EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 3
257-270
Year: 2021

DESIGN AND EVALUTION OF SUSTAINED RELEASE ENTERIC COATED DOSAGE FORM OF FLUOXETINE HYDROCHLORIDE

***V. Mounika and A. Kiran Kumar**

Pharmaceutics, Sahasra Institute of Pharmaceutical Sciences, Hasanparthy Mandal, Vangapahad Village, Warangal, Telangana India.

***Corresponding Author: V. Mounika**
Pharmaceutics, Sahasra Institute of Pharmaceutical Sciences, Hasanparthy Mandal, Vangapahad Village, Warangal, Telangana India.
DOI: https://doi.org/10.17605/OSF.IO/MWZ3H

Article Received on 05/01/2021 **Article Revised on 25/01/2021** **Article Accepted on 15/02/2021**

ABSTRACT
An enteric coating is a barrier that controls the location of oral medication in the digestive system where it is absorbed. The word "enteric" indicates small intestine. Therefore enteric coatings will prevent the release of medication before it reaches the small intestine. Preformulation studies have been performed to study the nature of API and compatibility of API with excipients by physical observation and FT-IR studies. The results showed that there was no interaction between API and all the excipients selected. The results of micromeritic properties indicates that the flow property of all formulation were good. All formulations possessed uniform thickness. The prepared tablets also possessed good mechanical strength and uniform hardness. All formulations of Fluoxetine Hydrochloridetablets passed the weight variation, friability test and disintegration test. The percentage drug content was found in the range of 98.55% to 102.16% for all the formulations, which was within the I.P acceptable limits.In the *in vitro* dissolution study, formulation F-IV and F-V showed maximum drug release of 95.78% and 100.67% at the end of 45 min. Hence formulation F-IV and F-V were selected for enteric coating and coated with protectab enteric M1 as coating polymer in different concentration. 4% coating thickness was applied in formulation F-IV and 8% in formulation F-V. Both the formulations were evaluated for various parameters. Formulation F-IV failed in disintegration test of enteric coated tablets. So formulation F-V was taken as best formulation and the drug release of formulation F-V was compared with marketed enteric coated tablet of Duloxetine hydrochloride. In the comparative *in vitro* dissolution study, formulation F-V showed better drug release than the marketed product. Formulation (F-V) was selected for the stability study and stored at 25±2°C/60%±5% RH and 40±2ºC/75%±5%RH for 3 months. The results indicated that there was no significant change found in appearance, thickness, weight variation, disintegration time, drug content and *in vitro* dissolution study. The study results showed that the formulation F-V was stable even after stored at 25±2°C/60%±5% RH and 40±2ºC/75%±5% RH for 3 months.

KEYWORDS: Delayed release, Fluoxetine HCl, Microcrystalline cellulose-PH, Povidone-K30.

INTRODUCTION
An enteric coating is a barrier that controls the location of oral medication in the digestive system where it is absorbed. The word "enteric" indicates small intestine. Therefore enteric coatings will prevent the release of medication before it reaches the small intestine. The enteric coated polymers remain unionise at low pH and therefore remain insoluble. But as the pH increases in the GIT, the acidic functional group capable of ionisation and the polymer swells or becomes soluble in the intestinal fluid. Materials used for enteric coating includes E.g. Cellulose acetate phthalate (CAP), Cellulose acetate trimellitate (CAT), Polyvinyl acetate phthalate (PVAP), Hydroxy propyl methylcellulose phthalate (HPMCP), fatty acids, waxes, shellac and plant fibres.

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) and as the name suggests, it exerts it's therapeutic effect by inhibiting the presynaptic reuptake of the neurotransmitter serotonin. As a result, levels of 5-hydroxytryptamine (5-HT) are increased in various parts of the brain. Further, fluoxetine has high affinity for 5-HT transporters, weak affinity for noradrenaline transporters and no affinity for dopamine transporters indicating that it is 5-HT selective. IUPAC name is methyl ({3-phenyl-3-[4-(trifluoromethyl)phenoxy] propyl}) amine hydrochloride. Molecular Weight 345.78 g/mol. The melting range of fluoxetine hydrochloride is 158.4-158.9ºC. Fluoxetine hydrochloride is freely soluble in methanol and ethanol; soluble in acetonitrile, chloroform, and acetone; slightly soluble in ethyl acetate, dichloromethane, and water.

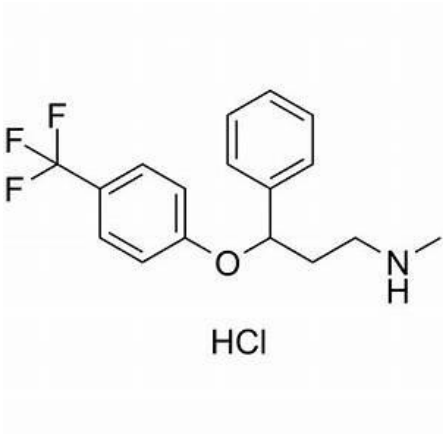

Fig 1: Chemical structure of Fluoxetine Hydrochloride.

MATERIALS

The Fluoxetine hydrochloride was supplied by MetroChem API Pvt. Ltd, Hyderabad, India, Microcrystalline cellulose-PH from Accent Microcell Pvt. Ltd, Mannitol anhydrous was purchased from Shandong Tianli Pharmaceutical Co.Ltd, Methanol was of high performance liquid chromatography (HPLC) grade. All other reagents and solvents were of analytical reagent grade

METHODOLOGY

PREFORMULATION STUDIES[1]

Preformulation is defined as a stage of development during which the physico-chemical properties of the drug substance is characterized and established. A complete knowledge of the relevant therapeutic and physico-chemical properties of the drug enables determination of its proper formulation and delivery method.

ORGANOLEPTIC PROPERTIES

The organoleptic properties like color, odor and taste of the API was evaluated.

Color: A small quantity of Floxetine HCl was taken in a butter paper and viewed in a well-illuminated place.

Taste and odor: Very less quantity of Duloxetine HCl was used to assess the taste with the help of tongue as well as smelled to get odor.

SOLUBILITY TEST[2]

Solubility of Floxetine HCl in water, methanol and ethanol was determined by using sonicator at roomtemperature.

DRUG - EXCIPIENT COMPATIBILITY STUDIES

In the tablet dosage forms the drug is in intimate contact with one or more excipients, the latter could affect the stability of the drug. Knowledge of drug-excipient interactions is very useful to the formulators in selecting appropriate excipients.

Method

Compatibility study was performed by preparing blends of different excipients with API. The blends were stored at room temperature for 30 days. Physical observation has been carried out at the initial stage, after 15 days and after 30 days. The drug excipients compatibility profiles were shown in table: 5.

Table: 1. Drug- Excipient Compatibility Study.

S.No.	Composition	Ratio (Drug : Excipient)
1.	Fluoxetine hydrochloride	1
2.	Fluoxetine Hydrochloride+ Mannitol anhydrous	1:1
3.	Fluoxetine Hydrochloride+ Calcium carbonate	1:1
4.	Fluoxetine Hydrochloride+ Microcrystalline cellulose	1:1
5.	Fluoxetine Hydrochloride+ Povidone-K30	1:1
6.	Fluoxetine Hydrochloride+ Colloidal silicon dioxide	1:1
7.	Fluoxetine Hydrochloride+ Croscarmellose sodium	1:1
8.	Fluoxetine Hydrochloride+ Magnesium stearate	1:1

FT- IR SPECTRAL ANALYSIS[3]

Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and excipients was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using hydraulic press at 10 tons pressure and scanned between 4000 - 400 cm^{-1} in a shimadzu FT-IR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

EVALUATION OF PRECOMPRESSION PARAMETERS

ANGLE OF REPOSE[4,5]

Angle of repose is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane. The angle of repose is designated by θ. It can be determined by funnel method. The powder blend was passed through funnel so that they form a pile. The height (h) of the pile and the radius of the pile (r) were measured and angle of repose was calculated using following formula.

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

Where,
θ = Angle of repose. h = Height of the pile. r = Radius of the pile.
The flow properties and corresponding angle of repose as per USP was listed in table: 6.

BULK DENSITY AND TAPPED DENSITY[6,7]
An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_0) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus (bulk density apparatus). The density apparatus was set for 100 taps and after that, the volume (V_f) was measured and the operation was continued till the two consecutive readings were equal. MEASUREMENT OF

POWDER COMPRESSIBILITY
Compressibility Index[8]
The term compressibility is the ability to reduce the volume under pressure. The compressibility index of the powder was determined by the carr's compressibility index. It is used as an indication of the flowability of a powder. A compressibility index greater than 25 is an indication of poor flowability and below 15 indicates good flowability.

Determination of Hausner's Ratio
The hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ideal range should be 1.2 - 1.5. Hausner's ratio was determined by the ratio of tapped density and bulk density. The scale of flowability was shown in table: 7.

$$\text{Compressibility index} = \frac{\square\square\square\square\square\square\ \square\square\square\square\square\square - \square\square\square\square\ \square\square\square\square\square\square}{\square\square\square\square\square\square\ \square\square\square\square\square\square\square} \times 100$$

$$\text{Hausner's ratio} = \frac{\square\square\square\square\square\square\ \square\square\square\square\square\square\square}{\square\square\square\square\ \square\square\square\square\square\square\square} \times 100$$

FORMULATION OF FLUOXETINE HYDROCHLORIDE UN COATED TABLETS
Fluoxetine Hydrochloridetablets (20 mg) were prepared by direct compression method as per the composition shown in Table: 8. Five formulations (F-I to F-V) were prepared by direct compression method. Various steps (sieving, dry mixing, lubrication and compression) involved in the tablet production by direct compression method were mentioned below.

DIRECT COMPRESSION METHOD[9]
Sieving
The active ingredient was passed through the sieve # 40. The other ingredients given in the formulation table were passed separately through the same sieve.

Dry mixing
All the materials (including the active ingredient) were taken in a poly bag and mixed for 10 minutes for uniform mixing.

Lubrication
Magnesium stearate and talc were passed through the sieve # 60 and mixed together with the powder mixture in a polybag for 5 minutes to get a uniform blend.

Compression
Finally, the powder mixture was compressed into tablets using rotary tablet compression machine of 7.14 mm round shape punches and dies.

ENTERIC COATING OF TABLETS
Seal coating
Accurately weighed ethyl cellulose was milled using colloidal mill for 20 minutes to reduce particle size and dissolved in acetone to form uniform coating solution and applied into uncoated tablets.

Moisture Prior coating
The solid material of insta coat moisture shield white was dissolved in isopropyl alcohol and then mixed with methylene dichloride and uniformly mixed by using colloidal mill for 30 minutes and then applied into uncoated tablets. This process of moisture prior coating is performed after seal coating process.

Enteric coating
Protectab enteric M1 bharath coat (methacrylic acid co polymer) powder was mixed with isopropyl alcohol. Iron oxide red was added to this solution and milled using colloidal mill to form uniform coating solution and then applied into uncoated tablets.

Polish coating

The tablets obtained are smooth and evenly colored but have a dull surface appearance. Polishing is carried out in canvas lined coating pans and the process consists of applying thin layer of waxy materials to impart shine to the finished tablets.

Packing details

The prepared tablets were packed in Alu-Alu Blister packing.

Table: 2. Composition of Fluoxetine Hydrochloride Enteric Coated Tablets.

Ingredients	Quantity per Tablet (mg) FORMULATION CODE				
	F-I	F-II	F-III	F-IV	F-V
Fluoxetine hydrochloride	20.00	20.00	20.00	20.00	20.00
Mannitol anhydrous	50.00	45.00	45.00	40.00	40.00
Microcrystalline cellulose - PH 112	45.00	45.00	35.00	30.00	30.00
Calcium carbonate	-	5.00	15.00	25.00	25.00
Povidone-K30	10.00	10.00	10.00	10.00	10.00
Croscarmellose sodium	16.00	16.00	16.00	16.00	16.00
Colloidal silicon dioxide	1.00	1.00	1.00	1.00	1.00
Magnesium stearate	3.00	3.00	3.00	3.00	3.00
Average weight of each uncoated tablet	**145.00**	**145.00**	**145.00**	**145.00**	**145.00**
Seal Coating					
Insta coat moist shield white	-	-	-	3.00	3.00
Isopropyl alcohol	-	-	-	20.00	20.00
Methylene dichloride	-	-	-	10.00	10.00
Enteric Coating					
Protectab Enteric M1	-	-	-	5.80	11.80
Isopropyl alcohol	-	-	-	30.00	60.00
Methylene dichloride	-	-	-	30.00	60.00
Ironoxide red	-	-	-	0.20	0.20
Polish Coating					
Insta coat glow	-	-	-	1.00	1.00
Isopropyl alcohol	-	-	-	3.50	3.50
Methylene dichloride	-	-	-	3.50	3.50

POST COMPRESSION PARAMETERS

The compressed tablets were evaluated for the following parameters.

GENERAL APPEARANCE

The tablets should be free from cracks, depressions, pinholes etc. The color and polish of the tablets should be uniform on whole surface. The surface of the tablets should be smooth. The tablets were examined externally under a biconvex lens for surface cracks, depressions and pinholes.

THICKNESS TEST

Thickness of the tablet was measured by using vernier caliper. Tablet thickness should be controlled within a ± 5% variation of standard value. Thickness values were expressed in millimeter.

HARDNESS TEST[10]

"Hardness is defined as the resistance of the tablet against the applied force till it breaks". Hardness (diametric crushing strength) is the force required to break a tablet across the diameter. To determine the need for pressure adjustments on the tablet compression machine, hardness can affect the disintegration. For each formulation, the hardness of 5 tablets was determined using a Monsanto hardness tester. The tablet is placed across the diameter in between the spindle and anvil. The knob is adjusted to hold the tablet in position. The pressure is increased slowly to break the tablet. The value was expressed in Kg/cm^2.

WEIGHT VARIATION TEST[11]

Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. Not more than two of the tablets weight should deviate from the average weight by more than the percentage deviation listed in the accompanying table and none should deviate from the average weight by more than twice that percentage deviation mentioned in table: 3.

Table: 3. Weight Variation of Tablets and Percentage Deviation.

Average Weight of Tablets in I.P (mg)	Percentage Deviation (%)
130 or less	± 10
130 – 324	± 7.5
More than 324	± 5

FRIABILITY[12]

Friability is the phenomenon where the surface of the tablet is damaged or shown a site of damage due to mechanical shock. It is tested by using Roche friabilator. Friabilator is made up of a plastic drum fixed with a machine which rotates at 25 rpm for 100 revolutions. Tablet falls from 6 inches height in each turn within the apparatus. The percentage friability of the tablets were calculated by the formula.

$$\text{Percentage Friability} = W1 - W2/W1 \times 100$$

Where,

W1 = Weight of tablets before testing. W2 = Weight of tablets after testing.

According to B.P/I.P = Percentage of friability should be not more than 0.8% - 1.0%.

DISINTEGRATION TEST[13]

The disintegration test was carried out according to I.P procedure on six tablets using disintegration test apparatus with disks in 0.1 N HCl (pH 1.2) maintained at $37^0C \pm 2^0C$ for 2 hours. After 2 hours 0.1 N HCl was replaced with phosphate buffer 6.8 pH. A disk was added to each tube and operated for further 60 minutes. The disintegration time of each tablet was recorded.

STABILITY STUDIES[14]

Stability is defined as the capacity of a drug substance or drug product to remain within the established specifications which maintains its identity, strength, quality and purity throughout the retest or expiration dating period. The objective of stability study is to determine the shelf life, namely the time period of storage at a specified condition within which the drug product still meets its established specifications. Stability study is of three types that is physical, chemical and microbial stability. Various factors like oxygen, water, temperature, pH, moisture, light and concentration affect the stability.

Purpose of Stability Testing[15]

The purpose of stability testing is to provide evidence of how the quality of an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) varies with time under the influence of a variety of environment factors such as temperature, humidity and light. The stability programme also includes the study of product-related factors that influences its quality, for example, interaction of API with excipients, container closure systems and packaging materials.

ACCELERATED STABILITY STUDIES[16]

Procedure

Stability studies were carried out for optimized formulation (F-V) at 25±2°C/60%±5%RH and 40±2°C/75%±5%RH for 3 months. The selected clear ALU-ALU packed formulations were stored at 25±2°C/60%±5%RH and 40±2°C/75%±5%RH for 3 months and their physical appearance, average weight, thickness, hardness, friability, disintegration test, assay and in vitro drug release were evaluated at specified intervals of time (every month).

RESULTS AND DISCUSSION

Fluoxetine Hydrochlorideis an acid labile drug which degrades in acidic environment of the stomach thus leading to therapeutic inefficiency. The present study was aimed to formulate enteric coated tablets of Fluoxetine Hydrochlorideto avoid degradation and to bypass the acidic pH of the stomach. The work was carried out to delay the release of Fluoxetine Hydrochloride by using enteric polymer. The powder blends of different fomulations were evaluated for precompression parameters such as angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The prepared tablets were evaluated for various post compression parameters such as general appearance, hardness, thickness, weight variation, friability, disintegration time and in vitro drug release study. The optimized formulation was subjected for stability study. The results were presented in appropriate tables and figures.

PREFORMULATION STUDIESDRUG – EXCIPIENTS COMPATIBILITY STUDIES

Compatibility study was performed by preparing blends of different excipients with API. The blends were stored at room temperature for 30 days. Physical observation has been carried out at the initial stage, after 15 days and after 30 days. The drug excipients compatibility profiles were shown in table: 4.

Table: 4. Drug - Excipients Compatibility Study.

S. No.	Composition	Description		
		INITIAL PERIOD	AFTER 15 DAYS	AFTER 30 DAYS
1.	Fluoxetine hydrochloride	White to off white powder	NCC*	NCC
2.	Fluoxetine Hydrochloride+ Mannitol anhydrous	White to off white powder	NCC	NCC
3.	Fluoxetine Hydrochloride+ Microcrystalline cellulose	White to off white powder	NCC	NCC
4.	Fluoxetine Hydrochloride+ Calcium carbonate	White to off white powder	NCC	NCC
5.	Fluoxetine Hydrochloride+ Povidone	White to off white powder	NCC	NCC
6.	Fluoxetine Hydrochloride+ Croscarmellose sodium	White to off white powder	NCC	NCC
7.	Fluoxetine Hydrochloride+ Colloidal silicon dioxide	White to off white powder	NCC	NCC
8.	Fluoxetine Hydrochloride+ Magnesium stearate	White to off white powder	NCC	NCC
9.	Fluoxetine Hydrochloride+ Insta coat moist shield	White to off white powder	NCC	NCC

Note: *NCC – No Characteristic Change

From the drug excipients compatibility study, it was observed that there was no characteristic change found between drug and excipients. Thus it was concluded that the excipients selected for the formulation were compatible with Fluoxetine Hydrochlorideand suitable for formulation development.

FT-IR SPECTRAL STUDIES

FT- IR studies of the pure Duloxetine hydrochloride, excipients and combination of drug and excipient was carried out to found any interaction between drug and excipients used in the formulation. FT-IR study was performed using IR spectroscopy (SHIMADZU). The I.R spectra of drug and excipients were shown in fig: 2 to 6 and in table: 6 to 10 respectively.

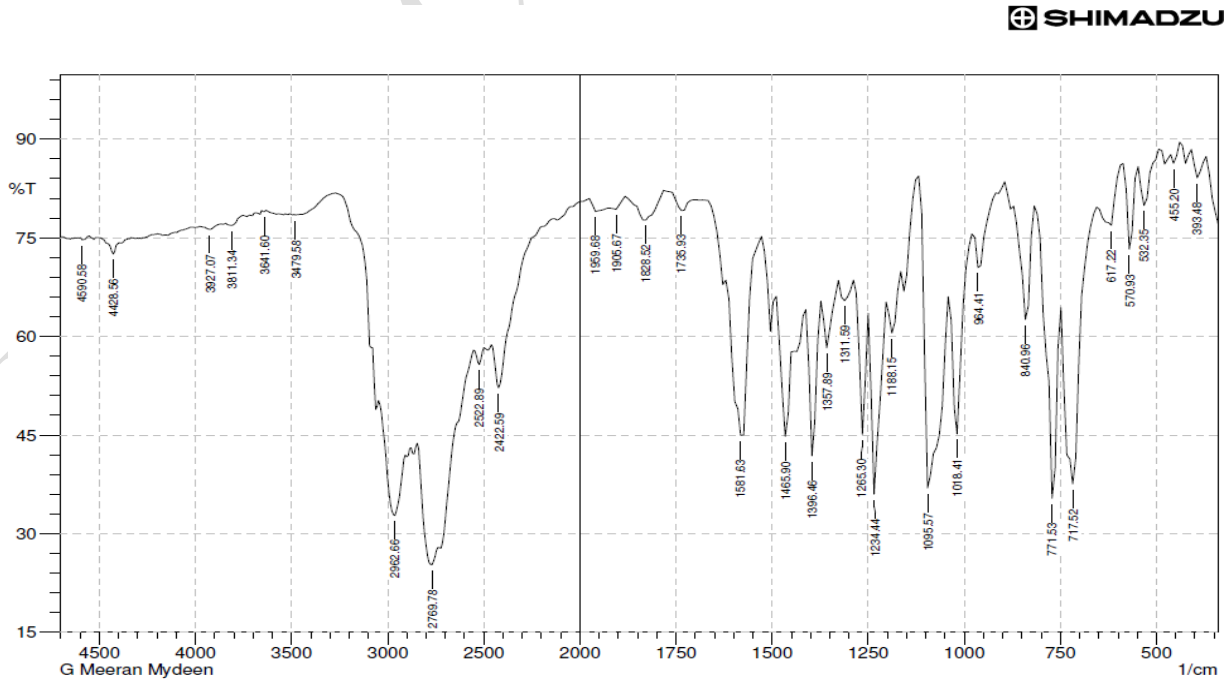

Fig: 2 FT- IR Spectrum of Pure Fluoxetine Hydrochloride.

Table: 5. FT- IR Spectral Data of Pure Fluoxetine Hydrochloride.

S. No.	Wave Number (cm^{-1})	Functional Group
1	2962	Aromatic C- H stretching
2	2769	Alkane C- H stretching
3	1581	Aromatic N- H bending
4	1465	Aromatic C = C stretching
5	1396	Alkane C- H bending
6	1234	Aromatic C - N stretching

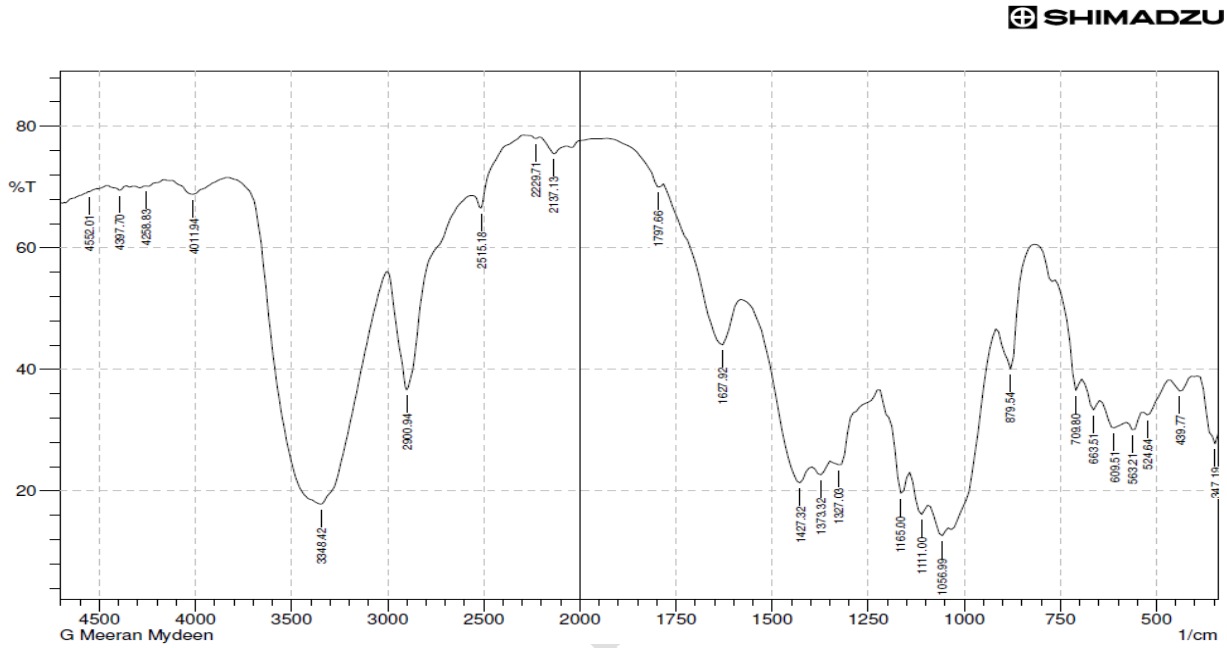

Fig: 3 FT- IR Spectrum of Croscarmellose sodium.

Table: 6. FT- IR Spectral Data of Croscarmellose sodium.

S. No.	Wave Number (cm^{-1})	Functional Group
1	3348	Alcoholic O - H stretching
2	2900	Alkane C - H stretching
3	1427	Alkane C - H bending
4	1056	Alcoholic C - O stretching

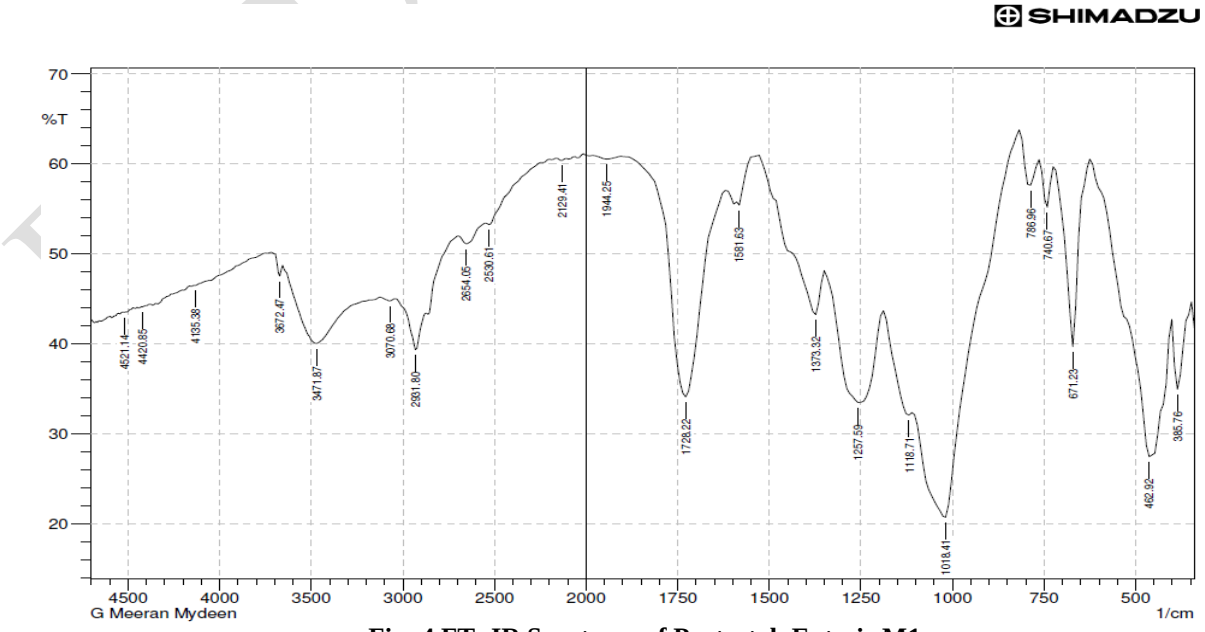

Fig: 4 FT- IR Spectrum of Protectab Enteric M1.

Table: 7. FT- IR Spectral Data of Protectab Enteric M1.

S. No.	Wave Number (cm^{-1})	Functional Group
1	2931	O - H stretching
2	1728	C = O stretching
3	1373	Alkane C - H bending
4	1257	Acid C - O stretching
5	1018	C -O stretching

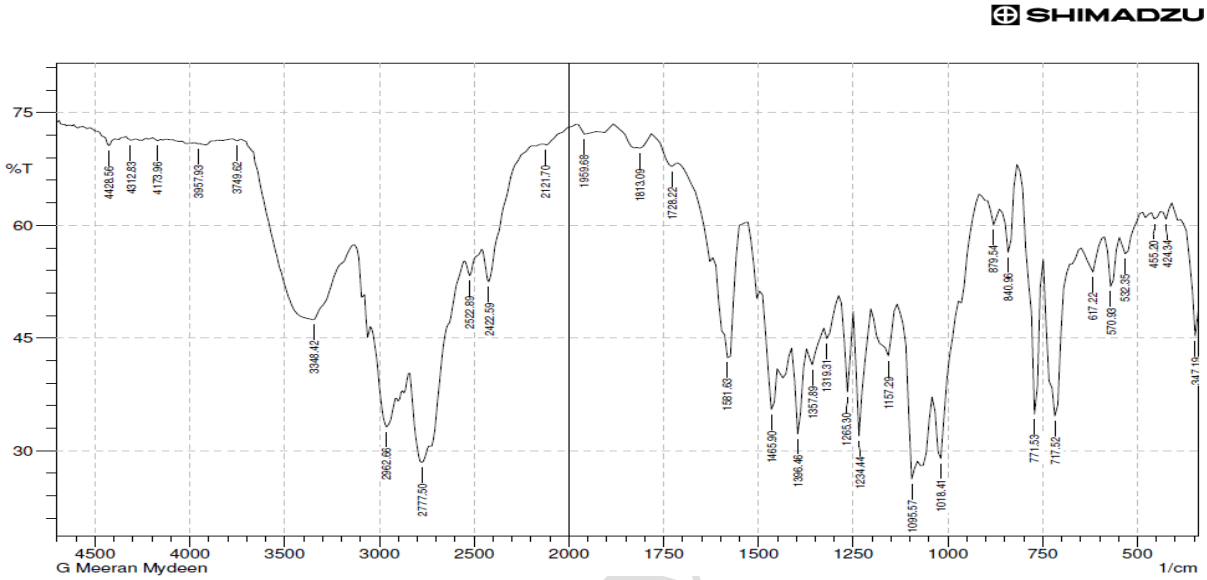

Fig: 5 FT- IR Spectrum of Fluoxetine Hydrochloride+ Croscarmellose sodium.

Table: 8. FT- IR Spectral Data of Fluoxetine Hydrochloride+ Croscarmellose sodium.

S. No.	Wave Number (cm^{-1})	Functional Group
1	2962	Aromatic C - H stretching
2	2777	Alkane C - H stretching
3	1581	Amine N - H bending
4	1396	Alkane C - H bending
5	3348	Alcoholic O - H stretching
6	2422	Alkane C - H stretching
7	1465	Aromatic C = C stretching
8	1095	Ether C – O stretching

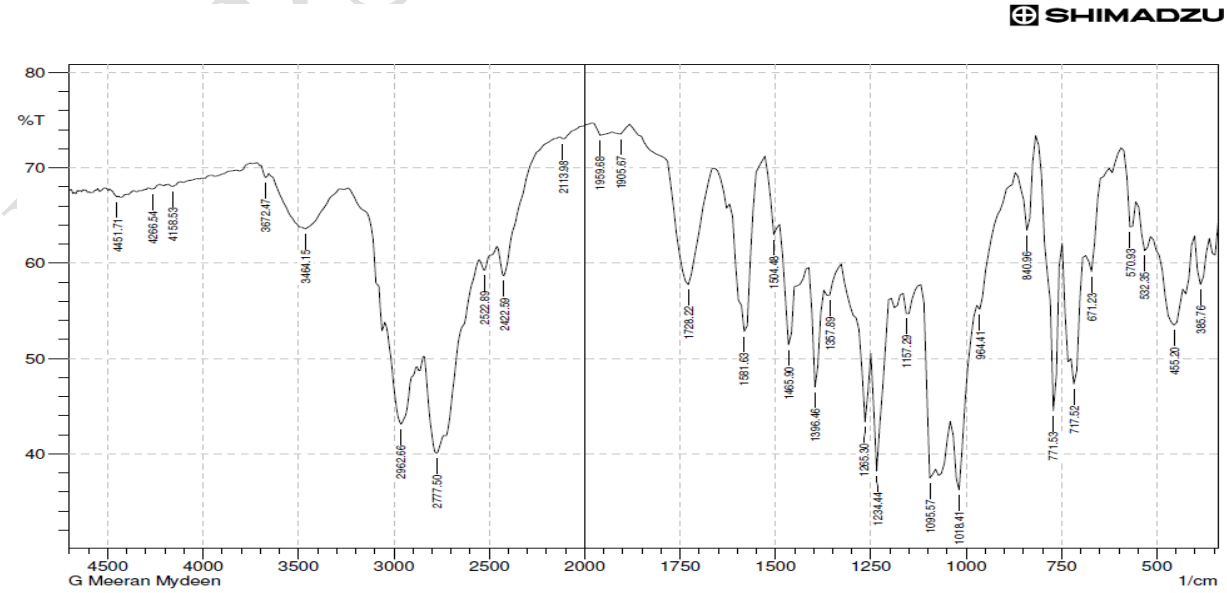

Fig: 6 FT-IR Spectrum of Fluoxetine Hydrochloride+ Protectab Enteric M1.

Table: 9. FT-IR Spectral Data of Fluoxetine Hydrochloride+ Protectab Enteric M1.

S. No.	Wave Number (cm^{-1})	Functional Group
1	2962	Aromatic C- H stretching
2	1581	Aromatic N- H bending
3	1465	Aromatic C = C stretching
4	1396	Alkane C- H bending
5	1234	Aromatic C - N stretching
6	1095	Ether C - O stretching

Table: 10. Comparative FT- IR Spectral Data of Drug and Excipients.

Compounds	Functional Groups						
	Aromatic C - H stretching	Alkane C - H stretching	N-H Amine bending	Aromatic C = C stretching	Alkane C-H bending	Aromatic C-N stretching	C- O Ether stretching
Drug (Flouxetine hydrochloride)	2962	2769	1581	1465	1396	1234	1095
Drug + CCS	2962	2777	1561	1465	1396	1234	1095
Drug + Protectab enteric M1	2962	2769	1581	1465	1372	1234	1095

FT-IR spectroscopic studies indicated that the drug is compatible with all the excipients. The FT-IR spectrum of physical mixture showed all the characteristic peaks of Flouxetine hydrochloride, thus conforming that no interaction of drug occurred with the components of the formulation.

MICROMERITIC PROPERTIES

Table: 11. Precompression Parameters.

Formulation Code	Angle of Repose (θ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index (%)	Hausner's Ratio
F-I	28.56±0.3	0.562±0.2	0.690±0.5	18.55±0.7	1.15±0.7
F-II	30.09±0.7	0.640±0.1	0.745±0.3	14.09±0.2	1.16±0.6
F-III	25.46±0.2	0.305±0.3	0.351±0.5	13.11±0.1	1.15±0.2
F-IV	24.98±0.6	0.317±0.7	0.367±0.1	13.63±0.6	1.15±0.5
F-V	24.23±0.1	0.310±0.5	0.360±0.2	13.89±0.3	1.17±0.3

***All the values are expressed as mean ± SD, n=3.**

Fluoxetine Hydrochloridepowder blends were evaluated for different precompression parameters and the results are mentioned in table: 11.

Angle of Repose

Angle of repose of Fluoxetine Hydrochloridepowder blend was found in the range of 24º.23' to 30°.09'. This values are well within the limit of 25° – 30° which indicates the flow of Fluoxetine Hydrochloridewas excellent. The above results revealed that the all the formulations (F-I to F-V) possess excellent flow.

Bulk Density and Tapped Density

Bulk density of Fluoxetine Hydrochloridewas found between 0.305 ± 0.3 to 0.640 ±0.1 g/cm^3. Tapped density ranges between 0.351 ± 0.5 to 0.745 ± 0.3 g/cm^3.

Compressibility Index and Hausner's Ratio

Compressibility index values was found to be in the range of 13.11 ± 0.1 to 18.55 ±0.7 % and the hausner,s ratio lies between 1.15 ± 0.5 to 1.17 ± 0.3. Compressibility index of formulation - I belongs to fair flow and compressibility index of other formulations indicates that the blend belongs to good flow property.

EVALUATION OF FLUOXETINE HYDROCHLORIDETABLETS

POST COMPRESSION PARAMETERS

GENERAL APPEARANCE

The general appearance of all formulations (F-I to F-V) were examined and found as follows,

Color – Yellow **Shape –** Round **Surface** – Smooth

Cracks, depressions, pinholes – Absent

The prepared tablets were evaluated for various post compression parameters. The results are mentioned in table: 12.

Table: 12. Post Compression Parameters.

Formulation Code	Thickness (mm)	Hardness (kg /cm^2)	Weight Variation (mg)	Friability (%)	Disintegration (min)
F-I	3.22 ± 0.055	7.20 ± 0.32	145.50 ±1.55	0.14 ±0.007	8 min 30 sec
F-II	3.35 ± 0.010	6.60 ± 0.29	144.50 ±1.20	0.12 ±0.004	8 min
F-III	3.40 ± 0.017	7.00 ± 0.27	145.25 ±1.08	0.10 ±0.010	5 min 45 sec
F-IV	3.36 ± 0.016	7.50 ± 0.49	145.00 ± 0.13	0.16 ±0.005	7 min 30 sec
F-V	3.29 ± 0.020	7.20 ± 0.24	146.03 ± 0.12	0.12 ±0.003	9 min 30 sec

***All the values are expressed as mean ± SD, n=3.**

Thickness and Hardness

The thickness of tablets was found in the range of 3.22 ± 0.055 to 3.40 ± 0.017mm. This may be due to the presence of upper and lower punches adjustment during the compression process. All the formulations showed uniform thickness. Hardness of Fluoxetine Hydrochloridetablets was found in the range of 6.60 ± 0.29 to 7.50± 0.49 kg/cm^2. All the formulations possessed good mechanical strength.

Weight Variation Test

Twenty tablets of each formulation were randomly selected for weight variation test. The accepted percentage deviation was ± 7.5 for 130 – 324 mg tablet weight as per I.P. The results showed that the weight of tablets ranges from 144.50 ± 1.20 to 146.03 ± 0.12 for all the formulations that is well within the I.P limit (± 7.5). Hence all the tablets passed the weight variation test.

Friability Test

The friability test carried was out by using Roche friabilator. The maximum weight loss should not be more than 1%. The friability values of formulations (F-I to F-V) were found to be in the range of 0.10 ± 0.010 to 0.16 ± 0.005% respectively. Hence all the tablets passed the friability test.

Disintegration Test

Disintegration test of Fluoxetine Hydrochlorideuncoated tablets ranges from 5 min 45 sec to 9 min 30 sec. The acceptable disintegration time of uncoated tablet limit as per I.P is NMT 15 minutes. Hence all the tablets passed the disintegration test.

IN VITRO DISSOLUTION STUDIES

The in vitro drug release of Fluoxetine Hydrochloridetablets were given in table: 13 and fig: 7

Table: 13. Comparative In Vitro Drug Release Studies of Fluoxetine Hydrochloride Tablets.

Time (min.)	Percentage Drug Release (%)				
	Formulation Code				
	F-I	F-II	F-III	F-IV	F-V
5	6.70 ± 0.32	24.78 ± 0.32	34.97 ± 0.20	66.98 ± 0.32	93.78 ± 0.22
10	8.78 ± 0.22	24.98 ± 0.39	36.98 ± 0.38	74.87 ± 0.21	94.67 ± 0.23
15	9.74 ± 0.36	25.32 ± 0.32	37.87 ± 0.37	78.98 ± 0.32	96.89 ± 0.22
20	10.96 ± 0.27	26.96 ± 0.34	43.96 ± 0.31	84.67 ± 0.16	97.78 ± 0.16
30	11.57 ± 0.22	27.97 ± 0.22	50.78 ± 0.28	87.96 ± 0.37	99.79 ± 0.080
45	12.57 ± 0.28	28.96 ± 0.10	64.50 ± 0.13	95.78 ±0.22	100.67 ± 0.11

***All the values are expressed as mean ± SD, n=3.**

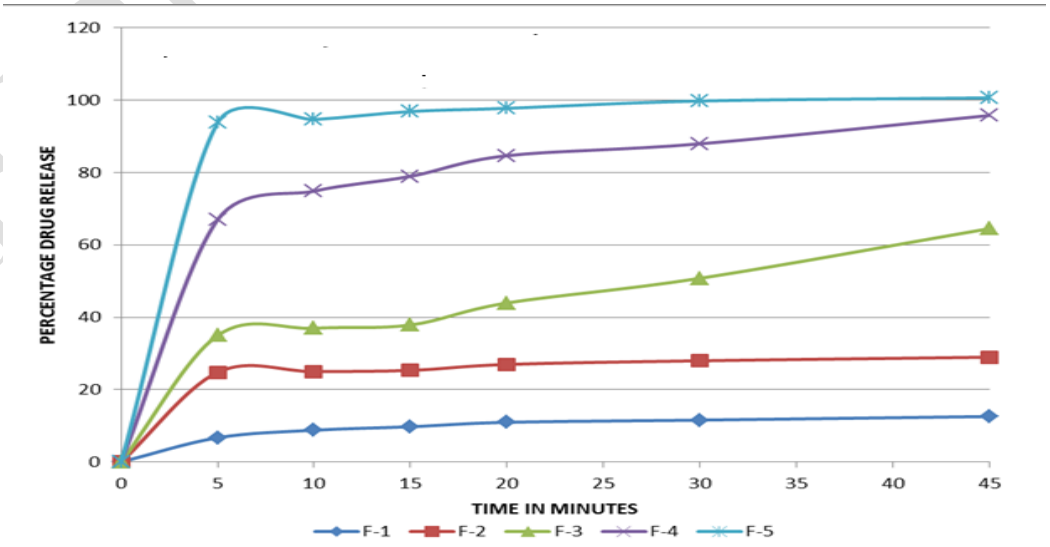

Fig: 7 Comparative In Vitro Drug Release Studies of Fluoxetine Hydrochloride.

1. Fluoxetine Hydrochloridetablets (F-I to F-V) were prepared by direct compression method and subjected to in vitro drug release studies. Formulation F-I showed only 12.57% of drug release at the end of 45 min. So to increase the drug release it was planned to add calcium carbonate as an alkalizing agent in formulation F–II and F-III. 5% of calcium carbonate was added in formulation F–II and 15% in formulation F–III. But formulation F–II and F-III showed only 28.96% and 64.50% drug release at the end of 45 min. So in formulation F–IV calcium carbonate content was further increased to 25%. In formulation F–V 25% calcium carbonate is added. Formulation F–IV and F-V showed maximum drug release at the end of 45 min (95.78% and 100.67%). This may be due to the alkaline pH nature due to the addition of calcium carbonate in formulation F–IV and F-V which showed more drug release than other formulations.
2. Hence formulation F–IV and F-V were selected as the best formulations based on drug release. The best formulations F-IV and F-V was coated with 5.80 mg and 11.80 mg of protectab enteric M1 polymer and evaluation of enteric coated tablets were performed
3. In comparison of formulation F-IV and F-V, the only difference is coating thickness. 4% coating thickness is applied in F-IV and the thickness was increased upto 8% in F-V. EVALUATION OF FLUOXETINE HYDROCHLORIDE ENTERIC COATED TABLETS

Table: 14 Evaluation of Fluoxetine Hydrochloride Enteric Coated Tablets.

Formulation Code	Thickness (mm)	Weight Variation (mg)	Disintegration Time (min)	
			0.1N HCl	pH 6.8 Phosphate Buffer
F-IV	3.48 ± 0.071	158.12±2.25	50 min	-
F-V	3.42± 0.026	160.50±1.90	-	15 min 30 sec
Marketed Sample	2.90± 0.055	210.00±2.50	-	15 min 40 sec

***All the values are expressed as mean ± SD, n=3.**

Formulation F–IV showed increased thickness after coating process. The weight of tablets also improved further upon addition of 4% coating solution. But formulation F-IV failed in disintegration test as it does not withstand in 0.1 N HCI for 2 hr. So in formulation F-V the coating thickness was further increased upon addition of 8% coating solution. Formulation F-V withstand in 0.1 N HCl for 2 hr and disintegrate in alkaline medium after 15 min and 30 seconds which is almost similar compared to the marketed Duloxetine HCl enteric coated tablets. Hence formulation F-V was considered as best formulation and the drug release behavior of formulation F-V was compared with the marketed Duloxetine HCl enteric coated tablets.

IN VITRO DRUG RELEASE STUDIES

The in vitro drug release of Fluoxetine Hydrochloride enteric coated tablets are given in table: 15 and fig: 8.

Table: 15. Comparative In Vitro Drug Release Data of Fluoxetine HydrochlorideMarketed Sample and Formulation (F-V)

Dissolution Medium	Sampling Time	Percentage Drug Release (%)	
		F-V	Marketed Sample
0.1 N HCl	2 hr	1.20 ± 0.25	2.75 ± 0.75
Simulated intestinal fluid (6.8 pH Phosphate buffer)	5 min	10.23 ± 0.74	12.50 ± 0.85
	10 min	20.56 ± 0.28	19.20 ± 0.24
	15 min	46.29 ± 0.45	40.31 ± 0.24
	20 min	72.30 ± 0.38	70.42 ± 0.46
	30 min	85.30 ± 0.63	87.25 ± 0.53
	45 min	100.53 ± 0.85	97.98 ± 0.52

All the value are expressed as mean ± SD, n=3

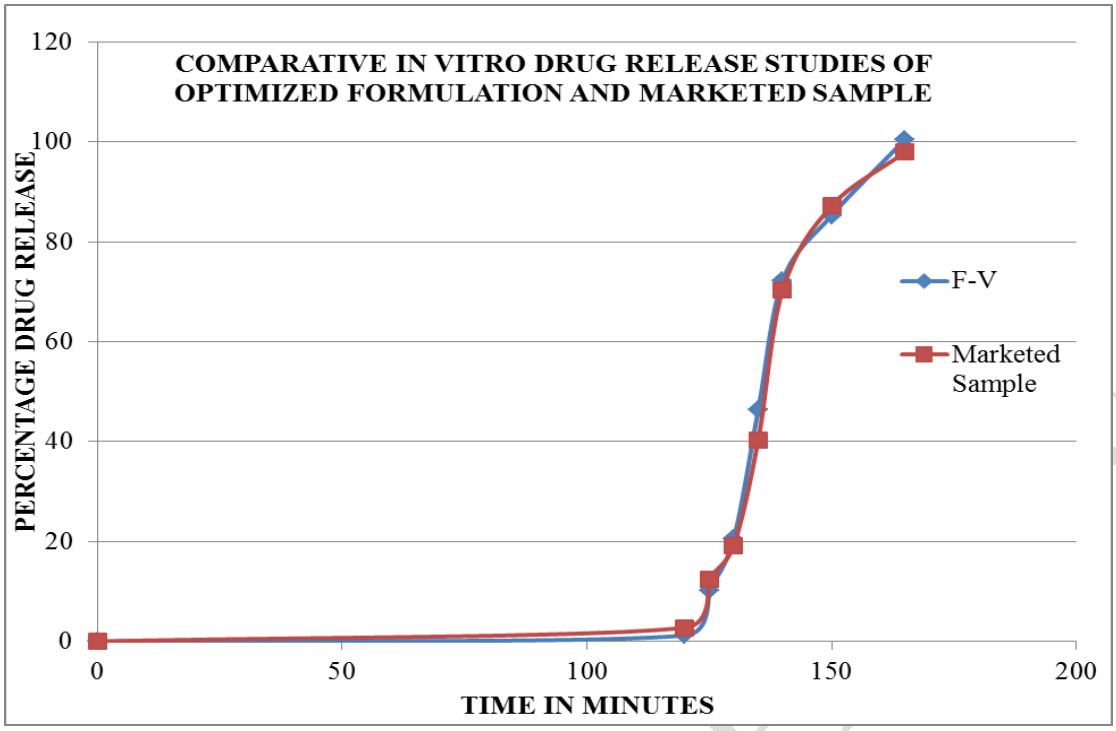

Fig: 8 Comparative In Vitro Drug Release Profiles of Fluoxetine HCI Marketed Sample and Formulation (F-V)

The percentage drug release of marketed sample and formulation (F-V) was found to be 97.98±0.52% and 100.53±0.85 % at end of 2 hour and 45 minutes.

The drug release from formulation F-V was found to be better than the marketed product. This may be due to increase in addition of calcium carbonate as an alkalizing agent in formulation F-V.

STABILITY STUDIES

The best formulation (F-V) was selected for the stability study and stored at 25±2^{0}C/60%±5% RH and 40±2^{0}C/75% ±5% RH for 3 months. The tablets were evaluated for various parameters like physical appearance, average weight, thickness, hardness, disintegration, in vitro drug release and drug content at every one month. The results are presented in table: 16 and 17.

Table: 16. Stability Study Data of Formulation F-V Stored at 25 ± 2°C/60% ± 5% RH.

S. No.	Storage Conditions: 25± 2°C/60%±5% RH					
	Tests		Initial Period	1st Month	2nd Month	3rd Month
1.	Physical Appearance		Orange color, round shaped tablets	Complies	Complies	Complies
2.	Average Weight (mg)		160.50	160.37	160.25	160.11
3.	Thickness (mm)		3.42	3.42	3.42	3.42
4.	Hardness (kg/cm^2)		7.10	7.20	7.26	7.28
5.	Disintegration Time (min)	0.1 N HCl	-	-	-	-
		pH 6.8 phosphate buffer	15 min 30 sec	14 min 15sec	16 min 45sec	16 min 30 sec
6.	In Vitro Dissolution Study	Acid Medium- 120 min (NMT 10%)	1.20 ± 0.25	1.70 ± 0.65	2.50 ± 1.15	3.00 ± 1.35
		Alkaline medium (at the end of 45 min) (%)	99.98 ± 0.52	98.99 ± 0.25	99.40 ± 0.74	98.25 ± 0.97
7.	Assay % (Limit: 90 to 110)		100.45±1.10	99.45 ± 0.26	99.40 ± 0.96	99.52 ± 0.85

Table: 17. Stability Study Data of Formulation F-V Stored at 40 ± 2^{0}C/75% ± 5% RH.

S. No.	Storage Conditions: 40±2^{0}C/75% ±5% RH					
	Tests		Initial Period	1st Month	2nd Month	3rd Month
1.	Physical Appearance		Orange color, round shaped tablets	Complies	Complies	Complies
2.	Average Weight (mg)		160.50	161.25	160.89	162.53
3.	Thickness (mm)		3.42	3.42	3.42	3.42
4.	Hardness (kg/cm^2)		7.20	7.25	6.95	6.95
5.	Disintegration Time (min)	0.1 N HCl	-	-	-	-
		pH 6.8 phosphate buffer	15 min 30 sec	18 min 30sec	14 min 15sec	12 min 45 sec
6.	In Vitro Dissolution Study	Acid Medium – 120 min (NMT 10%)	1.20 ± 0.25	1.30 ± 0.25	2.86 ± 0.12	3.20 ± 1.95
		Aslkaline medium (at the end of 45 min) (%)	99.98 ± 0.52	98.29 ± 0.35	99.50 ± 0.94	99.55 ± 0.50
7.	Assay % (Limit: 90 to 110)		100.45±1.10	100.27 ± 0.56	99.65 ± 0.37	99.55 ± 0.11

Stability studies revealed that there was no significant changes found in physical appearance, average weight, thickness, hardness, disintegration, in vitro drug release and assay during the period of three months even after stored at 25±2ºC/60%±5% RH and 40±2ºC/75%±5% RH. The study revealed that the formulation F-V was stable at 25±2°C/60%±5%RH and 40±2ºC/75%±5% RH even after stored for three months.

CONCLUSION

A total of five formulations (F-I to F-V) of Fluoxetine Hydrochloride tablets were developed by direct compression method. The work was carried out to delay the release of Fluoxetine Hydrochloride by using enteric polymer.

From all the above observation it was concluded that the formulation F-V containing calcium carbonate as an alkalizing agent along with mannitol and microcrystalline cellulose as diluent was selected as the best formulation among the five formulations and 8% coating solution of Protectab enteric M1 polymer was applied as enteric coating. Formulation F-V showed better drug resistance in acidic medium and release the drug in alkaline medium as per I.P specification and showed rapid drug release in intestine than marketed Fluoxetine Hydrochloride enteric coated tablet. Hence the study concluded that formulation F-V satisfied all the criteria for enteric coating tablets.

REFERENCES

1. USP NF 2007, Asian edition, Volume 2, pg.no.242, 243, 273.
2. Sandeep Kumar and Pritam Singh. Various techniques for solubility enhancement: An overview. The Pharma Innovation Journal, 2016; 5(1): 23-28.
3. P. Ravi Prasad and K. Bhuvaneswari. Quantitative determination of domperidone and paracetamol in combined dosage form by FT-IR spectroscopy. Journal of Chemical and Pharmaceutical Research, 2012; 4(1): 180-185.
4. Rinal Mistry and Chirag Dalal. Determination of angle of repose of pharmaceutical materials based on image processing using lab view. International Journal of Advanced Research in Electrical, Electronics and Instrumentation Engineering, 2017; 11(3): 1127-1129.
5. H.M. Beakawi Al-Hashemi and O.S. Baghabra Al-Amoudi. Powder technology, 2018; 330: 397–417.
6. Sourav Tribedi, Mahantesh Ananthapur, J.S. Sabitha. Formulation and evaluation of enteric coated tablets of pantoprazole. International Journal of Pharmaceutical and Chemical Sciences, 2013; 2(3): 1455-1457.
7. Prasanna Kumar Desu, G. Vaishnavi, K. Divya and U. Lakshmi. An Overview on preformulation studies. Indo American Journal of Pharmaceutical Sciences, 2015; 2(10): 1399-1407.
8. Gregory E. Amidon, Pamela J. Secreast and Deanna Mudie. Particle, powder and compact characterization. Developing Solid oral dosage forms. 1st Ed. USA, Elseiver, 2009; 165-167.
9. B. Shibu, S. Suresh and M. Purushothaman. Formulation and evaluation of enteric coated tablets by wet granulation method. International Journal of Pharmaceutical Research and Analysis, 2014; 2(7): 193-199.
10. M. E. Aulton. Pharmaceutics-The sciences of dosages form design. 3rd edition, Churchill Livingstone, London, 2007; 419-421.
11. S. Gilbert Banker, T. R. Christopher. Preformulation. In: Modern pharmaceutics. 4th edition, Marcel D. Inc. New York, 2005; 167-185.
12. P. Bhargavi, B. Naveen Kuma and Anita. Formulation and evaluation of Ranolazine extended release tablets by using pH dependent and

independent polymers. International Journal of Pharmaceutical & Biological Archives, 2013; 4(6): 1164 – 1171.
13. M. Preethi, P. Srinivas, R. Venkataramana and M. Sadanandam. Formulation and evaluation of Fluoxetine Hydrochloridedelayed release, enteric coated capsules. International Journal of Pharmaceutical & Biological Science, 2011; 2(3): 152- 172.
14. S. K. Patel, N. J. Patel, K. M. Patel, P. U. Patel and B. H. Patel. Estimation of Fluoxetine Hydrochloridein pharmaceutical formulations by RP-HPLC method. Indian Journal of Pharmaceutical Sciences, 2008; 70(6): 825.
15. Murat–Turkoglu. Tableting and stability evaluation of enteric coated omeprazole pellets. European Journal of Pharmaceutics and Biopharmaceutics, 2004; 2(6): 279-286.
16. U.S. Pharmacopoeial Convention, Inc., The United States Pharmacopoeia 23/National Formulary 18, Author, Rockville, MD, 1995; 11: 1940-1941, 1959- 1963.
A. Sambasivarao1, Chandra Sekhara Rao Baru and M. Hareesh Reddy. Accelerated stability testing of dosage forms as per international conference of hormonization (ICH) guidelines. World Journal of Pharmaceutical and Medical Research. 2016; 2(3): 99-103.
17. N. Amruth Kumar and V. S. Thiruvengada Rajan. A review on stability studies an overview. International Journal of Review in Life Science, 2011; 2(3): 106-111.
18. T. Hemant Krishna and Vamsi. UV spectrophotometric determination of Duloxetine HCl. Asian Journal of Pharmaceutical Sciences, 2009; 21(6): 4951 - 4953.