FORMULATION AND *INVITRO* EVALUATION OF ESCITALOPRAM OXALATE ORAL DISINTEGRATING TABLETS

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DECLARATION

I here by declare that the dissertation work entitled **"FORMULATION AND EVALUATION OF ESCITALOPRAM OXALATE ORAL DISINTEGRATION TABLETS BY INVITRO AND STABLILITY STUDIES"** is based on the original work carried out by me in **Annai Veilankanni's Pharmacy College, Saidpet, Chennai** and formulation and evaluation in **CEEGO LABS Pvt.Ltd.** for the award of Degree Master of pharmacy in pharmaceutics. The work is original and has not been submitted in part or full for any other diploma or degree of this or any other submission to The Tamilnadu Dr.M.G.R Medical University in the partial fulfillment of the requirement university. The information furnished in this dissertation is genuine to the best of my knowledge.

Chennai,

Date :27.08.2015 261311058

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LIST OF ABBREVIATIONS

ODTs	Oro- dispersible tablets
FDTs	Fast Dissolving Tablets
MCC	Micro Crystalaline Cellulose
PEG	Polyethylene Glycol
HPMC	Hydroxy Propyl Methyl Cellulose
SSG	Sodium starch glycolate
TD	Tapped Density
BD	Bulk Density
IP	Indian pharmacopoeia
DSC	Gastrointestinal Scanning Calorimetry
GIT	Gastrointestinal Tract
FDA	Food and Drug Administration
SSF	Simulated salivary Fluid
RDT	Rapid disintegrating Tablet
SEM	Scanning Electron Microscopy
XRPD	S-Ray powder diffraction
g	Gram
mm	Millimeter
mg	Milligram
kg	Kilogram
API	Active pharmaceutical ingredient

1. INTRODUCTION

Oral route of drug administration is most appealing route for delivery of drugs of various dosage forms. The tablets is one of the most preferred dosage form because of its ease of administration, accurate dosing and stability as compared to oral liquid dosage forms and when compared to capsules, tablets are more temper evident.

1.1 TABLETS1:

Tablets may be defined as solid unit pharmaceutical dosage forms containing drug substance with or without suitable Excipients and prepared by either compression or molding mehtods[1]. The first step in the development of dosage form is Preformulation, which can be defined as investigation of physicochemical properties of drug substance alone and when combined with Excipients. The main objective of Preformulation studies, is to develop stable and bioavilabel dosage form and study of factors affecting such stability, bioavailability and to optimize so as to formulate the best dosage form, here optimization of formulation means finding the best possible composition[2]. compressed tablets are formed by applying pressure, for which compression machines (tablet presses) are used and they are made from powdered crystalline or granular material, alone or in combination with binder, disintegrants, release polymers, lubricants and diluents and in some cases colorant.

1.1.1 Various types of tablets[2]

A) Oral tablets for ingestion

These tablets are meant to be swallowed intact along with a sufficient quantity of potable water. Exception is chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction.

1. Standard compressed tablets
2. Multiple compressed tablets
    a. Compression coated tablet
    b. Layered tablet
    c. Inlay tablet
3. Modified Release tablet
4. Delayed action tablet
5. Targeted tablet
    a. Floating tablet
    b. Colon targeting tablet
6. Chewable tablet
7. Dispersible tablet

B) Tablets used in the oral cavity

The tablets under this group are aimed release active pharmaceutical ingredient in oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity.

1. Lozenges and troches
2. Sublingual tablet
3. Buccal tablet
4. Dental cones
5. Mouth dissolved tablet

C Tablets administered by other routes

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application.

1. Vaginal tablet
2. Implants

D Tablets used to prepare solution

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parentral application or for topical use depending upon type of medicament used.

1. Effervescent tablet
2. Hypodermic tablet

1.2 FORMULATION OF TABLETS:

In addition to active pharmaceutical agent (API), the tablets contain non drug substances called as Excipients, which include:

Table-1.1 Excipients in Tablet Formulation and their Functions[2,3]

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/ Granulating agents	Provides cohesiveness to powders, thus providing the necessary bonding to form granules.
Disintegrates	Facilitate a breakup or disintegration of the tablet when placed in an aqueous environment.
Antifrictional Agents	

Lubricants	Reduce the friction during tablet formation in a die and also during ejection from die cavity.
Anti adherents	Reduce sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall.
Glidants	Promote the flow of tablet granulation or powder mixture from hopper to the die cavity by reducing friction between the particles.
Miscellaneous	
Wetting agents	Aid water uptake during disintegration and assist drug dissolution.
Dissolution retardants	Retards the dissolution of active pharmaceutical ingredients.
Dissolution enhancers	Enhance the dissolution rate of active pharmaceutical ingredients.
Adsorbents	Retain large quantities of liquids without becoming wet; this property allows many oils, fluid extracts to be incorporated into tablets.
Buffers	Provide suitable micro environmental pH to get improved stability and / or bioavailability.
Antioxidants	Prevents oxidation and maintains the product stability.
Chelating agents	Protect against autoxidation; they act by forming complexes with the heavy metal ions which are often required to initiate oxidative reactions.
Preservatives	Prevent the growth of micro-organisms.
Colors & flavors	Provides attractiveness, increase patient compliance and product identification.
Sweeteners	Sweeteners are added to mask bitter taste of tablets

1.3 Tablet: Manufacturing Methods[2, 3, 4]

1.3.1 Wet granulation

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing, drying and compression.

Raw materials → Weighing → Screening → wet mass → Sieving/Milling → drying → screening → Mixing → Compression

1.3.2 Dry granulation

In dry granulation process the powder mixture is compressed without the use of heat and solvent. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is pre compressed and the resulting tablet or slug are milled to yield the granules and the compressed to tablets.

Raw material → Weighing → Screen → Mixing → Slugging →Milling → Screening → Mixing → Compression

1.3.3 Direct compression

Direct compression is a more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.

Raw material →Weighing → screening → Mixing → Compression

1.3.4 Defects in tablet manufacturing [2, 3]

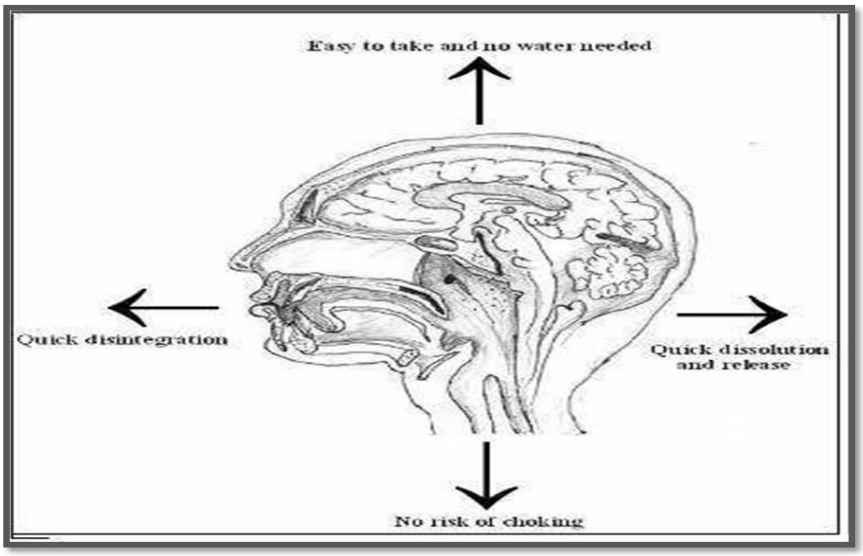
- **Lamination:** Separation of a tablet into two or more distinct horizontal layers.

- **Capping:** Partial or complete separation of top or bottom crowns of a tablet.
- **Chipping:** Breaking of tablet edges during compression or coating.
- **Cracking:** Fine cracks observed on the upper and lower central surface of tablets, or very rarely on the sidewall are referred to as 'Cracks'.
- **Picking:** In picking the tablet material adheres to the surface of the punches resulting in tablets with a pitted surface instead of a smooth surface.
- **Sticking:** The tablet material adhers to the die wall.
- **Mottling:** Unequal distribution of colour on the surface of coloured tablets.
- **Blotting:** Appearance of light or dark spots of colour on the tablet surface.
- **Double Impression:** It involves only those punches, which have a monogram or other engraving on them. Free travel or free rotation of either upper punch or lower punch during ejection of a tablet causes double impression.

1.4 ORAL DISINTEGRATING TABLETS

The most important drug delivery route is undoubtedly the oral route. It offers advantages of convenience of administration and potential manufacturing cost savings. Drugs that are administered orally, solid oral dosage forms in general and tablets in particular represent the preferred class of product. Today drug delivery companies are focusing on solid oral drug delivery systems that offer greater patient compliance and effective dosages. Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing. Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medication as prescribed. In a survey conducted by Honda and Nakano, half of the patients experienced difficulty taking medication, such as tablet and capsule which results in a high incidence of non-compliance and

ineffective therapy. The difficulty is experienced in particular by paediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water.[5] Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing. United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute. [6]



1.41 Historical perspective of ODT

Products of ODT technologies entered the market in the 1980's, have grown steadily in demand, and their product pipelines are rapidly expanding. The first ODT form of a drug to get approval from the US (FDA) was a Zydis ODT of Claritin (Loratadine) in December 1996. It was followed by a ZYDIS ODT formulation of Klonopin (Clonazepam) in December 1997, and a ZYDIS ODT formulation of Maxalt (Rizatriptan) in June 1998. CATALENT PHARMA SOLUTIONS in the U.K., CIMA LABS in the U.S. and TAKEDA Pharmaceutical Company in Japan lead in the development of ODTs[7].

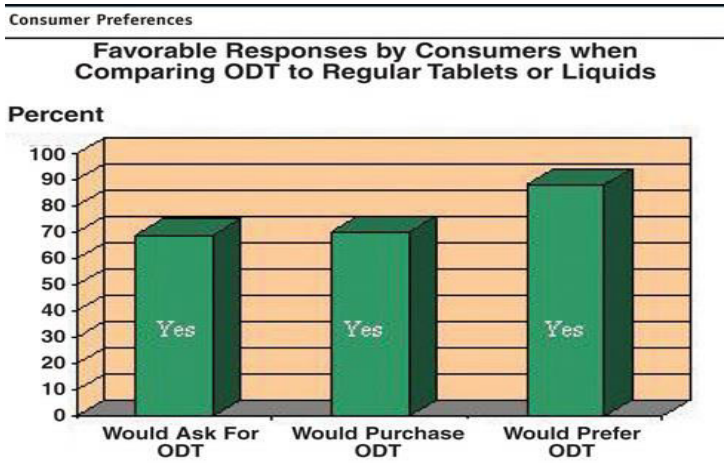


Figure-1.1 Consumer Preferences for ODT's[8]

Recent market studies indicate that most of the patient population prefers ODTs to other dosage forms and would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%). In addition, several business needs are driving ODT technology development and the commercialization of new products such as the need for expanded product lines, improved life-cycle management, extended patent life, and marketing advantages[7,8].

1.42 Drug Selection Criteria

The ideal characteristics of a drug for oral dispersible tablet include [9]

- Ability to permeate the oral mucosa.

- At least partially non-ionized at the oral cavity pH.
- Have the ability to diffuse and partition into the epithelium of the upper GIT.
- Small to moderate molecular weight.
- Low dose drugs preferably less than 50 mg.
- Short half life and frequent dosing drugs are unsuitable for ODT.
- Drug should have good stability in saliva and water.
- Very bitter or unacceptable taste and odour drugs are unsuitable for ODT.

1.43 Important Criteria for Excipients used in the Formulation of ODTS:

- It must be able to disintegrate quickly.
- Their individual properties should not affect the ODTs.
- It should not have any interactions with drug and other excipients.
- It should not interfere in the efficacy and organoleptic properties of the product.
- When selecting binder a (single or combination of binders) care must be taken in the final integrity and stability of the product.
- The melting points of excipients used will be in the range of 30-350C.
- The binders may be in liquid, semi liquid, solid or polymeric mixtures[10].
- (Ex: Polyethylene glycol, cocoa butter, hydrogenated vegetable oils)

1.44 Advantages [11, 12]

- Easy to administer to the patient who cannot swallow such as pediatric, geriatric, bedridden, stroke victim and institutionalized patient (specially for mentally retarded and psychiatric patients)

- Pregastric absorption leading to increased bioavaibility rapid absorption of drugs from mouth, pharynx and oesophagus as saliva passes down to stomach, also avoids hepatic metabolism.
- Convenient for administration to travelling patients and busy people who do not have accesses to water.
- Excellent mouths feel property produced by use of flavours and sweetners help to change the perception of "medication as bitter pill" especially in pediatric population.
- Fast disintegration of tablets leads to quick dissolution and rapid absorption which may produce rapid onset of action.
- ODTs offer all the advantages of solid dosage forms and liquid dosage forms.
- Convenience of administration and accurate dosing compared to liquids.

1.45 Challenges in the Formulation of Orally Disintegrating Tablets

Palatability[13, 14]

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance

Mechanical strength[15, 16, 17]

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow

them to be packaged in multidose bottles, such as Wowtab® by Yamanouchi-Shaklee, and Durasolv® by CIMA labs.

Hygroscopicity[18]

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging

Amount of drug[13, 19]

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

Aqueous solubility[20, 21]

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as Mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

Size of tablet[22]

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Table-1.2 Drugs Explored for Orally Disintegrating Tablets.[23]

Category	Drug
NSAIDS	Ketoprofen, Piroxicam, Paracetomol, Rofecoxib, Nimesulide, Ibuprofen
Anti ulcer	Famotidine, Lansoprazole
Anti parkinsonism	Selegiline
Anti depressants	Mitraxepine, Fluoxetine, Escitalopram Oxalate
Anti migrane	Sumatriptan, Rizatriptan benzoate, Zolmitriptan
Anti histaminics	Loratadine, Diphenhydramine, Meclizine
Hypnotics sedatives	Zolpidem, Clonazepam, Atenolol
Anti psychotics	Olanzepine, Pirenzepine, Risperidone
Anti emetics	Ramosetoron HCl, Ondansetron
Miscellaneous	Ethenzamide, Baclofen, Hydrochlorthiazide, Tramodol Hcl, Propyphenazone, Spiranolactone, Phloroglucinol, Sildenafil

1.5 Various Approaches Employed in Manufacture of ODTS

There are number of techniques generally employed in the formulation of orally disintegrating dosage forms. These techniques have their own advantages as well as disadvantages and are described below:

1.51 Direct compression

Direct compression is one of the popular techniques for preparation of these dosage forms. The advantages of this method include easy implementation, use of conventional equipments along with commonly available excipients, limited number of processing steps and cost effectiveness. Disintegration and solubilization of directly compressed tablets depend on single or combined action of disintegrants, water-soluble excipients and effervescent agents. The basic principle involved in

development of these dosage forms using this technique is addition of Superdisintegrants in optimum concentrations so as to achieve rapid disintegration along with pleasant mouth feel [24]. It is considered as the best method to prepare orally disintegrating dosage forms since the prepared tablets offer higher disintegration due to absence of binder and low moisture contents [25]. This approach is also considered as disintegrant addition technology.

1.52 Freeze drying

Freeze drying or lyophilization is a process in which solvent is removed from a frozen drug solution or suspension containing structure forming excipients. Tablets formulated by this technique are usually very light and porous in nature which allows their rapid dissolution. Glassy amorphous porous structure of excipients as well as the drug substance produced with freeze drying results in enhanced dissolution. Freeze drying process normally consists of three steps:

- Material is frozen to bring it below the eutectic point.
- Primary drying to reduce the moisture around 4% w/w of dry product.
- Secondary drying to reduce the bound moisture upto required final volume.

Entire freeze drying process is carried out at non elevated temperature; therefore, nullifying adverse thermal effects that may affect drug stability during processing[24]. R.P. Scherer patented *zydis technology* utilizing lyophilization or freeze drying process in development of mouth dissolving tablets on the basis of patents issued to Gregory *et al* [26,27]. Corveleyn Sam *et al* also prepared rapidly disintegrating tablets by lyophilization [28]

1.53 Sublimation

Because of low porosity, compressed tablets containing highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in water. Some inert volatile substances like urea, urethane, ammonium carbonate,

naphthalene, camphor etc. are added to other tablet excipients and blend is compressed into tablet. Removal of volatile substances by sublimation generates a porous structure. Various steps involved in sublimation process are shown in Figure 1. Additionally several solvents like cyclohexane and benzene etc. can also be used as pore forming agents.

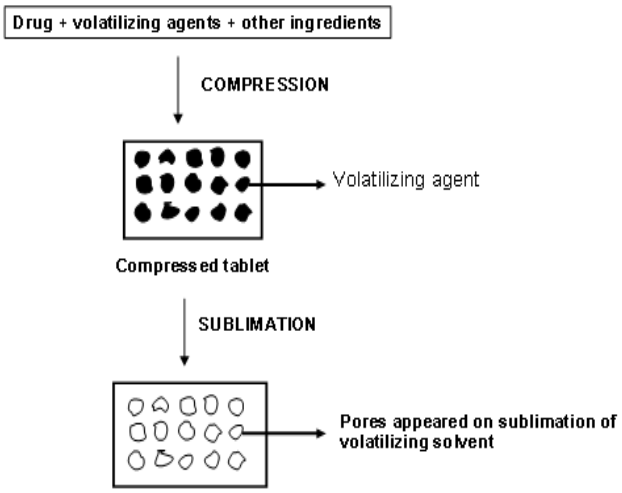


Figure 1.2: Steps involved in sublimation process

Koizumi *et al* formulated rapidly saliva soluble tablets using camphor as subliming agent. The tablets were subjected to vacuum at 80ºC for 30 min. to eliminate camphor and thus create pores in the tablet. Porous tablet exhibits good mechanical strength and dissolve quickly[29]. Gohel M. *et al* prepared mouth dissolving tablets of nimesulide using vacuum drying technique and found that it would be an effective alternative approach compared to the use of more expensive adjuvants in the formulation of these dosage forms [30]

1.54 Moulding

Moulded tablets are designed to facilitate the absorption of active ingredients through mucosal linings of mouth. This is achieved by complete and rapid dissolution of the tablet using water soluble ingredients. Moulded tablets disintegrate more rapidly and offer improved taste because of the dispersion matrix which is

generally prepared from water soluble sugars. Powdered blend (containing drug and excipients like binding agents - sucrose, acacia, PVP etc.) is pushed through a very fine screen (to ensure rapid dissolution) and then moistened with a hydroalcoholic solvent and moulded into tablets under pressure lower than employed for conventional compressed tablets. The solvent is later removed by air drying. A porous structure that enhances dissolution prepared by using water soluble ingredients meant to be absorbed through mucosal lining of mouth, thus increasing bioavailability and decreasing first pass metabolism of certain drugs.

1.55 Spray drying

This technique is based upon the use of a particulate support matrix prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. Allen *et al* utilized this process for preparing ODTs. These formulations consisted of hydrolyzed/unhydrolyzed gelatin as supporting agent for matrix, mannitol as bulking agent, and sodium starch glycolate or croscarmellose sodium as disintegrating agent. Disintegration and dissolution were further improved by adding effervescent components, i.e. citric acid and sodium bicarbonate. The formulation was finally spray dried to yield a porous powder [31].

1.56 Mass extrusion

This technology consist of softening the active blend using a solvent mixture of water soluble Polyethylene glycol with methanol and expulsion of softened mass through the extruder or syringe to obtain cylinder of the product into even segments employing heated blade to form tablet. The dried cylinder can also be utilized for coating the granules of bitter drugs and thereby masking their taste[31,32]

1.57 Cotton candy process

This process is so named as it utilizes an inimitable spinning mechanism to produce floss like crystalline structure, which mimics cotton candy. This technique involves formation of matrix of polysaccharides or saccharides by simultaneous

action of flash melting and spinning. The matrix formed is partially recrystallized to have better flow properties and compressibility. This matrixis milled and blended with active ingredients as well as excipients and subsequently compressed to ODTs. This process can accommodate high doses of drug and offers improved mechanical strength. However, high process temperature limits the use of this process[31.]

1.58 Phase transition

Kuno *etal* proposed a novel method to prepare ODTs with sufficient hardness by involving the phase transition of sugar alcohol. In this technique, ODTs are produced by compressing and subsequently heating tablets that contain two sugar alcohols, one with high and other with a low melting point. Heating process enhances the bonding among particles leading to sufficient ardness of tablets which was otherwise lacking owing to low/little compactibility [33].

1.59 Melt granulation

Melt granulation is a process in which pharmaceutical powders are efficiently agglomerated by the use of binder which can be a molten liquid, a solid or a solid that melts during the process. For accomplishing this process, high shear mixers are utilized, where the product temperature is raised above the melting point of binder by a heating jacket or by the heat of friction generated by impeller blades. Perissutti *et al* prepared carbamazepine fast-release tablets by melt granulation technique using polyethylene glycol 4000 as a melting binder and lactose monohydrate as hydrophilic filler [34, 35.]

1.6 Important Patented Technologies for Fast Dissolving Tablets[36-40]

Zydis Technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is

composed of many material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration while various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process.

Durasolv Technology:

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of drug, filler and a lubricant. Tablets are prepared by using conventional tabletting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring low amounts of active ingredients.

Orasolv Technology:

CIMA labs have developed Orasolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable.

Flash Dose Technology:

Flash dose technology has been patented by fuisz. Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self-binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing.

Wow tab Technology

Wow tab technology is patented by Yamanouchi Pharmaceutical Co.WOW means "Without Water". In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (eg. lactose, glucose, and mannitol) and granulated with a high mouldability saccharide (eg. Maltose, oligosaccharides) and compressed into tablet.

Flash tab Technology:

Prographarm laboratories have patented the Flash tab technology. Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like oacervation, micro encapsulation and extrusion spheronisation. All the processing utilized conventional tabletting technology.

OraQuick:

The OraQuick fast-dissolving/disintegrating tablet formulation utilizes a patente taste masking technology. KV Pharmaceutical claims its microsphere technology,known as MicroMask, has superior mouthfeel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production.

Quick –Dis Technology:

Lavipharm Laboratories Inc. (Lavipharm) hass invented an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intraoral drug delivery system, trademarked Quick- Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The Quick-Dis™ drug delivery system can be provided in various packaging

configurations, ranging from unitdose pouches to multiple-dose blister packages. The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. drug delivery system is 50% released within 30 seconds and 95% within 1 minute.

Durasolv Technology

DuraSolv is Cima's second-generation fast-dissolving/disintegrating tablet formulation. Produced in a fashion similar to OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. DuraSolv tablets are prepared by using conventional tabletting equipment and have good rigidity (friability less than that 2%). The DuraSolv product is thus produced in a faster and more costeffective manner. DuraSolv is so durable that it can be packaged in traditional blister packaging, pouches or vials. One disadvantage of DuraSolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Unlike OraSolv, the structural integrity of any taste masking may be compromised with high drug doses. The drug powder coating in DuraSolv may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, the DuraSolv technology is best suited for formulations including relatively small doses of active compound.

Sheaform Technology

This technology make Sheaform matrix consisting of floss preparation. Floss is produced by subjecting to a feedshock containing a sugar to flash heat processing.

Ceform Technology

In this technology microspheres containing active ingredient are prepared.Basic requirement of this technology is placing dry powder containing either pure drug or special blend of drug and excipients. The microspheres then mixed and compressed into previously selected oral dosage form.

Lyoc (Laboratories L. Lafon, Maisons Alfort, France)

Lyoc utilizes a freeze drying process but differ from Zydis in that the product is frozen on the freeze dryer shelves. To prevent inhomogeneity by sedimentation during this process, these formulations require a large proportion of undissolved inert filler (mannitol), to increase the viscosity of the inprocess suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets with disintegration rates that are Comparable with the loosely compressed fast melt formulations.

Pharmaburst technology

Pharmaburst™ is a "Quick Dissolve" delivery system patented by SPI Pharma. Pharmaburst is a co-processed excipient system with specific excipients, which allows rapid disintegration and low adhesion to punch facesmouldablilty saccharides are used to obtain rapid melting strong tablet. The active ingredient mixes with low mouldablilty saccharides.

Frosta technology

Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing them at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastic material, water penetration enhancer, and binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of tablet.

Nano technology

For fast dissolving tablets, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in

dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal™ Fast dissolving technology provides for:

- Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix
- Product differentiation based upon a combination of proprietary and patent-protected technology elements.
- Cost-effective manufacturing processes that utilize conventional, scalable unit operations.

Table-1.3 ODT Patented Technologies and Corresponding Commercial Products [41]

Technologies	**Company name**	**Products on market**
DuraSolv®, OraSolv®	CIMA	Tempra®, Quicklet/Tempra®, FirsTabs, Trimainic ®, Softchews (several formulations), Remeron®, SolTabs, Zomig® Rapimelt, Nulev®, Alavert®, FazaClo, Parcopa, Niravam, Clarinex Redi Tabs
Flash Dose	Biovail	Neruofen
Flashtab	Ethypharm	Nurofen
Kryotab	Biotron	None
OraQuick	KV Pharmaceutical	None
Quick-Dis	Lavipharm	Lab Film none
Rapitrol™	Shire Lab	None
Slow-Dis™	Lavipharm Lab	Film none
WOWTAB	Yamanouchi	Benadryl Fastmelt
Advatab	Eurand	None
Zydis	Cardinal Health	Maxalt MLT, Claritin Reditabs, Zyprexa Zydis, Zofran ODT
Lyoc	Cephalon	Proxalyoc (piroxicam), Paralyoc (paracetamol), SpasponLyoc (loperamide)

1.7 Possible Benefits of Orally Disintegrating Drugs[42, 43].

Clinical

- ✓ Improved drug absorption
- ✓ Faster onset of action
- ✓ Minimized first-pass effect
- ✓ Improved bioavailability

Medical

- ✓ No tablet or capsule to swallow or chew.
- ✓ Better taste, no water needed.
- ✓ Improved safety and efficacy.
- ✓ Improved compliance
- ✓ The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.

Technical

- ✓ More accurate dosing than liquid products.
- ✓ Can use sugars and other excipients that are generally recognized as safe.
- ✓ Improved stability because of unit-dose packaging.
- ✓ Manufacturing with common process and conventional equipment.

Business

- ✓ Unique product differentiation
- ✓ Value-added product line extension
- ✓ Marketing exclusivity

- ✓ Extended patent protection
- ✓ Product differentiation
- ✓ Line extension and life cycle management.
- ✓ Exclusivity of product promotion

1.8 Super Disintegrants and ODT[44]

Superdisintegrant plays the major role in oral disintegrating tablet. The disintegration efficiency is based on the force-equivalent concept (the combined measurement of swelling force development and amount of water absorption). Superdisintegrants are generally used at a low level in the solid dosage form, typically 1 – 10 % by weight relative to the total weight of the dosage unit.

Common disintegrants used are Croscarmellose sodium (Vivasol, Ac-Di-Sol), Crospovidone (Polyplasdone), Carmellose (NS-300), Carmellose calcium (ECG-505), Sodium starch glycolate (SSG) etc. Recently few ion exchange resins (e.g. Indion 414) are found to have superdisintegrant property and are widely used in pharmaceutical industry.

1.8.1 Method of Addition of Disintegrants

Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment. There are three methods of incorporating disintegrating agents into the tablet:

I. Internal Addition (Intragranular)

II. External Addition (Extragranular)

III. Partly Internal and External

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression. In Internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules. When these methods are used, part of disintegrant can be added internally and part

externally. This provides immediate disruption of the tablet into previously compressed granules while the disintegrating agent within the granules produces further erosion of the granules to the original powder particles.

1.8.2 Mechanism of Tablet Disintegrants[44]

The tablets are broken into small pieces and then produces a homogeneous suspension which is based on the following mechanisms:

Capillary action/ Water wicking

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. The ability of a disintegrant to draw water into the porous network of a tablet is essential for effective disintegration. Wicking is not necessarily accompanied by a volume increase.

By Swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate into the tablet and disintegration again slows down.

Air expansion /Heat of wetting

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet.

Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Non-swelling particles cause

disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

Due to deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

Due to release of gases

Carbon dioxide is released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

By Enzymatic reaction

Here, enzymes presents in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration.

Mechanism of Action of Superdisintegrant

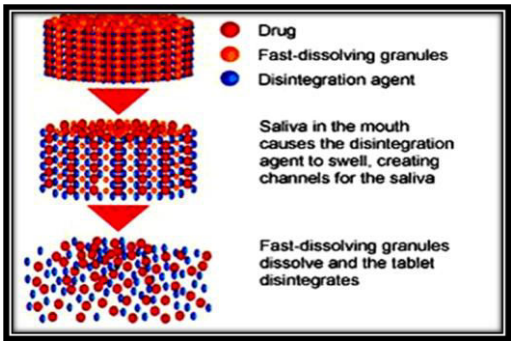


Figure1.3: Mechanism of action of Superdisintegrant

Table-1.4 Superdisintegrants employed in ODTs.[45,46.]

Superdisintegrant	Nature	Properties	Mechanism
Crosspovidone	Crosslinked homo polymer of N-vinyl-2-pyrrolidone	Particle size - 100ìm. Insoluble in water. Gives smoother mouth feel.	Both swelling and wicking
Cross carmellose sodium	Cross-linked form of sodium CMC	Particle size - 200ìm. Insoluble in water.	Swelling
Sodium starch glycolate	Crosslinked low substituted carboxy methyl ether of poly-glucopyranose	Particle size - 140mesh. Insoluble in organic solvents, disperses in cold water and settles in the form of a highly saturated layer.	Water uptake followed by rapid and enormous swelling.
Acrylic acid derivatives	Poly (acrylic acid) super porous hydrogel	Particle size - 106ìm. DT – 15 + 2 s	Wicking action
Effervescent mixture	Citric acid, tartaric acid, sodium bicarbonate.	Crystalline nature	Effervescence
Sodium alginate	Sodium salt of alginic acid	Slowly soluble in water, hygroscopic in nature	Swelling
L-HPC	Low hydroxy propyl cellulose	Particle size - 106ìm. DT – 90 s	Both swelling and wicking

Table-1.5 ODT Products Available in International Market.[47]

Brand name	Active ingredient	Company
Alavert	Loratadine	Wyeth Consumer Healthcare
Cibalginadue FAST	Ibuprofen	Novartis Consumer Health
Hyoscyamine Sulfate ODT	Hyoscyamine sulfate	ETHEX Corporation
NuLev	Hyoscyamine sulfate	Schwarz Pharma
Fluoxetine ODT	Fluoxetine	Bioavail
Benadryl Fastmelt	Diphenhydramine	Pfizer
Nurofen flash tab	Ibuprofen	Boots Healthcare
Zomig ZMT & Rapimelt	Zolmitriptan	Astra Zeneca
Fluoxetine ODT	Fluoxetine	Bioavail
Excedrin Quick Tabs	Acetaminophen	Bristol-Myers Squibb
Claritin RediTabs	Loratadine	Sching Corporation
Remeron SolTab	Mirtazepine	Organon Inc
Feldene Melt	Piroxicam	Pfizer
Propulsid Quicksolv	Cisapride monohydrate	Janssen
Imodium Instant melts	Loperamide HCL	Janssen

2. REVIEW OF LITERATURE

Syama sundar.b **et al,** [48] carried out 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.

Chaudhari et al, [49] developed simple, rapid, accurate and precise assay procedure based on Spectrophotometric method has been developed for the estimation of Escitalopram oxalate (ESC) in Pharmaceutical formulation. The method was based on the bromination of ESC with a known excess amount of bromate-bromide mixture in acid medium followed by the determination of surplus bromine by reacting with dye methyl orange and measuring the absorbance at 507 nm. The proposed method was linear over the range of 2-14 μg/mL with the correlation co-efficient (r) of 0.9983 and the mean recovery for ESC was 100.5 %. The intermediate precision data obtained under different experimental setup, the calculated value of co-efficient of variance (CV, %) was found to be 1.14 % for both day to day and within a day variation. The proposed method can be successfully applied for the analysis of tablet formulations.

Sanjay Sharma et al, [50] developed a method to estimate Escitalopram oxalate and Clonazepam in combination are available as tablet dosage forms in the ratio of 20:1. A simple, precise, accurate, reproducible and efficientmethod for the simultaneous determination of Escitalopram oxalate and Clonazepam tablet dosage

form was developed. The proposed method is based on thesimultaneous estimation by UV Spectroscopy, using multi-component mode of analysis. 80% (v/v) aqueous methanol was used as blank (reference solvent). Thedeveloped method was validated and successfully applied to estimation of Escitalopram oxalate and Clonazepam in combination in tablet formulations.

Tapobana samanta et al, [51] *study* indicates a simple, accurate and precise RP-HPLC method for the estimation of Escitalopram in bulk and in pharmaceutical formulations. The mobile phase used was phosphate buffer with pH 7.0 and an organic mixture solvent (acetonitrile and methanol in the ratio of 1:1 v/v). Then the mobile phase was prepared by mixing buffer solution and mixture of organic solvents in the ratio of (55: 45 v/v) respectively. The specification of the chromatographic system 150 mm ×4.6 mm Xterra RP 18, 5 µm, flow rate 1.2ml/min, detection 238nm, injection volume 10µl and run time 10 min. Only very few HPLC procedures have been reported in the literature for the determination of Escitalopram in pharmaceutical formulations and biological fluids. There are no reports for the determination of Escitalopram by HPLC in pure form. Hence I have made an attempt to develop a HPLC method for the determination of Escitalopram in bulk and in pharmaceutical formulations.

Kanij Fatema et al, [52]Nefopam and Escitalopram are INN drugs and as such it has not been yet included in the BP or USP. The objective of this work is to develop a simple, sensitive, accurate, precise and reproducible UVS pectrophotometric method for quantitative estimation of Nefopam and Escitalopram in tablet dosage forms. Various solvents were used to find out the medium for maximum solubility of each drug. The _max of Nefopam and Escitalopram was 266nm and 284nm in water respectively. Both drugs obey Beer- Lambert's law in the range of 50-400µg/ml for Nefopam and 25-200µg/ml for Escitalopram. The correlation coefficients of std. curves were 0.998 and 0.995. The values of SD were 0.131 and 0.081 respectively. %RSD (Relative standard deviation) of interday absorbance of Nefopam was 0.766 and Escitalopram was 0.854. The LOD (Limit of Detection) were 0.393 and 0.243 and LOQ (Limit of Quantification) were 1.310 and 0.810 respectively. The percent potencies were 92.16 and 102.06 for Nefopam and

Escitalopram. The potency of these tablets complied with their claimed quantity (±10%).

Sharma. S et al, [53]developed a new, simple, fast and reliable zero order spectrophotometric method has been developed for determination of Escitalopram Oxalate in bulk and tablet dosage forms. The quantitative determination of drug was carried out using the zero order values (absorbance) measured at 238 nm. Calibration graph constructed at 238 nm was linear in concentration range of 2-20 µg/ml with correlation coefficient 0.9999. The method was found to be precise, accurate, specific, and validated as per ICH guidelines and can be used for determination of Escitalopram Oxalate in tablet formulations.

Kakde R. B. et al, [54] carried out a accurate and precise spectrophotometric method has been developed for simultaneous estimation of escitalopram oxalate and clonazepam in combined dosage form. Simultaneous equation method is employed for simultaneous determination of escitalopram oxalate and clonazepam from combined dosage forms. In this method, the absorbance was measured at 238 nm for escitalopram oxalate and 273 nm for clonazepam. Linearity was observed in range of 5-100 µg/ml and 5-50 µg/ml for escitalopram and clonazepam respectively. Recovery studies confirmed the accuracy of proposed method and results were validated as per ICH guidelines. The method can be used for routine quality control of pharmaceutical formulation containing escitalopram and clonazepam.

Kalpesh gur et al, [55]developed the fast disintegrating tablets of aceclofenac were prepared by subliming method with a view to enhance patient compliance. In this paper, two super-disintegrants, viz., crospovidone and sodium starch glycolate were used in different ratio (2-8 % w/w) with camphor (30 % w/w) as subliming agent. The prepared batches of tablets were evaluated for thickness, weigh variation, hardness, friability, drug content uniformity, wetting time, water absorption ratio, in-vitro disintegration time and in-vitro drug release. Based on disintegration time (approximately 21 second), three formulations were tested for the in-vitro drug release pattern (in ph 7.4 phosphate buffer). Among the three promising formulations, the formulation prepared by using 8% w/w of crospovidone

and emerged as the overall best formulation based on the in-vitro drug release characteristics.

Uma vasi reddy et al, [56]compared the effect of superdisintegrants on the mouth dissolving property of salbutamol sulphate tablets. Orodispersible tablets of salbutamol sulphate of prepared using sodium starch glycollate, crosscarmellose sodium as superdisintegrants. The results revealed that the tablets containing subliming agent had a good dissolution profile. The optimized formulation showed good release profile with maximum drug being released at all time intervals. This work helped us in understanding the effect of formulation processing variables especially the super disintegrants on the drug release profile. The present study demonstrated potentials for rapid absorption improved bioavailability effective therapy and patient compliance.

Prameela rani. A et al, [57] metformin hcl (met.hcl) is an orally administered hypoglycemic agent, used in the management of non-insulin-dependent (type-2)diabetes. As precision of dosing and patient's compliance become important prerequisite for a long term antidiabetic treatment, there is a need to develop formulation for this drug which overcomes problems such as difficulty in swallowing, inconvenience in administration while travelling and patient's acceptability. Hence in the present study an attempt has een made to prepare fast disintegrating tablets of met.hcl in the oral cavity with enhanced dissolution rate. The tablets were prepared with isphagula husk, natural superdisintegrant and crosspovidone, synthetic superdisintegrant. The pure drug and formulation blend was examined for angle of repose, bulk density, tapped density, commpressibility index and haussner's ratio. The tablets were evaluated for hardness, tensile strength, drug content, friability and were found satisfactory. The disintegration time in the oral cavity was also tested and was found to be around 10sec. Based on dissolution rate the disintegrants can be rated as isphagula husk > crosspovidone. Hence ishagula husk was recommended as suitable disintegrant for the preparation of direct compression melt-in-mouth tablets of met.hcl. All the dissolution parameters were calculated and compared with market tablet. A 3.78 fold increase in the dissolution rate was observed with f4 formulation when compared to market tablet(glucophage).

It was concluded that the rapidly disintegrating tablets with proper hardness, rapid disintegration in the oral cavity with enhanced dissolution rate can be made using super disintegrants.

Basani g et al, [58] baclofen is a muscle relaxant and anti spastic. The present investigation deals with the formulation of oral disintegrating tablets of baclofen that disintegrate in the oral cavity upon contact with saliva and there by improve therapeutic efficacy. The odts were prepared by direct compression technique. The optimized formulation was also prepared by effervescent method. The influence of superdisintegrants, Crospovidone, croscaremellose sodium and sodium starch glycolate at three levels on disintegration time, wetting time and water absorption ration were studied. Tablets were evaluated for weight and thickness variation, disintegration time, drug content, in vitro dissolution, wetting time and water absorption ratio. The in vitro disintegration time of the best odts was found to be 14 sec and 28sec by direct compression and by effervescent method, respectively. Tablets containing crospovidone exhibit quick disintegration time than tablets containing croscaremellose sodium, sodium starch glycolate and effervescent mixture. Good correlation was observed between water absorption ratio and dt. The directly compressible rapidly disintegrating tablets of baclofen with shorter disintegration time, acceptable taste and sufficient hardness could be prepared using crospovidone and other excipients at optimum concentration.

Jyotsana madan et al, [59]the objective of this work was to prepare and evaluate fast dissolving tablets of the nutraceutical, freeze dried aloe vera gel.fast dissolving tablets of the nutraceutical, freeze-dried aloe vera gel, were prepared by dry granulation method. The tablets were evaluated for crushing strength, disintegration time, wetting time, friability, drug content and drug release. A 32 full factorial design was applied to investigate the combined effect of two formulation variables - amounts of microcrystalline cellulose and mannitol. The results of multiple regression analysis revealed that in order to obtain a fast dissolving tablet of the aloe vera gel, an optimum concentration of mannitol and a higher content of microcrystalline cellulose should be used. A response surface plot was also provided to graphically represent the effect of the independent variables on the disintegration

time and wetting time. The validity of the generated mathematical model was tested by preparing a check point batch.conclusion: this investigation has demonstrated that satisfactory fast dissolving aloe vera gel tablets can be formulated. It also showed the potential of experimental design in understanding the effect of formulation variables on the quality of fast dissolving tablets.

Jashanjit singh et al, [60]purpose: the objective of this study was to formulate and optimize an orodispersible formulation of meloxicam using a 2 factorial design for enhanced bioavailability.the tablets were made by non-aqueous wet granulation using crospovidone and mannitol. A 2 factorial design was used to investigate the amount of crospovidone and taste masking, soothening hydrophilic agent (mannitol), as independent variables, and disintegration time as dependent response. Formulated orodispersible tablets were evaluated for weight variation, friability, disintegration time, drug content, wetting time, water absorption ratio and in vitro drug release. The results show that the presence of a superdisintegrant and mannitol is desirable for orodispersion. All the formulations satisfied the limits of orodispersion with a dispersion time of less than 60 sec. For example, formulation f4 showed a disintegration time of 32.1 sec, crushing strength of 4.93 kg/cm2, drug content of 98.5% and fast drug release rate of 99.5% within 30 min, as compared with the conventional tablet (49.5%) . It is feasible to formulate orodispersible tablets of meloxican with acceptable disintegration time, rapid drug release and good hardness, which could be amenable to replication on an industrial scale.

furtado et al, [61] purpose of the present research was to the effect of camphor as a subliming agent on the mouth dissolving property of famotidine tablets. Method: orodispersible tablets of famotidine were prepared using camphor as subliming agent and sodium starch glycollate together with crosscarmellose sodium as superdisintegrants. The formulations were evaluated for weight variation, hardness, friability, drug content, wetting time, in vitro and in-vivo dispersion, mouth feel and in vitro dissolution. Result: all the formulations showed low weight variation with dispersion time less than 30 seconds and rapid in vitro dissolution. The results revealed that the tablets containing subliming agent had a good dissolution profile. The drug content of all the formulations was within the

acceptable limits of the united states pharmacopoeia xxvii. The optimized formulation showed good release profile with maximum drug being released at all time intervals. Conclusion: this work helped in understanding the effect of formulation processing variables especially the subliming agent on the drug release profile. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Anand et al,[62] prepare taste-masked orally disintegrating tablets (odts) of prednisolone (pdl) by incorporation of microspheres in the tablets for use in specifi c populations viz. Pediatrics, geriatrics and patients experiencing diffi culty in swallowing. Methods: microsphere containing pdl were prepared by the solvent evaporation method using acetone as solvent for ph-sensitive polymer and light liquid paraffi n as the encapsulating medium. Prepared microspheres were characterized with regard to the yield, drug content, particle size and size distribution, surface features, in vitro drug release and taste. Tablets, prepared by direct compression containing microspheres, were evaluated with regard to crushing strength, friability, disintegration time, drug content and in vitro drug release and taste. Results: the results obtained showed that the average size of microspheres is infl uenced greatly by the speed of stirring. Microspheres prepared by the solvent evaporation method in acetone were of a regular spherical shape with satisfactory results in terms of the size and size distribution. The comparison of the dissolution profi les of microspheres in different media shows that microspheres produce a retarding effect in ph 6.8 buffer. Taste evaluation studies confi rmed that microspheres of pdl having a drug to polymer ratio of 1: 10 are tasteless and these were further used for formulation into odts. Compression of microspheres resulted in breaking of a fraction of the microspheres but this did not dversely affect the taste. Conclusion: effective taste-masking was achieved for pdl using the technique of icroencapsulation and odts of acceptable characteristics were obtained by disintegrant addition and direct compression.

Venkata ramana reddy S et al,[63] develop oral disintegrating tablets (odt) of low bitter hypertensive drugs like amlodipine besylate using tastem enhancers as a taste asking agents. Odt of amlodipine besylate were prepared using different

superdisintegrants by direct compression method. Mannitol was used as a diluent and sodium lauryl sulphate was used as a wetting (surfactant) agent. Aspartame and acesulfame potassium were used for unpleasant taste masked from the amlodipine besylate by cosifting and serial of blending with other excipients. The mixed final blend was then compressed into tablets. The formulations were evaluated for weight variation, hardness, friability, wetting time, disintegrating time, dissolution, taste valuation study and in vitro dissolution. All the formulation showed low weight variation with different disintegration time and rapid in vitro dissolution. The results revealed that the tablets containing taste enhancers had a good palatability for the patients. The optimized formulation showed good taste masking, less disintegration time (<30seconds) and release profile with maximum drug being released at all time intervals. The present study demonstrated potentials for rapid disintegration in oral cavity without water, improved taste masking and patient compliance.

Anantha lakshmi pallikonda et al, [64] formulate and evaluate domperidone mdt's. It acts as an ant emetic used in the treatment of motion sickness. Different batches of tablets were prepared using higher and lower concentrations of superdisintegrants like croscarmellose sodium, crospovidone (c.p), sodium starch glycolate (ssg), while mcc was used as diluents. Tablets were prepared by slugging method. Different evaluations tests like hardness, friability, wetting and disintegration times, % drug release were performed. Tablets containing along with crospovidone were disintegrate rapidly below 20sec and % drug release is 99% at 4th minute. Tablets with added patient benefits and increased consumer satisfaction.

Mahaveer pr. Khinchi et al, [65] super disintegrants (such as ac-di-sol, crospovidone, sodium starch glycolate), diluents (dibasic calcium phosphate) along with sweetening agent (aspartame) were used in the formulation of tablets. The tablets were evaluated for hardness, friability, water absorption ratio, in-vitro disintegration time (dt), in-vitro disintegration time in oral cavity and in vitro drug release. Using the same excipients, the tablets were prepared by direct compression and were evaluated in the similar way. Maximum drug release and minimum dt were observed with crospovidone excipient prepared by direct compression.

Dr. Raghavendra rao n. et al, [66] carried out the study on novel co-processed super disintegrants were developed by solvent evaporation method using crospovidone and sodium starch glycolate in different ratios (1:1, 1:2 and 1:3) for use in the fast dissolving tablet formulations. The developed excipients were evaluated for angle of repose, carr's index and hausner's ratio in comparison with physical mixture of superdisintegrants. Fast dissolving tablets of felodipine were prepared using the above co-processed superdisintegrants and evaluated for pre-compression and postcompression parameters. Effect of co-processed superdisintegrants (such as crospovidone, and sodium starch glycolate) on wetting time, disintegrating time, drug content, in-vitro release, and stability parameters have been studied. From this study, it can be concluded that dissolution rate of felodipine could be enhanced by tablets containing co-processed superdisintegrant.

Suhas m. Kakade et al, [67] Orally disintegrating tablets prepared by direct compression and using super disintegrants like crospovidone, croscarmellose sodium and sodium starch glycolate designate, designated as three different groups of formulation (a, b and c) respectively were prepared and evaluated for the precompression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content, disintegration time and in-vitro dissolution profile and found satisfactory. Among the three groups, group (c) containing crospovidone emerged as the best formulation and showed maximum dissolution rate with 98.49% drug release in 15 min. All three groups of formulations released the drug at faster rates than that of marketed conventional tablets of sertraline.

Deshpande kiran bhaskar et al, [68] carrriedout the study was aimed, which can disintegrate or dissolve rapidly once placed in the oral cavity. Propranolol hydrochloride is a antihypertensive drug, which undergoes extensive hepatic degradation (96%), which have poor oral bioavailability (26%) for overcoming this problem orodispersible tablets of propranolol hydrochloride can be formulated which avoids extensive first pass metabolism and improvement in dissolution efficacy, disintegration time which results in improvement in bioavailability. The advantage of this formulation is such that in case of hypertension attack patient can

take the drug without the usage of water. Therefore the main objective of the present work is to develop orodispersible tablets of propranolol hydrochloride to improve bioavailability, disintegration time, dissolution efficacy and patient compliance.

Tejash serasiya et al, [69]orodispersible tablets of pheniramine maleate were prepared by direct compression method using various superdisintegrants like crospovidone, croscarmellose sodium, sodium starch glycolate, low substituted hydroxypropyl cellulose, pregelatinized starch. The prepared tablets were evaluated for uniformity of weight, hardness, friability, wetting time, in-vitro disintegration time, in-vitro dispersion time and drug release study. All the formulation exhibited hardness between 3.3 – 3.6 kg/cm2. The tablets were disintegrating in–vitro within 20 to 51 sec. Dissolution studies revealed that formulations containing 10% crospovidone and formulation containing 10% croscarmellose sodium showed 100% of drug release, at the end of six min. The concentration of superdisintegrants had an effect on disintegration time and in-vitro drug dissolution whereas hardness and friability of resulting tablets were found to be independent of disintegrant concentration. The two formulations, one containing 10% of crospovidone and second containing 10% croscarmellose sodium were found to give the best results.

Pankaj p. Amrutkar et al, [70]. Carried out the work on lamotrigine used in the treatment of depression and bipolar disorder. But it is a bitter drug and slightly soluble in water. Thus, in the work under taken, an attempt was made to mask the taste and to formulate into a chewable dispersible tablet by complexation with precirol ato-05, which also acts as taste masking agent. Since, these tablets can be swallowed in the form of dispersion; it is suitable dosage form for paediatric and geriatric patients. Drug-precirol ato-05 was prepared in drug to precirol ato-05 ratio of 1:2, 1:1.5, 1:1, 1:0.5. The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, taste evaluation, mouth feel, in vitro disintegration time, and in vitro dissolution studies. Tablets with precirol ato-05 have shown good disintegrating features, also, the dispersion not showing any bitter taste, indicate the capability of precirol ato-05 used, both as taste masking agents. Almost more than 90 percent of drug was released from the formulation within 1 h. Further formulations were subjected to stability testing for 3 months at temperatures

25±5ºc/60±5%rh; 30±5ºc/65±5%rh and 40±5ºc/75±5%rh. Tablets have shown no appreciable changes with respect to taste, disintegration, and dissolution profiles.

Ganesh kumar gudas et al,[71]. Study an attempt has been made to prepare fast dissolving tablets of chlorpromazine hcl in the oral cavity with enhanced dissolution rate. The tablets were prepared with five superdisintegrants eg: sodium starch glycolate , crospovidone ,croscarmellose, l-hpc, pregelatinised starch , the blend was examined for angle of repose, bulk density, tapped density , compressibility index and hausners ratio. The tablets were evaluated for hardness, friability, disintegration time, dissolution rate, drug content, and were found to be within 1 min. It was concluded that the fast dissolving tablets with proper hardness, rapidly disintegrating with enhanced dissolution can be made using selected superdisintegrants.

Sradhanjali patra et al,[72] metronidazole is an antiemetic and prokinetic drug used in the treatment of motion sickness in adults and children.as precision of dosing and patient's compliance become important prerequisite for quick relief from motion sickness, there is a need to develop a formulation for this drug which overcomes problems such as difficulty in swallowing, inconvenience in administration while traveling and better compliance. Hence in the present research work mouth dissolving tablets of metronidazole were developed with superdisintegrants like crospovidone, indion 414, l – hpc and pregelatinised starch in various concentrations like 8 % and 10 % w/w by wet granulation method. All formulations were evaluated for physical characteristics of compressed tablets such as weight variation, hardness, friability, drug content, disintegration time and in vitro dissolution study. Among all, the formulation f4 (containing 10% w/w concentration of crospovidone) was considered to be the best formulation, having disintegration time of 27 sec, hardness 2.56 kg/cm2 and in vitro drug release of 92.23% in 15 min. All the formulation follows higuchi order release kinetics.

Prajapati et al, [73]carriedout the work on piroxicam which has bad taste, half life of 30 hrs and poor water solubility. In the present work to develop taste masked orally disintegrating tablets of piroxicam, preformulation parameters like

solubility, particle size, tapped density, bulk density,hausner ratio, carr's compressibility index, angle of repose, and differential scanning calorimetry study were performed. Out of twelve formulations (f-1 to f-12), f-11 formulation containing crospovidone xl 10 %, drug: polymer 1:0.35 , aspartame 6% and sodium lauryl sulphate 0.5%, showed optimum characteristics of orodispersible tablet (odt) of piroxicam with sufficient crushing strength (5.5 to 6.5 kp), friability (0.18%), wetting time (28 sec) and disintegration time (22 sec). In-vitro dissolution profile studies revealed that 82.3% drug was released within 5 min. The study concluded that crospovidone xl and eudragit epo can successfully be used as superdisintegrant and taste masking excipient respectively.

P***asupathi et.al,***[74].carried out the ork on lamotrigine chewable-dispersible tablet was prepared by using crosspovidone xl10, as a disintegrating agent, different grades of mannitol (pearlitol 160 c, pearlitol sd 200, pearlitol 500dc) as a diluents, pvp k30 as a binder and carried out studies for weight variation, thickness, hardness, content uniformity, disintegrating time, dispersion time, wetting time, in vitro drug release and stability study. Tablets were prepared by using direct compression method and wet granulation method. Furthermore, impact of different punches and superdisintegrants (sodium starch glycolate, and sodium crosscarmalose) were carried on f16 formulation.

Ashok Kumar et al, [75] investigation was to develop orally disintegrating tablets of terbutaline sulphate. Granules containing drug, diluent, subliming agents, aspartame were prepared by wet granulation technique using alcoholic solution of polyvinyl pyrrolidone K25 (10% w/v) as a binder. The dried granules were then mixed with lubricant magnesium stearate and glidant talc and compressed into tablets. Subliming agents was sublimed from the tablet by exposing it to drying at 65 0C. The tablets were evaluated for percentage friability, hardness, weight variation, disintegration time and percentage drug content. Menthol containing tablets resulted in rapid disintegration as compared with tablets containing ammonium bicarbonate and camphor. Formulations F4 showed the minimum disintegration time of 16s. Formulations tested for all the official tests for tablets and were found to be within limits.

Madhusudan rao Y et al, [76] deals with formulation of orodispersible tablets (ODT) of buspirone that disintegrate in the oral cavity upon contact with saliva and thereby should improve therapeutic efficacy. The ODTs were prepared by wet granulation and direct compression techniques. The optimized formulation was also prepared by freeze drying method. The influence of superdisintegrants, crospovidone, croscarmellose sodium and sodium starch glycolate at three levels on disintegration time, wetting time and water absorption ratio were studied. Tablets were evaluated for weight and thickness variation, disintegration time, drug content, *in vitro* dissolution, wetting time and water absorption ratio.

Pandey Shivanand et al,[77]development of taste masked orally disintegrating tablets are to increase patient compliance, ease of administration, safety and appropriate dosing. Orally disintegrating formulations also provide benefits for pharmaceutical companies like lifecycle management, line extension, market expansion, cost effective drug development programs. This technology has perceived faster onset of action (only if engineered for absorption in the oral cavity or stomach) as the dosage form is disintegrated prior to reaching the stomach and is ideal for acute diseases like hypertension and heart failure and particularly applicable to manage breakthrough symptoms. Fast dissolving tablets (FDT), tablet that disintegrates and dissolves rapidly in saliva without need of drinking water. The FDT usually dissolve in the oral cavity in about 10 seconds to 3 minutes. Faster the drug goes into solution, the quicker absorption and onset of clinical effect.

PK Bhoyar et al, [78] present work was to mask the taste of ondansetron hydrochloride and to formulate its patient-friendly dosage form. Complexation technique using indion 234 (polycyclic potassium with carboxylic functionality) and an ion-exchange resin was used to mask the bitter taste and then the taste-masked drug was formulated into an orodispersible tablet (ODT). The drug loading onto the ion-exchange resin was optimized for mixing time, activation, effect of pH, mode of mixing, ratio of drug to resin and temperature. The resinate was evaluated for taste masking and characterized by X-ray diffraction study and infrared spectroscopy. ODTs were formulated using the drug–resin complex. The developed tablets were evaluated for hardness, friability, drug content, weight variation, content uniformity,

friability, water absorption ratio, *in vitro* and *in vivo* disintegration time and in vitro drug release. The tablets disintegrated in vitro and in vivo within 24 and 27 s, respectively. Drug release from the tablet was completed within 2 min. The obtained results revealed that ondansetron HCl has been successfully taste masked and formulated into an ODT as a suitable alternative to the conventional tablets.

Shailesh Sharma et al, [79]formulate promethazine theoclate fast-dissolving tablets that offer a suitable approach to the treatment of nausea and vomiting The solubility of promethazine theoclate was increased by formulating it as a fast-dissolving tablet containing _-cyclodextrin, crospovidone, and camphor, using direct compression method. A 33 full factorial design was used to investigate the combined influence of three independent variables – amounts of camphor, crospovidone and _-cyclodextrin - on disintegration time, friability and drug release after 5 min. The optimization study, involving multiple regression analysis, revealed that optimum amounts of camphor, crospovidone and _-cyclodextrin gave a rapidly disintegrating/dissolving tablet. A Check point batch was also prepared to verify the validity of the evolved mathematical model. The optimized tablet should be prepared with an optimum amount of _-cyclodextrin (3.0 mg), camphor (3.2mg) and crospovidone (2.61 mg) which disintegrated in 30 s, with a friability of 0.60 % and drug release of 89 % in 5 min.

3. AIM AND OBJECTIVE

AIM OF STUDY

- ✓ To carry out preformulation study of excipients and their compatibility with the API.
- ✓ Development of various formulations and preparation of ODT's by direct compression technique.
- ✓ Selection and optimization of the best formulation.
- ✓ To conduct accelerated stability testing to the finished dosage form as per ICH guidelines

OBJECTIVE OF STUDY

- ✓ To carry out literature survey of drug molecules
- ✓ To analyse the trial samples
- ✓ To optimize the final formula
- ✓ To conduct the stability studies of final formula

4. PLAN OF WORK

The present work was carried out to formulate Oral Disintegrating Escitalopram Oxalate tablets and to evaluate the invitro and stability studies for the prepared Escitalopram Oxalate tablets. It was planned to carry out this work as outlined below.

- ✓ Characterization of drug substances and other excipients.
- ✓ Formulation development of Escitalopram Oxalate Orally Disintegrating tablets by Direct Compression Technique.
- ✓ Evaluation of the pre compressional parameters.
- ✓ To evaluate the formulated Escitalopram Oxalate tablets for the following parameters.
    a) Tablet thickness.
    b) Weight variation.
    c) Tablet friability.
    d) Wetting time.
    e) Tablet hardness.
    f) Disintegration.
    g) In vitro dispersion time
    h) Dissolution
    i) Moisture absorption studies
    j) Assay
- ✓ To carry out the stability studies for finalized formula of Orally Disintegrating Escitalopram Oxalate Tablet as per ICH guidelines.

5. DRUG PROFILE [81, 82, 83]

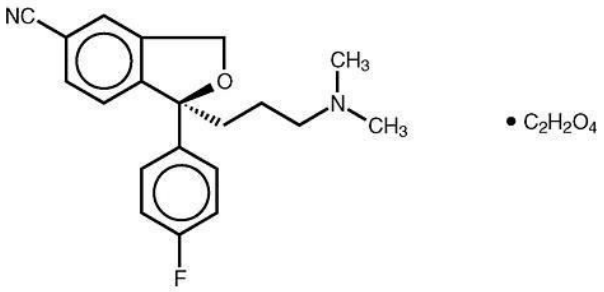
5.1 ESCITALOPRAM OXALATE

Category : Antidepressant agent

Chemical Name : 1-[3-(Dimethylamino) propyl]-1-(4-fluorophenyl)-1, 3-dihydro-S-(+)-5- isobenzofurancarbonitrile oxalate

Description : A white to off white crystalline powder.

Molecular Structure



Molecular Formula : $C_{20}H_{21}FN_2O \bullet C_2H_2O_4$

Molecular weight : Escitalopram 324.392g/mol ; 414.43 as oxalate ion

Bioavailability : 80%

Half life : 27-32 hours

Solubility : Soluble in Dimethlyformide**,** in Dimethylsulfoxide, Sparingly soluble in methanol & slightly soluble in Dichloromethane.

Uses:

Escitalopram is an antidepressant (selective serotonin reuptake inhibitor-SSRI) used to treat depression and anxiety. It works by restoring the balance of certain natural substances (neurotransmitters such as serotonin) in the brain. Escitalopram may improve your feelings of well-being and energy level and decrease nervousness.

5.2 CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT).

Pharmacodynamics

In vitro and in vivo studies in animals suggest that escitalopram is a highlyselective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake. Escitalopram is at least 100-fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Tolerance to a model of antidepressant effect in rats was not induced by long-term (up to 5 weeks) treatment with escitalopram. Escitalopram has no or very low affinity for serotonergic ($5\text{-}HT_{1\text{-}7}$) or other receptors including alpha- and beta-adrenergic, dopamine ($D_{1\text{-}5}$), histamine ($H_{1\text{-}3}$), muscarinic ($M_{1\text{-}5}$), and benzodiazepine receptors. Escitalopram also does not bind to, or has low affinity for, various ion channels including Na^+, K^+, Cl^-, and Ca^{++} channels. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular side effects of other psychotropic drugs.

Pharmacokinetics

The single- and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 27-32 hours. With once-daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of escitalopram in plasma in young healthy subjects was 2.2-2.5 times the plasma concentrations observed after a single dose. The tablet and the oral solution dosage forms of escitalopram oxalate are bioequivalent.

Absorption and Distribution

Following a single oral dose (20 mg tablet or solution) of escitalopram, peak blood levels occur at about 5 hours. Absorption of escitalopram is not affected by food.

The absolute bioavailability of citalopram is about 80% relative to an intravenous dose, and the volume of distribution of citalopram is about 12 L/kg. Data specific on escitalopram are unavailable.

The binding of escitalopram to human plasma proteins is approximately 56%.

Metabolism and Elimination

Following oral administrations of escitalopram, the fraction of drug recovered in the urine as escitalopram and S-demethylcitalopram (S-DCT) is about 8% and 10%, respectively. The oral clearance of escitalopram is 600 mL/min, with approximately 7% of that due to renal clearance.

Escitalopram is metabolized to S-DCT and S-didemethylcitalopram (S-DDCT). In humans, unchanged escitalopram is the predominant compound in plasma. At steady state, the concentration of the escitalopram metabolite S-DCT in

plasma is approximately one-third that of escitalopram. The level of S-DDCT was not detectable in most subjects. *In vitro* studies show that escitalopram is at least 7 and 27 times more potent than S-DCT and S-DDCT, respectively, in the inhibition of serotonin reuptake, suggesting that the metabolites of escitalopram do not contribute significantly to the antidepressant actions of escitalopram. S-DCT and S-DDCT also have no or very low affinity for serotonergic ($5\text{-}HT_{1\text{-}7}$) or other receptors including alpha- and beta-adrenergic, dopamine ($D_{1\text{-}5}$), histamine ($H_{1\text{-}3}$), muscarinic ($M_{1\text{-}5}$), and benzodiazepine receptors. S-DCT and S-DDCT also do not bind to various ion channels including Na^+, K^+, Cl^-, and Ca^{++} channels.

In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of escitalopram.

Marked formulations **:** Anxiest, lexapro, cipraplex, seroplex, lexamil

Drug Interactions

5-HT 1 agonists (eg, sumatriptan)

Risk of serotonin syndrome may be increased. If coadministration is clinically warranted, carefully observe the patient, particularly when starting treatment or during dose increases.

Alcohol

May potentiate the effects of alcohol; use of alcohol is not advised.

Aspirin, NSAIDs (eg, ibuprofen), warfarin

Risk of bleeding may be increased. Use with caution and carefully monitor the patient.

Beta-blockers (eg, metoprolol, propranolol)

Excessive beta-blockade (eg, bradycardia) may occur, increasing the risk of cardiac and CNS toxicity. Use with caution.

Buspirone, opioid analgesics (eg, meperidine), sibutramine, SNRIs (eg, duloxetine), St. John's wort, sympathomimetics (eg, amphetamine), tramadol

The risk of serotonin syndrome may be increased. Closely monitor patients. Serotonin syndrome requires immediate medical attention, including withdrawal of the serotonergic agent and supportive care.

Citalopram

Escitalopram is the active isomer of racemic citalopram; do not coadminister these two agents.

CNS drugs Use with caution.

Cyproheptadine

May decrease the pharmacologic effect of escitalopram. If there is a decrease in the efficacy of escitalopram, consider discontinuing cyproheptadine.

Dosage

Usual adult dose for anxiety

10 mg orally once a day in the morning or evening with or without food. The dose may be increased to 20 mg, after a minimum of one week.

Escitalopram (10 to 20 mg orally daily) has been shown to be well tolerated and effective in the treatment of generalized anxiety disorder for up to 6 months.

Usual adult dose for depression

10 mg orally once a day in the morning or evening with or without food. The dose may be increased to 20 mg, after a minimum of three weeks.

Usual pediatric dose for depression

12to17years:

10 mg orally once a day in the morning or evening with or without food. The dose may be increased to 20 mg, after a minimum of three weeks.

Marketed Formulations:

- **Lexapro filim coated 5,10,20 mg tablets**
- **Lexapro solution 1mg/ml**
- **Cipralex**
- **Seroplex**
- **Anxiset**

6. EXCIPIENTS PROFILE[84-86]

6.1 MANNITOL

Nonproprietary names

BP; PhEur; USP**:** Mannitol

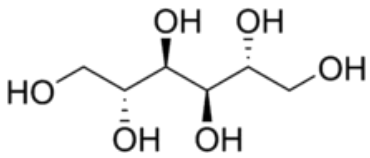
JP**:** D-Mannitol

Synonyms : Cordycepic acid, Manna sugar, D-mannite, Mannitolum; Mannogem.

Chemical Name : D-Mannitol

Empirical Formula: $C_6H_{14}O_6$

Structural Formula



Molecular Weight : 182.17

Functional Category: Plasticizer, sweetening agent, tablet and capsule diluent.

Solubility

Freely soluble in water, soluble in alkaline solutions, slightly soluble in pyridine, very slightly soluble in alcohol, practically insoluble in ether.

Applications in Pharmaceutical Formulation or Technology:

Mannitol is widely used as a diluent (10–90% w/w) in tablet formulations, since it is not hygroscopic and may thus be used with moisture sensitive active ingredients. It may be used in direct compression tablet applications, for which the granular and spray dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. It is commonly used as an excipient in the manufacture of chewable tablet formulations and also used as a diluent in rapidly dispersing oral dosage forms.

Description

It occurs as a white, odourless, crystalline powder, or free flowing granules. It has a sweet taste and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol.

Mannitol grades

Grade	Description	Applications
Pearlitol 100 SD	Fine particle size	Excellent Diluent-binder for direct compression applications (Fast Dissolving, chewable, oral dispersible, effervescent tablets.
Pearlitol 200 SD	Medium particle size	

Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.(19) Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic. Sodium cephapirin at 2 mg/mL and 30 mg/mL concentration is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.

Safety

Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities. If it is used in foods as a bodying agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement 'excessive consumption may have a laxative effect'.

6.2 CROSPOVIDONE

Nonproprietary names

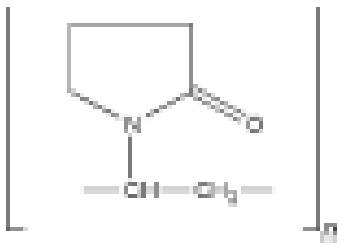
BP; PhEur; USP-NF: Crospovidone

Synonyms:

Crospovidonum, Crospopharm, crosslinked povidone, Kollidon CL, Kollidon CL-M, Polyplasdone XL, Polyplasdone XL-10, Polyvinyl polypyrrolidone.

Chemical Name : 1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula and Molecular Weight: $(C_6H_9NO)n$ >1000000



Functional Category: Tablet disintegrant

Solubility

Practically insoluble in water and in most common organic solvents.

Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water insoluble tablet disintegrant and dissolution agent used in tablets prepared by direct compression or wet and dry granulation methods. It can also be used as a solubility enhancer. Crospovidone can be used to enhance the solubility of poorly soluble drugs.

Description

Crospovidone is a white to creamy white, finely divided, free flowing, practically tasteless, odourless, hygroscopic powder.

Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level

Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Crospovidone grades

Grade	Description	Applications
Kollidon CL	Standard Grade	Used as a super disintegrant in tablets for improving release of active substances
Kollidon CL-F	Fine particle size	Fine Grade is ideal for small tablets
Kollidon CL-SF KollidonCL-M	Super fine Grade Micronized Grade	Micronized Grade is used as a stabilizer for suspensions

.

6.3 CELLULOSE, MICROCRYSTALLINE

Nonproprietary names

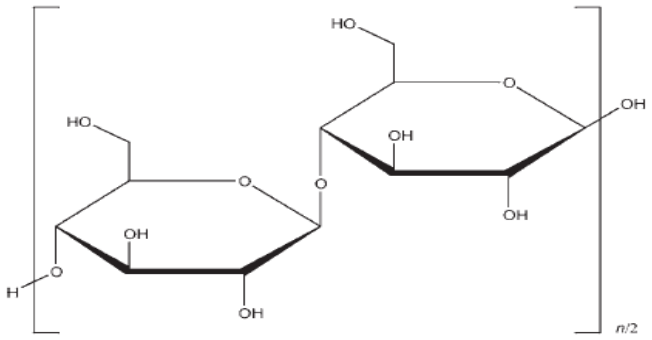
BP; JP; PhEur; USP-NF: Microcrystalline Cellulose

Synonyms:

Avicel PH, Cellulose gel, Hellulosum microcristallinum, Ceolus KG, Crystalline cellulose, Emcocel, Fibrocel, Pharmacel, Tabulose.

Chemical Name: Cellulose

Empirical Formula and Molecular Weight: $(C_6H_{10}O_5)n$; 36 000 where n -220.



Functional Category:

Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.

Solubility

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

Applications in Pharmaceutical Formulation or Technology

It is as a binder/diluent in oral tablet and capsule formulations in both wet granulation and direct compression processes. In addition it also has some lubricant and disintegrant properties.

Description

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

6.4 ASPARTAME

Nonproprietary names

BP; PhEur; USP-NF: Aspartame

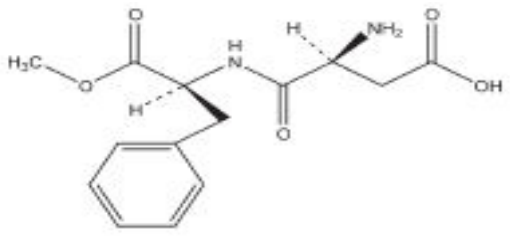
Synonyms:

Aspartamum, Aspartyl phenylamine methyl ester, Natra Taste, NutraSweet, Pal Sweet, Pal Sweet Diet.

Chemical Name : N-L-a-Aspartyl-L-phenylalanine 1-methyl ester

Empirical Formula and Molecular weight: $C_{14}H_{18}N_2O_5$; 294.30

Molecular Structure



Functional category: Sweetening agent.

Solubility

Slightly soluble in ethanol (95%), sparingly soluble in water.

Applications in Pharmaceutical Formulation or Technology

It is used as a sweetening agent in tablets, powder mixes, and vitamin preparations. The approximate sweetening power is 180–200 times that of sucrose. Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal).

Description

It occurs as an off white, almost odourless crystalline powder with an intensely sweet taste.

6.5 TALC

Nonproprietary Names

BP: Purified Talc

JP, PhEur USP: Talc

Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Imperial; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore; talcum.

Chemical Name and CAS Registry Number: Talc [14807-96-6]

Empirical Formula and Molecular Weight

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$.

It may contain small, variable amounts of aluminum silicate and iron.

Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, , although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Uses of talc.

Use	**Concentration** (%)
Dusting powder	90.0–99.0
Glidant and tablet lubricant	1.0–10.0
Tablet and capsule diluents	5.0–30.0

Description

Talc is a very fine, white to grayish-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittine

Stability and Storage Conditions

Talc is a stable material and may be sterilized by heating at 1608C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

6.6 HYDROXYPROPYL CELLULOSE, LOW-SUBSTITUTED

Non-proprietary Names

JP: Low Substituted Hydroxypropylcellulose

USP-NF: Low-Substituted Hydroxypropyl Cellulose

Synonyms

Cellulose, 2-hydroxypropyl ether; 2-hydroxypropyl ether (lowsubstituted) cellulose; hyprolose, low-substituted; L-HPC; oxypropylated cellulose.

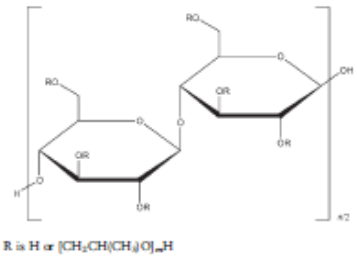
Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether (low-substituted) [9004-64-2]

Empirical Formula and Molecular Weight

The USP32–NF27 describes low-substituted hydroxypropyl cellulose as low-substituted hydroxypropyl ether of cellulose. Compared to hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose has only a small proportion of the three free hydroxyl groups per glucose subunit converted to a hydroxypropyl ether.

When dried at 1058C for 1 hour, it contains not less than 5.0% and not more than 16.0% of hydroxypropoxy groups (—OCH2CHOHCH3). Low-substituted hydroxypropyl cellulose is commercially available in a number of different grades that have different particle sizes and substitution levels.



R is H or $[CH_2CH(CH_3)O]_mH$

Functional Category

Tablet and capsule disintegrant; tablet binder.

Applications in Pharmaceutical Formulation or Technology

- Low-substituted hydroxypropyl cellulose is widely used in oral solid-dosage forms. It is primarily used as a disintegrant, and as a binder for tablets and granules in wet or dry granulation.
- It has been used in the preparation of rapidly disintegrating tablets produced by direct compression methods.
- In addition, low substituted hydroxypropyl cellulose has been used as a binder/ disintegrant included in the powder layering process on spherical cores and to prepare pellets by extrusion/spheronization.
- Low particle size and high hydroxypropyl content is recommended to produce round spheres and rapid dissolution.
- There are a number of grades that have different particle sizes and substitution levels.

- ✓ LH-11 has the longest fibrous particles, and is typically used as an ant capping agent and disintegrant for direct compression.
- ✓ LH-21 is less fibrous and is used as a binder and disintegrant for tablets through the wet-granulation process.
- ✓ LH-31 is a small-particle grade used especially for extrusion to produce granules, as it has a small particle size that is better for passing a screen.
- ✓ LH-B1 is the nonfibrous, high-density grade designed for fluid-bed granulation, and can be used for direct compression and/ or formulations with a high low-substituted hydroxypropyl cellulose loading. Lower substitution grades
- ✓ LH-22 and LH-32 can be used for better disintegration capability, depending on the characteristics of the active ingredients. The typical content of low-substituted hydroxypropyl cellulose in a formulation is approximately 5–50%.

Description

Low-substituted hydroxypropyl cellulose occurs as a white to yellowish white powder or granules. It is odourless or has a slight, characteristic odor, and it is tasteless

Stability and Storage Conditions

Low-substituted hydroxypropyl cellulose is a stable, though hygroscopic, material. The powder should be stored in a well closed container

Colloidal Silicon Dioxide

Nonproprietary Names

BP: Colloidal Anhydrous Silica

JP: Light Anhydrous Silicic Acid

PhEur: Silica, Colloidal Anhydrous

USP-NF: Colloidal Silicon Dioxide

Synonyms

Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica; fumed silicon dioxide; hochdisperses silicum dioxid; SAS; silica colloidalis anhydrica; silica sol; silicic anhydride; silicon dioxide colloidal; silicon dioxide fumed; synthetic amorphous silica;

Chemical Name and CAS Registry Number: Silica [7631-86-9]

Empirical Formula and Molecular Weight: SiO_2 60.08

Functional Category

Adsorbent; ant caking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

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
- 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 and 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.

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

Description

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

6.7 KYRONT-31[85]

Synonyms:

Kyron T-314 is derived from cross linked polymer of Polycarboxylic acids as per USP/NF & has the K^+ ionic form. It is a very high purity polymer used in pharmaceutical formulations as a super fast disintegrant as well as dissolution improver in solid dosage forms like tablets, capsules, pellets etc. It is available in

white free flowing powder hence it is suitable for the both wet granulation as well as direct compression system for tablet formulations.

APPLICATIONS

As Disintegrating agent:

Kyron T-314 has a very high swelling tendency of hydration either in contact with water or G.I. fluids causing fast disintegration without the formation of lumps and thus acts as an effective tablet super disintegrant. Required quantity is from 0.5% to 4.0% to get fast disintegration.

As Dissolution Improver:

Kyron T-314 breaks the tablets into very smaller particles, thus it increases the effective surface area for the absorption of the active substances and thus it increases the dissolution and bioavailability of the active substances. Required quantity is from 2.0% to 6.0% for dissolution improvement.

- Rapid disintegrating agent
- Elimination of lump formation
- Compatible with all therapeutic agents and excipients
- Imparts excellent strength to the tablets
- Elimination of the sticking problems to the dies and punch
- Improves bioavailability of the drug
- Uniformly mix with low dose tablets blend or formulations
- Smooth surface after storage
- Provide smooth cream-like mouth feel, so more suitable for ODT
- Suitable for both direct compression and wet granulation methods
- Cost effective
- White in color
- Directly compressible grade
- Dissolution improver
- Effective at very low concentration (0.5 to 4.0%).

Toxicity

Kyron T-314 is high molecular weight polymer, so doesn't get absorbed by body tissue and is safe for human consumption. It has no physiological action at recommended dosage and it is non toxic.

Storage

Store in tightly closed container. Keep away from moisture. If moisture is absorbed then dry at 90°C to 100°C to remove moisture content and make it below 10%.

6.8 PROSOLV ODT [86]

PROSOLV ODT is an orally disintegrating tablet Excipient matrix. It allows a rapid formulation development and quality tablet manufacture.

PROSOLV ODT addresses formulation and manufacturing challenges with robust functional performance required for high speed tablet manufacture. Patients experience a tablet with pleasing mouth feel and fast disintegration in the oral cavity without needing water. With no licensing and, royalty agreements required, JRS PHARMA makes **PROSOLV ODT** ready to use for scientists, manufacturing, and business professionals alike.

PROSOLV ODT is simple-to-use co-processed composite derived from JRS PHARMA's patented **PROSOLV Technology**. Its primary application is for the development and manufacture of orally disintegrating tablets allowing the discrete and convenient administering of medicines without water for high patient compliance.

Offering Advantages for

- Formulation Development
- Manufacturing Ease
- Business Simplicity
- Patient Compliance

INGREDIENTS	CONCENTRATION
Microcrystalline Cellulose	15-30%
Colloidal Silicon Dioxide	1.5-2.5%
Mannitol	30-40%
Fructose	30-40%
Crospovidone	4-6%

7. MATERIALS AND METHODS

7.1 LIST OF EQUIPMENTS:

Table -7.1 List of equipments used

Equipment	Manufacturer	Model
Electronic single pan balance	Sartorius Essae	LA1205 TE2145
Mechanical Sifter with sieve 40 and 60	Retsec	AS100
Tapped Density apparatus	Electro lab	ETD 1020
LOD	Satorious	MAB5
Analytical Sieve Shaker	Retsec	AS200
Blender	Rimec	410AG
Compression Machin	Chamundi Pharma Machinery	PPM406300210
Friabilator	Electro lab	Ef-2
Dissolution Apparatus	Electro lab	TDTO8L
Ultra voilet-visible spectroscopy		UV 2400PC series
Disintegration Apparatus	Electro Lab	ED2AL
Moisture analyzer	Sartorius	---
pH meter	Eutech cyber scan 100	---

7.2 LIST OF CHEMICALS:

Table7.2 List of chemicals used

Ingredients	Supplier
. Escitalopram Oxalate	Hetero Drugs Limited, Hyderabad
Cross Povidone CL-F	Shanhung Industries Co.Ltd
LHPC-21	SGN ETSU Chemicals Co.Ltd
Kyron T314	Coral pharma
Aspartame	Newtrasweet company, Augusta
Orange	Frimerich
Peppermint	Frimerich
Lake sunset yellow	Amerind colors & Chemicals pvt.ltd
Aerosil	Wacker Chemicals
Prosolv ODT	JRS Pharma Pvt Ltd
MCC (Cyclocel pH112)	FMC Biopolymer
Mannitol SD200 (Peritol)	Merck Pvt.Ltd
Talc	Analyst, Udaipur, India

7.3 PREFORMULATION STUDIES

API CHARACTERIZATION

Identification of Escitalopram oxalate By UV Spectroscopy

25mg of Escitalopram oxalate standard dissolved in 100 ml of methanol and further diluted and scanned in the UV region.

Bulk Density[1]:

It's a measurement to describe packing of particles. Bulk density/apparent density is used to determine the amount of drug that occupies the volume (gm/ml).

$$Bulk\ Density = \frac{Mass\ of\ the\ blend}{Untapped\ volume}$$

Determination of Bulk density:

Weighed quantity of Escitalopram Oxalate (25gm) was transferred into 100 ml measuring cylinder without tapping during transfer. The volume occupied by the drug was measured. Bulk density was measured by using formula $\rho_b = m / V_b$. The values obtained are reported in the table.

Tapped density[87]:

25 gm of Escitalopram Oxalate was taken in 100 ml measuring cylinder that was placed in Electro lab tapped density apparatus (method USP-I). Initial volume (V_0) of the cylinder was noted and then the cylinder was tapped 500 times and volume was measured. Then further an additional 750 tapings were repeated. No difference was noted between the volumes of the two tapings (500 and 750). The final volume (V) was considered after completion of 750 taps. Tapped density was measured by using formula $\rho_t = m / V_t$. The values obtained are reported in the table.

Compressibility Index[87, 88]:

Weighed amount of Escitalopram Oxalate (25gm) was transferred to 100ml-graduated cylinder and subjected to 500,750 &1250 taps in tap density tester (Electro lab). The difference between two taps should be less than 2%. The % of compressibility index calculated using formula

Compressibility Index = $100 * (\rho_{tapped} - \rho_{bulk}) / \rho_{tapped}$

Hausner's ratio[87]:

It is measurement of frictional resistance of the drug .the ideal range should be 1.2 –1.5.it is the determined by the ratio of tapped density and bulk density.

Hausners ratio = $\rho_{tapped} / \rho_{bulk}$

Table7.3 Scale of Flow ability

Compressibility index (%)	Flow character	Hausner 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[87]:

It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane, which is given by the equation:

$$\text{Angle of repose} = \tan^{-1}\left(\frac{\text{heigh of the pile}}{\text{radius of the pile}}\right)$$

Procedure: Weighed quantity of the drug was passed through a funnel kept at a height 2 cm from the base. The powder is passed till it forms a heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated by using the above formula.

Table 7.4 Flow properties and corresponding angle 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
Very, very poor	>66

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

Loss on drying (LOD):

1 gm of the drug was placed in the LOD apparatus and percentage loss on drying was observed.

Melting point: melting point was observed by capillary tube method.

7.4 DRUG EXCIPIENT COMPATIBILITY STUDIES

Drug-Excipient compatibility studies lay the foundation for designing a chemically stable formulation for clinical and commercial development. Drug excipient compatibility studies are conducted during preformulation to select the most appropriate excipients.

Objective To study compatibility of the active ingredients with selected excipients and to prove that the selected excipients are compatible with the active ingredient.

Table 7.5 Compatibility study ratio for solid dosage forms

S.NO	Ingredients	Ratio
1	Escitalopram oxalate	
2	Escitalopram oxalate + LHPC-21	1:1
3	Escitalopram oxalate + Crospovidone CL-F	1:1
4	Escitalopram oxalate + Kyron T-314	1:1
5	Escitalopram oxalate + Aspartame	1:0.05
6	Escitalopram oxalate + Powdarome pippermint	1:0.05
7	Escitalopram oxalate + Powdarome orange	1:0.05
8	Escitalopram oxalate + Lake Sunset Yellow	1:0.05
9	Escitalopram oxalate + Aerosil	1:0.25
10	Escitalopram oxalate + MCC pH 112	1:10
11	Escitalopram oxalate + Mannitol	1:10
12	Escitalopram oxalate + Talc	1:0.05

The active ingredients and the excipients were mixed in the selected ratios using a mortor and pestle. The mixtures are transferred into glass vials and sealed. The samples were placed as first set of initial samples and second set of samples were kept at 40°C±2°C/75%±5 % RH for 4 weeks. The samples were analyzed for physical parameters.

Drug and excipients were weighed accurately in the above ratios and well by using motor and pestle this was transferred into a glass vials. Vials were closed using rubber stopper and labeled the condition and stored in respective conditions 40°C±2°C/75%±5 % RH for 4 weeks. The samples were withdrawn every week and analyzed for physical parameters.

Standard calibration curve of the Escitalopram oxalate

25mg of the dug was dissolved in the 50ml of methanol and sonicated for few minutes and further diluted to 100ml with methanol. From this above solution futher dilutions were carried out to obtained 2,4,6,8,10 µg/ml using methanol. The absorbance of the above concentration was measured at 239nm using UV spectroscopy.

Formulation of Escitalopram oxalate tablets

As the amount of drug substance weighed may not be equivalent to the desired weight (because of the presence of moisture).Therefore the quantity of substance to be weighed was calculated as follows;

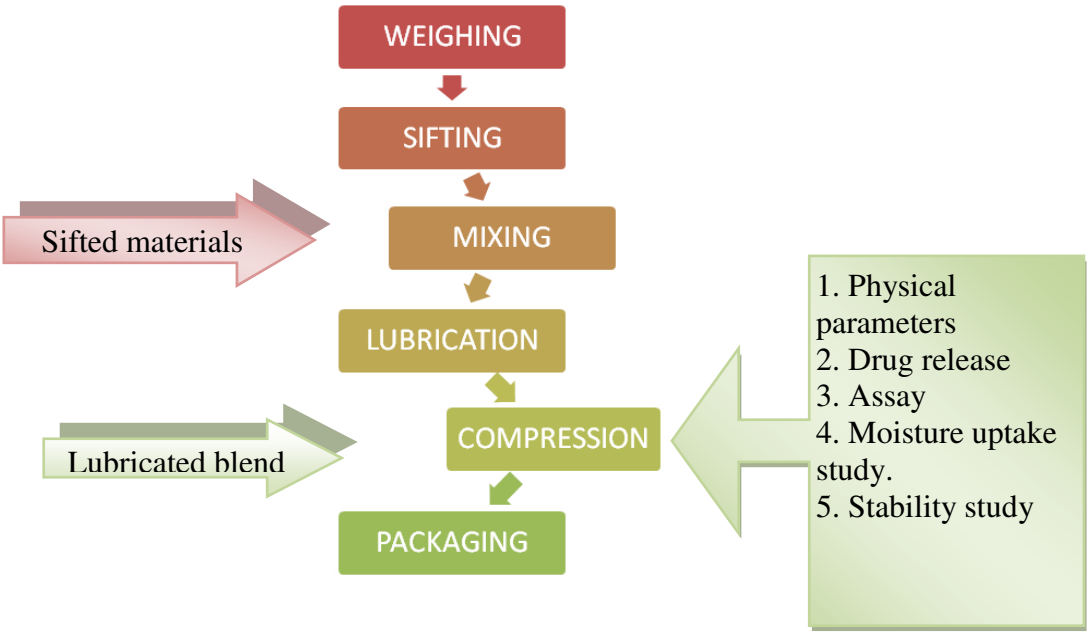
$$\text{Amount of Drug to be taken} = \frac{\text{Strength of the tablet} \times 100 \times 100 \times \text{batch size}}{\text{Assay of the sample} \times (100 - \text{LOD}) 1000}$$

Table 7.7 Formulation Developmental Trails

Excipients /Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9
Escitalopram Oxalate	20	20	20	20	20	20	20	20	20
Crospovidone CL-F	5	5	10	10	10	10	10	10	10
LHPC-21	5	5	10	10	10	10	10	10	10
Kyron T314	0	10	15	15	15	15	15	15	15
aspartame	5	5	5	5	5	5	5	5	5
orange	5	8	8	8	8	8	8	8	8
Peppermint	0	8	8	8	8	8	8	8	8
Lake sunset yellow	1	1	1	1	1	1	1	1	1
Aerosil	20	20	20	20	0	5	15	20	20
Prosolv ODT	0	0	0	0	120	65	25	0	0
MCC(CyclocelpH112)	136	81	50	40	0	0	0	0	0
Mannitol SD200(Peritol)	0	40	50	60	0	50	80	100	100
Talc	3	3	3	3	3	3	3	3	3
Total weight(mg)	200	200	200	200	200	200	200	200	200

Note: Quantities in mg

Figure -7.1 MANUFACTURING PROCESS



7.5 NARRATIVE DESCRIPTION OF MANUFACTURING PROCESS

Formulation of oral disintegrating tablets of Escitalopram oxalate20 mg was carried out by direct compression technique

Procedure for F1

- Escitalopram oxalate, Crospovidone CL-F, LHPC-21, Aspartame, Powdarome Orange& Aerosil were weighed and sifted through #40 mesh.
- Lake sunset yellow was shifted separately through 80# mesh.
- Micro crystalline cellulose pH112 was shifted separately through 40# mesh.
- Above three blends was co shifted through 40# mesh and then blended in poly bag for 10 mins
- The lubricant, Talc was shifted through 40 # separately and added to the above blend.

- The final blend was mixed thoroughly in polythene bag for 10-15 mins and compressed under 8mm flat bowled edge punches.

Procedure for F2

In this formula different formulas were assumed with different concentrations of flavours and sweeteners for their optimisation. The below procedure was followed for the preparation of the blend and taste was evaluated.

- Escitalopram oxalate, Crospovidone CL-F, LHPC-21, Aspartame, KyronT314, Powdarome Orange & Aerosil were weighed and sifted through #40 mesh.
- Lake sunset yellow was shifted separately through 80# mesh.
- Micro crystalline cellulose pH112 was shifted separately through 40# mesh.
- Mannitol SD200 was shifted separately through 40# mesh
- Above blends was co shifted through 40# mesh and then blended in poly bag for 10 mins.
- The lubricant, Talc was shifted through 40 # separately and added to the above blend.
- The final blend was mixed thoroughly in polythene bag for 10-15 mins.

Above blends were prepared with different concentrations of powdarome orange, aspartame and powdarome peppermint.

Table 7.8 Optimizing concentrations of flavours

	Trail-A	**Trail-B**	**Trail-C**	**Trail-D**
Escitalopram Oxalate	20	20	20	20
Crospovidone CL-F	5	5	5	5
LHPC-21	5	5	5	5
Kyron T314	10	10	10	10
Aspartame	5	5	5	5
Orange	0	5	5	8
Peppermint	0	0	5	8
lake sunset yellow	1	1	1	1
Aerosil	20	20	20	20
Prosolv ODT	0	0	0	0
MCC(CyclocelpH112)	91	86	81	75
Mannitol SD200(Peritol)	40	40	40	40
Talc	3	3	3	3
Total weight	200	200	200	200

As the different concentrations was prepared and taste was evaluated and therefore finally Trail-D was considered as the best among the four trails and the blend was used for the compression of tablets using 8mm flat bowled edge punches.

Procedure for F3

- Escitalopram oxalate, Crospovidone CL-F, LHPC-21, Aspartame, KyronT314, Powdarome Orange, powdarome peppermint & Aerosil were weighed and sifted through #40 mesh.
- Lake sunset yellow was shifted separately through 80# mesh.

- Micro crystalline cellulose pH112 was shifted separately through 40# mesh.
- Mannitol SD200 was shifted separately through 40# mesh
- Above blends was co shifted through 40# mesh and then blended in poly bag for 10 mins
- The lubricant, Talc was shifted through 40 # separately and added to the above blend.
- The final blend was mixed thoroughly in polythene bag for 10-15 mins and compressed under 8mm flat bowled edge punches.

Procedure for F4

- Escitalopram oxalate, Crospovidone CL-F, LHPC-21, Aspartame, KyronT314, Powdarome Orange, powdarome peppermint & Aerosil were weighed and sifted through #40 mesh.
- Lake sunset yellow was shifted separately through 80# mesh.
- Micro crystalline cellulose pH112 was shifted separately through 40# mesh.
- Mannitol SD200 was shifted separately through 40# mesh
- Above blends was co shifted through 40# mesh and then blended in poly bag for 10 mins
- The lubricant, Talc was shifted through 40 # separately and added to the above blend.
- The final blend was mixed thoroughly in polythene bag for 10-15 mins and compressed under 8mm flat bowled edge punches.

Procedure for F5

- Escitalopram oxalate, Crospovidone CL-F, LHPC-21, Aspartame, KyronT314, Powdarome Orange& powdarome peppermint were weighed and sifted through #40 mesh.

- Lake sunset yellow was shifted separately through 80# mesh.
- Prosolv ODT was shifted separately through 40# mesh.
- Above blends was co shifted through 40# mesh and then blended in poly bag for 10 mins
- The lubricant, Talc was shifted through 40 # separately and added to the above blend.
- The final blend was mixed thoroughly in polythene bag for 10-15 mins and compressed under 8mm flat bowled edge punches.

Procedure for F6

- Escitalopram oxalate, Crospovidone CL-F, LHPC-21, Aspartame, KyronT314, Powdarome Orange, powdarome peppermint & Aerosil were weighed and sifted through #40 mesh.
- Lake sunset yellow was shifted separately through 80# mesh.
- Mannitol SD200 was shifted separately through 40# mesh
- Prosolv ODT was shifted separately through 40# mesh.
- Above blends was co shifted through 40# mesh and then blended in poly bag for 10 mins
- The lubricant, Talc was shifted through 40 # separately and added to the above blend.
- The final blend was mixed thoroughly in polythene bag for 10-15 mins and compressed under 8mm flat bowled edge punches.

Procedure for F7

- Escitalopram oxalate, Crospovidone CL-F, LHPC-21, Aspartame, KyronT314, Powdarome Orange, powdarome peppermint & Aerosil were weighed and sifted through #40 mesh.
- Lake sunset yellow was shifted separately through 80# mesh.
- Mannitol SD200 was shifted separately through 40# mesh

- Prosolv ODT was shifted separately through 40# mesh.
- Above blends was co shifted through 40# mesh and then blended in poly bag for 10 mins
- The lubricant, Talc was shifted through 40 # separately and added to the above blend.
- The final blend was mixed thoroughly in polythene bag for 10-15 mins and compressed under 8mm flat bowled edge punches.

Procedure for F8

- Escitalopram oxalate, Crospovidone CL-F, LHPC-21, Aspartame, KyronT314, Powdarome Orange, powdarome peppermint & Aerosil were weighed and sifted through #40 mesh.
- Lake sunset yellow was shifted separately through 80# mesh.
- Mannitol SD200 was shifted separately through 40# mesh.
- Above blends was co shifted through 40# mesh and then blended in poly bag for 10 mins
- The lubricant, Talc was shifted through 40 # separately and added to the above blend.
- The final blend was mixed thoroughly in polythene bag for 10-15 mins and compressed under 8mm flat bowled edge punches.

Procedure for F9

- Reproducibility batch for F8

7.6 PRE-COMPRESSION PARAMETERS[89]

ANGLE OF REPOSE

The internal angle between the surface of the pile of blend and the horizontal surface is known as the angle of repose.

Method

The Angle of repose was known by passing the blend through a funnel fixed to a burette stand at a particular height (4 cm). A graph paper was placed below the funnel on the table. The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula.

$$Angle\ of\ repose = \tan^{-1}\left(\frac{Height\ of\ the\ pile}{Radius\ of\ the\ pile}\right)$$

BULK DENSITY

Bulk density is used as a measure to describe packing materials or granules.

Method

Bulk density is the ratio of given mass of powder and its bulk volume. It was determined by transferring an accurately weighed amount of powder sample to the graduated cylinder with the aid of a funnel. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated.

$$Bulk\ density = \frac{Mass\ of\ the\ blend\ (W)}{Untapped\ volume(Vo)}$$

TAPPED DENSITY

Method

Tapped density was measured by transferring a known quantity of blend into a graduated cylinder and was placed on the tapped density apparatus. The initial volume was noted. The apparatus was set for 500, 750 and 1250 taps. The tapped density was determind as the ratio of mass of the blend to the tapped volume.

$$Tap\ density = \frac{Mass\ of\ the\ blend\ (W)}{tapped\ volume(Vf)} gm/ml$$

COMPRESSIBILITY INDEX

It is the propensity of a powder to be compressed.

Method

It is measured by tapped density apparatus for 500, 750 and 1250 taps for which the difference should be not more than 2%. Based on the apparent bulk density and tapped density the percentage compressibility of the blend was determined using the following formula.

$$\%Compressability = \frac{(Tap\ density - Bulk\ denisty)}{Tap\ density} \times 100$$

HAUSNER RATIO

It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powders is called Hausner ratio.

$$Hausner\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Table 7.9 Flow properties and Compressibility index

S No.	Flow Properties	Angle of Repose (è)	Compressibility Index (%)	Hausner Ratio
1	Excellent	25-30	<10	1.0-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Possible	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.59
7	Very very poor	>66	>38	>1.60

7.7 POST COMPRESSION PARAMETERS

PHYSICAL APPEARANCE

The physical appearance of the compressed tablets involves the measurement of a number of attributes like tablet shape, smoothness, chipping, cracks, surface texture, colour etc.

THICKNESS

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm**.** The tablet thickhness should be controlled within a ± 5% variation of a standard.

WEIGHT VARIATION

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

Average weight of tablet (mg)	% difference
130 or less	10 %
From 130 to 324	7.5%
> 324	5%

HARDNESS TEST

The crushing load which is the force required to break the tablet in the radial direction was measured using a Schluenzier hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in kp or kg/cm^2.

PERCENTAGE FRIABILITY

In friability testing the tablets are subjected to abrasion and shock. It gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping.

Method

If the tablet weight is ≥ 650 mg 10 tablets were taken and initial weight was noted. For tablets of weight less than 650 mg the number of tablets equivalent to a weight of 6.5 g were taken. The tablets were rotated in the Roche Friabilator for 100 revolutions at 25 rpm. The tablets were dedusted and reweighed. The percentage friability should be not more than 1%w/w of the tablets being tested.

The percentage friability is expressed as the loss of weight and is calculated by the formula:

$$\%Friability = \frac{(Intial\ weight\ of\ tab - Final\ weightof\ tab)}{Final\ weightof\ tab} \times 100$$

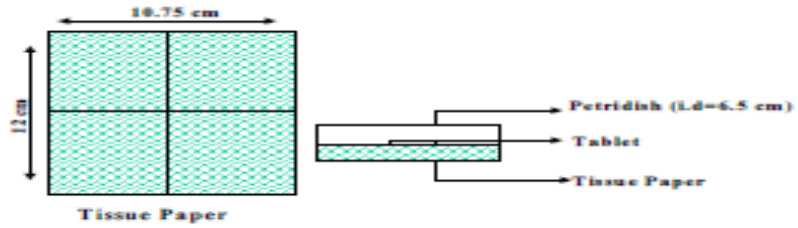
DISINTEGRATION TIME

Disintegration time is the time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 ml which is maintained at 37±2^{0}C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (# 10) was considered as the disintegration time of the tablet. The disintegration time that patients can experience for oral disintegrating tablets ranges from 5 to 30seconds.

Wetting time and water absorption ratio:

Wetting time of dosage form is related to with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure[55]. Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ration the weight of the tablet before keeping in the petridish is noted (Wb). The wetted tablet from the petridish is taken and reweighed (Wa). The water absorption ratio,*R* can be the determined according to the following equation.

$R = 100 (Wa-Wb) / Wb$



Simple Method for the Measurement of Wetting Time of a Tablet

In vitro dispersion time

In vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of Sorenson's buffer (pH6.8). Six tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

DISSOLUTION STUDIES

Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified conditions.

Method

The dissolution test was carried out in USP Apparatus Type II (paddle) with 0.1 N Hydrochloric acid as the dissolution medium. The samples were drawn at 5, 10, 15 and 30 min. Fresh volume of the medium were replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed for the percentage of drug released.

Dissolution Parameters

Dissolution Apparatus	**:**	USP Apparatus Type II (Paddle)
Dissolution Medium	**:**	0.1N Hydrochloric acid
Volume	**:**	900 ml
Temperature	**:**	37±2° C
Rpm	**:**	50
Sampling Intervals (min)	**:**	5, 10, 15&30min

Assay:

About 6 tablets were grinded to fine powder in a dry mortar and a quantity of powder equavalent to 100mg of Escitalopram Oxalate was transferred into 100ml volumetric flask. To this 50ml of methanol was added and sonicated to dissolve the drug and diluted to volume with methanol and mixed thoroughly. The solution was filtered through what man filter paper no 1.and futher diluted to get a requied ppm

UV parameters:

Instrument Type	:	UV – 2400PC series
Measuring mode	:	Absorbance
Wavelength range	:	200.00nm to 300.00nm
Scan speed	:	Medium
Slit width	:	2.0nm

Calculation

$$\frac{Sample\ absorbance}{Standard\ absorbance} \times \frac{Standard\ dilution}{Sample\ dilution} \times \frac{Average\ Weight}{Label\ claim} \times 100$$

STABILITY STUDIES

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity etc.

Objective:

To generate documented evidence that the tablets manufactured comply with the finished product specifications under accelerated and long term stability conditions as per ICH guidelines.

Design Plan

Accelerated study: The product is subjected to accelerated stability studies at 40°C±2°C/75% ±5% RH for 6 months.

Long term study: The product is subjected to long term studies at 25°C±2°C/60% ±5%RH for 12 months

Table 7.9 Stability Sampling withdrawl schedule

S.NO.	STORAGE CONDITION	TEST PERIOD
1.	40°C±2°C/75% ±5% RH	1st month
		2nd month
		3 months
		6 months
2.	25°C±2°C/60% ±5% RH	3 months
		6 months
		9 months
		12 months

8. RESULTS AND DISCUSSION

8.1 API CHARACTERIZATION

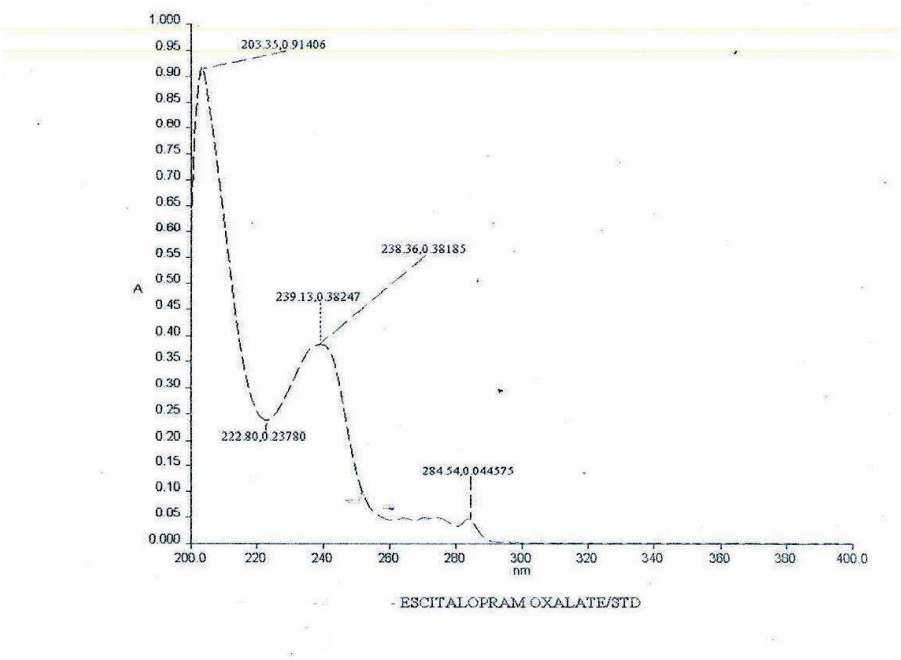


Figure-8.1 UV Spectroscopy of Escitalopram oxalate API

The Escitalopram Oxalate API (10µg/ml) was scanned in the UV between 200-400nm observed that at 239 nm shows maximum absorbance.

Raw Material analysis of Escitalopram Oxalate

The raw material analysis of the Escitalopram oxalate was carried out the results were as follows.

Table 8.1 Flow properties of Escitalopram oxalate API

S.NO	TEST	RESULT
1	Bulk density(g/ml)	0.200gm/ml
2	Tap density(g/ml)	0.384
3	Compressibility Index	48%
4	Hausner Ratio	0.1923
5	Angle of Repose	44.645

INFERENCE:-

From the above results flow property of the drug shows very poor

Table 8.2 Raw material analysis of the Escitalopram oxalate drug

TEST	SPECIFICATION	RESULT
Description	A white to half white crystalline powder	A white crystalline powder
Melting point (^{0}C)	Between 148-156.0	152.1to 153.9
Water content by Kf (%w/w)	NMT1.5	0.7
Solubility	Soluble in Dimethyl formide, in Dimethyl Sulfoxide, Sparingly soluble in methanol& slightly soluble in Dichloromethane	Compiles
Loss on drying (%)	NMT 1.00%w/w	0.30% w/w
Particle size (µ)	NMT 30µ	11.1µ
Assay (%)	NLT 98.0%& NMT 102.0%	99.7%
Residue on ignition (%w/w)	NMT0.20% w/w	0.06%
In House Specifications		

Table 8.3 Drug Excipient Compatibility Studies

S.no	Ingredient	Ratio	Description				
			Initial	Final 40°C±2°C/75%±5			
				I week	II week	III week	IV week
1	Escitalopram oxalate		White to half white crystalline powder	NC	NC	NC	NC
2	Escitalopram oxalate + LHPC-21	1:1	White to half white crystalline powder	NC	NC	NC	NC
3	Escitalopram oxalate + Crospovidone CL-F	1:1	White to half white crystalline powder	NC	NC	NC	NC
4	Escitalopram oxalate + Kyron T-314	1:1	White to half white crystalline powder	NC	NC	NC	NC
5	Escitalopram oxalate + Aspartame	1:0.05	White to half white crystalline powder	NC	NC	NC	NC
6	Escitalopram oxalate + Powdarome peppermint	1:0.05	White to half white crystalline powder	NC	NC	NC	NC
7	Escitalopram oxalate + Powdarome orange	1:0.05	White to half white crystalline powder	NC	NC	NC	NC
8	Escitalopram oxalate + Lake Sunset Yellow	1:0.05	Slight orange crystalline powder	NC	NC	NC	NC
9	Escitalopram oxalate + Aerosil	1:0.25	White to half white crystalline powder	NC	NC	NC	NC
10	Escitalopram oxalate + MCC pH 112	1:10	White amorphous powder	NC	NC	NC	NC
11	Escitalopram oxalate + Mannitol	1:10	White coloured amorphous powder	NC	NC	NC	NC
12	Escitalopram oxalate + Talc	1:0.05	White to half white crystalline powder	NC	NC	NC	NC

NC-No change observed

INFERENCE:

From the above physical observation that all the excipients shows a good compatability with the drug no interactions or color changes observed.

Table 8.4 Standard calibration curve of the Escitalopram oxalate

Concentration(µg/ml)	Absorbance at 239nm
0	0
2	0.0813
4	0.1586
6	0.2349
8	0.3087
10	0.3824
Slope(m)	0.381
Intercept	0.003
Correlation	0.999

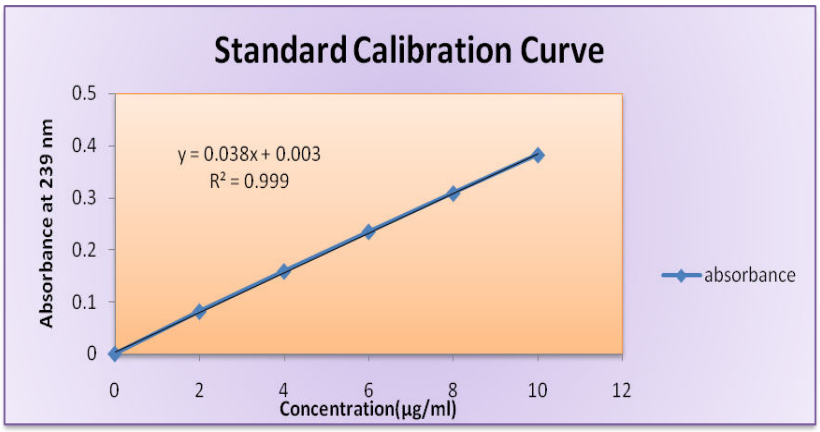


Figure-8.2 Standard calibration curve of the Escitalopram oxalate

Table 8.5 Results of Pre Compression Parameters

BATCH NOS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of repose	48.32	37.45	34.76	32.98	40.5	38.04	32.56	29.65	28.98
Bulk density	0.25	0.605	0.631	0.586	0.387	0.59	0.384	0.486	0.463
Tap density	0.384	0.741	0.728	0.681	0.54	0.74	0.45	0.532	0.509
Compressibility index	34.89	18.35	13.32	13.95	28.33	20.27	14.66	8.64	9.03
Hausner ration	1.53	1.22	1.15	1.16	1.39	1.254	1.17	1.09	1.09

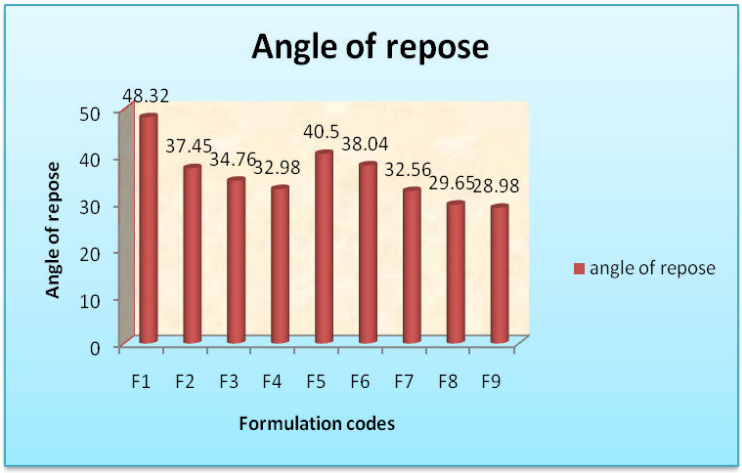


Figure –8.3 Comparison of Angle of Repose of All Formulations

INFERENCE:

Preformulation studies shows that Escitalopram Oxalate API dose not shows good flow property so it should be improved by the addition of the From this graph the initial batch F1 shows poor flow property where the filler used was MCC it was improved by the addition of Mannitol in F2,F3,F4 in increasing concentrations shows good flow properties . again the flow property was decresad by addition of Prosolv ODT at last in the final formula only the Mannitol filler shows the Excellent flow property in F8&F9.

Table 8.6 Results of Post Compresional Parameters

Physical Appearance: - slight orange coloured tablets with break line

Formulation Code	**Average weight (mg) ±7.5%**	**Thickness (mm) ±5%**	**Hardness (kp)**	**Percentage Friability (%) 0.1-0.9%**	**In vitro Disintegration Time (sec)**	**In vitro dispersion time(sec)**	**Wetting time (sec)**	**Assay**
F1	201	3.55	2.5	0.31	180	>7min	240	99.87%
F2	199.6	3.54	2.3	0.20	68	132	118	97.91%
F3	202.5	3.71	2.0	0.22	55	110	97	100%
F4	200	3.89	2.2	0.10	49	65	45	101%
F5	198.5	3.45	2.1	0.60	54	165	120	99.56%
F6	202.1	3.56	2.7	0.34	32	121	104	97%
F7	200	3.67	2.5	0.11	21	45	48	100%
F8	200	3.71	3.4	0.09	14	34	24	101.05%
F9	200	3.70	3.5	0.09	16	31	28	101.43%

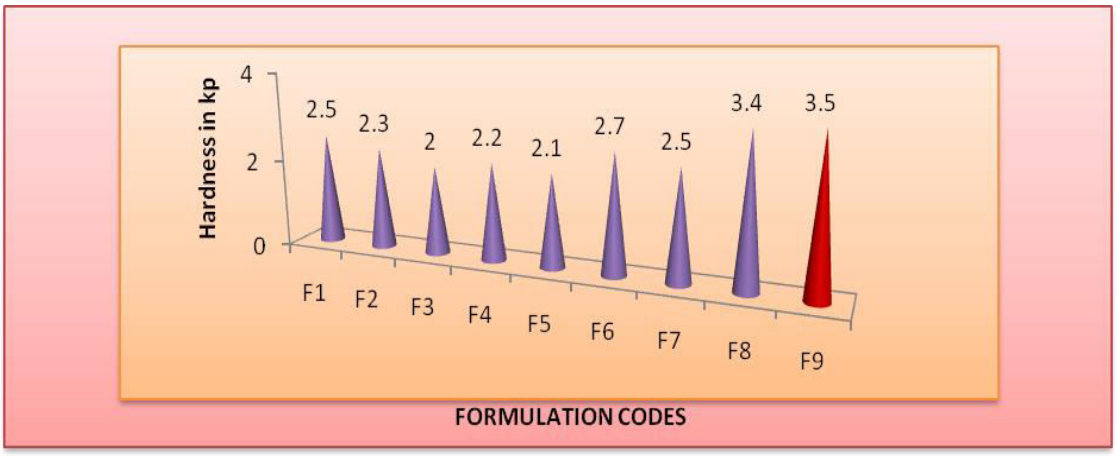


Figure-8.4 Comparison of hardness of different formulations

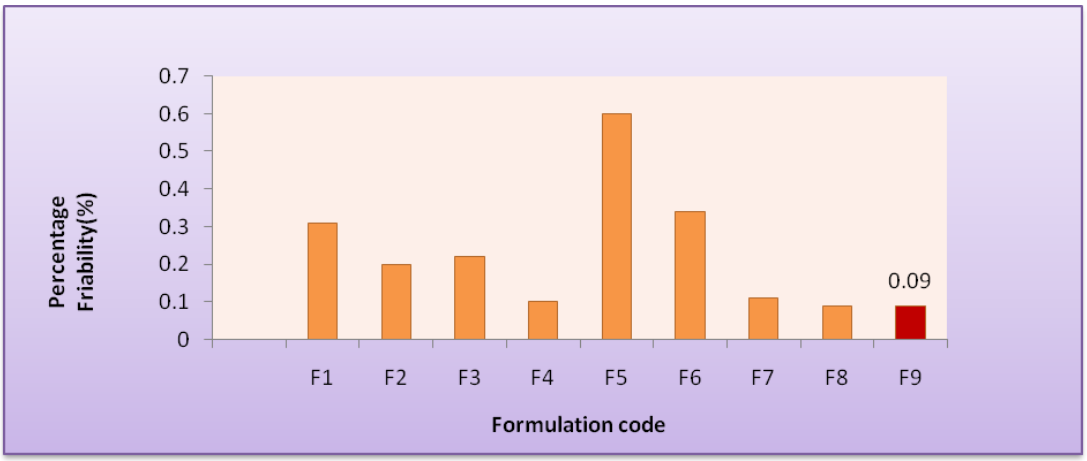


Figure-8.5 Comparison of percentage weight loss of different formulations

INFERENCE:

From the figure12 &13 initially the hardness was low and the friability was more it was observed to improve by replacing the MCC by Mannitol increasing concentration of Mannitol results in the optiminsed hardness (3.5±0.5) and low friability (0.09%) in the final formulas F7,F8,F9.

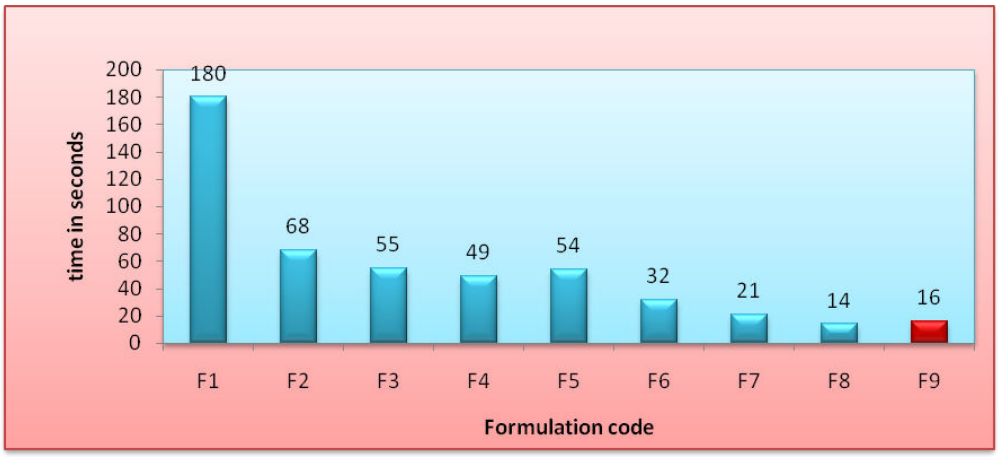


Figure-8.6 Comparison of in vitro disintegration time

INFERENCE:

Initially the tablet took more than 5 minutes to disintegrate. Since mannitol has multiple properties such as diluent, sweetenting agent and as well as disintegrant , the concentration of mannitol was increased to make the tablet disintegrate at a faster rate. Optimization of disintegration time was made by studying the inclusion of super disintegrants such as LHPC-21, kyron T-314 and Crospovidone CL-F. Addition of cros povidone showed positive results in disintegration time of the tablets. Optimized disintegration time was obtained by increasing the % of super disintegrates. The above figure shows the disintegration time of various formulations. From the figure it could be inferred that formulation F_9 got an optimized disintegration time of 16 ±3sec.

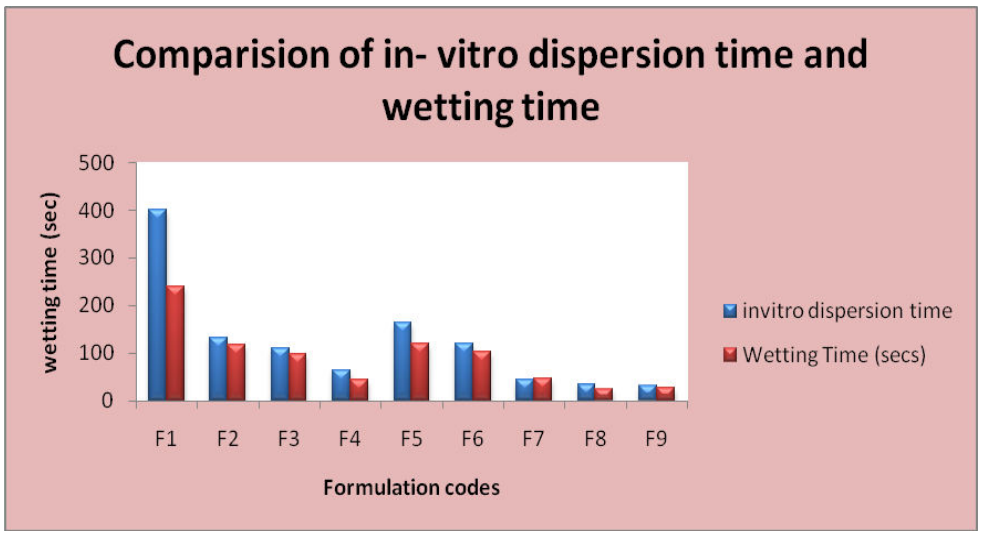


Figure-8.7

INFERENCE:

'Wetting time' is an important parameter to be considered while preparing an oral disintegrating tablet. Wetting time is carried out to determine the absorption capacity of the tablet which effects its disintegration. Initially the wetting time was around 4 minutes. Addition of the Mannitol with micro crystalline cellulose increased compactability and hardness of the tablet and results in decreased its wetting time. Wetting time was further more decreased by enhancing the disintegrating capacity of the tablet by inclusion of super disintegrates and increasing the concentration of the filler (Mannitol) in the final trials. The above figure shows the wetting time of various formulations of Escitalopram oxalate orally disintegrating tablets. From the figure it could be inferred that the wetting time was optimized and brought to 28 Seconds at F_9.

Invitro dispersion time

Initially the in vitro dispersion time was observed to be more than 5 mins it was gradually reduced by increasing the concentration of the super disintegrants and by increasing the concentration of the Mannitol as filler the above figure shows the in vitro dispersion time of various formulations of escitalopram oxalate orally disintegrating tablets. From the figure it could be observed that the wetting time was optimized and bought to 31seconds for F9.

TABLE 8.7 Dissolution study of Escitalopram Oxalate Oral Disintegrating Tablets

Cumulative percentage of drug release (%)									
Time (min)	**F 1**	**F 2**	**F 3**	**F4**	**F5**	**F6**	**F7**	**F 8**	**F9**
0	0	0	0	0	0	0	0	0	0
5	92.99	98.66	99.44	102.59	101.28	102.48	103.14	103.04	103.13
10	96.3	98.74	100.71	102.37	102.46	102.66	103.65	103.54	103.65
15	96.49	100.77	101.72	102.33	103.59	103.2	103.51	103.29	103.71
20	98.83	102.14	102.27	101.47	101.02	101.22	102.75	101.79	103.75
30	101.79	102.04	102.25	101.26	101.87	101.4	102.84	101.85	102.84

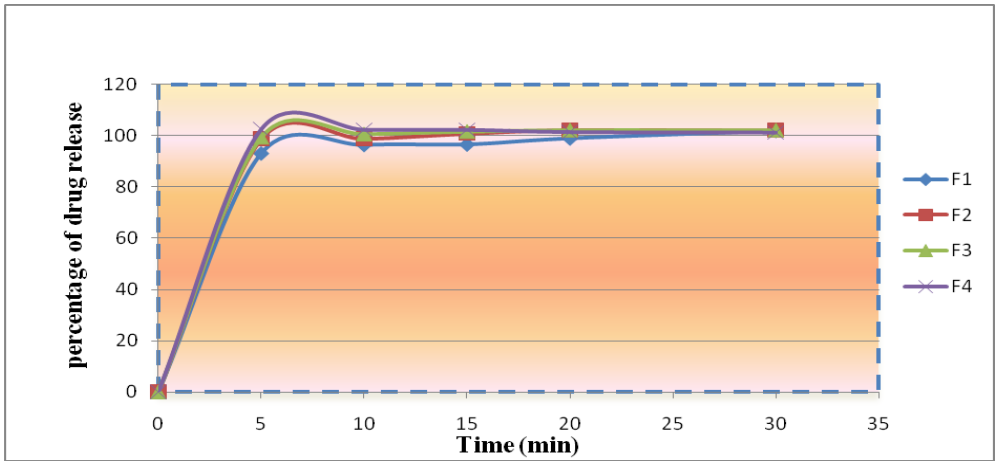


Figure-8.8 Comparative dissolution profile of Different Formulations (F1, F2, F3, F4)

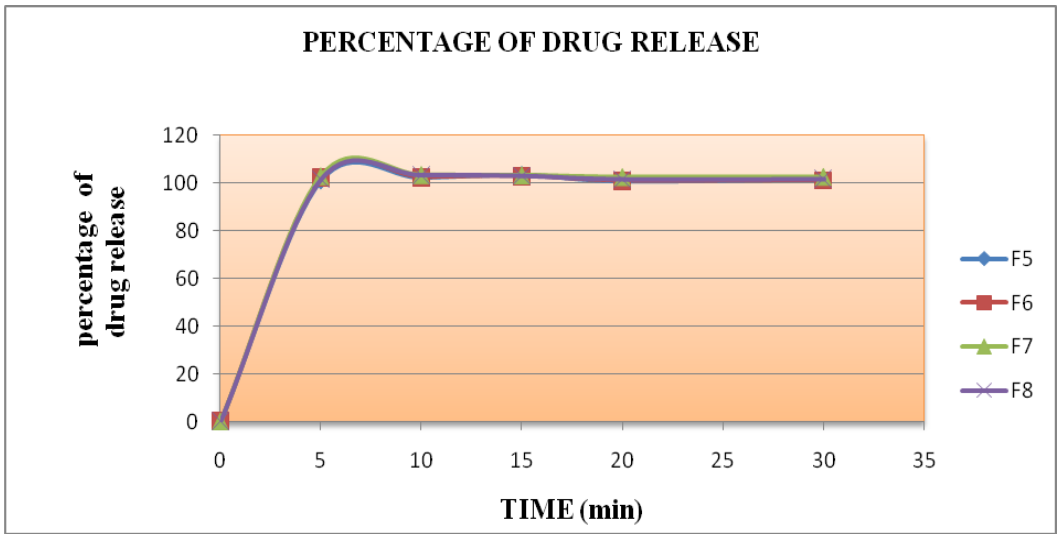


Figure-8.9 Comparative dissolution profile of Different Formulations (F5, F6, F7, F8)

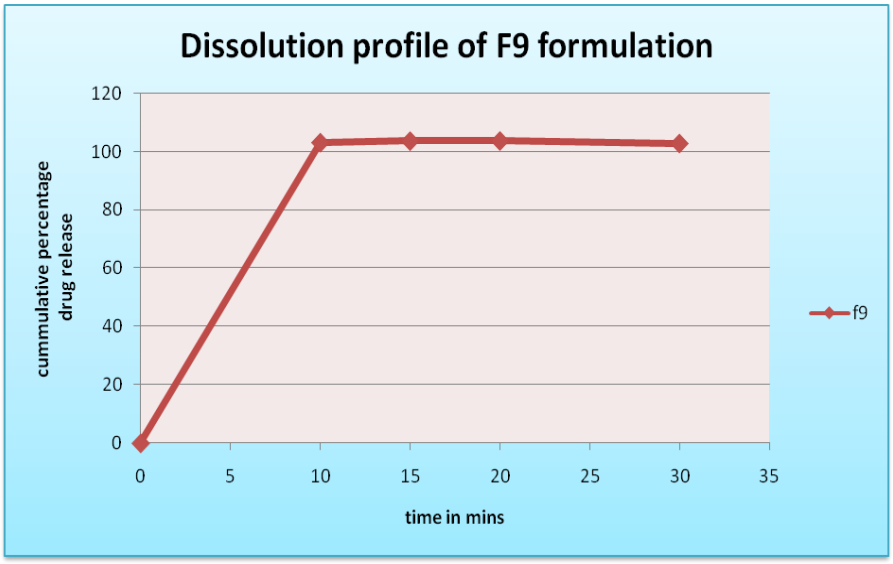


Figure-8.10 Dissolution profile of F9 Formulation

RESULTS OF STABILITY DATA

Table 8.8 Stability study data

PARAMETERS TESTED	STORAGE CONDITIONS		
	INITIAL	$40^0C \pm 2^0C$ / 75% ±5% RH	
		1st month	2nd month
Description	Light orange coloured round tablet with break line	No change	No change
Average weight (mg)	200	201	201
Thickness (mm)	3.71	3.71	3.73
Hardness (kp)	3.4	3.4	3.3
% Friability	0.09	0.12	0.17
Disintegration time (sec)	14	18	20
In vitro dispersion time	34	39	51
Water content (%)	2.41	2.33	2.45

Table 8.9 Dissolution data of stability study sample(percentage of drug release)

Time Interval (min)	Initial	$40^0C±2^0C$ / 75% ±5% RH	
		Ist month	2nd month
0	0	0	0
5	101.71	101.52	101.28
10	103.52	102.60	102.46
15	103.2	103.19	103.00
20	101.77	101.76	101.02
30	101.83	101.82	101.07

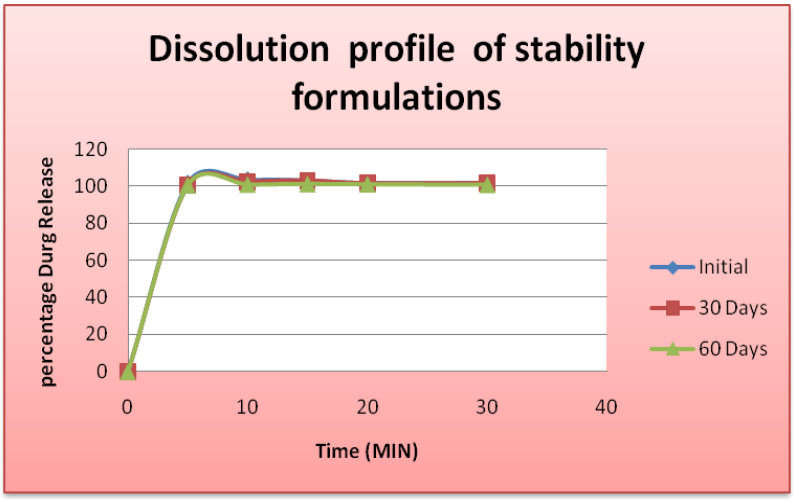


Figure-8.11

Table 8.10 Assay of stability samples

Storage conditions		Escitalopram oxalate
Initial		100.45%
$40^0C±2^0$ C / 75% ±5% RH	1st month	99.87%
	2nd month	100.23%

DISCUSSION

Formulation F1

F1 was carried Microcrystalline cellulose (Cyclocel pH112) as diluent, Crosspovidone XL (2.5%) & L-HPC (2.5%) as superdisintegrant. Aerosil is used as a glident the disintegration time was more than 3mins and in-vitro dispersion time was more than 7mins.

Improvisation of trial

- ✓ Addition of the another super disintegrate Kyron T314 (5%)

Formulation F2

During the F2 batch trails were performed for optimizing the concentrations of the sweeteners and flavouring agents four different trials A, B, C and D. It was observed that Trial D showed good mouth feel. Hence the tablets were compressed with the formula for Trial D.

F2 was carried Microcrystalline cellulose (Cyclocel pH112) as diluent, Crosspovidone XL (2.5%) & L-HPC(2.5%) & KyronT314(5%) as superdisintegrant. Hence e disintegration time was reduced to 68 seconds but fails in the in-vitro dispersion time and wetting time.

Improvisation of trial

- ✓ Increasing the concentration of the superdisintegrants
- ✓ Addition of spray dried mannitol as a diluent

For the improvement of the wetting time and in-vitro dispersion time

Formulation (F3)

F3 Formulation was carried out by increasing the concentrations of the super disintegrate Crosspovidone (5%), kyron (7.5%), L-Hpc (5%).and using the combination of the diluent Micro crystalline cellulose and mannitol. Hence the disintegration time was reduced but still the wetting time was not yet improved

Improvisation of trial

- ✓ Further increasing in the concentration of the spray dried mannitol 30% as diluent

Formulation (F4)

Formulation F4 was carried out with increased concentration of the mannitol (30%) as diluent results in good improvement in the disintegration time(65sec) and wetting time(45 sec).

Improvisation of trial

- ✓ Replacing the excipients with PROSOLV ODT which is a combination of the Microcrystalline Cellulose, Colloidal Silicon Dioxide, Mannitol, Fructose, and Crospovidone.

Formulation (F5)

F5 was carried out by using the Prosolv ODT (60%) as excipent specially designed for the orally disintegrating tablet here the disintegration time was increased and wetting time was also increased and the sticking problem was also observed during compression.

Improvisation of trial

- ✓ Decreasing the concentration of the Prosolv ODT and addition of the spray dried mannitol.
- ✓ Additions of crospovidone as super disintegrate.

Formulation (F6)

F6 formulation was carried out with addition of spray dried mannitol (25%) and Aerosil (2.5%) and crospovidone (5%) hence observed improvisation in the wetting time and disintegration time

Improvisation of trial

- ✓ Increase in concentration of Spray dried mannitol and Aerosil

Formulation (F7)

F6 formulation was carried out with addition of spray dried mannitol (40%) and aerosil (7.5%) as a suspending agent hence observed improvisation in the wetting time (48sec) and disintegration time (21) hence concluded that Prosolv ODT does not show the impact on this formulation.

Improvisation of trial

- ✓ Replacing the Prosolv ODT with Spray dried mannitol and Aerosil

Formulation (F8)

F8 formulation was carried out with mannitol as a filler and crospovidone, KyronT314 & L-Hpc 21 as a super disintegrates results in good wetting time (24sec)and disintegration time (14sec).

Formulation (F9)

Reproducibility batch of F8

All the pre compression and the post compression parameters showed good results

9. SUMMARY

A recent advance in Novel Drug Delivery System aims to enhance safety to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is Orally Disintegrating Tablet.

The present study was to formulate and standardize of an Anti depressant drug Escitalopram Oxalate. Escitalopram Oxalate orally disintegrating tablets formulated in the present study are beneficial to the pediatrics and elderly patients. It is also beneficial to the person having Dysphagia and mentally ill.

Preformulation studies were carried out during the early stages of this work. It was found that Escitalopram oxalate is having maximum absorbance at wavelength 239 nm. The drug-polymer compatibility study was carried out to determine the interactions between the drug and the polymers used in the study.

The orally disintegrating tablets were formulated using the above mentioned difrent super disintegrants by direct compression technique. Crospovidone, LHPC-21 and Kyron T-314 were used as super disintegrants .

Prepared tablets were evaluated for Pre-Compression Parameters and Post compression Parameters.

Flow properties –Angle of repose, Bulk density, Tap Density and also %compressability was determined to all formulations which showed good flow property.

Formulation F1 was carried Microcrystalline cellulose (Cyclocel pH112) as diluents, Crosspovidone XL (2.5%) & L-HPC (2.5%) as Superdisintegrants. Aerosil is used as a glident. here shows the DT more than 3mins to improve the disintegration time the addition of the super disintegrants KYRONT-314 ,the

disintegration time was improved but still the wetting time and the invitro dispersion time were not improved for this reason the Spray dried Mannitol was used as diluents and concentration of super disintegrants was increased in F3.As the increasing the concentration of the diluents Mannitol results in the good wetting time and invitro dispersion.

F5,F6,F7 were prepared by using Prosolv ODT which does not give good results so the increasing concentration of Mannitol and the cross provide were used again gives the best result. F8 were carried out with Mannitol as filler and Crospovidone, Kyron T-314 &L-HPC 21 as super disintegrates results in good wetting time 24 sec and disintegration time 14 seconds.

The final trials F8, F9 were optimized with various tablet parameters like Thickness (3-4)mm; Hardness (3-4) kp; Percentage Friability (<1%) and Disintegration time (14±3 seconds), which were within the specified limits. The Dissolution and Assay results of F8 and F9 were good

Moisture uptake studies for the final batch were performed at 29, 43% RH The reproducibility batch F9 was loaded for long term and accelerated stability studies at 40±2°C/75±5% RH. The results of stability data for 1st and 2nd month (40±2°C/75±5% RH) were found to be good. Not much variation or changes found during study period.

10. CONCLUSION

Escitalopram Oxalate used as Antidepressant. They are formulated as oral disintegrating tablets which show better patient acceptability and compliance with improved efficacy when compared with conventional dosage forms.

Direct compression was the preferred technology for the preparation of oral disintegrating tablets of Escitalopram Oxalate.

Based on the preliminary studies various formulation trials (F1-F9) were carried out with different concentrations of Superdisintegrants, filers and lubricants. From the various formulations it was concluded that the formulation F9, the reproducibility batch of F8 was finalized as the optimized formula.

Formulation F9 showed satisfactory results with various physicochemical evaluation parameters like Hardness, Percentage weight loss, Disintegration time, Dissolution profile, Assay and Moisture content. When subjected to accelerated stability studies the tablets were found to be stable.