FORMULATION AND EVALUATION OF ESCITALOPRAM OXALATE IMMEDIATE RELEASE TABLETS

A Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In the partial fulfillment of the requirement for

the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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Place: Chennai

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"I deeply grateful to my family members, staffs and my friends for their Love, Encouragement and guidance"

Aravapalli V S A Kumar

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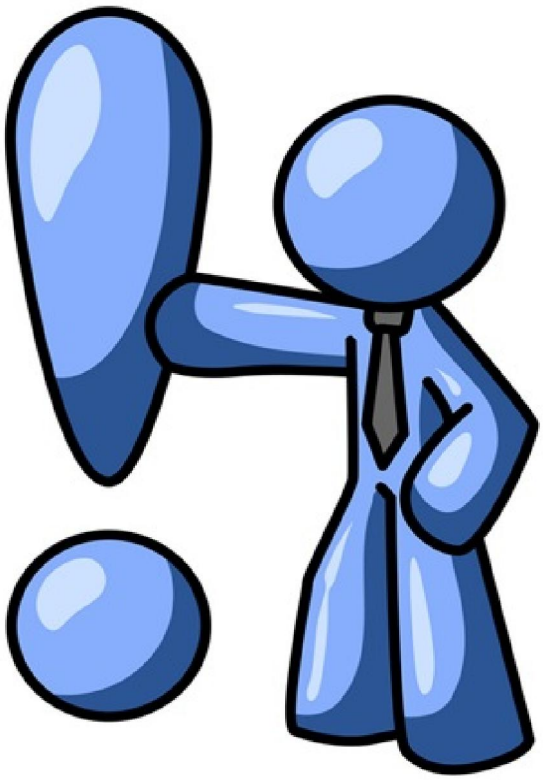

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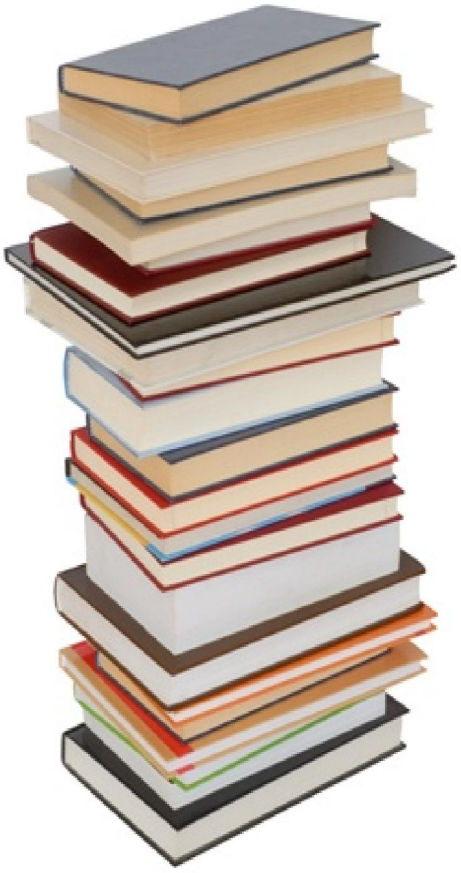

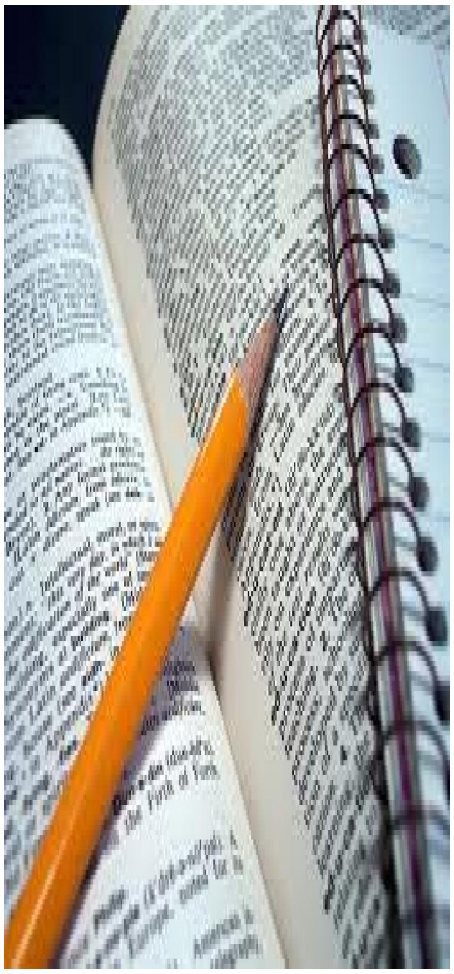

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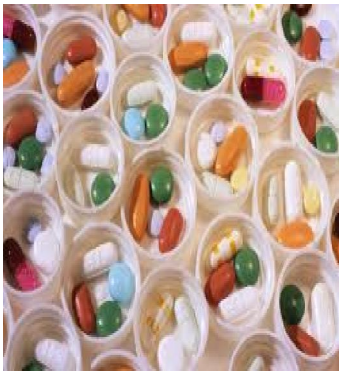
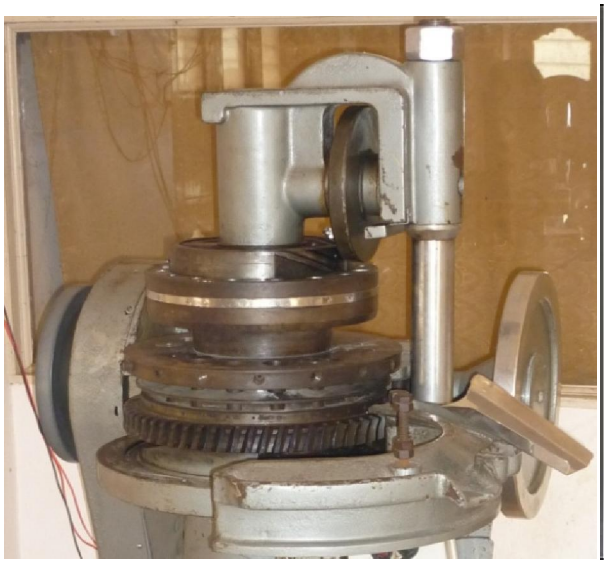


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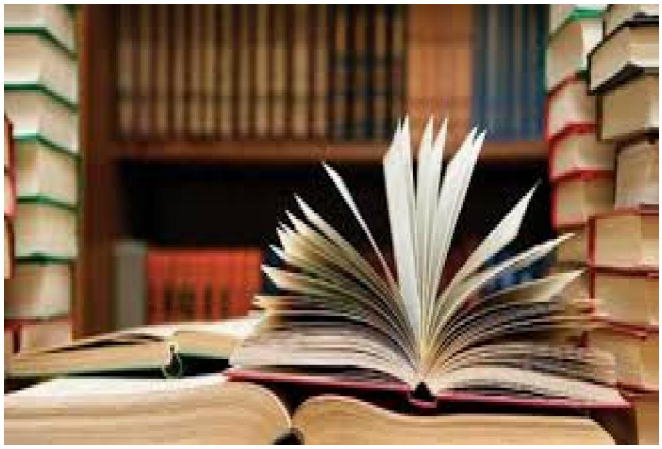

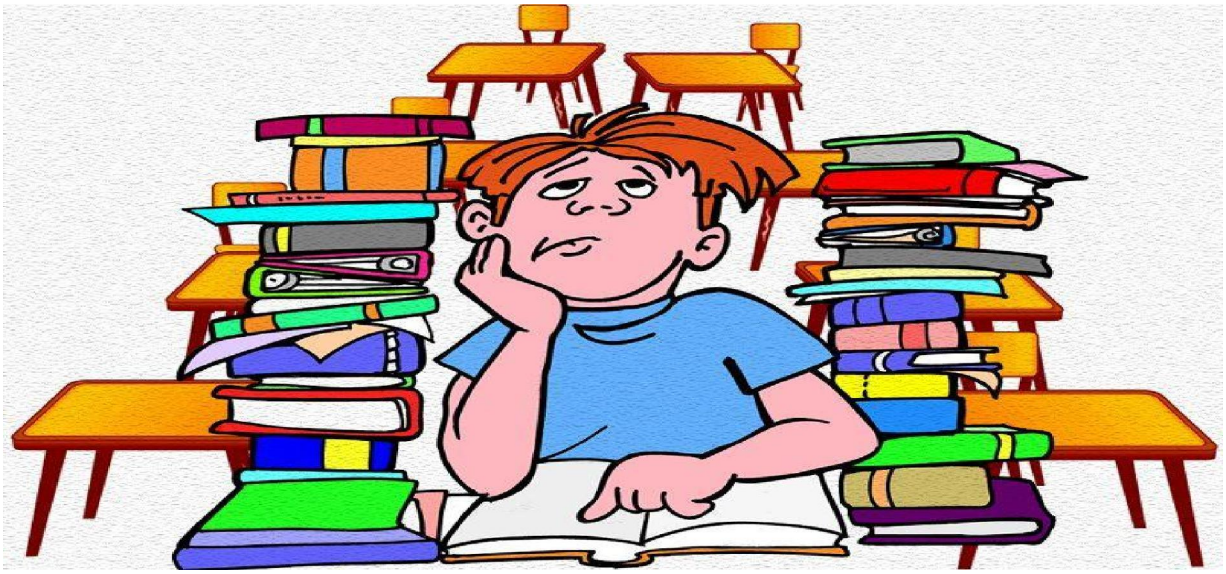

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GLOSSARY OF ABBREVIATIONS

F	=	Formulation
API	=	Active pharmaceutical ingredient
HPMC	=	Hydroxypropylmethylcellulose
Mg.stearate	=	Magnesium Stearate.
IPA	=	Iso Propyl Alcohol
h	=	Hour
n	=	Diffusion coefficient
Sec	=	Second
UV	=	Ultra violet
W/w	=	Weight by weight
µg	=	microgram
IR	=	Immediate release
IP	=	Indian Pharmacopoeia
BP	=	British Pharmacopoeia
USP	=	United States Pharmacopoeia
^{o}C	=	Degree centigrade
FT-IR	=	Fourier TransformInfra-Red
M	=	Molarities
µg	=	Microgram
mg	=	Milligram
ml	=	Milliliters
min	=	Minutes
%	=	Percent/percentage

N	=	Normality
NMT	=	Not More Than
NLT	=	Not Less Than
PPM	=	Parts PerMillion
RPM	=	Revolutions Per Minute
RH	=	Relative Humidity
VF	=	VolumetricFlask
w/w	=	Weight by weight
#	=	Sieve number
Conc.	=	Concentration
DC	=	Direct compression
CI	=	Car's index
HR	=	Hausner's ratio
ECS	=	Excipient compatibility studies

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ABSTRACT

Escitalopram Oxalate is a class of drug with selective serotonin (5-HT) reuptake inhibitor (SSRIs). SSRIs are broad spectrum antidepressants that are effective for major depressive disorder and several anxiety disorders. The main objective of the present study was to develop a pharmaceutically equivalent, stable, cost effective and quality improved formulation of immediate release tablets of Escitalopram Oxalate using different concentration of superdisintegrants like croscarmellose sodium and sodium starch glycolate. Preformulation studies were performed prior to formulation. The tablets were compressed using microcrystalline cellulose, colloidal silicon dioxide, talc, magnesium stearate and opadry white was used for coating the tablets. The tablets were formulated by wet granulation with non aqueous binder and the fabricated tablets were evaluated for various micromeritic properties like bulk density, tapped density, compressibility index, Hausner'sratio, angle of repose and post compression characteristics like thickness, hardness, friability, disintegration time and drug release. Croscarmellose sodium was used as the disintegrant in the formulation of immediate release tablets of Escitalopram Oxalate. The stability studies were carried out for the optimized batch for six months. The results of the present study showed that among all the formulations, F12 was better in all terms of preformulation and post compression parameters and showed comparably a good dissolution profile like that of the marketed product(cipralex).

Keywords: EscitalopramOxalate; antidepressants; wet granulation; stability studies.

AIM AND OBJECTIVE OF STUDY

The aim of this work is to develop a stable and robust formulation of the drug Escitalopram Oxalate, which is an orally administered tablet with Antidepressant and Anxiolytic activity.

The tablet produced should be a stable, bioequivalent to the Innovator sample (Cipralex).

To achieve this goal, various trials were performed and evaluated with respect to various quality parameters such as bulk density, sieve analysis, drug uniformity and dissolution.

Objectives of the present study are

- To design and develop an oral tablet dosage form comprising Escitalopram Oxalate API characterization.
- Conducting Excipient Compatibility Studies.
- Formulation development of tablets via selecting suitable tablet manufacturing method and different excipients.
- Quality control of formulated tablets
    1. Testing for weight variation, hardness, thickness, friability, disintegration time etc.
    2. In vitro-dissolution study.
- Comparison of optimized formulation tablets with commercial marketed tablets (Cipralex).

- Stability study of optimized formulation as per ICH guidelines of storage conditions for three months at 40 ºC/75 % RH, 30 ºC / 65 % RH and 25 ºC /60 % RH.
- Evaluating Pharmaceutical Equivalence of formulated Tablets with that of the commercial formulation using dissimilarity (f1) and similarity (f2) factors.

1. INTRODUCTION

Drugs are not generally given as pure chemical drug substances but are formulated as finished dosage forms (drug products) such as tablets, capsules, ointments, etc, before being administered to patients for therapy. Among these, tablets are the ruling dosage forms in the market. Formulated drug products usually include the active drug substance and selected ingredients (excipients) that make up the dosage form. Drug products are designed to deliver drug for local or systemic effects.[1-2]

Over the last hundred years tablet manufacturers have developed materials and processes that can produce compressed tablet containing precise amount of an active pharmaceutical ingredient (API) at high speed and at relatively low cost. The development in the field of API, excipients, and tableting machinery during the past decade has made tablet manufacturing a science and tablets the most commonly used dosage form[3]

1.1. Solid Dosage Forms[4]

Solid dosage forms are widely prevalent due to their age-old application. Especially, oral solid formulations hold a high potential as they serve to be most convenient for the administration of drugs. These have been developed into a wide range of formulations from conventional dosage forms to targeted drug dosage forms. Oral route is the most convenient and commonly used method of drug delivery. More than 50% of drug delivery systems available in the market are oral drug delivery systems. They offer convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost.

Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules.

These dosage forms are designed either for improving the physical and mechanical properties of materials during manufacture and/or for providing a desired drug delivery system. The tabletsand capsules can be made directly from powders or from granules and pellets, or from film coated multiple units.

1.1.1 TABLETS[5-10]

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, 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 tablet. All medicaments are available in the tablet form except where it is difficult to formulate or administer.

1.1.2 ADVANTAGES OF TABLETS

1. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.

2. Cost is lowest of all oral dosage form.

3. Lighter and compact.

4. Easiest and cheapest to package and strip.

5. Easy to swallowing with least tendency for hang-up.

6. Sustained release product is possible by enteric coating.

7. Objectionable odour and bitter taste can be masked by coating technique.

8. Suitable for large scale production.

9. Greatest chemical and microbial stability over all oral dosage form.

10. Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

1.1.3 DISADVANTAGES OF TABLETS

1. Difficult to swallow in case of children and unconscious patients.

2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.

3. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

4. Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.

1.1.4 CLASSIFICATION OF TABLETS

Basing on the route of administered or the function, the tablets are classified as follows

(A) Tablets ingested orally

1. Compressed tablet, e.g. Paracetamol tablet

2. Multiple compressed tablet

    i) Layered Tablets

    ii) Compression coated Tablets

3. Repeat action tablet

4. Delayed release tablet, e.g. Enteric coated Bisacodyl tablet

5. Sugar coated tablet, e.g. Multivitamin tablet

6. Film coated tablet, e.g. Metronidazole tablet

7. Chewable tablet, e.g. Antacid tablet

(**B) Tablets used in oral cavity**

1. Buccal tablet, e.g. Vitamin-C tablet

2. Sublingual tablet, e.g. Vicks Menthol tablet

3. Troches and lozenges

4. Dental cones

(C) Tablets administered by other route

1. Implantation tablet

2. Vaginal tablet, e.g. Clotrimazole tablet

(D) Tablets used to prepare solution

1. Effervescent tablet, e.g. Dispirin tablet (Aspirin)

2. Dispensing tablet, e.g. Enzyme tablet (Digiplex)

3. Hypodermic tablet

4. Tablet triturates e.g. Enzyme tablet (Digiplex)

1.1.5 EXCIPIENTS USED IN TABLETS

In addition to active ingredients, tablet contains a number of inert materials known as additives or excipients.

1.2. Definition of excipients

Excipients play a key role in transforming pharmacologically active substances into dosage forms, medicinal products and devices which are acceptable to the patient.

The International Pharmaceutical Excipients Council (IPEC) defines excipients as Pharmaceutical excipients are any substance other than the active drug or prodrug that has been appropriately evaluated for safety and is included in a drug delivery system to either:

1. Aid processing of the system during manufacture.
2. Protect, support or enhance stability, bioavailability or patient acceptability.
3. Assist in product identification.
4. Enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use.

Salient features of excipients

1. It should not accelerate the chemical and/or physical degradation of API(S).
2. It should not interfere with the biological availability of active ingredient.
3. It should be compatible with all the adjuvant present in the formulation.
4. It should be physiologically inert.
5. It should not interfere with the disintegration or dissolution of the active ingredient.
6. It should be colorless and tasteless.
7. It should be relatively cost effective and available in desired time.
8. It should show batch-to-batch reproducibility of physical and physico-mechanical properties.

1.3.Formulation design and selection of excipients:

The final composition of a product will be influenced by a range of factors, both objective and subjective. Many of the factors are interrelated. The final formulation will be a balance of all the factors. The choice of final product, e.g. hard gelatin capsule, tablet, coated tablet will often be dictated by factors outside the control of the formulator, via:

- Company policy
- Market research
- Competitor products
- Dose
- Production preferences
- Costs

Different excipients are

1. Diluents

2. Binders and adhesives

3. Disintegrents

4. Lubricants

5. Antiadherants

6. Glidants

Table 1: Excipients with their functions in tablet formulation[5, 8, 11]

EXCIPIENT	FUNCTION
Diluents or Fillers	Diluents make the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size.
Binders or Granulating agents or Adhesives	Binders are added to tablet formulations to add cohesiveness to powders, thus providing the necessary bonding to form granules, which under compaction form a cohesive mass or a compact which is referred to as a tablet.
Disintegrants	A disintegrant is added to most tablet formulations to facilitate a breakup or disintegration of the tablet when placed in an aqueous environment.
Lubricants	Lubricants are intended to reduce the friction during tablet formation in a die and also during ejection from die cavity.
Antiadherents	Antiadherents are added to reduce sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall.
Glidants	Glidants are intended to promote the flow of tablet granulation or powder mixture from hopper to the die cavity by reducing friction between the particles.

1. Diluents: Diluents are fillers used to make required bulk of the tablet when the drug dosage itself is inadequate to produce the bulk. Secondary reason is to provide better tablet properties such as improve cohesion, to permit use of direct compression manufacturing or to promote flow.

Carbohydrate substances such as sugars, starches and celluloses may also function as binders during wet granulation process whereas when used in direct compression system, they serve as the diluent. The inorganic diluents, do not exhibit binding properties when used in wet granulation and direct compression. Tablet diluent or filler may also be classified on the basis of their solubility in water as soluble and insoluble.

Table 2: Classification of diluents[11, 12]

INSOLUBLE TABLET FILLERS OR DILUENTS	**SOLUBLE TABLET FILLERS OR DILUENTS**
Starch	Lactose
Powdered cellulose	Sucrose
Microcrystalline cellulose	Mannitol
Calcium phosphates	Sorbitol

Commonly used tablet diluents

1. Lactose-anhydrous and spray dried lactose

2. Directly compressed starch-Sta Rx 1500

3. Hydrolyzed starch-Emdex and Celutab

4. Microcrystalline cellulose-Avicel (PH 101,PH 102 and PH 200)

5. Dibasic calcium phosphate dehydrate

6. Calcium sulphatedihydrate

7. Mannitol

8. Sorbitol

9. Sucrose- Sugartab, DiPac, Nutab

10. Dextrose

2. Binders and Adhesives[13]

Binder is one of an important excipient to be added in tablet formulation. In simpler words, binders or adhesives are the substances that promote cohesiveness. It is utilized for converting powder into granules through a process known as Granulation.

Purpose of Granulation[14]

Powders/Granules intended for compression into tablets must possess two essential properties: flow property and compressibility.

Flow property/Fluidity is required to produce tablets of a consistent weight and uniform strength. Compressibility is required to form a stable, intact compact mass when pressure is applied. These two objectives are obtained by adding binder to tablet formulation and then

proceeding for granulation process. Granules so formed should possess acceptable flow property and compressibility. Some drugs exhibit poor fluidity and compressibility. In such cases binders have to be added for improving flow property and compressibility.

Other reasons for Granulation process are to improve appearance, mixing properties, to avoid dustiness, to densify material, to reduce segregation, in general to either eliminate undesirable properties or to improve the physical and chemical properties of fine powders.

In wet granulation and dry granulation/slugging methods binders are added in solution/suspension form and in dry form respectively.

In direct compression, binders possessing direct compressibility characteristics are used. Binder when used in liquid form gives better binding action as compared to when used in dry form.

Table 3: Classification of binders[15]

SUGARS	NATURAL BINDERS	SYNTHETIC/SEMISYNTHETIC POLYMERS
Sucrose	Acacia	Methyl Cellulose
Liquid Glucose	Tragacanth	Ethyl Cellulose
--	Gelatin	Hydroxy Propyl Methyl Cellulose (HPMC)
--	Starch Paste	Hydroxy Propyl Cellulose
--	Pregelatinized Starch	Sodium Carboxy Methyl Cellulose
--	Alginic Acid	Polyvinyl Pyrrolidone (PVP)
--	Cellulose	Polyethylene Glycol (PEG)

--	--	Polyvinyl Alcohols
--	--	Polymethacrylates

3. DISINTEGRANTS[13]

Disintegrants are added to a tablet formulation to facilitate its breaking or disintegration when it contacts water in the GIT. Disintegrants, an important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants. The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet.

Mechanism of TabletDisintegration[11]

The tablet breaks to primary particles by one or more of the mechanisms listed below

i. By capillary action

ii. By swelling

iii. Because of heat of wetting

iv. Due to disintegrating particle/particle repulsive forces

v. Due to deformation

vi. Due to release of gases

vii. By enzymatic actionExample: Starch- 5-20% of tablet weight. Starch derivative – Primogel and Explotab (1-8%) Clays- Veegum HV, bentonite 10% level in colored tablet only Cellulose, Cellulose derivatives- Ac- Di-Sol (sodium carboxy methyl cellulose)

Superdisintegrants[16]

As days passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate disintegrants i.e. superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. Superdisintegrants swells up to ten fold within 30 seconds when contact water. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs. Superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

Table 4: List of superdisintegrants

List of super disintegrants	**Example of Super disintegrants**	**Mechanism of Action**	**Special Comment**
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol®	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free

CrosspovidoneCrosspovidon M® Kollidon®	Crosslinked PVP	-Swells very little and returns to original size after compression but act by capillary	-Water insoluble and spongy in nature so get porous tablet

2. DRUG PROFILE

2.1.Escitalopram oxalate

Escitalopram oxalate is an Antidepressant and also act as anxiolytic drug. Escitalopram oxalate is chemically designated as (1*S*)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-3*H*-2-benzofuran-5-carbonitrile oxalate, and it has the following chemical structure:

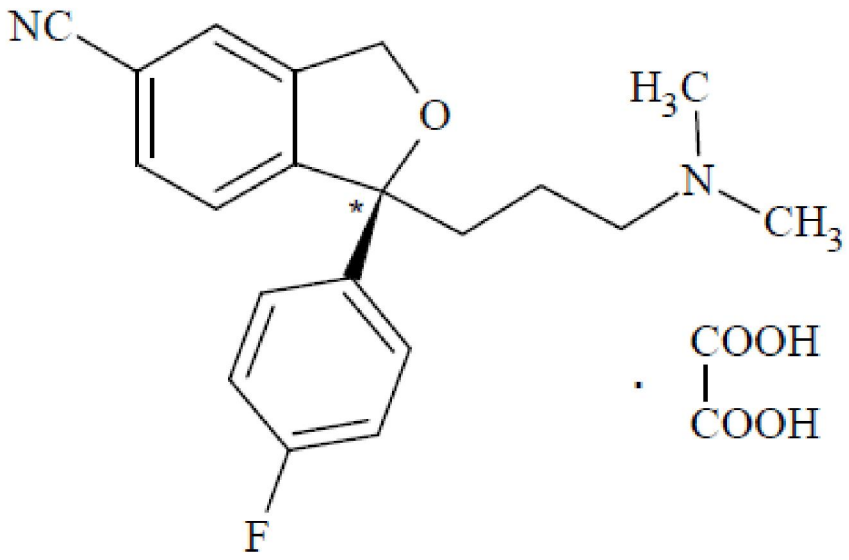


Fig 1: Structural Formula of Escitalopram Oxalate

The empirical formula is $C_{20}H_{21}FN_2O.C_2H_2O_4$, representing a molecular weight of 414.4.

DESCRIPTION

Escitalopram oxalate is a fine white to off-white powder.

SOLUBILITY

Soluble in dimethyl formamide, dimethylsulfoxide, sparingly soluble in methanol and slightly soluble in dichloromethane.

CLINICAL PHARMACOLOGY

Mechanism of Action: Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000 fold lower affinity. Escitalopram has no or low affinity for a number of receptors including 5-HT1A, 5-HT2, DA D1 and D2 receptors, α1-, α2-, β-adrenoceptors, histamine H1, muscarine cholinergic, benzodiazepine, and opioid receptors. The inhibition of 5-HT re-uptake is the only likely mechanism of action explaining the pharmacological and clinical effects of Escitalopram.

Pharmacokinetics:

Absorption :

Escitalopram is rapidly absorbed, with peak serum concentrations attained about 3–4 hours after dosing. The pharmacokinetic profile of escitalopram is linear. The absolute bioavailability of Escitalopram is approximately 80%, implying limited first-pass metabolism, and co-administration of food does not affect the kinetics of escitalopram. Mean steady state concentrations following 10 mg/day are approximately 50 nmol/l.

Distribution :

Escitalopram is widely distributed, with an apparent volume of distribution of about 20 l/kg. Plasma protein binding is low (average 56%) over a wide range of concentrations,

Indicating a low potential for drug displacement interactions.

Metabolism

Escitalopram is metabolized by cytochrome P450 (CYP) enzymes to demethylEscitalopram, and further to barely detectable levels of didemethyl metabolite. By inference from results with racemic citalopram, the propionic acid derivative is a pharmacologically inactive metabolite, possibly formed by the action of monoamine oxidases. In addition, an *N*-oxide metabolite and glucuronides of citalopram have been identified. All of these derivatives are therapeutically inactive. The metabolism of escitalopram to desmethylescitalopram is mediated in parallel by three CYP isozymes: CYP3A4, 2C19 and 2D6 whereas only CYP2D6 mediates further demethylation to the didemethyl metabolite.

Elimination

The escitalopram elimination half-life is about 30 hours, consistent with once-daily dosing, and the plasma clearance following oral administration is about 0.6 l/min .The pharmacokinetics is linear in the investigated dose range. The renal clearance values of escitalopram and it'sdemethyl metabolite are 2.7 and 6.9 l/h, respectively, corresponding to excretion of about 8% and 10% of the dose in urine.

Drug Interactions:

Contraindications: Hypersensitivity to escitalopram or to any of the excipients. Concomitant treatment with non-selective, irreversible monoamine oxidase inhibitors (MAO-inhibitors) is contraindicated due to the risk of serotonin syndrome with agitation, tremor, hyperthermia etc. The combination of escitalopram with reversibleMAO-A inhibitors (e.g. moclobemide) or the

reversible non-selectiveMAO-inhibitor linezolid is contraindicated due to the risk of onset of a serotonin syndrome.

Mechanism of action

The inhibition of serotonin (5-hydroxytryptamine; 5-HT) reuptake is the only mechanism of action explaining the pharmacological and clinical effects of escitalopram. Escitalopram is a selective inhibitor of serotonin reuptake, with high affinity for the primary binding site on the SERT protein, where conventional selective serotonin reuptake inhibitors (SSRIs) and the serotonin–noradrenaline reuptake inhibitors (SNRIs) venlafaxine and duloxetine bind. Escitalopram also binds to the allosteric site on SERT, which decreases the dissociation rate of escitalopram from the primary site, i.e. it appears to have a stabilising, or self-potentiating, effect on the escitalopram– transporter complex. This allosteric binding has led to escitalopram being described as an ASRI, an allosteric serotoninreuptake inhibitor The impact of R-citalopram on escitalopram SERT binding. Pharmacological, functional and behavioural experiments have established that escitalopram (the S-enantiomer of citalopram) has a greater activity and an earlier onset of effect than its racemic parent, citalopram. The R-enantiomer, having negligible uptake-inhibiting effect in itself has recently been shown unexpectedly to inhibit the effect of the S-enantiomer on the SERT protein via an allosteric mechanism that decreases the time that S-citalopram occupies the primary site.In other words, one enantiomer appears to counteract the activity of the other at the same target a unique property among antidepressants.A recent *in vitro* study provided further evidence of R-citalopram's allosteric effects at the human SERT (hSERT), by indicating that it produced a conformational change in the transporter protein. Moreover, *in vitro* binding studies showed that R-citalopram attenuated the association rates of Escitalopram and paroxetine (which is also known to act upon allosteric

sites, although to a lesser degree) with hSERT, but had no effect on the association rate of fluoxetine, which has no affinity for the SERT allosteric sites.

Excipients Profile

2.2. Microcrystalline Cellulose[24]

Synonyms: AvicelpH ,cellulose gel, crystalline cellulose, E460.

Chemical Name: Cellulose

Empirical Formula and Molecular Weight: $(C_6H_{10}O_5)_n$ ≈36 000 where $n \approx 220$.

Structural Formula:

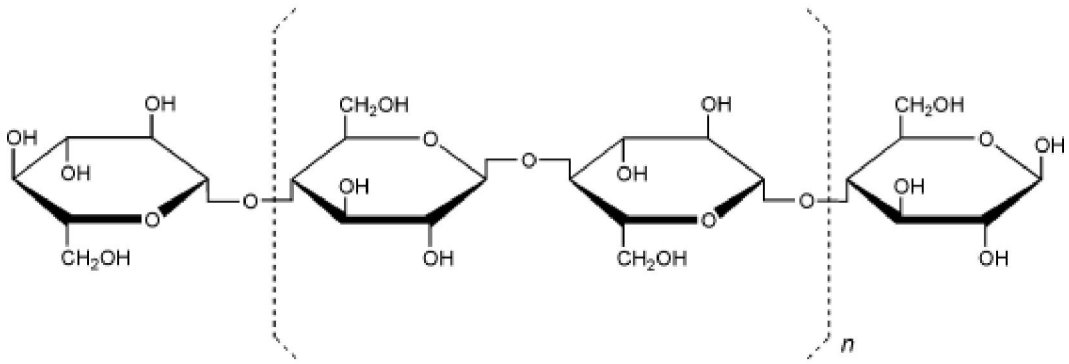


Fig 2:Structural Formula of MCC

Functional Category: Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.

Description:

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Typical Properties

Angle of repose: 49°

Density (bulk): 0.32 g/cm^3

Density (tapped): 0.45 g/cm^3

Density (true): 1.512–1.668 g/cm^3

Flowability: 1.41 g/s

Melting point: Chars at 260–270°C

Moisture content: Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

Particle size distribution: Typical mean particle size is 20–200 μm. Different grades may have a different nominal mean particle size.

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids, and most organic solvents.

Specific surface area: 1.06–1.12 m^2/g

Applications in Pharmaceutical Formulation or Technology:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Table 5: Uses of microcrystalline cellulose

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluents	20–90
Tablet disintegrant	5–15
Tablet binder/diluents	20–90

Stability and Storage Conditions: Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Microcrystalline cellulose is incompatible with strong oxidizing agents.

2. 3.Hydroxy Propyl Methyl Cellulose (Methocel E-5) [25]

Synonyms: Hydroxypropyl methylcellulose, HPMC, methylcellulose propylene glycol ether, methyl hydroxypropylcellulose.

Chemical Name: Cellulose hydroxypropyl methyl ether

Empirical Formula and Molecular Weight: $CH_2CH(OH)CH_3$, calculated on a dried basis. Molecular weight is approximately 10,000–1,500,000.

Structural Formula

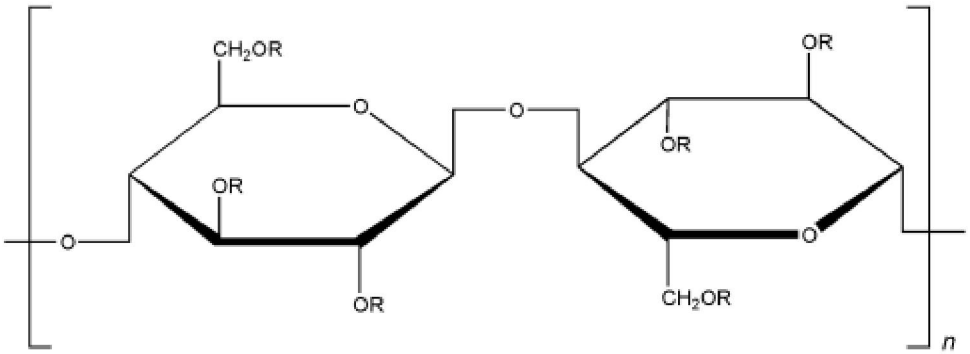


Fig 3: Structural Formula of HPMC(E5)

Where R is H, CH_3, or $CH_3CH(OH)CH_2$

Functional Category: Coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Description: Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Typical Properties

Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous solution.

Ash: 1.5–3.0%, depending upon the grade and viscosity.

Auto ignition temperature: 360°C

Density (bulk): 0.341 g/cm^3

Density (tapped): 0.557 g/cm^3

Density (true): 1.326 g/cm^3

Melting point: Browns at 190–200°C, chars at 225–230°C. Glass transition temperature is 170–180°C.

Moisture content: Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

Solubility

Soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Specific gravity: 1.26

Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Hypromellose is also used as a

suspending and thickening agent in topical formulations. Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

2.4.Sodium starch glycolate

Synonyms: Carboxymethyl starch, sodium salt; carboxymethylamylumnatricum; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.

Chemical Name: Sodium carboxymethyl starch

Structural Formula

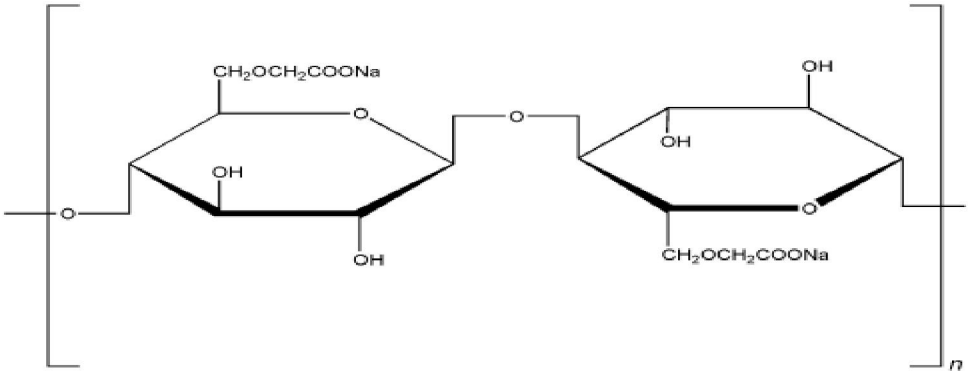


Fig 4: Structural Formula of Sodium Starch Glycolate

Functional Category: Tablet and capsule disintegrant.

Description: Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. The PhEur 2005 states that it consists of oval or spherical granules, 30–100 mm in diameter, with some less-spherical granules ranging from 10–35 mm in diameter.

Typical Properties

Acidity/alkalinity: pH = 5.0–7.0 in aqueous dispersions.

Density (bulk): 0.529 g/cm^3

Density (tapped): 0.819 g/cm^3

Density (true): 1.543 g/cm^3

Particle size distribution: NMT 2% retained on a #200 (73.7 μm) mesh and not more than 10% retained on a #325 (44.5 μm) mesh.

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

Specific surface area: 0.81–0.83 m^2/g

Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules.

In tablet formulations, sodium starch glycolate may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the sodium starch glycolate should be added in both the wet and dry stages of the process (intra- and extra granularly) so that the wicking and swelling ability of the disintegrant is best utilized. sodium starch glycolate at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Table 6: Uses of sodium starch glycolate

Use	Concentration (%)
Disintegrant in capsules	10–25
Disintegrant in tablets	0.5–5.0

Stability and Storage Conditions

Sodium starch glycolate is a stable though hygroscopic material.

A model tablet formulation prepared by direct compression, with sodium starch glycolate as a disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months.

sodium starch glycolate should be stored in a well-closed container in a cool, dry place.

Incompatibilities

The efficacy of disintegrants, such as sodium starch glycolate, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol.

Sodium starch glycolate is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

2.5. Colloidal Silicondioxide[26]

Synonyms: Aerosil, Cab-O-Sil, Cab-O-Sil M-5P, colloidal silica, fumed silica, fumed silicon dioxide, SAS, silica colloidalisanhydrica, silica sol, silicic anhydride, silicon dioxide colloidal, silicon dioxide fumed, synthetic amorphous silica, Wacker HDK.

Chemical Name: Silica

Empirical Formula and Molecular Weight: SiO2 and 60.08

Structural Formula: $[CH_3(CH_2)_{16}COO]_2Mg$

Functional Category: Adsorbent, anticaking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity-increasing agent.

Description:

Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

Typical Properties

Acidity/alkalinity pH: 3.8–4.2 (4% w/v aqueous dispersion) and 3.5–4.0 (10% w/v aqueous dispersion) for Cab-O-Sil M-5P

Density (bulk): 0.029–0.042 g/cm3

Melting point: 1600^0C

Particle size distribution: Primary particle size is 7–16 nm. Aerosil forms loose agglomerates of 10–200 mm.

Refractive index: 1.46

Solubility: Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid, soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water. For Aerosil, solubility in water is 150 mg/L at 258C (pH 7).

Specific gravity: 2.2

Specific surface area: 100–400 m^2/g depending on grade.

Applications in Pharmaceutical Formulation or Technology:

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling. Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. With other ingredients of similar refractive index, transparent gels may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than nonpolar liquids). Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity in aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders. Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate. Colloidal silicon dioxide is also used as an adsorbent during the preparation of wax microspheres, as a thickening agent for topical preparations, and has been used to aid the freeze-drying of nanocapsules and nanosphere suspensions.

Table 7: Uses of colloidal silicon dioxide.

Use	Concentration (%)
Aerosols	0.5–2.0

Emulsion stabilizer	1.0–5.0
Glidant	0.1–1.0
Suspending and thickening agent	2.0–10.0

Stability and Storage Conditions:

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 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. Colloidal silicon dioxide powder should be stored in a well-closed container.

Incompatibilities:

Incompatible with diethylstilbestrol preparations.

2.6. Magnesium Stearate[27]

Synonyms: Magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid, magnesium salt.

Chemical Name: Octadecanoic acid magnesium salt

Empirical Formula and Molecular Weight: $C_{36}H_{70}MgO_4$, 591.34

Structural Formula: $[CH_3(CH_2)_{16}COO]_2Mg$

Functional Category: Tablet and capsule lubricant.

Description:

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Typical Properties

Crystalline forms: High-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk): 0.159 g/cm^3

Density (tapped): 0.286 g/cm^3

Density (true): 1.092 g/cm^3

Flash point: 250°C

Flowability: Poorly flowing, cohesive powder.

Melting range: 126–130°C

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in warm benzene and warm ethanol (95%).

Specific surface area: 1.6–14.8 m^2/g

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

2.7.Isopropyl alcohol

Synonyms: Alcohol isopropylicus, dimethyl carbinol, IPA, isopropanol, petrohol,2-propanol,sec-propyl alcohol; rubbing alcohol.

Chemical Name: Propan-2-ol

Empirical Formula and Molecular Weight: C3H8O 60.1

Structural Formula

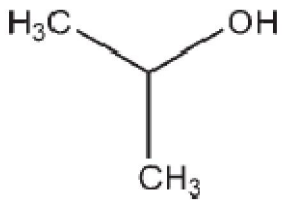


Fig 5: Structural Formula of IPA

Functional Category: Disinfectant, solvent.

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

Typical Properties

Antimicrobial activity Isopropyl alcohol is bactericidal, at concentrations greater than 70% v/v it is a more effective antibacterial preservative than ethanol (95%). The bactericidal effect of aqueous solutions increases steadily as the concentration approaches 100% v/v. Isopropyl alcohol is ineffective against bacterial spores.

Boiling point 82.48°C

Dielectric constant D20 = 18.62

Flash point 11.78C (closed cup); 138C (open cup).

Melting point _88.58

Solubility Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt solutions.Forms an azeotrope with water, containing 87.4% w/w isopropyl alcohol (boiling point 80.378C).

Specific gravity 0.786

Viscosity (dynamic) 2.43 mPa s (2.43 cP) at 208C

Applications in Pharmaceutical Formulation or Technology

Isopropyl alcohol is used in cosmetics and pharmaceutical formulations, primarily as a solvent in topical formulations. It is not recommended for oral use owing to its toxicity, Although it is used in lotions, the marked degreasing properties of isopropyl alcohol may limit its usefulness in preparations used repeatedly. Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation. It has also been shown to significantly increase the skin permeability of nimesulide from carbomer 934.Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.

Stability and Storage Conditions

Stability and Storage Conditions Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

Incompatibilities

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition.

3. LITERATURE REVIEW

1. **SrinivasGangula et.Al**[17] worked on identification, synthesis and spectral characterization of impurities in process development of Escitalopram, identified, synthesized (starting from racemic substrates), developed robust analytical methods and characterized the four process related impurities present in escitalopram particularly those are close to 0.10%. The characterization of these compounds is based on LC–MS, IR and NMR spectral data followed by their independent syntheses in order to meet the regulatory requirements as per ICH guidelines.

2. **Patrick Crowley**[18] identified the Drug Excipient interactions, although considered pharmacologically inert, excipients can initiate, propagate or participate in chemical or physical interactions with drug compounds, which may compromise the effectiveness of a medication. Excipients may also contain impurities or form degradation products that in turn cause decomposition of drug substances. Here interactions are necessary prerequisite to the development of dosage forms that are stable and of good quality.

3. **N. Dogan and T.H.Mchugh**[19]worked on the Effects of Microcrystalline Cellulose on Functional Properties of Hydroxy Propyl Methyl Cellulose Microcomposite Films, investigate the use of nanosize MCC fillers for the purpose of preparing edible microcomposite films. It was shown that through the incorporation of fillers such as MCC, edible film mechanical properties can be significantly improved without reducing film barrier properties. These findings are expected to have a significant impact on the food industry by enabling them to manufacture edible films with improved tensile strengths, while maintaining their elongation and water vapor permeability values. The size, configuration, and water bonding properties of filler materials as

well as their compatibility with the matrix affect the microstructure and overall functional properties of films. These results will allow food scientists to envision a new generation of composite edible films and barriers and not be restricted to emulsified and bilayer films for current and new applications.

4. **Hareesha chamarthi**[20]worked on Formulation and evaluation of oro dispersible tablet of Escitalopram oxalate by super disintegrates addition method, direct compression method is useful for the preparation for oro dispersible tablet of Esitalopram oxalate. crosscarmellose sodium and crosspovidone mixture is useful for this preparation.

5. **Ngoc Do, Jason Hansell, and Thomas P. Farrell**[21]worked on Modulating Dissolution Profiles of Immediate Release Tablets Using Methocel E5 LV and a Direct Compression Process, The drug release rate of tablets depends on several formulation variables such as the concentration and viscosity of the polymers as well as the concentration and water solubility of the drugs. The purpose of this study was to investigate the ability of singleMethocel premium cellulose ether, E5 LV grade to modulate the dissolution profiles of immediate release tablets prepared by different types of compression methods. The dissolution rate of all tablets decreases with increasing concentration of Methocel E5 LV. The slow-down effect of Methocel E5 LV also depends on the water solubility characteristics of the drug – i.e. lower water solubility drugs had slower dissolution rates at the highest METHOCEL E5 LV concentrations. Film coating with Opadry II 85 Series has no effect on the dissolution profiles of all tablets containing METHOCEL E5 LV...

6. **Rohokale BS, Jadhav VM, Kadam VJ**[22]worked related to the studies in optimization of non aqueous film coating parameters. At lower spray rate un-uniform coating was reported and at high rate white spot, sticking and picking problem was recorded. Variation in atomization air pressure affect over quality of coating process because at high atomization air pressure small droplet was formed and at low atomization air pressure big droplet was formed. As distance between tablet bed and spray gun increased disturbed spray spray pattern was observed even at minimum distance sticking & white spot over tablet noted. At low inlet air temperature rough surface, sticking, picking & white spot was observed and at high temperature white spot & rough surface observed. As pan DP reduced spray was disturbed. Higher RPM of pan increase the mixing and distributions of spray over the tablet. At high % solid content create problem like roughness over tablet.

7. **Suresh Pareek, ChetanRajsharad, Ashok Mohanty&Aditi Golatkar**[23]worked on theEffect of solvents on tablet coating. The film coating of Pharmaceutical dosage forms is done by dispersing the polymers, plasticizers, opacifier Lubricant & pigments or Ready to use film coating material like Instacoat in the solvent system. The solvent system could be Organic, Aqueous or a combination of Organic and Aqueous. The most commonly used organic solvents are IPA and Methylene chloride. The Instacoat coating material used for conducting various coating trials proved to the effect in different type of solvent system. It proved to be very coat effective in case of aqueous coating. The final product finish was also much better in case of aqueous coating in White colour. In case of Indigo carmine, the colour shade of the finish product should be decided based on the solvent system.

8. **Sanil Kumar Ramachandra Nair,2012**Escitalopram Oxalate is a class of drug with selective serotonin (5-HT) reuptake inhibitor (SSRIs). The tablets were compressed using microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, talc, magnesium stearate and opadry white was used for coating the tablets. The tablets were formulated by direct compression. Croscarmellose sodium was used as the disintegrant in the formulation of immediate release tablets of Escitalopram Oxalate. The stability studies were carried out for the optimized batch for six months. The results of the present study showed that among all the formulations, F4 was better in all terms of preformulation and post compression parameters and showed comparably a good dissolution profile like that of the marketed product.

9. Ramesh Kannuri1*, HareeshaChamarthi2 ,2012 developed Orally disintegrating tablets of escitalopram Oxalate. Orally disintegrating tablets offers a solution for paediatrics, geriatrics; psychiatric or mentally ill people and those have difficulty in swallowing tablets/capsules resulting in improved patient compliance. The aim is to formulate Orally disintegrating tablets of escitalopram oxalate using different ratios of Superdisintegrants LHPC-21, Kyron and Crospovidone, while Microcrystalline cellulose, Mannitol, Prosolv ODT used as fillers. Tablets were prepared by direct compression method. The tablets were evaluated for hardness, thickness, friability, and weight variation and disintegration time, dispersion times and %drug release studies were performed. Tablets containing Crospovidone, Kyron as disintegrants and Mannitol as filler were disintegrate rapidly below 20 sec and 100% drug release below 5mins.

10. **Suneetha.A,2011**A simple, specific, accurate and precise RP-HPLC method was developed and validated for the determination of escitalopram oxalate in tablet dosage forms. A hypersil BDS C8, 5- column having 250x4.6mm internal diameter in isocratic mode with mobile phase containing methanol: disodium hydrogen phosphate: acetonitrile (28:44:28v/v, pH

7.0±0.05) was used. The flow rate was 1.5ml/min and effluents were monitored at 226nm. The retention time of escitalopram oxalate was 8.45 min. The linearity range is 250-1500-g/ml with coefficient of correlation 0.9999. The method was validated in terms of accuracy, precision, repeatability. The percentage recovery for escitalopram oxalate was found to be 99.0%. The proposed method was successfully applied for quantitative determination of escitalopram oxalate in single dosage form for routine analysis.

11. **Patel, JigarA, et al**. prepared immediate release tablets using a suitable diluents and super-disintegrants. Faster disintegration of the tablet administrated orally minimizes absorption time and improves its bioavailability in less time. Immediate Release tablet of Antibiotic drug is formulated using dry granulation using super disintegrantcroscarmellose sodium. One of the important studies included in the present investigation is of study on process parameter effect on performance of the Immediate Release tablets. The effect of selected process parameters on critical properties of immediate release (IR) tablets were studied, like effect of disintegration time, friability, dissolution profile. The optimized formulation F5 was evaluated for *in vitro* drug release in pH 5.0, 6.8 for 60min using BP type II dissolution apparatus at 50 rpm. Hence Antibiotic drug can be successfully formulated as an immediate release tablet by dry granulation method.

12. **B.G.Shiyani*et al.*, 2009** compares the disintegrants efficiency of the 3 superdisintegrants(Ac-Di-Sol, Polyplasdone XL and Explotab) and also to compare disintegrant properties disintegrant efficiency of agar (AG) and gellan gum (GG) with treated agar (TAG) and treated gellan gum (TGG) by formulating metoclopramide HCl immediate release tablets by direct compression method. In the present investigation, the attempted first time reporting TGG as disintegrant. Disintegration efficiency of powder disintegrants were compared by swelling

&hydration capacity of disintegrants. While efficiency of disintegrants in tablets compared by various test like disintegration time, dissolution test, wetting time & maximal water uptake study of metoclopramide HCl immediate release tablets.

13. **Biljana Govedarica,2011,**Paracetamol (PAR) crystals exhibit poor compressibility, poor flowability and its tablets show a tendency to cap. To improve the mechanical strength of tablets several kinds of "Paracetamol for direct compression" are present on the market. Current research demonstrated the best tablet properties with coated paracetamol, Furthermore, coated paracetamol in combination with both investigated superdisintegrants such as Vivasol® and Polyplasdone® XL-10 shows faster disintegration time and dissolution rate in comparison to paracetamol for direct compression. Eventually, the major advantages of the formulation with coated paracetamol for industrial production are decrease of friability and superiority in terms of flowability, compressibility, quick disintegration and dissolution.

4.Materials and Equipment

4.1.List of Materials Used

The materials and their supplier names which are used in the formulation development of Escitalopram oxalate Immediate Release tablets are listed below.

Table 8: List of Materials used

S. No.	MATERIAL	NAME OF SUPPLIER
1.	Escitalopram oxalate	Finoso Pharma Pvt. Limited
2.	Microcrystalline cellulose	FMC Biopolymer
3.	Hydroxypropyl methyl cellulose	Dow Chemical Company
4.	Isopropyl alcohol	Rankem limited
5.	Croscarmellose sodium	FMC Biopolymer
6	Colloidal silicon dioxide	Evonik Degussa
7.	Magnesium stearate	Ferro corporation, Cleveland
8.	Opadry white	Colorcon

4.2. List of Equipments The following are the list of equipments used for the formulation development.

Table 9: List of Instruments used

S.No.	Name of Instrument	Manufacturer
1	Automatic tablet dissolution apparatus USP II	Electro lab
2	Digital Vernier calipers	Fischer scientific
3	Friability tester	Electrolab
4	Tablet hardness tester	Dr Schleunizer tablet tester 8m
5	Halogen Moisture Analyzer	Sartorious MA 100
6	Electro magnetic sieve shaker	Electrolab
7	Tap Density Apparatus	Electrolab
8	Mini roll compactor	Chamunda
9	Electronic weighing balance	SartoriousPrecision balance
10	17 station rotatory tabletting machine	Cadmach
11	Coating machine	Neocota
12	Rapid dryer	Retsch
13	Moisture Content (KF Titrino)	Metrohm
14	UV – Spectrometer	Shimadzu
15	High pressure liquid chromatographic apparatus	Azulent
16	pH meter	Thermo

4.3.PREFORMULATION STUDY

Preformulation study was an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It was the first step in the rational development of dosage forms.

4.3.1. Objective /Purpose of Preformulation study:-

Pre-formulation studies on active pharmaceutical ingredients (API), inactive ingredients (Excipients), and their combinations were carried out to serve following purposes:

i) To Finalize specifications of active pharmaceutical ingredients (API)

ii) To Study the compatibility between active and inactive ingredient

iii) Characterization of reference product.

4.3.2. Scope:-

The use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

4.3.3. Class: - Preformulation study can divide in to two Subclasses.

4.3.3.1 API characterization,

4.3.3.2. Compatibility study

4.3.3.1. Active pharmaceutical ingredient (API) characterization:-

Organoleptic Evaluation:-These are preliminary characteristics of any substance which is useful in identification of specific material. Following physical properties of API were studied.

a) Color

b) Odor

Table 10: Organoleptic and Solubility Analysis of Escitalopram Oxalate

Parameter	Escitalopram Oxalate
Organoleptic Evaluation	White to off white powder
Solubility Analysis	Soluble in dimethyl formamide, dimethylsulphoxide, sparingly soluble in methanol and slightly soluble in dichloromethane.

Loss on drying:-1.5g of sample of Escitalopram Oxalate was accurately weighed and the powder was kept in a moisture balance apparatus for 5 min at 105ºC and the moisture content was calculated.

Bulk density:-

Bulk density was determined by pouring gently 25 gm of sample (Escitalopram Oxalate) into 100 ml graduated cylinder. The volume occupied by the sample was recorded. Bulk density was calculated as:

Bulk density *= weight of sample in gram /volume occupied by the sample*

Tapped density:-

Tapped density was determined by using Electro lab density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%.

A sufficient number of taps should be employed to assure reproducibility for the material in question.

Volume was noted and tapped density is calculated using following formula.

Tapped density *= Wt. of sample in gm / Tapped volume*

Compressibility Index and Hausner ratio:-

In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics.

Both the compressibility index and the Hausner ratio were determined by using bulk density and the tapped density of a powder.

C.I=tapped density-untapped density*100/tapped density.

$$\text{Carr's index} = \frac{\text{Tapped desnity} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Table no.11: Relation of flow property with HR & CI

Compressibility Index (%)	**Flow Character**	**Hausner's Ratio**
≤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
>38	Very very poor	>1.60

Angle of Repose:

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

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

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

Where **θ** = angle of repose, **h** = height, **r** = radius.

A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed .Determine the angle of repose by measuring the height of the cone of powder and radius of the heap of powder.

Table 12: Flow Properties and Corresponding Angles of Repose

Flow Property	**Angle of Repose (degrees)**
Excellent	25–30
Good	31–35
Fair - aid not needed	36–40
Passable - may hang up	41–45
Poor - must agitate, vibrate	46–55
Very poor	56–65

Table 13: Flow properties of Escitalopram Oxalate (API)

Parameters	
Bulk density	0.199 gm/ml
Tap density	0.384 gm/cc
Compressibility / Carr's index (%)	48%
Hausner's ratio	0.1923
Angle of repose	44.625

From the above results it is evident that the drug has very poor flow properties, as the compressibility index, Hausner's ratio and Angle of repose values are high.

Particle size:

Sieve analysis:

The main aim of sieve analysis is to determine the different size of drug particles present. A series of standard sieves were stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed by sieves of decreasing pore size (larger sieve number) towards the bottom.

Procedure: Clean and dry#60, # 80, # 100, # 120, and collector were collected and individual weights of each sieve were noted. These sieves were arranged in ascending order. Weighed quantity of Escitalopram Oxalate (100gm) was placed in #60 mesh. Sieve shaker was set for 5 min at amplitude of 40 (Intermittent shaking).

Remove the set up from the sieve shaker after 5 min and weigh the each mesh individually and calculate % drug retained in each size of mesh with the following formula.

$$\% \text{ Retained} = \frac{\text{Final weight} - \text{initial weight}}{\text{Total weight taken}} \times 100$$

Sieve analysis of Escitalopram Oxalate

Table 14: Results of sieve analysis

Sieve No.	Sieve size (micron)	Initial Wt. (gm)	Final Wt. (gm)	% Retained
#60	250	269.5	271	1.5
#80	180	247.5	254.0	6.5
#100	150	268.5	279.0	42
#120	125	238.0	250.5	50
Collector		343.5	343.5	0
		Total		100

Inference: Based on the above results, it has been inferred that around 50% of API of size 75µ were retained in #200 mesh. Similarly 42%, 6%, 2% of API having size of 106µ, 63µ and 150µ were retained in #140, #230, and #100 meshes respectively.

4.3.4. DRUG EXCIPIENT COMPATIBILITY STUDIES

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

As a part of the product development, the compatibility of various excipients with active was evaluated.

According to the functional category these excipients were mixed in different ratios with drug.

Excipients are mixed with the Escitalopram Oxalate (API) in following ratios.

Vial in exposed condition for 1 month. Observations for physical appearance are made at initial, 2 week, and 4week, the samples were withdrawn for analysis of following parameter:

- **Description**
- **Related substances**

Results of the above excipients were used to fabricate robust formulation of Escitalopram Oxalate Tablets.

Rationale for selection of the below mentioned ratios of actives with the excipients:

The percentages of excipients were taken based on their maximum usage limits (as mentioned in the literature) along with Escitalopram Oxalate.

Sample preparation:

The individual excipient(s) were weighed as per the formula and mixed well with the API. From the individual drug mixtures made, 2 g was placed in each vial.

1. The vials were closed with the stoppers and labeled with all the details.
2. 3 vials were kept at each of the below mentioned intervals under study.
3. 2 gm of the active weighed into three vials (per interval) and placed this along with drug – excipient blends for study.

Table15: Composition for ECS studies

S No	Composition	Ratio
1.	API (Escitalopram oxalate)	-
2.	API + Microcrystalline Cellulose pH 200	1:10
3.	API + Microcrystalline Cellulose pH 112	1:10
4.	API + Microcrystalline Cellulose pH 102	1:10
5.	API + Lactose monohydrate	1:10
6.	API + Lactose anhydrous	1:10
7.	API + Maize starch B	1:5
8.	API + Methocel E5 (HPMC)	2:1

9.	API + Povidone (Kollidon 30)	2:1
10.	API + Sodium starch glycolate (Glycolys)	2:1
11.	API + Croscarmellose sodium (Ac-di-sol SD 711)	2:1
12.	API + Magnesium stearate (Synpro Magnesium stearate VG)	2:1
13.	API + Colloidal silicon dioxide (Aerosil 200 pharma)	2:1
14.	API + Talc (Luzenac Pharma UM)	2:1
15.	API+ Opadry white	4:1

Sampling Schedule

The prepared drug and excipient mixtures were evaluated at various intervals for Related Substances by HPLC as per the following conditions and time intervals

S. No.	Storage condition / Packing	Sampling intervals
1	Initial	Initial
2	40 ± 2 °C / 75 ± 5% RHGlass vial	2 weeks 4 weeks
3	25°C/60% RH Glass Vial	2 weeks,4 weeks
4	Room temperature	Control sample

4.3.5.SOLUBILITY STUDIES

Escitalopram Oxalate is classified under class I according to BCS i.e; highly permeable and highly soluble. Solubility studies of Escitalopram oxalate were conducted at all pH ranges

from 1 to 12. The solubility of API was determined by dissolving the highest unit dose of the drug in 250 ml of buffer adjusted between pH 1.0 and 12.0

Solubility Study:

- Solubility study was performed at room temperature or ambient temperature.
- 250 ml of solvent or medium was taken into 250 ml volumetric flask in which the solubility of the Escitalopram Oxalate was to be established.
- Escitalopram Oxalate equivalent to 18 mg was added
- Ultrasonicated for 15 minutes with handshaking until the material was completely dissolved.
- Solution was filtered through 0.45 µm filter to get clear solution. Filtered solution was diluted to get a concentration approximately equal to that of standard preparation.
- Content of Escitalopram Oxalate was estimated by HPLC method.

Amount of the Escitalopram Oxalate dissolved was calculated by using the following formula.

The quantity of the Escitalopram Oxalate dissolved in percentage (wt/v):

$$Q = \frac{A}{B} \times \frac{\text{Std.wt.}}{\text{Std. dil}} \times \frac{\text{Test dil.}}{\text{test wt.}} \times \frac{\text{Std. purity}}{100} \times \frac{100}{\text{Test purity}}$$

A= Response of the test solution.

B= Response of the standard solution.

The actual amount of Escitalopram Oxalate dissolved in mg

$$m = \frac{Q \times Wt}{100}$$

4.4. FORMULATION DEVELOPMENT OF ESCITALOPRAM OXALATE TABLETS 20 mg

Based on preformulation data and literature review, following strategies are used for formulation development i.e

1. Direct compression method
2. Dry granulation method
3. Wet granulation method
    a. Aqueous granulation
    b. Non aqueous granulation

After formulating the finished dosage forms by any of the above strategy, the finished dosage forms are charged for stability according to ICH guidelines. Finally the samples are analyzed by HPLC whether the release of drug from the formulation is within the specifications or not and for drug content.

4.4.1.DIRECT COMPRESSION METHOD

STEPS IN DIRECT COMPRESSION

STEP 1. WEIGHING:

Weighed the required quantities of API other dry mix materials as per table given separately.

STEP2. SIFTING:

Sifted the API and other dry mix materials through #40 mesh and mixed the blend in a poly bag for uniform distribution of API.

STEP3. LUBRICATION:

Required amount of Magnesium stearate was weighed, passed through #80 mesh and blended with blend from step 2 for 5 min.

STEP4. COMPRESSION:

The granules obtained were compressed with 11.64 × 7.0 mm oval shaped standard concave punches using 17 station compression machine.

S.no	CONTENTS	F1 (Mg/ tab)	F2 (Mg/ tab)	F3 (Mg/ tab)
1	Escitalopram Oxalate	25.55	25.55	25.55
2	Microcrystalline cellulose (Avicel PH102)	209.45	207.45	-
3	Microcrystalline cellulose (Avicel PH112)	-	-	107.45
4	Microcrystalline cellulose (Avicel PH200)	-	-	100
5	Sodium starch glycolate	10	10	10
6	Colloidal silicondioxide	2.5	3.5	2.5
7	Magnesium stearate	2.5	3.5	4.5

Total tablet weight(mg)	250	250	250

Formulations with Direct compression strategy:

Table 16: Compilation of Escitalopram oxalate tablet by DC Strategy

Lubricated blend parameters:

S.No	Parameters	F1	F2	F3
1	Bulk density(g/ml) Premix	0.373	0.41	0.412
2	Tapped density	0.552	0.508	0.477
3	Cars index	32.42	19.5	13.62
4	Hausners ratio	1.48	1.24	1.16

Table 17: Parameters for DC strategy:

Tablet parameters:

S.No	Parameters	F1	F2	F3
1	Weight(mg)	250	250	250
2	Hardness(kp)	15.3-17.0	15.5-17.3	17.7-19.6
3	Thickness(mm)	4.89-4.94	4.88-4.92	4.09-4.19
4	Disintegration Time	4.55-5.32	4.59-5.21	4.57-5.24

4.4.2.DRY GRANULATION METHOD

STEPS IN DRY GRANULATION

STEP 1. WEIGHING:

Weighed the required quantities of all the dry mix materials as per table given separately.

STEP2. SIFTING:

Sifted the drug and other dry mix materials through #40 mesh and mixed the blend in a poly bag for uniform distribution of API.

STEP3. COMPACTION:

Sifted blend is compacted into ribbons/flakes using roll compactor.

STEP5. SIZING & BLENDING OF GRANULES:

The ribbons/flakes obtained were sized through #30 mesh. Required quantity extra granular material was weighed and passed through #40 mesh and blended along with granules for 15 min.

STEP6. LUBRICATION: Required amount of Magnesium stearate was weighed, passed through #80 mesh and blended with blend from step 5 for 5 min.

STEP7. COMPRESSION:

The granules obtained were compressed with 11.64 × 7.0 mm Oval shaped standard concave punches using 17 station compression machine.

Formulations with Drug in dry mix.

Table 18: Compilation of Escitalopram oxalate Tablet by Dry Granulation

S.no	Contents	F4 (mg/tab)	F5(mg/tab)
1	Escitalopram Oxalate	25.55	25.55
2	Microcrystalline cellulose (avicel PH102)	204.45	-
3	Microcrystalline cellulose(avicelPH101)	-	204.45
4	Hydroxy propyl methyl cellulose (methocel E5 PR LV)	5	5
Extra granular material			
5	Sodium starch glycolate	10	
6	Colloidal silicondioxide	2.5	
7	Magnesium stearate	2.5	
Average weight(mg) of core tablet		250	

Table 19: Parameters for Dry Granulation Strategy

Parameters	**F4**	**F5**
Bulk density(g/ml) Premix	0.338	0.341
Tapped density(g/ml)	0.466	0.439
Carr's index	27.46	22.32
Hausners ratio	1.378	1.29

Compressed tablet parameters:-

Parameters	**F4**	**F5**
Weight(mg)	250	250
Hardness(kp)	12-14	12-14
Thickness(mm)	6.1-6.5	6.1-6.5
Disintegration Time	5.01-5.49	5.08-5.37

4.4.3.WET GRANULATION

STEP 1. WEIGHING:

Weighed the required quantities of API and other intra-granular materials as per table given separately.

STEP2. SIFTING:

Sifted the API and other intra-granular materials through #40 mesh and mixed the blend in a poly bag for uniform distribution of API.

STEP3. GRANULATION:

Sifted mixture is granulated using required amount of water for aqueous granulation and ipa for non-aqueous granulation.

STEP4. **DRYING:**Granules were dried at temperature at 60 °C until optimum LOD was obtained.

STEP5. SIZING & BLENDING OF GRANULES:

The granules obtained were sized through #30 mesh. Required quantity extra granular material was weighed and passed through #40 mesh along with granules.

STEP6. LUBRICATION:

Required amount of Magnesium Stearate was weighed, passed through #80 mesh and blended with blend from step 5 for 5 min.

STEP7. COMPRESSION: The granules obtained were compressed with 11.6 × 7.10 mm oval shaped standard concave punches using 17 station compression machine.

Table 20: Compilation of Trials by Wet granulation process

S.no	Contents	F6	F7	F8	F9	F10	F11	F12
1	Escitalopram Oxalate (mg)	25.55	25.55	25.55	25.55	25.55	25.55	25.55
2	Microcrystalline cellulose (avicel PH101) (mg)	206.2	204.2	203.2	200.2	200.2	200.2	200.2
3	HPMC (mg)	3	5	5	5	5	5	5
Binder addition								
4	Water	q.s	q.s	q.s	q.s	-	-	
5	IPA	-	-	-	-	q.s	q.s	q.s
Extra granular materials								
6	Sodium starch glycolate (mg)	10	10	10	13	13	13	13
7	Colloidal silicondioxide	2.5	2.5	2.5	2.5	2.5	2.5	2.5
8	Magnesium stearate (mg)	2.75	2.75	3.75	3.75	3.75	3.75	3.75

Average weight(mg) of core tablet	250	250	250	250	250	250	250
Average weight(mg) of coated tablet	260	260	260	260	260	260	260

Table 21: Parameters for Wet Granulation strategy

Parameters	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Bulk density(g/ml) Premix	0.338	0.341	0.39	0.465	0.39	0.342	0.343
Hardness(kp)	9-10.5	12.1-13.7	11.5-13.2	10.3-11.2	10.7-11.8	12.4-13.3	13.6-14.1
Thickness(mm)	4.65-4.80	3.95-3.99	3.99-4.02	3.99-4.01	4.31-4.33	4.23-4.27	4.26-4.28
Disintegration Time	4.10-4.31	4.44-4.49	4.37-5.09	5.31-5.54	5.24-5.37	5.05-5.28	5.28-5.43

4.5.ANALYSIS OF REFERENCE/INNOVATOR PRODUCT

With the help of analysis of the innovator product we will able to compare the results obtained of our formulated product and it was helpful for calculation of the (f1) dissimilarity & (f2) similarity dissolution factor.

Analysis of the innovator product was carried out for various physical parameters and In-vitro dissolution profile.

For tablet (Parameters):-

- Shape.
- Thickness test.
- Hardness test.
- Friability test.
- Weight Variation test.
- In-vitro dissolution studies.

4.6.EVALUATION OF TABLETS

The compressed tablets were evaluated for different official and nonofficial tests .i.e.

1) WEIGHT VARIATION TEST:

Individual weights of 20 tablets were taken and the average weight was calculated by using the following formula.

$$\text{Weight variation} = \frac{\text{(Weight of tablet-Average weight)}}{\text{Average weight of tablets}} \times 100$$

Weight variation should not be more than 5%.

2) HARDNESS:-

Hardness of the tablets was observed by the use of hardness tester. Desired hardness was 13.0Kp

3) THICKNESS:-

Thickness of the tablets was calculated by the use of Digital Vernier calipers. Desired thickness was 4.20 to 4.40mm.

4) DISSOLUTION:-

The compressed tablets were evaluated for dissolution release profiles. It is carried out for 1 hr study using USP-II (paddle type) apparatus.

DISSOLUTION STUDY:

Medium: 0.1N HCl

Type of apparatus: USP-II (paddle type)

RPM: 50 rpm

Volume: 900ml

Temperature: 37ºC± 0.5

Time: 1 hr

Time intervals: 5, 10,20,30,45 and 60 mins

Preparation of Dissolution media (0.1M HCl buffer): Add 16.6ml of HCl in a 2l volumetric flask and with some distilled water. Swirl to mix and add distilled water up to the mark of the volumetric flask.

Test and Method of analysis

Assay by HPLC

Chromatographic conditions

Instrument : Shimadzu 1200 series, Injector, UV Detector and Recorder.

Column : ACE C18column, 100-mm × 4.6-mm column that contains 3-µm

Wave Length: 239 nm.

Flow rate : 1.0 ml / min.

Injection Volume: 10µl.

Column Temperature: 45ºC

Run time: 10 min.

Diluent: 0.1NHcl

Retention time : About 6.4 minutes.

Mobile Phase is PH5.2 buffer: methanol: ACN: 600:330:70

Buffer Preparation

Dissolve accurately about 1.5 gms of anhydrous sodium acetate and 0.4ml of glacial acetic acid was added into one liter of water and ph 5.2 was adjusted to with 1N NaOH solution.

Preparation of standard solution: (22.464 µg/ml): Weigh and transfer accurately about 36 mg of Escitalopram oxalate working standeard in 50 ml of volumetric flask and dissolve and dilute upto the mark with diluent. Pipette out 2 ml of the above solution in 250 ml volumetric flask and dilute upto mark with diluent.

Preparation of test solution: Take a tablet dissolved in 900ml dissolution medium.

Procedure of injection sequence: Injected 10 µl portion of the dissolution medium as blank, standard preparation, test preparation into the chromatogram, record the chromatogram and measure the response for the analyte peak.

Calculations:

Quantity of Escitalopram oxalate dissolved in nth time interval as

$$\% \text{ of labeled amount} = \frac{AT * Ws * 2 * 900 * P}{AS * 50 * 50 * LC * 100}$$

Where,

AT = average peak area of Escitalopram oxalate for test preparation, in the nth time interval

AS = average peak area of Escitalopram oxalate for standard preparation

Ws = weight of Escitalopram oxalate working standard taken in mg.

P = potency of Escitalopram oxalate working standard calculated as API.

LC = labeled amount of Escitalopram oxalate working standard calculated as API.

n = time points

5) ASSAY:- Assay is an indicative of the amount of the drug present in the dosage form. Here it gives the insight information about the substances of the process and about effect of changes. Decrease in assay % was insignificant and within limits for the formulations.

Mobile Phase Preparation: ph5.2 buffer : methanol : ACN : 600:330:70 (v/v).

Buffer Preparation: Dissolve accurately about 1.5 gms of anhydrous sodium acetate and 0.4ml of glacial acetic acid was added into one liter of water and ph 5.2 was adjusted to with 1N NaoH solution.

Preparation of standard solution: (99.84 μg/ml):

Weigh and transfer accurately about 32 mg of Escitalopram oxalate working standeard in 50 ml volumetric flask ,add 5ml of methanol and dissolve completely and sonicate for few seconds and make to the volume to 50ml with mobile phase and then further dilute 5 ml to 25

ml with water. Pipette out 2 ml of the above solution in 250 ml volumetric flask and dilute upto mark with diluent.

Preparation of test solution: (100 µg/ml):

Weigh accurately 20 tablets of Escitalopram oxalate tablets crush and weigh the crushed powder equivalent to 100mg of Escitalopram into a 200ml volumetric flask, to this add 20 ml of buffer shake vigoursly for 10 mins add 100ml of methanol to this flask shake for one additional min and sonicate for 10 mins and make up the volume with mobile phase with up to the mark filter through 0.45micrometer filter further dilute 5ml to 25ml with water.

Procedure of injection sequence:

Injected 10 µl portion of the dissolution medium as blank, standard preparation, test preparation into the chromatogram, record the chromatogram and measure the response for the analyte peak.

Chromatographic conditions

Instrument : Shimadzu 1200 series, Injector, UV Detector and Recorder.

Column : ACE C18column, 100-mm × 4.6-mm column that contains 3-µm

Wave Length : 239 nm.

Flow rate : About 1.0 mL / min.

Injection Volume : 10µl.

Column Temperature: 45ºC

Run time : 10 min.

Diluent : pH 5.2 buffer : methanol : ACN(600:330:70)

Retention time : About 6.4 minutes.

Procedure: Inject 10 µl portion of the diluents as blank, standard preparation, test preparation into the chromatogram, record the chromatogram and measure the response for the analyte peak.

Calculations:-

Assay : Assay(mg/tab) : AT* WR*5*200*25*PR*Avg Wt*324.4*100

AR*50*25*WS*5*LA*100*414.4

Where,AT = avearge peak area of Escitalopram oxalate for test preparation.

AR = average peak area of Escitalopram oxalate for standard preparation.

WR = weight of Escitalopram oxalate in slandered solution in mg

Ws = weight of Escitalopram oxalate sample taken in sample preparation mg.

PR = purity of Escitalopram oxalate working standard calculated as API.

LA = labeled amount of Escitalopram oxalate per tablet

5.1. PREFORMULATION STUDIES

5.1.1. Evaluation of tablet

Table 22: Results of physical evaluation of tablet

Physical parameter	F1	F2	F3	F4	F5	F6
Weight variation (%)	8	5.5	5	4.7	4.1	1.5
Hardness (Kp)	15.3-17.0	15.5-17.3	17.7-19.6	12.4-14.1	12.9-14.5	22.5-24.7
Thickness (mm)	4.89-4.94	4.88-4.92	4.09-4.19	6.1- 6.5	6.1- 6.5	3.98-4.04
Disintegration Time	4.55-5.32	4.59-5.21	4.57-5.24	5.01-5.49	5.08-5.37	4.10-4.31

Table no.23. Results of physical evaluation of tablet

Physical parameter	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Weight variation (%)	0.9	0.2	0.17	0.44	0.21	0.17
Hardness (Kp)	18.9-19.7	11.7-12.9	14.3-15.3	10.7-11.8	12.4-13.3	13.6-14.1
Thickness (mm)	4.01-4.07	4.14-4.19	4.05-4.10	4.31-4.33	4.23-4.27	4.26-4.28
Disintegration Time	4.24-4.49	4.37-5.09	5.31-5.54	5.24-5.37	5.05-5.28	5.28-5.43

5.1.2. Drug-Excipient Compatibility Studies

Table no.24

S. No	Composition	Ratio	Initial Observation	Final observation (40°C/75% RH)		Final observation (25°C/60% RH)		Conclusion
				2nd week	4th week	2nd week	4th week	
1	API (Escitalopram oxalate)	-	White	White	White	White	White	Compatible
2	API + Microcrystalline Cellulose pH 200	1:10	White	White	White	White	White	Compatible
3	API + Microcrystalline Cellulose pH 112	1:10	White	White	White	White	White	Compatible
4	API + Microcrystalline Cellulose pH 102	1:10	White	White	White	White	White	Compatible
5	API + Lactose monohydrate	1:10	White	White	White	White	White	Compatible
6	API + Lactose anhydrous	1:10	White	White	White	White	White	Compatible

7	API + Maize starch B	1:05	White	White	White	White	White	Compatible
8	API + Methocel E5 (HPMC)	2:01	White	White	White	White	White	Compatible
9	API + Povidone (Kollidon 30)	2:01	White	White	White	White	White	Compatible
10	API + Sodium starch glycolate (Glycolys)	2:01	White	White	White	White	White	Compatible
11	API + Croscarmellose sodium (Ac-di-sol SD 711)	2:01	White	White	White	White	White	Compatible
12	API + Magnesium stearate (Synpro Magnesium stearate VG)	2:01	White	White	White	White	White	Compatible
13	API + Colloidal silicon dioxide (Aerosil 200)	2:01	White	White	White	White	White	Compatible
14	API + Talc (Luzenac Pharma UM)	2:01	White	White	White	White	White	Compatible
15	API+ Opadry white	4:01	White	White	White	White	White	Compatible

5.1.3. Estimation of λmax

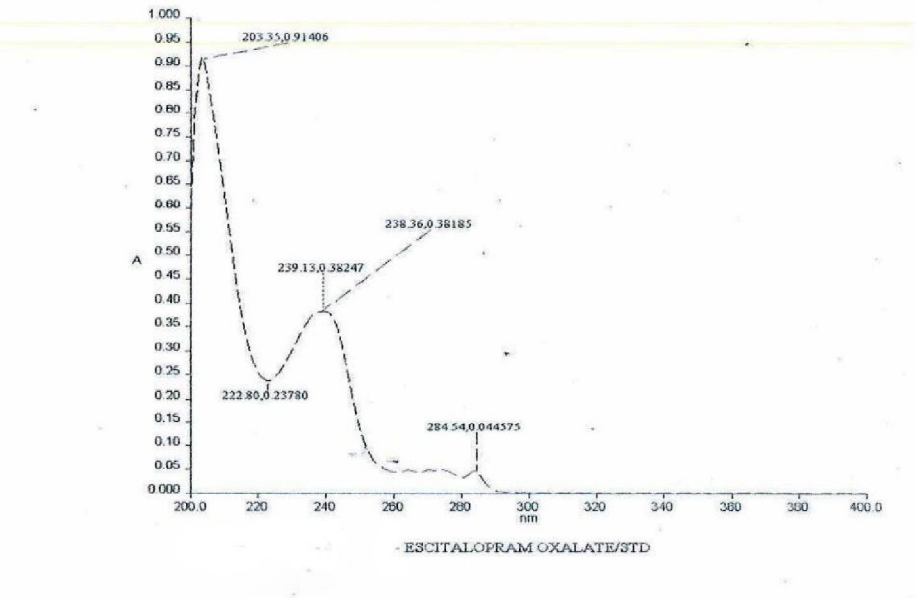


Fig no.1 Estimation of λmax

5.2. Standard calibration values:

Table no.25

Conc(µg/ml)	Absorbance(nm)
0	0
2	0.0813
4	0.1586
6	0.2349
8	0.3087
10	0.3824

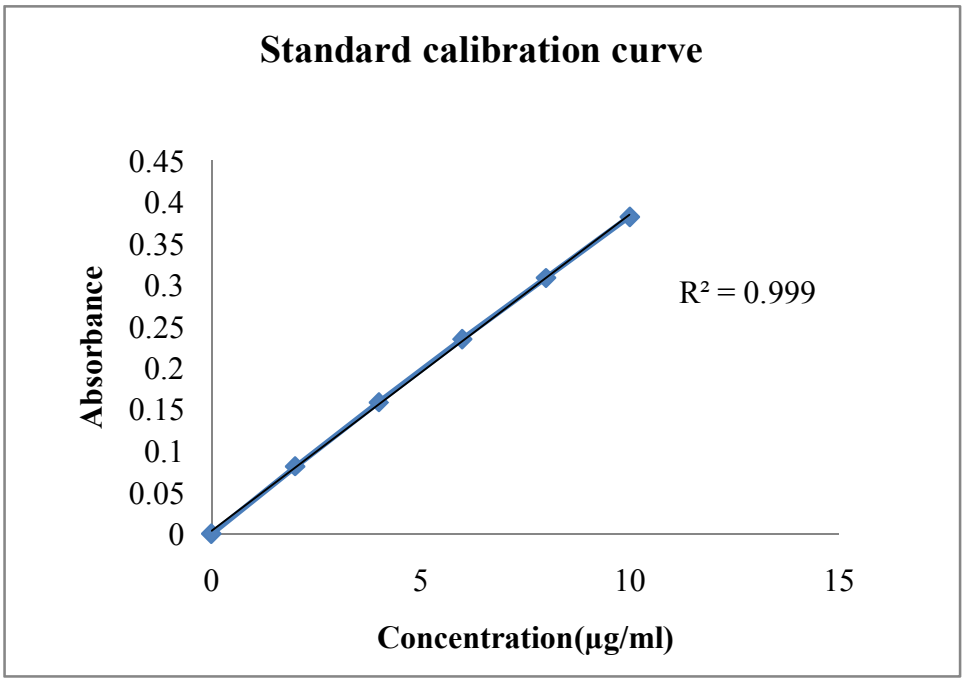


Fig no.2 Standard Calibration Profile of Escitalopram oxalate

5.3. DISSOLUTION STUDIES

Dissolution profile for Escitalopram oxalate tablets:

Table 26: Reference tablet dissolution study data

S.no	Time (min)	% Drug Dissolved						
		Sample-1	**Sample-2**	**Sample-3**	**Sample-4**	**Sample-5**	**Sample-6**	**MEAN(Q)**
1	0	0	0	0	0	0	0	0
2	5	73	78	76	79	74	75	76.3
3	10	81	83	82	82	83	86	82.8
4	15	91	92	92	91	91	91	91.3
5	20	96	98	97	98	97	98	97.3
6	30	101	102	101	101	101	104	101.6
7	45	102	102	101	101	101	102	101.5
8	60	101	102	101	101	101	101	101.1

Dissolution data of innovated drug product:

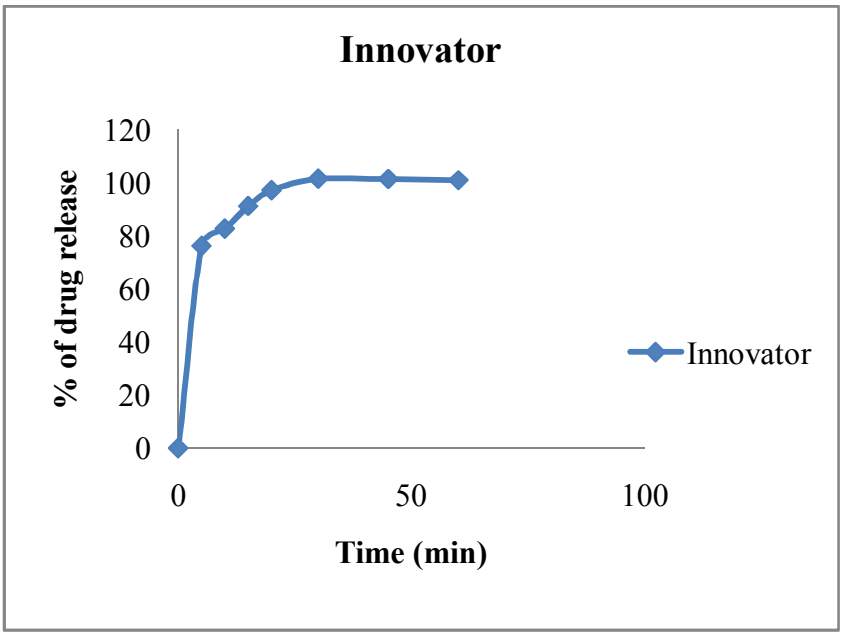


Fig no.2. Dissolution profile of innovated drug product

Comparative dissolution profiles:

Table no.27: Dissolution profile of F1:

S.no	Time (min)	%Drug Dissolved						
		Sample-1	Sample-2	Sample-3	Sample-4	Sample-5	Sample-6	MEAN(Q)
1	0	0	0	0	0	0	0	0
2	5	73	89	64	72	91	60	74.83
3	10	101	91	98	94	81	68	74
4	15	101	96	108	112	91	86	99
5	20	102	109	112	114	99	90	104.3
6	30	102	112	114	101	106	101	106
7	45	101	106	102	104	111	101	104.1
8	60	99	101	101	102	104	100	101.1

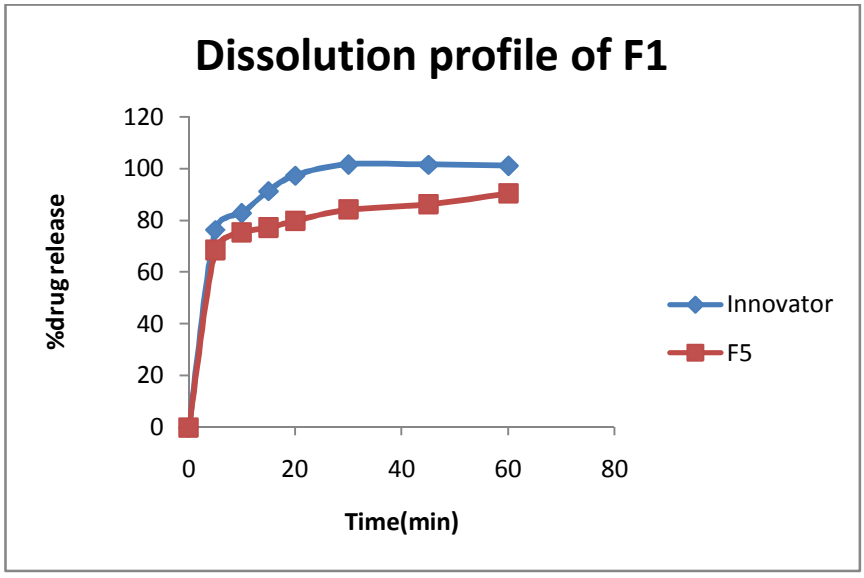


Fig no.3. Dissolution profile of F1

Table no.28. Dissolution profile of F2

S.no	Time (min)	% Drug Dissolved						
		Sample-1	Sample-2	Sample-3	Sample-4	Sample-5	Sample-6	MEAN(Q)
1	0	0	0	0	0	0	0	0
2	5	76	64	72	71	61	59	67.1
3	10	79	71	74	76	79	81	76.6
4	15	81	66	78	81	84	85	79.1
5	20	89	96	92	101	93	98	94.8
6	30	106	89	101	111	102	102	101.8
7	45	101	92	98	112	101	99	100.5
8	60	102	98	99	104	98	100	100.1

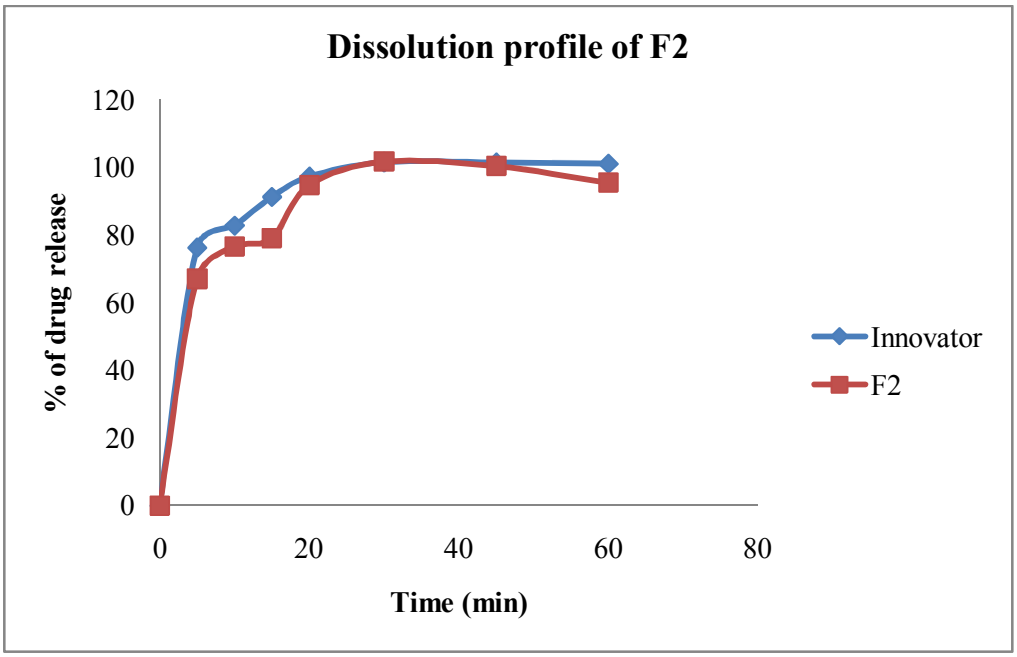


Fig no.4. Dissolution profile of F2

Table no.29. Dissolution profile of F3

S.no	Time (min)	% Drug Dissolved						
		Sample-1	Sample-2	Sample-3	Sample-4	Sample-5	Sample-6	MEAN(Q)
1	0	0	0	0	0	0	0	0
2	5	82	79	76	81	74	79	78.5
3	10	91	89	93	92	91	89	90.8
4	15	96	92	93	93	92	90	92.6
5	20	108	109	107	109	110	109	108.6
6	30	111	109	108	109	111	109	109.5
7	45	111	109	108	109	111	110	109.6
8	60	106	104	102	102	104	101	103.1

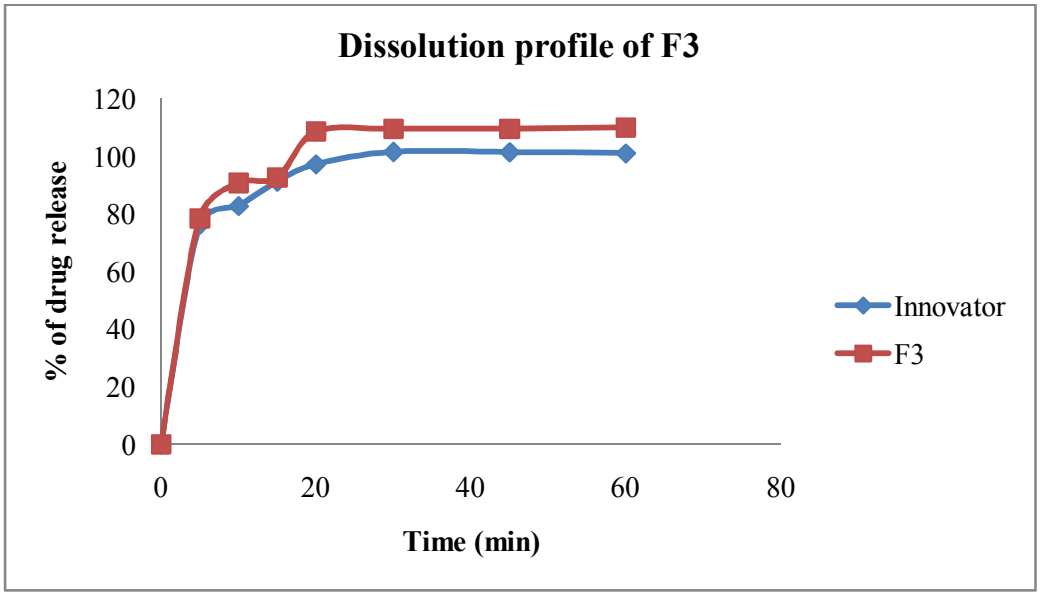


Fig no.5. Dissolution profile of F3

Table no.30. Dissolution profile of F4

Sn.n0	Time(min)	%drug release						
		Sample-1	Sample-2	Sample-3	Sample-4	Sample-5	Sample-6	Mean-(Q)
1	0	0	0	0	0	0	0	0
2	5	54	59	61	55	51	49	54.8
3	10	69	71	66	63	59	58	64.3
4	15	71	75	72	64	66	60	69.1
5	20	74	78	77	69	71	74	73.8
6	30	78	80	81	75	75	76	77.5
7	45	81	85	86	81	86	82	83.5
8	60	81	86	87	81	86	84	84.1

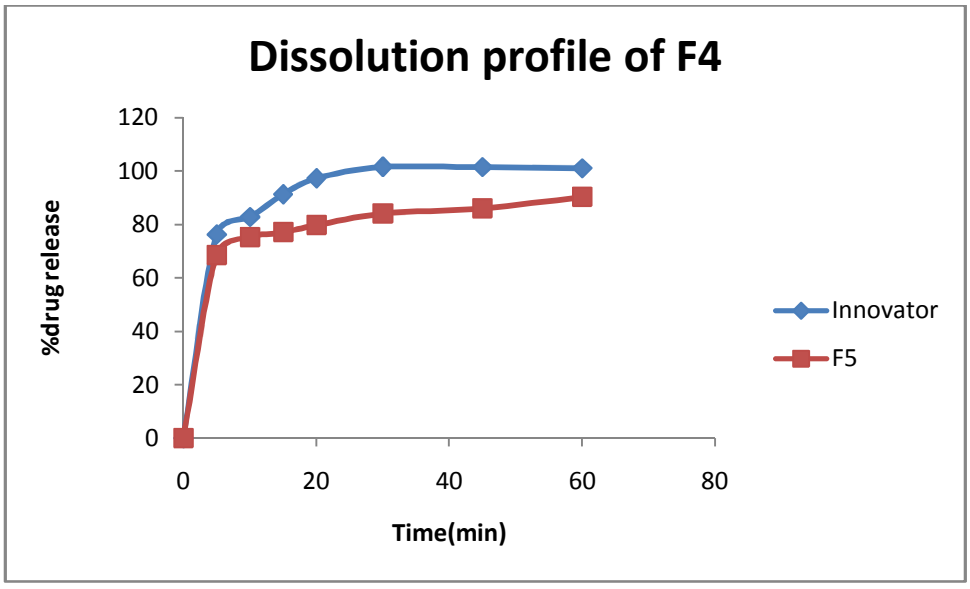


fig no.6. Dissolution profile of F4

Table no.31:Dissolution profile of F5

S.No	Time(min)	% drug release						
		Sample-1	Sample-2	Sample-3	Sample-4	Sample-5	Sample-6	Mean-(Q)
1	0	0	0	0	0	0	0	0
2	5	69	74	66	67	66	69	68.5
3	10	71	77	79	71	76	78	75.3
4	15	74	78	79	75	77	80	77.1
5	20	78	79	81	79	80	82	79.8
6	30	80	82	84	86	86	87	84.1
7	45	82	85	86	87	88	89	86.1
8	60	86	89	90	91	92	94	90.3

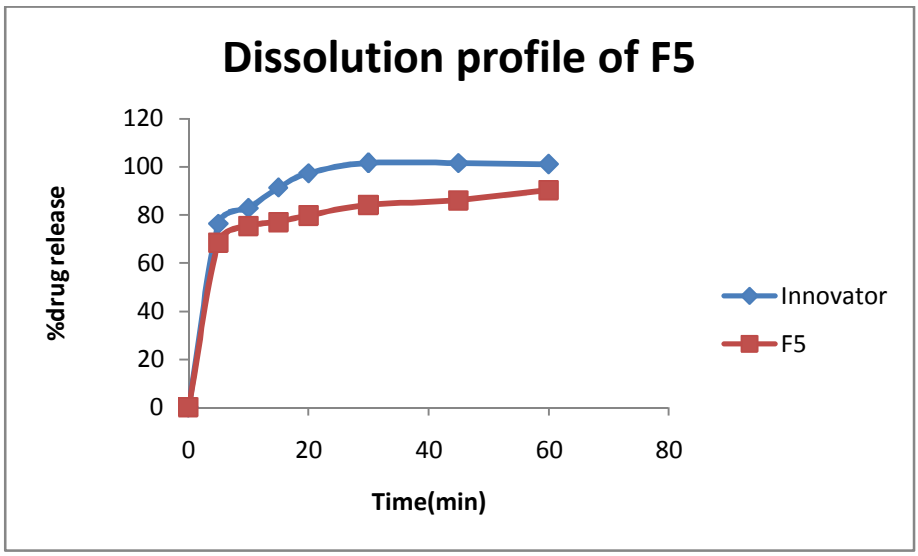


Fig no.7. Dissolution profile of F5

Table no.32. Dissolution profile of F8

S.no	Time (min)	% Drug Dissolved						
		Sample-1	Sample-2	Sample-3	Sample-4	Sample-5	Sample-6	MEAN(Q)
1	0	0	0	0	0	0	0	0
2	5	59	66	68	71	66	67	66.1
3	10	71	69	76	72	69	76	72.1
4	15	82	81	80	86	89	79	82.8
5	20	88	92	86	88	91	84	88.1
6	30	91	90	92	89	88	88	89.6
7	45	92	91	92	90	88	96	91.5
8	60	92	91	93	90	88	91	90.8

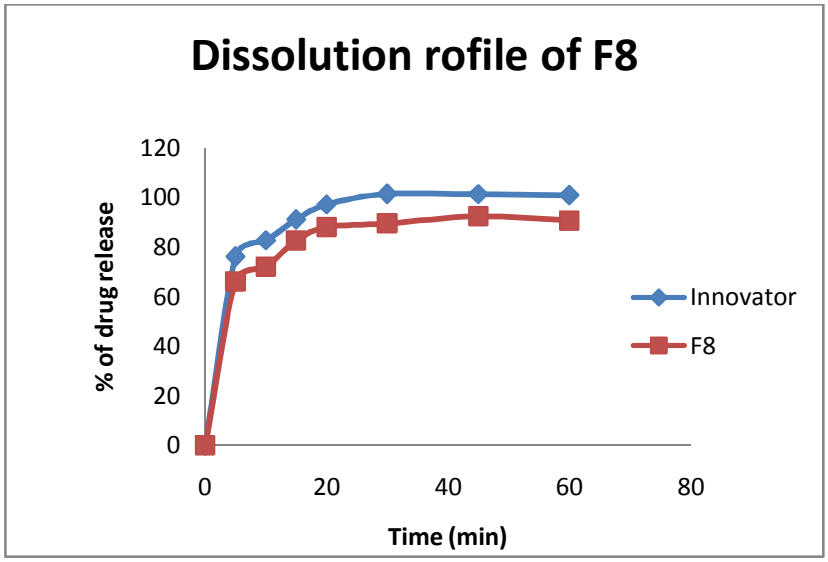


Fig no.8 Dissolution rofile of F8

Table no.33. Dissolution profile of F9

S.No	Time in Mins	%Drug Dissolved						
		Sample-1	**Sample-2**	**Sample-3**	**Sample-4**	**Sample-5**	**Sample-6**	**MEAN(Q)**
1	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
2	5	82	83	81	88	89	87	85
3	10	86	87	88	89	91	88	88.1
4	15	99	98	98	96	98	99	98
5	20	104	103	106	102	99	98	102
6	30	104	104	102	101	100	99	101.6
7	45	101	102	102	101	101	100	101.1
8	60	101	102	103	102	101	99	101.3

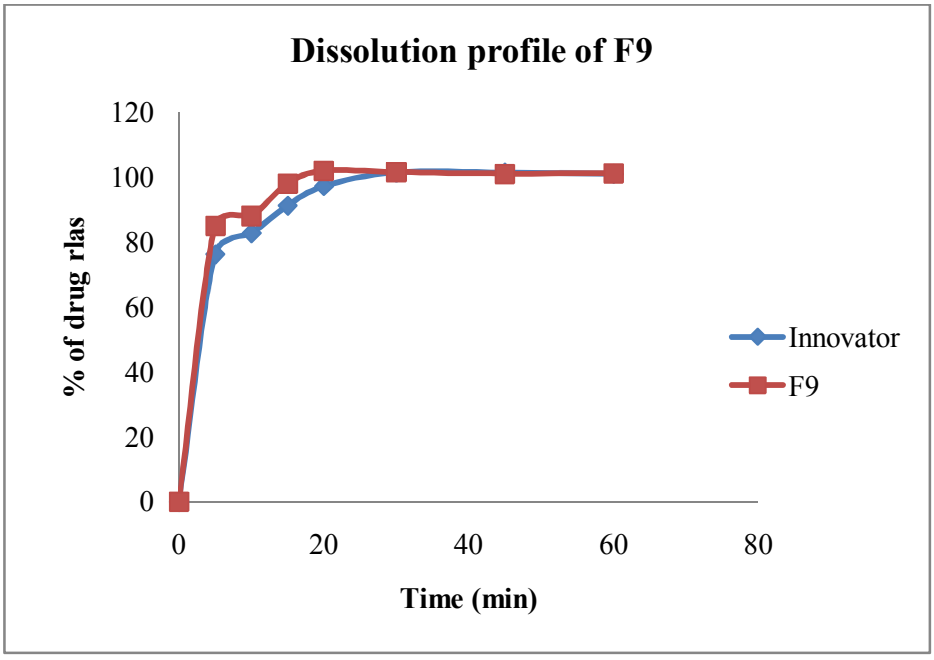


Fig no.9 Dissolution profile of F9

Table no.34 Dissolution Profile of F9 (40^0C/75% RH – 1 month)

S.No	Time in Mins	% Drug Dissolved						
		Sample-1	Sample-2	Sample-3	Sample-4	Sample-5	Sample-6	MEAN(Q)
1	0	0	0	0	0	0	0	0
2	5	40	43	38	40	39	42	28
3	10	49	53	52	47	49	49	33
4	15	53	57	59	65	56	63	58.8
5	20	68	67	70	72	71	70	47
6	30	81	78	79	76	78	75	61
7	45	84	83	87	85	84	86	72
8	60	98	101	94	94	95	97	78

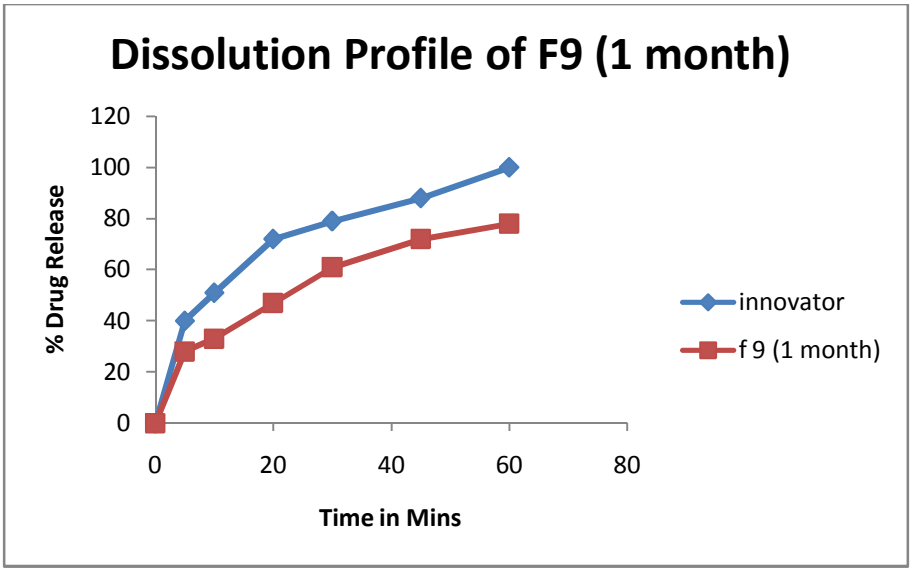


Fig no.10. Dissolution Profile of F9 (1 month)

Table no.35Dissolution profile of F10

S.No	Time (min)	% Drug Dissolved						
		Sample 1	**Sample 2**	**Sample 3**	**Sample 4**	**Sample 5**	**Sample 6**	**MEAN (Q)**
1	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
2	5	69	61	68	66	71	67	67
3	10	81	89	82	84	79	82	82.8
4	15	84	90	87	89	85	93	88
5	20	95	92	96	99	99	101	97
6	30	99	98	99	97	101	102	99.3
7	45	101	103	100	101	106	108	103.1
8	60	101	103	101	101	101	102	101.5

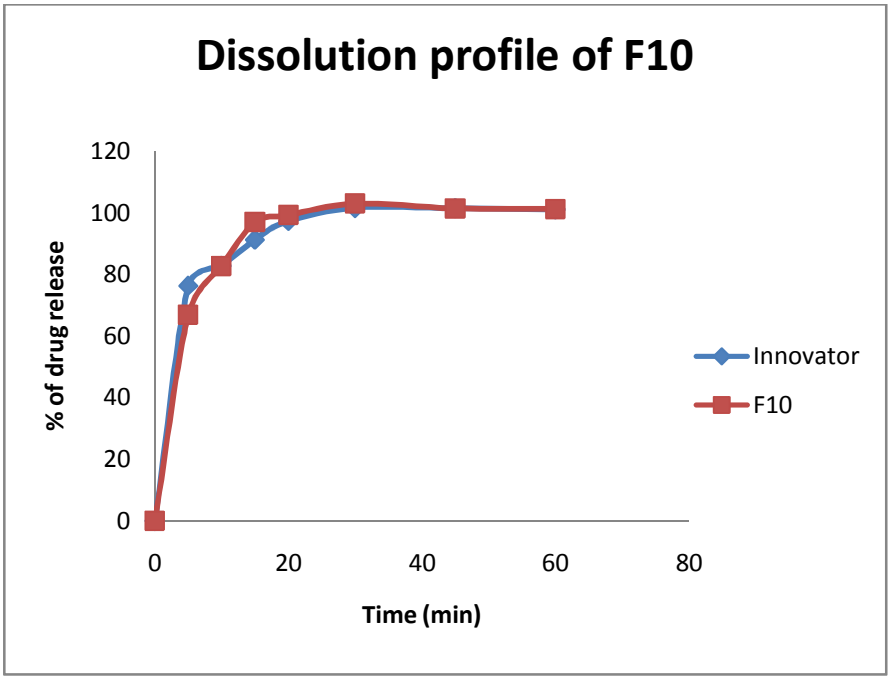


Fig no.11 Dissolution profile of F10

Table no.36. Dissolution profile of F11

S.No	Time (min)	% Drug Dissolved						
		Sample 1	**Sample 2**	**Sample 3**	**Sample 4**	**Sample 5**	**Sample 6**	**MEAN (Q)**
1	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
2	5	80	69	69	70	76	78	73.6
3	10	82	85	89	83	91	93	87.1
4	15	86	91	92	95	99	96	93.1
5	20	91	96	98	99	101	101	97.6
6	30	100	102	101	101	101	101	101
7	45	103	103	104	102	101	99	102
8	60	102	101	101	100	100	101	100.8

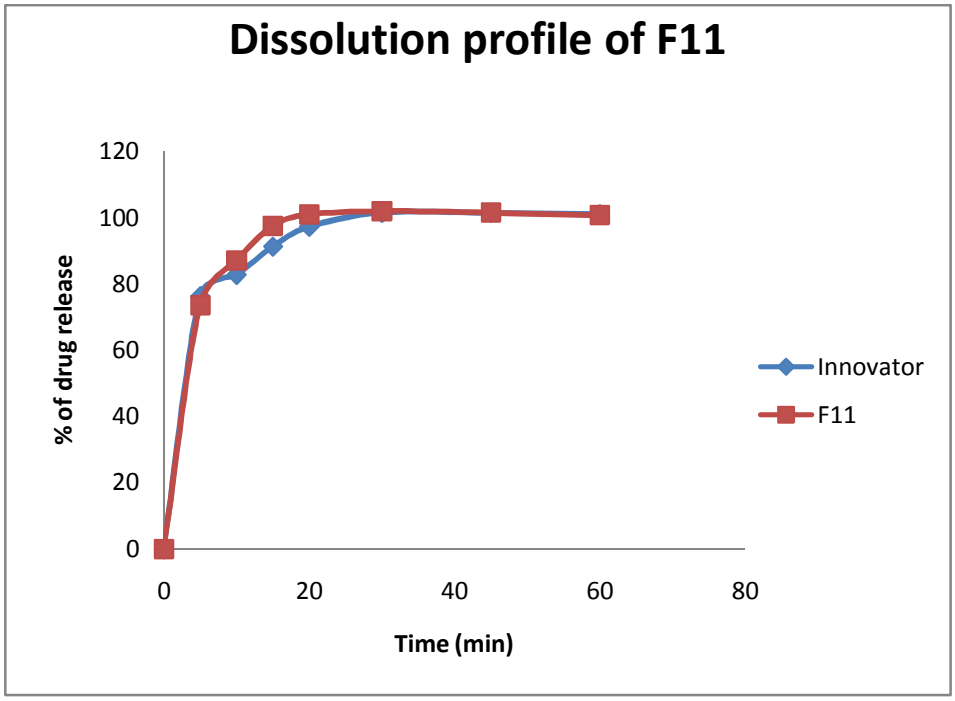


Fig no.12. Dissolution profile of F11

Table no37 Dissolution profile of F12

S.No	Time (min)	% Drug Dissolved						
		Sample 1	**Sample 2**	**Sample 3**	**Sample 4**	**Sample 5**	**Sample 6**	**MEAN (Q)**
1	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
2	5	80	84	86	81	88	84	83.8
3	10	91	92	91	90	94	92	91.6
4	15	95	94	96	92	95	96	94.6
5	20	96	98	98	97	96	98	96.6
6	30	102	99	99	101	101	99	100.1
7	45	101	102	102	101	99	102	101.1
8	60	101	101	103	102	101	102	101.6

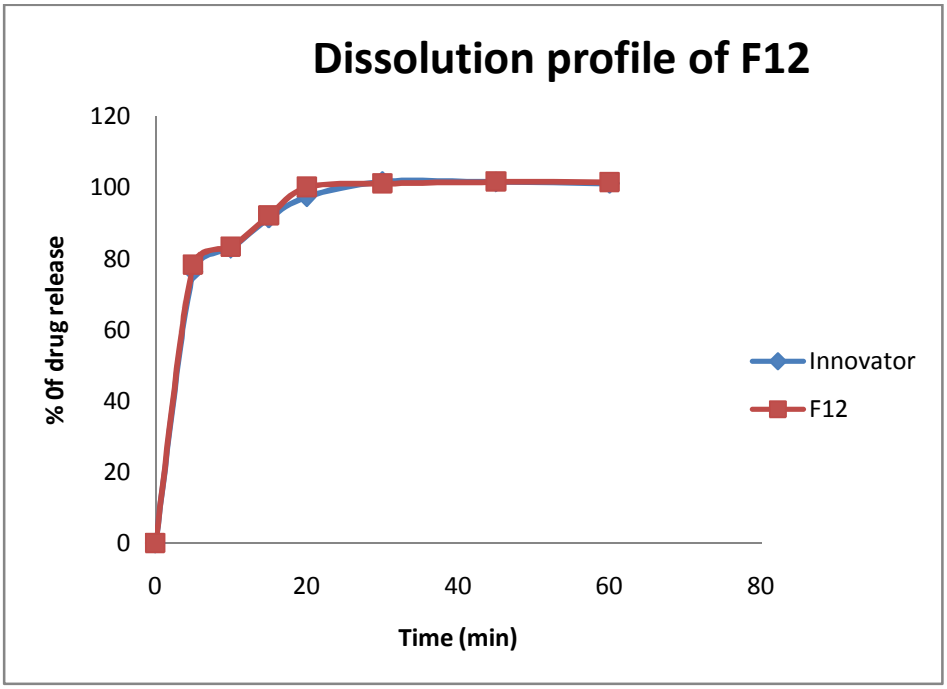
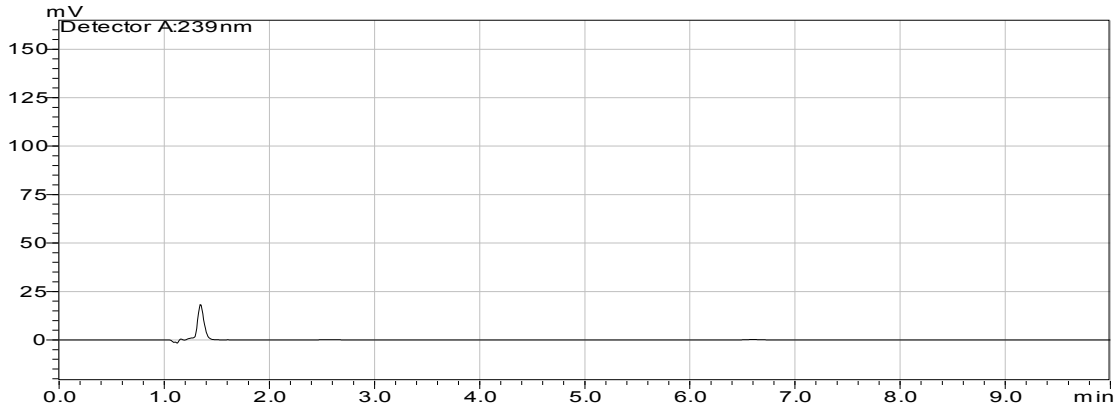


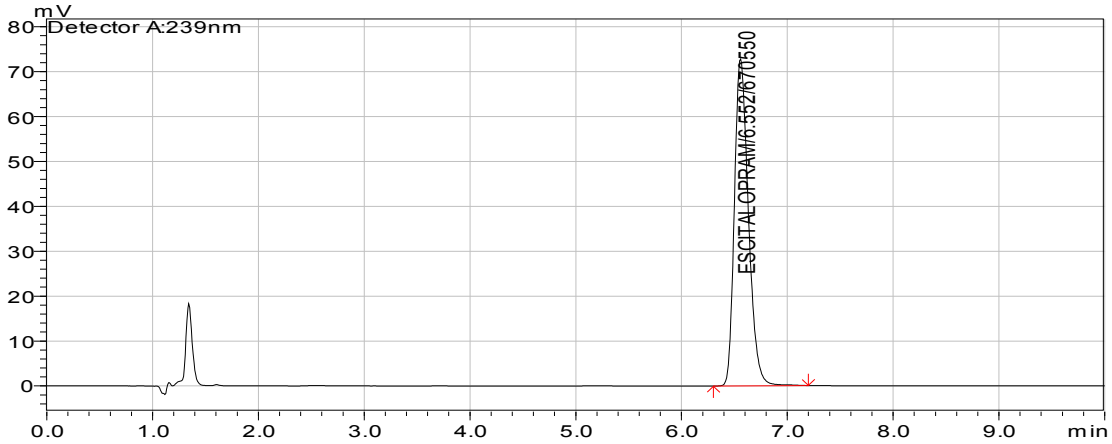
Fig no.13. Dissolution profile of F12

CHROMATOGRAMS FOR CONFIRMATORY BATCH

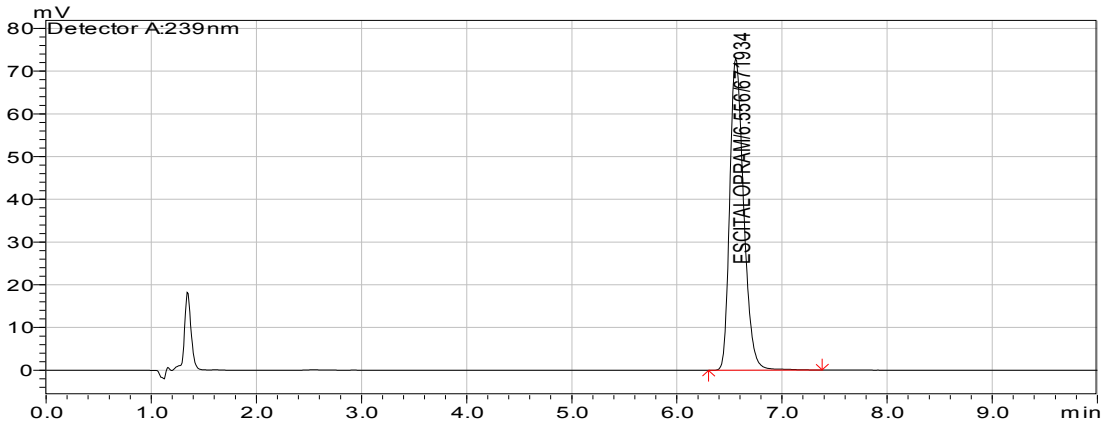
DISSO BLANK



DISSO STANDARD



DISSO SAMPLE



STABILITY STUDIES

Table 38: Related Substances (25/60) after 15 days

S.No	Name of Drug/ Excipient	Ratio	Related Substances			
			Imp-A	Imp-B	Imp-C	Total
1	API + Microcrystalline Cellulose pH 112	1:10	0.004	0.09	0.003	0.04
2	API + Microcrystalline Cellulose pH 102	1:10	0.004	0.08	0.006	0.03
3	API + Lactose monohydrate	1:10	0.004	0.06	0.061	0.033
4	API + Lactose anhydrous	1:10	0.043	0.07	0.004	0.037
5	API + Maize starch B	1:05	0.07	0.09	0.067	0.005
6	API + Sodium starch glycolate (Glycolys)	2:01	0.025	0.049	0.0053	0.05
7	API + Magnesium stearate (Synpro Magnesium stearate VG)	2:01	0.004	0.08	0.006	0.03

Table 39: Related Substances (25/60) after 30 days

S.No	Name of Drug/ Excipient	Ratio	Related Substances			
			Imp-A	**Imp-B**	**Imp-C**	**Total**
1	API (Escitalopram oxalate)	-	0.07	0.07	0.09	0.24
2	API + Microcrystalline Cellulose pH 112	1:10	0.004	0.09	0.003	0.04
3	API + Microcrystalline Cellulose pH 102	1:10	0.004	0.08	0.006	0.03
4	API + Lactose monohydrate	1:10	0.004	0.06	0.061	0.033
5	API + Lactose anhydrous	1:10	0.043	0.07	0.004	0.037
6	API + Maize starch B	1:05	0.07	0.09	0.067	0.005
7	API + Sodium starch glycolate (Glycolys)	2:01	0.025	0.049	0.0053	0.05
8	API + Magnesium stearate (Synpro Magnesium stearate VG)	2:01	0.004	0.08	0.006	0.03

Table 40: Related Substances (40/75) after 15 days

S.No	Name Of Drug/ Excipient	Ratio	Related Substances			
			Imp-A	Imp-B	Imp-C	Total
1	API (Escitalopram oxalate)	-	0.15	0.15	0.07	0.37
2	API + Microcrystalline Cellulose pH 200	1:10	0.025	0.05	0.0053	0.061
3	API + Microcrystalline Cellulose pH 112	1:10	0.005	0.09	0.003	0.041
4	API + Microcrystalline Cellulose pH 102	1:10	0.004	0.026	0.006	0.036
5	API + Lactose monohydrate	1:10	0.004	0.06	0.061	0.125
6	API + Lactose anhydrous	1:10	0.023	0.07	0.004	0.033
7	API + Maize starch B	1:05	0.07	0.09	0.067	0.022
8	API + Sodium starch glycolate (Glycolys)	2:01	0.025	0.049	0.0053	0.042
9	API + Croscarmellose sodium (Ac-di-sol SD 711)	2:01	0.004	0.09	0.003	0.047
10	API + Magnesium stearate (Synpro Magnesium stearate VG)	2:01	0.004	0.08	0.006	0.09
11	API + Talc (Luzenac Pharma UM)	2:01	0.033	0.07	0.002	0.037

Table 41: Related Substances (40/75) after 30 days

S.No	Name Of Drug/ Excipient	Ratio	Related Substances			
			Imp-A	Imp-B	Imp-C	Total
1	API (Escitalopram oxalate)	-	0.15	0.15	0.1	0.4
2	API + Microcrystalline Cellulose pH 200	1:10	0.025	0.049	0.0053	0.21
3	API + Microcrystalline Cellulose pH 112	1:10	0.004	0.09	0.03	0.04
4	API + Microcrystalline Cellulose pH 102	1:10	0.004	0.08	0.006	0.09
5	API + Lactose monohydrate	1:10	0.04	0.06	0.061	0.033
6	API + Lactose anhydrous	1:10	0.043	0.07	0.004	0.054
7	API + Maize starch B	1:05	0.07	0.09	0.067	0.19
8	API + Povidone (Kollidon 30)	2:01	0.08	0.09	0.05	0.22
9	API + Sodium starch glycolate (Glycolys)	2:01	0.025	0.049	0.0047	0.08
10	API + Croscarmellose sodium (Ac-di-sol SD 711)	2:01	0.004	0.09	0.009	0.11
11	API + Magnesium stearate (Synpro Magnesium stearate VG)	2:01	0.004	0.08	0.009	0.092
12	API + Colloidal silicon dioxide (Aerosil 200)	2:01	0.004	0.06	0.056	0.12
13	API + Talc (Luzenac Pharma UM)	2:01	0.041	0.06	0.004	0.105
14	API+ Opadry white	4:01	0.07	0.1	0.067	0.12

6.Results & Discussions

The present study was undertaken to formulate Escitalopram oxalate immediate release tablets. The study involves pre-formulation studies of drug and excipients, formulation and processing development along with evaluation of tablets made with the optimized formulation. Finally tablets were evaluated by in vitro methods.

6.1.PREFORMULATION STUDIES

Drug Excipients Compatibility Study

Physical observation

Compatibility with excipients was confirmed by HPLC studies. The pure drug and along with its formulation excipients were subjected to compatibility studies & studies were carried out by mixing definite proportions of drug and excipients and kept in glass vials which are stored at 40°C ±2°C&75± 5%RH and 25°C ±2°C + 60% RH for one month .Physical observation of sample was done every week for any colour change or lump formation, the results of the physical observation and Related Substances were shown in Table no.24

6.2.DISSOLUTION STUDIES

F1: In the first trial F1, 25.55mg/tab of API (equivalent to 20mg of Escitalopram), 209.45mg/tab of microcrystalline cellulose (Avicel PH 102), were sifted through #40 and then blended and lubricated with extra granular material and finally compressed to tablets.which is shown in table no.27

Conclusion: Physical parameters of tablets were found to be unsatisfactory. Very poor flow of blend was observed. Picking of tablets observed at the time of compression.

F2: Same composition as of F1 but diluent decreased by 2mg and colloidal silicon dioxide and magnesium stearate was increased by 1 mg, then blended and lubricated, finally compressed to tablets.shown in table no.28

Conclusion: Flow of blend was improved. Poor content uniformity of tablets observed. Dissolution studies were found to be on lower side. Only 82% of drug dissolved in 1hr. Dissolution rate was also low when compared to Reference. (100% at 1 hr).

F3: In these formula diluents were changed from Avicel PH102 to mixture of Avicel PH200 and Avicel PH 112 (100mg + 107.45mg). The above materials were sifted through #40, blended and lubricated with extra granular material and finally compressed to tablets.shown in table no.29

Conclusion: Flow of blend was good. Tablet assay is found to be on higher side i.e.,108% (standard limit 95 to 105%). Poor content uniformity of tablets observed.

F4

Objective: To take a trial by Dry granulation process.

Conclusion: compacts are formed with very low hardness, poor flow of final blend was observed. Dullness of tablet observed.shown in table no.30

F5

Objective: To take a trial by change of diluent.

Conclusion: Flow was improved when compared to F4 but still rat holing was observed when observed through funnel. Compacts are formed with low hardness, no change in strength of compacts observed even with increasing pressure between rollers.shown in table no.31

F6: In the first trial F6, API and other intragranular materials were sifted through #40. The above materials were granulated using water as granulating agent. Final dried granules were sifted through #30, blended and lubricated with extra granular material and finally compressed to tablets.shown in table no.32

Conclusion: fines percentage is very high in the dried blend. Physical parameters of tablets were found unsatisfactory.

F7: Same composition as that of F6 but amount of HPMC was increased 2mg more in intra-granular portion. The above materials were granulated using water as granulating agent. Final dried granules were sifted through #30, blended and lubricated with extra granular material and finally compressed to tablets.shown in table no.33

Conclusion: Physical parameters of tablets were found satisfactory. But sticking problem is appearing

F8: Same composition as that of F7 but stearate was increased by 1 mg in extra-granular portion. The above materials were granulated using water as binding agent. Final dried granules were sifted through #30, blended and lubricated with extra granular material and finally compressed to tablets.shown in table no.34

Conclusion: Physical parameters of tablets were found satisfactory. Dissolution studies were found to be on lower side. 90% of drug dissolved at 1hr of dissolution study. Dissolution rate was improved when compared to f2 but less when compared to Reference where 100% of drug was dissolved at 1hr.

F9: In this batch disintegrant quantity was increased by 3mg in extra-granular portion which is compensated with the diluent. The above materials were granulated using water as granulating agent. Final dried granules were sifted through #30, blended and lubricated with extra granular material and finally compressed to tablets.shown in table no.35

Conclusion: Granulation and Compression parameters were found to be satisfactory. Dissolution data was found to be similar when compared to Reference. Complete release of drug was observed in a similar way to that of Reference product. Then tablets were packed in PVC blister and stored at ICH conditions (25˚C/60%RH, 30˚C/65%RH and 40˚C/75%RH). Dissolution drop was observed after 1 month of stability charging and even the hardness of the tablet was increased.

F10: Same Formula as that ofF9but the above materials were granulated using IPA as granulating agent instead of water and temperature was reduced to 45˚C during drying. Final dried granules were sifted through #30, blended and lubricated with extra granular material and finally compressed to tablets and coated with aqueous dispersed coating solution.shown in table no.36

Conclusion: Granulation parameters were found satisfactory. Compression parameters were found to be satisfactory. Dissolution studies were found to be good. But in final tablets IPA content crosses the official limit. (3000 ppm)

F11: In this trial, same formula as of F10 and compression was done and tablets are coated with non-aqueous coating solution (IPA: DCM with 40:60).shown in table no.36

Conclusion: Here also IPA content is more than the permitted limit.

F12: In the formula same as F11 but granules drying temperature was increased to 55˚C and remaining process was same as above.(Final dried granules were sifted through #30, blended and lubricated with extra granular material and finally compressed to tablets and coating done with mixture of IPA and DCM in the ratio40:60.) shown in table no.37

Conclusion: Granulation parameters were found satisfactory. Compression parameters were found to be satisfactory. Dissolution studies were found to be good and final tablets IPA content is also complying official limits.

6.3.Stability studies:

Impurity was less than 0.5% According to guidelines on impurity of drug product the drug product containing 20 mg dose /day acceptance criteria is 0.5%.shown in table no.38,39,40,41.

Conclusions: By observing the data obtained from compatibility study, which includes physical appearance and related substances done for the samples it can be concluded that:

- No change in physical description was observed.
- No significant increase in impurities was observed.

Hence it can be concluded that the excipients used in the formulation are considered compatible with the active ingredient and it will be further concluded in the final formulation stability studies.

7. SUMMARY AND CONCLUSION

The aim of this study was to develop stable Escitalopram oxalate Immediate Release tablets which have more chances for drop in dissolution during stabiltiy and comparing with marketed product. Escitalopramoxalate comes under the category of Antidepressant and anxiolytic. In this study Escitalopram oxalate tablets were prepared by using a range of excipients including diluents and functional excipients and formulated by direct compression, dry granulation and wet granulation of which direct compression and dry granulation process were failed due to poor content uniformity of dosage form and wet granulation was successful in which non aqueous granulation with non aqueous coating was found to be good which showed very less impurity generation during stability studies. Different invitro studies were performed and were compared with that of reference and the one with wet granulation were found to be satisfactory.

The conclusion of the study is as follows:

- The tablets prepared were found to be within the official limits with respect to hardness, weight variation, drug content, thickness etc

- Among all the formulations done, the formulation with non aqueous granulation was found to be good which showed very less drop in the dissolution profile during stability where in the drop of dissolution was high in aqueous granulation during its stability study.

CONCLUSION

It can be concluded that wet granulation process with non aqueous granulation(with IPA) and with non aqueous coating was found to be optimum for the manufacturing of Escitalopram oxalate tablets as the stability results were found to be good with no impurity issues and stable dissolution data. The tablets prepared are comparable with that of the reference in all aspects and is a stable formulation.

Formulation-F12 containing Escitalopram oxalate 25.55 mg per tablet and developed using non aqueous granulation with non aqueous coating is similar and equal to the innovator product in respect of all tablets properties and dissolution profile.

Hence the study resulted in the development of Escitalopram oxalate tablets comparable to the innovator product for Escitalopram oxalate which is stable.

BIBLIOGRAPHY

1. Swarbrick J. Encyclopedia of Pharmaceutical Technology. 3rded. New York: informa healthcare; 2007.p. 164-72.

2. Shargel L, Wu-Pong S and YU ABC. Applied Biopharmaceutics and Pharmacokinetics; 5 th ed. New York: McGraw Hill; 2008:p.453.\

3. M.C.Gohel and P.D.Jogani "A review of co-processed directly compressible excipients" J Pharm PharmaceutSci (www.cspscanada.org) 8(1):76-93, 2005

4. Shayne Cox Gad;Pharmaceutical manufacturing handbook; production and processes, Volume 10, 235-266.

5. Lachman L, Liberman H and Kanig J. The Theory and Practice of Industrial Pharmacy. 3rd ed. Washington: Lee &Febriger 1991; 293-345, 346-373.

6. Aulton M. Pharmaceutics: The Science of Dosage Form Design; International Student Edition: 304-321, 347-668.

7. Ansel HC, Allen LV and Popovich NG. Pharmaceutical Dosage Forms and Drug Delivery Systems; 8 th ed. Philadelphia: Lipincott Williams & Wilkins 2005: p.227-56.

8. Lachman L, Liberman L and Schwartz J. Pharmaceutical Dosage Forms: Tablets. 2nd ed. New York: Marcel Dekker 1989; 1:p. 131-138.

9. Remington J. The Science and Practice of Pharmacy. 19th ed. Philadelphia: Lipincott Williams & Wilkins 2008; 2: 1615-1641.

10. Rawlins EA. Bentley‟s Text book of Pharmaceutics. New Delhi: BaillierTindall 2002: p.269-309.

11. Banker G and Rhodes C. Drug and Pharmaceutical Sciences: Modern Pharmaceutics. 3rd ed. New York: Marcel Decker 2002; 72: 333-394.

12. Swarbrick J and Boylan J. Encyclopedia of Pharmaceutical Technology. New York: informa healthcare; 4: 37-84, 85-106.

13. Swarbrick J and Boylan J. Encyclopedia of Pharmaceutical Technology. New York: informa healthcare; 7: 121-160.

14. Augsburger LL, Hoag SW. Pharmaceutical Dosage Forms: Tablets. 3 rded. New York: informa healthcare 2008 1: 261-293.

15. Swarbrick J and Boylan J. Encyclopedia of Pharmaceutical Technology. New York: informa healthcare 1: 451-464.

16. Augsburger LL, Hoag SW. Pharmaceutical Dosage Forms: Tablets. 3 rded. New York: informa healthcare 2008; 2: 235-239.

17. Augsburger LL, Hoag SW. Pharmaceutical Dosage Forms: Tablets. 3 rded. New York: informa healthcare 2008; 2: 251-264.

18. Shayre CG. Pharmaceutical Manufacturing Handbook. New Jersey: John Wiley & Sons Inc 2008: p. 181.

19. Gibson M. Pharmaceutical Preformulation and Formulation. Florida: CR Press 2004: p.403-36.

20. Augsburger LL, Hoag SW. Pharmaceutical Dosage Forms: Tablets. 3 rded. New York: informa healthcare 2008; 1: 303-332.

21. Rowe RC, Sheskey PJ, Owens SC. "Handbook of Pharmaceutical Excipients" 6th ed. London Pharmaceutical Press; pg 129- 133

22. Rowe RC, Sheskey PJ, Owens SC. "Handbook of Pharmaceutical Excipients" 6th ed. London Pharmaceutical Press; pg 359- 362

23. Rowe RC, Sheskey PJ, Owens SC. "Handbook of Pharmaceutical Excipients" 6th ed. London Pharmaceutical Press: pg 364- 369

24. Rowe RC, Sheskey PJ, Owens SC. "Handbook of Pharmaceutical Excipients" 6th ed. London Pharmaceutical Press: pg 206- 207

25. Rowe RC, Sheskey PJ, Owens SC. "Handbook of Pharmaceutical Excipients" 6th ed. London Pharmaceutical Press: pg 326- 329

26. Rowe RC, Sheskey PJ, Owens SC. "Handbook of Pharmaceutical Excipients" 6th ed. London Pharmaceutical Press: pg 185- 188

27. Rowe RC, Sheskey PJ, Owens SC. "Handbook of Pharmaceutical Excipients" 6th ed. London Pharmaceutical Press: pg 404- 407

28.Srinivas Gangula,1 Naveen Kumar Kolla, GERF Bulletin of Biosciences, June 2011, 2(1):1-5 "Identification, synthesis and spectral characterization of impurities in process development of Escitalopram".