Formulation and Evaluation of Immediate Release Pellets of Escitalopram oxalate.

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ABSTRACT

Multiparticulate systems prove to be promising system for oral drug delivery. Pelletization is a process in which fine powders or granules are converted into free flowing semi-spherical units referred as pellets. Pellets are the multiple unit dosage forms which can be formulated in the form of suspensions, capsules or disintegrating tablets. This review outlines manufacturing and evaluation of spherical pellets. In many cases immediate onset of action is required than conventional therapy. To overcome these drawbacks, immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms. Escitalopram, an anti-depressant drug belonging to the SSRI class used for treating depression and generalized anxiety disorder in adults and children of age above 14 years. It is the (S)-stereoisomer (enantiomer) of the drug Citalopram. In the present study, an attempt was made to prepare immediate release pellets of Escitalopram, Pellets were prepared by Drug loading method using pelletizing agents that can contribute to the faster dissolution and thereby improve the solubility of the drug. Different super disintegrants like Crospovidone, Croscarmellose sodium and sodium starch glycolate were tried in order to improve dissolution profile and HPMCE15 was used as a binder. The pellets were characterized for friability, disintegration time, thickness, flow properties, infrared spectroscopy and dissolution profile. Formulated pellets have shown clear and better dissolution profile.

Keywords: Multiparticulate systems, Immediate release, Escitalopram, Pellets, Drug layering method, Crospovidone.
INTRODUCTION

1.1. PELLETIZATION

Traditionally, pellets have been described as agglomerates that are produced from different types of raw materials. Specifically, with respect to pharmaceutical sector, pellets can be defined as agglomerates of fine powders or granules made up of drugs and pharmaceutical Excipients. Pellets range in size typically between 0.5 to 1.5mm and are mostly preferred for oral route of drug delivery \(^1,2\).

Pellets can be defined as small, free flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and intended usually for oral administration, manufactured by the agglomerates of fine powders or granules of bulk drugs and excipients using appropriate processing equipment. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today\(^3\).

Pellets offer greater degree of flexibility throughout the design and development of oral dosage forms. They can be divided into different dose strengths without any process changes and can be used to deliver incompatible biologically active agents all together or particles with different release profiles at same site or at different site of gastrointestinal tract. Pellets are the multiple unit dosage forms which can be formulated in the form of suspensions, capsules or disintegrating tablets.

Multiple unit systems hold significant advantages over single unit systems. They are less dependent on gastric emptying when compared to single unit dosage forms. Due to their, they pass through the pyloric sphincter easily which minimizes the inter and intra-subject variability in gastrointestinal transit time. Pellets exhibit high loading capacity of active ingredients without producing extensive large particles. Pellets are less susceptible to dose dumping when compared to single unit systems. Pellets can be coated easily due to their spherical shape and low surface to volume ratio and hence no extra coating material is required to fill the irregularities on the surface\(^1,4\).

1.1.1. Criteria for pellets

- Regardless of which manufacturing process is used, pellets have to meet the following requirements. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.
The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000mm.

The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.

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Regardless of which manufacturing process is used, pellets have to meet the following requirements. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.

1.1.1.1. SIGNIFICANCE OF PELLETS

Pellets may have varied applications in varied industries. It just requires an innovative bend to use it to derive maximum profitability. The smooth surface & the uniform size of the pellets allow uniform coating not only for each pellet but also from batch to batch.

Highlighted below are some of the few instances where smooth surfaced uniform pellets are being successfully used:

1. Improved appearance of the products. Coating of pellets can be done with different drugs to enable a controlled release rate.
2. In case of immediate Release Products larger surface area of pellets enables better distribution.
3. Chemically incompatible products can be formed into pellets & delivered in a single dose by encapsulating them.

4. In the chemical industries it is used to avoid powder dusting.
5. Varied applications are possible in the pellet form. Eg: sustained release.
6. Pellets ensure improved flow properties, and flexibility in formulation development and manufacture.
7. The coating material may be colored with a dye material so that the beads of different coating thickness will be darker in color and distinguishable from those having fewer coats.
8. The beads or granules of different thickness of coatings are blended in the desired proportions to give the desired effect.
9. The thickness of the coat on the pellets dictates the rate at which the drug/contents are released from the coated particles. A smooth surface of the pellets & uniform coating thickness for each pellet.
10. By selecting the proper formulation, processing conditions and processing equipment it is possible to attain smooth surfaced & uniform pellets.

1.1.1.2. Advantages of Pellatization:

Multiple unit systems hold significant advantages over single unit systems.

- They are less dependent on gastric emptying when compared to single unit dosage forms. Due to their, they pass through the pyloric sphincter easily which minimizes the inter and intra-subject variability in gastrointestinal transit time.
- Pellets exhibit high loading capacity of active ingredients without producing extensive large particles.
- Pellets can be coated easily due to their spherical shape and low surface to volume ratio and hence no extra coating material is required to fill the irregularities on the surface.
- Improved appearance of the product and the core is pharmaceutically elegant.
- Pellatization offers flexibility in dosage form design and development.
- Pellets are less susceptible to dose dumping.
- It reduces localized concentration of irritative drugs.
- It improves safety and efficacy of a drug.
- Pellets offer reduced variation in gastric emptying rate and transit time.
- Pellets disperse freely in G.I.T. and invariably maximize drug absorption and also reduce peak plasma fluctuation.
- Pellets ensure improved flow properties in formulation development.

1.1.2. Theory of pellet formation

In order to judiciously select and optimize any Pellatization/granulation process, it is important to understand the fundamental mechanisms of granule formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. As the conventional granulation, the most thoroughly studied, most classified Pellatization process, which involves a rotating drum, a pan or a disc, has been divided into three consecutive regions: nucleation, transition and ball growth. However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer.
1.1.3. METHODS OF PREPARING PELLETS.

Compaction and drug layering are the most widely used Pellatization techniques in pharmaceutical industry. Of the compaction techniques, extrusion and Spheronization is the most popular method. Recently, however, melt Pellatization has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer. Other Pellatization methods such as globulation, balling and Compression are also used in development of pharmaceutical pellets although in a limited scale.

**Powder layering:**

Powder layering involves the deposition of successive layers of dry powders of drugs and excipients on preformed nuclei or cores with the help of binding liquids. As powder layering involves simultaneous application of binding agents and dry powders, hence it requires specialized equipments like spheronizer. The primary requirement in this process is that the product container should be solid walls with no perforation to avoid powder lose beneath the product chute before the powder is picked off by the wet mass of pellets that is being layered.

**Solution / suspension layering:**

Solution/suspension layering involves the deposition of successive layers of solution or suspensions of drug substances and binder over the starter/non-pareil seeds, which is an inert material or crystals/granules of the same drug. In fact the coating process involved in general is applicable to solution or suspension layering technology. Consequently conventional coating pans, fluidized beds, centrifugal granulators, wurster coaters have been used successively to manufacture pellets by this method. The efficiency of the process and the quality of the pellets produced are in part related to the type of equipment used.

**PELLETIZATION BY EXTRUSION AND SPHERONIZATION:**

The process involves first making extrudes from the powder material and then converting the extrudes into beads using the spheronizer. The powder material could be any kind of powder (drug powder, ayurvedic powder, food ingredient powder, detergent powder, nuclear powder etc). Beads as fine as 0.6mm can also be made.
OTHER PELLETIZATION METHODS

Other Pellatization methods such as globulation, cryopellatization, balling and compression are also used, although a limited scale in the preparation of pharmaceutical pellets.

Globulation or droplet formation consists two related processes, spray drying and spray congealing.

Spray drying: It is the process in which drugs in the suspension or solution without excipients are sprayed in to a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates; hence bioavailability of poorly soluble drugs.

Spray congealing:

It is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets. Both immediate and controlled release pellets can be prepared in this process depending on the physiochemical properties of the ingredients and other formulation variables.

Cryopellatization:

It is a process in which the liquid formulation is converted in to solid spherical particles or pellets in the presence of liquid nitrogen as fixing medium. The shape depends up on the distance the droplet travel before contacting liquid nitrogen.

Compression:

It is one type of compaction technique for preparing pellets. Compacting mixtures or blends of active ingredients and excipients under pressure prepare pellets of definite sizes and
shapes. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablets manufacturing.

**Balling:**

It is the Pellatization process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixtures. The process consists of conversion of finely divided particles into spherical particles upon the addition of appropriate amounts of liquid.

**1.1.4. Excipients for pellets:**

Formulation aids or excipients are added to pharmaceutical dosage forms mainly to produce satisfactory delivery of the drug to the intended site, to impart favorable characteristics to the dosage form and to facilitate the manufacture of the product. Excipients, disintegrant, surfactants, pH adjusters, Separating agents, Spheronization enhancers, glidants and release modifiers etc. some examples of such excipients are given in Table 1

**Table: 1. Excipients used in Pellatization**

<table>
<thead>
<tr>
<th>Filler</th>
<th>MCC, starch, sucrose, lactose, mannitol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binder</td>
<td>Gelatin, HPC, HPMC, MC, PVP, sucrose, starch</td>
</tr>
<tr>
<td>Lubricant</td>
<td>Calcium stearate, glycerin, PEG, Mg. Stearate</td>
</tr>
<tr>
<td>Separating agent</td>
<td>Kaolin, talc, silicon dioxide</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>Alginites, Croscarmellose sodium</td>
</tr>
<tr>
<td>pH adjuster</td>
<td>Citrate, phosphate, meglumine.</td>
</tr>
<tr>
<td>Surfactant</td>
<td>Polysorbate, SLS</td>
</tr>
<tr>
<td>Spheronization enhancer</td>
<td>MCC, sodium CMC</td>
</tr>
<tr>
<td>Glidants</td>
<td>Talc, starch, Mg stearate.</td>
</tr>
<tr>
<td>Release modifier</td>
<td>Ethyl cellulose, carnauba wax, shellac.</td>
</tr>
</tbody>
</table>

**NON PAREIL SEEDS: (NEUTRAL PELLETS)**

**SUGAR SPHERES:**

Sugar spheres contain NMT 92% of sugar, calculated on dry basis. The remainder consists of maize starch” defined according to European pharmacopoeia. Possibility to analyze the sugar spheres according to the Ph. Eur., USP/NF and JP produced accordance with the GMP.
1.1.5. COATING EQUIPMENTS:

Most of the coating processes use one of three general types of equipment.

1. The standard Coating pan
2. The Perforated Coating pan
3. The Fluidized bed coater

1.1.5.1. Conventional pan system:

The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand, the pan is rotated on its horizontal axis by a motor, the hot air is directed into the pan and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan. Coating solutions are applied by spraying the material on the bed surface.

1.1.5.2. The Perforated Coating pan:

Neocota is an automatic coating system for tablets and pellets. Neocota is a completely updated automatic coating system having a batch capacity of 500 g to 1 kg. This model efficiently carries out the following operations: Aqueous film coating of tablets/pellets; Non-aqueous organic solvent based film coating of tablets/pellets; and enteric film coating of tablets/pellets.

The basic units of the system are: Coating pan has perforations along its cylindrical portion. It is driven by a variable speed drive with a flame-proof motor. Supply of hot air and exhaust of drying air are arranged to facilitate the coating system through stainless steel plenums positioned on both sides of the perforated coating pan. The pan is enclosed in a cylindrical airtight housing provided with a suitable door and front glass window. This housing of pan with drive is a stainless steel cabinet accommodating the gearbox, AC variable drive, power panel, hot air unit, exhaust unit and an air fitter.

Liquid spray system is complete with stainless steel liquid storage vessel, variable flow-rate liquid dosing pump, automatic spray gun, and inter-connecting flexible hoses.

1.1.5.3. The Fluidized bed coater:

The Fluid Bed Technology offers a very efficient coating technique. The major advantage of the Fluid Bed Systems is that it is a closed system and not only coating but granulation and pellet formation is also possible in the same machine.
Fluidized bed coating is a process that takes place inside a fluidized bed whereby a coat is introduced to cover the intended object in order to protect it or modify its behavior. Particulate coating is a form of fluidized bed coating involving the coating of solid particles inside the bed.

In the process, a layer is deposited onto the surface of fluidized solid particles by spraying with a solution of the coating material. The fluidizing gas is also used to dry the deposited solution to form a coat on the surface of the particle. Fluidized beds are used for coating because of their high energy and mass transfer. Fluidized beds for film coating can be divided into three groups,

- Top-spray,
- Tangential-spray
- Bottom-spray equipment.

**Top spray:**

The expansion chamber is lengthened to allow powder to remain fluidized longer and to move with a higher velocity, so that agglomeration is minimized. The expansion chamber is conically shaped to allow uniform deceleration of air stream. The filter housing is larger and designed to shake the fines back into the bed interrupting fluidization; this reduces agglomeration tendencies. The nozzle is positioned low in the expansion chamber so that coating material impinge on the fluidized particle a short distance from the nozzle; this reduces droplet spray drying and provides for longer subsequent drying of the coated particles. The top spray coater has been used to apply aqueous and organic solvent based film coatings, controlled release coatings.

**Bottom spray coating: (wurster process, Make-GLATT)**

The wurster machine employs a cylindrical product container with a perforated plate. Inside the container is a second cylinder (coating partition) with is raised slightly above the perforated plate, centered in the plate below this partition is a spray nozzle used to dispense the coating solution. The perforated plated is designed with large holes in the area under the coating partition and smaller holes in the remainder of the plate, except for one ring of large holes at the perimeter. The design allows the substrate particles to be pneumatically transported upward through the coating partition, and downward outside this partition. Material passing through coating partition receives a layer of coating material, dries in the expansion chamber, and falls back in a semi fluidized state. Material circulates rapidly in this fashion and receives layer of coating material, dries in the expansion chamber, and falls back in a semi fluidized state material circulates rapidly in this fashion and receives a layer of coating on each pass through the coating.
partition. The ring of large holes on the periphery of perforated plate prevents the accumulation of material at the container wall. It has been used for coating small particles, pellets and tablets.

Table 2: Parameters Used in Bottom Spray Equipment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inlet temperature</td>
<td>38-42°C</td>
</tr>
<tr>
<td>Product temperature</td>
<td>32-36°C</td>
</tr>
<tr>
<td>Exhaust temperature</td>
<td>32-38°C</td>
</tr>
<tr>
<td>Spray rate</td>
<td>8-12mg/min</td>
</tr>
<tr>
<td>Peristaltic pump</td>
<td>12-18 rpm</td>
</tr>
</tbody>
</table>

1.1.5.4. FLUID BED COATING

Particles smaller than approx. 2mm should be coated in fluid bed equipments, because with decreasing particle diameter the specific surface area of a substrate increase dramatically. thus, the required coating weight gain is much higher than tablet coating processes. In order to achieve acceptable process times, the high efficiency of fluid bed compared to pan coating equipment shows clear advantages in particles coating processes.

SHAPE In order to achieve good flow properties, spherical particles with smooth surfaces are preferred, while needle shaped particles show poor flow properties and tend to form lumps. Another advantage of the latter is the increased risk of breakage during the coating process, creating uncoated spaces and leading to an increased coating weight gain. besides crystals and pellets, granules can be used as substrates.

SIZE Usual particle sizes are in arrange of 0.2-1.2mm. smaller particles may have problematic flow properties in higher scale and may tend to break if the length /diameter-ratio is 1:2.

TOP/ BOTTOM / TANGENTIAL SPRAY. The top spray method is known and used for particle coating and granulation processes. Compared to other fluid bed coating technologies, the top spray method is susceptible for porous film structure, especially if organic coating formulations are processed. bottom spraying (wurster process) is the usual method in particle coating. due to a more uniform particle movement, better film structures can be achieved compared to the top spray method, and the required polymer weight gain for a certain function is usually lower to some extent. A disadvantage is that in case of nozzle blockage during the coating process, the product must be discharged before the nozzles can be cleaned. Tangential
spraying system, which is commonly fitted with a rotating bottom plate, can achieve film quantities nearly as good as bottom–spraying system. The rotation of the plate nicely supports product movement, so that the required air amount is mainly used for drying process and only to a smaller degree for the product movement.

**NOZZLES FOR THE PARTICLE COATING:** Common spray gun is air-borne with a round spray pattern. Some equipment is fitted with a double air supply which is used for common atomizing air and extra microclimate air, which surrounds the spray pattern, preventing over wetting of the product and reducing spray drying effects.

**PUMP SYSTEM:** Peristaltic pumps fitted with silicon tubing are standard. Tubing can be selected in a wide range of internal diameters in order to keep the flow speed high and hence to prevent sedimentation. Therefore the use of tubing with small internal diameters recommended. Alternative pump systems include gear pumps and piston pumps.

**ROATING DISK GRANULATION:** These techniques have been extended to coating operations and combined with an expansion chamber to form the rotating disk granulator and coater fluid bed device. The basic design employs a rotating disk in the product container. The disk can be moved up or down to create a variable slit opening between the outer perimeter of the disk and the sidewall of the container. Air is drawn into the product container through the slit under negative pressure. This fluidizes the material along the circumferential surface of the product container. At the same time the disk rotates at varying speeds and moves the product by the centrifugal force to the outer portions where it is lifted by the fluidizing air stream into the expansion chamber. As the material decelerates, it descends to the center of the disk and repeats the same sequence.

### 1.2. ANTIDEPRESSANTS

An **antidepressant** is a psychiatric medication used to alleviate mood disorders, such as major depression and dysthymia and anxiety disorders such as social anxiety disorder, antidepressants are often used to treat other conditions, such as anxiety disorders, obsessive compulsive disorder, eating disorders, chronic pain, and some hormone-mediated disorders such as dysmenorrhea.

#### 1.2.1. Classification of Anti-Depressants

- Selective serotonin reuptake inhibitors
- Serotonin-nor epinephrine reuptake inhibitors
- Noradrenergic and specific serotonergic antidepressants
- Nor epinephrine (noradrenalin) reuptake inhibitors
Nor epinephrine-dopamine reuptake inhibitors
Selective serotonin reuptake enhancers
Nor epinephrine-dopamine disinhibitors
Tricyclic antidepressants
Monoamine oxidase inhibitor
Nicotine
Augmenter drugs

Selective serotonin reuptake inhibitors
The Selective serotonin reuptake inhibitors (SSRIs) are the class of antidepressants commonly used as the first line treatment for depression because they have a favorable side-effect profile and low toxicity. Depression can be treated by increasing the amount of available serotonin, a chemical used in the brain to transmit signals between neurons. SSRIs are said to work by preventing the reuptake of serotonin (also known as 5-hydroxytryptamine, or 5-HT) by the presynaptic neuron, thus maintaining higher levels of 5-HT in the synapse. This class of drugs includes:

- Citalopram
- Dapoxetine
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Paroxetine
- Sertraline

Serotonin-nor epinephrine reuptake inhibitors
Serotonin-nor epinephrine reuptake inhibitors (SNRIs) are a newer form of antidepressant that works on both nor epinephrine and 5-HT. They typically have similar side-effects to the SSRIs, though there may be a withdrawal syndrome on discontinuation that may necessitate dosage tapering. These include:

- Desvenlafaxine
- Duloxetine
- Milnacipran
- Venlafaxine

The mechanism of these types of antidepressants involves affecting the neurotransmitters that are used to communicate between brain cells; they interfere with re-uptake process of the specific chemical messengers. Re-uptake is the process by which a terminal button retrieves the...
molecules of transmitter substance that it has just released; terminates the effect of the transmitter substance on the receptors of the postsynaptic neuron.

There are some general side effects with the use of SNRIs which includes:

- Nausea
- Dry Mouth
- Dizziness
- Insomnia (numbness)
- Sleepiness
- Constipation
- Increased Blood Pressure

Noradrenergic and specific serotonergic antidepressants

Noradrenergic and specific serotonergic antidepressants (NaSSAs) form a newer class of antidepressants which purportedly work to increase nor epinephrine (noradrenaline) and serotonin neurotransmission by blocking presynaptic alpha-2 adrenergic receptors while at the same time blocking certain serotonin receptors. Side-effects may include drowsiness, increased appetite, and weight gain.

Examples include:

- Mianserin
- Mirtazapine

Nor epinephrine (nor adrenaline) reuptake inhibitors

Nor epinephrine (nor adrenaline) reuptake inhibitors (NRIs) act via nor epinephrine (also known as nor adrenaline). These include:

- Atomoxetine
- Mazindol
- Reboxetine
- Viloxazine

Nor epinephrine-dopamine reuptake inhibitors

Nor epinephrine-dopamine reuptake inhibitors inhibit the neuronal reuptake of dopamine and nor epinephrine (nor adrenaline). These include:
- Bupropion

Selective serotonin reuptake enhancers

- Tianeptine

Nor epinephrine-dopamine disinhibitors
Nor epinephrine-dopamine disinhibitors (NDDIs) act by antagonizing the serotonin $\text{5HT}_2C$ receptor, which normally acts to inhibit nor epinephrine and dopamine release, thereby promoting outflow of these neurotransmitters.

- Agomelatine

Tricyclic antidepressants
Tricyclic antidepressants are the second oldest class of antidepressant drugs. Tricyclics block the reuptake of certain neurotransmitters such as nor epinephrine (nor adrenaline) and serotonin. They are used less commonly now due to the development of more selective and safer drugs.

Side-effects include increased heart rate, drowsiness, dry mouth, constipation, urinary retention, blurred vision, dizziness, confusion, and sexual dysfunction.

Tertiary amine Tricyclic antidepressants:

- Amitriptyline
- Clomipramine
- Doxepin
- Imipramine
- Trimipramine

Secondary amine Tricyclic antidepressants

- Desipramine
- Nortriptyline
- Protriptyline

Monoamine oxidase inhibitor
Irreversible monoamine oxidase inhibitors (MAOIs) may be used if other antidepressant medications are ineffective. MAOIs work by blocking the enzyme monoamine oxidase, which breaks down the neurotransmitters dopamine, serotonin, and nor epinephrine (nor adrenaline). The MAOI group of medicines include:

- Isocarboxazid
- Moclobemide
- Phenelzine
- Selegiline
- Tranylcypromine

**Nicotine**

Nicotine is believed to act as an anti-depressant via it stimulating the release of Dopamine and nor epinephrine; additionally nicotine is believed to exert an antidepressant effect due to the desensitization of nicotinic receptors which occurs as a result of tolerance. Varenicline, a nicotinic receptor acting drug used to wean people off of nicotine dependence has also demonstrated antidepressant properties.

**Augmenter drugs**

Psycho stimulants, such as amphetamine, methylphenidate or Modafinil are sometimes added to an antidepressant regimen. Modafinil is unique in its effect on sleep: it increases alertness and reduces drowsiness while the patient is active, but does not inhibit normal sleep. Stimulants are known to trigger manic episodes in people suffering from bipolar disorder.

**Lithium**

It remains the standard treatment for bipolar disorder and is often used in conjunction with other medications, depending on whether mania or depression is being treated. Lithium's potential side-effects include thirst, tremors, light-headedness, nausea, and diarrhea.

1.2. **IMMEDIATE RELEASE DRUG DELIVERY SYSTEM**: 

In many cases immediate onset of action is required than conventional therapy. To overcome these drawbacks, immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms. There are novel types of dosage forms that act very quickly after administration. The development of immediate release therapy also provides an opportunity for a line extension in the marketplace.

**DEFINITION**
The term “immediate release” pharmaceutical formulation includes any formulation in which
the rate of release of drug from the formulation and/or the absorption of drug, is neither
appreciably, nor intentionally, retarded by galenic manipulations.

In this context, the term “release” includes the provision (or presentation)
of drug from the formulation to the gastrointestinal tract, to body tissues and/or into systemic
circulation.

1.3.1. DIFFICULTIES WITH EXISTING ORAL DOSAGE FORM

- Patient may suffer from tremors therefore they have difficulty to take powder and liquids. In dysphasia physical obstacles and adherence to an esophagus may cause gastrointestinal ulceration.
- Swallowing of solid dosage forms like tablet and capsules and produce difficulty for young adult of incomplete development of muscular and nervous system and elderly patients suffer from dysphasia.
- Liquid medicaments (suspension and emulsion) are packed in multi dose container; therefore achievement of uniformity in the content of each dose may be difficult.
- Buccal and sublingual formation may cause irritation to oral mucosa, so patients refused to use such medications.
- Cost of products is main factor as parenteral formulations are most costly and discomfort.

1.3.2. DESIRED CRITERIA FOR IMMEDIATE RELEASE DRUG DELIVERY SYSTEM

Immediate release dosage form should have the character like

- In the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.
- In the case of liquid dosage form it should be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- It should not leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensivity to environmental condition as humidity and temperature.
- Be manufactured using conventional processing and packaging equipment at low cost.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.

Advantages of Immediate Release Drug Delivery System⁹:
• Improved compliance/added convenience
• Improved stability
• Suitable for controlled/sustained release actives
• Allows high drug loading.
• Ability to provide advantages of liquid medication in the form of solid preparation.
• Adaptable and amenable to existing processing and packaging machinery
• Cost-effective

1.3.3. EXCIPIENTS used in Immediate Release Drug Delivery System

Excipients balance the properties of the actives in immediate release dosage forms. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

BULKING MATERIALS:

Bulking materials are significant in the formulation of fast-melting tablets. The material contributes functions of a diluents, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition.

The bulking agents generally used are like
• mannitol,
• lactitol,
• DCL (direct compressible lactose)
• starch hydrolystate etc

EMULSIFYING AGENTS:

Emulsifying agents are important excipients for formulating immediate release formulations as they aid in rapid disintegration and drug release. They stabilize the immiscible blends and enhancing bioavailability. The emulsifiers generally used are
• alkyl sulfates,
• propylene glycol esters,
• lecithin,
• sucrose esters etc
LUBRICANTS:

Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

FLAVOURS AND SWEETENERS:

Flavors and taste-masking agents make the products more palatable and pleasing for patients, overcomes bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavors can be used to improve the organoleptic characteristics. The sweeteners generally used are
- sugar,
- dextrose
- fructose,
- sodium saccharin
- Sucralose.

SUPER DISINTEGRANTS: 10,11
A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment.

ADVANTAGES:

- Effective in lower concentrations
- Less effect on compressibility and flow ability
- More effective intragranularly

Some Super Disintegrants are:
- Sodium Starch Glycolate
- Cross-linked Povidone (Crospovidone)
- Low-substituted Hydroxy Propyl cellulose,
- Cross linked carboxy methyl cellulose sodium (Croscarmellose sodium)
- Gas producing disintegrants
1.3.4. POTENTIAL CANDIDATE FOR IMMEDIATE RELEASE ORAL DOSAGE FORM

**Analgesics and Anti-inflammatory Agents**: Aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofen calcium, flurbiprofen, ibuprofen etc

**Anthelmintics**: Albendazole, bephenium, hydroxynaphthoate, cambendazole, Dichlorophen, Ivermectin, Mebendazole etc

**Anti-Arrhythmic Agents**: Amiodarone HCl, Disopyramide, Flecainide acetate, Quinidinesulfate etc

**Anti-bacterial Agents**: Benethamine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, Cloxacillin etc

**Anti-coagulants**: Dicoumarol, Dipyridamole, Nicoumalone, Phenindione etc

**Anti-depressants**: Amoxapine, ciclazindol, Escitalopram Oxalate, maprotiline HCl, mianserin HCl, nortriptyline HCl, trimipramine maleate etc

**Anti-diabetics**: Acetohexamide, Chlorpropamide, Glibenclamide, Gliclazide, Glipizide, Tolbutamide etc

**Anti-epileptics**: Carbamazepine, clonazepam, methsuximide, phenacemide, phenytoin, valproic acid etc

**Anti-fungal Agents**: Amphotericin, butoconazolene, clotrimazole, fluconazole, griseofulvin, ketoconazole etc

**Anti-hypertensive Agents**: Amlodipine, carvedilol, darodipine, Diltiazem HCl, isradipine, monoxide, nimodipine, reserpine etc

**Anti-malarial**: Amodiaquine, chloroquine, chlorproguanil HCl, mefloquine HCl, pyrimethamine, quinine sulphate etc

**Anti-muscarinic Agents**: Atropine, benzhexol HCl, biperiden, ethopropazine HCl, hyoscine butyl bromide, hyoscyamine, tropicamide etc
Anti-neoplastic Agents and Immunosuppressants: Aazathioprine, busulphan, chlorambucil, cyclosporine, methotrexate, procarbazine HCl etc

Anti Protozoal Agents: Benznidazole, clioquinol, decoquinate, diloxanidefuroate, dinitolmide etc

Anti-thyroid Agents: Carbimazole, propylthiouracil.

Anxiolytic, Sedatives, Hypnotics and Narcoleptics: Alprazolam, amylobarbitone, barbitone, bentazepam, bromazepam, clozapine, diazepam etc

Cardiac Inotropic Agents: Amrinone, digitoxin, digoxin, enoximone, lanatoside C etc

Corticosteroids: Beclomethasone, betamethasone, budesonide, cortisone acetate, dexamethasone, fluticasone propionate, prednisolone etc

Diuretics: Acetazolamide, amiloride, bendrofluazide, bumetanide, chlorothiazide, chlorthalidone, ethacrynic acid, frusemide, metolazone, spironolactone, triamterene.

Enzymes: All the enzymes.

Anti Parkinsonian Agents: Bromocriptinemesylate, lysuride Maleate etc

Gastro-intestinal Agents: Bisacodyl, cimetidine, Domperidone, famotidine, loperamide, Omeperazole, ondansetron HCl, Ranitidine HCl etc

Histamine H1-Receptor Antagonists: Acrivastine, astemizole, cinnarizine, cyclizine, loratadine, meclozine HCl etc

Lipid Regulating Agents: Bezafibrate, clofibrate, fenofibrate, gemfibrozil, probucol.

Local Anesthetics: Lidocaine

Nero muscular Agents: Pyridostigmine.

Nitrates and other Anti anginal Agents: Amyl nitrate, glyceryltrinitrate, isosorbidedinitrate, isosorbide, mononitrate etc

Nutritional Agents: Betacarotene, vitamin A, vitamin B2, vitamin D, vitamin E, vitamin K etc
Analgesics: codeine, dextropropoxyphene, diamorphine, dihydrocodeine, morphine, meptazinol, nalbuphine, pentazocine etc

Oral Vaccines: Vaccines designed to prevent or reduce the symptoms of diseases of which the following is a representative Influenza, Tuberculosis, Meningitis, Hepatitis, Polio, Tetanus, Diphtheria, Malaria, Cholera, Herpes, Typhoid, HIV, AIDS, Measles and auto-immune Disease conditions affecting companion and farm animals etc.

Proteins, Peptides and Recombinant drugs: Insulin, glucagon, growth hormone (somatotropin), interferons, LHRH, GHRH, secretin, bradykin antagonist, vasopressin and factor VIII, G-CSF (granulocyte-colony stimulating factor), EPO (erythropoietin) etc

Sex Hormones: Clo miphenecitrate, danazol, methyl testosterone, norethisterone, norgestrel, oestradiol, testosterone etc

Spermicidal: Nonoxynol etc

Stimulants: Amphetamine, dexamphetamine, dexfenfluramine etc

2. NEED FOR THE STUDY

Multiparticulate dosage forms are receiving an immense attention as alternative drug delivery system for oral drug delivery even though single unit dosage forms have been widely used for decade. It was sensed that some of the formulating and clinical problems (free flowing property, dose dumping, dysphasia, etc.) comes along with the single dose formulations. To overcome the above problems, Multiple unit dosage forms (MUDFs), are formulated as granules, pellets, or mini tablets. The concept of this multiple unit dosage forms answers many formulating problems and is a common strategy to control the release of drug as showing the reproducible release profiles when compared to SUDFs.

Pellets are MUDFs which are described to be produced systematically, as geometrically defined agglomerate obtained from diverse starting materials using different processing conditions. They are free-flowing, spherical or semi-spherical solid units with a size range of about 0.5 mm to 1.5 mm and that are intended mostly for oral administration.

Pellets were selected due to the following features.
- Improved aesthetic appearance of products.
- Coating of drug pellets with different polymers to achieve controlled release rate of drugs.
- For immediate release products larger surface area of pellets enables better distribution, dissolution and absorption.
- Chemically incompatible products can be formulated into pellets and delivered in a single dosage form by encapsulating them.
- This technique is used to avoid powder dusting in chemical industries.
- Pellets ensure improved flow properties and flexibility in formulation development and manufacture.

Escitalopram is the highly selective serotonin reuptake inhibitor (SSRI) used for the treatment of adults and children over 12 years of age with major depressive disorder, generalized anxiety disorder (GAD), Obsessive Compulsive Disorder (OCD)\(^\text{12}\). Escitalopram is selected as a model drug due to following reasons:

- It is mainly used for the treatment of several diseases including depression, GAD and OCD.
- Escitalopram is also applied for the treatment of social anxiety disorder (social phobia), depression associated with mood disorders and used on occasion in the treatment of body dysmorphic disorder and anxiety\(^\text{13}\).
- It represents an appropriate and effective therapeutic option for patients with a wide range of depression symptoms and is popularly prescribed.
- It is having longer biological half-life which varies from 27 to 37 hr, can be used as an immediate release product.

3. OBJECTIVES
The rationale of this study is to design and characterize an immediate release pellets containing Escitalopram, which can be used effectively in the treatment of depression etc. In the present research project, we have attempted to develop an immediate release pellets by using pan coating method.

3.1. Plan of Work:

1. Literature survey
2. Selection of drug and polymer
3. Procurement of drug and polymer
4. Experimental work
5. Preformulation study
6. Identification of drug
   - Organoleptic Properties
   - Solubility Study
   - Determination of Melting Point
   - FTIR
   - UV Spectrophotometry Study
   - Assay of Escitalopram Oxalate.
7. Formulation of Pellets
   - Pan coating method
8. Evaluation of Escitalopram Oxalate Pellets
   - Appearance
   - FTIR
   - Friability test
   - Disintegration time
• Moisture content
• Loss on Drying
• *In vitro* Dissolution Studies.
• Stability Study

9. Results and discussion

10. Summary and Conclusion

11. Future prospectus


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4. DRUG AND EXCIPIENTS PROFILE

4.1. ESCITALOPRAM OXALATE: 7,14,15

Escitalopram Oxalate, a structurally novel antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. Escitalopram is the (S)-stereoisomer (enantiomer) of the drug Citalopram. It is designed as (S)-1-[3-(dimethyl amino) Propyl]-1-(4-fluoro phenyl )-1,3- dihydroisobenzofuran-5-carbonitrile.and has the empirical formula **C₂₀H₂₁FN₂O**.

Table 3. Details of drug Escitalopram Oxalate

<table>
<thead>
<tr>
<th>Chemical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structure of Escitalopram Oxalate" /></td>
</tr>
</tbody>
</table>
**Clinical Pharmacology:**

Escitalopram is the highly selective serotonin reuptake inhibitor (SSRI) used for the treatment of adults and children over 12 years of age with major depressive disorder, generalized anxiety disorder (GAD), Obsessive Compulsive Disorder (OCD). It is used to treat the depression associated with mood disorders and used on occasion in the treatment of body dysmorphic disorder and anxiety.\(^\text{16}\)

**MECHANISM OF ACTION\(^\text{17}\):**

SSRIs including Escitalopram Oxalate work by affecting neurotransmitters in the brain, the chemical messengers that nerves use to communicate with one another. Neurotransmitters are
made and released by nerves and then travel to other nearby nerves where they attach to receptors on the nerves. Some neurotransmitters that are released do not bind to receptors and are taken up by the nerves that produced them. This is referred to as "reuptake." Many experts believe that an imbalance of neurotransmitters is the cause of depression. Escitalopram prevents the reuptake of one neurotransmitter, serotonin, by nerves, an action which results in more serotonin in the brain to attach to receptors. It is a highly selective SSRI with minimal effects on nor epinephrine and dopamine neuronal reuptake.

**PHARMACOKINETICS**:  

Table 4: Pharmacokinetics of Escitalopram Oxalate.

| Absorption | Following oral administration, Escitalopram Oxalate is rapidly absorbed and reaches maximum plasma concentrations in approximately 3-4 hrs after either single or multiple dose administration. The absorption of Escitalopram is not affected by food. The absolute bioavailability of Citalopram is about 80% relative to an intravenous dose. |
| Distribution | Widely distributed throughout tissues, with an apparent volume of distribution during the terminal phase after oral administration (V (z)/F) of about 1100L. |
| Metabolism | Mainly hepatic. Escitalopram undergoes N-demethylation to S-demethylcitalopram (S-DCT) and S-didemethylcitalopram (S-DDCT). CYP3A4 and CYP2C19 are the enzymes responsible for this N-demethylation reaction. |
| Excretion | Following oral administration, 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). |
| Adverse effects | Constipation, decreased sexual desire or ability; diarrhea, coma, dizziness, drowsiness, dry mouth, vomiting, nausea, headache, light-headedness when you stand or sit up, loss of appetite, Itching, difficulty in breathing. |
| Interaction | Co-administration of Escitalopram 20mg following steady-state administration of cimetidine or Omeperazole led to a 72% and 51% increase, |
respectively.

- Escitalopram should not be combined with drugs in the monoamine oxidase (MAO) inhibitor class of antidepressants such as isocarboxazid, phenelzine, tranylcypromine, Selegiline and procarbazine.
- Escitalopram has negligible inhibitory effects on CYP isoenzymes and P-glycoprotein, suggesting that drug is unlikely to cause clinically significant drug-drug interactions.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Half life</strong></td>
<td>Elimination half-life of 27-32hrs</td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td>Moderate (approximately 56%) bound to plasma protein.</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>80%</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>Store at Room temperature of 15-30°C</td>
</tr>
</tbody>
</table>

**PHARMACO DYNAMICS**

Escitalopram Oxalate has no significant affinity for adrenergic (alpha1, alpha2, beta), cholinergic, GABA, dopaminergic, histaminergic, serotoninergic (5HT₁A, 5HT₁B, 5HT₂), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anti cholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of Escitalopram was found to down regulate neither brain nor epinephrine receptors, as has been observed with other drugs effective in the treatment of major depressive disorder. Escitalopram does not inhibit monoamine oxidase.

**4.2. CROSCARMELLOSE SODIUM**
Figure 2. Chemical structure of Croscarmellose Sodium\(^{19}\)

**Synonyms:** Ac-Di-Sol, Explocel, Solutab.

**Chemical Name:** Cellulose, carboxy methyl ether

**Chemical Formula:** Croscarmellose sodium is a cross linked Polymer of Carboxy methyl cellulose sodium and its chemical formula is \(\text{C}_{12}\text{H}_{10}\text{Ca}_{3}\text{O}_{14} \cdot 4\text{H}_{2}\text{O}\)

**Molecular Weight:** 570.49gms

**Functional Category:** Tablet and capsule disintegrant.

**Applications in Pharmaceutical Formulation or Technology:**
- Increases dissolution rate, increase the pellet micro pore volume
- It is used in oral Pharmaceutical formulations as a disintegrant for capsules, tablets and granules.
- Concentrations up to 5% w/w may be used as a tablet disintegrant.

**Description:** Odourless, white or greyish-white powder.

**Melting point:** 25°C

**\(\text{pH}\):** 6.0-8.0

**Solubility:** Soluble in water, although Croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. Practically it is insoluble in acetone and ethanol.

**Stability and Storage Conditions:** It is a stable though hygroscopic material. It should be stored in a well-closed container in a cool and dry place.

**Incompatibilities:** Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as Aluminium, mercury and zinc.

**Safety:** It is mainly used as a Disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and non-irritant material.

### 4.3. CROSPOVIDONE
Figure 3. Chemical structure of Crospovidone

**Synonyms:** Polyvinyl Polypyrrolidone, Crospolividone, E1202

**Chemical Name:** Poly [1-(2-oxo-1-pyrrolidinyl) ethylene] 1-Ethenyl-2-pyrrolidone homopolymer1-Vinyl-2-pyrrolidinon-Polymere Crospovidone

**Molecular formula:** \((\text{C}_6\text{H}_9\text{NO})_n\)

**Molecular mass:** 2.500 - 2.5000.000 g·mol\(^{-1}\)

**Functional Category:** Tablet and Capsule disintegrant.

**Applications in Pharmaceutical Formulation:**

- The cross linked form of PVP is used as a disintegrant in pharmaceutical tablets and capsules.
- It is used as a fining to extract impurities.

**Description:** White, free flowing, compressible powder. A synthetic homo polymer of cross-linked N-vinyl-2-pyrrolidone.

**Solubility:** Completely insoluble in water, acids, alkalis, and all organic solvents. Hygroscopic, swells rapidly in water. Rapidly disperses in water, but does not gel even after prolonged exposure.

**Melting point:** 150 - 180 °C (glass temperature)

**pH:** 5.0-8.0 (1%w/v aqueous slurry)

**COMPATIBILITY:** Chemically inert. Has a high adsorptive capacity, forms reversible physical complexes with many molecules without the formation of covalent chemical bonds.

**STORAGE AND HANDLING:**

Crospovidone products have excellent stability when stored in their original container with a routine re-test period of 36 months. It is hygroscopic therefore suitable precautions should be taken to avoid excessive exposure to moisture. Crospovidone does not present a human or environmental health risk in the form in which it is supplied. Sensible precautions should be taken to avoid inhalation.
4.4. SODIUM STARCH GLYCOLATE

![Chemical structure of Sodium Starch Glycolate](image)

**Figure 4. Chemical structure of Sodium Starch Glycolate**

**Synonyms:** Carboxy Methyl starch, Explotab, Primojel

**Chemical Name:** Sodium carboxy methyl starch[9063-38-1]

**Molecular formula:** $C_2H_4O_3xNax$

**Molecular weight:** 500000-1000000

**Functional Category:** Disintegrant, Dissolution Aid, Suspending Agent.

**Applications in Pharmaceutical Formulation:**

- Increases dissolution rate, increase the pellet micro pore volume
- Tablets and pellets prepared with sodium starch glycolate show good stability.
- Sodium starch glycolate is widely used in oral pharmaceuticals as a dissolution aid for tablets, capsules and pellets.
- Absorbs water rapidly, resulting in swelling which leads to rapid disintegration of tablets and granules.

**Description:** Sodium salt of Carboxymethyl ether of starch. White to off-white, tasteless, odorless, relatively free flowing powder.

**pH:** 5.5-7.5

**Melting point:** 338°C

**Solubility:** Practically insoluble in water and not soluble in organic solvents.

**Stability and storage conditions:** Sodium starch glycolate is stable and should be stored in a well closed container to protect it from wide variations in humidity and temperature that may cause caking. The physical properties remain unchanged for up to 4 years if stored at moderate...
temperatures and humidity.

4.5. Hydroxy Propyl methylcellulose

Figure 5. Chemical structure of Hydroxy Propyl methylcellulose\textsuperscript{19,20,21}

Synonyms: HPMC, Methocel, Benecel MHPC, Methyl hydroxyl Propyl cellulose, Methylcellulose propylene glycol ether, Metolose.

Chemical Name and CAS Registry Number: Cellulose Hydroxypropyl methyl ether[9004-65-3]

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

Physicochemical Properties:
Description: White to slightly off white powder, free flowing powder

Particle size: Minimum 95% through a #40 US standard sieve

pH (1% content): 5.5-8

Solubility: HPMC K100M is a medium viscosity polymer which is soluble in water.

HPMC is available in 4 different chemistries (E, F, J, and K series) based on the varying degrees of hydroxyl Propyl and methyl substitutions. The K series is premium series meaning it has the fastest hydration rate. The K100M polymer thus has fast hydration, has a viscosity of 100,000 cps and is termed medium viscosity as per the “M” designation. HPMC K100M is a hypromellose 2208 which meets the requirements of the USP and European Pharmacopoeia and has been certified kosher.

Viscosity (dynamic): A wide range of viscosity types are commercially available. Aqueous
solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions. See table 5.

<table>
<thead>
<tr>
<th>Methocel product</th>
<th>USP 28 designation</th>
<th>Nominal viscosity (mPas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methocel K100 Premium LVEP</td>
<td>2208</td>
<td>100</td>
</tr>
<tr>
<td>Methocel K4 Premium</td>
<td>2208</td>
<td>4000</td>
</tr>
<tr>
<td>Methocel K15 Premium</td>
<td>2208</td>
<td>15000</td>
</tr>
<tr>
<td>Methocel K100MPremium</td>
<td>2208</td>
<td>100000</td>
</tr>
<tr>
<td>Methocel E4M Premium</td>
<td>2910</td>
<td>4000</td>
</tr>
<tr>
<td>Methocel F50Premium</td>
<td>2906</td>
<td>50</td>
</tr>
<tr>
<td>Methocel E10MPremium</td>
<td>2906</td>
<td>10000</td>
</tr>
<tr>
<td>Methocel E3 Premium</td>
<td>2906</td>
<td>3</td>
</tr>
<tr>
<td>Methocel E5 Premium</td>
<td>2906</td>
<td>5</td>
</tr>
<tr>
<td>Methocel E6 Premium</td>
<td>2906</td>
<td>6</td>
</tr>
<tr>
<td>Methocel E15 Premium</td>
<td>2906</td>
<td>15</td>
</tr>
<tr>
<td>Methocel K4 E50Premium</td>
<td>2906</td>
<td>50</td>
</tr>
<tr>
<td>Methocel 60SH</td>
<td>2910</td>
<td>50, 4000, 10000</td>
</tr>
<tr>
<td>Methocel 65SH</td>
<td>2906</td>
<td>50, 400, 1500, 4000</td>
</tr>
</tbody>
</table>
Stability and storage: Hypromellose powder is stable material, although it is hygroscopic after drying. Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling. The gel point is 50-90°C, depending upon the grade and concentration of material.

Applications in Pharmaceutical Formulation:

- Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.
- In oral products, Hypromellose is primarily used as a tablet binder, in film coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation process.
- Depending upon the viscosity grade, concentrations of 2-20% w/w are used for film-forming solutions to film-coat tablets. Examples of film-coating materials that are commercially available include Any Coat C, spectracel, and Pharma coat.
- Hypromellose is also used as suspending agent in topical formulations. Compared with methyl cellulose, Hypromellose produces aqueous solutions of greater clarity, therefore preferred in formulations for ophthalmic use.
- Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.
- In addition, it is also widely used in cosmetics and food products.
5. LITERATURE REVIEW

Vishal Guptha et al\textsuperscript{22}, (2011) designed an oral controlled release matrix pellets of water insoluble drug Olanzapine using blend of sodium alginate, glyceryl palmito-stearate as matrix polymers. MCC as spherizer enhancer and SLS as pore forming agent. OZ formulations were developed by the Pellatization technique by drug loaded pellets and characterized with regard to the drug content, size distribution, Scanning Electron Microscopy (SEM), Differential Scanning Colorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR) and X-ray Diffraction study (XRD). The drug content was in the range of 93.34\textendash 98.12 %. The mean particle size of the drug loaded pellets was in the range 1024 to 1087\textmu m. The compatibility between drug and polymers in the drug loaded pellets were confirmed by DSC and FTIR studies. Stability studies indicated that pellets are stable. Drug release was controlled for more than 24 hrs and mechanism of the drug release followed by Fickian diffusion. It may be concluded that F5 is an ideal formulation for once a day administration.

Rakhee Surana et al\textsuperscript{23}, (2011) formulated phenyl Propanolamine Hydrochloride sustained release pellets and evaluated the impact of different solvent composition of polymer solution which is used in this formulation. Eight batches of pellets were fabricated by solution/suspension layering technique. The impact of different solvent composition on polymer solution used for sustained release pellets was compared from in vitro dissolution studies. The pellets were evaluated for shape, size analysis, density, content uniformity. The results were obtained satisfactory.

Subhabrota et al\textsuperscript{24}, (2011) designed Multi particulate formulation compressing colon specific pellets of Ketoprofen by powder layering technology. to evaluate the effect of 59\% methoxylated pectin and 45 cps ethyl cellulose on coating label These are successfully evaluated by gamma scintigraphy method to evaluate the transit behavior of drug loaded pellets and compared with uncoated pellets to evaluate its specific release. The transit behavior and scintigraphy image clearly indicates that the formulation can delay the drug release prior to colon. Formulation containing pectin and ethyl cellulose with suitable coating label may be suitable as a coating.
formulation for colon delivery of ketoprofen and can be successfully evaluated by gamma scintigraphy method.

**Raveendra Pai et al** (2011) studied a new approach of compression of matrix pellets into disintegrating tablet to overcome the rupture of polymer coat during compression of reservoir pellets. Sertaline hydrochloride was used as model drug. Sodium alginate (kelton LV CR) was used in levels of 10, 20, and 30% w/w for preparing matrix pellets by Spheronization method. In vitro drug release from alginate containing pellets was complete within 4hrs. The drug release from the uncompressed pellet and compressed tablet was identical, as each pellet was behaving like a monolithic mini matrix system. Scanning electron micrographs of the pellets obtained after completion the dissolution test were found to be left with empty sac like structure releasing the drug indicating anomalous type drug release.

**Xing tang et al** (2011) prepared immediate release pellets with an improved stability in gastric fluid using Omeperazole as a model drug. The immediate-release Omeperazole core beads were prepared by extrusion-Spheronization combined with previous milling. Powder coating technique was employed to prepare powder coated pellets using sodium bicarbonate. The results showed that, by raising the gastric fluid pH immediately and previously, the sodium bicarbonate coated on PCP formed a built-in buffer to protect the subsequently dissolved Omeperazole from acid degradation. The apparent rate of absorption of Omeperazole from PCP ($t_{max} = 42$ min) and PMP ($t_{max} = 41$ min) was markedly faster than that from enteric-coated capsules ($t_{max} = 110$ min). Milling with bead mill indeed enhanced the dissolution rate of Omeperazole. The PCP not only exhibited rapid absorption and identical bioavailability with commercial enteric-coated capsules but also showed a much more stable absorption compared with PMP. The pharmaceutical potential of Omeperazole is further improved.

**Amit Bhat et al** (2011) The objective of this study was to develop and evaluate a pulsatile drug delivery system based on impermeable capsule body filled with theophylline pellets and sealed with erodible polymer plug placed in the opening of capsule body. Erodible plugs were prepared by direct compression followed by placing the pellets in the capsule by congealing directly a melt able plug material directly within the capsule opening. The theophylline pellets were prepared in four batches with PVP K30, water as binder solution and evaluated for the
surface morphology, particle size, drug content and in-vitro release profile and from the obtained results; one best formulation was selected for further fabrication of pulsatile capsule. Different hydrogel polymers were used as plugs, to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. The lag time prior to pulsatile drug release correlated well with erosion properties of the plugs and, besides the composition of the plug, could be controlled by the thickness of the plug. Programmable pulsatile release has been achieved from a capsule device over a 2–36 hour period, consistent with the requirement of chronopharmaceutical drug delivery.

**Farrukh zeeshan et al**28, (2010) developed a novel modified-release pellet based tablet system with different release profiles. Lortadine Hydrochloride and Pseudoephedrine Hydrochloride were used as model drugs by using extrusion–Spheronization method. The pellets of pseudoephedrine hydrochloride were coated to prolong the drug release up to 12 h. Both immediate and prolonged-release pellets were filled into hard gelatin capsule and also compressed into tablets using inert tableting granules of microcrystalline cellulose CeolusKG-801. The in vitro drug dissolution study conducted using high-performance liquid chromatography method showed that both multiple-unit capsules and multiple-unit tablets released loratadine completely within a time period of 2 h, whereas the immediate-release portion of pseudoephedrine hydrochloride was liberated completely within the first 10 min. On the other hand, the release of pseudoephedrine hydrochloride from the prolonged release coated pellets was prolonged up to 12 hr and followed zero-order release kinetic. The pellets were subjected for various evaluation parameters like particle size, flow properties, bulk density, friability, hardness and in vitro drug release studies.

**Golam kibria et al**29, (2010) studied the influence of the formulation and operating conditions on pellet preparation by the pan technique of Domperidone Maleate. Pellets were prepared by layering of powdered drug on sugar-based cores. Scanning electron microscopy was employed to image the surface morphology of the prepared pellets. Drug loading efficiency, % yield, size, and shape uniformity, drug content and dissolution study were performed by HPLC and UV-Visible method. About 50% and 80% drug was released within 7.72 m and 13.66 m respectively in 0.1N HCl media (pH 1.2). This study also showed the good performance of the conventional coating
pan system in obtaining instant release Domperidone pellets prepared by the powder layering technique.

Rahman et al\textsuperscript{30}. (2008) The Multiparticulate formulation of Sodium Para aminosalicylate for oral administration was developed by Extrusion and Spherization technique microcrystalline cellulose was used as filler in conc. of 14.4% w/w. Pellets were coated by Eudragit L30D55 using fluidized bed processor. Different weight gain of acrylic polymer were applied on the pellets and evaluated for in vitro dissolution behavior in 0.1N HCL for 2 hours. And then media was charged to pH6.8 phosphate buffer. A 60% w/w coating level of Eudragit L30D55 has Produce the most acceptable result.3% seal coat of HPMC E5 was also applied in order to protect the drug from migration into the Eudragit coat and film coat was applied in order to prevent aggregation of pellets in dissolution media. Morphological characteristics of developed pellets were also investigated by scanning electron microscopy and found to be smooth and spherical. Developed system was found to be suitable for the delivery of Sodium Para aminosalicylate).

S.Eskandari et al\textsuperscript{31}. (2007) formulated an extended release pellets using powder layering technology or centrifugation (rotary fluid bed granulation).Indomethacin was used as modern drug. Layered nonpareil pellets composed of sugar, Avicel PH 101 and lactose were prepared using FREUND CF granulator and were treated by a binder solution (HPC-L) applied by spray gun. Drug content of pellets was determined by HPLC method. The results have shown that the increasing amount of Eudragit NE 30 D, Opadray and SDS in coating solution adjusts release of pellets. The dissolution profile achieved from pellets containing 500 g nonpareil, 400 g Indomethacin, 400 ml HPC 8%, 61g talc, 50 g Opadray\textsuperscript{®} and coating consisted of 37.5 g Eudragit NE 30 D,1.8 g SDS, 7.5 g Opadray\textsuperscript{®} have passed USP30 standards for Indomethacin release and was comparable with retard Indocid\textsuperscript{®}75 Capsule from MDS company.

WIPO PATENT\textsuperscript{32}. (2007) Lansoprazole is acid labile Benzimidazole derivative very effective for GERD, peptic ulcer, Lansoprazole having poor stability in the solid state it degrade in the presence of heat, moisture, light and having solution or suspension. Its stability deceases with decreasing pH. Sub coat the prepared pellets in order to avoid a reaction between the API and the outer acidic enteric coating. It shows degradation and prone towards discoloration of API. Avoid
anti tacking agent in the nucleus form. Salt form was used in the pellets of Lansoprazole e.g. Calcium, Magnesium, Hydroxide, Sodium, Potassium, Citrate. In above preparation SCMC, Povidone K30, used as binder and Polymethacrylic acid used for gastric resistance, Triethyl Citrate used as plasticizer.

Nisar-Ur-Rahman et al. (2005) A release controlling film coat around Diltiazem pellets was developed with Eudragit NE40 and the effects of percent drug layering, pH and stirring speed of dissolution media on drug release were also evaluated. Diltiazem HCL aqueous solutions were applied onto inert pellets to produce drug pellets, which were subsequently coated with aqueous polymer dispersion using bottom spray Fluidized-bed coater. Coated pellets were cured at 370°C for 24 h. The release profile of coated pellets was found to be inversely proportional to the thickness of the polymer coat and desirable controlled release characteristics could be achieved by manipulating the coating levels. The percent drug layering onto inert pellets had no effect on the release rate of coated pellets. Moreover, Diltiazem HCL release was fairly independent of pH and stirring speed.

J. Balasubramaniam et al. In this preliminary study, Multiparticulate pellets containing Esomeprazole magnesium have been prepared using an Extrusion Spheronization process, employing Povidone and Crospovidone as non-traditional processing aids. Attempts have been made to prepare pellets of various sizes and ultimately investigate the levels of enteric coating that need to be applied in order to achieve a suitable delayed-release dissolution profile. While acceptable pellets, displaying appropriate drug delayed-release characteristics have been achieved, it is evident from this initial study that further formulation and processing refinements, with respect to the formation of the initial pellets, need to be made in order to create pellets with optimal sphericity characteristics and narrower particle size distributions.

Claudio et al. (2000) The goal of the present study was to evaluate the influence of the formulation and operating conditions on pellets preparation by pan technique application of powdered drug on sugar based cores. Inert cores were intermittently treated with micronized drug powder and adhesive solution. Drug layering by GS automated pan coating system. Core resulting in the production of pellets that can further coated by different polymers to obtain modified release formulations different procedures have been used to evaluate a series of
important parameters such as initial cores weight. Speed of powder application, speed type and position of the atomizers, atomization degree, temperature and air spray. At first covered with seal coating then followed by enteric coating.

Tanberk et al\textsuperscript{36}, (1997) In the production of Omeperazole pellets the inert core based on sacharose, starch, glucose. The inert core covered with the micronized and sieved active substance which is in a buffered dispersion being added within anionic surface active agent. In order to finally receive an enteric covering in a fluidized bed with HPMC Phthalate, Diethyl Phthalate, Acetone, Ethyl Alcohol, being afterwards dried to obtain water content of less than 1%. Then sieved, weighted and encapsulated in gelatin capsule. Inert core prepared by 65-85\% of Sacharose, 2-6\% of Glucose being sieved through 150 mesh & dispersing in a buffered aqueous dispersion at pH 7.1 with addition of anionic surface active agent.

J. G. HARDY et al\textsuperscript{37}, (1991) An enteric-coated, pellet formulation of naproxen has been evaluated in eight healthy subjects. Each volunteer was dosed with Sm-labelled, enteric-coated pellets on two occasions, once whilst fasted and once after breakfast. Gastrointestinal transit was followed using gamma scintigraphy and drug absorption compared with that from uncoated naproxen pellets dosed on a separate occasion. The pH in the stomach and intestines was monitored using radio telemetry capsules. Gastric emptying was delayed by dosing after breakfast, but small intestinal transit of the enteric-coated formulation was the same on both occasions. The highest pH recorded from the stomach was 4.0 and in all subjects the pH rose to at least 7.3 in the small intestine. The onset of drug absorption was fastest from the uncoated formulation and slowest from the coated pellets taken after breakfast. The total amount of drug absorbed was the same on all three occasions.
6. METHODOLOGY

6.1. PREFORMULATION STUDIES

Preformulation studies were carried out to standardize the estimation for Escitalopram oxalate and to investigate any possible drug polymer interaction. Drug polymer interaction was studied by carrying out Fourier transform infrared (FTIR) spectral studies.

6.1.1. Standardization of Escitalopram Oxalate.

Standard curves of Escitalopram were prepared in distilled water, 0.1N HCl, using UV Spectrophotometry method of estimation.

6.1.1.1. Preparation of primary stock solution

100 mg sample was dissolved in 100 ml of distilled water, 0.1N HCl to give a concentration of 1mg / mL.

6.1.1.2. Preparation of working standard

Standard solution of 1 mL volume was taken in a 10 mL volumetric flask and the volume was made up with distilled water, 0.1N HCl or phosphate buffer (pH 6.8) to obtain a concentration of 100 g / mL.

Different concentration of the drug ranging from 2 µg / mL to 12 µg / mL were prepared by taking suitable volumes of working standard solution in 100 mL volumetric flask and making up the 0.1N HCl. Absorbance’s of different dilutions were measured using UV spectrophotometer (Shimadzu 1800, Japan, UV-visible spectrophotometer) at 239.40 nm and were plotted against respective concentrations to obtain calibration curve.

6.1.2. FTIR Spectral studies
FTIR spectra of pure drugs and their physical mixtures (stored at 40 ± 2 °C /75% ± 5% RH for 2 months) were recorded. The samples were prepared by potassium bromide disc method and scanned for absorbance.

6.1.3. Micrometric properties of Escitalopram Oxalate

6.1.3.1. Determination of bulk density and tap density: An accurately weighted quantity of the powder (W) was carefully poured into the granulated cylinder and volume (V₀) was measured. Then the graduated cylinder was closed with lid set into the density determination apparatus (bulk density apparatus) the density apparatus was set for 100 taps. After that the volume (Vᵢ) was measured and continued the operation till the two consecutive reading were equal. The bulk density and the tapped density were calculated using the formulas.

\[
\text{Bulk Density} = \frac{W}{V₀}
\]

\[
\text{Tapped Density} = \frac{W}{Vᵢ}
\]

Where,

\(W\) - Weight of the powder.

\(V₀\) - Initial volume.

\(Vᵢ\) - Final volume.

6.1.3.2. Percentage compressibility index (Carr’s Index)

Based on the bulk density and tapped density, the % compressibility of the powder blend was computed using the compressibility index.

\[
\text{Compressibility Index} = 100 \times \left( \frac{\rho\text{tapped} - \rho\text{bulk}}{\rho\text{tapped}} \right)
\]
Table No 6: Range of Hausner’s ratio and compressibility index and their properties

<table>
<thead>
<tr>
<th>Compressibility index</th>
<th>Properties</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10</td>
<td>Excellent</td>
<td>1.00 -1.11</td>
</tr>
<tr>
<td>11-15</td>
<td>Good</td>
<td>1.12-1.18</td>
</tr>
<tr>
<td>16-20</td>
<td>Fair</td>
<td>1.19-1.25</td>
</tr>
<tr>
<td>21-25</td>
<td>Passable</td>
<td>1.26-1.34</td>
</tr>
<tr>
<td>26-31</td>
<td>Poor</td>
<td>1.35-1.45</td>
</tr>
<tr>
<td>32-37</td>
<td>Very poor</td>
<td>1.46-1.59</td>
</tr>
<tr>
<td>&gt;38</td>
<td>Very very poor</td>
<td>&gt;1.60</td>
</tr>
</tbody>
</table>

6.1.3.3. Hausner’s ratio:

It indicates the flow properties of the powder and measured by the ratio of Tapped density to bulk density.

**Hauser ratio = Tapped density /Bulk density**
6.1.3.4. Angle of repose (θ):

Angle of repose was performed using funnel method by keeping a funnel vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom was closed and 10 gm of powder was filled in the funnel. Then the funnel was opened to releases the powder on the paper to form a smooth conical heap. The radius of the heap (r) and the height of the heap (h) was measured. The \( \tan^{-1} \) of the height of the pile / radius of its base gave the angle of repose.

\[
\theta = \tan^{-1} \frac{2h}{r}
\]

Where:
- \( \theta \) = Angle of repose.
- \( h \) = Height of the particles pile.
- \( r \) = Distance from the center of the pile to the edge.

6.1.3.5. **Sieve Analysis**: The main aim of sieve analysis was to determine the different size of drug particles present. Series of standard sieve were stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed by sieve of decreasing pore size (large sieve number) towards the bottom.

Procedure - A series of sieves were arranged in the order of their decreasing pore diameter (increasing sieve number) i.e. sieve no. ASTM 40, 60, 80, 100 with 40 grams of drug were weighed accurately and transferred to sieve 40 which were kept on top. The sieves were shaken for about 5-10 minutes. Then the drug retained on each sieve were taken, Weighted separately and expressed in terms of percentage.

6.2. FORMULATION STUDIES

6.2.1. **Preparation of Escitalopram pellet formulations**

Accurately weighed lactose Pellets were coated with mixture solution of PVP (6%) and the drug. The coated pellets were dried. The above dried pellets were seal coated with HPMC E15 (1%) and were kept for drying. The above dried pellets were coated with different concentrations of
Super disintegrants like Crospovidone, Croscarmellose sodium, Sodium starch glycolate which are the rate defining factors

Immediate release pellets of Escitalopram were prepared by Pan coating method.

6.2.2. Manufacturing Process: 38, 39, 40

In suspension layered method pellets were prepared by 3 sequential coatings

- Drug coating
- Seal coating
- Final coating

- **Drug Coating:**
  - **Preparation of drug suspension:** Escitalopram was added to the mixture solution of methanol and dimethyl sulfoxide under continuous stirring (step 1)
  - PVP K30 (6%) was added to IPA using lab stirrer (step 2)
  - Step 2 preparations was added to step 1 preparation and stirred for 30 minutes. This preparation is called primary suspension
  - Lactose spheres #20/25 were loaded into conventional coating pan and were coated with primary suspension
  - Drug loaded pellets were collected (step 3)

- **Seal Coating:**
  - Preparation of barrier suspension: HPMC E15 (1%) was added to sufficient quantity methanol under continuous stirring to prepare barrier suspension
  - Coating of barrier suspension: Step 3 pellets were loaded into coating pan and were coated with above prepared barrier suspension.

- **Final Coating:**
The barrier coating pellets were divided into nine batches.
The divided pellets were coated with different super disintegrants like Croscarmellose sodium, Crospovidone and sodium starch glycolate with different concentrations like 2%, 4% and 6% respectively.

Table 7. Formulation for preparation of Escitalopram Oxalate pellets.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>FR1</th>
<th>FR2</th>
<th>FR3</th>
<th>FR4</th>
<th>FR5</th>
<th>FR6</th>
<th>FR7</th>
<th>FR8</th>
<th>FR9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>PVP K 30</td>
<td>06</td>
<td>06</td>
<td>06</td>
<td>06</td>
<td>06</td>
<td>06</td>
<td>06</td>
<td>06</td>
<td>06</td>
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<tr>
<td>Lactose pellets</td>
<td>168</td>
<td>164</td>
<td>160</td>
<td>168</td>
<td>164</td>
<td>160</td>
<td>168</td>
<td>164</td>
<td>160</td>
</tr>
<tr>
<td>HPMC E15</td>
<td>02</td>
<td>02</td>
<td>02</td>
<td>02</td>
<td>02</td>
<td>02</td>
<td>02</td>
<td>02</td>
<td>02</td>
</tr>
<tr>
<td>Croscarmellosesodium</td>
<td>04</td>
<td>08</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>04</td>
<td>08</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sodiumstarchglycolate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>04</td>
<td>08</td>
<td>12</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
</tr>
<tr>
<td>Methanol</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
<td>Q.S</td>
</tr>
<tr>
<td>Total</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

* Quantity in mg
6.3. EVALUATIONS

The pellets of every batch were evaluated for in-process and finished product quality control tests i.e. thickness, weight uniformity test, friability, drug content and in vitro drug release studies.

6.3.1. Evaluation tests for Escitalopram Oxalate Pellets:

Friability test

The friability was determined using friability test apparatus (Ketan, Koshish Industries, Bombay, India, Model No: SS153) and expressed in percentage (%). The drug loaded beads from each batch were weighed separately ($W_{\text{initial}}$) and placed in the friabilator, which was then operated for 10 min at 24 rpm. The pellets were reweighed ($W_{\text{final}}$) and the percentage friability was calculated for each batch by using the following formula.

$$F(\%) = \frac{(W_{\text{initial}}) - (W_{\text{final}})}{(W_{\text{initial}})} \times 100$$

Disintegration time

Accurately weighed 1 g pellets cores from each batch were placed in three 100 mL conical flasks containing 50mL of 0.1 mol/L hydrochloric acid (37±2OC). The flasks were rotated every 30 s. The experiment was continued until total disintegration of the granulated mass. The total disintegration time was determined at the moment when there were no particles bigger than 0.5 mm. Sieve Retch (Retsch, Hann, Germany) 0.5 mm mesh diameter was used.

Assay

1. Assay procedure of Standard Solution: Accurately Weighed Escitalopram Oxalate (68mg) was transferred into 100ml volumetric flask. The contents were ultra sonicated for 15min with 20ml of HPLC methanol and made up to the mark with same. The resulting solution was allowed to settle for about an hour. About 5.0ml of above solution was transferred into a 50ml volumetric flask. It was diluted with diluents and mixed thoroughly to calculate the percentage purity of drug.
2. Assay procedure of Test preparation: Twenty capsule contents were weighed accurately. The average weight was determined and was ground to a fine powder. A quantity equivalent to 20mg was transferred to a 100ml volumetric flask. The contents were ultra sonicated for 15min with 50ml of HPLC methanol and was made up to the mark with same. The resulting solution was allowed to settle for about an hour. The solution was filtered using 0.45μm membrane filter. The drug content per capsule (on an average weight basis) was calculated.

\[
\% \text{ Assay} = \frac{\text{Sample area} \times \text{Std. wt} \times \text{Avg. wt} \times \text{std. purity} \times \text{dilution factor}}{\text{Std. area} \times \text{Sample wt.} \times 100}
\]

6.3.2. In vitro drug release study of Escitalopram Oxalate pellets

In vitro release studies were carried out in the dissolution test apparatus USP XXIII Type II (paddle method). The tests were carried out in 900 ml of 0.1N HCl for 30min at 50 rpm at 37±0.5°C. 10 ml of the aliquot was withdrawn at different predetermined time intervals (5, 10, 15, 20, 30) and was filtered. The required dilutions were made with 0.1N HCl and the solution was analyzed for the drug content by UV spectrophotometer detecting at \( \lambda \) max 239.40 nm. The dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. From this, percentage drug release was calculated and this was plotted against function of time to study the pattern of drug release.

6.4. Accelerated stability studies of selected formulation

The stability studies were carried out of the most satisfactory formulation to assess the drug and formulation stability. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. Formulation was stored at various temperatures viz. 25 ±2°C, 60 ± 5% RH and at 30± 2 °C, 65± 5% RH as per ICH guidelines and various physicochemical parameter (appearance, percentage drug content and release profile) were monitored periodically for 2 months.

6.5. Scanning electron microscopy

Scanning electron microscope (SEM) was used to study the morphology of the prepared pellets as such without any coating around the pellets during analysis. The selected formulations were
chosen on the basis of results obtained from the disintegration studies and dissolution studies. SEM was performed using Hitachi (Model: S-3400 N, Japan) scanning electron microscope at 5 kV having different magnifications.

7. Results and Discussions

7.1. Preformulation Studies

Preformulation studies of drug were performed to characterize the API. The powder flow properties of API were studied. The results obtained are bulk density 0.42 mg/ml, tapped density was 0.50 mg/ml and Hausner’s ratio 1.19. Angle of repose of the drug was 23.26. The results showed that the compressibility of the API was 16 which indicate that the drug has fair flow properties. 69.4% of Escitalopram Oxalate powder has passed through #100 (NLT 65% should pass through 100 mesh).

- **Solubility:** Freely soluble in methanol.
- **Melting Point:** 192°C
- **Description:** White power

### 7.1.1. Determination of λ max of Escitalopram Oxalate

The λ max of Escitalopram Oxalate was estimated by carrying out UV scan between the wavelength 200 to 400 nm which gave a highest peak at 272 nm and the same was selected for Escitalopram.

### 7.1.2. Standard graph of Escitalopram Oxalate with 0.1N HCL

Standard curves of Escitalopram Oxalate were prepared in 0.1N HCl. Escitalopram Oxalate showed maximum absorbance in 0.1N HCL at 239.40 nm. The solution obeyed Beer-Lambert’s law for concentration range of 2 µg / mL to 12 µg / mL with regression coefficient of 0.999. Standard curve of Escitalopram prepared in 0.1N HCL is shown below in Table 8 and Figure 4.

### Table 8. Calibration data of Escitalopram Oxalate in 0.1N HCL

<table>
<thead>
<tr>
<th>Concentration(µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.199</td>
</tr>
<tr>
<td>4</td>
<td>0.34</td>
</tr>
<tr>
<td>6</td>
<td>0.486</td>
</tr>
</tbody>
</table>
7.2. Drugs Polymer Interaction Study by FTIR spectrophotometer

The spectra obtained from the physical mixtures showed all the principal peaks at or around the requisite wave numbers of pure drugs and individual polymers. IR spectrum for pure drug and physical mixture of drug- polymers were obtained and analyzed for principle peaks at 3181.72 cm\(^{-1}\) (alkynes C-H stretching), 1752 cm\(^{-1}\) (ketones C=O stretching), 1362.77 cm\(^{-1}\) (Aromatic ring C=C stretching), 1680 cm\(^{-1}\) (Amines N-H bending), 913 cm\(^{-1}\) (CH Deformation). Thus it may be concluded that there was no interaction between drug and polymers, the purity and integrity of drug was maintained in the physical mixture.

<table>
<thead>
<tr>
<th>Concentration (µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>0.626</td>
</tr>
<tr>
<td>10</td>
<td>0.769</td>
</tr>
<tr>
<td>12</td>
<td>0.89</td>
</tr>
</tbody>
</table>

**Figure 6. Standard Curve of Escitalopram Oxalate in 0.1N HCL**
Table 9. Standard band frequency of Escitalopram Oxalate.

<table>
<thead>
<tr>
<th>Wave number in cm(^{-1})</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>3181.72</td>
<td>C-H</td>
</tr>
<tr>
<td>1752</td>
<td>C=O</td>
</tr>
<tr>
<td>1362.77</td>
<td>C=C</td>
</tr>
<tr>
<td>1680</td>
<td>N-H</td>
</tr>
<tr>
<td>913</td>
<td>CH Deformation</td>
</tr>
</tbody>
</table>

The FTIR Spectra were shown in the Figures 7-20.

Figure 7. FTIR Spectrum of Escitalopram Oxalate
Figure 8. FTIR Spectrum of physical mixture Escitalopram Oxalate and Croscarmellose sodium

Figure 9. FTIR Spectrum of physical mixture Escitalopram Oxalate and Sodium Starch glycolate
Figure 10. FTIR Spectrum of physical mixture Escitalopram Oxalate and Crospovidone

Figure 11. FTIR Spectrum of physical mixture Escitalopram Oxalate and HPMCE15
Figure 12. FTIR Spectrum of physical mixture Escitalopram Oxalate and PVPK30
7.3. Micrometric properties of Escitalopram Oxalate pellet formulations

Table 10. Micrometric properties of Escitalopram Oxalate pellet formulations

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Bulk density (gm/cm²)</th>
<th>Tap density (gm/cm²)</th>
<th>Carr’s index (%)</th>
<th>Hausner’s ratio</th>
<th>Angle of repose (Ø)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FR1</td>
<td>0.6060</td>
<td>0.625</td>
<td>9.0909</td>
<td>1.1</td>
<td>25.61</td>
</tr>
<tr>
<td>FR2</td>
<td>0.625</td>
<td>0.66</td>
<td>5.2030</td>
<td>1.056</td>
<td>26</td>
</tr>
<tr>
<td>FR3</td>
<td>0.645</td>
<td>0.6890</td>
<td>6.386</td>
<td>0.936</td>
<td>25.34</td>
</tr>
<tr>
<td>FR4</td>
<td>0.595</td>
<td>0.645</td>
<td>7.751</td>
<td>1.084</td>
<td>25.73</td>
</tr>
<tr>
<td>FR5</td>
<td>0.602</td>
<td>0.604</td>
<td>0.331</td>
<td>1.003</td>
<td>27.55</td>
</tr>
<tr>
<td>FR6</td>
<td>0.573</td>
<td>0.595</td>
<td>3.7</td>
<td>1.038</td>
<td>29</td>
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<tr>
<td>FR7</td>
<td>0.595</td>
<td>0.67</td>
<td>10.74</td>
<td>1.12</td>
<td>31</td>
</tr>
<tr>
<td>FR8</td>
<td>0.612</td>
<td>0.66</td>
<td>7.3</td>
<td>1.07</td>
<td>28.66</td>
</tr>
<tr>
<td>FR9</td>
<td>0.582</td>
<td>0.596</td>
<td>2.35</td>
<td>1.02</td>
<td>29</td>
</tr>
</tbody>
</table>
7.4. EVALUATIONS

7.4.1. Physical properties of Escitalopram Oxalate pellet formulations.

Table 11: Physical properties of Escitalopram Oxalate pellet formulations.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FR1</th>
<th>FR2</th>
<th>FR3</th>
<th>FR4</th>
<th>FR5</th>
<th>FR6</th>
<th>FR7</th>
<th>FR8</th>
<th>FR9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friability [%]</td>
<td>0.21</td>
<td>0.25</td>
<td>0.32</td>
<td>0.24</td>
<td>0.21</td>
<td>0.37</td>
<td>0.25</td>
<td>0.25</td>
<td>0.31</td>
</tr>
<tr>
<td>Disintegration time [min]</td>
<td>2.8</td>
<td>2.1</td>
<td>2.4</td>
<td>2.6</td>
<td>2.4</td>
<td>2.3</td>
<td>3.3</td>
<td>2.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Moisture content [%]</td>
<td>1.87</td>
<td>1.9</td>
<td>1.80</td>
<td>1.88</td>
<td>1.86</td>
<td>1.82</td>
<td>1.84</td>
<td>1.85</td>
<td>1.87</td>
</tr>
<tr>
<td>Loss on drying [%]</td>
<td>0.9</td>
<td>0.8</td>
<td>0.8</td>
<td>0.9</td>
<td>0.7</td>
<td>0.7</td>
<td>0.9</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Assay [%]</td>
<td>99.05</td>
<td>99.3</td>
<td>98.6</td>
<td>98.85</td>
<td>99.2</td>
<td>98.65</td>
<td>99.05</td>
<td>99.65</td>
<td>99.75</td>
</tr>
</tbody>
</table>

7.5. Accelerated stability studies of selected formulation (FR 8)

The selected formulation was subjected for accelerated stability studies as per the ICH guidelines. There were no changes in appearances and percentage drug content of pellets stored at different temperature for drug remaining vs. time at 25 ±2ºC, 60 ± 5% RH and 30± 2 ºC, 65±5%RH. All the parameters were within the limit after 60 days.

7.6. Scanning electron microscope

Scanning electron micrographs suggested that pellets have a larger surface area, so they easily came into contact with the dissolution media and quick dissolution of the drug might also be enhanced. The burst release can be explained by the cracking present in the pellets surface which
enhances the dissolution medium to penetrate into the core of the pellets. This was shown in the below figures 16 and 17.

Figure 14.Scanning Electron Micrographs of pellet of formulation (FR 2)

Figure 15.Scanning Electron Micrographs of pellet of formulation (FR 8)
CONCLUSION

Immediate release of pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. The basic approach used in development of pellets is the use of super disintegrants like Croscarmellose sodium, Sodium starch glycolate, Polyvinylpyrrolidone etc. which provide instantaneous disintegration of pellet after administration.

Standard plots of Escitalopram Oxalate in 0.1N HCl were prepared by UV Spectrophotometry which showed good correlation coefficient ($R^2$) values. The drug-polymer interaction studies were performed by FTIR Spectrophotometry and it was found that there was no interaction between the drug and various polymers used in the formulation.

The Escitalopram Oxalate pellets are composed of three layers, a drug containing layer, hydrophobic polymer (HPMC E15) coat and final coat consisting of super disintegrants like Crospovidone, Croscarmellosesodium and Sodium starch glycolate.

The flow properties of the drug were evaluated. The drug has shown fair compressibility. The formulated pellets were evaluated for parameters namely angle of repose, bulk density, tapped density and Carr’s Index for the flow ability nature, angle of repose, thickness. The results shown by all the pellet formulations were found within the official pharmacopoeia limits. All the formulations showed favorable drug loading with uniformity of drug content in the pellets and friability percentage. Based on the friability, formulation FR1 and FR5 was selected as best formulations. All the formulations of pellets showed almost uniform size, shape and appearance. The physico-chemical properties of all the formulations (FR1-FR9) like thickness, friability lies within pharmacopoeia limits.

In vitro release of Escitalopram Oxalate pellet formulations FR2 and FR8 coated with Croscarmellose sodium and Sodium Starch Glycolate with 4% each respectively have shown maximum drug release within 15 minutes. The other formulations FR1, FR3, FR4, FR5, FR6, FR7 and FR9 also showed a better drug release.
The immediate release of the drug has been achieved from the pellets of formulation FR2 and FR8 with 97.36% and 99.54% respectively which meet demand of immediate release dosage form.

9. BIBLIOGRAPHY

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