FORMULATION OF NOVEL MANNITOL COATED ESOMEPRAZOLE DELYAED RELEASE COLON SPECIFIC PELLETS

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ABSTRACT:

This research focuses on the formulation of delayed-release esomeprazole magnesium-loaded pellets employing mannitol sub-coating and HPMC E5 polymers to enhance drug stability under acidic conditions typical of the gastrointestinal tract. Esomeprazole magnesium, a potent proton pump inhibitor, is widely used for its efficacy in managing acid-related disorders such as gastro-esophageal reflux disease (GERD), peptic ulcers, and Zollinger-Ellison syndrome. Achieving delayed release of esomeprazole is crucial for ensuring targeted delivery to the site of action, allowing optimal inhibition of gastric acid secretion over an extended period. Through systematic formulation optimization, the study evaluates the impact of various pellet compositions on drug release kinetics and resistance to acid degradation. The findings reveal a notable increase in acid resistance with the concentration of mannitol, while maintaining consistent drug release kinetics. The F7 formulation percentage drug release in acid stage and release profile in buffer stage complies with the innovator. To confirm this further trial was conducted with mannitol and plasticizer concentration.From the results, F7 formulation was found to be optimized formulation of Esomepraprazole magnesium delayed release pellets. Rest all the formulations were found to deviate from the reference.This underscores the significance of mannitol as a key component in improving the acid stability of delayed-release formulations of Esomeprazole magnesium, thus offering promising prospects for enhanced therapeutic outcomes in acid-sensitive conditions.

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INTRODUCTION

Pellets:

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration. Implants of small, sterile cylinders formed by compression from medicated masses are also defined as pellets in pharmacy. Pellets can be prepared by many methods, the compaction and drug-layering techniques being the most widely used today.

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 1000 µm.
- The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.

In the last two decades, pellets have established their position for many reasons. Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets. Successful film coating can be applied onto pellets due to their ideal spherical shape and a low surface area-to-volume ratio. Pellets composed of different drugs can be blended and formulated in a single dosage form. This approach facilitates the delivery of two or more drugs, chemically compatible or incompatible, at the same sites or different sites in the gastrointestinal tract. Even pellets with different release rates of the same drug can be supplied in a single dosage form.

The pelletised products can improve the safety and efficacy of the active agent. These multiple-unit doses are usually formulated in the form of suspensions, capsules or disintegrating tablets, showing a number of advantages over the single-unit dosage system. The pelletised product can freely disperse in the gastrointestinal tract as a subunit, thus maximising drug absorption and reducing peak plasma fluctuation. Consequently, potential side effects can be minimized without impairing drug bioavailability. Local irritation derived from high local concentrations of a drug from a single-unit dose, can be avoided.

The most important reason for the wide acceptance of multiple-unit products is the rapid increase in popularity of oral controlled-release dosage forms. Controlled-release oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time. With pellets, the above mentioned goals can be obtained through the application of coating materials (mainly different polymers), providing the desired function or through the formulation of matrix pellets to provide the desired effect.

The advantage of multiple-unit products as a controlled-release dosage form is believed to be their behaviour in vivo because of their advantageous dispersion pattern in the gastro intestinal tract and their special size characteristics. The transit time of a gastrointestinal drug delivery system along the gastrointestinal tract is the most limiting physiological factor in the development of a controlled-release gastrointestinal drug delivery system targeted to once-a-day medication. Gastro-intestinal transit time, greatly affects the bioavailability of a drug from an orally administered controlled release preparation. Gastric transit of both single and multiple-unit solid dosage forms is prolonged in a fed stomach compared to a fasting one. Plastic spheres of 7 mm remained in the food-filled stomach even as food itself expelled steadily. Once the stomach had emptied, the spheres began to transit in clusters. It has been reported that pellets smaller than about 2.4 mm in diameter, are free from the digestive function of the stomach and the closing system of the pyloric sphincter to be emptied from the stomach. A maximum pellet diameter of 1.5 mm has been recommended for an optimal multiple-unit formulation. Kelly 1981 and Devereux 1987 clearly showed that the threshold size must be below 1 mm. According to Khosla et al. (1989), there is no actual cut-off size for gastric emptying, but as the size of the pellets increase, predictable emptying from the fed stomach becomes uncertain and highly variable. However, it has been demonstrated that gastric emptying is not only dependent on the size but also on some other important factors, such as density of pellets and inter-subject variation. Clarke et al.

1993 and Tuleu et al.1999 showed that both density and size of the pellets affect the gastrointestinal transit time. The higher density of the pellets prolonged the gastric transit time, while the larger size slightly prolonged the small gut transit time but not the gastric transit time. Controversial results have also been reported to the effect of pellets densities on the transit times through the gastrointestinal tract.

Ideal properties of pellets:

- Spherical shape and smooth surface is considered as desired characteristic for uniform film coating.
- The particle size of pellets should be in range of 500-1500µm.
- The quantity of the active ingredient in pellets should be maximum in order to maintain size of pellet.

Reasons for pellatization:

The pharmaceutical industry has developed a great interest in pellatization due to a variety of reasons-

- Prevention of segregation of co-agglomerated components, resulting in an improvement of uniformity of content.
- The defined shape and weight improves the appearance of the product.
- Improved flow properties and ease of packing resulting in uniform and reproducible fill weight of tablets and capsules.
- Controlled release application of pellets due to the ideal low surface area to volume ratio that provides an ideal shape for the application of film coatings.
- Improvement of handling properties due to the free flowing properties.
- Improved safety and efficacy of active ingredient.
- Decreased handling hazards and easier transport.
- Improvement of the hardness and friability of pellets.
- Increasing bulk density and decreasing bulk volume.
- High drug loading capacity without producing extensively large particles.
- When formulated as modified release preparation pellets are less susceptible to dose dumping and thus lowering the risk of side effects.
- Uniform size with narrow size distribution.
- The wide distribution of spherical particles in the gastrointestinal tract limits localized buildup of the drug, avoiding the irritant effect of some drugs on the gastric mucosa.

- Peak plasma level of the drug can be reduced by the use of spherical particles with different release rates and side effects can be minimized without markedly lowering drug bio-availability.
- Pellets disperse freely in GIT fluids due to their small size, providing larger surface area for drug absorption.
- Prevention of dust formation, resulting in an improvement of the process safety.
- Pellets offer reduced variation in gastric emptying rate and intestinal transit time thus reducing inter and intra subject variability.
- Pellatization can be used or taste masking of unpalatable drugs.
- No crystallization or precipitation of solution and suspension and decreased hygroscopicity.

Disadvantages of pellets:

- Often pellets cannot be pressed into tablets because they are too rigid. So they have to be encapsulated into capsules.
- The production of pellets is quite an expensive process and requires highly specialized equipment and trained personnel.
- The control of production process is difficult (e.g., the amount of water to be added is critical for the quantity of the pellets and over-wetting can occur very easily).

Theory of pellets formulation and growth:

In order to judiciously select and optimise any pellatisation/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. Some of these theories are derived from experimental results while others are confined to visual observations. Results obtained from the experiments with some form of tracer technique are regarded as acceptable and convincing. As the conventional granulation, the most thoroughly studied, most classified pellatisation 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 Nucleation (Figure 1A) is a common stage in all pelletisation/granulation processes and occurs whenever a powder is wetted with liquid. The primary particles are drawn together to form three-phase air-water-liquid nuclei and are attached together by liquid bridges which are pendular in nature. The bonding strength is improved by reduction of particle size. The sizes of the primary particles, the moisture content, the viscosity of the binding particles, the wet ability of the substrate and the processing conditions, such as tumbling and drying rates, influence the size, the rate and the extent of nuclear formation.

Both the mass and the number of nuclei in the system change as a function of time, which is an important feature of nucleation. Nucleation is followed by a transition phase, and the growth mechanisms affecting the transition region are coalescence and layering.

Coalescence is defined as the formation of large-sized particles by random collision of well-formed nuclei, and the mechanism requires slight excess moisture on the nuclear surface. Although the number of nuclei is progressively reduced, the total mass of the system remains unchanged during this step.

Layering is a slow growth mechanism and involves the successive addition of fragments and fines on an already formed nucleus. In the layering step, the number of particles remains the same, but the total mass in the system increases due to increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction. that occurs due to attrition, breakage and shatter. The fines and the fragments that are produced through size reduction are picked up by large pellets. Production of fines and subsequent coalescence and layering continues until the number of favourable collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth region, is reached.

In the ball growth phase the main mechanism affecting the slow growth of agglomeration is the abrasion transfer which involves the transfer of materials from one granule formed to another without any preference in either direction. This situation does not result in a change in the total number or mass of the particles. The particles, however, undergo a continuous change in size as long as the conditions that lead to the transfer of material exist.

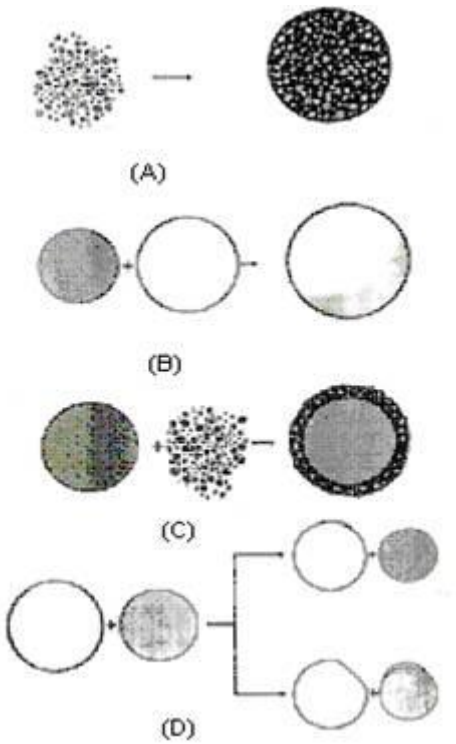


Figure :1 Theory of pellets formulation and growth.

Pellatization techniques:

- ✓ Extrusion-spheronisation
- ✓ Drug layering
- ✓ Cryopellatization
- ✓ Freeze pellatization
- ✓ Globulation
- ✓ Compression
- ✓ Balling

1. Extrusion and spheronisation:

Extrusion and spheronisation is a multistage process for obtaining pellets with uniform size from wet granules.

The method involves the following steps:-

- The dry mixing of ingredients, in order to achieve homogenous powder dispersions.
- Wet massing, in which the powders are wet-mixed to form a sufficiently plastic mass.
- An extrusion stage, in which the wet mass is shaped into cylindrical segments with a uniform diameter.
- The spheronisation stage, in which the small cylinders are rolled into solid, spheres (spheroids).
- The drying of the spheroids, in order to achieve the desired final moisture content.
- Screening to achieve the desired narrow size distribution.

Dry mixing:-

Different types of mixers like twin shell blender, high shear mixer, tumbler mixer and planetary mixer are used for dry mixing to obtain homogenous powder dispersions.

Wet massing:-

In wet massing powders are mixed to form a sufficiently plastic mass. Mostly planetary mixer is used for both mixing and granulation operations.

Extrusion:-

Extrusion process involves application of pressure to a wet mass until it passes through the calibrated openings of a screen or die plate of extruder and further shaped into small extrudate segments.

As the mass passes through the extruder screen, the resulting extrudates eventually break under their own weight. The extrudates must have enough plasticity in order to deform, but an excessive plasticity may lead to sticking of extrudates each other as they are collected and further processed in the speroniser. The diameter of the segments and the final size of the spheroids depend on the diameter of the openings in the extruder screen. Feed rate, powder consumption, dies temperature and compression chamber pressure should be monitored to get reproducible results.

Spheronisation:-

Spheronisation includes formation of spherical particles from the small rods produced by extrusion. It consists of three stages, breaking of cylindrical segments or extrudates, agglomeration of broken segments and smoothing of particles. The breaking of cylindrical segments occurs due to interaction of extrudates with rotating grooved or smooth plate, stationary wall or other extrudates particles. Spherical particles are formed during smoothing stage by generation of rotational motion of each granule about its axis in constantly changing planes. These fragments will subsequently be rounded into pellets when there is adequate surface plasticity under stress for remodelling and the mass is sufficiently cohesive to remain as an entity under the frictional stress during spheronisation.

Drying of spheroids:-

The pellets are dried at room temperature or elevated temperature in a tray drier or in a fluidized bed drier to achieve desired final moisture content.

Screening of pellets:-

Screening is done to avoid pellets having high poly dispersity index and to achieve the desired narrow size distribution.

2. Drug layering:-

Drug layering process involves deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of same material or inert starter seeds. It comprises the simultaneous application of the binding liquid and dry powder. The dissolved material crystallizes forming solid bridges between the cores and initial layers of drug substance and among successive layers of drug substance and polymer. The process is continued until desired layer of drug or polymer is formed.

In powder layering method, the binding liquid helps in forming successive layers of dry powder of drug and other components on starting cores by forming liquid bridges which are eventually replaced by solid bridges. It involves continuous and successive layering of drug and binder solution until the desired pellet size is achieved. The mixing is a function of pan shape, tilt angle, baffle arrangement, rotational speed of pan, etc. Equipments used for powder layering process are tangential spray granulator and centrifugal fluid bed granulator.

The process of solution or suspension layering consists of preparing a solution or suspension of drug particles and other components in application medium. The particle size of drug is an important factor to be considered.

If the particle size of the drug in the solution suspension is large, the amount of binder required to immobilize the particles onto the core will be high and thus pellets of low potency are produced. Micronized drug particles provide pellets with smooth appearance which is a desirable property during film coating for controlled release applications.

3. Cryopellatization:-

Cryopellatization is a process of conversion of droplets of a liquid formulation into solid spherical particles or pellets by using liquid nitrogen as the fixing medium. It involves production of drug loaded pellets by allowing droplets of liquid formulation such as solution, suspension or emulsion to come in contact with liquid nitrogen at -1600^{0}C. The procedure includes instantaneous and uniform freezing of the processed material due to rapid transfer of heat between the droplets and liquid nitrogen. Then the pellets are dried to remove water or organic solvent in conventional freeze dryers.

The equipment used for cryopellatization consists of a container equipped with perforated plates, a reservoir, conveyor belt with transport baffles and storage container. The perforated plates that fall and freeze instantaneously when they come in contact with the liquid nitrogen below. The frozen pellets are transported out of the nitrogen bath into a storage container at -600^{0}C before drying. The critical step is droplet formation and is influenced by formulation related variables like viscosity, surface tension and solid content, equipment design and process variables. This technique may be used to produce drug loaded pellets for immediate as well as controlled release formulation.

Compression:

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

Balling:

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

Globulation:

Spray drying and spray congealing known as globulation processes, involve atomization of hot melts, solutions or suspensions to produce spherical particles or pellets. The droplet size is maintained small to maximize the rate of evaporation or congealing and the particle size of pellets produced is usually very small.

Spray drying is the process in which drugs in solution or suspension without excipients are sprayed into a hot stream to produce dry and more spherical particles. As the atomized droplets come in contact with hot air, evaporation of the application medium is initiated. This drying process continues through a series of stages where by the viscosity of the droplets constantly increases until finally almost the entire application medium is driven off and solid

particles are formed. Generally, sprayed dried pellets tend to be porous. This process is commonly used for improving the dissolution rates and bioavailability of poorly soluble drugs.

Spray congealing 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. This process consists of suspending the particles in a molten coating material and pumping the resultant slurry into a spray dryer in which cold air is circulated. The slurry droplets congeal on contact with air. The coating agents normally employed is low melting materials such as waxes. The congealing process require higher ratio of coating agents to active material than does the spray drying, because only molten coating agent constitute the liquid phase. Spray congealing can used for both immediate and controlled release pellets depending on the physicochemical properties of the ingredients and other formulation variables.

4. Freeze pellatization:

Freeze pellatization is a novel and simple technique in which solid carrier along with a dispersed active ingredient is introduced as droplets into an inert and immiscible column of liquid. By this method pellets with narrow size distribution can be produced.

The solid carriers are introduced as droplets in molten state into the immiscible liquid and drying is not required as pellets are solid at room temperature. Depending on their density with respect to the liquid in the column, the droplets can move either in upward or downward direction and solidify into spherical pellets. The carriers used are solid at room temperature with melting point below 100^0C so that degradation of active constituent can be minimized. The hydrophilic or hydrophobic carriers are melted at a temperature 5-10^0C higher than melting point of carrier solids.

Two types of equipments are used for freeze pellatization- freeze pellatizer I and freeze pellatizer II. In freeze pellatizer I, the molten solid carrier is introduced from the upper portion of the column. The density of solid carriers is more than that of liquid used in the column and the carriers solidify in the bottom portion. Hydrophilic carriers such as polyvinyl alcohol, polyethylene glycol and low melting point sugars (dextrose, maltose) are used. Suitable liquids for column are low density oil such as mineral oil, vegetable oil and silicone oil. In case of freeze pellatizer II, the molten solid carrier is introduced from the bottom of the column because density of the solid carrier is low as compared to the liquid used in the column and the solid solidify at the top. For freeze pellatizer II, hydrophobic carriers of low density oil such as glycerol palmitostearate, glycerol behenate and glycerol monostearate are used as solid carriers. High density liquids such as liquid polyethylene glycol, ethyl alcohol, glycerine and water are used as liquids for the column. For sustained release pellets containing mixture of hydrophobic and hydrophilic solids, liquids that are immiscible with both hydrophilic and hydrophobic molten solids are used as cooling liquid in the column.

Enteric coating:

The techniques involve in entering coating is protection of the core pellets from disintegration in acidic environment of stomach by emptying pH sentive polymer which swell or solubilise in response to an increase in pH to release the drug.

Reason for enteric coating:

- To prevent degradation of acid sensitive active pharmaceutical ingredient.
- To prevent irritation of stomach by certain drug like sodium salicylate.
- Delivery of active pharmaceutical ingredient into intestine
- To provide a delayed release component for repeat action pellets.

Ideal properties of entering coating material are summarized as below

- Resistant to digestive fluid
- Susceptible /permeable to intestinal fluid
- Compatibility with most coating solution component and the drug substance
- Formulation of continuous film
- Nontoxic cost effective and ease of application

Enteric coating system are obtained by coating the pellets with enteric coating material such as ethyl cellulose(EC), cellulose acetate phthalate(CAP), cellulose acetate phthalate trimellilate (CAT), hydroxyl propyl methyl cellulose phthalate (HPMC CP), methacrylic acid , methacrylic ester co polymer , polyvinyl phthalate (PVAP), hydroxyl propyl methyl acetate succinate etc.

Excipients

Formulation aids or excipients are added to pharmaceutical dosage forms mainly to produce satisfactory delivery of the drug to the intended site, to impart favourable characteristics to the dosage form and to facilitate the manufacture of the product. Since pellets are intended to be administered orally, the excipients used in the pellet dosage forms are typically the same as those used in tablet or capsule formulations.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 Examples of commonly used excipients

Filler	MCC, starch, sucrose, lactose, mannitol
Binder	Gelatin, HPC, HPMC, MC, PVP, sucrose, starch
Lubricant	Calcium stearate, glycerine, PEG, Mg. stearate
Separating agent	Kaolin, talc, silicon dioxide
Disintegrant	Alginates, croscarmellose sodium
pH adjuster	Citrate, phosphate, meglumine.
Surfactant	Polysorbate, SLS
Spheronization enhancer	MCC , sodium CMC
Glidant	Talc, starch, Mg stearate.
Release modifier	Ethyl cellulose, carnauba wax, shellac.

PEPTIC ULCER DISEASE:

Peptic ulcer are open sores or erosion in the gut lining of the stomach , duodenum , oesophagus. A peptic ulcer of the stomach is called gastric ulcer of the duodenum as duodenum ulcer: and of the oesophagus, an oesophageal ulcer. An ulcer occur when the lining of these organ is corroded by the acidic digestive juice which are secreted by the stomach cells.

Signs and symptoms:

- Abdominal pain with a burning or gnawing sensation
- Pain 2-3 hour after eating.
- Pain is often aggrieved by an empty stomach for example night time pains is common.
- Pain may be relieved by antacid or milk.
- Heartburn
- Indigestion(dyspepsia)
- Belching
- Nausea

- Vomiting
- Poor appetite
- Weight loss

Causes:

Peptic ulcer disease (PUD) can start when the protective barrier that lines the stomach or intestine is injured, exposing the underlying tissue to stomach acid. A variety of things can harm the protective lining of the stomach or intestine. The causes are listed below.

- ❖ Helicobacter pylori-a bacterial organism is responsible for most ulcer this organism weaker than protective coating of the stomach and duodenum and allows the damaging digestive juices to irritate the sensitive lining below.
- ❖ Non-steroidal anti-inflammatory drug (NSAIDs)- ongoing use of this class of mechanism is the second most common cause of ulcer. These drugs which include aspirin, ibuprofen, naproxen, diclofenac, tolmetin, fenoprofen,indomethacin) are acidic they block prostaglandins substance in the stomach that help maintain blood flow and protect the area from injury.
- ❖ Zoolinger – Ellison syndrome people with this uncommon condition have tumors in the pancreas and duodenum that produce gastric a hormone that stimulate gastric acid production. Other cause of ulcer are conditions that can result indirect damage to the wall of the stomach or duodenum such as heavy use of alcohol radiation therapy, burns and physical injury.
- ❖ Risk factor:
- ❖ Genetic factor
- ❖ Increasing age
- ❖ Chronic pain, from any cause such an arthritis, fibromyalsia respective stress injuries or persistent back pain leading to ongoing use of aspirin as NSAIDs
- ❖ Alcohol abuse

Treatment of Peptic ulcer: following are the approaches used for the treatment of peptic ulcer disease.

- o Proton pump inhibitors, including omeprazole, lansprazole, pantoprazole, rabeprazole and esomeprazole, decrease gastric acid secretion. This is the best medication for treating ulcer.
- o H2 blocker such as cimetidine , ranitidine ,nizatidine and famotidine, reduce gastric acid secretion
- o Anticholinergic these are of little important in the treatment of ulcer . they reduce acid secretion by 35-40%. These are used along with antacids.

- Sucralfate makes a coating over the ulcer protecting it from further damage
- Antacids may relatively heart burns or indigestive but will not treat ulcer.

Gastroesophageal reflux disease (**GERD**), **gastro-oesophageal reflux disease** (**GORD**):

Gastric reflux disease, or acid reflux disease is a chronic symptom of mucosal damage caused by stomach acid coming up from the stomach into the oesophagus. GERD is usually caused by changes in the barrier between the stomach and the oesophagus, including abnormal relaxation of the lower oesophageal sphincter, which normally holds the top of the stomach closed, impaired expulsion of gastric reflux from the oesophagus, or a hiatal. These changes may be permanent or temporary.

The most-common symptoms of GERD are:

- Heartburn
- Regurgitation
- Difficulty in swallowing (dysphagia)
- Pain with swallowing/sore throat (odynophagia)
- Increased salivation (also known as water brash)
- Nausea
- Chest pain

GERD sometimes causes injury of the oesophagus. These injuries may include:

- Reflux esophagitis – necrosis of oesophageal epithelium causing ulcers near the junction of the stomach and oesophagus
- Oesophageal strictures – the persistent narrowing of the oesophagus caused by reflux-induced inflammation
- Barrett's oesophagus – intestinal metaplasia (changes of the epithelial cells from squamous to intestinal columnar epithelium) of the distal oesophagus
- Oesophageal adenocarcinoma – a rare form of cancer
- sinusitis
- recurrent ear infections, and
- idiopathic pulmonary fibrosis are due to GERD
- coughing,
- belching or burping

—

Causes:

GERD is caused by a failure of the lower oesophageal sphincter. In healthy patients, the "Angle of His"—the angle at which the oesophagus enters the stomach—creates a valve that prevents duodenal bile, enzymes, and stomach acid from traveling back into the oesophagus where they can cause burning and inflammation of sensitive oesophageal tissue.

Factors that can contribute to GERD:

- Hiatal hernia, which increases the likelihood of GERD due to mechanical and motility factors.[9][10]
- Obesity: increasing body mass index is associated with more severe GERD.[11] In a large series of 2000 patients with symptomatic reflux disease, it has been shown that 13% of changes in oesophageal acid exposure is attributable to changes in body mass index.[12]
- Zollinger-Ellison syndrome, which can be present with increased gastric acidity due to gastrin production.
- Hypercalcemia, which can increase gastrin production, leading to increased acidity.
- Scleroderma and systemic sclerosis, which can feature oesophageal dysmotility.
- The use of medicines such as prednisolone.
- Visceroptosis or Glénard syndrome, in which the stomach has sunk in the abdomen upsetting the motility and acid secretion of the stomach.

GERD has been linked to a variety of respiratory and laryngeal complaints such as laryngitis, chronic cough, pulmonary fibrosis, earache, and asthma, even when not clinically apparent. These atypical manifestations of GERD is commonly referred to as laryngopharyngeal reflux or as extraoesophageal reflux disease (EERD).

Treatment : The treatments for GERD include lifestyle modifications, medications, and possibly surgery. Initial treatment is frequently with a proton-pump inhibitor such as omeprazole ,esomeprazole

Proton-pump inhibitors

According to the Biopharmaceutical Classification System (BCS), drug substances are classified as follows:

Class I	-	HighPermeability, High Solubility
Class II	-	High Permeability, Low Solubility
Class III	-	Low Permeability, High Solubility
Class IV	-	Low Permeability, Low Solubility

- Class I drugs are likely to exhibit few bioavailability problems.

- Class II drugs are prone to dissolution rate– limited absorption.
- Class III drugs are likely to exhibit permeation rate–limited absorption.
- Class IV drugs may present serious obstacles to oral bioavailability, and some may be best formulated in a solubilized form such as a liquid filled or semisolid-filled capsule.

Group of Proton Pump inhibitors includes derivatives of Benzimidazole like Omeprazole, Lansoprazole, Dexlansoprazole, Pantoprazole, Rabeprazole. Etc.

Dexlansoprazole belongs to a class of compounds called proton pump inhibitors (PPI) substituted benzimidazoles which inhibit the final common step in gastric acid secretion.

Esomeprazole belongs to **Class II drugs** of the BCS characterized by low solubility and high permeability. The dissolution rate was chosen as the dependent factor to monitor any effects of changes in the formulation parameters.

The key action mechanism of the PPI's is inhibition of H+/K+ -adenosine triphosphate (also known as acid pump or proton pump), an enzyme present in the gastric parietal cells (Horn J. 2000). This effect on the final step of the gastric acid formation thereby reducing gastric acid output both during basal conditions and simulated acid secretion , irrespective of stimulus.

Absorption of the most PPI's takes place in the proximal small intestine (Horn.J et al., 2000). All of the currently availed delayed –release proton pump inhibitors have a short elimination half-life (t1/2) of between 1 and 2 hours. Aside from bioavailability in the first few days oforal dosing, there are no substantive differences among currently available delayed release PPI's with respect to pharmacokinetics (Horn J.et al., 2000).

Table-2:Pharmacokinetics of Delayed Release Proton Pump Inhibitors :

PPI's Parameter	**Omeprazole**	**Lansoprazole**	**Pantoprazole**	**Rabeprazole**	**Esomeprazole**
IUPAC	5-methoxy-2-[(4-methoxy-3,5dimethyl-pyridin-2-yl)methylsulfinyl]-3H-benzimidazole	2-[(3-methyl-4-(2,2,2-trifluoroethoxy)pyridine-2-yl)methylsulfinyl]-1H-benzimidazole	5-(difluoromethoxy)-2[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-3H-benzimidazole	2-[(4-(3-methoxypropoxy)-3-methyl-pyridin- 2-yl)methyl sulfinyl]-1H-benzimidazole	(S)-5-methoxy-2-[(4-methoxy3,5-dimethylpyridin-2-yl)methylsulfinyl]-3H-benzimidazole
Chemical Name	$C_{17}H_{19}N_3O_3S$	$C_{16}H_{14}F_3N_3OS$	$C_{16}H_{14}F_2N_3NaO_4S$	$C_{18}H_{20}N_3NaO_3S$	$C_{17}H_{19}N_3O_3S$

Molecular Weight	345.4	369.363	383.371	359.444	345.417
Bioavailability	30 – 40%	>80%	77%	52%	50 – 90%
Metabolism	Hepatic (CYP2C19)	Hepatic (CYP2C19, CYP3A4)	Hepatic (CYP2C19, CYP3A4)	Hepatic (CYP2C19, CYP3A4)	Hepatic (CYP2C19, CYP3A4)
Elimination half-life	1 – 1.2 hours	1 – 1.5 hours	1 hour	1 – 1.5 hours	1 – 1.5 hours
Tmax	0.5 – 3.5	1.7	2.5	2 – 5	0.5 – 3.5
Excretion	80% Renal 20% Faecal	Renal – 33% Biliary/faces – 66%	Renal – 71% as metabolites Feces – 18% as metabolites	Renal – 90% as metabolites Feces- 10% as metabolites	80% Renal 20% Faecal
Proprietary Name	PRILOSEC	PREVACID	PROTONIX	ACIPHEX	NEXIUM
Year of Approve(USFDA)	Jan 15, 1998	May 10, 1995	Feb 2000	Aug 19, 1999	Feb 20, 2001
Route of Dosage	Oral, IV	Oral, IV	Oral, IV	Oral	Oral, IV

Drug Delivery Systems

The treatment of acute diseases or chronic illness has been achieved by delivery of drugs to the patients for many years. A number of oral dosage forms are available. Some are liquids (e.g., syrups, elixirs, tinctures, suspensions, and emulsions), whereas the most common ones are solids (e.g., tablets & capsules). Tablets and capsules are generally formulated to release the drug immediately after oral administration to hasten systemic absorption. These are called immediate- release products. Other products like modified-release dosage forms have been developed to release the drug at a controlled rate. The purpose is generally either to avoid contact with gastric fluids (acidic environment) or to prolong drug input in systemic circulation.

These drug delivery systems include tablets, parenteral, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used.

The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body.

Conventional Drug Delivery System:

These therapies require periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic window. Conventional forms often cause problems to the patient, because they maintain therapeutic drug level for only brief duration. This gives rise to sharp fluctuations of drug levels in plasma and in tissue. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels.

To overcome these problems, controlled drug delivery systems were introduced into the market. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience. The goal of controlled drug delivery systems is to improve the effectiveness of drug therapies. Conventional dosage forms are rapidly absorbed, with the ascending and descending portions of the concentrations versus time curve reflecting primarily the rate of absorption and elimination, respectively. Because of the rapid rate of absorption from conventional dosage forms, drugs are usually administered more than once daily, with the frequency being dependent on biological half-life ($t_{1/2}$) and duration of pharmacological effect.

Disadvantages of conventional drug delivery system:

- In Conventional oral drug delivery systems, thereis little or no control over the release of the drug and effective concentration at the target site can be achieved by intermittent of excessive doses.
- The dosing pattern in Conventional dosage formsresults in constantly changing, unpredictable and often sub-therapeutic plasma concentrations, leading to marked side effects in some cases.
- The rate and extent of absorption of drug from conventional formulations may vary greatly, depending on the factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food. pH of the gastrointestinal motility and so on.

Modified Drug Delivery Systems:

Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location. Drug release only occurs sometime after the administration or for a prolonged period of time or to a specific target in the body. Modifications in drug release are often desirable to increase the stability, safety and efficacy of the drug, to improve the therapeutic outcome of the drug treatment and/or to increase patient compliance and convenience of administration.

Classification:

Modified Release dosage form may be classified as

- Extended Release
  - Sustained Release
  - Controlled Release
- Delayed Release

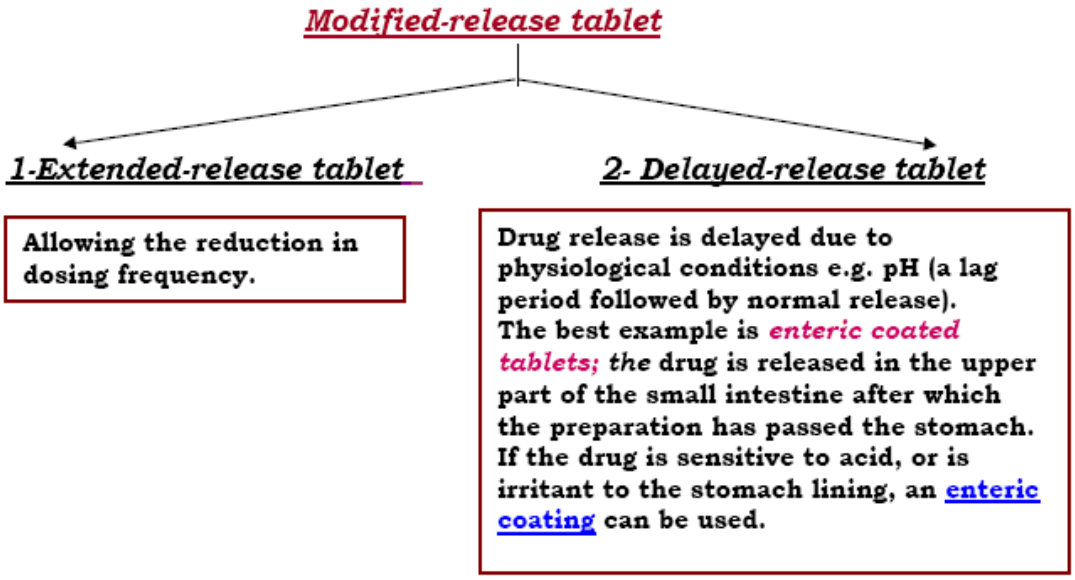


Figure: 2Types of modified release tablets

Extended Release oral DDS allows the drug to be released over prolonged time periods. By extending the release profile of a drug, the frequency of dosing can be reduced. Extended release can be achieved using sustained or controlled-release dosage forms.

The term **Sustained Release** is constantly used to describe a pharmaceutical dosage form formulated to retard the release of the therapeutic agent such that its appearance in the systemic circulation is delayed and prolonged and its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed, on the duration of its therapeutic effect is sustained.

Controlled Release Dosage form is generally accomplished by attempting to obtain "zero-order" release from the dosage form which independent of the amount of drug in the delivery system (i.e., a constant release rate). Sustained Release systems generally do not attain this type of release and usually try to mimic zero order release by providing drug in a slow first order fashion (i.e., concentration dependent).

Delayed Release:

A Delayed Release dosage form is designed to release the drug at a time other than promptly after administration. Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location.

Delayed Release oral dosage forms can control where the drug is released, e.g. when the dosage form reaches the small intestine (enteric-coated dosage forms) or the colon (colon-specific dosage forms). Delayed Release systems release a bolus of the drug after a predetermined time in a predetermined location, i.e. they do not release the drug immediately after ingestion, for example enteric-coated tablets, pulsatile-release capsules.

Delayed Release dosage forms are designed to provide spatial placement or temporal targeted delivery of a drug to the distal human gut. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to desired rate of drug release to target tissue over a specified period of time. The primary aim of using delayed release products is to protect the drug from gastric fluids, to reduce gastric distress caused by drugs particularly irritating to the stomach or to facilitate gastrointestinal transit for drugs that are better absorbed from intestine. Delayed Release products are typically enteric-coated or targeted to the colon.

The oral route of drug delivery is typically considered the preferred and most patient-convenience means of drug administration. The release of drug from an oral dosage form may be intentionally delayed until it reaches the intestine.

The correct selection and balance of excipients and processes in solid dosage formulations are designed either for improving the micromeritic or macromeritic properties of materials during manufacture and/or for providing a desired drug delivery system. The most commonly used pharmaceutical delayed release solid oral dosage forms today include tablets, capsules, granules and pellets.

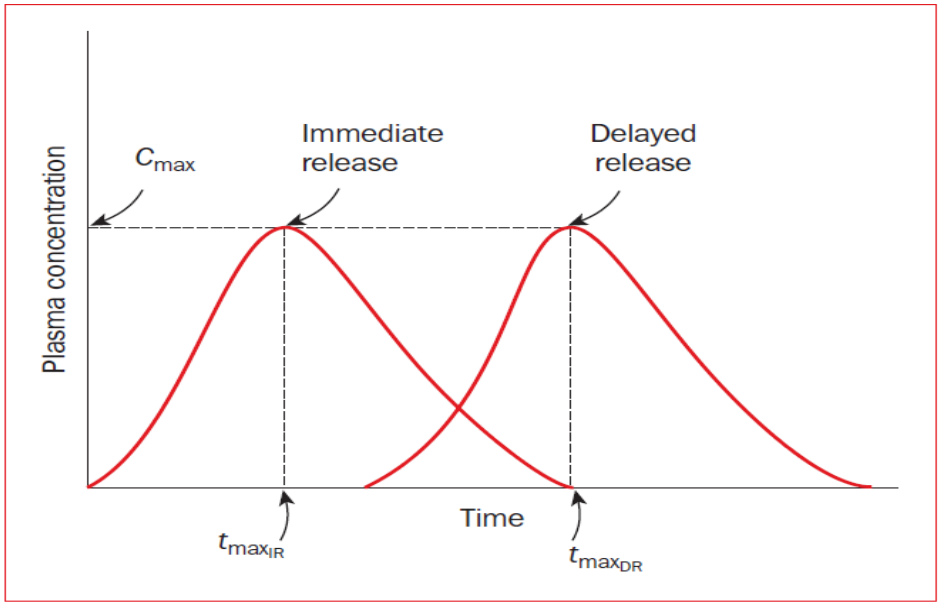


Figure : 3 Plasma concentration vs Time graph of Oral modified release Dosage Form Compared to an Immediate-Release Dosage Form

T_{max}ofIR is the time for maximum plasma concentration of the drug released from an immediate-release dosage form and $T_{max}$of DR is the time for maximum plasma concentration of the drug released from a delayed-release dosage form.

Significance of Delayed Release Systems:

The design of such system involves release of drugs only at a specific site in the gastrointestinal tract. The drugs contained in such a system are those that are:

- Destroyed in the stomach or by intestinal enzymes
- Known to cause gastric distress
- Absorbed from a specific intestinal site
- Meant to exert local effect at a specific gastrointestinal site

In these cases drug release should be delayed until the dosage form has reached the small intestine. Often polymers are used to achieve this aim. The dosage form (for example, a tablet or the granules before tabletting) can be coated with a suitable polymer. The polymer dissolves as a function of pH, so when the dosage forms travel from the low-pH environment of the stomach to the higher-pH environment of the small intestine, the polymer coat dissolves and the drug can be released. Once this occurs, the release is again immediate and the resulting plasma concentration versus time curve is similar to the one for immediate release dosage forms.

The two types of delayed release systemsare:

- Intestinal Release System
- Colonic Release System

Intestinal Release System: A drug may be enteric coated for intestinal release for several known reasons such as to prevent gastric irritation, prevent destabilization in gastric pHetc.

Colonic Release System: Drugs are poorly absorbed through colon but may be delivered to such a site for two reasons

- Local action in the treatment of ulcerative colitis
- Systemic absorption of protein and peptide drugs

The development of colon-specific drugs and dosage forms may be advantageous for the treatment of local and systemic disease including colorectal cancer and Crohn’s disease. Especially for peptide and protein drugs, this form of release may also be advantageous for systemic administration given the more favourable pH conditions in the colon compared to the stomach and the generally lower enzymatic activity compared to the small intestine.

Advantage is taken of the fact that pHsensitive bio erodible polymers like polymethacrylates release the medicament only at the alkaline pH of colon or use of divinylbenzene cross-linked polymers that can be cleaved only by the azo-reductase of colonic bacteria to release free drug for local effect or systemic absorption.

General Considerations for Design of Colonic Formulations:

The proper selection of a formulation approach is dependent upon several important factors, which are listed below.

- Pathology and pattern of the disease, especially the affected parts of the lower GI tract or physiology and physiological composition of the healthy colon if the formulation is not intended for localized treatment.
- Physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery and the desired release profile of the active ingredient.
- The most common physiological factor considered in the design of delayed release colonic formulations is pH gradient of the GI tract. In normal healthy subjects, there is a progressive increase in luminal pH from the duodenum (pH = 6.6 + 0.5) to the terminal ileum (pH = 7.5 + 0.4), a decrease in the cecum (pH = 6.4 + 0.4) and then a slow rise from the right to the left colon with a final value of pH 7.0 + 0.7. Some reports suggest that alterations in GI pH profiles may occur in patients with inflammatory bowel disease, which should be considered in the development of delayed release formulations.

pH Dependent (or Delayed Release) Systems:

Solid formulations for colonic delivery that are based on pH-dependent drug release mechanism are similar to conventional enteric-coated formulations but they differ in target site for delivery and therefore type of enteric polymers. In contrast to conventional enteric-coated formulations, colonic formulations are designed to deliver drugs to the distal (terminal) ileum and colon, and utilize enteric polymers that have relatively higher threshold pH for dissolution. Most commonly used polymers are derivatives of acrylic acid and cellulose. These polymers have ability to withstand an environment ranging from low pH (1.2) to neutral pH (7.5) for several hours.

Apparently, it is highly desirable for pH-dependent colonic formulations to maintain their physical and chemical integrity during passage through the stomach and small intestine and reach the large intestine where the coat should disintegrate to release the drug locally. It should be however noted that GI fluids might pass through the coat while the dosage form transits through the small intestine. This could lead to premature drug release in the upper parts of GI tract and as a result loss of therapeutic efficacy may occur. One approach to overcome this problem is to apply higher coating levels of enteric polymers; however, this also allows influx of GI fluids through the coat, and the thicker coats often rupture under the influence of contractile activity in the stomach. In general, the amount of coating required depends upon the solubility characteristics (solubility, dose/solubility ratio) of the drug, desired release profile and surface area of the formulation, and composition of the coating solution/dispersion.

Classification of Delayed release solid oral dosage forms:

Delayed release solid oral dosage forms are available either as single–unit (non divided formulations-tablets, capsules) or as multiple- unit (divided formulations – pellets, mini-tablets) forms.

Solid unit dosage forms-

The single-unit dosage forms usually refer to diffusion controlled systems which include monolithic systems (Fan L.T et. Al., 1989b) reservoir or multi-layered matrix systems, where the diffusion of the drug through the polymer coating or layer of the system is the rate-limiting step. However, generally release of drugs will occur by a mixture of these two mechanisms (Ansel C.H et al., 1995).

Multiparticulate drug delivery systems-

Multiparticulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm.

To deliver the recommended total dose, these subunits are filled into a sachet or encapsulated or compresses into a tablet. The mechanism of drug release from Multiparticulate can occur by either Diffusion or Erosion or Osmosis.

- The use of pellets as vehicle for drug delivery at a controlled rate has recently received significant attention. Applications are found not only in the pharmaceutical industry but also in the agribusiness (such as in fertilizer and fish food) and in the polymer industry. There are numerous advantages offered by multiple unit dosage forms.
- Pharmaceutical pellets are agglomerates of fine powder particles or bulk drugs and Excipients, small, free-flowing, spherical or semi-spherical solid units, size ranges from about 0.5mm to 1.5mm (ideal size for oral administration) obtained from diverse starting materials utilizing different processing techniques and conditions.

MATERIALS AND METHODS

Table-3 : Materials used in formulation of pellets

Ingredients	Reference	Qty Taken
Esomeprazole	USP	330 gms
Mannitol	BP/EP	291.5 gms
Sucrose(Dilute)	BP/EP	153.5 gms
Sucrose (#30/40) crystals for pellets	BP/EP	155.5 gms
SURCOSE (FOR SYRUP PREPARATION)	BP/EP	24.3 gms
Di sodium hydrogen phosphate	BP	15.5 gms
Calcium Carbonate	BP/EP	29.1 gms
Hydrogen propyl methyl cellulose(HPMC E5)	USP	0.0812 gms
Acetyl alcohol	BP/EP	15 gms
Acetone	BP/EP	1.5 litrs
Iso Propyl alcohol	BP/EP	1 lit

Table-4:**List of equipment's used for Esomeprazole magnesium delayed release pellets.**

S. No	EQUIPMENT	MANUFACTURER	Model No.
1	Digital semi micro analytical Balance	LCGC RADWAG Hyderabad	XA/82/220/X
2	Mesh # 16, 18,20	Retsec	ASL00
3	Tap density tester`	Electro lab	ETD-1020
4	Electromagnetic Sieve Shaker	Electro labs Mumbai	EMS-8
5	Cone Blender	Likeetha	410AG
6	Coating pan	SKMS techno mech	48GMP
7	Fluid bed coater	Perfect labs	PPTFBC-06
8	Tray dryer	Retsch	RDE-030
9	Ultra sonicat both	Ram sit scientific enterprises Hyderabad	D-50/1H
10	Cyclomixture	Remi equipment RTD manufacture.	CMB4D
11	P^Hmeter	POLMON hyd	LP-139SA
12	Karl fisher titrator.	Lasco lab services.	KFT-A

13	Electronic balance	TULAMAN Hyderabad.	HTJS
14	Friabilator	Electro lab USP	RDE-015
15	UV-visible spectrometer.	TOSHVIN analytic pvt ltd.	UV-1700
16	Dissolution test apparatus	Electro labs Mumbai.	TDT-08L
17	HPLC	Schinaduspinco bio tech pvt ltd.	LC-2010CHT
18	Karl fisher manual	RASCO lab services.	KFT-M

Preformulation Studies:

Bulk density:

The sample equivalent to 10g was accurately weighed and filled in a 50 ml graduated cylinder, the powder was leveled, and the untapped volume, V0 was noted. The bulk density was calculated in g/cm3 by the following equation.

Db = M / V0

Where, M= Mass of powder, V0= Bulk volume of the powder.

Tapped density:

The mechanical tapping of the cylinder was carried out using tapped density tester at a nominal rate of 300 drops per min for 500 times initially and the tapped volume Vt was noted.

Dt = M / Vt

Where, M = Mass of powder, Vt = Tapped volume of the powder.

Hausner's ratio:

The ratio of Tapped density and bulk density gives the Hausner's ratio and it was calculated using the following equation.

HR= Dt / Db

Where, Dt = Tapped density of the powder, Db = Bulk density of the powder**.**

Table-5: Limits as per USP

Hausner's ratio	**Powder flow**
1.0-1.11	Excellent
1.1-1.18	Good
1.19-1.25	Fair
1.26-1.34	Possible
1.35-1.45	Very poor
>1.60	Very poor

Compressibility index:

The bulk density and tapped density was measured and compressibility index was calculated by the following equation.

IC = Dt - Db / Dt*100

Where, Dt = Tapped density of the powder, Db = Bulk density of the powder

Table6:Limits as per USP

Compressibility index	Powder flow
<10	Excellent
11-15	Good
16-20	Fair
21-25	Possible
26-31	Poor
31-37	Very poor
>38	Very poor

Angle of Repose:

Accurately weighed powder were poured from a funnel that can be raised vertically until a maximum cone height (h), was obtained. Diameter of heap, (D), was measured. The angle of repose (è) was calculated by the following equations.

tan θ = h / r

where, h= max height of cone, r = radius of heap

Table 7: Limits as per USP

Angle of repose	Powder flow
<25	Excellent
25-30	Good
30-40	Possible
>40	Very poor

Water content:

a) **Karl-Fisher :**Take a suitable quantity of anhydrous methanol in the titration flask & titrate with Karl Fisher reagent till the end point. Crush the pellets to fine powder in a dry mortar, weigh accurately about 0.5g of the sample, transfer quickly to the titration flak, dissolve by stirring and titrate with Karl Fisher reagent to the end point.

Calculation:

$$\% \text{ Moisture} = \frac{V \times F \times 100}{W_T}$$

V = Volume of Karl Fisher reagent consumed for sample

F = Factor of Karl Fisher reagent

W_T = weight of sample taken in mg.

b) LOD: Loss on drying is determined by IR moisture analyzer at 105ºC. About 1gm of sample was placed in analyzer and observed until required temperature was attained. Then loss on drying was determined.

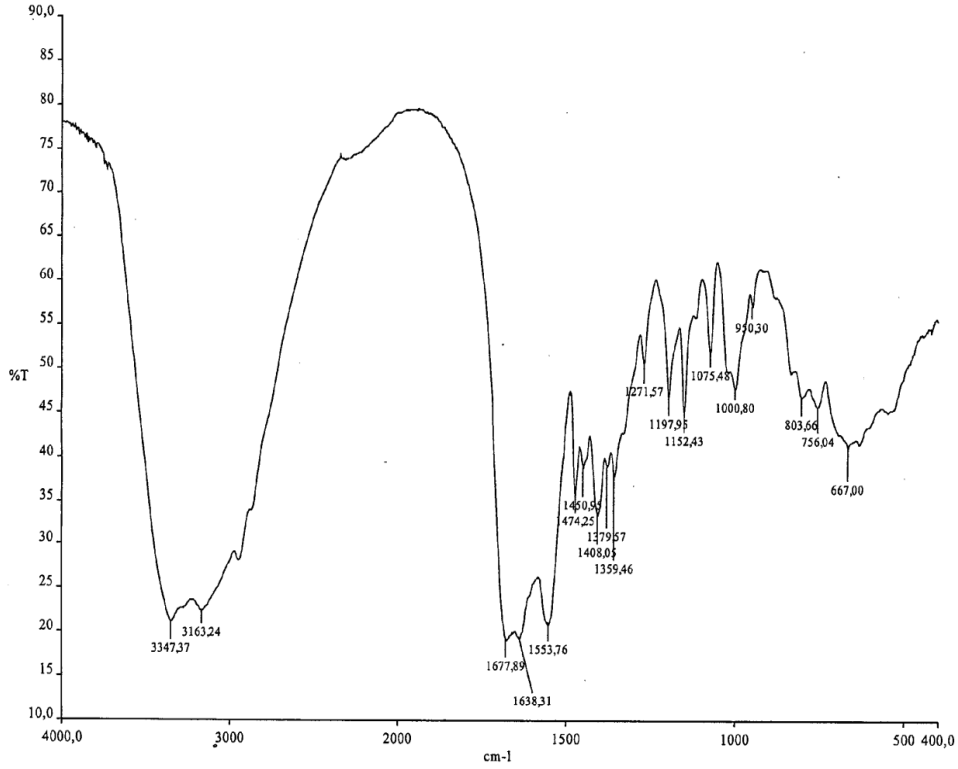
Sieve Analysis:

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 deceasing pore diameter (increasing sieve number) i.e. sieve no. ASTM 40, 60, 80, 00 with 40grams 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 sieves were taken, weighted separately and expressed in terms of percentage.

Figure 5:Study of API with Excipients by FTIR spectroscopy:



FORMULATION DEVELOPMENT METHODS

Preparation of Esomeprazole Magnesium Pellets:

- Mannitol, sucrose, disodium hydrogen phosphate, sodium carboxy methyl cellulose pulverize these materials in a clean pulverizer. Mill fitted with 0.5mm mesh and collect it.
- Pass the milled materials through a clean shifter, fitted with 20#sieve and collect it.
- Load the above materials into a double cone blender along with Esomeprazole magnesium and calcium carbonate. Blend the contents for 45 mins and collect it.
- Purified water taken into water kettle heat to boiling transfer the above hot purified water into a clean vessel.
- Add sodium methyl paraben and sodium propyl paraben to the stirring vessel and continue the stirring until complete dissolution, add sucrose to the above under stirring to get clear solution filter the solution in clean stainless steel kettle.
- Charge the sucrose crystals 30#40 into a dry coating pan .
- Coat the above sucrose crystals with syrup solution till the sugar crystals are wetted.
- Feed the blended drug and excipients on to the above sugar crystals slowly till unform distribution .
- Continue the process of wetting of crystals with syrup and feeding of blended API with excipients till the required size ,if necessary, sieve in between and feed under sized pellets with the blended drug and excipients on to the above sugar crystals slowly till uniform size pellets are obtained.
- The coated pellets taken into clean stainless steel tray and spread them uniformly. Load the trays into clean hot air drier.
- Dry the pellets at 50-55°c for 8hrs. Record the dryer temperature once in every 30 min occasionally.
- Determine the moisture content not more than 3%.
- Switch off the dryer transfer to clean &dry mesh #16 and pass dried pellets collect the 16 tops.
- Fix clean mesh dry mesh #20 and pass the 16 bottoms collect the upper size pellets separately in clean dry polythene bags.

Sub Coating with Mannitol:

- We have taken sucrose in required qty of water for syrup preparation.
- Now switch on the coating pan .Then Esomeprazole Mg pellets were taken in the coating pan.
- Now Mannitol is added to the pellets by wetting them with sugar syrup.
- After the completion of the addition of mannitol then the pellets are taken out and keep in tray drier.
- It is kept for 3 hours in the tray drier and then taken out.
- Then these pellets are sieved in #16 and #20 mesh.

Enteric Coating of Pellets:

- **Preparation of enteric coating solution:**
  - ❖ Collect IPA, acetone to a clean beaker kept under homogenizer add acetyl alcohol, titanium dioxide& HPMCHP55 under stirring continue the stirring until to get homogeneous solution.
  - ❖ Fix the suitable label &keep the vessel in closed condition till use load the mannitol coated pellets into fluid bed coater.
  - ❖ Start enteric coating with coating suspension.
  - ❖ Maintain air pressure at 2-2.5kg/cm²and bed temperature 38-40°c (note down bed temperature &air pressure every half an hour).
  - ❖ Weigh the mannitol coated pellets loaded.
  - ❖ Dry the enteric coated pellets at 38-40°c for 30min &allow to cool.
  - ❖ Unload the dried enteric coated pellets into polythene bags.
  - ❖ Sieve the enteric coated pellets to the required size #16 remove the agglomerates.

Table 8:Enteric coating parameters

Inlet temp	38-40ºC
Bed temp	40-42ºC
Outlet	26-30 ºC
Blower	1600-1900rpm
Atomizing air pressure	2-2.5 bars
Spray Rate	2-6rpm

Table 9: Formulations

Formulations	**Esomeprazole (mg)**	**Mannitol (mg)**	**Sucrose crystals (mg)**	**Sucrose (mg)**	**Disodium hydrogen phosphate (mg)**	**Calcium carbonate (mg)**	**HPMC(E5) (mg)**
F1	40	50	6.22	0.972	0.62	1.16	0.0032
F2	40	75	6.22	0.972	0.62	1.16	0.0032
F3	40	100	6.22	0.972	0.62	1.16	0.0032
F4	40	125	6.22	0.972	0.62	1.16	0.0032
F5	40	150	6.22	0.972	0.62	1.16	0.0032
F6	40	175	6.22	0.972	0.62	1.16	0.0032
F7	40	200	6.22	0.972	0.62	1.16	0.0032

Formulations	Sodium propyl paraben (mg)	Sodium methyl paraben (mg)	Isopropyl alcohol (ml)	Titanium dioxide (mg)	Acetone (ml)	Acetyl alcohol (mg)	Purified water(for syrup &hpmc solution)
F1	0.00006	0.00006	0.4	0.6	0.04	0.6	Q.S
F2	0.00006	0.00006	0.4	0.6	0.04	0.6	Q.S
F3	0.00006	0.00006	0.4	0.6	0.04	0.6	Q.S
F4	0.00006	0.00006	0.4	0.6	0.04	0.6	Q.S
F5	0.00006	0.00006	0.4	0.6	0.04	0.6	Q.S
F6	0.00006	0.00006	0.4	0.6	0.04	0.6	Q.S
F7	0.00006	0.00006	0.4	0.6	0.04	0.6	Q.S

EVALUATION OF PELLETS

Acid resistance(0.1 HCl): Dissolution rate test apparatus filled with paddle:

Apparatus : USP Apparatus II

RPM : 100

Detector : UV 302nm

Medium : 0.1N HCl, 300ml

Temperature : 37°C ± 0.5°C

Sampling interval : 2hours

Diluent: pH 11.0

Dissolve 5.24gms of tribasic sodium phosphate dedecahydrate in water .Add 110ml of 0.5M dibasic sodium phosphate solution ,and dilute with water to 1000ml.

Standard preparation:

Weigh accurately about 10 mg of Esomeprazole working standard, into a 250ml volumetric flask, dissolve in about 10ml of alcohol, add 40ml dilute to volume with water.(conc.0.04mg/ml).

Sample preparation:

Weight and transfer the pellets equivalent to20mg of esomeprazole magnesium individually in each of the dissolution flasks, containing 300ml of 0.1 N Hcl previously which has been equilibrated to the temperature of 37°c±0.5°c. Immediately start the apparatus and run for 2hrs.After 2hrs lift the paddles. Drain the medium completely without losing any pellets. Carefully transfer the pellets into a 100ml volumetric flask individually with the aid of a funnel, add 60 ml of diluent and shake for 20min to dissolve the pellets .Sonicate for few mins if needed, to completely dissolve .Add 20ml of alcohol and sonicate for few min. Cool ,and dilute to volume with dilute mix and filter. Transfer 2.0ml of the solution into a 10ml volumetric flask and dilute to the volume with water and mix (conc. 0.04mg/ml).

Calculation:

For Acid stage:

$$\text{\% labelled amount dissolved} = \frac{A_t \times W_s \times 100 \times 10 \times 100}{A_S \times 250 \times W_T \times 2 \times \text{Assay}} \times P$$

Where:

- At : Peak area due to Esomeprazole Magnesium in sample preparation.
- As : Peak area due to esomeprazole magnesium trihydrate in working standard preparation
- Ws: Weight of Esomeprazole magnesium trihydrate working standard taken in mg
- Wt. : Weight of sample taken in mg.
- Assay : Assay obtained in mg per gm.
- P : Potency of esomeprazole magnesium trihydrate working standard used (on anhydrous basis)

Dissolution in pH 6.8 buffer by UV Spectroscopy:

Dissolution rate test apparatus filled with paddle.

Apparatus : USP Apparatus II

RPM : 100

Medium : pH 6.8 buffer, 1000ml

Temperature : 37°C ±0.5°C

Sampling interval : 60 minutes

Apparatus : UV Spectrophotometer 302nm.

Standard preparation:

Weigh accurately about 40.0 mg of Esomeprazole Magnesium trihydrate working standard ,into a 20ml volumetric flask, dilute to the volume with alcohol.Trasfer 1.0ml of the solution into 100 ml

volumetric flask and dilute to the volume with pH 6.8 phosphate buffer. Take 10ml of this solution, Add of 0.24M sodium hydroxide and mix well.

[Note: Do not allow the solution to stand before adding the sodium hydroxide solution].

Sample preparation:

Weight and transfer the pellets equivalent to 20mg of Esomeprazole Magnesium individually in each of the dissolution flasks, containing 300ml of 0.1M HCL previously which has been equilibrated to the temperature of 37℃ ±0.5℃.Immediately start the apparatus and run for 2 hrs .After 2hrs add 700ml of 0.086M dibasic sodium phosphate ,to a pH of 6.8 phosphate buffer ,collect the sample at regular intervals and filter .Take 5.0ml of the filtrate and add 1.0ml of 0.25M sodium hydroxide, mix observe the absorbance.

For Buffer stage:

$$\text{\% labelled amount dissolved} = \frac{A_T \times W_S \times 1 \times 1000 \times 100}{A_S \times 20 \times 100 \times W_T \times \text{Assay}} \times P$$

Where:

- At : Peak area due to esomeprazole magnesium in sample preparation
- As : Peak area due to esomeprazole magnesium trihydrate in buffer standard preparation
- Ws: Weight of Esomeprazole magnesium trihydrate working standard in mg.
- Wt. : Weight of sample taken in mg.
- Assay : Assay obtained in mg per gm
- P : Potency of esomeprazole magnesium trihydrate working standard used (on anhydrous basis)

RESULTS AND DISCUSSION:

Table-10: Standard Calibration Curve:

S.no	Concentration(µg/ml)	Absorbance
1	5	0.15
2	10	0.30
3	15	0.45
4	20	0.61
5	25	0.76
6	30	0.92

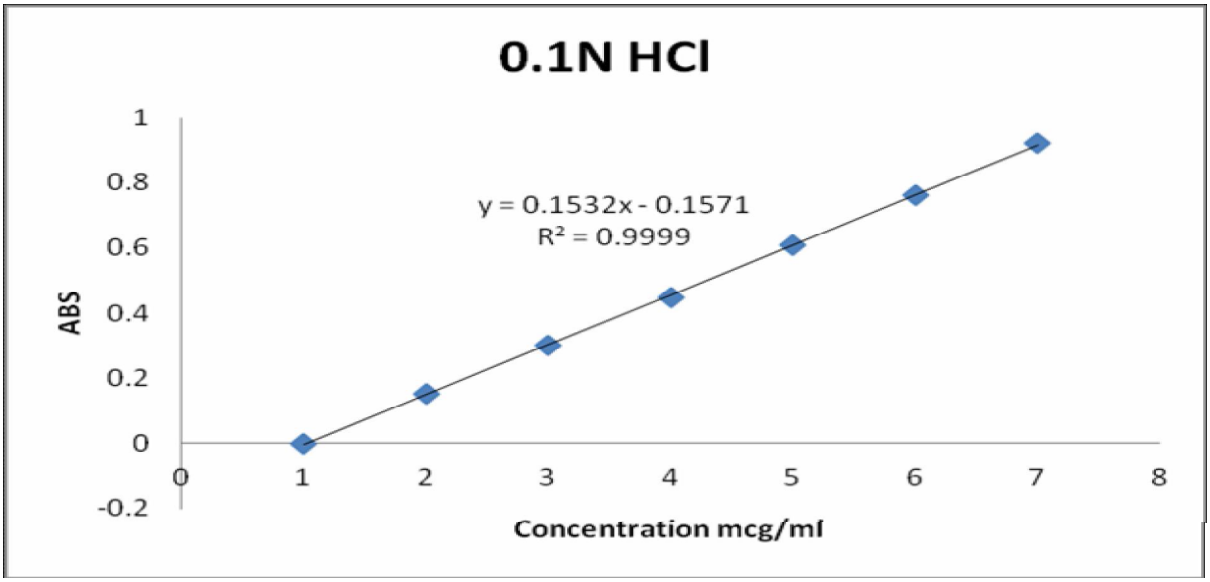


Figure :6 Standard graph

Preformulation studies:

Table-11:Bulk density and Tapped density:

S. no	Formulations	Bulk density(gm/cc)	Tapped density(gm/cc)
1	F1	0.714	0.719
2	F2	0.719	0.724
3	F3	0.724	0.735
4	F4	0.725	0.729
5	F5	0.735	0.719
6	F6	0.724	0.735
7	F7	0.719	0.719

Table-12 :Compressibility index and Hausner's ratio:

S.no	Formulations	Compressibility index (%)	Hausner's ratio
1	F1	0.690	1.006
2	F2	1.496	1.015
3	F3	2.176	1.022
4	F4	2.162	1.022

5	F5	2.176	1.022
6	F6	2.05	1.021
7	F7	1.371	1.013

Table-13 : Angle of Repose and Percentage of water:

S.no	Formulations	Angle of repose	Percentage of water
1	F1	25°80′	2.35
2	F2	25°91′	2.16
3	F3	25°12′	2.76
4	F4	28°34′	2.02
5	F5	27°15′	2.60
6	F6	27°30′	2.81
7	F7	27°18′	2.84

Table-14 :Drug Excipients Compatibility Study

S. No.	Composition Details	40ºC/ 75%RH		
		1M	2M	3M
1	Esomeprazole alone	NCC	NCC	NCC
2	Esomeprazole +Mannitol	NCC	NCC	NCC
3	Esomeprazole +HPMC E5	NCC	NCC	NCC
4	Esomeprazole+Calcium carbonate	NCC	NCC	NCC
5	Esomeprazole +Sucrose	NCC	NCC	NCC
6	Esomeprazole +HPMC HP55	NCC	NCC	NCC
7	Esomeprazole+HPMC HP55	NCC	NCC	NCC
8	Esomeprazole +Disodiumhydragen phosphate	NCC	NCC	NCC
9	Esomeprazole +Cetyl alcohol	NCC	NCC	NCC
10	Esomeprazole +Titanium dioxide	NCC	NCC	NCC

Dissolution Studies:

Comparative Invitro Dissolution Studies

Percentage labeled amount of Lansoprazole dissolved in 0.1N HCl =Percentage labeled amount of Lansoprazole (assay) - Percentage labeled amount of Lansoprazole retained in 0.1N HCl (acid resistance).

%labelled amount of drug dissolved in 0.1N HCl =%labelled amount(assay) -

Release kinetics

Zero order release kinetics

It defines a linear relationship between the fractions of drug released versus time.

$$\mathbf{Q = k_o t}$$

Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant.A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First order release kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

$$\mathbf{\ln (1-Q) = -k_1 t}$$

Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant.Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$\mathbf{Q = k_2 t^{1/2}}$$

Where, K_2 is the release rate constant.

A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent.

Erosion equation

This equation defines the drug release based on tablet erosion alone.

$$\mathbf{Q = 1 - (1 - K_3 t)^3}$$

Where, Q is the fraction of drug released at time t, K_3 is the release rate constant. Thus, a plot between $(1-Q)^{1/3}$ against time will be linear if the release obeys erosion equation.

Table -15: *In vitro* Release Profile of Percentage Cumulative Drug Release from Various formulations and Acid Resistance Dissolution Data:

Time in Minutes	**F1**	**F2**	**F3**	**F4**
Dissolution profile				
0	0.00	0.00	0.00	0.00
5	24± 0.91	32.16±0.38	33.41±0.28	30.09±0.75
10	33.6± 0.72	40.09±0.80	47.29±0.18	38.96±0.78
15	50.08±0.75	60±0.73	62±0.38	58.82±0.48
30	61.48±0.81	72.59±0.58	76±0.48	70.05±0.57
45	77.74±0.81	81.8±0.68	90±0.48	80±0.29
60	92.36±0.97	97±0.89	99.58±0.69	96.64±0.72
Acid Resistance Dissolution Data				
0	0.00	0.00	0.00	0.00
60	0.90±0.21	1.50±0.56	2.5±0.25	2.00±0.30
120	1.5±1.22	2.48±1.53	3.2±1.23	2.27±1.27

Timein minutes	**F5**	**F6**	**F7**	**INNOVATOR**
	Dissolution profile			
0	0.00	0.00	0.00	0.00
5	36.63±0.45	34.45±0.67	39±0.67	23.38±0.68
10	40.03±0.26	41.23±0.76	41.13±0.89	35.06±0.75
15	58.38±0.89	51.53±0.65	60±0.26	52.11±0.93
30	74.51±0.18	73.29±0.48	78±0.67	63.96±0.78
45	87.13±0.48	87.79±0.59	88.62±0.84	75.43±0.51
60	98.65±0.84	97.41±0.43	99.12±0.51	93±0.57
	Acid resistance Dissolution profile			

0	0.00	0.00	0.00	0.00
60	1.50±0.90	2.62±0.26	1.00±0.28	0.9±0.51
120	2.86±1.87	2.84±2.1	2.91±2.6	1±2.47

Each value represents the Mean ± s.d. (n=3).

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to popular release models such as zero-order, first-order, Higuchi equation, erosion and peppas equations. The order of drug release from matrix systems was determined by using zero order kinetics or first order kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation, erosion and Peppas equation.

Figure-7:Zero order release dissolution Release Profiles for Formulations Trails-Innovator:

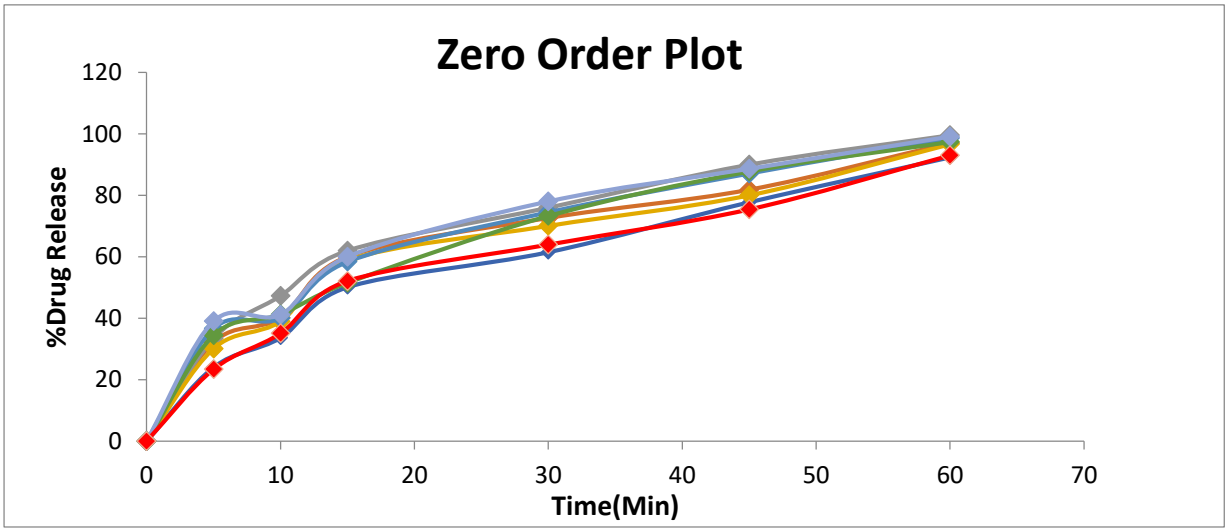
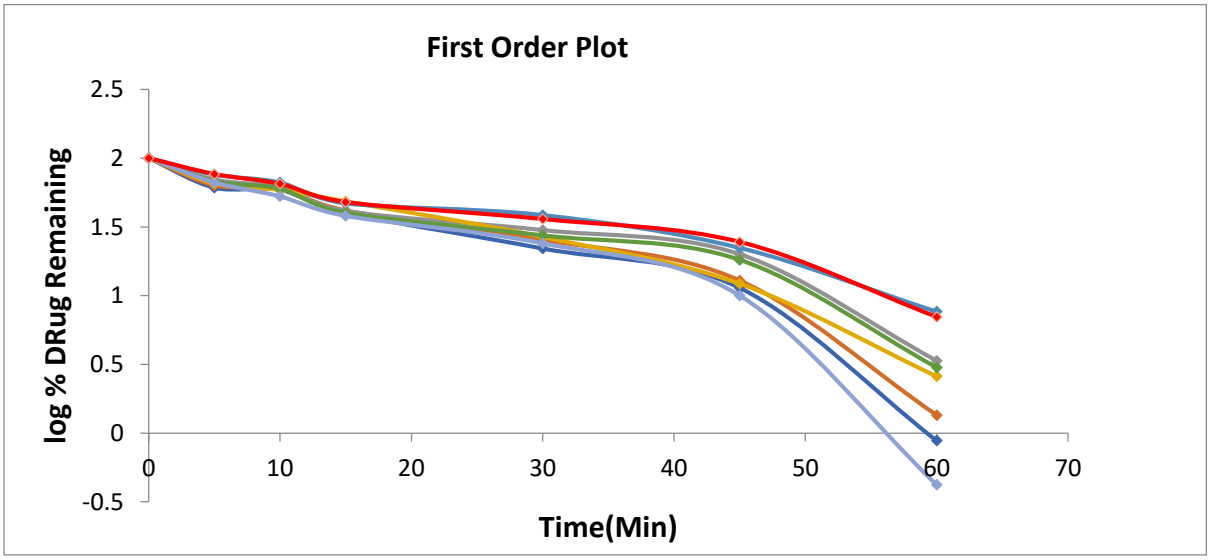
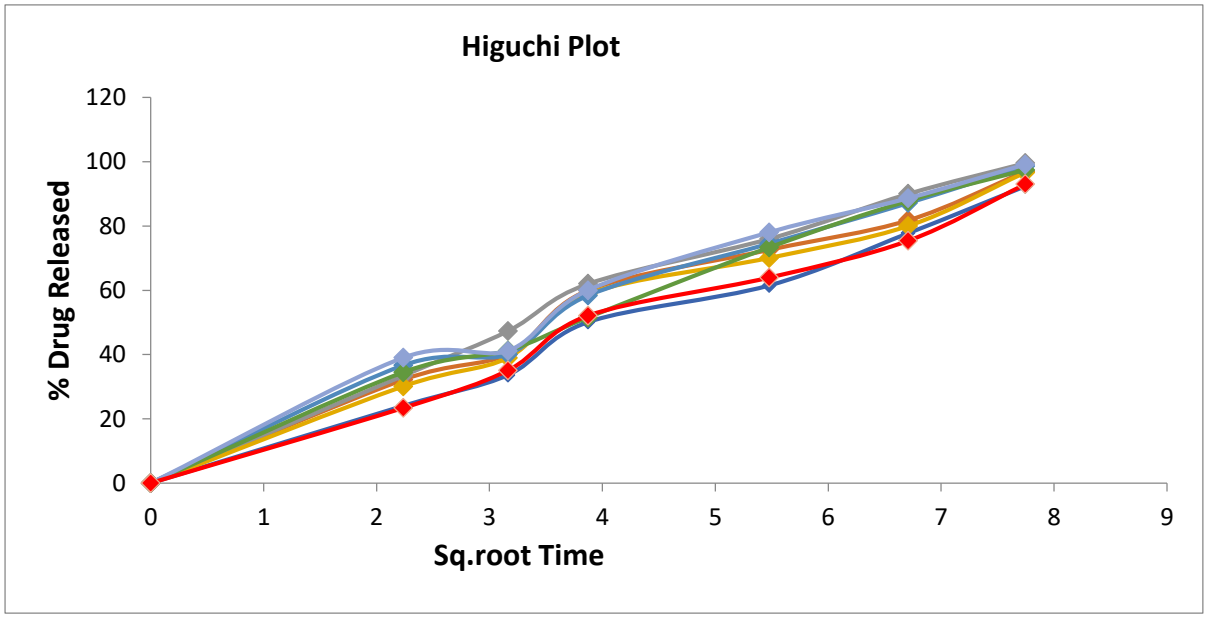


Figure-8:First Order Drug Release Profiles for Formulations Trails-Innovator:



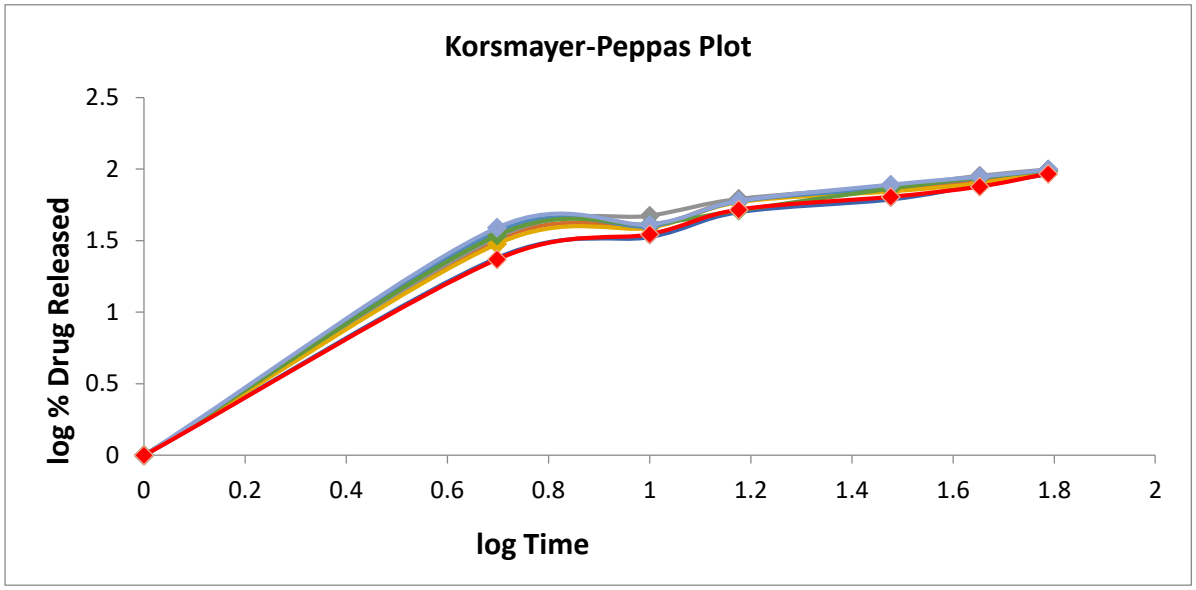
First Order Release Profile

Figure-9:Higuchi Pharmacokinetic Release Profiles for Formulations F7-Innovator:



Higuchi Release Profile

Figure-10:Korsmayer-Peppas Pharmacokinetic Release Profiles for Formulations F7-Innovator:



Korsmayer-Peppas Release Profiles

Kinetic Release Profiles for Optimized F7 Formulation:

Figure-11:Zero Order Release profile for Optimized F7 Formulation:

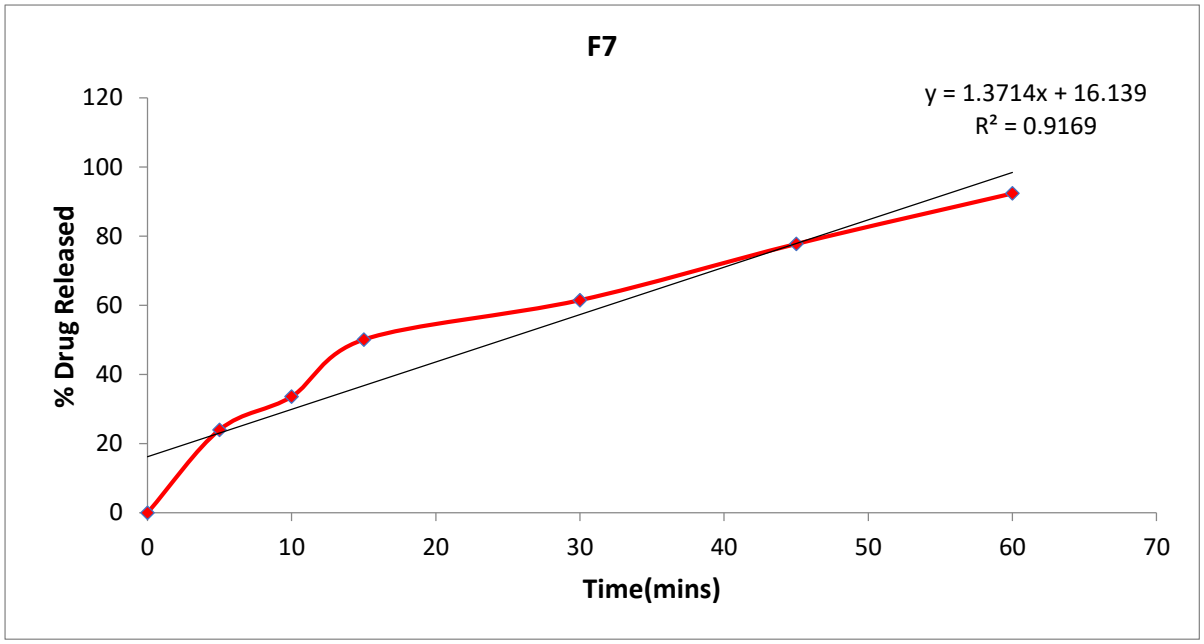
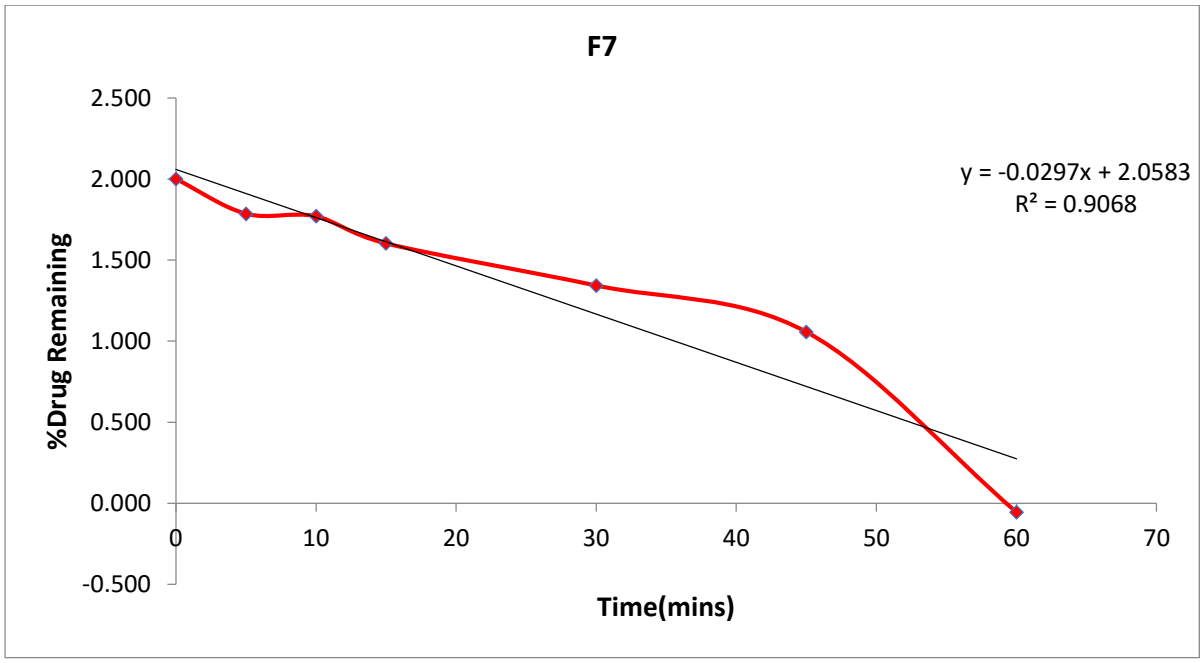


Figure-12:First Order Release profile for Optimized F7 Formulation:



First Order Release profile

Figure-13:Higuchi Release profile for Optimized F7 Formulation:

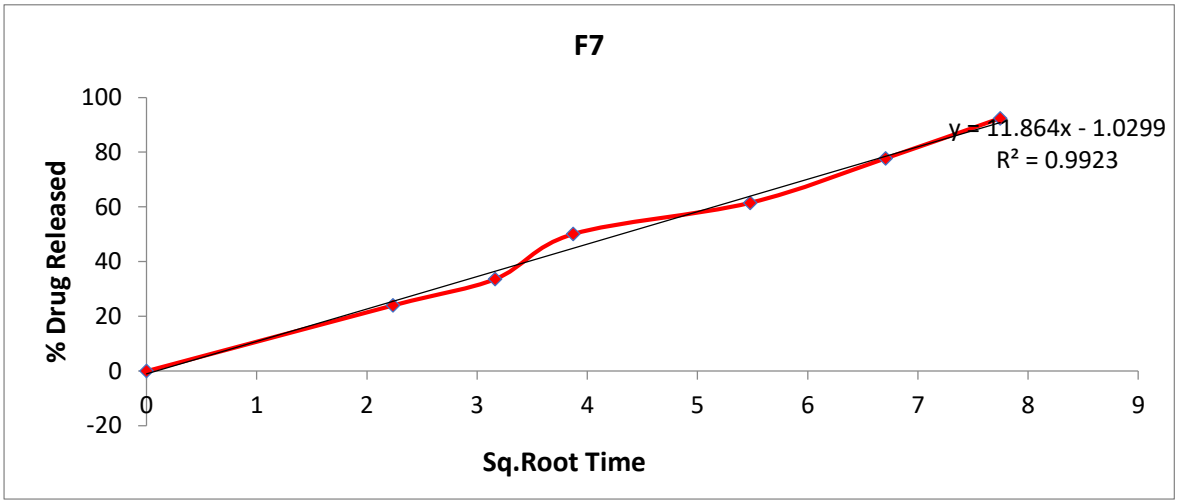
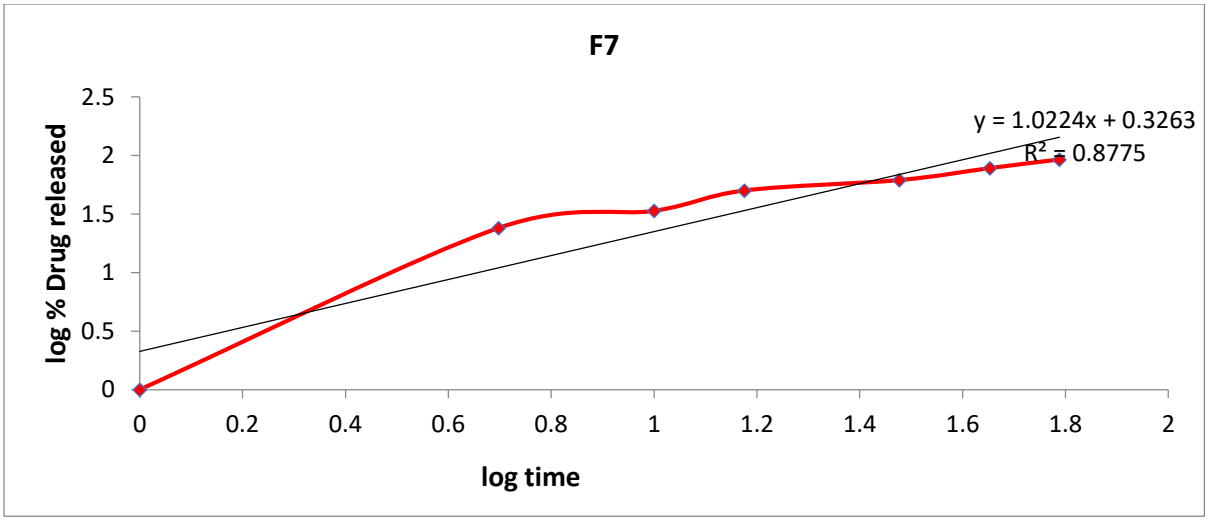


Figure-14:Korsmayer-Peppas Release profile for Optimized F7 Formulation:



Kinetic Release Profiles for Innovator Formulation:

Figure-15:Zero Order Release profile for innovator:

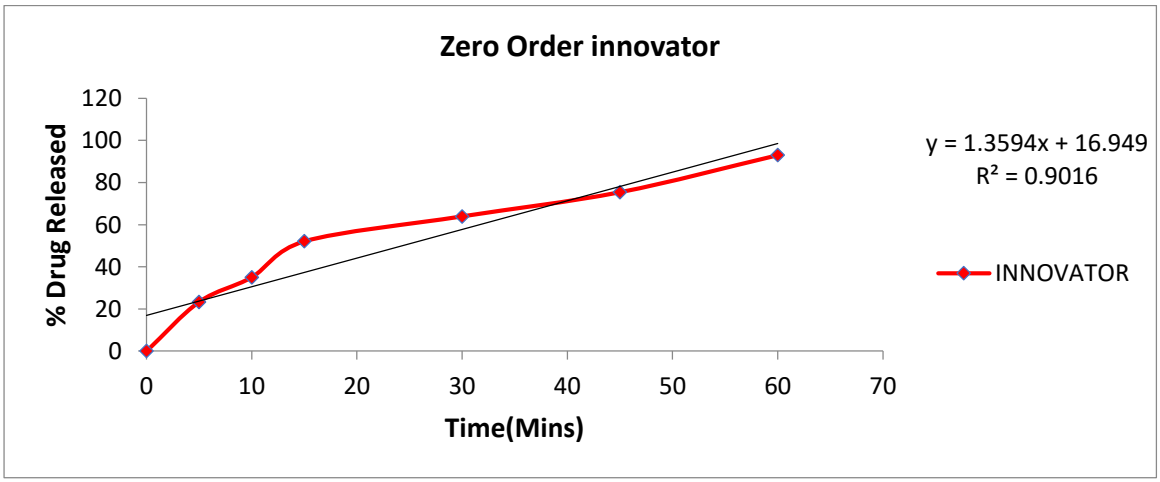


Figure-16:First Order Release profile for innovator:

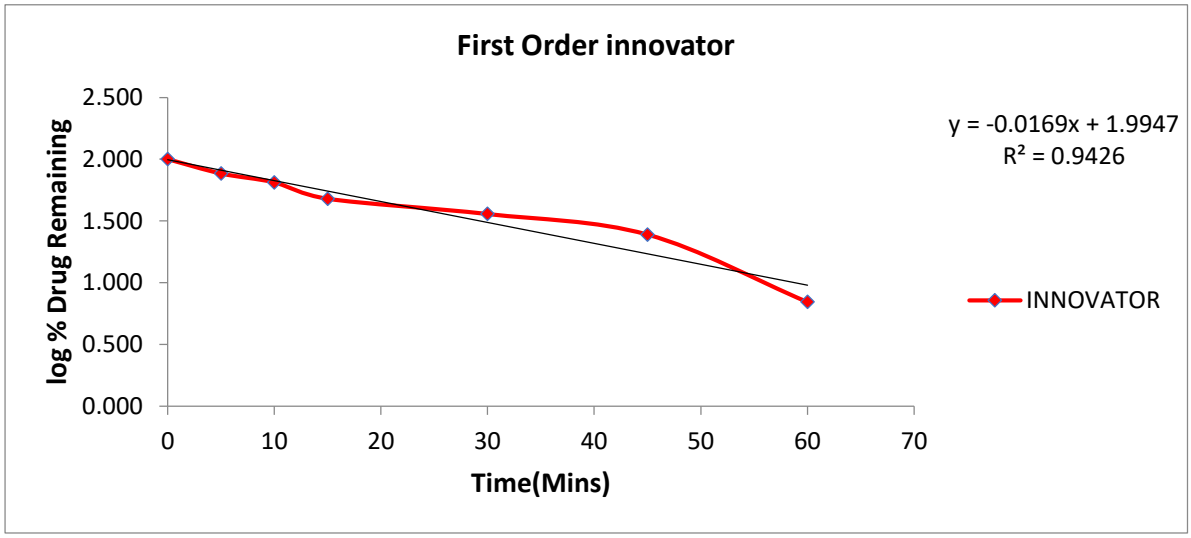


Figure-17:Higuchi Release profile for innovator:

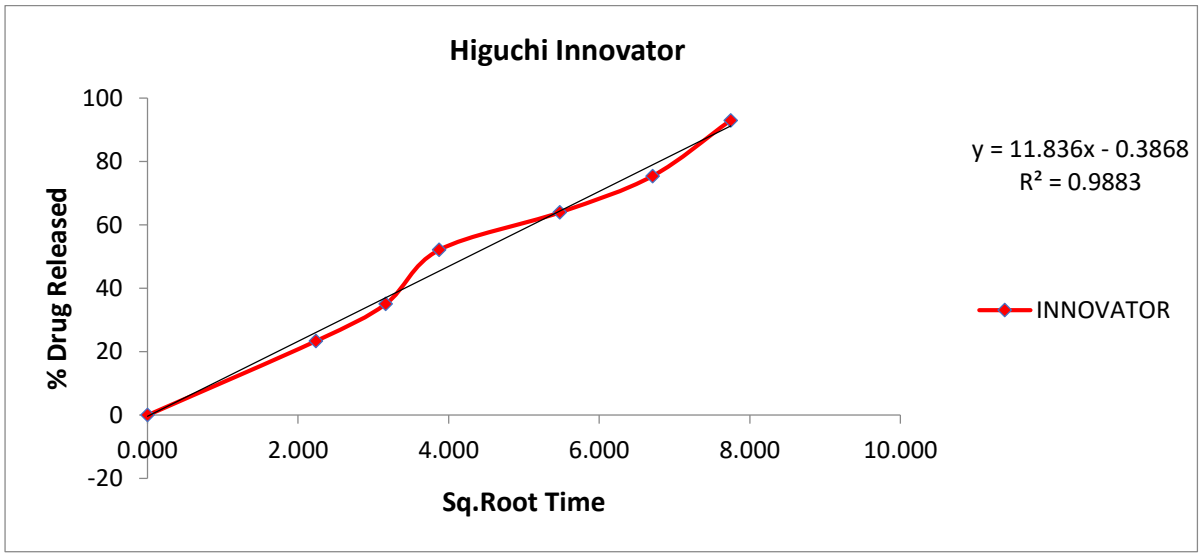


Figure-18:Korsmayer-Peppas Release profile for innovator:

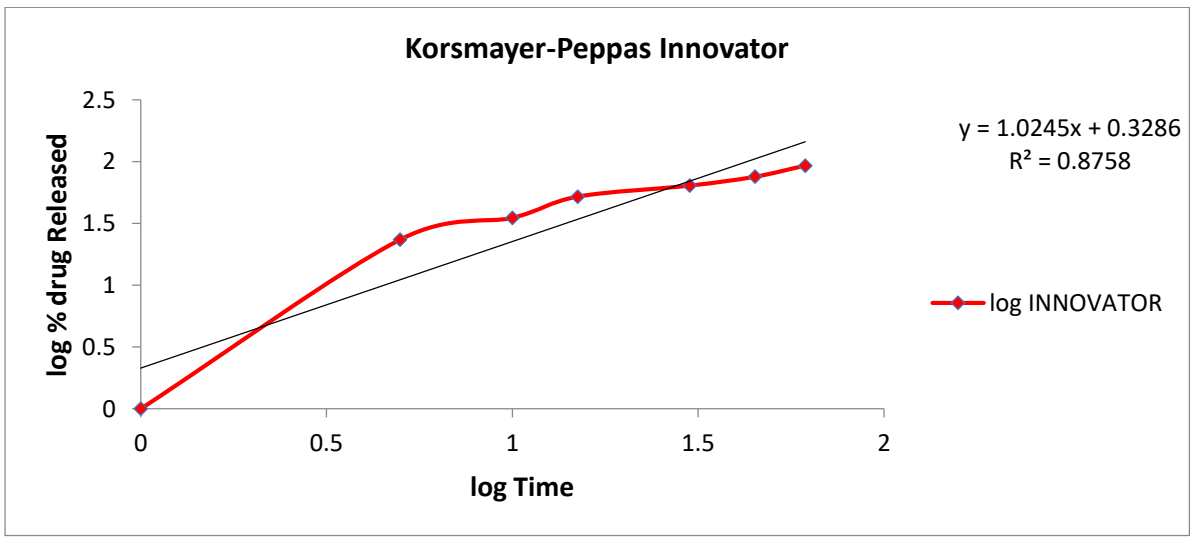
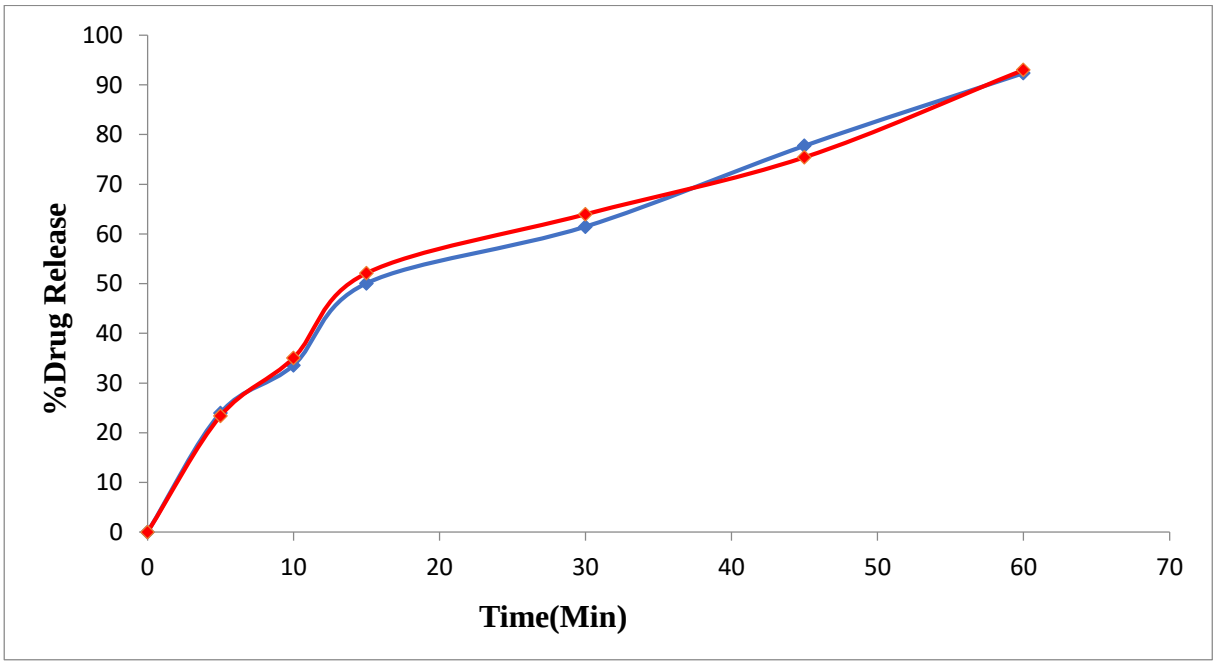


Table - 16:Comparative Dissolution Profile of F7 with Innovator

TIME	F7	INNOVATOR
0	0.00	0.00
5	39±0.67	23.38±0.68
10	41.13±0.89	35.06±0.75
15	60±0.26	52.11±0.93
30	78±0.67	63.96±0.78
45	88.62±0.84	75.43±0.51
60	99.12±0.51	93±0.57

Figure-17:Comparative Dissolution Profile of F7 with Innovator



The F7 formulation percentage drug release in acid stage and release profile in buffer stage complies with the innovator. To confirm this further trial was conducted with mannitol and plasticizer concentration.From the above results, F7 formulation was found to be optimized formulation of Esomepraprazole magnesium delayed release pellets. Rest all the formulations were found to deviate from the reference.

Table-17*: In-vitro* Release Kinetic Data:

Formulation Code	Zero Order (r^2)	First Order (r^2)	Higuchi (r^2)	Peppas (r^2)
F1	0.916	0.906	0.992	0.877
F2	0.853	0.913	0.981	0.837
F3	0.843	0.913	0.985	0.830
F4	0.865	0.959	0.982	0.844
F5	0.862	0.956	0.986	0.826
F6	0.886	0.921	0.995	0.837
F7	0.844	0.875	0.980	0.819
Innovator	0.901	0.942	0.988	0.875

Dissolution profile for stability samples at different storage conditions

- **Acid stage:** 0.1 N HCl, 500ml, Basket, 100rpm, 120 minutes.
- **Buffer stage:** pH 6.8 phosphate buffer, 900ml, Basket, 100rpm,

  Sampling points 10, 20, 40, 50, 60 minutes.

Table 18: Dissolution profile of stability samples

Time(min)	40°C / 75% RH% drug release		
	1 month	**2 month**	**3 month**
0	0	0	0
10	40.01	40.05	40.10
15	41.20	41.26	41.30
30	60.04	60.10	60.14
45	89.02	89.25	89.31
60	99.25	99.29	99.34

Optimized formulation (F7) was kept for stability studies and observed the dissolution profile. There was no significant change in i*nvitro* release profile. It shows that formulation F7 is stable.

CONCLUSION

- ✓ Esomeprazole magnesium is a proton pump inhibitor and is used in the treatment of ulcers.
- ✓ It is acid sensitive drug. It degrades in the acidic pH . So we have to protect in acidic environment. Drug should release in basic environment so that I had formulated enteric coated pellets.
- ✓ In this study sub coating is done by mannitol. Mannitol is used for drug loading pellets as a sub coating with various concentrations.
- ✓ The prepared pellets were evaluated for Bulk density, tapped density, Drug-Excipient interaction study, Drug content, and in-vitro Dissolution of various formulations. From that optimized batch was selected and compared with Innovator's product.

From the present study, the fallowing conclusion can be drawn:

1. Esomeprazole magnesium pellets were formulated by layering technique. The obtained pellets were found to be good.
2. IR studies indicate that the drug is compatible with polymer.
3. The drug content was found to be uniform in all the formulations of prepared pellets.
4. Drug release was found to approximately follow Zero order kinetics.

From the reproducible results obtained from the executed experiments it can be concluded that:

1. Mannitol layer is the barrier layer between drug layer and enteric layer. If it is not present degradation of the drug occur.
2. Calcium Carbonate is the ingredient acts as base used for the stability of the pellets.
3. In optimized formulation the percentage drug in acid stage and in buffer stage complies with innovator.
4. Optimized formulation was kept for stability studies and observed the dissolution profile. There is no significant change in invitro release.
5. HPMC E5 and HPMC E55 controls the drug release in acidic environment because it is pH sensitive polymer. It solubilizes at the pH of 5.5.

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