FORMULATION AND EVALUATION OF ENTERIC COATED TABLETS OF DULOXETINE HYDROCHLORIDE

A Dissertation submitted to

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Submitted by

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INTERNAL EXAMINER **EXTERNAL EXAMINER**

Date: Date:

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ABBREVIATIONS

E/C	Enteric Coated
GIT	Gastro Intestinal Tract
U/C	Uncoated
U.S.P	United State Pharmacopoeia
I.P	Indian Pharmacopoeia
F.D.A	Food & Drug Administration
HPLC	High Performance Liquid Chromatography
UV	Ultra Violet
FT-IR	Fourier Transform Infra-Red Spectrophotometer
API	Active Pharmaceutical Ingredient
ICH	International Council For Hormonization
CAN	Acetonitrile
CI	Compressibility Index
MCC	Microcrystalline Cellulose
MDC	Methylene Di Chloride
HCl	Hydrochloric Acid
PVP	Poly Vinyl Pyrrolidone
CONC.	Concentration
NLT	Not Less Than
NMT	Not More Than
RT	Retention Time
DT	Disintegration Time
TD	Tapped Density
BD	Bulk Density
MG	Milligram
ºC	Degree Celsius
RPM	Rotation Per Minute
MM	Millimeter
µG	Microgram
ML	Milliliter
NM	Nanometer
GM	Gram
W/V	Weight By Volume

CHAPTER-1

INTRODUCTION

The oral route of drug administration is the most important method of administering drugs for systemic effect. The 90% of drugs used to produce systemic effects are administered by oral route. Among the drugs that are administered orally, solid oral dosage form such as tablet represent the preferred class of products. The reasons for this preference are as follows. Tablet is an unit dosage form in which one usual dose of the drug has been accurately placed by compression. Liquid oral dosage forms, such as syrups, suspensions, emulsions, solutions and elixirs are usually designed to contain one (or) more dose of medication in 5 to 30ml. The patient is then asked to measure his or her own medications using, tablespoon or other measuring device. Such dosage measurements are typically in error by a factor ranging from 20-50% when the drug is self-administered by the patient.

1.1. TABLETS[1]

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. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablets. All medicaments are available in the tablet form except where it is difficult to formulate or administer. Although a variety of tablets exist, with few exceptions (primarily sugar lozenges) tablets are formed by the compression of a powder held within a confined space. The tablet consists of one or more drugs (active ingredients) as well as series of other substances used in the formulation of a complete preparation. Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use the drug must be released from the tablet.

1.1.1.Advantages of Tablets:

- They are unit dosage form and they offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- They offer lowest cost of all oral dosage forms.
- They are the lightest and most compact oral dosage forms.
- They are in general the easiest and cheapest to package and strip.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They may provide the greatest ease of swallowing with the least tendency for "hang up" above the stomach.
- They lend themselves to certain special release profile products such as enteric or delayed release products.
- Objectionable odour and bitter taste can be masked by coating technique.
- Greatest chemical and microbial stability over all oral dosage forms.
- They are better suited to large scale production than other unit oral dosage forms[2,3]

1.1.2.Disadvantages of Tablets[4,5]:

- Difficult to swallow in case of children and elderly patients.
- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low density character.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, poor absorption in the GI tract or any combination of this features may be difficult or impossible to formulate and manufacture as a tablet.
- Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression or the tablets may require coating.

1.2. ADDITIVES USED IN TABLETS

Excipients are pharmacologically inactive substances included in the formulation which is used as a carrier of active ingredient[6]. The excipients used in the tablet formulation includes,

1. Diluents/fillers
2. Binders
3. Disintegrants
4. Lubricants
5. Glidants
6. Anti-Adherents
7. Miscellaneous

Diluents

Diluents are used to increase the bulk content of the dosage form. This is done in a situation where the active constituent to be incorporated in the formulation is of less quantity. For example if the active ingredient is just 5 mg, in such a case a tablet of just 5 mg is very difficult to manufacture and handle too, thus the bulk content is increased by addition of inactive excipients. Round tablets of weight 120mg to 700mg and oval tablets of weight 800mg are easy to handle. The following are examples of diluents used in tablet formulations .E.g. Lactose, lactose anhydrous, lactose spray dried, direct compressible starch, hydrolyzed starch, MCC, other cellulose derivatives, dibasic calcium phosphate dihydrate, mannitol, sorbitol, sucrose, calcium sulphate dehydrate, dextrose, etc[7].

Binders[8]

These are the dry powders or liquid which are added during wet granulation to promote granules or to promote cohesive compact during direct compression. They provides mechanical strength to the tablets. Binders can be in powder form and liquid form. Examples of the binders are

1. Powder binders**:** Methyl cellulose, polyvinyl pyrolidone, PEG.
2. Solution binders**:** Gelatin, PVP, HPMC, PEG, sucrose, starch.

Disintegrants

Disintegrants are added to the formulation as it breaks the dosage form into smaller particles when it comes in contact with the liquid. These smaller fragments have greater surface area which will increase the dissolution of the drug. When the tablet comes in contact with the liquid, the liquid penetrates into the pores of the tablets and breaks it into fragments. To improve the water uptake into the pores, certain hydrophilic polymers are added to the formulation[9]. E.g. starch, starch derivatives, clay, cellulose, alginates, polyvinyl pyrolidone, cross linked sodium carboxy methyl cellulose, etc.

Lubricants

Lubricants are used to reduce the friction between the tablets and die cavity when the tablet is getting ejected from the die. Lack of lubricant can lead to problems like capping, scratch on the sides of the tablet, fragmentation of the tablet, shape out etc. For a lubricant the time of addition, concentration in which it is to be added and the combination are the important parameters. E.g. stearic acid, stearic acid salts, stearic acid derivatives, talc, PEG, surfactants, waxes, calcium stearate and magnesium stearate are the most commonly used lubricants[10].

Glidants

Glidants are used to improve the flow property of the formulation. It reduces the friction between the particles and between the hopper and particles and die cavity and particles. Actually glidant, lubricant and anti-adherent have a close relation to each other. They have some functions in common. Most of the glidants used are hydrophobic, thus they are to be carefully added (i.e) concentration regulated. E.g. talc, colloidal silicone dioxide, corn starch.

Anti-Adherents

Anti-Adherents are added to prevent adhesion of tablet material to the punches and dies.
E.g. Talc, magnesium stearate, starch.

Miscellaneous

Apart from the above mentioned principal ingredients, the following excipients also improve the dosage form characters. They are adsorbents, flavoring agents, colouring agents and sweetening agents.

Adsorbents

Adsorbents are used when there is a need to add a liquid or semisolid ingredient in the formulation. Adsorbents are capable of sorbing the liquid component on to the dry powder. Thus oil or liquid component can be incorporated into the powder. E.g.Magnesium oxide, kaolin,bentonite,etc.

Flavoring agents

They are incorporated into the formulation to improve the flavor or to give a pleasant taste to the formulation. Flavoring agents are mostly restricted to the formulations in which are intended to be released in the mouth or chewable tablets. They are usually added in along with the granules .E.g. Chocolate flavor, peppermint flavor, vanilla flavor, Trusil orange flavor etc.

Coloring agents

Colorants are added to the formulation in order to increase the appeal, patient compliance or for identification of the formulation. Usually the colorants are added in the form of insoluble powder or in liquid form. E.g. FD&C and D&C dyes and lakes.

Sweetening agents

Sweetening agents are added to control the taste and hence the acceptability of tablets. These agents are of particular importance if the conventional tablet contains a bitter drug or, more importantly, if it is a chewable tablet. E.g.Aspartame, sucralose, sucrose, glycerin, mannitol, sorbitol, acesulfame potassium, saccharin sodium etc.

1.3. DIFFERENT TYPES OF TABLETS[11]

Tablets are solid dosage form manufactured either by dry granulation, wet granulation or direct compression containing medicaments with or without excipients, intended to produce desired pharmacological response. Various types of tablets are being manufactured according to the route of administration and type of dosage form. They are

Tablets ingested orally includes

1. Sugar coated tablet
2. Chewable tablet
3. Film coated tablet
4. Compressed tablet
5. Multiple compressed tablet
6. Enteric coated tablets

Sugar coated tablets:

These are compressed tablets which are coated with sugar, in order to mask the bitter taste or odor of the drug.

Chewable tablets:

These are big sized tablets which are difficult to swallow. Hence they are made in such a way that they are consumed by chewing the tablet. Most of antacid tablets are chewable types.

Film coated tablets:

These are compressed tablets covered with a thin layer or film of a water soluble material. A number of polymeric substances may be used for film coating. Film coating imparts the same general characteristics as sugar coating, in addition it offers reduced time period required for the coating operation[12].

Compressed tablets:

These tablets are prepared by compression technique in which tablets are not coated with any material. It comprises a mixture of active substances and excipients usually in powder form, pressed or compacted into a solid dose[13].

Multiple compressed tablets:

These tablets are prepared to separate physically or chemically incompatible ingredients or to produce repeat action or prolonged action products. A special type of tablet making machine is used which provides compressions.

Enteric coated tablets:

These are compressed tablets which are coated with substance which disintegrates in intestine. A tablet that has special outer covering designed to dissolve in the small intestine. Once the enteric coating is dissolved, the tablet disintegrates and the active ingredient gets absorbed in the systemic circulation.

Tablets used in oral cavity includes

1. Sublingual tablets

2. Buccal tablets

Buccal tablets and Sublingual tablets:

These are small flat oval tablets, intended to be dissolved in the buccal pouch (buccal tablets) or beneath the tongue (sublingual tablets) for absorption through the oral mucosa[14].

Tablets used to prepare solution includes

1. Effervescent tablets

2. Molded tablets

2. Dispensing tablets

Effervescent tablets:

They contain sodium bicarbonate and an organic acid such as tartaric or citric acid along with the drug. In the presence of water, they react liberating carbon dioxide which acts as a distintegrator and thus produces effervescence.

Molded tablets:

Tablet Triturates are molded tablets made of powders created by moistening the powder mixture with alcohol and water. They are used for compounding potent drugs.

Dispensing tablets:

These tablets contain excipients which gets dissolved quickly to form a clear solution. These tablets are highly toxic if taken orally by mistake. The medicaments commonly incorporated in these tablets include mild silver proteinate, bichlorides of mercury merbromin and quaternary ammonium compounds.

Tablets which are administered via other route includes:

1. Vaginal tablet
2. Implantation tablets

Vaginal tablets:

These tablets are meant to dissolve slowly in the vaginal cavity. The tablets are typically ovoid or pear shaped to facilitate retention in the vagina. These tablets are used to release steroids, antibacterial agents or astringents to treat several vaginal infections.

Implantation tablets:

These are the tablets meant to be put in the body sub-surfaces mostly below the skin or into muscles. These implants once inserted into the body tissues, they release the drug slowly over a period of months to year. Drugs like contraceptives, steroids are given in this route. There is no need for regular administration of the drug if these implants are used. But they can cause pain and sometimes release excess drug leading to toxicity[15].

1.4. MANUFACTURING PROCESS OF TABLETS[16]

The typical manufacturing process of tablets are given in table.1

Table: 1. Typical Unit Operation Involved In Wet Granulation, Dry Granulation and Direct Compression methods.

Wet granulation	Dry granulation	Direct compression
1.Milling and mixing of drugs and excipients	1.Milling and mixing of drugs and excipients	1.Milling and mixing of drugs and excipients
2.Preparation of binder solution	2.Compression into slugs	2.Compression of tablet
3.Wet massing by addition of binder solution or granulating solvent	3.Milling and screening of slugs	–
4.Screening of wet mass	4.Mixing with lubricant and disintegrant	–
5.Drying of the wet granules	5.Compression of tablet	–
6.Screening of dry granules	–	–
7.Blending with lubricant and disintegrants	–	–
8.Compression of tablet	–	–

1.5. 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 a coating 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.

1.5.1.Objectives of Tablet Coating

1. To mask the disagreeable odor, color or taste of the tablet.
2. To offer a physical and or chemical protection to the drug.
3. To control and sustain the release of the drug from the dosage form.
4. To incorporate another drug which create incompatibility problems.
5. To protect an acid-labile drug from the gastric environment.
6. To increase the mechanical strength of the dosage form.

In a coating process, it is most desirable that the coating should be uniform and should not crack under stress. Hence, various techniques were designed for the application of the coating on the tablet surface. Generally, the coating solution are sprayed onto the uncoated tablets as the tablets are being agitated in a pan, fluid bed, etc. As the solution is being applied, a thin film is formed which sticks into each tablets. The liquid portion of the coating solution is then evaporated by passing hot air over the surface of the tumbling pans[17].

1.5.2.Advantages of Tablet Coating

1. Tablet coating must be stable and strong enough to survive the handling of the tablet, must not make tablets stick together during the coating process and must follow the fine contours of embossed characters or logos on tablets.
2. Coating is necessary for tablets that have an unpleasant taste and a smoother finish makes large tablets easier to swallow.
3. Coating provides physical and chemical protection, protects the drug in the stomach and control its release profile.
4. The colorful tablets can also be prepared by the use of dye in the coating solution
5. Drugs that are sensitive to oxygen may require coating[18].

1.5.3.Disadvantages of Tablet Coating

1. The uneven coat may produce rough surface of the tablet.
2. The coating solutions used to coat the tablet may be toxic in nature.
3. The coating may increase the bulk and weight of the tablet.
4. Relatively high cost[19].

1.5.4.Basic Principles Involved in Tablet Coating

Tablet coating is the application of coating composition to moving bed of tablets with concurrent use of hot air to facilitate evaporation of solvent.

1. Coating solution which influences the release pattern as little as possible and does not markedly change the appearance.
2. Color coating which provides insulation.
3. To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibilities or to provide sequential drug release.
4. To improve the pharmaceutical elegance by use of special colors and contrasting printing[20].

1.6. 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

The coating process is usually a batch operating task consisting of the following phases:

- Identification of batch and Recipe selection (film or sugar coating)
- Loading/Dispensing (accurate dosing of all required raw materials)
- Warming
- Spraying (Both application and rolling are carried out simultaneously)
- Drying
- Cooling
- Unloading

1.6.1.Coating Equipment

A modern tablet coating system combines several components such as[21]:

- A coating pan.
- A spraying system.
- An air handling unit.
- A dust collector.

1.6.2.Tablet Coating Defects:

- Sticking and picking
- Roughness
- Orange peel effect
- Bridging and filling
- Blistering
- Hazing / Dull film
- Color variation
- Cracking

Sticking and Picking:

Over wetting or excessive film tackiness causes tablets to stick to each other or to the coating pan. On drying, at the point of contact, a piece of the film may remain adhered to the pan or to another tablet, giving a "picked" appearance to the tablet surface and resulting in a small exposed area of the core. It is caused by over-wetting of the tablets or under-drying or by poor tablet quality.

Roughness:

A rough or gritty surface is a defect often observed when the coating is applied as a spray. Some of the droplets may dry rapidly before reaching the tablet bed, resulting in deposits of spray dried particles on the tablet surface. Moving the nozzle closer to the tablet bed or reducing the degree of atomization can decrease the roughness due to spray drying. Roughness also increase with pigment concentration and polymer concentration in the coating solution.

Orange Peel Effect:

Inadequate spreading of the coating solution before drying causes a bumpy or orange peel effect on the coating. This indicates that spreading is impeded by too rapid drying or by high solution viscosity. Thinning the solution with additional solvent may correct this problem.

Bridging and Filling:

During drying, the film may shrink and pull away from the sharp corners of intagliation or bisect resulting in a bridging of the surface. Filling is caused by applying too much solution, resulting in a thick film that fills and narrows the monogram or bisect.

Blistering:

When coated tablets require further drying in oven, too rapid evaporation of the solvent from the core and the effect of high temperature on the strength, elasticity and adhesion of the film may result in blistering.

Hazing / Dull Film:

It is also called as "Bloom." It can occur when too high processing temperature is used for a particular formulation. It can also occur if the coated tablets are exposed to high humidity conditions and partial salvation of film results.

Color Variation:

This problem can be caused by processed conditions or the formulation. Improper mixing, un even spray pattern and insufficient coating may result in color variation. Migration of soluble dyes, plasticizers and other additives during drying may give the coating a mottled or spotted appearance.

Cracking:

It occurs if internal stresses in the film exceed the tensile strength of the film. The tensile strength of the film can be increased by using higher molecular weight polymers or polymer blends. Internal stresses in the film can be minimized by adjusting the plasticizer type and concentration and the pigment type and concentration[22].

1.7. ENTERIC COATING

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. An ideal enteric polymer will;

- Protect drug from being destroyed by gastric contents, either enzymes or highly acidic gastric fluids. E.g. Low pH destroys some drugs (Erythromycin).
- Prevent or reduce nausea and vomiting associated with a drug's irritation of gastric mucosa. E.g. Aspirin.
- Deliver the drug to its absorption site in the intestine.
- Deliver the drug intended for local action in the intestine. E.g. Intestinal antibacterial or antiseptic agent.
- Minimize first pass metabolism[23].

1.7.1. Advantages of Enteric Coated Tablets

1. Enteric coating is employed for a number of therapeutic, safety and medical reasons. (E.g) Some drugs when directly exposed to the gastric mucosa, including aspirin and vigorous electrolytes such as NH_4Cl produce gastric irritation.
2. The low pH of the stomach may destroy some drugs and hence enteric coating may deliver the drugs in highest concentration possible within the intestine.
(E.g) Anthelmintic drugs.
3. Protect the active pharmaceutical ingredients, from the acidic environment of the stomach (E.g. Enzymes and certain antibiotics).
4. Minimize first pass metabolism of drugs[24].

1.7.2.Disadvantages of Enteric Coated Tablets

1. Relatively high cost, long acting time and high bulk led to the use of other coating materials.
2. This process is tedious and time consumed and it requires the expertise of highly skilled technician[25].

1.7.3.Enteric Coating – Imperative:

When a tablet is swallowed it travels down the oesophagus to the stomach. In the stomach the tablet is churned and gyrated in highly acidic digestive secretions with pH (1- 4) for 45 min to 2 hours. If anything left of tablet, it will be passed through the duodenum to the small intestine. Stomach acid breaks down the tablets to prematurely release active ingredients (i. e) enzymes. The highly acidic environment of the stomach destroys the majority of the enzymes activities. The enteric coating was done on different types of dosage forms like tablets, capsules, pellets and granules as these are most commonly used when compared to other dosage forms.[26]

1.8. COMPOSITION OF ENTERIC COATED TABLETS

An enteric coating composition includes 0.01% - 10% resin and about 0.01% - 10% polymer. The enteric coating composition may be applied to a substrate, such as pharmaceutical, neutraceutical, fruit, vegetable, agriculture or industrial product to form an enteric coating on the substrate. After the forming of tablet core, the tablet core are first coated with separating layer and then with the enteric coating layer. The Enteric coated formulation usually contains the following components[27]

a) Polymer.
b) Plasticizer.
c) Solvent.
d) Colorant

a) Polymer

Polymers are substance containing a large number of structural units joined by the same type of linkage. These substances often form into a chain-like structure. Starch, cellulose and rubber all possess, polymeric properties. Enteric coating polymers with an acid-resistant property generally possess free carboxylic acid groups on the polymer backbone. They are insoluble in acidic media but become deprotonated and dissolved in basic media at pH nearly neutral values (pH>5).

E.g.Alginate, Polyvinyl acetate phthalate (PVAP), Methacrylic acid copolymer dispersion (Eudragit L30D-55).

b) Plasticizer

Success of enteric coating efficiency mostly relies on the addition of plasticizer. Plasticizers are a group of auxiliary components that improve elasticity of the polymeric film. The type of plasticizer should be selected carefully as it influences the film brittleness, compatibility with the coating substrates and product stability. A wide range of plasticizers are available to the formulator such as phthalate esters, phosphate esters, other esters like citrates, stearates, sebacate, oleate, adipate etc. E.g. Tri ethyl citrate, PEG (Polyethylene Glycol), TEC (Triethyl Citrate).

c) Solvent

Solvents are used to dissolve or disperse the polymers and other additives and convey them to substrate surface. Generally enteric coating polymers dissolve well in organic solvents, giving stable coating solution that facilitates faster coating processes due to easy evaporation of organic solvents. The solvents used in enteric coating process are listed below

1. Water.
2. Alcohols.
3. Ketones.
4. Esters.
5. Chlorinated Hydrocarbons.

d) Colorant

Colorants are mainly used to impart a distinctive appearance to the pharmaceutical dosage forms. There are many types of pharmaceutical formulations which need to be colored such as tablets, tablets coatings, capsules (hard gelatin, soft gelatin), liquid orals, tooth pastes, ointments and salves etc. The purpose of coloring varies with different formulations. Coloring may be required to increase the aesthetic appearance or to prolong the stability or to produce standard preparations or for identifications of a particular formulation. The commonly used colorants in coating are water soluble dyes. However, the overall colour effect of these dyes depend on the dye concentration at a particular point, thickness of film at that point and the residual moisture content in the film at that point. E.g. FD and C lakh yellow NO-5.

1.9. 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. The precompression parameters evaluated during tableting are outlined below[28].

Pre-compression Parameters

- ✓ Loss on drying
- ✓ Bulk density
- ✓ Tapped density
- ✓ Carr's index
- ✓ Hausner's ratio

Evaluation of enteric coated tablets are outlined below

Evaluation of Tablets

- ✓ Tablet appearance
- ✓ Hardness test
- ✓ Thickness test
- ✓ Weight variation test
- ✓ Disintegration test
- ✓ Drug content
- ✓ *In vitro* dissolution test
- ✓ Stability studies

CHAPTER-2

REVIEW OF LITERATURE

Naresh *et al.*, (2015)[29] formulated enteric coated tablets of Duloxetine hydrochloride by direct compression technique using polymer hydroxy propyl methylcellulose phthalate, sodium starch glycolate and other excipients like talc, calcium phosphate, magnesium stearate. Hydroxy propyl methylcellulose phthalate was used for preventing drug release in stomach. Sodium starch glycolate was used to reduce the disintegration time of tablet in intestine. Press coated tablets were prepared with different concentrations of enteric coated material like hydroxy propyl methylcellulose phthalate. Press coated tablets were evaluated in terms of their pre compression parameters, physical characteristics, weight variation, hardness, drug content and further tablets were evaluated for *in vitro* drug release. In the dissolution study no drug release was observed in formulation F30 and F31 in acidic medium at first 2 hrs. Gradually drug release was increased in alkaline medium. Hence it can be concluded that enteric coated tablets by press coating technology can be prepared by using different concentrations of HPMCP to reduce the gastrointestinal tract side effects.

V Rajitha *et al.*, (2017)[30] formulated and evaluated Duloxetine hydrochloride tablets by using different enteric polymers like Acryl EZE, HPMC phthalate HP 55, HPMC phthalate HP 55 S, HPMC phthalate HP 50. The prepared tablets were evaluated for various post compression parameters. With Acryl EZE only 5% drug release was observed in pH 5.5 phosphate buffer even after 90 minutes. The Enteric coating suspension was very viscous and the process was very slow when HPMC phthalate HP 55 S was used as enteric polymer. HPMC Phthalate (HP 55) showed poor drug release in pH 5.5 phosphate buffer, whereas the drug release pattern with HPMC phthalate HP 50 was high when compared to innovator. So a combination of HPMC Phthalate (HP 55) and HPMC Phthalate (HP 50) were used and different ratios of HPMC Phthalate (HP 55) and HPMC Phthalate (HP 50) were tried out. The release profile of E12 formulation matched with that of the innovator product (HP 55: HP 50=6:4). Different solvent systems like IPA/DCM-1:1, Acetone/water in the ratio 1:1 and 8:2 were tried out as enteric solvents. Acetone/water in the ratio 8:2 was optimized. The Different kinetic models were applied to optimize enteric coated formulation (E12) and observed that it follows zero order kinetics with Higuchi diffusion mechanism. The stability studies were conducted at 40ºC/75%RH (accelerated stability testing) for 2 months. The overall results

revealed that the assay, acid resistance, dissolution release profile of optimized enteric coated formulation (E12) complies with that of innovator product and was found to be stable.

P.Rajesh *et al.*, (2013)[31] formulated Duloxetine delayed release (DR) pellets. Duloxetine is a novel anti-depressant drug used widely for treatment of depression and generalised anxiety disorder, but it is having disadvantage of forming a toxic product of alpha-naphthol when comes in contact with 0.1N HCl. So in order to prevent toxic product formation and to promote the enteric release, the present research work was directed towards the development of a delayed release dosage form of Duloxetine in the form of capsules. In the present study polymers such as HPMC E5, HPMC HP 55 was used as coating polymers which helps in providing delayed release. The di ssolution studies of the dosage form was performed and analysed by HPLC. Different evaluation parameters such as drug - excipient compatibility by FT-IR, XRD and DSC were done and *in vitro* drug release was performed which showed dissolution profile as per specification. Different polymers are optimized on the basis of release pattern. The marketed formulation was evaluated for the *in vitro* release studies and formulated product is compared with the marketed delayed release pellets. The study concluded that the Duloxetine delayed release formulation containing 10% HPMC E5 and 15% HPMC HP 55 showed good release pattern and can be used for future research in developing enteric release capsule formulation for acid labile drugs.

Preethi Mylavarapu *et al.*, (2011)[32] formulated Duloxetine hydrochloride delayed release enteric coated pellets in capsules. Since Duloxetine hydrochloride degrades in the acidic environment, it is important to bypass the acidic pH of the stomach. Protection of drug from acidic environment is done by coating the drug with enteric polymers by using suspension layering technique in Fluidized bed processor (FBP) with different enteric polymers like PVAP (Poly Vinyl Acetate Phthalate), Kollicoat MAE 30 DP, Eudragit L30 D55 (Methacrylic acid copolymer) and HPMCP (Hydroxy propyl methyl cellulose phthalate). The prepared pellets were studied for their *in vitro* release studies and were analyzed by using HPLC technique. The release kinetics was analyzed using the zero-order model, first-order model and Higuchi's square root equation. FT-IR (Infrared spectroscopy) and DSC (Differential Scanning Colorimetry) studies were performed to know the compatibility of the drug with various excipients and SEM (Scanning Electron Microscopy) analysis were performed to know the particle size and morphology of the pellet. The results depicted that HPMCP gave a good dissolution profile and process suitability compared to Eudragit L30

D55, Kollicoat MAE 30DP and PVAP and hence optimized based on the similarity factor (F2 value). It can be concluded that the optimized formulation (E10) of Duloxetine Hydrochloride delayed release pellets in capsules was found to achieve the effective drug levels in the intestine.

Sk Zakir Hussain *et al.*, (2011)[33] developed delayed release pellets of Duloxetine hydrochloride with a suitable polymer by using suspension layered method. Drug loaded nuclei was prepared using suspension layered technique in a Fluidized Bed Processor, the nuclei was coated with an acid resistant acrylic polymer (Eudragit L30-D55) and compared the acid resistant properties with HPMC phthalate. The entire coating process was performed in a Fluidized Bed Processor with different thickness. The *in vitro* dissolution studies were conducted in 0.1N HCl for 2 hours followed by phosphate buffer (pH 6.8) for 1 hour with USP dissolution tester (Type II). The results generated in this study showed that proper selection of polymer material based on their physicochemical properties as well as polymer load is important in designing delayed release pellets with best fit of dissolution profile. It may be concluded that the F8 formulation is selected as an optimized formulation compared to other formulations since, the drug release in 3.5 hour's fulfills all the requirements of enteric coated pellets.

Sudipta Das *et al.*, (2008)[34] developed Duloxetine hydrochloride enteric coated tablets using Hypromellose phthalate (HP-55) as enteric coated materials in various proportions. Three formulations were prepared and all of them had same amount of ingredients but only difference is in percentage of coating applied. FT-IR study revelead that there was no interference to the drug with excipients. *In vitro* evaluation were carried out by using USP dissolution testing apparatus. The prepared tablets and commercial tablet showed a fair uniformity of drug content of 99 to 101 %. Physical parameters were observed fairly good in the present study conforming to requirements. Average weight of tablet of all three formulations was found in the range of 129 to 136 mg. In the present study hardness of all tablet formulations was observed in the range of 6 to 8 kg/cm^2. Thickness of all three tablet formulations were found in the range of 3. 11 to 3.17 mm. Friability for all the formulations in the study was in the range of 0.028 to 0.068%. *In vitro* release profile was done in 0.1 N HCl for 2 h and then pH 6.8 phosphate buffer. The commercial tablet after 2 h of operation in 0.1 N HCl, followed by pH 6.8 phosphate buffer media showed 100 % release at

45 min. In formulation 1 (6% enteric coating), two out of six tablets failed in 0.1 N HCl media. In formulation 2 (8 % enteric coating), one tablet failed in 0.1 N HCl media and in formulation 3 (10% enteric coating), all the six tablets passed in 0.1 N HCl media and showed good release profile at 45 min in phosphate buffer. Hence formulation 3 (10% enteric coating) fulfilled all the criteria for enteric coated tablets.

Surya Bhan Singh Rathore *et al.*, (2013)[35] formulated enteric coated tablets of Ilaprazole to reduce the gastrointestinal tract side effects. Four formulations of core tablets were prepared and one which showed rapid disintegration (around three minutes) was selected for enteric coating. Enteric coat was optimized using two different polymers such as HPMCP 50 and Eudragit L 100 in different concentrations. The prepared tablets were evaluated in terms of their pre-compression parameters, physical characteristics and *in vitro* release study. 2.5% seal coating on core tablets was optimized and 9% enteric coating on seal coated tablets was performed using HPMC P 50 (60%), triethyl citrate (10%) and IPA: DCM (60:40) which gives the highest dissolution release profile and f2 value. The stability results revealed that there was no change in the formulation even after 1 month accelerated stability study. So, prepared delayed release tablet of proton pump inhibitor was stable. Hence it can be concluded that delayed release tablets of Ilaprazole could be successfully developed using HPMCP 50 as enteric polymer to reduce the GIT side effects.

Srilakshmi N *et al.*, (2015)[36] formulated Metronidazole enteric coated tablets using various synthetic hydrophilic polymers to control the drug delivery and target the drug to the intestine. The aim of the study was to formulate core tablets using different polymers such as HPMC K 15M and HPMC K100M in different ratios and the core tablets were coated with an enteric polymer. The prepared tablets were evaluated for weight variation, hardness, friability, content uniformity and *in vitro* drug release study. The angle of repose values obtained for the formulations ranged from 25.48^0 to 30.40^0. The compressibility index values for the formulations ranged from 11.36 to 21.8%. The Hausner's ratio values for the formulations ranged from 1.12 to 1.25. This indicates the powder blend has good flow property. The weight variation of the tablets was within the limits of 5%. The measured hardness of tablets in all batches was ranged from 6.0 – 6.2 kg/cm^2. Friability values were found to be less than 1% in all prepared formulations and considered to be satisfactory. Drug content was in the range of 99.17 to 100.2 % indicating good content uniformity in the all formulations. Formulation F12 showed good controlled drug delivery, as it showed 96% drug

release for 24 hrs and it follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism. Thus, the formulated enteric coated tablets seem to be a potential candidate for targeted and sustained drug delivery of Metronidazole for the treatment of diseases in colon.

Rabia Bushra *et al.*, (2010)[37] developed enteric coated Ibuprofen tablets to avoid gastric mucosal irritation and to let active ingredient to be absorbed easily in small intestine. The formulation was developed through the direct compression process. Enteric coating was done using an opadry white sub coating and an aqueous coating dispersion of Acryl-Eze. Enteric coated formulation was subjected to disintegration and dissolution tests by placing in 0.1 M hydrochloric acid for 2 h and then 1 h in phosphate buffer with a pH of 6.8. About 0.05% of drug was released in the acidic phase and 99.05% in the basic medium. Dissolution and disintegration results showed strong acid resistance whereas the drug was freely released in 6.8 buffer solution. The results of stability testing were satisfactory, indicating that coated Ibuprofen tablets were stable under the testing conditions. These results reflect that Ibuprofen can be successfully enteric coated in order to prevent its release in the stomach and facilitate rapid release of the drug in the duodenum, due to the presence of super disintegrant.

Malay R Patel *et al.*, (2012)[38] formulated Doxycycline hydrochloride delayed release tablets by dry mix method. This drug is universal antibiotic and can be targeted to the specific site of absorption by enteric coating using pH dependant polymers. Pre formulation studies like angle of repose, bulk density, tapped density, porosity, carr's index, hausner's ratio were performed. Enteric coating was carried out using different polymers like Eudragit L-30, D-55, hydroxy propyl methylcellulose phthalate, cellulose acetate phthalate and acryl-EZE. The prepared tablets were evaluated for hardness, friability, weight variation, drug content, disintegration and *in vitro* dissolution. Values for the angle of repose were found in the range of $22.1^0 – 27.7^0$. The prepared blends showed good flow properties. Hardness was found to be in the range of 7 to 11 (kg/cm^2) in all the formulations indicating good mechanical strength. In all the formulations the friability value is less than 1% giving an indication that tablets formulated are mechanically stable. The percentage weight variation was within the limits. Drug content was found to be between 90% to 110% and it was within the limits. Formulation D5 and D8 remain intact in 0.1 N HCl and dissolved fastly in pH 6.8 phosphate buffer. Hence it can be concluded that the formulation D5 and D8 containing Eudragit L 30 and D 55 showed better results compared to the formulation containing hypromellose phthalate and cellulose acetate phthalate.

Pranav Palshikar *et al.*, (2013)[39] developed enteric coated tablets of Sodium valproate using cellulose acetate phthalate as enteric coating material. Core tablets were prepared by non-aqueous granulation method and seal coated with PVP K-30 which act as moisture barrier. This seal coated tablet was further coated with cellulose acetate phthalate to dissolve in the intestinal fluid. The *in vitro* release result showed that enteric coating was capable of restricting the drug release in the acidic media. The optimized batch was found to be capable of releasing the drug in same manner of a marketed formulation of Sodium valproate. Hence it can be concluded that, enteric coated Sodium valproate tablets can be prepared by non aqueous granulation method to release the drug in the intestine.

Farha Amna Shaik *et al.*, (2014)[40] formulated Rabeprazole delayed release enteric tablets by direct compression method. Five formulations were developed by preparing core tablets using mannitol as diluent and crospovidone as super disintegrant in different proportions and varying the compositions of sub coating and enteric coating using opadry white and enteric yellow. In the pre formulation studies the micromeritic flow properties of the API were assessed by determining angle of repose, compressibility index and hausner's ratio. The results indicated good free flow of Rabeprazole. Formulation F5 is considered as an efficient delayed release formulation of Rabeprazole as it was comparable to the innovator product. The developed delayed release tablet formulation is quite stable with regard to drug content, physical properties and dissolution rate in the accelerated stability testing. Hence it can be concluded that enteric coated formulation F5 could be successfully prepared to achieve effective drug levels in the intestine.

Sourav Tribedi *et al.*, (2013)[41] developed Pantoprazole sodium enteric coated tablets by direct compression method using different concentration of microcrystalline cellulose as filler, mannitol and dicalcium phosphate as diluents, croscarmellose sodium as disintegrating agent, magnesium stearate and talc as glidant and lubricant respectively. The prepared tablets were evaluated for hardness, weight variation, friability and drug content uniformity and it was found that the results complied with official standards. The prepared tablets were coated using enteric coating polymer such as cellulose acetate phthalate, Eudragit L100 by dip coating method. The *in vitro* release was studied using acidic buffer pH 1.2 and phosphate buffer pH 6.8. Among all formulations C2F9 was found best, with hardness 6.3 ± 0.14 (Kg/cm^2), drug content 98.54 ± 0.12(%), disintegration time 6.02± 0.21(min) and percentage cumulative drug release which started after 120 min and reached 99.72% after 180 min.

Stability studies indicated that the developed tablets were stable and retained their pharmaceutical properties at room temperature and at 40 °C / 75% RH for a period of 3 month.

Madusudhan RaoYamsani *et al.*, (2015)[42] developed enteric coated sustain release tablets of Lansoprazole by using enteric polymers like Kollicoat MAE 30DP and Eudragit L 100. Primary characterization of the drug was done by performing the melting point, identification test by Fourier Transform Infrared Spectroscopy, solubility and assay. Using complexation technique different ratios of the drug were complexed with cyclodextrin to improve photo stability. The stability test results indicated that the inclusion complex was more stable than raw Lansoprazole in the light. It was observed that inclusion complex of Lansoprazole showed increased solubility by about 4.5 times. Among the four polymers chitosan, xanthum gum, locust bean gum and guar gum, chitosan was chosen for further coating process. Physico-chemical and *in vitro* drug release studies were performed for all the formulations. F4C formulation was found to be best formulation which showed better resistance in 0.1N HCl, sustained well and with *in vitro* release of 97.83± 0.39% release in 12h. The study concludes that Lansoprazole and β-CD complex improves the photostability of the enteric coated sustain release tablets of Lansoprazole.

N. Damodharan *et al.*, (2010)[43] developed small intestine targeting tablets of Doxycycline hydrochloride by wet granulation method and enteric coating of tablets using pH dependent polymers like Eudragit and HPMC Phthalate. Pre formulation studies like angle of repose, bulk density, tapped density, porosity, carr's index and hausner's ratio were performed. Six batches (F1 to F6) were formulated and evaluated for hardness, friability, weight variation, drug content, disintegration and *in vitro* dissolution. The prepared blends showed good flow properties. Hardness was found to be in the range of 6-8 (kg/cm^2) in all the formulations indicating good mechanical strength. In all the formulations the friability value is less than 1% giving an indication that tablets formulated are mechanically stable. The weight variation was found to be within the limits. Drug content was found to be between 90% to 110% and it was within the limits. It was observed that the drug release of DF1 (5% HPMC P-55) showed better enteric release of 87% at the end of 90 min and DF4 (5% Eudragit L100) showed drug release of 94% at the end of 90 min. The study concluded that formulation DF4 could be successfully used to protect the drug release in the hostile environment of upper GIT.

Prasanta Kumar Choudhury *et al.*, (2012)[44] formulated matrix tablets of Ornidazole by wet granulation method using matrix forming natural polymers like Guar gum and Xanthan gum in combination with different proportions. The further effect of enteric coat on the matrix tablets for colon specific drug release was investigated. The Ornidazole optimized matrix formulation OM1 showed drug release around 32.37±0.33% in 2 hrs. So it was further enteric coated with 5% Eudragit S100 and coded as OME1 which showed 44.09±0.16% of drug release after 12 hrs. All formulations were subjected to hardness test, friability test, determination of uniform diameter and thickness, drug content and *in vitro* release study. *in vitro* dissolution studies indicated that the drug release in upper part of GIT from matrix tablets of Ornidazole can be prevented by enteric coating with pH sensitive polymer (Eudragit S100), which releases the drug specifically in colonic region to achieve target delivery. Hence it can be concluded that guar gum, xanthan gum has the potentiality for colon specific drug delivery of Ornidazole and Eudragit S100 can be used to protect the drug release in the hostile environment of upper GIT.

Mohammed Sarfaraz *et al.*, (2014)[45] formulated enteric coated tablets of Salbutamol sulphate immediate release tablets by direct compression method using superdisintegrants like croscarmellose sodium, crospovidone and sodium starch glycolate in different concentrations (2.5 - 7.5% w/w) to improve disintegration time. The formulation, which showed best disintegration and dissolution profile, was coated with ethyl cellulose as inner layer and Eudragit S100 as outer enteric coating polymer. The optimized enteric coated formulation E6 containing 2.5% w/w of Eudragit S 100 and 30% w/w of ethyl cellulose as coating system inhibited the release of the drug in 0.1 N HCl and where as 99.04% of drug released in the intestinal medium. Thus, dissolution profiles indicated that E6 tablet containing 2.5% w/w of Eudragit S100 and 30% w/w of ethyl cellulose may be better alternative in the treatment of nocturnal asthma which overcomes the problems of conventional forms.

Ramesh Pastham *et al.*, (2017)[46] formulated Zileuton tablets by employing compression coating technology. Initially the core tablets were prepared by 30% concentrations of superdisintegrants, the formulated core tablets were then coated with the polymers by using compression coating technology. All the core and press coated tablet formulations were subjected to various physical and chemical evaluation tests. The thickness, hardness and weight variation shown by all the tablet formulations were found within the official

pharmacopoeias limits. *In vitro* release of Zileuton core tablet formulation F1 showed faster drug release after 15 min. Faster drug release can be correlated with the high disintegration and friability observed in this study. The enteric coated formulations C1, C3 showed maximum drug release after 4 hour. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C3, C6 and C9 with 95.5%, 94.76% and 97.48% respectively. Hence it can be concluded that the *in vitro* drug release of the optimized formulations is suitable for pulsatile drug delivery.

Anroop B Nair *et al.*, (2010)[47] formulated enteric coated tablets of Esomeprazole magnesium tri hydrate. Different core tablets were prepared and formulation (F-1) was selected for further enteric coating, based on the disintegration time. Seal coating was applied to achieve 3% weight gain using opadry. Enteric coating was carried out using different polymers like Eudragit L-30 D-55, hydroxy propyl methylcellulose phthalate, cellulose acetate phthalate and Acryl-EZE to achieve 5% weight gain. Disintegration studies showed that the formulations failed in 0.1N HCl media. Hence the quantity of enteric coating was increased to 8% w/w. *In vitro* analysis of the developed tablets was carried out. Results from disintegration time and dissolution rate studies indicate that all the Esomeprazole enteric tablets prepared possess good integrity, desirable for enteric coated tablets. Among the polymers studied, the methacrylic polymers exhibited better dissolution rate than the cellulose polymers. Stability studies indicate that the prepared formulations were stable for a period of three months when stored at 40°C ± 2°C / 75% ± 5% RH. This study concluded that enteric coated tablets of Esomeprazole can be prepared using any of the enteric coating polymer studied using a minimal weight gain of 8%.

Deepak Kashyap *et al.*, (2012)[48] developed enteric coated Ibuprofen tablets using PVPK-30 and starch as disintegrating agent. Methacrylic acid copolymer was used as an enteric coating material. The tablets were formulated using wet granulation method. Further *in vitro* drug release from Ibuprofen enteric coated tablets were studied using different percentage of coating material utilizing different dissolution mediums. Moreover, to achieve the maximum drug release, coating of 7% is desired. Hence it can be concluded that Ibuprofen enteric coated tablets prepared by wet granulation techniques, showed promising results. Methacrylic acid copolymer prevents the release of drug for the first 2hrs. The enteric coated tablets are economical and exhibit predictable release behavior. Moreover, with the specified percentage of coating material of 7% maximum release can be effectively achieved. The

coating with copolymer and non selective COX inhibitor properties makes the formulation an excellent candidate for colon specific drug delivery. The results suggested that the prepared enteric coated tablet is an excellent candidate for colon specific drug delivery.

V Kalvimoorthi *et al.*, (2011)[49] formulated Aspirin delayed release tablets to understand the kinetics of drug release by applying mathematical and model-dependent approaches. Six formulations of delayed release tablets were prepared by the direct compression method and simple pan coating using Drug coat N-100 and hydroxy propyl methyl cellulose phthalate (HPMCP) as enteric coating polymers. The *in vitro* drug release was studied in pH 1.2 HCl and 6.8 pH phosphate buffer using USP dissolution apparatus Type 2 at 100 rpm. Zero-order, first- order, higuchi and korsmeyer models were used to estimate the kinetics of drug release. The criteria for selecting the most appropriate model were based on the goodness of fit test and lowest sum of squares residual. Hardness was found to be in the range of 6-8 kg/cm^2 in all the formulations indicating good mechanical strength. In all the formulations the friability value is less than 1% giving an indication that tablets formulated are mechanically stable. Drug content was found to be between 90% to 110% and it was within the limits. The dissolution of F1, F2, F3, F4, F5 and F6 showed percentage drug release of 63.33%, 69.15%, 74.43%, 84.23%, 79.72% and 75.76% respectively at the end of 45 min in the phosphate buffer. Drug release from the optimal batch was explained by the Higuchi model. The difference in percent cumulative drug release of each point was highest for the optimum batch. F4 batch was considered to be the best enteric formula as it showed 84.23% drug release at end of 45 min in the phosphate buffer.

Ajit Patil *et al.*, (2011)[50] formulated enteric coated tablets of Azithromycin dihydrate to reduce the gastro intestinal tract side effects. Three formulations of core tablets were prepared and one showed rapid disintegration (below three minutes) was selected for enteric coating. Enteric coat was employed by using different polymers such as HPMC-55, Eudragit, Ethyl cellulose in different ratios. Combination of HPMC-55 and ethyl cellulose (10:1.5) exibited better dissolution, disintegration, hardness and friability properties. This combination remained intact for two hours in the acidic pH 0.1 N HCl and disintegrated completely in the phosphate buffer pH6.8 within half an hour. Combination of HPMC - 55 and the eudragit (10:1.5) was not intact more than one and half hour in the 0.1 N HCl, also HPMC-55 (F1) not remain intact in 0.1N HCl for more than one hour. So, the combination

of HPMC -55 and ethylcellulose (F2) (10:1.5) was best for the enteric coating, which have given hardness (4-5kg/cm^2), friability (0.8-1%), weight variation (490±10), content uniformity, percent drug release and disintegration within officially specified limits. This study concluded that enteric coated tablets of Azithromycin dihydrate can be prepared by using combination of polymers studied to reduce the GI tract side effects.

Deepak Kaushik *et al.*, (2016)[51] formulated enteric coated tablets of Benzimidazole derivative to enhance its stability. The tablets were coated with HPMC phthalate based enteric polymer with different amount of plasticizers and talc. Prior to enteric coating, core tablets were seal coated to prevent interaction between core and enteric layer. The core tablets were separated into three groups and seal coated with a colour coding scheme to coverage levels of 2% (white colour), 2.5% (yellow colour), 3% (orange colour) weight gains. The purpose of colour coding was to carry out the coating simultaneously to reduce the number of experiments and eliminate potential differences that may exist during separate coating processes. During each enteric coating process, a predetermined amount of labeled tablets were removed after attaining 6, 8 and 10% weight gains. Dissolution results revealed that all enteric coated formulations inhibited drug release for 2 h in 0.1 N HCl and drug release at most intermediate sampling time points in phosphate buffer, pH 6.8. Hence it can be concluded that the enteric coated tablets of proton pump inhibitor coated using polymeric dispersion of HPMC phthalate enhance the stability of drug by remaining intact in 0.1N HCl buffer.

Vaishali Thakkar *et al.*, (2012)[52] developed enteric coated tablets of Fluoxetine HCl by direct compression method and prepared nine batches using fenugreek mucilage at 40%, 50% and 60% concentration, HPMC at 10%, 15% and 20%; compritol ATO 888 at 10%, 15% and 20% and ethyl cellulose at 2%, 3% and 4% concentration. Fenugreek mucilage was extracted from dried ripe seeds of Trigonella foenum-graecum (Fabaceae). Cellulose acetate phthalate was used as an enteric coating agent. The tablets were characterized for weight variation, crushing strength, friability, drug content and *in vitro* drug release study. All the formulations complied with standard specifications. The drug excipients compatibility study was performed by DSC and IR Spectroscopy and no incompatibility was found. The results of *in vitro* dissolution studies indicated that formulations X2, X5 and X8 released 7.03%, 7.03%, 4.75% of Fluoxetine respectively at the end of 2 hour and 98.17%, 78.12%, 65.45% of Fluoxetine respectively at the end of 24 hour. Drug release rate was increased in polymer

order HPMC K 100M > ethyl cellulose > compritol ATO 888. Formulation X2 (50% fenugreek mucilage and 15% HPMC K 100M) could extend drug release upto 24 hour and it exhibited satisfactory drug release within first 2 hours and total release pattern was very close to marketed product. The mechanism of drug release was found to be diffusion coupled with erosion. Optimized formulation was found to be stable when exposed to 40^0C/75% RH. Hence the study concluded that the optimized formulation containing 50% fenugreek mucilage and 15% HPMC K 100M was found to be stable at all the stability conditions and exhibited drug release profile similar to marketed product.

Gobinath T *et al.*, (2014)[53] formulated Pantoprazole sodium enteric coated tablets by direct compression method using different concentration of microcrystalline cellulose as filler, mannitol and di calcium phosphate as diluents, croscarmellose sodium as disintegrating agent, magnesium stearate and talc as glidant and lubricant respectively. The prepared tablets were evaluated for hardness, weight variation, friability and drug content uniformity and it was found that the results comply with official standards. The prepared tablets were coated using enteric coating polymer such as cellulose acetate phthalate, Eudragit L100 by dip coating method. The *in vitro* release was studied using acidic buffer pH 1.2 and phosphate buffer pH 6.8. Stability studies indicated that the developed tablets were stable and retained their pharmaceutical properties at room temperature and 40 °C / 75% RH for a period of 3 month. Among all batches C2F9 was found best, with hardness 5.60 ± 0.24 (Kg/cm^2**)**, drug content 99.08 ± 0.35(%), disintegration time7.02 ± 0.21(min) and percentage cumulative drug release which started after 120 min and reached 99.72 % after 180 min.

Sachin D Bali *et al.*, (2013)[54] developed delayed release enteric coated tablets of Sulfasalazine using different enteric coat polymer to increase bioavailability and to prevent acid degradation, delivering the drugs to its local site of action in the intestine. Core tablets of Sulfasalazine were prepared and evaluated. The cellulose acetate phthalate, HPMC-P polymers were used to coat the core tablet. On the basis of weight gain and USP specification the tablets were coated. The design of enteric coating based on the transit time required for passage to the intestine may be accomplished through coatings of sufficient thickness. The formulation with 6% weight gain was selected as optimized batch which released 98.40% drug in pH 7.5 phosphate buffer. It is concluded that, the enteric coat polymer gives promising dosage form to target the organ and prevent the loss of Sulfasalazine. Hence it can

be concluded that the combination of CAP and HPMC-P have promising delay release property and can achieve higher bioavailability of Sulfasalazine.

Vivek P Chavda et al., (2015)[55] formulated enteric coated Paracetamol tablets to protect the drug from being released in stomach. Core tablets were prepared with and without superdisintegrant using wet granulation method. Dip coating method is used for coating were different concentration of Eudragit L100 is used as coating agent. Preformulation studies like angle of repose, bulk density, tapped density, porosity, carr's index, hausner's ratio were performed. The FDT2 batch showed the highest drug release at the end of total 135 min of 94.13 % which are the satisfactorily promising results. So, we can conclude that the FDT2 is the optimized batch among all three batches. From the reproducible results obtained from the executed experiments it can be concluded that Eudragit L 100 can be used as enteric coated polymer. These results reflected that Paracetamol tablets can be successfully enteric coated in order to prevent its release in the stomach and facilitate rapid release of the drug in the duodenum, due to the presence of superdisintegrant.

Roy Chowdhury Santanu et al., (2014)[56] formulated enteric coated tablets of Erythromycin stearate by wet granulation method. Enteric coating of Erythromycin stearate tablets were done using two polymers like ethyl cellulose and pectin by multivariate ANOVA method by alternating the 2 variables X and Yin rows and columns. Polyethylene glycol was used as a plasticizer while Isopropyl alcohol and water was incorporated as a solvent. The effects of polymers and Isopropyl alcohol as a binder on drug release profile, gastro-resistant properties and matrix integrity of tablet were investigated. Developed formulations were also evaluated for their physical characteristics, drug content, disintegration time, friability, hardness, thickness, swelling index, weight variation, in vitro drug release profile etc. On the basis of various physical characteristic parameters, it was found that all the formulations showed good result. On comparative kinetic modeling study such as (Zero order, First order, Higuchi model and Korsmeyer-Peppas) it was found that all the formulations followed Higuchi model and correlation coefficient (R2) values were nearer to unity. Among those formulations, F4 showed R2 value of Higuchi model more near as compared to the other formulations.

Y. Naveen Kumar *et al.*, (2017)[57] formulated Esmaprazole controlled release tablets by direct compression method using altered concentrations of Eudragit-S 100, Eudragit-L 100 and Eudragit-RSPO. Esomeprazole dose was fixed as 20 mg. Total weight of the tablet was considered as 100 mg. Polymers were used in the concentration of 20 and 40 mg. The pre compression blend of all formulations were subjected to various flow property tests and all the formulations were passed the tests. Prepared compositions were evaluated for various physicochemical parameters such as weight variation, hardness, friability, thickness and drug content. All the compositions showed results within the Pharmacopoeial limits. Dissolution studies showed that the formulation (F-6) showed better desired drug release pattern (i.e.) 97.47% in 24 hours and it followed Zero order release kinetics mechanism. The optimised formula shall be utilized for the formulation development and other studies like bioequivalence study, for triumphant initiation of the product. Hence it can be concluded that the prepared Esmaprazole controlled release tablets may improve the bioavailability, reduce the number of doses and increase patient compliance.

CHAPTER - 3

AIM AND PLAN OF WORK

3.1 AIM OF WORK

Duloxetine hydrochloride is one of the most commonly used antidepressant drug which is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) used to balance the Hormones such as dopamine, serotonin and norepinephrine.

Duloxetine hydrochloride is an acid labile drug which degrades in acidic environment of the stomach thus leading to therapeutic inefficiency.

The study was aimed to formulate enteric coated tablets of Duloxetine hydrochloride using methacrylic acid copolymer (Protectab enteric M1) to avoid degradation and to bypass the acidic pH of the stomach to improve the therapeutic efficacy and to increase the Duloxetine release in the intestine compared to the marketed Duloxetine hydrochloride enteric coated tablets.

Enteric coating was done by using following polymers such as INSTA COAT MOIST SHIELD WHITE (ICMS), Enteric polymer protectab enteric M1.

3.2. PLAN OF THE WORK

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.

1. To carry out the preformulation studies such as

- Evaluation of API
- Description
- Solubility
- Drug – excipient compatibility study

2. To carry out the pre-compression parameters of the powder blend such as

- Angle of repose
- Bulk density
- Tapped density
- Compressibility index
- Hausner'ratio

3. To carry out the drug and excipient interaction study by FT-IR.s

4. To formulate Duloxetine hydrochloride tablets by direct compression method.

5. To carry out the evaluation of uncoated tablets such as

- Hardness
- Thickness
- Weight variation
- Estimation of drug content
- Disintegration time
- *In- vitro* release studies

6. To carry out the enteric coating of best formulation using methacrylic acid copolymer (Protectab enteric M1).

7. To carry out the evaluation of enteric coated tablets such as

- Thickness
- Weight variation
- Hardness
- Disintegration time
- Assay
- *In vitro* dissolution studies

8. To carry out the stability study for the best formulation at 25±2°C/60%±5%RH and 40±2°C/75% ±5% RH for 3 months.

CHAPTER - 4

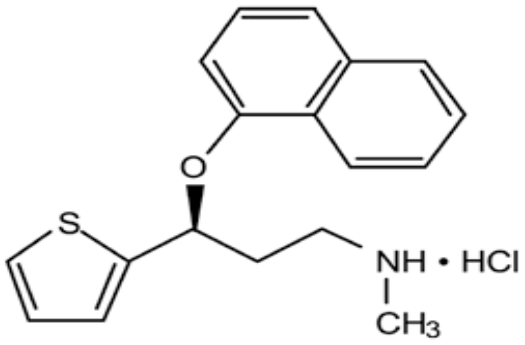
MATERIALS AND METHODS

4.1 LIST OF MATERIALS USED AND MANUFACTURERS

Table: 2. List of Materials Used and Manufacturers

S. No.	Materials	Manufacturers
1.	Duloxetine hydrochloride	MetroChem API Pvt. Ltd, Hyderabad, India.
2.	Mannitol anhydrous	Shandong Tianli Pharmaceutical Co. Ltd, China**.**
3.	Microcrystalline cellulose-PH 112	Accent Microcell Pvt. Ltd, Gujarat, India.
4.	Calcium carbonate	Par Drugs and Chemicals Pvt. Ltd, Vadodara, India.
5.	Povidone-K30	Boai NKY Pharmaceuticals Ltd, China.
6.	Croscarmelose sodium	Prachin Chemicals Pvt. Ltd, Ahmedabad, India.
7.	Colloidal silicon dioxide	Rasula Pharmaceuticals and Fine Chemicals, Hyderabad, India.
8.	Magnesium stearate	Par Drugs and Chemicals Pvt. Ltd, Vadodara, India.
9.	Instacoat moist shield	Ideal Cures Pvt. Ltd, Mumbai, India.
10.	Isopropyl alcohol	Deepak Fertilizers and Petrochemicals Corporation Limited, Pune, India.
11.	Methylene dichloride	Chemplast Sanmer Plant Ltd, Salem, Tamilnadu.
12.	Protectab Enteric MI	Bharat Coats, Chennai, India.
13.	Iron oxide red	Koel Colours Pvt. Ltd, Mumbai, India.
14.	Insta coat glow	Ideal Cures Pvt. Ltd, Mumbai, India.

4.2 DRUG PROFILE[58]

DRUG	:	DULOXETINE HYDROCHLORIDE
STRUCTURAL FORMULA	:	
MOLECULAR FORMULA	:	$C_{18}H_{20}ClNOS$.
MOLECULAR WEIGHT	:	333.88g/mol.
CHEMICAL NAME	:	(S)-N-Methyl-3(naphthalen-1yloxy)-3-(thiophen-2yl)propan-1-amine hydrochloride(s)- Duloxetine HCl.
CATEGORY	:	Selective serotonin and norepinephrine reuptake inhibitor (SSNRI).
DOSE	:	60-120mg/day.
DESCRIPTION	:	White to slightly brownish white solid, crystalline powder.
SOLUBILITY	:	Slightly soluble in water but soluble in ethanol, methanol.
MELTING POINT	:	169ºC - 171ºC.

MECHANISM OF ACTION[59]

Duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate and GABA receptors. The antidepressant and pain inhibitory actions of Duloxetine are believed to be related to its potentiation of serotonergic and nor adrenergic activity in the CNS. The mechanism of action of Duloxetine in stress urinary incontinence (SUI) has not been determined, but is thought to be associated with the potentiation of serotonin and nor epinephrine activity in the spinal cord, which increases urethral closure forces and thereby reduces involuntary urine loss.

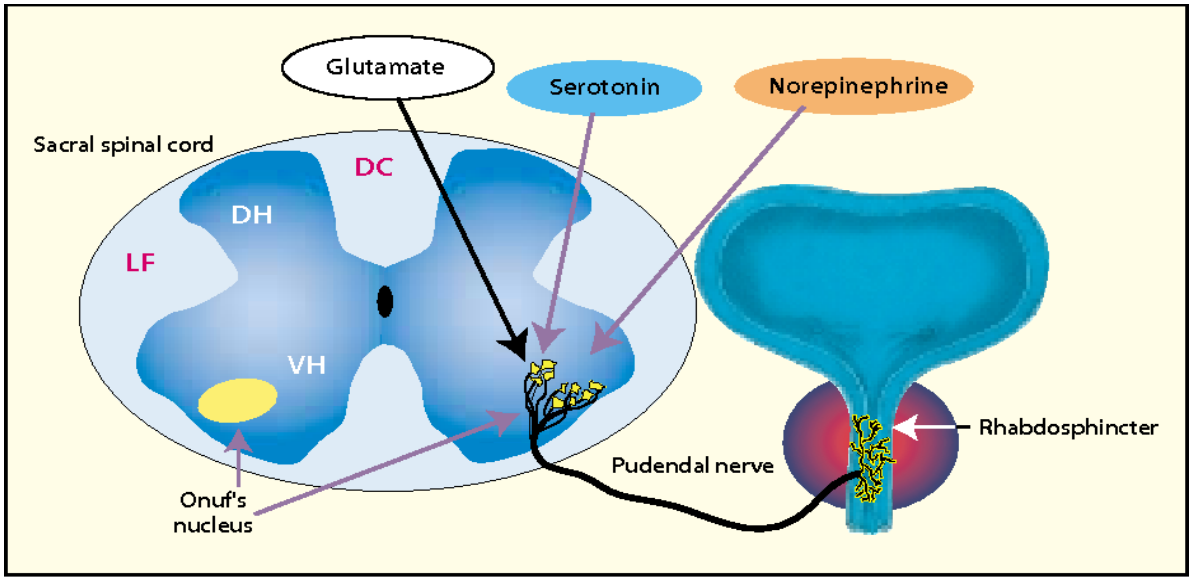


Fig: 1 Mechanism of Action of Duloxetine Hydrochloride

PHARMACOKINETICS[60]

Absorption : Duloxetine is well absorbed by oral rote. The time to reach $\mathbf{C_{max}}$ was typically in the range of 4 to 6 hours in healthy adult volunteers.

Distribution : Volume of distribution is 10-14L/kg. Duloxetine was highly bound to plasma proteins (≥95%).

Metabolism : *In vitro* studies suggest that Duloxetine may inhibit CYPZD6 and can be metabolized by both CYP1A2 and CYPZD6 into multiple inactive metabolites.

Elimination : The elimination halif-life of Duloxetine is about 12 hrs. Trace amount of (≤1%) unchanged Duloxetine was found in urine and about 20% excreted in faeces.

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DRUG INTERACTIONS[61]

Duloxetine is a moderate inhibitor of CYP2D6 and therefore, caution is advisable if administering Duloxetine together with other CYP2D6 inhibitors. Concomitant use of Duloxetine with drugs undergoing CYP2D6 metabolism may result in higher concentrations of the latter. Duloxetine with potent inhibitors of CYP1A2, like Fluvoxamine, Ciprofloxacin or Enoxacin, will result in higher concentrations of Duloxetine and therefore co-administrations is contraindicated.

ADVERSE EFFECTS

Central Nervous System **:** Dizziness, headache, tiredness, weakness, drowsiness.

Gastro Intestinal Tract **:** Constipation, nausea, vomiting, dry mouth, stomach pain.

Musculo Skeletal System **:** Muscle pain or cramps, fibromyalgia.

Skin **:** Rashes, blisters or peeling skin.

INDICATIONS[62]

Duloxetine is indicated for the treatment of :

- Major depressive disorder
- Generalized anxiety disorder
- Diabetic peripheral neuropathy
- Fibromyalgia
- Chronic musculoskeletal pain

DOSAGE AND ADMINISTRATION[63]

Treatment of major depressive disorder:

Adult: 20-30 mg bid or 60 mg once daily.

Maximum dose: 60 mg daily.

Treatment of moderate to severe stress urinary incontinence in women:

Adult: 40 mg bid.

Diabetic neuropathy:

Adult: 60 mg once daily.

Maximum dose: 120 mg daily.

CONTRAINDICATIONS

Duloxetine is contraindicated in patients with a known hypersensitivity to the drug. Concomitant use in patients taking monoamine oxidase inhibitors (MAOI) is contraindicated.

MARKETED PRODUCTS

Combac(tab), Delok(cap), Dulane(cap), Dulife(tab), Duluta-30(tab), Duvanta-30(tab), Dutin(cap), Sympta(tab), Nudep(cap).

4.3 EXCIPIENTS PROFILE

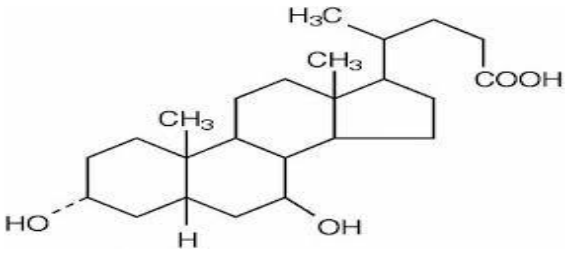
4.3.1 MICROCRYSTALLINE CELLULOSE[64]

NON PROPRIETARY NAMES : BP : Microcrystalline cellulose
JP : Microcrystalline cellulose
PhEur : Cellulose microcrystallinum
USP : Microcrystalline cellulose

SYNONYMS : Avicel, cellulose gel, crystalline cellulose, emcocel, fibrocel, tabulose, vivacel.

CHEMICAL NAME : Microcrystalline cellulose.

MOLECULAR STRUCTURE :



MOLECULAR WEIGHT : 404.481g/mol.

MELTING POINT : 260 to 270ºC.

DENSITY : 1.512 to 1.668 g/cm^3.

DESCRIPTION : Microcrystalline cellulose is a purified white, odorless, tasteless crystalline powder.

SOLUBILITY	**:**	Insoluble in water and organic solvent. Slightly soluble in 5% w/v NaoH solution.
FUNCTIONAL CATEGORY	**:**	Absorbent, suspending agent, diluent and tablet disintegrant.
APPLICATIONS	**:**	Microcrystalline cellulose is used in pharmaceutical industries primarily as binder/ diluent for tablets and capsules in both wet granulation and direct compression process and also possess lubricant and disintegrant properties. It is also used in cosmetics and food products.
STORAGE	**:**	It should be stored in a well closed container in a cool, dry place.
STABILITY	**:**	Microcrystalline cellulose is stable, though hygroscopic material.
INCOMPATIBILITIES	**:**	Microcrystalline cellulose is incompatible with strong oxidizing agents.

4.3.2 MANNITOL ANHYDROUS

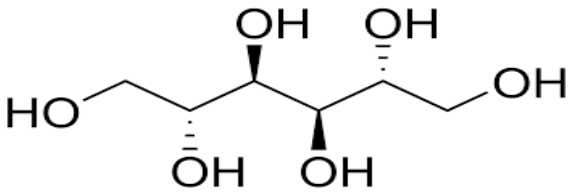
NON PROPRIETARY NAMES[64] **:** BP: Mannitol.
JP: D-Mannitol.
PhEur: Mannitol.
USP: Mannitol.

SYNONYMS **:** Cordycepic acid, emprove, manna sugar, D-mannite, mannite, mannitolum, mannogem, pearlitol.

CHEMICAL NAME **:** D-Mannitol.

EMPIRICAL FORMULA **:** $C_6H_{14}O_6$.

MOLECULAR STRUCTURE **:**



MOLECULAR WEIGHT[65] **:** 182.17g/mol.

MELTING POINT **:** 166-168°C.

DESCRIPTION **:** Mannitol occurs as a white, odorless, crystalline powder or free-flowing granules.

SOLUBILITY : Soluble in alkalis and practically insoluble in ether.

FUNCTIONAL CATEGORY : Diluent, plasticizer, sweetening agent, tablet and capsule diluent and tonicity agent.

APPLICATIONS : Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10-90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients. Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available or in wet granulations.

STORAGE : The bulk material should be stored in a well-closed container in a cool, dry place.

STABILITY : Mannitol is stable in the dry state and in aqueous solutions.

INCOMPATIBILITIES : Mannitol solution, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. Precipitation has been reported when a 25% w/v mannitol solution was allowed to contact plastic. Mannitol was found to reduce the oral bioavailability of Cimetidine.

4.3.3 CROSCARMELLOSE SODIUM[66]

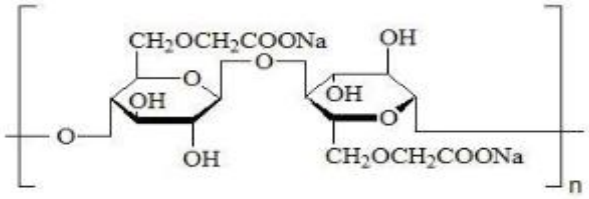
NON PROPRIETARY NAMES : BP: Croscarmellose sodium
JP: Croscarmellose sodium
PhEur: Croscarmellose sodium
USP-NF: Croscarmellose sodium.

SYNONYMS : Ac-Di-Sol, carmellosum natricum conexum, crosslinked carboxymethylcellulose sodium, Pharmacel XL, primellose, solutab, vivasol.

CHEMICAL NAME : Cellulose, carboxymethyl ether, sodium salt, crosslinked.

EMPIRICAL FORMULA : $C_{12}H_{30}NA_8O_{27.}$

MOLECULAR STRUCTURE :



MOLECULAR WEIGHT : 90,000 – 700,000.

MELTING POINT[64] : More than 205°C.

DESCRIPTION : Croscarmellose sodium occurs as an odorless, white or greyish white powder.

SOLUBILITY : Insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

FUNCTIONAL CATEGORY : Tablet and capsule disintegrant.

APPLICATIONS : Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules.

STORAGE : Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

STABILITY : Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30ºC for 14 months.

INCOMPATIBILITIES : The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury and zinc.

4.3.4 COLLOIDAL SILICON DIOXIDE[67]

NON PROPRIETARY NAMES : BP: Colloidal anhydrous silica.
JP: Light anhydrous silicic acid
PhEur: Silica, colloidal anhydrous
USP-NF: Colloidal silicon dioxide

SYNONYMS : Aerosil, Cab-O-Sil, Cab-O-Sil M-5P, colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride and silicon dioxide fumed.

CHEMICAL NAME : Silica.

MOLECULAR STRUCTURE : SiO_2.

MOLECULAR WEIGHT : 60.08g/mol.

DESCRIPTION : Colloidal silicon dioxide is a light, loose, white colored, odorless, tasteless, non-gritty amorphous powder.

SOLUBILITY[64] : Practically insoluble in organic solvents, water and acids except hydrofluoric acid. Soluble in hot solutions of alkali hydroxide, forms a colloidal dispersion with water.

FUNCTIONAL CATEGORY : Absorbent, anticaking agent, glidant, suspending agent, tablet disintegrant.

APPLICATIONS : Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics and food products. Colloidal silicon dioxide is also used to stabilize emulsions and as a thickening and suspending agent in gels and semisolid preparations.

STORAGE : It should be stored in a well-closed container in a cool, dry place.

STABILITY : Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at pH range from 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates.

INCOMPATIBILITIES : Incompatible with diethylstilbestrol preparation.

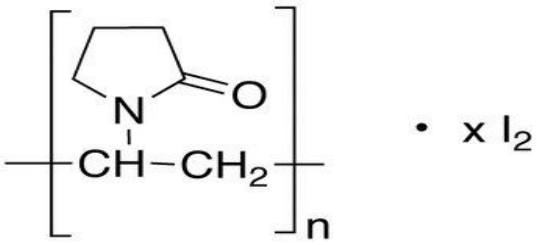
4.3.5 POVIDONE[68]

NON PROPRIETARY NAMES : BP: Povidone.
JP: Povidone.
PhEur: Povidone.
USP: Povidone.

SYNONYMS : Kollidon, Polyvidone, Polyvinyl Pyrrolidone, povidonum, Povipharm, PVP.

CHEMICALNAME : 1-Ethenyl-2-pyrrolidione homo polymers.

MOLECULAR STRUCTURE :



MOLECULAR WEIGHT : 40,000g/mol.

MELTING POINT[64] : 150°C.

DENSITY : 1.2 g/cm^3.

DESCRIPTION : Povidone occurs as a fine, white to creamy white colored or colorless, almost odourless, hygroscopic powder

SOLUBILITY : Freely soluble in acids, chloroform, menthol ethanol (95%), ketones and water. Practically insoluble in ether, hydrocarbon and mineral oil.

FUNCTIONAL CATEGORY : Disintegrant, dissolution enhancer, suspending agent and tablet binder.

APPLICATIONS : In tableting, povidone solutions are used as binders in wet-granulation process.

STORAGE : The powder is hygroscopic; it should be stored in an airtight container in a cool place, dry place.

STABILITY : Povidone darkens to some extent on heating at 1800C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110ºC-130°C. Aqueous solutions are susceptible to mold growth and consequently require addition of suitable preservatives.

INCOMPATIBILITIES : It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin and other compounds.

4.3.6 CALCIUM CARBONATE[69]

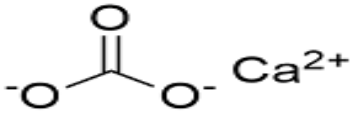
NON PROPRIETARY NAMES : BP: Calcium carbonate
JP: Precipitated calcium carbonate
PhEur: Calcium carbonate
USP: Calcium carbonate

SYNONYMS : Calcii carbonas, calcium carbonate carbonic acid calcium salt, precipitated carbonate of lime, precipitated chalk

CHEMICAL NAME : Carbonic acid, calcium salt

EMPIRICAL FORMULA : $CaCO_3$.

MOLECULAR STRUCTURE :



Calcium carbonate

MOLECULAR WEIGHT : 100.09g/mol.

MELTING POINT : Melting point Decomposes at 825°C.

DESCRIPTION : Calcium carbonate occurs as an odorless and tasteless white powder or crystals.

SOLUBILITY[64]	:	Practically insoluble in ethanol (95%) and water. Solubility in water is increased by the presence of ammonia.
APPLICATIONS	:	Calcium carbonate is employed as a pharmaceutical excipient, mainly in solid-dosage forms as a diluent. It is also used as a base for medicated dental preparations, as a buffering agent and as a dissolution aid in dispersible tablets. Calcium carbonate is used as a bulking agent in tablet sugar-coating process and as an opacifier in tablet film-coating. Calcium carbonate is also used as a food additive and therapeutically as an antacid and calcium supplement.
FUNCTIONAL CATEGORY	:	Buffering agent, coating agent, colorant, opacifier, tablet binder, tablet and capsule diluent, therapeutic agent.
STORAGE	:	Calcium carbonate should be stored in a well-closed container in a cool, dry place.
STABILITY	:	Calcium carbonate is stable in room temperature.
INCOMPATIBILITIES	:	Incompatible with acids and ammonium salts.

4.3.7 MAGNESIUM STEARATE[70]

NON PROPRIETARY NAMES	**:**	BP: Magnesium stearate JP: Magnesium stearate PhEur: Magnesium stearate USP-NF: Magnesium stearate.
SYNONYMS	**:**	Dibasic magnesium stearate, Magnesium distearate, Magnesia stearas, Magnesium octadecanoate, Octadecanoic acid, Magnesium salt, Stearic acid, Magnesium salt.
CHEMICAL NAME	**:**	Octadecanoic acid magnesium salt.
MOLECULAR STRUCTURE	**:**	$[CH_3(CH_2)_{16}COO]_2Mg$.
MOLECULAR WEIGHT	**:**	591.24g/mol.
MELTING POINT[64]	**:**	117–150ºC.
DENSITY	**:**	1.092 g/cm^3.
DESCRIPTION	**:**	It occurs as a fine, white precipitated or milled impalpable powder with a faint odor and a characteristic taste.

SOLUBILITY	**:**	Practically insoluble in ethanol, ethanol ether and water, slightly soluble in warm benzene and warm ethanol (95%).
FUNCTIONAL CATEGORY	**:**	Lubricant.
APPLICATIONS	**:**	It is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet formulations at concentrations between 0.2- 5.0 percent.
STORAGE	**:**	It should be stored in a well-closed container in a cool, dry place.
STABILITY	**:**	Magnesium stearate is stable at room temperature.
INCOMPATIBILITIES	**:**	Incompatible with strong acids, alkalis and iron.

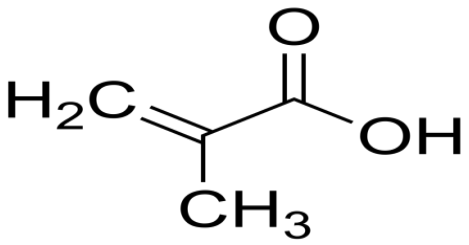
4.3.8 METHACRYLIC ACID COPOLYMER[71]

NON PROPRIETARY NAMES : BP: Methacrylic acid–ethyl acrylate copolymer
PhEur: Ammonio methacrylate copolymer,
USP-NF: Ammonio methacrylate copolymer, Ethyl acrylate and methyl methacrylate copolymer, Methacrylic acid copolymer dispersion.

SYNONYMS : Acryl-EZE, Acryl-EZE MP, Eastacryl 30D, Protectab Enteric M1; Bharath Coat, Polymeric Methacrylic Acid.

CHEMICAL NAME : Poly (methacrylic acid, ethyl acrylate) 1:1.

MOLECULAR STRUCTURE :



MOLECULAR WEIGHT[64] : About 2,50,000.

DESCRIPTION : Synthetic cationic and anionic polymers of dimethyl amino ethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios.

DENSITY : 0.390 g/cm^3.

ACID VALUE : 300-330.

SOLUBILITY	**:**	Miscible in acetone and alcohols, 0.1N HCl, Petrolium ether.
FUNCTIONAL CATEGORY	**:**	Film-forming agent, tablet binder, tablet diluent.
APPLICATIONS	**:**	Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents.
STORAGE	**:**	Stored at temperatures between 5 and 25ºC.
STABILITY	**:**	Stable at temperatures less than 30°C.
INCOMPATIBILITIES	**:**	Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent.

4.3.9 ISOPROPYL ALCOHOL[72]

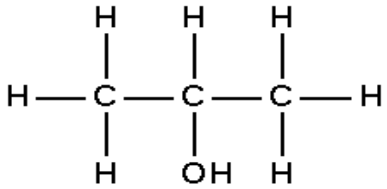
NON PROPRIETARY NAMES : BP: Isopropyl alcohol
JP: Isopropanol
PhEur: Isopropyl alcohol
USP: Isopropyl alcohol

SYNONYMS : Alcohol isopropylico, dimethyl carbinol, isopropanol, petrohol, 2-propanol, rubbing alcohol.

CHEMICAL NAME : Propan-2-ol.

EMPIRICAL FORMULA : C_3H_80.

MOLECULAR STRUCTURE :



MOLECULAR WEIGHT : 60.1g/mol.

MELTING POINT[64] : - 88.5^0C.

DESCRIPTION : Isopropyl alcohol is a clear, colorless, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone. It has a slightly bitter taste.

SOLUBILITY : Miscible with benzene, chloroform, ethanol (95%), ether, glycerin and water. Soluble in acetone, insoluble in salt.

FUNCTIONAL CATEGORY : Disinfectant, solvent.

APPLICATIONS : Isopropyl alcohol is used in cosmetics and pharmaceutical formulations, primarily as a solvent in topical formulations. Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation.

STORAGE : It should be stored in an air tight container in a cool, dry place.

STABILITY : Isopropyl alcohol is stable at room temperature.

INCOMPATIBILITIES : Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition. Isopropyl alcohol may be salted out from aqueous mixtures by the addition of sodium chloride, sodium sulfate and other salts or by the addition of sodium hydroxide.

4.3.10 METHYLENE DI CHLORIDE[73]

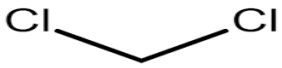
NON PROPRIETARY NAMES : Methylene di chloride

SYNONYMS : Solmethine, narkotil, solaesthin.

CHEMICAL NAME : Dichloromethane.

EMPIRICAL FORMULA : CH_2Cl_2.

MOLECULAR STRUCTURE :



MOLECULAR WEIGHT : 84.93g/mol.

MELTING POINT : -97^0C.

DESCRIPTION : Colorless, transparent, volatile liquid with pungent smell, soluble in water of about 50 times the volume, soluble in phenol, aldehyde, ketone, acetic acid, tri ethyl phosphate, ethyl acetoacetate, cyclohexylamine. Miscible with other chlorinated hydrocarbons and ethanol.

SOLUBILITY[64] : Miscible in ethyl acetate, alcohol, hexanes, methanol, diethyl ether, n-octanol, acetone.

APPLICATIONS : Dichloromethane is largely used in the manufacture of safe film, polycarbonate, the rest used as paints, solvents, metal degreasing agent, gas aerosol spray, polyurethane foam, mold release agent and paint remover. It is also used as the reaction medium in the pharmaceutical industry for the preparation of Ampicillin, Ampicillin and Cephalosporin.

STORAGE : Methylene dichloride should be stored at room temperature in air tight container in a cool, dry place.

STABILITY : In the absence of moisture at ordinary temperature dichloromethane is relatively stable.

INCOMPATIBILITIES : Methylene di chloride is incompatible with alkali metals, strong oxidizing agents, strong bases and oxides of nitrogen, zinc, aluminum, water, magnesium and amines. Liquid methylene chloride will attack some forms of plastics, rubber and coatings.

4.3.11 LAKE IRON OXIDE RED[74]

NON PROPRIETARY NAMES : Iron oxide.

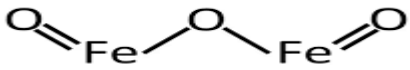
SYNONYMS : Anhydrous ferric oxide, anhydrous iron oxide, ferroxide, hematite, pigment red, red ferric oxide, sicovit.

CHEMICAL NAME : Iron oxide red.

EMPIRICAL FORMULA : Fe_20_3.

MOLECULAR WEIGHT : 159.70g/mol.

MOLECULAR STRUCTURE :



DESCRIPTION : Iron oxides occur as yellow, red, black or brown powder. The color depends on the particle size, shape and crystal structure.

SOLUBILITY[64] **:** Soluble in mineral acids, insoluble in water.

FUNCTIONAL CATEGORY **:** Colorant.

APPLICATIONS **:** Iron oxides are widely used in cosmetics, foods and pharmaceutical applications as colorants and UV absorbers. As inorganic colorants they are becoming of increasing importance as a result of the limitations affecting some synthetic organic dyestuffs.

STORAGE **:** Iron oxides should be stored in well-closed containers in a cool, dry place.

STABILITY **:** Iron oxide red is stable at room temperature.

INCOMPATIBILITIES **:** Iron oxide is incompatible with common organic acids, mineral acids and oxidizing agents.

4.4 INSTRUMENTS USED AND MANUFACTURERS

Table: 3. List of Instruments Used and Manufacturers

S. No	INSTRUMENTS	MANUFACTURERS
1.	Single pan electronic balance	Sartorious, Germany.
2.	12 Station D/B Tooling compression machine	Fluid pack, Ahmedabad, india.
3.	R&D Mini coater	Ideal Cure Pvt Ltd, Mumbai, India.
4.	Vernier calipers	Mitutoyo, Japan.
5.	Dissolution Test Apparatus	Electro lab, Mumbai, India.
6.	Hardness Tester	Campbell electronics, Mumbai.
7.	Friability Test Apparatus	Electro lab, ED-2L, India.
8.	Sieves	Jayant Scientific Ind, Mumbai, India.
9.	Disintegration Test Apparatus	Electro lab, ED-2L, India.
10.	FT-IR spectrophotometer	IR Affinity-1S Shimadzu, Japan.
11.	HPLC	LC-10, Shimadzu, Japan.
12.	UV- spectrophotometer	UV-1800, Shimadzu, Japan.
13.	Stability chamber	Thermo lab, Mumbai
14.	Blister packing machine	Elmach Packages Pvt Ltd, Mumbai, India.

4.5 METHODOLOGY

4.5.1 PREFORMULATION STUDIES[72]

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. The overall objective of preformulation testing is to generate information useful in developing the formulation which is stable and bio-available. Further the use of preformulation parameter maximize the chances in formulating an acceptable, safe, efficacious and stable product. The goals of preformulation 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.

Objectives of preformulation 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.

4.5.1.1 ORGANOLEPTIC PROPERTIES

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

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

4.5.1.2 SOLUBILITY TEST [73]

Solubility of Duloxetine HCl in water, methanol and ethanol was determined by using sonicator at room temperature. The solubility specifications as per I.P was mentioned in table: 4.

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

4.5.1.3 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

4.5.2 FT- IR SPECTRAL ANALYSIS[74]

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.

4.5.3 EVALUATION OF PRECOMPRESSION PARAMETERS

4.5.3.1 MICROMERITIC PROPERTIES

4.5.3.1.1 ANGLE OF REPOSE[75, 76]

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.

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

4.5.3.1.2 BULK DENSITY AND TAPPED DENSITY[77, 78]

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. The bulk density and tapped density were calculated using the following formulas

Bulk density = W/V_0

Tapped density = W/V_f

Where,

W= Weight of powder,

V_0= Initial volume of powder,

V_f = Final volume of powder.

4.5.3.1.3 MEASUREMENT OF POWDER COMPRESSIBILITY

A) Compressibility Index[79]

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.

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

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.

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

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

4.5.4 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.

DIRECT COMPRESSION METHOD[80]

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.

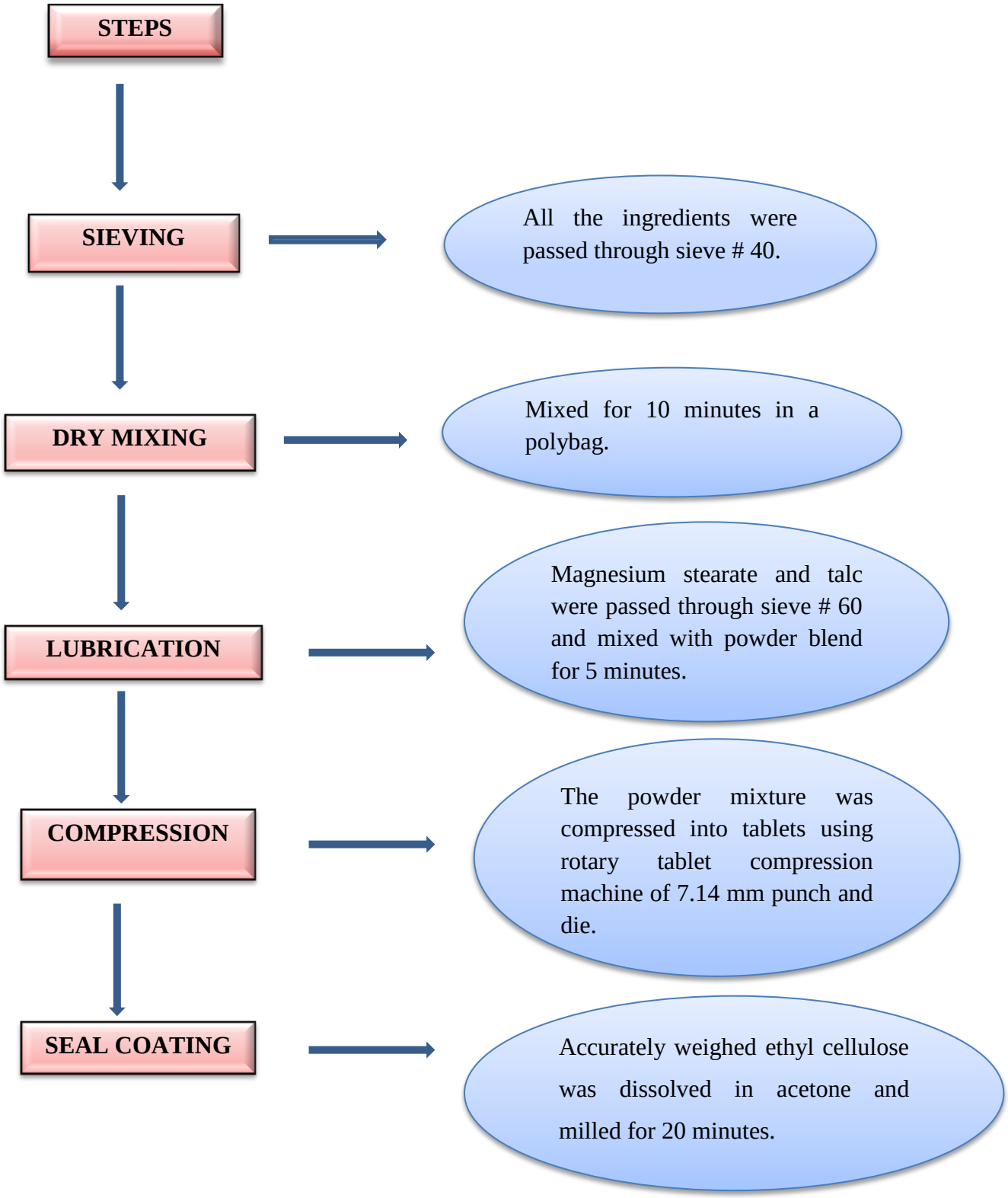
Polish coating

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.

FORMULATION FLOW CHART OF DIRECT COMPRESSION METHOD



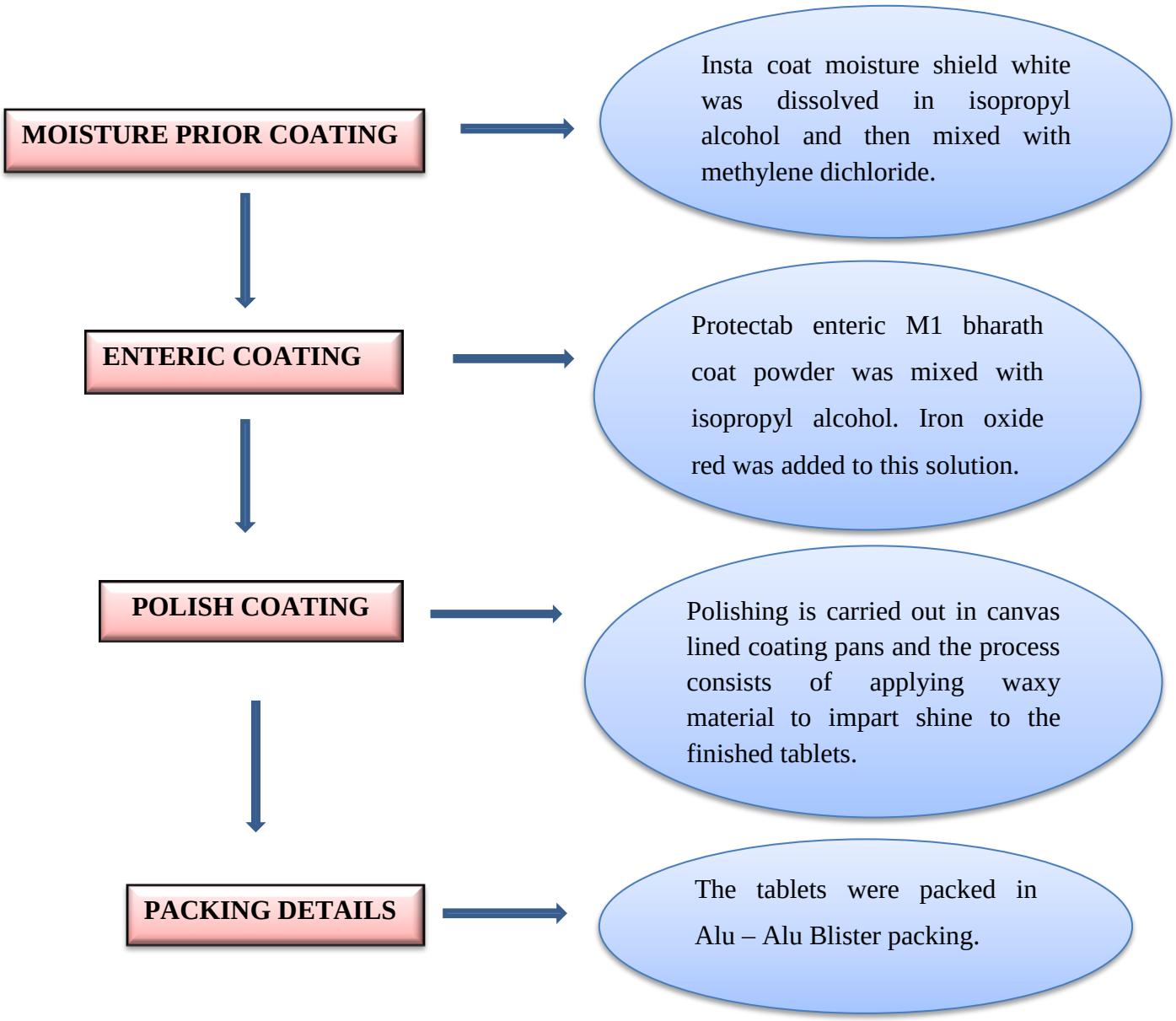

MOISTURE PRIOR COATING
Insta coat moisture shield white was dissolved in isopropyl alcohol and then mixed with methylene dichloride.
ENTERIC COATING
Protectab enteric M1 bharath coat powder was mixed with isopropyl alcohol. Iron oxide red was added to this solution.
POLISH COATING
Polishing is carried out in canvas lined coating pans and the process consists of applying waxy material to impart shine to the finished tablets.
PACKING DETAILS
The 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**

4.5.5 POST COMPRESSION PARAMETERS

The compressed tablets were evaluated for the following parameters.

4.5.5.1 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.

4.5.5.2. 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.

4.5.5.3. HARDNESS TEST[81]

"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.

4.5.5.4. WEIGHT VARIATION TEST[82]

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.

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

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

4.5.5.5 FRIABILITY[83]

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%.

4.5.5.6 DISINTEGRATION TEST[84]

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.

4.5.5.7 ASSAY OF DULOXETINE HYDROCHLORIDE BY HPLC METHOD[85]

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.

4.5.5.8 *IN VITRO* DRUG RELEASE STUDIES[86]

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.

4.5.5.9 STABILITY STUDIES[87]

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.

4.5.5.9.1 Purpose of Stability Testing[88]

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.

4.5.5.9.2 ACCELERATED STABILITY STUDIES[89]

Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid the undesirable delay, the principles of accelerated stability studies are adopted by accelerating the parameters such as temperature, humidity and light.

The International Council for Harmonization (ICH) guidelines titled stability testing for new drug substances and product (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and United States of America. ICH guidelines specifies the length of study and storage conditions.

- ✓ Long term testing: 25 ± 2°C/60% ± 5% RH for 12 months.
- ✓ Accelerated testing: 40 ± 2°C/75% ± 5% RH for 6 months.

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).

CHAPTER-5

RESULTS AND DISCUSSION

Duloxetine hydrochloride is 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 Duloxetine hydrochloride to avoid degradation and to bypass the acidic pH of the stomach. The work was carried out to delay the release of Duloxetine 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.

5.1 PREFORMULATION STUDIES

5.1.1 ORGANOLEPTIC PROPERTIES

The organoleptic properties of Duloxetine hydrochloride was 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

Discussion:

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.

5.1.2 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

Discussion:

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.

5.1.3 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

Discussion:

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.

5.2 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: 13 to 17 respectively.

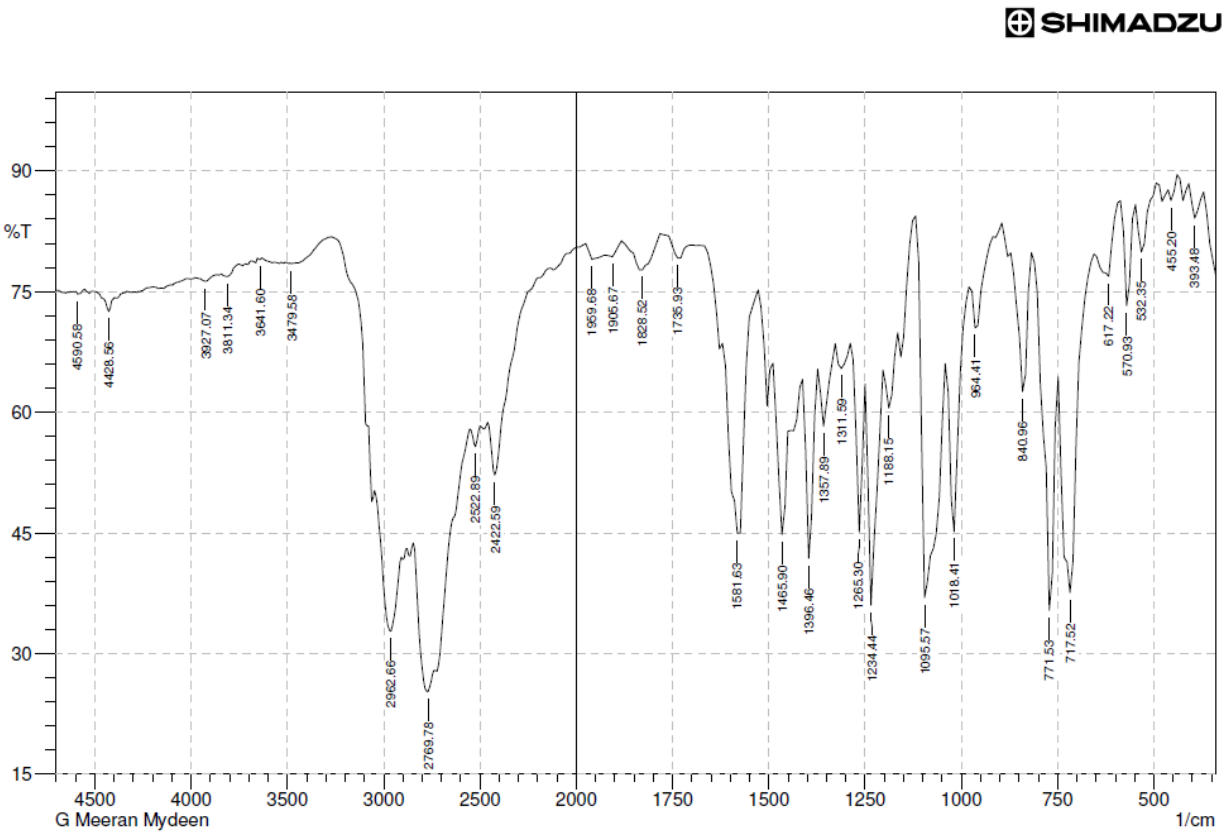


Fig: 2 FT- IR Spectrum of Pure Duloxetine Hydrochloride

Table: 13. FT- IR Spectral Data of Pure Duloxetine 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
7	1095	Ether C - O stretching

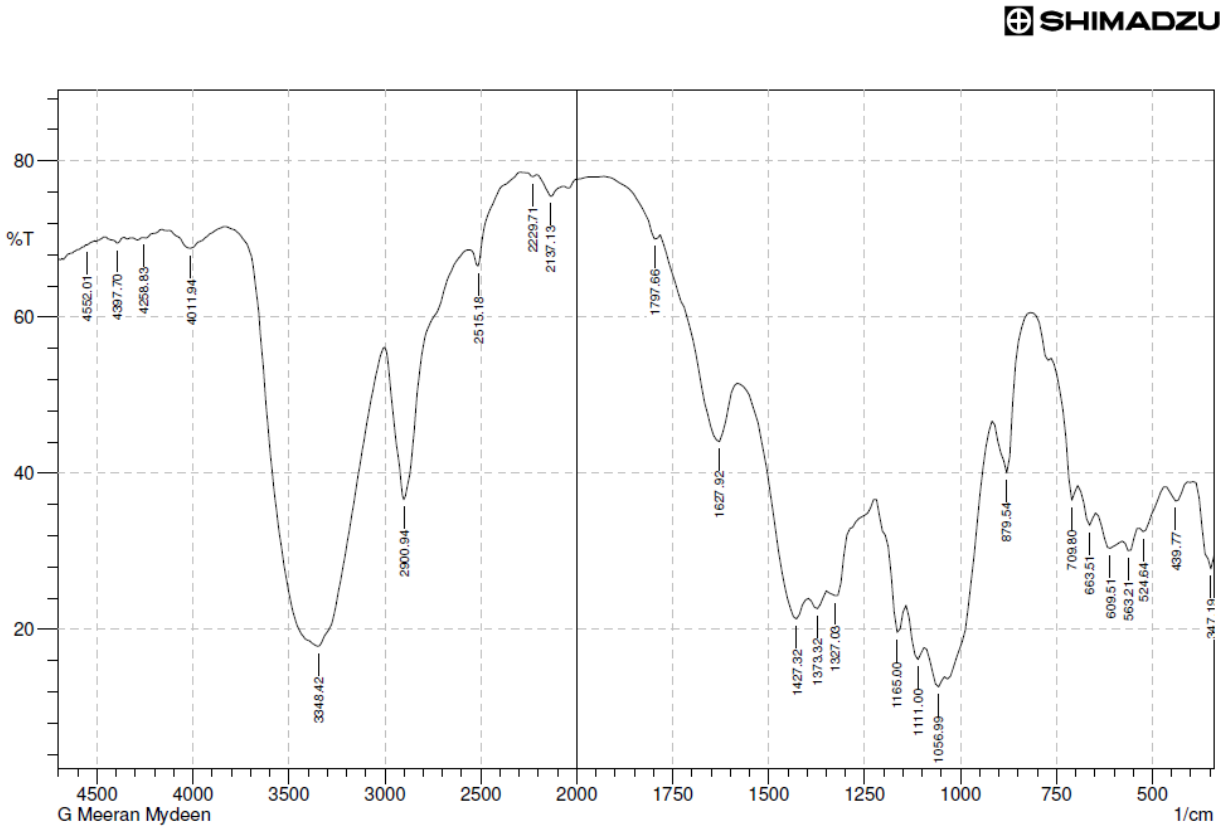


Fig: 3 FT- IR Spectrum of Croscarmellose sodium

Table: 14. 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

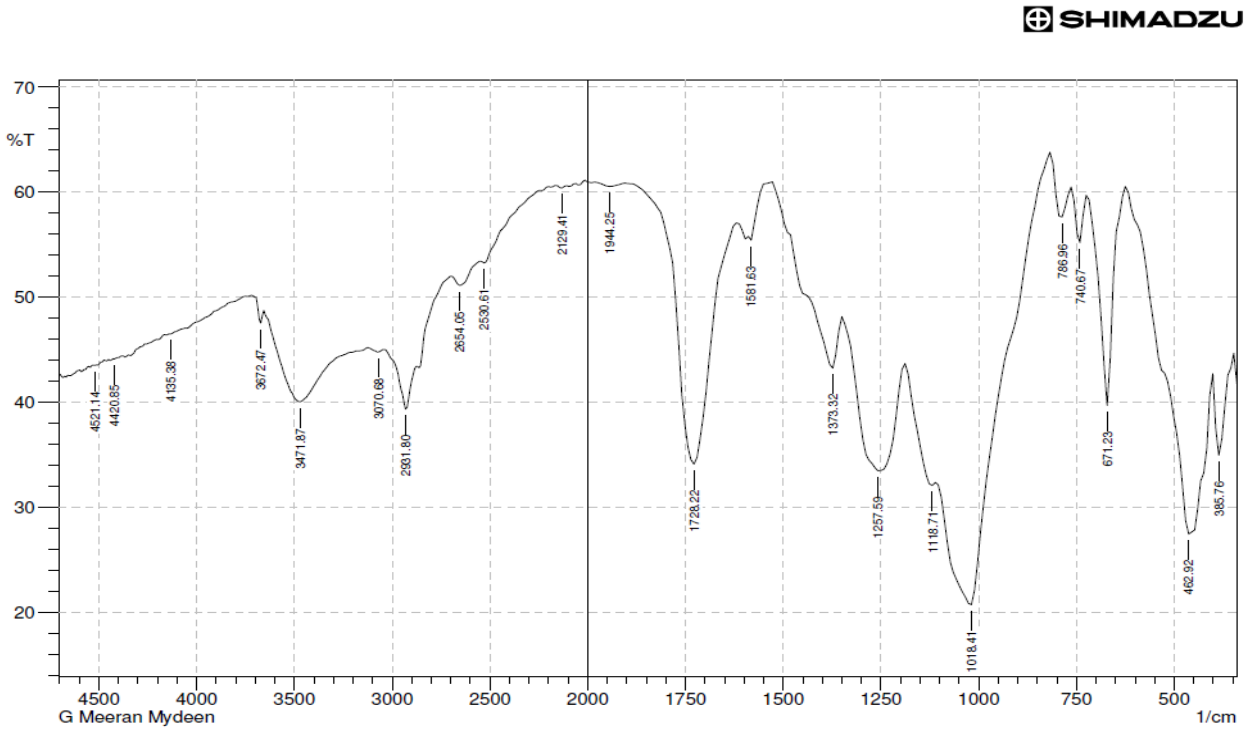


Fig: 4 FT- IR Spectrum of Protectab Enteric M1

Table: 15. 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

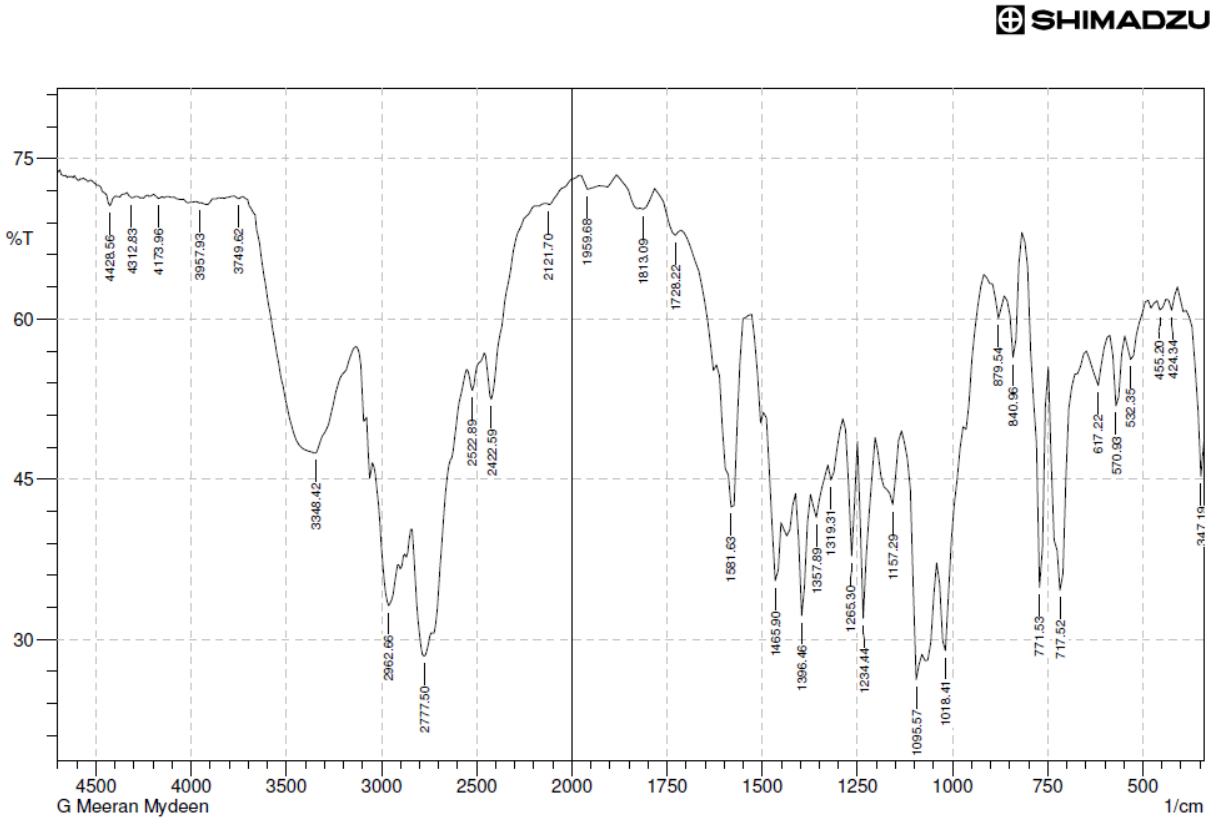


Fig: 5 FT- IR Spectrum of Duloxetine Hydrochloride + Croscarmellose sodium

Table: 16. FT- IR Spectral Data of Duloxetine 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

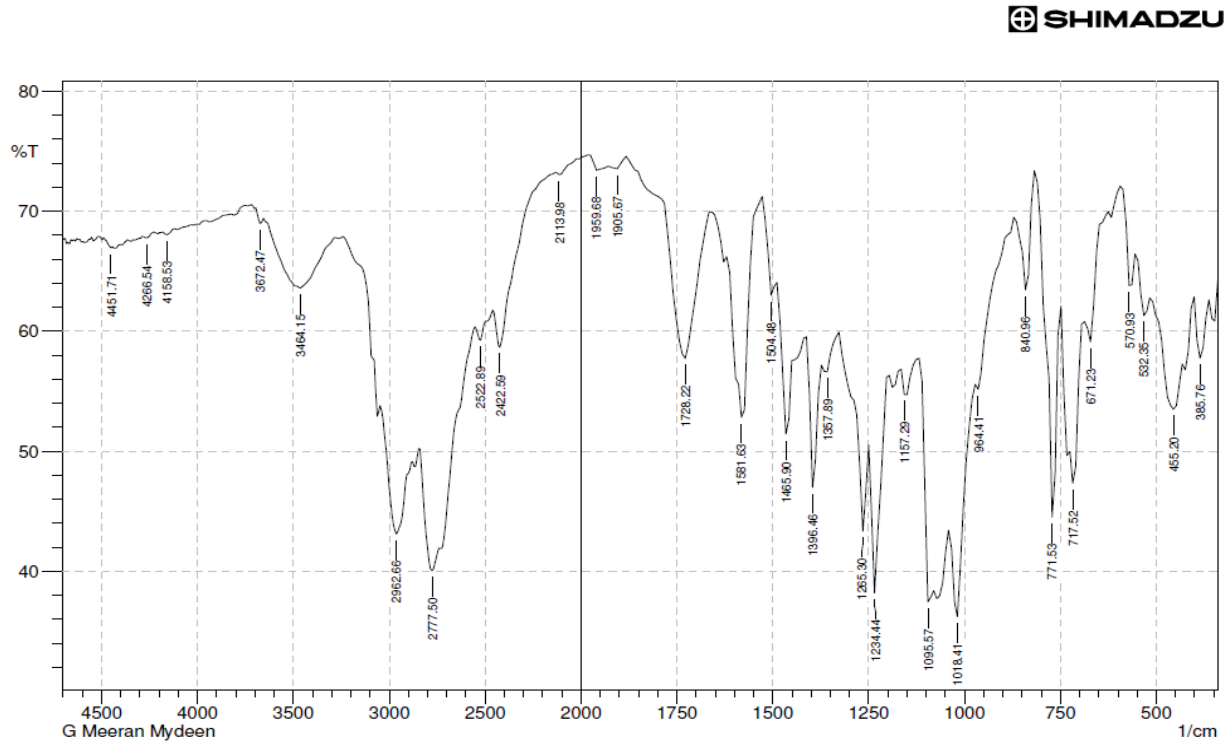


Fig: 6 FT-IR Spectrum of Duloxetine Hydrochloride + Protectab Enteric M1

Table: 17. FT-IR Spectral Data of Duloxetine 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: 18. 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 (Duloxetine 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

Discussion:

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 Duloxetine hydrochloride, thus conforming that no interaction of drug occurred with the components of the formulation.

5.3 MICROMERITIC PROPERTIES

Table: 19. 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.**

Discussion:

Duloxetine hydrochloride powder blends were evaluated for different precompression parameters and the results are mentioned in table: 19.

Angle of Repose

Angle of repose of Duloxetine hydrochloride powder 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 Duloxetine hydrochloride was 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 Duloxetine hydrochloride was 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.

5.4 EVALUATION OF DULOXETINE HYDROCHLORIDE TABLETS

5.4.1 POST COMPRESSION PARAMETERS

5.4.1.1 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: 20.

Table: 20. 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.**

Discussion:

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 Duloxetine hydrochloride tablets 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

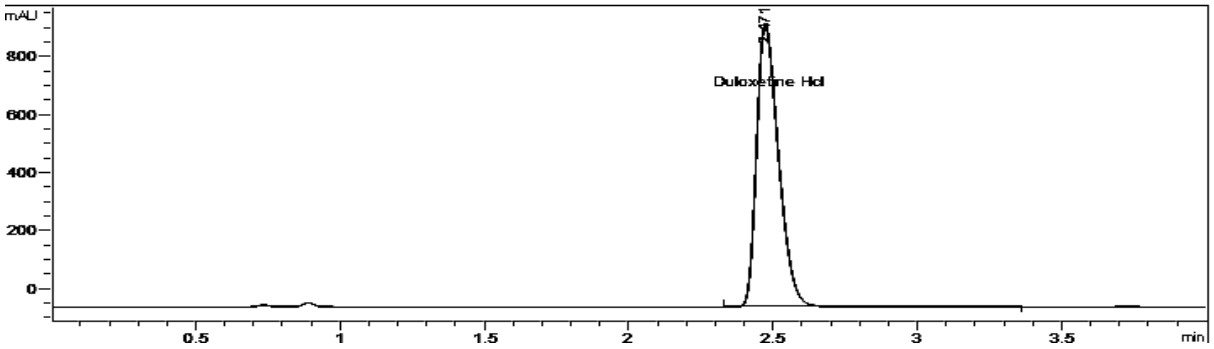
The friability test carried was out by using Roche friabilator. The maximum weight loss should not be more than 1%. The friability values of formulations (F-I to F-V) were found to be in the range of 0.10 ± 0.010 to 0.16 ± 0.005% respectively. Hence all the tablets passed the friability test.

Disintegration Test

Disintegration test of Duloxetine hydrochloride uncoated 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.

5.4.2 ASSAY OF DULOXETINE HYDROCHLORIDE BY HPLC METHOD

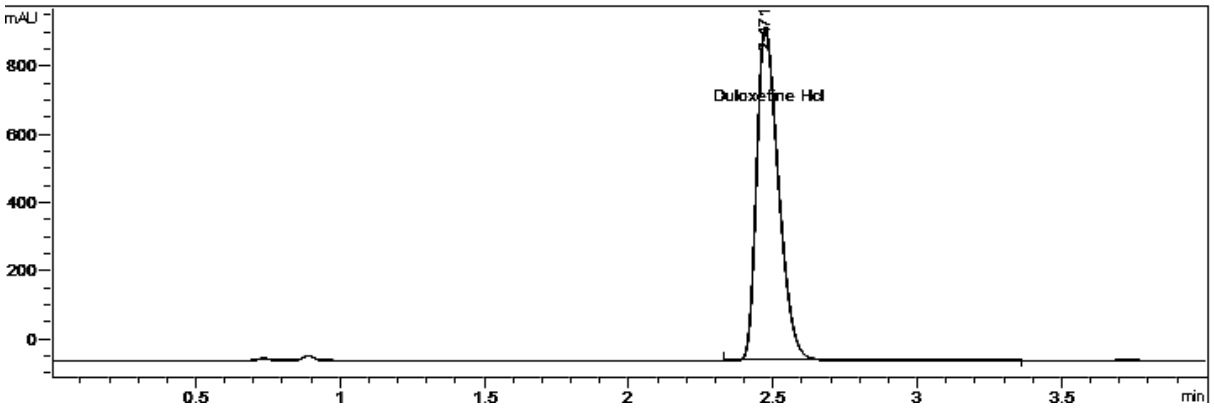
The assay was carried out by HPLC method as per the procedure given in methodology part. The HPLC chromatogram of Duloxetine hydrochloride standard and sample formulations were shown in fig no: 7 to 12 and in table: 20 respectively.



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

***RT – Retention Time**

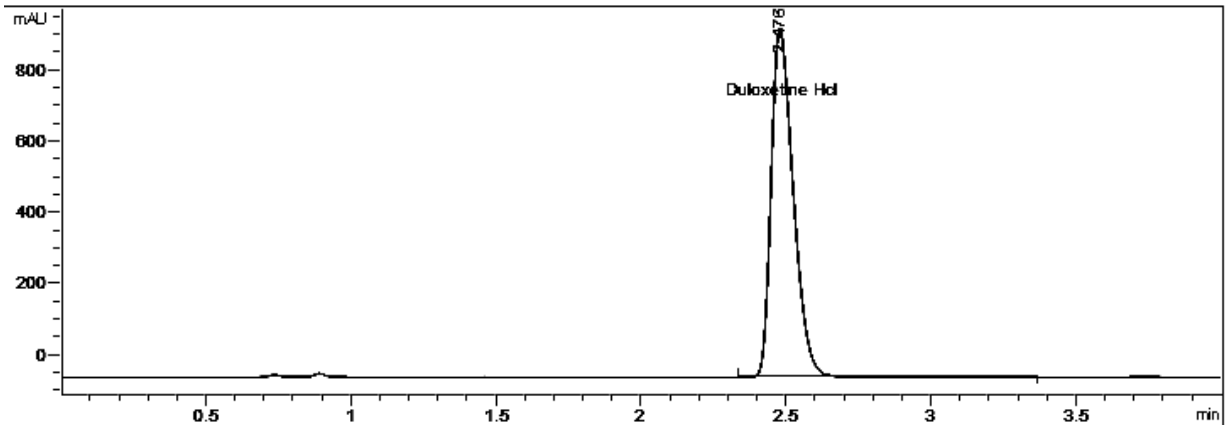
Fig: 7 HPLC Chromatogram of Duloxetine HCI (Standard)



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

***RT – Retention Time**

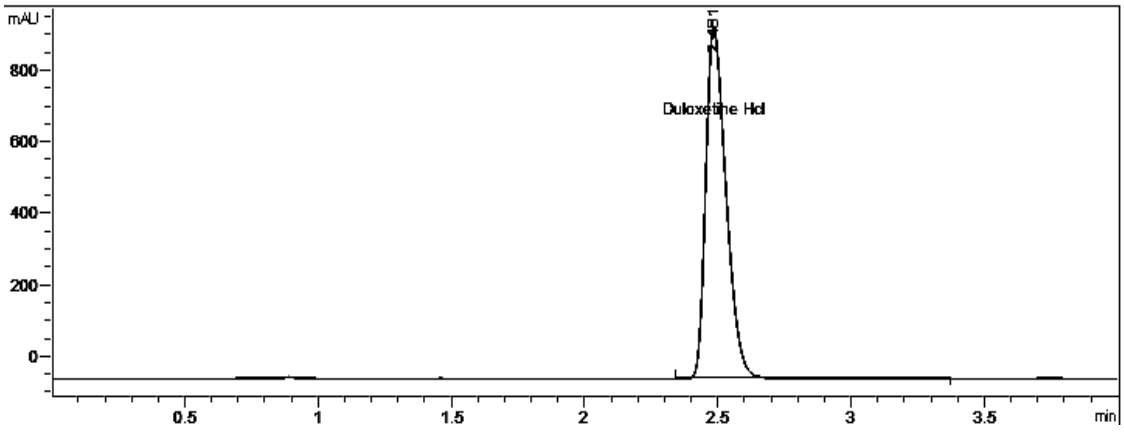
Fig: 8 HPLC Chromatogram of Formulation F-I



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

***RT – Retention Time**

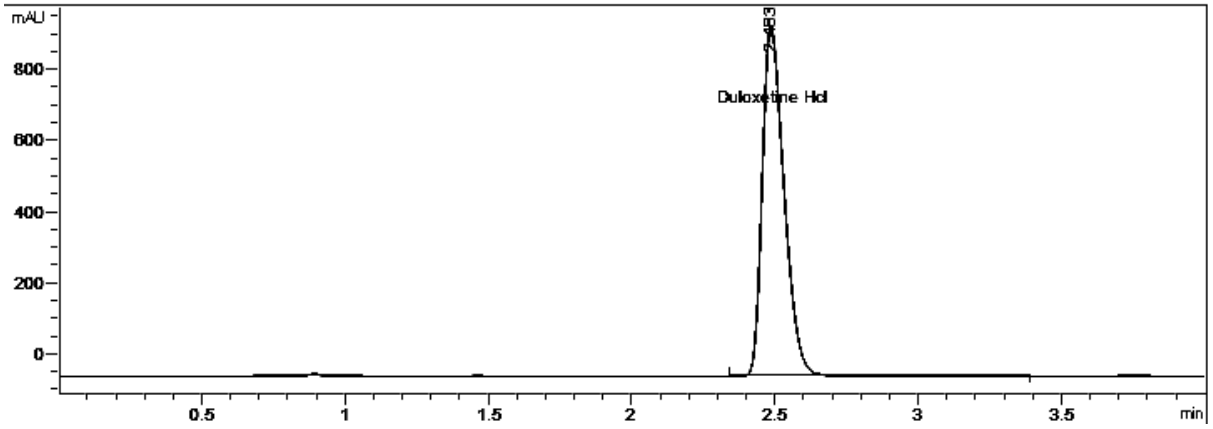
Fig: 9 HPLC Chromatogram of Formulation F-II



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

***RT – Retention Time**

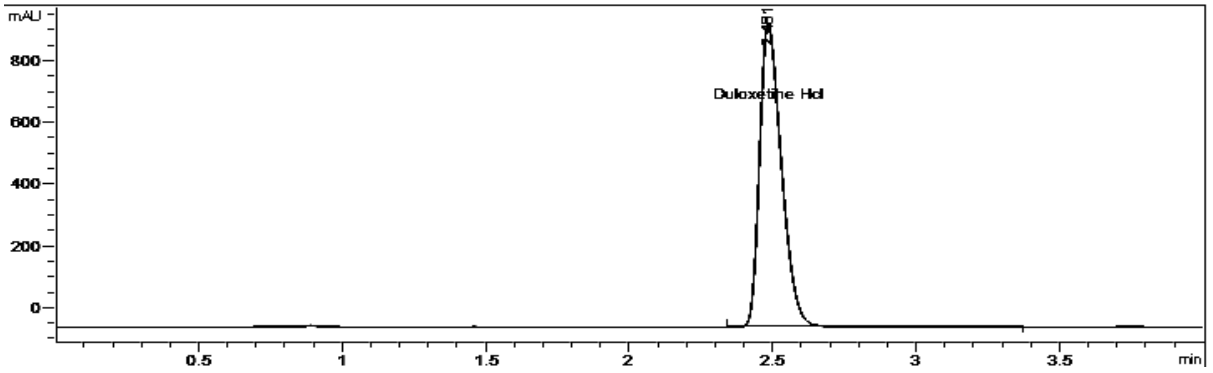
Fig: 10 HPLC Chromatogram of Formulation F-III



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

Discussion:

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.

5.4.3 STANDARD CURVE OF DULOXETINE HYDROCHLORIDE[90]

Preparation of pH 6.8 Phosphate Buffer

Place 7.20 gm of dihydrogen phosphate and 2.86 gm of potassium hydrogen phosphate in a 500 ml volumetric flask and make upto 500 ml with de-mineralized water.

Preparation of Standard Curve of Duloxetine Hydrochloride

0.025 gm of Duloxetine hydrochloride was accurately weighed and dissolved first in methanol and the volume was made upto 50 ml with methanol to get a concentration of 500µg/ml. From this 5 ml was pipetted out and transferred into a 50 ml volumetric flask and make upto required volume using pH 6.8 phosphate buffer to get a concentration of 50 µg/ml, from this is secondary stock solution different concentrations of drug (3, 5, 10, 15, 20, 25 and 30 µg/ml) were prepared using pH 6.8 phosphate buffer. The absorbance of the resulting solutions were measured at 290 nm using UV spectrophotometer. Standard curve of Duloxetine hydrochloride was mentioned in table: 22 and fig: 13.

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

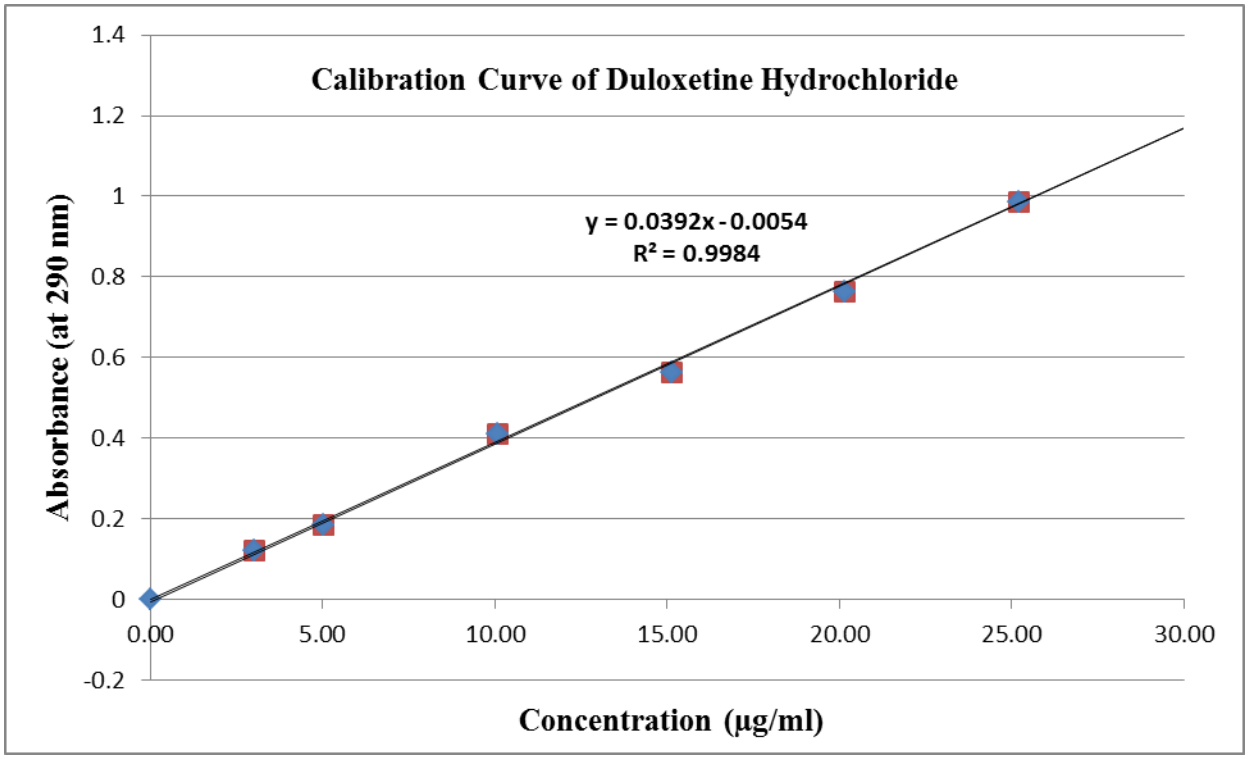


Fig: 13 Calibration Curve of Duloxetine Hydrochloride

5.4.4 *IN VITRO* DISSOLUTION STUDIES

The *in vitro* drug release of Duloxetine hydrochloride tablets were 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.**

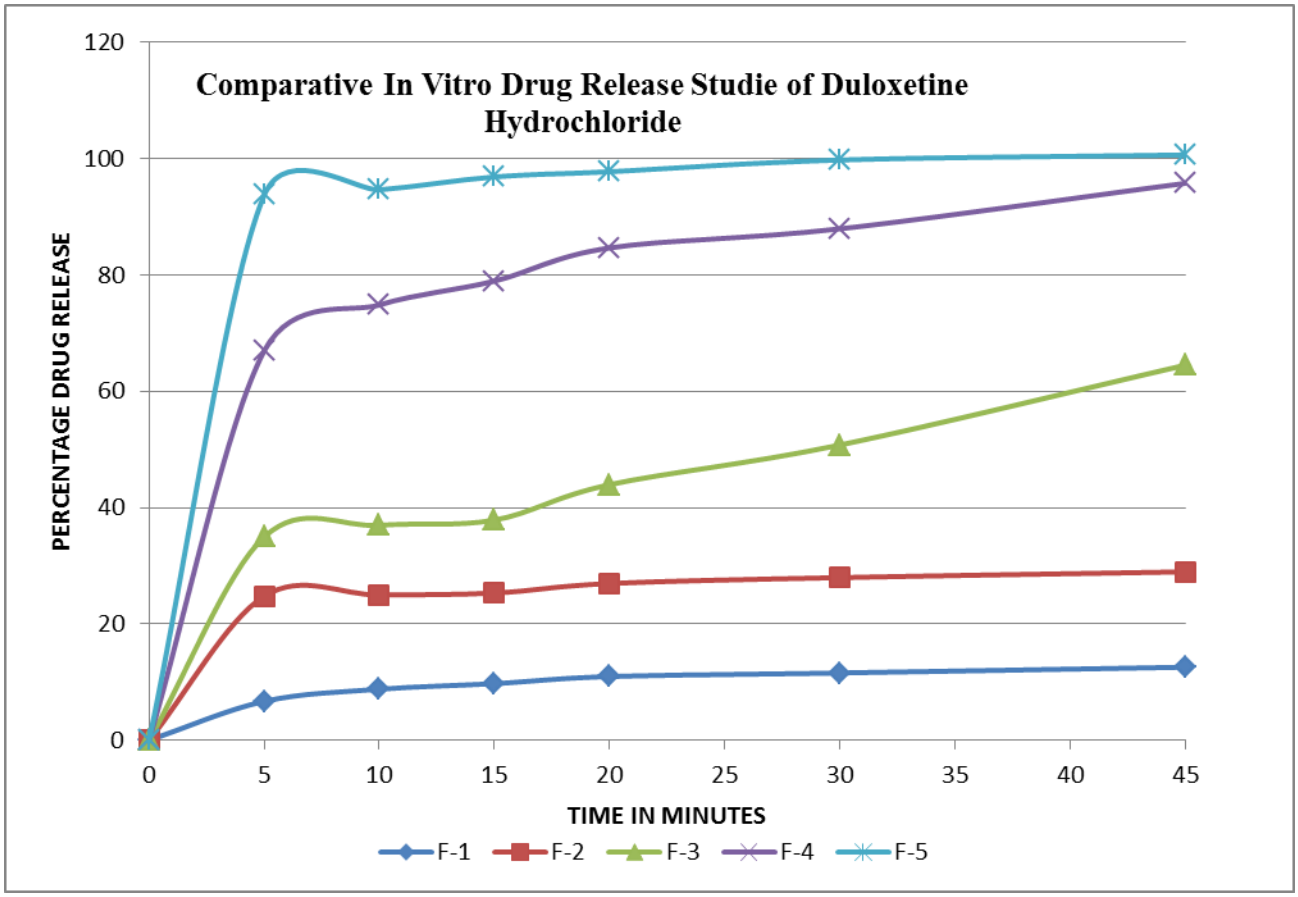


Fig: 14 Comparative *In Vitro* Drug Release Studies of Duloxetine Hydrochloride

Discussion:

1. Duloxetine hydrochloride tablets (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 and the results are given in table: 23.
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.

5.4.5 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.**

Discussion:

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.

5.4.6 *IN VITRO* DRUG RELEASE STUDIES

The *in vitro* drug release of Duloxetine hydrochloride enteric coated tablets are 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

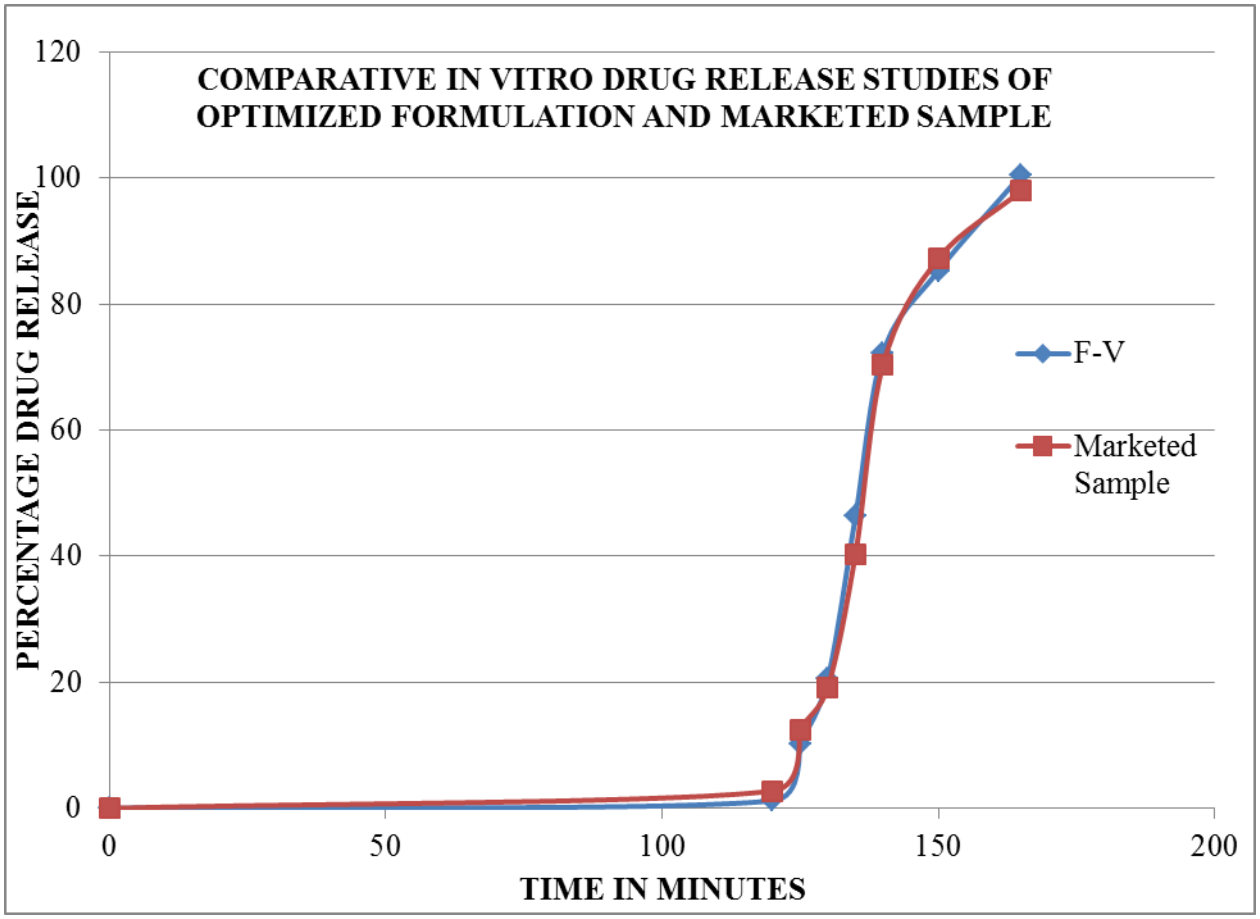


Fig: 15 Comparative *In Vitro* Drug Release Profiles of Duloxetine HCI Marketed Sample and Formulation (F-V)

Discussion

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.

5.4.7 STABILITY STUDIES

The best formulation (F-V) was selected for the stability study and stored at 25 ± 2^0C/60%±5% RH and 40 ± 2^0C/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: 26 and 27.

Table: 26. 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: 27. 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
		Alkaline 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

Discussion:

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.

CHAPTER – 6

SUMMARY AND CONCLUSION

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.

The preformulation study of API such as organoleptic properties, solubility, compatibility study and FT-IR drug – excipient interaction study were carried out.

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.

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 were 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.
- ✓ 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.

CONCLUSION

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.

CHAPTER- 7

7. FUTURE PLAN

Formulation (F-V) may be further investigated for following studies.

The present work may explore the following aspects in the future which may become valuable assets in the field of pharmaceutical science.

- Manufacture Acid labile drug into formulations as cost effective & stable pharmaceutical composition.
- The *in vitro* studies can be extended to *in vivo* studies by leading to a final conclusion of a successful formulation which can be marketed thereafter.
- Duloxetine hydrochloride enteric coated tablet formulation may be evaluated for various pharmacokinetic parameters.

CHAPTER-8

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