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FORMULATION AND EVALUATION OF DULOXETINE HYDROCHLORIDE ENTERIC COATED TABLETS

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ABSTRACT
The present study was undertaken to formulate and evaluate enteric coated tablets of Duloxetine hydrochloride using calcium carbonate as an alkalizing agent to improve the solubility of drug and to convert micro pH environment to alkaline nature. Five formulations (F-I to F-V) of Duloxetine hydrochloride tablets were prepared by direct compression method. The prepared blend was evaluated for precompression parameters like angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The prepared tablets were evaluated for post compression parameters such as hardness, thickness, weight variation, friability, assay, disintegration test and dissolution study. A total of five formulations (F-I to F-V) of Duloxetine hydrochloride tablets were developed by direct compression method. The work was carried out to delay the release of Duloxetine 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 Duloxetine hydrochloride enteric coated tablet. Hence the study concluded that formulation F-V satisfied all the criteria for enteric coating tablets.

KEYWORDS: Duloxetine hydrochloride, enteric coated tablet, Protectab, polymers.

INTRODUCTION
The oral route of drug administration is the most important method of administering drugs for systemic effect. Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to Indian pharmacopoeia, pharmaceutical tablets are solid, flat or biconvex dishes. Tablets are prepared by compressing a drug or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration.[1]

Tablet coating
Tablet coating can be described as a process of applying an edible paint on the surface of a pharmaceutical dosage form to achieve specific benefits. This is an additional process in tableting which causes an increase in the cost of tablet production. Coating can be applied to several kinds of solid dosage forms like tablets, pellets, pills, drug crystal, etc. When acoating solution is applied to a batch of tablets in a coating pan, the surfaces of the tablet get covered with a tacky polymeric film. The tablets are then allowed to dry and the film eventually forms a non-sticky dry surface. The coating technique involves parameters such as the spray pattern, drop size and nozzle spacing (in addition to multiple other non-spray related parameters) which must all be precisely controlled in order to ensure uniform distribution of the coating material.[2]

Coating process design and control
In most coating methods, when the tablets are being agitated in a pan, fluid bed, etc. spraying of coating solution on tablets takes place. As the solution is being sprayed, a thin film is formed that adheres directly to each tablet. The coating may either be formed by a single application or may be built up in layers through the use of multiple spraying cycles. Firstly, uncoated tablets are placed in the pan, which is typically tilted at an angle from the horizontal, and then the liquid coating solution is introduced into the pan while the tablets are tumbling. By passing hot air over the surface of the tumbling tablets, the liquid portion of the coating solution is then

evaporated. In comparison, a fluid bed coater operates by passing hot air through a bed of tablets at a velocity sufficient to support and separate the tablets as individual units. Once separation takes place, then the tablets are sprayed with the coating composition.[3,4]

The present work was carried out to formulate enteric coated tablets of Duloxetine hydrochloride and to evaluate the tablets for various parameters. It was planned to carry out this work as outlined below.

Evaluation of enteric coated tablets

Tablets when formulated may undergo physical and chemical changes, which may alter their bioavailability. Therefore, the tablets are to be evaluated before dispensing to ensure their stability and bioavailability throughout their shelf life.[5]

Preformulation Studies

Preformulation is defined as a stage of development during which the physico-chemical properties of the drug substance are 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. The overall objective of pre-formulation testing is to generate information useful in developing the formulation which is stable and bio-available. Further the use of pre-formulation parameter maximizes the chances in formulating an acceptable, safe, efficacious and stable product. The goals of pre-formulation studies are to choose the correct form of the drug substance, evaluate its physical properties and generate a thorough understanding of the material's stability under the conditions that will lead to development of an optimal drug delivery system.[6]

Objectives of pre-formulation studies

To develop the elegant dosage forms (stable, effective & safe).

To understand the physical description of a drug substance before dosage form development.

Rational development of a dosage form of a drug substance before dosage form development.

It provides information to the formulator to design an optimum drug delivery system.

Solubility Test

Solubility of Duloxetine HCl in water, methanol and ethanol was determined by using sonicator at room temperature.[7] The solubility specifications as per I.P was mentioned in table: 1.

Table 4: Solubility Specifications.

Solubility	Approximate Volume of Solvent in ml per gm of Solute
Very soluble	Less than 1
Freely soluble	1 to 10
Soluble	10 to 30
Sparingly soluble	30 to 100
Slightly soluble	100 to 1000
Very slightly soluble	1000 to 10000
Practically insoluble	More than 10000

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 5: Drug- Excipient Compatibility Study.

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

EVALUATION OF PRECOMPRESSION PARAMETERS

MICROMERITIC PROPERTIES

ANGLE OF REPOSE

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.[8,9]

$$\text{Tan } \theta = h/r$$

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

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.

Table 6: Flow Properties and Corresponding Angle of Repose as per USP.

Flow Property	Angle of Repose (θ)
Excellent	25 – 30
Good	31 – 35
Fair	36 – 40
Passable	41 – 45
Poor	46 – 55
Very Poor	56 – 65
Very Very Poor	> 66

BULK DENSITY AND TAPPED DENSITY

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V0) 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 (Vf) was measured and the operation was continued till the two consecutive readings were equal. The bulk density and tapped density were calculated using the following formulas.[10,11]

$$\text{Bulk density} = W/V_0$$

$$\text{Tapped density} = W/V_f$$

Where,
W= Weight of powder,
V_0= Initial volume of powder,
V_f = Final volume of powder.

MEASUREMENT OF POWDER COMPRESSIBILITY

A) Compressibility Index

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.[12]

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

B) 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.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \times 100$$

Table 7: Scale of Flowability.

Compressibility Index (%)	Flow Character	Hausner's Ratio
01-10	Excellent	1.00-1.11
11- 15	Good	1.12-1.18
16- 20	Fair	1.19-1.25
21- 25	Passable	1.26-1.34
26- 31	Poor	1.35-1.45
32- 37	Very poor	1.46-1.59

FORMULATION OF DULOXETINE HYDROCHLORIDE UNCOATED TABLETS

Duloxetine Hydrochloride tablets (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.

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 8: Composition of Duloxetine Hydrochloride Enteric Coated Tablets.

Ingredients	Quantity per Tablet (mg)				
	FORMULATION CODE				
	F-I	F-II	F-III	F-IV	F-V
Duloxetine 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
Average weight of each enteric coated tablet	-	-	-	**155.00**	**161.00**

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

"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.[13]

WEIGHT VARIATION TEST

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: 9.[14]

Table 9: 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

Percentage deviation of the tablets were calculated by using the following formula

$$\text{Percentage deviation} = \frac{(\text{Weight of tablet (mg)} - \text{Average weight of tablet (mg)})}{\text{Average weight of tablet (mg)}} \times 100$$

FRIABILITY

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 was calculated by the formula.[15]

Percentage Friability = W1 – W2/W1 × 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

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 370C ± 20C 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.[16]

ASSAY OF DULOXETINE HYDROCHLORIDE BY HPLC METHOD[80]

Chromatographic Conditions

Column	Inertsil ODS (250x 4.6 mm) C8 column.
Mobile phase	55:37:8 V/V (Buffer: acetonitrile (ACN): methanol.
Buffer	0.3% w/v solution of potassium dihydrogen phosphate. Adjust to pH 5.7 with orthophosphoric acid.
Flow rate	2.0 ml/minute.
Injection volume	20 µl.
Wavelength	240 nm.
Column Temperature	30ºC.

Preparation of Mobile Phase

Buffer pH 5.7, ACN and methanol were mixed in the ratio of 55:37:8 v/v.

Preparation of Standard Solution

Accurately weighed 20 mg of Duloxetine hydrochloride was transferred to a 20ml volumetric flask, dissolved and diluted to the mark with methanol to obtain a standard solution of 1000 µg/ml. This solution (1 ml) was further diluted to 10 ml with mobile phase to obtain a working standard stock solution of 100µg/ml for the HPLC method.

Preparation of Sample Solution

Twenty tablets were weighed and finely powdered. A mass equivalent to 20 mg of Duloxetine hydrochloride was weighed and transferred in a 100 ml volumetric flask, mixed with methanol (60 ml) and sonicated for 20 min. The solution was filtered through whatman filter paper and the residue was washed thoroughly with methanol. The filtrate and washings were combined in a 100 ml volumetric flask and diluted to the mark with methanol. An aliquot of this solution (0.2 ml) was further diluted to 10 ml with methanol to obtain a solution containing 4 µg/ml of Duloxetine hydrochloride and subjected to HPLC analysis.

Sample Injection Procedure

20 µl of filtered sample solution and standard solution were separately injected into HPLC system. The chromatogram was recorded and responses were measured for major peaks.

The content of Duloxetine hydrochloride in the powder mixture was calculated by using the following equation.

$$\text{Content of Duloxetine hydrochloride} = \frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Standard weight}}{\text{Sample weight}} \times \frac{P}{100} \times \text{Avg. Wt}$$

Where,

P – Purity of Duloxetine hydrochloride.

Avg. Wt – Average weight in mg.

IN VITRO DRUG RELEASE STUDIES[16]

Dissolution Parameters

Type of apparatus	U.S.P. Type II (paddle)
Medium	0.1N HCL for 2hr, Phosphate buffer pH 6.8 for 45 min
RPM	100
Temperature	37°C ± 0.5ºC
Volume of medium	900 ml
Sampling intervals	5, 10, 15, 20, 30, 45 min.
Sampling volume	10 ml
Method of analysis	UV Spectrophotometer
Wavelength	289 nm.

Preparation of 0.1 N Hydrochloric Acid

Place 8.5 ml of concentrated hydrochloric acid into the 1000 ml volumetric flask and the volume was made up with de-mineralized water.

Preparation of pH 6.8 Phosphate Buffer

Place 14.40 gm of dihydrogen phosphate and 5.72 gm of potassium hydrogen phosphate in a 1000 ml volumetric flask and make upto 1000 ml with de-mineralized water.

Procedure

Drug release studies were carried out by using USP Type II paddle dissolution test apparatus at 100 rpm for 2 hrs in 0.1 N HCI (900ml) maintained at 37°C ± 0.5ºC. 10 ml of sample was taken and analyzed by using UV spectrophotometer at 289 nm. Then the dissolution medium was replaced with 6.8 pH Phosphate buffer (900 ml) and tested for drug release for 45 minutes at 37°C ± 0.5ºC temperature and 100 rpm speed. After 5, 10, 15 and 45 minutes, 10ml samples were taken out and 10 ml volume of fresh phosphate buffer pH 6.8 was added to kept volume of dissolution medium constant and sample was analyzed using UV spectrophotometer at 289 nm.

STABILITY STUDIES

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.[17]

Purpose of Stability Testing

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.[18]

PREFORMULATION STUDIES

ORGANOLEPTIC PROPERTIES

The organoleptic properties of Duloxetine hydrochloride were presented in table: 10.

Table 10: Organoleptic Properties of Duloxetine Hydrochloride (API)

Tests	Specifications as per I. P	Observation
Color	White	White
Taste	Bitter	Bitter
Odor	Odorless	Odorless

The organoleptic properties like color, odor and taste of the API were evaluated. The color of Duloxetine hydrochloride was found to be white. Duloxetine hydrochloride does not show any characteristic odor and the taste was found to be bitter. Duloxetine hydrochloride showed similar color, taste and odor as per the I.P specifications.

SOLUBILITY TEST

The solubility profile of Duloxetine hydrochloride was mentioned in table: 11.

Table 11: Solubility Profile of Duloxetine HCl (API)

Raw Material (API)	Solubility
Duloxetine hydrochloride	Very soluble in DMSO
	Soluble in methanol
	Sparingly soluble in water

The solubility studies of drug (API) revealed that Duloxetine HCI was very much soluble in DMSO, soluble in methanol, ethanol and sparingly soluble in water.

DRUG – 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: 12.

Table 12: Drug - Excipients Compatibility Study.

S. No.	Composition	Description		
		INITIAL PERIOD	AFTER 15 DAYS	AFTER 30 DAYS
1.	Duloxetine hydrochloride	White to off white powder	NCC*	NCC
2.	Duloxetine hydrochloride + Mannitol anhydrous	White to off white powder	NCC	NCC
3.	Duloxetine hydrochloride + Microcrystalline cellulose	White to off white powder	NCC	NCC
4.	Duloxetine hydrochloride + Calcium carbonate	White to off white powder	NCC	NCC
5.	Duloxetine hydrochloride + Povidone	White to off white powder	NCC	NCC
6.	Duloxetine hydrochloride + Croscarmellose sodium	White to off white powder	NCC	NCC
7.	Duloxetine hydrochloride + Colloidal silicon dioxide	White to off white powder	NCC	NCC
8.	Duloxetine hydrochloride + Magnesium stearate	White to off white powder	NCC	NCC
9.	Duloxetine 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 Duloxetine hydrochloride and suitable for formulation development.

EVALUATION OF DULOXETINE HYDROCHLORIDE TABLET (POST COMPRESSION PARAMETERS)

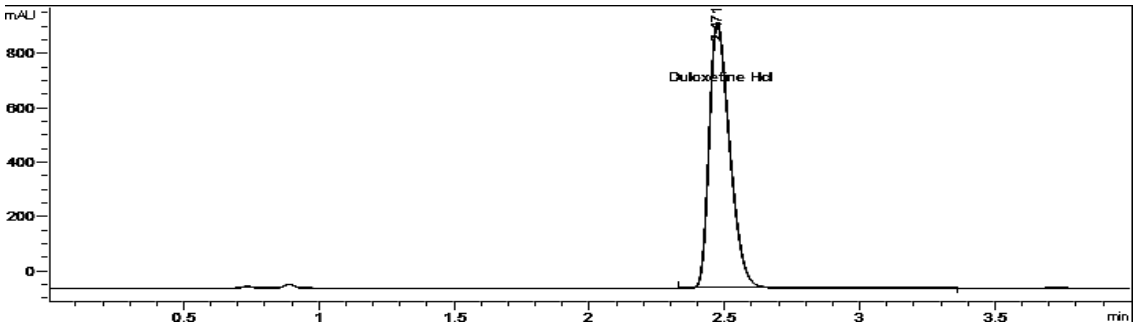
Table 20: Post Compression Parameters.

Formulation Code	Thickness (mm)	Hardness (kg /cm2)	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.**

ASSAY OF DULOXETINE HYDROCHLORIDE BY HPLC METHOD

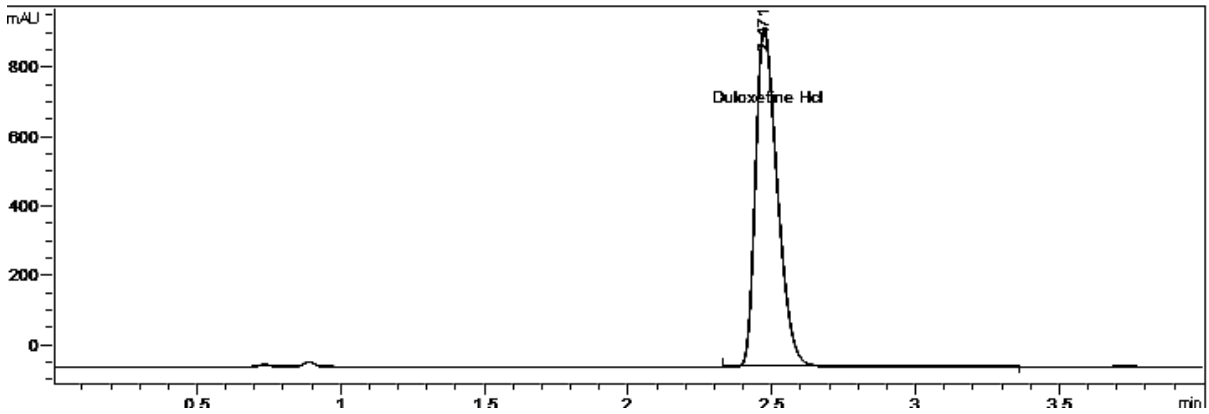
The assay was carried out by HPLC method as per the procedure given in methodology part. The HPLC chromatogram of Duloxetine hydrochloride standard and sample formulations were shown in fig no: 7 to 12 and in table: 20 respectively.



S.No.	DRUG	RT*	Area	Plate count	Symmetry
1	Duloxetine HCI	2.471	5179018	5282	0.91

***RT – Retention Time**

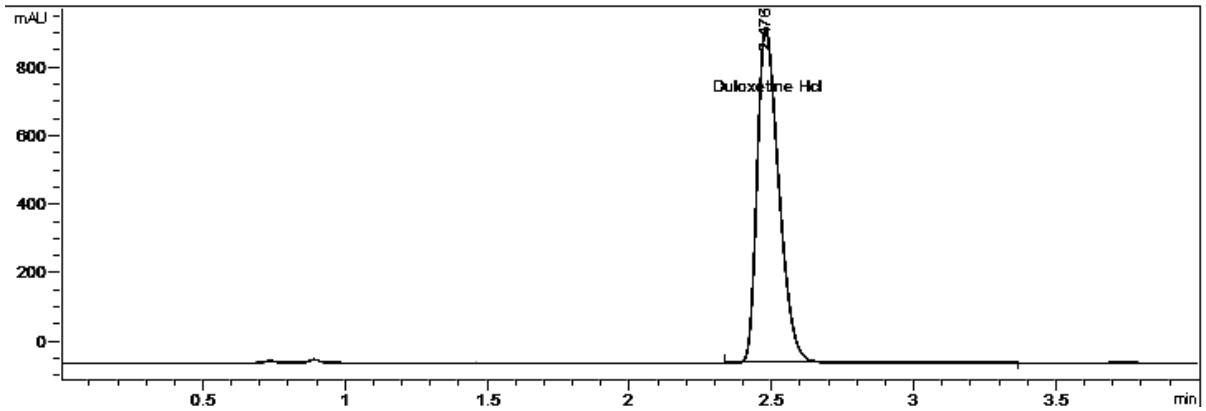
Fig: 7 HPLC Chromatogram of Duloxetine HCI (Standard).



S.No.	DRUG	RT*	Area	Plate count	Symmetry
1	Formulation F-I	2.471	5178834	5282	0.91

***RT – Retention Time**

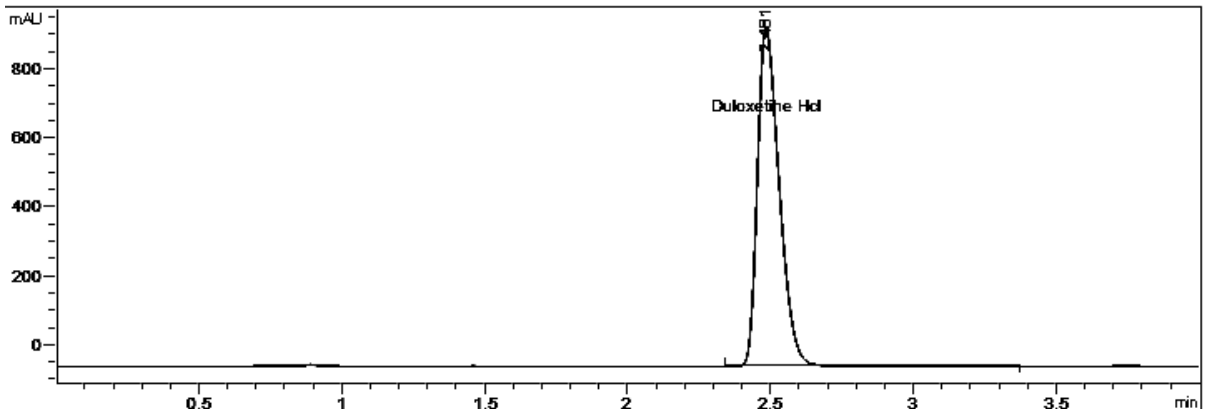
Fig: 8 HPLC Chromatogram of Formulation F-I.



S.No.	DRUG	RT*	Area	Plate count	Symmetry
1	Formulation F-II	2.476	5204743	5305	0.91

***RT – Retention Time**

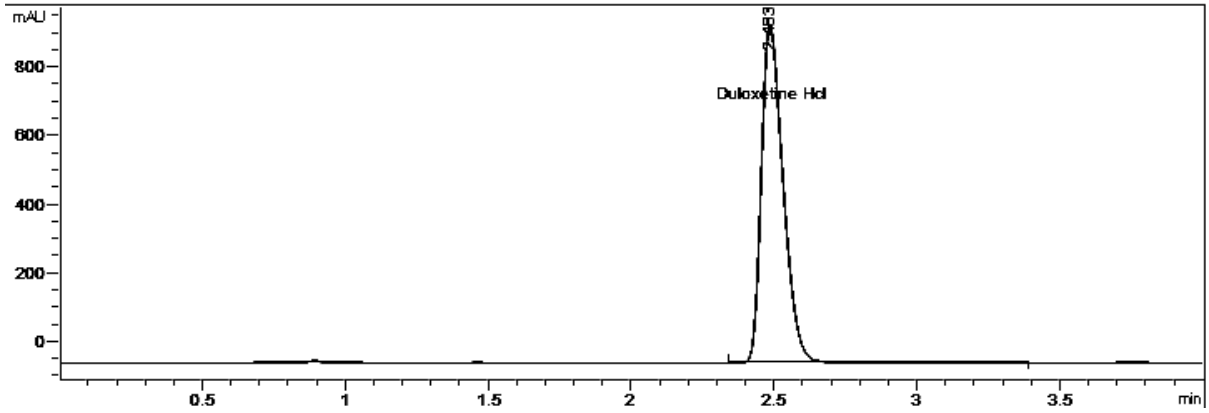
Fig: 9 HPLC Chromatogram of Formulation F-II.



S.No.	DRUG	RT*	Area	Plate count	Symmetry
1	Formulation F-III	2.481	5207273	5330	0.91

***RT – Retention Time**

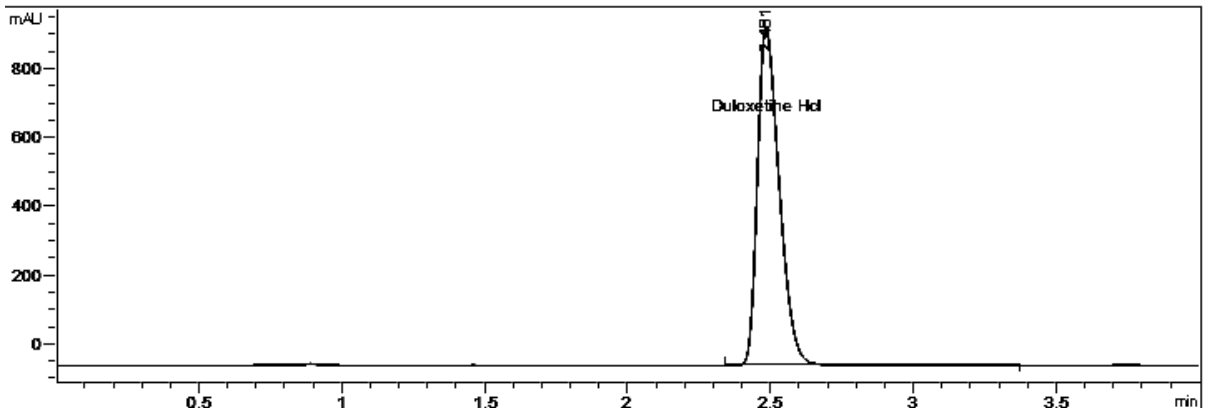
Fig: 10 HPLC Chromatogram of Formulation F-III.



S.No.	DRUG	RT*	Area	Plate count	Symmetry
1	Formulation F-IV	2.483	5210035	5335	0.91

***RT – Retention Time**

Fig: 11 HPLC Chromatogram of Formulation F-IV.



S.No.	DRUG	RT*	Area	Plate count	Symmetry
1	Formulation F-V	2.481	5217624	5332	0.91

***RT – Retention Time**

Fig: 12 HPLC Chromatogram of Formulation F-V.

Table 21: Assay of Duloxetine Hydrochloride Tablets.

Formulation Code	Limit (%)	Assay (%)
F-I	90 – 110%	99.42
F-II		98.55
F-III		98.70
F-IV		102.16
F-V		100.45
Marketed sample		99.02

The content of Duloxetine hydrochloride in all formulations were found in the range of 98.55% to 102.16% which was within the acceptable I.P limits.

Table 22: Standard Curve Data of Duloxetine Hydrochloride.

Concentration (µg/ml)	Absorbance at 290 nm
3	0.122
5	0.184
10	0.410
15	0.563
20	0.762
25	0.987
30	1.20

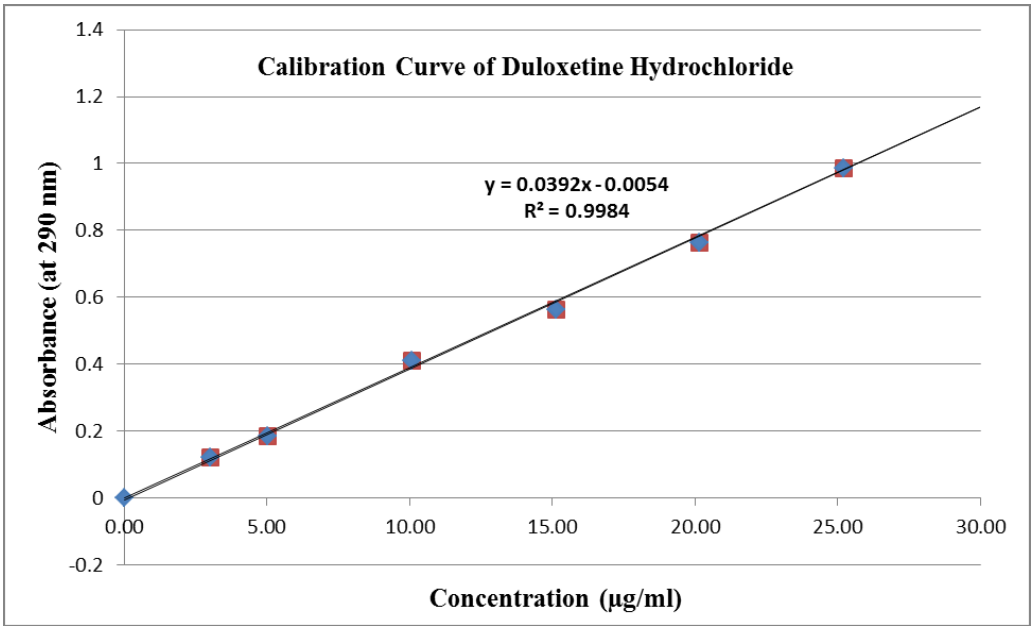


Fig: 13 Calibration Curve of Duloxetine Hydrochloride.

***IN VITRO* DISSOLUTION STUDIES**

The in vitro drug release of Duloxetine hydrochloride tablets was given in table: 23 and fig: 14

Table 23: Comparative In Vitro Drug Release Studies of Duloxetine 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.**

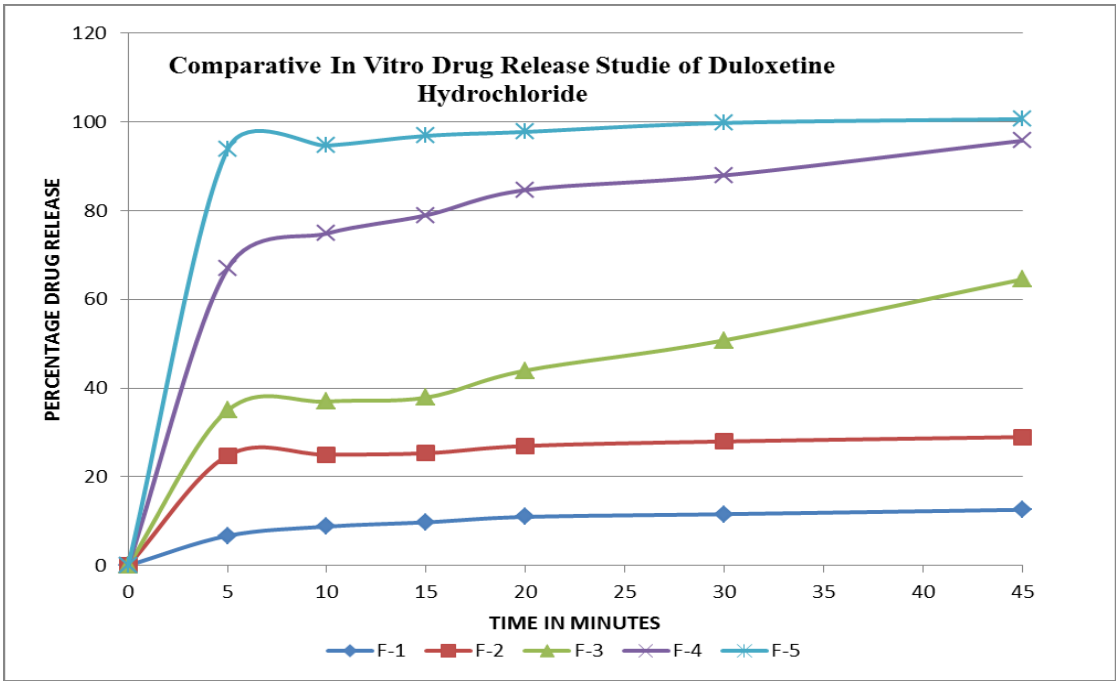


Fig: 14 Comparative In Vitro Drug Release Studies of Duloxetine Hydrochloride.

EVALUATION OF DULOXETINE HYDROCHLORIDE ENTERIC COATED TABLETS

Table 24: Evaluation of Duloxetine 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.**

***IN VITRO* DRUG RELEASE STUDIES**

The in vitro drug release of Duloxetine hydrochloride enteric coated tablets is given in table: 25 and fig: 15.

Table 25: Comparative In Vitro Drug Release Data of Duloxetine Hydrochloride Marketed 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

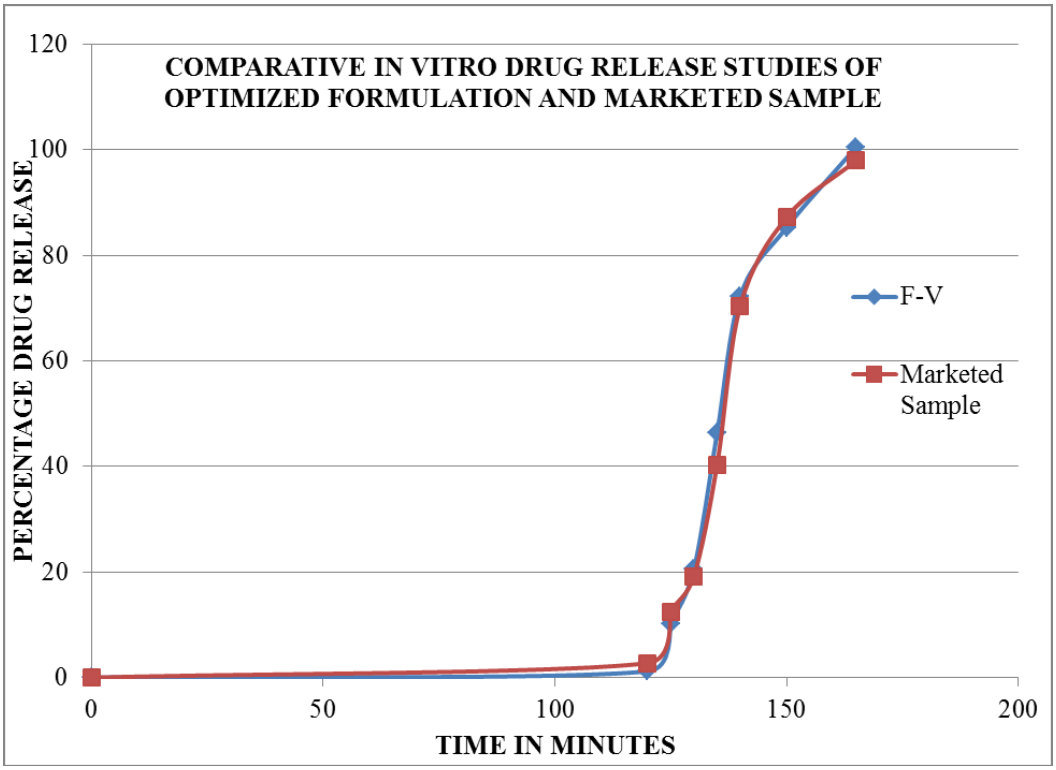


Fig: 15 Comparative In Vitro Drug Release Profiles of Duloxetine HCI Marketed Sample and Formulation (F-V).

CONCLUSION

From the experimental results, the following points can be summarized.

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 was good.

All formulations possessed uniform thickness. The prepared tablets also possessed good mechanical strength and uniform hardness.

All formulations of Duloxetine hydrochloride tablets 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.

In view of the discoveries, it was resolved that the definition F-V, which contained calcium carbonate as an alkalizing specialist as well as mannitol and microcrystalline cellulose as diluent, was awesome of the five plans, and a 8 percent covering arrangement of Protectab intestinal M1 polymer was utilized as intestinal covering. Detailing F-V beat the popularized Duloxetine hydrochloride intestinal covered tablet as far as medication obstruction in acidic media, drug discharge in basic medium, and medication discharge in the stomach. Accordingly, the review discovered that detailing F-V met each of the necessities for intestinal covering tablets.

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Conflict of interest
No conflicts of interest is declared by the author.

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