5	26	23	87
6	T6	19	22	107
7	T7	60	57	108
8	T8	55	50	99
9	T9	30	25	95

Table 7: Percentage Cumulative drug release of tablets in 6.8pH phosphate buffer

Time (min)	T1	T2	T3	T4	T5	T6	T7	T8	T9
2	30.67	43.65	50.36	33.12	68.85	56.3	64.05	69.02	70.15
5	39.15	58.05	64.2	46.24	87.75	61.4	71.95	73.15	82.05
10	50.9	76.95	76.11	66.1	90.1	84.65	74.4	86.75	86.6
15	67.06	87.15	83.49	74.94	99.2	89.7	87.95	91.85	90.2
30	84.23	91.5	100.01	96.8	98.57	98.1	96.45	96.6	96
45	91.35	97.65	101.55	102.4	102.15	101.3	101	101.15	102.35
60	98.84	101.3	104.2	-	-	-	-	105.2	-

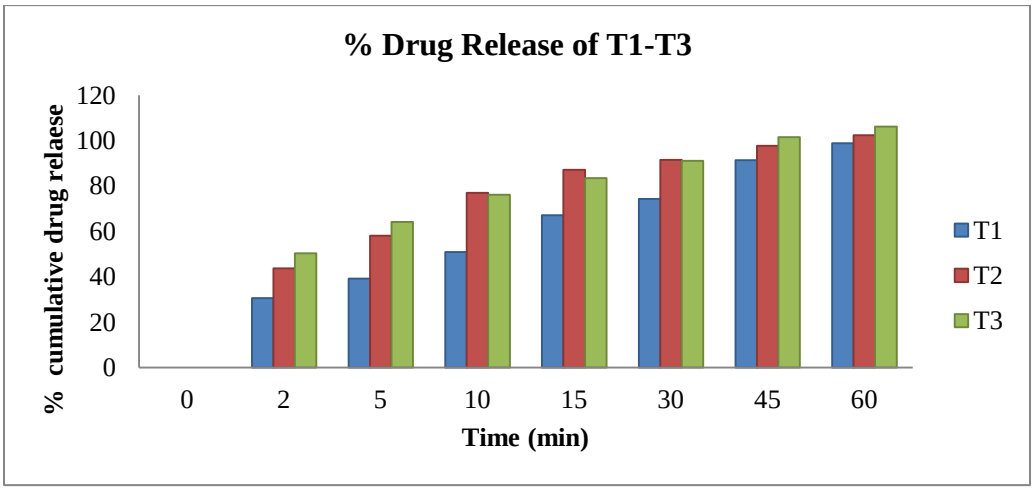

Fig 8: Cumulative percentage drug release of T1-T3 with Cross Povidone

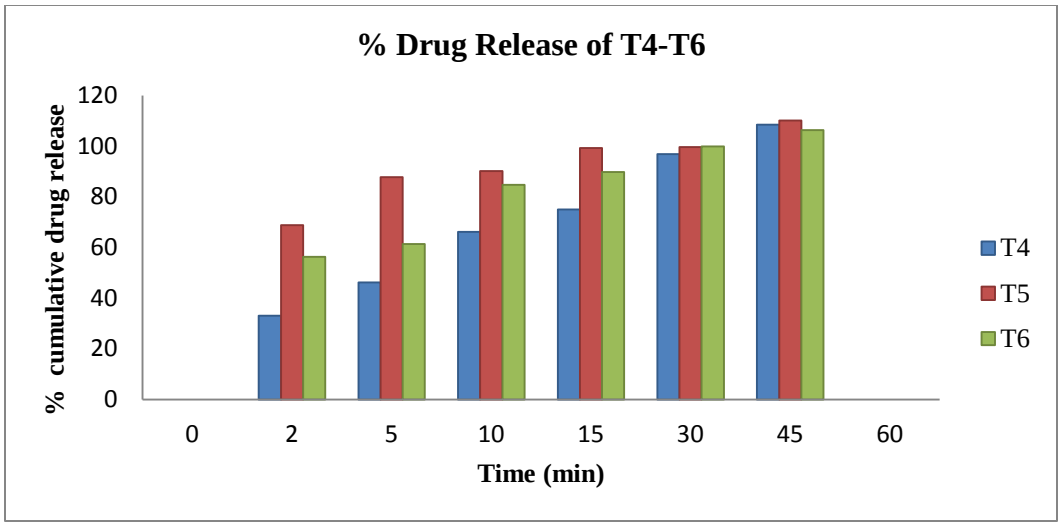

Fig 9: Cumulative percentage drug release of T4-T6 with Sodium Starch Glycolate

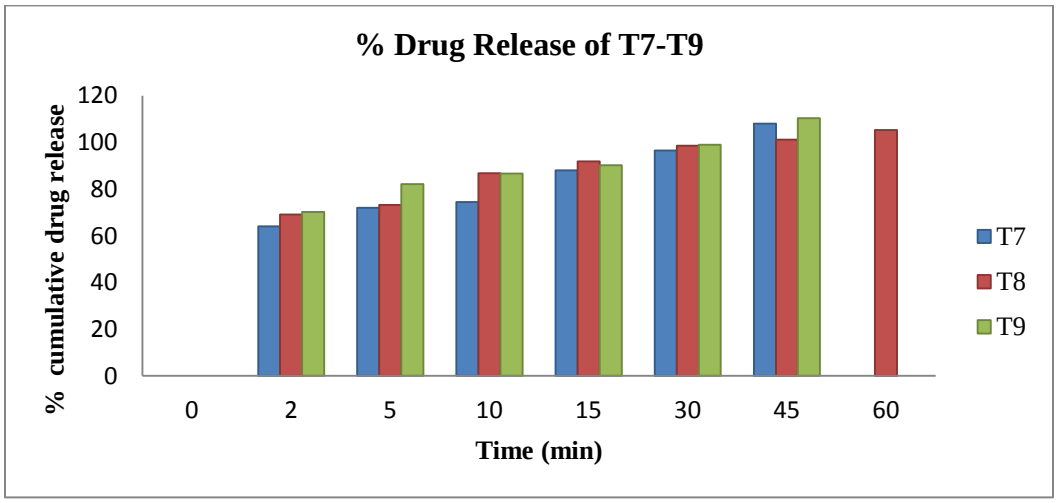

Fig 10: Cumulative percentage drug release of T7-T9 with Cross Carmellose Sodium

Comparison with marketed product

Brand Name: Allegra

Table 8: Comparison of Percentage Cumulative drug release of Optimized formulation (F13) of Fexofenadine Hydrochloride and the marketed tablet

Time (min)	% Cumulative Drug Release	
	T13	Marketed Tablet
2	99.63	69.3
5	99.82	76.95
10	99.91	82.55
15	100.62	94.69
30	101.83	99.99
45	102.94	100.26
60	103.56	101.49

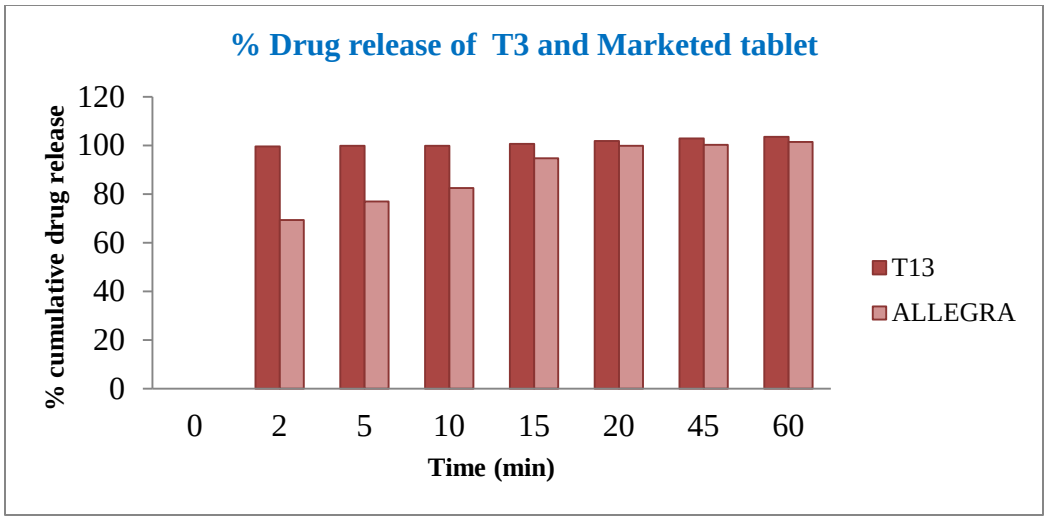

Fig 11: Comparison of percentage drug release between optimized and marketed formulation

Accelerated Stability Studies

Table 9: Accelerated Stability Study data of Optimized Formulation

Stability Period	% Drug Content	% In vitro Release
Initial	98±0.05	100±0.01
30 Days	97±0.86	99±0.24
60 Days	97±0.64	99±0.18
90 Days	97±0.02	99±0.05

*Values expressed as mean±SD, n=3

Oral disintegrating drug delivery system have an advantage over the conventional drug delivery system in pediatric, elderly, bed ridden, mentally retarted and patients suffering with dysphagia. As these kind of patients need special attention and monitoring, in the present study an attempt has been made to formulate and evaluate Rapid Dispersible tablets and films of Fexofenadine Hydrochloride by Direct Compression method using different superdisintegrants in different concentrations.

Solubility, Determination of of λ_{max}, Construction of calibration curve, Drug polymer compatibility studies

The solubility of Fexofenadine Hydrochloride reveals that it is sparingly soluble in water and chloroform, completely soluble in ethanol and methanol and insoluble in hexane.

In the Preformulation studies, the lambda max of Fexofenadine Hydrochloride was determined by Spectroscopic Method and it was found to be 224nm with 6.8pH phosphate buffer.

In this study at 224nm in 6.8pH phosphate buffer had good reproducibility in the concentration between 10-50µg/ml. Correlation between concentration and absorbance was found to be closer to 1 indicating that the method obeyed Beer-Lambert's Law.

Fourier-Transformed Infrared (FTIR) Spectrophotometer technique has been used to study the physical and chemical interaction between the drug and excipients used.

Table 10: FT-IR data interpretation

S. no	Formulations	Wave number in formulation (cm^{-1})	Characteristic wave number range(cm^{-1})	Bond nature and bond attributed
1	Pure drug	3292.48	3200-3400	NH stretching (2° amine)
2	CCS	1586.72	1400-1600	C=C ring stretch Benzene
3	SSG	3274.36	3200-3400	OH stretching (Bonded)
4	HPMC E 15	2897.56	2800-3000	C-H aldehyde stretching
5	Optimized Tablet	1702.14	1600-1800	C=O ketone stretching
6	Optimized Film	1039.87	1020-1250	C-N aliphatic stretching

The FT-IR spectrum of pure drug and different excipients and the optimized tablet and film formulation were studied. There was no significant difference between the absorption peaks of pure drug and optimized formulation. The results concluded that there was no interaction between pure drug and excipients.

Angle of repose, Bulk density, Tapped density, Carr's compressibility index and Hausner's Ratio

The angle of repose for the formulation blend was carried out and the results were shown. It can be concluded that the angle of repose for all formulation blends was obtained in the range of 20.02 to 22.32 thus falling in the range of official limits 25-30 (good flow). Hence all formulation blends possess good flow property.

Bulk density of the formulation blend plays an important role in the compression of the powder. Bulk density was carried out and the results were shown. The bulk density of the formulations was found to be in the range of 0.64g/cm^3 to 0.71g/cm^3.

Tapped density also plays an important role in knowing the compressibility of the formulation blend. It was found to be in the range of 0.72g/cm^3 to 0.83g/cm^3. It was noted that the tapped density of all the formulations were greater than their respective bulk density thus indicating that all the powder formulation had a good compressibility.

Carr's consolidation index was carried out and the results were shown. The CCI was calculated based on bulk density and tapped density. It was found to be in the range of 10.22 to 14.81 indicating that all formulation blends possess good flow property for compression.

Hausner's ratio is the ratio between tapped bulk density and loose bulk density. Hausner's ratio was calculated for all formulation blends and reported. All formulations having Hausner's ratio < 1.25

Weight variation, Thickness, Hardness, Friability, Disintegration Time, Water absorption ratio and Wetting time

The % weight variation was calculated for all formulations. All the formulations passed the weight variation test as the percentage weight variation was within the pharmacopoeia limits. The weights of all formulations were found to be uniform with low standard deviation values.

Thickness of all the formulations was found to be 2.33±0.14 to 2.52±0.03mm with low standard deviation values.

The crushing strength of the uncoated tablets of each batch ranged between 2.52±0.11 to 3.46±0.25 kg/cm^2. This ensures good handling characteristics of all batches.

The values of friability test were in the range from 0.45 to 0.69%. The percent friability of all the formulations was less than 1% ensuring that the tablets were stable.

The values of the disintegration time found in the range 10 to 60 seconds.T13 formulation was found to have less disintegration.

The formulations prepared shows water absorption ratio in the range 87-109%, formulations containing less superdisintegrant shows lower water absorption ratio when compared formulations containing more superdisintegrants, the water absorption ratio also decreases due to less swelling property.

Wetting time is closely related to the inner structure of the tablet. Promising formulations T13

and F3 showed a wetting time of 8 and 14 seconds respectively which facilitates faster dispersion in the mouth.

In vitro drug release studies

The in vitro drug release study plays an important part in the selection of best formulation among all. The in vitro drug release study for tablets of Fexofenadine Hydrochloride was carried out in 6.8pH phosphate buffer as a diffusion medium. The drug release from the formulation increased as the concentration of the super disintegrant increased.

Stability Studies

The selected formulation T3 was subjected to stability studies and the formulation was evaluated for physical parameters like size, colour, hardness, thicknesses were same. The percentage drug content and % cumulative drug release was tested at 30 days, 60 days and 90days, there were no significant changes in the values.

CONCLUSION

Rapid dispersible tablets of fexofenadine hydrochloride were prepared using cross povidone, cross carmellose sodium and sodium starch glycolate as superdisintegrants in different concentrations by Direct Compression method. Preformulation studies of Fexofenadine Hydrochloride were performed, from the FT-IR, the interference was verified and found that polymers did not interfere with the drug. Finally, it can be concluded that Fexofenadine Hydrochloride can be formulated as Rapid Dispersible Tablets successfully and gives best results. Also negligible side effects makes it superior and effective candidate for pediatric, geriatric, bedridden and psychotic patients.

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