DESIGN, DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE MULTIPLE UNIT PELLETS FOR POTENTIAL DELIVERY OF ANTIULCERANTS

THESIS

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Submitted by
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Under the guidance of
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This is to certify that the Ph.D., dissertation entitled "**DESIGN, DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE MULTIPLE UNIT PELLETS FOR POTENTIAL DELIVERY OF ANTIULCERANTS"** being submitted to The TN Dr.M.G.R Medical University, Chennai for the award of **Doctor of Philosophy** in **Faculty of Pharmacy** was carried out by **Mr**. **K.SELVARAJU** at KMCH College of Pharmacy, Coimbatore under my direct supervision and guidance to my fullest satisfaction. The content of this in full or in parts have not been submitted to any other institute or University for the award of any degree or diploma.

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DECLARATION

I hereby declare that the Ph.D., dissertation entitled **DESIGN, DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE MULTIPLE UNIT PELLETS FOR POTENTIAL DELIVERY OF ANTIULCERANTS** being submitted to The TN Dr.M.G.R.Medical University, Chennai for the award of **Doctor of Philosophy** in **Faculty of Pharmacy** was carried out under the direct supervision and guidance of **Dr.K.S.G.ARULKUMARAN**, Vice-Principal, KMCH College of Pharmacy, Coimbatore during the academic year 2013-2017.The content of this thesis in full or in parts have not been submitted to any other institute or University for the award of any degree or diploma.

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K.SELVARAJU

CONTENTS

LIST OF ABBREVATION

ABBREVATION	FULL FORM
MUPS	Multiple Unit pellets
mm	Millimeter
µm	Micrometer
GIT	Gastro intestinal Tract
API	Active pharmaceutical ingredients
MCC	Micro crystalline cellulose
%	Percentage
w/w	Weight by weight
FD & C	Food drug and cosmetic act
RPM	Rotation per minute
Hcl	Hydrochloric acid
g	Grams
RH	Relative humidity
HPMC	Hydroxy propyl methyl cellulose
AUC	Area under Curve
C_{max}	Maximum concentration
T_{max}	Maximum time
mg	Milligram
Kg	Kilogram
SEM	Scanning electron microscope
FTIR	Fourier transfer infrared
PVP	Polyvinyl pyrrolidine
UV	Ultra violet-visible
µg/ml	Micro gram per milliliter
p^H	Hydrogen ion concentration
ICH	International Conference on Harmonisation
PVP	Polyvinyl prrolidine
LOD	Loss on drying
KBr	Pottasium bromide
D_B	Bulk density
M	Mass of powder
V_b	Bulk volume of the powder
D_T	Tapped volume of the powder
V_t	Tapped volume of the powder
(θ)	Angle of repose
H	Height
R	Radius
D_t	Tapped density of the powder
D_b	Bulk density of the powder
I	Carr's index
q.s	Quantity sufficient
USP	United states of pharmacopeia
BP	British pharmacopeia
IP	Indian pharmacopeia

˚C	Degree Celsius
mL	Milliliters
Cm	Centimeters
Hrs	Hours
min	Minutes
sec	Seconds

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1. INTRODUCTION

Peptic Ulceration is one of the common disease affecting millions of people. It is now considered to be one of modern age epidemics affecting nearly 10 % of world population. This disease is triggered by an imbalance between host defence mechanism such as mucous secretion and cellular regeneration and damaging agents such as acid and pepsin secretion. Inadequate dietary habits, alcohol abuse, the prolonged use of Non Steroidal Anti Inflammatory drugs (NSAIDs), Stress, Helicobacter pylori and genetic factors may all cause inflammation of the gastric mucosa.

CLASSIFICATION OF PEPTIC ULCER:

By location:

- Duodenum (called duodenal ulcer)
- Esophagus (called esophageal ulcer)
- Stomach (called gastric ulcer)
- Meckel's diverticulum (called Meckel's diverticulum ulcer; is very tender with palpation)

Modified Johnson Classification of Peptic ulcer:

- Type **I**: Ulcer along the body of the stomach, most often along the lesser curve at incisures angularis along the locus minoris resistantiae. Not associated with acid hyper secretion.
- Type **II**: Ulcer in the body in combination with duodenal ulcers. Associated with acid oversecretion.
- Type **III**: In the pyloric channel within 3 cm of pylorus. Associated with acid over secretion.

- Type **IV**: Proximal gastro esophageal ulccerType **V**: Can occur throughout the stomach. Associated with the chronic use of NSAIDs (such as ibuprofen).

GASTRIC ULCERS

Incidence: Usually 50 and over

- Male: female ratio 1:1
- 15% of peptic ulcers are gastric
- ***Signs, Symptoms, and Clinical Findings***
- Normal—hypo secretion of stomach acid (HCl)
- Weight loss may occur
- Pain occurs 1⁄2 to 1 hour after a meal may be relieved by vomiting; ingestion of food does not help, sometimes increases pain
- Vomiting common
- Hemorrhage more likely to occur than with duodenal ulcer; hematemesis more common than melena

Risk Factors

- *pylori*, gastritis, alcohol, smoking, use of NSAIDs, stress

DUODENAL ULCERS

Incidence: Age 30–60

- Male: female ratio 2–3:1
- 80% of peptic ulcers are duodenal

Signs, Symptoms, and Clinical Findings

- Hyper secretion of stomach acid (HCl)
- May have weight gain
- Pain occurs 2–3 hours after a meal
- ingestion of food relieves pain

- Vomiting uncommon
- Hemorrhage less likely than with gastric ulcer, but if present melena more common than hematemesis
- More likely to perforate than gastric ulcers

Malignancy Possibility

- Rare

Risk Factors

- *pylori*, alcohol, smoking, cirrhosis, stress

ZOLLINGER ELLISON SYNDROME (ZES):

- ZES consists of severe peptic ulcers, extreme gastric hyperacidity, and gastrin-secreting benign or malignant tumors of the pancreas.
- ZES is suspected when a patient has several peptic ulcers or an ulcer that is resistant to standard medical therapy.
- It is identified by the following findings: hypersecretion of gastric juice, duodenal ulcers, and gastrinomas (islet cell tumors) in the pancreas.

STRESS ULCERS:

- *Stress ulcer* is the term given to the acute mucosal ulceration of the duodenal or gastric area that occurs after physiologically stressful events, such as burns, shock, severe sepsis, and multiple organ traumas.
- These are clinically different from peptic ulcer. These ulcers are most common in ventilator-dependent patients after trauma or surgery.
- Fiberoptic endoscopy within 24 hours after injury reveals shallow erosions of the stomach wall; by 72 hours, multiple gastric erosions are observed. As the stressful

condition continues, the ulcers spread. When the patient recovers, the lesions are reversed. This pattern is typical of stress ulceration.

- Stress ulcers should be distinguished from Cushing's ulcers and Curling's ulcers, two other types of gastric ulcers. Cushing's ulcers are common in patients with trauma to the brain. They may occur in the esophagus, stomach, or duodenum and are usually deeper and more penetrating than stress ulcers. Curling's ulcer is frequently observed about 72 hours after extensive burns and involves the antrum of the stomach or the duodenum.

ESOPHAGEAL ULCERS:

Esophageal ulcers occur as a result of the backward flow of HCl from the stomach into the esophagus (gastroesophageal reflux disease [GERD]).

PATHOPHYSIOLOGY:

Peptic ulcers occur mainly in the gastro duodenal mucosa because this tissue cannot withstand the digestive action of gastric acid (HCl) and pepsin.

The use of NSAIDs inhibits the secretion of mucus that protects the mucosa.

Patients with duodenal ulcer disease secrete more acid than normal, whereas patients with gastric ulcer tend to secrete normal or decreased levels of acid.

Ninety percent of tumors are found in the "gastric triangle," which encompasses the cystic and common bile ducts, the second and third portions of the duodenum, and the neck and body of the pancreas. Approximately one third of gastronomes are malignant.

CLINICAL MANAFESTATIONS:

Abdominal discomfort is the most common symptom of both duodenal and gastric ulcers. Felt anywhere between the navel and the breastbone, this discomfort usually is a dull or burning pain occurs when the stomach is empty—between meals or during the night may be briefly relieved by eating food, in the case of duodenal ulcers, or

by taking antacids, in both types of peptic ulcers lasts for minutes to hours comes and goes for several days or weeks

Other symptoms include

- weight loss
- poor appetite
- bloating
- burping
- nausea
- vomiting

Some people experience only mild symptoms or none at all.

Emergency Symptoms:

A person who has any of the following symptoms should call a doctor right away:

- sharp, sudden, persistent, and severe stomach pain
- bloody or black stools
- bloody vomit or vomit that looks like coffee grounds
- These “alarm” symptoms could be signs of a serious problem, such as
- Bleeding—when acid or the peptic ulcer breaks a blood vessel.
- Perforation—when the peptic ulcer burrows completely through the stomach or duodenal wall.
- Obstruction—when the peptic ulcer blocks the path of food trying to leave the stomach.

Fig:1.1 Gastrointestinal tract

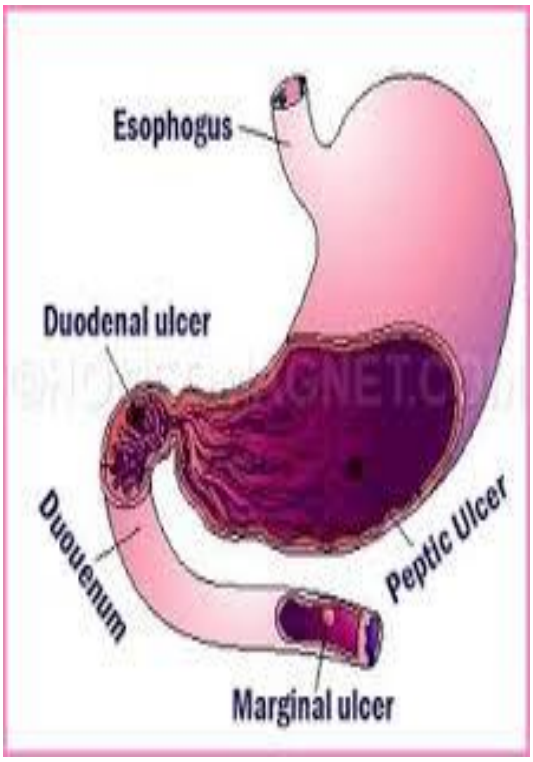


Fig:1.2 Peptic Ulcer

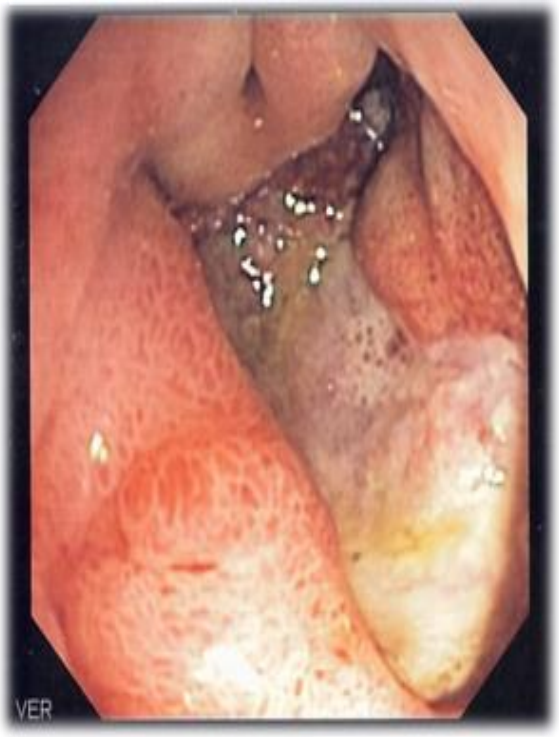


Fig:1.3 Peptic Ulcer

Fig:1.4 H.pylori

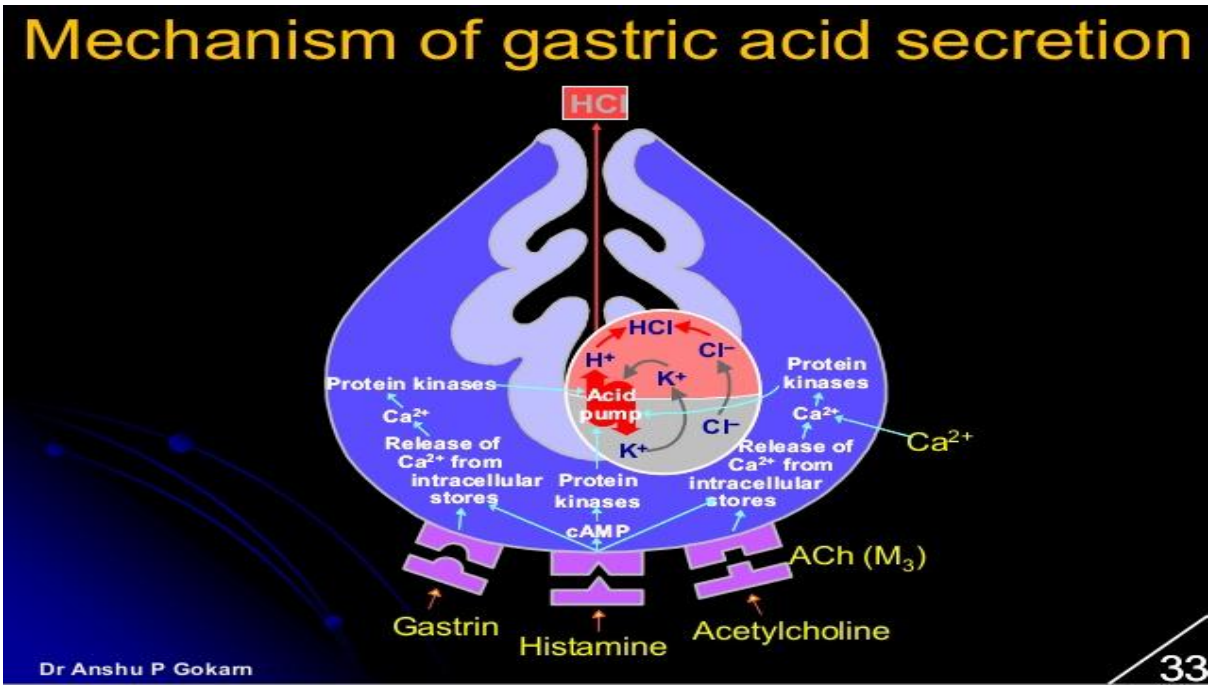


Fig:1. 5 Mechanism of gastric acid secretion

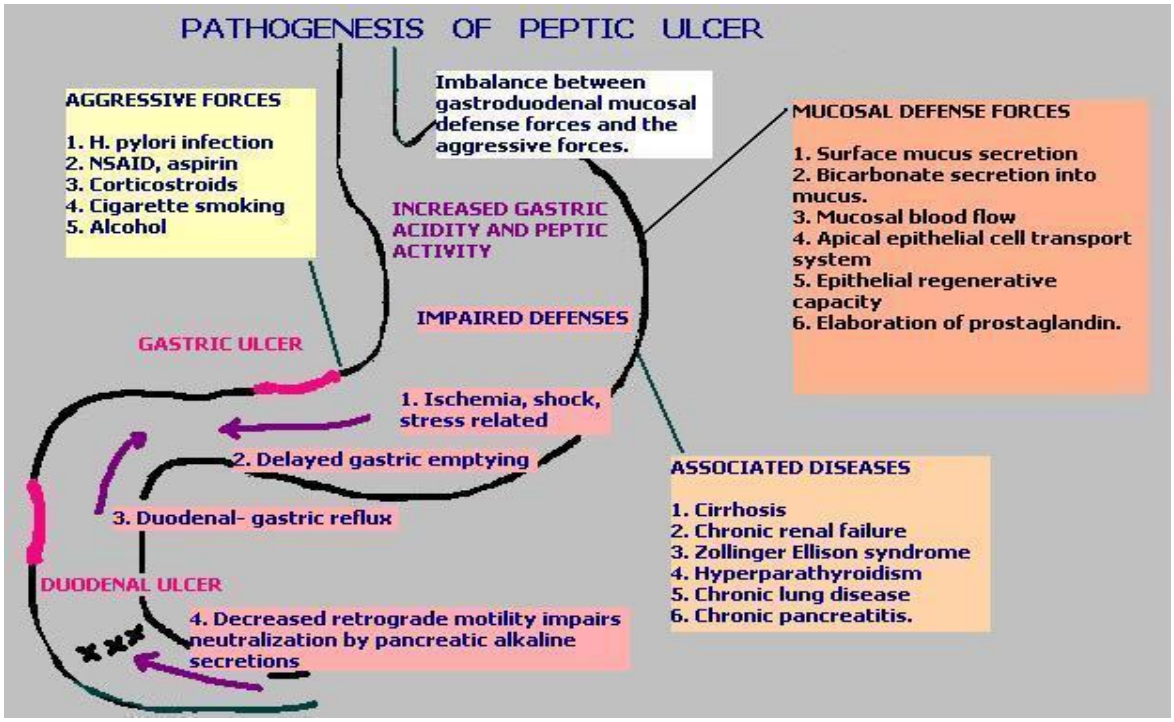


Fig:1.6 Pathogenesis of peptic ulcer

REGULATION OF GASTRIC ACID SECRETION :

The mechanism operating at the gastric parietal cells are summarized. The terminal enzyme H^+K^+ ATPase (proton pump) which secretes H^+ inos in the apical canaliculi of parietal cells can be activated by histamine, ACh and gastrin acting *via* their own receptors located on the baso lateral membrane of these cell. Out of the three physiological secretagogues,histamine ,acting through H_2receptors,play the dominant role , because the other two ,gastrin and ACh act partly directly and to a greater extent indirectly by releasing histamine from paracrine entrochromaffin -like cell called "histaminocytes" located in oxyntic glands. While H_2 receptor activate H^+K^+ ATPase by generating cAMP muscarinic and gastrin /cholecystokinin (CCK_2) receptors appear to function through the phospholipase C→IP_3-DAG pathway that mobilizes intracellular ca^{2+} . The cAMP mediated proton pump activation also involves Ca^{2+} . The cAMP mediated proton pump activation also involves Ca^{2+}. The secretomotor response to gastrin and cholinergic agonists is expressed fully only in the presence of cAMP generated by H_2 activation .As such, histamine participates in the acidresponse to gastrin and ACh at more than one levels and H_2 antagonists suppress not only histamine ,but also ACh, pentagastrin and in fact any gastric acid secretory stimulus.

Gastrin is secreted from the antrum in response to rise in antral pH, food constituents and vagally medicated reflexes. The dominant muscarinic receptor medicating vagal responses is of the M_1subtype.Its location on the ganglion cells of muscarinic receptor is of the M_3 subtype but the subtype of muscarinic receptor on histaminocytes has not been defined. Vagus releases ACh in close proximity to histaminocytes and gastrin secreting cells , but the apparently at a distance from the

parietal cell. As such, vagal effects are exerted largely indirectly through histamine and gastrin .

Prostoglandins have been ascribed a “cytoprotective” role in gastric mucosa by augmenting mucus and bicarbonate secretion byopposing cAMP generation (in parietal cell) and gastrin release (from antral cells).

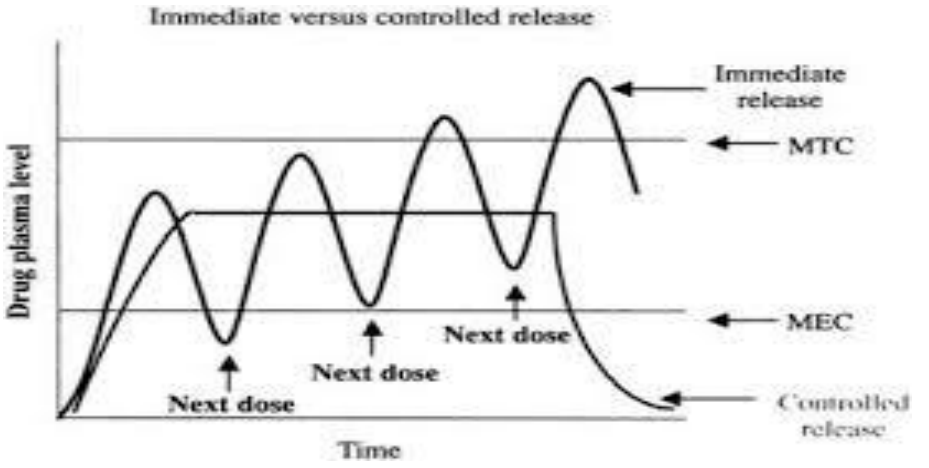
APPROACHES FOR THE TREATMENT OF PEPTIC ULCER ARE[1]:

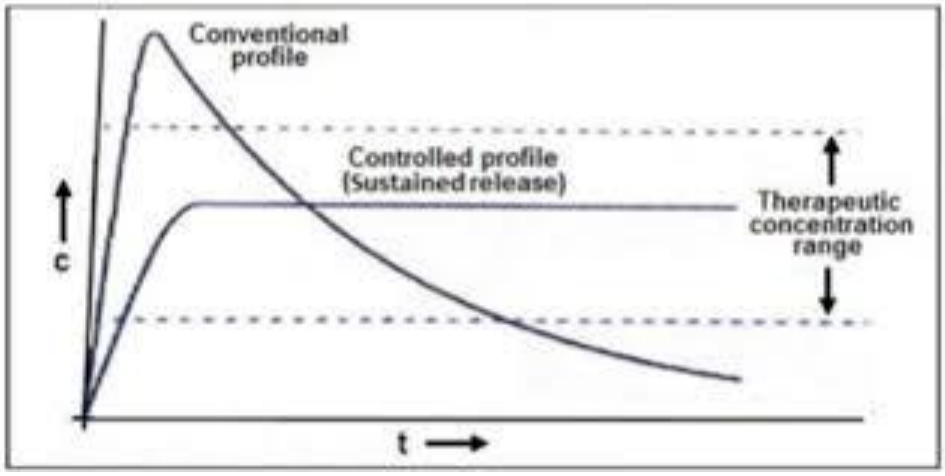
1. **Reduction of gastric acid secretion**
   a) H_2 antihistamines: Cimetidine ,Ranitidine,Famotidine, Roxatidine.
   b) Proton pump inhibitors: Omeprazole,Lansoprazole, Pantopraole,Rabeprazle, Esomeprazole
   c) Anticholinergics: Pirenzepine, Propantheline,Oxyphenonium
   d) Prostaglandin analogue : misoprostol
2. **Neutralization of gastric acid (antacids)**
   a) Systemic : Sodium carbonate, sodium citrate
   b) Non systemic: Magnesium hydroxide, Magnesium trisilicate, Aluminium hydroxide gel,Magaldrate, Calcium carbonate.
3. **Ulcer protectives:** sucralfate, colloidal bismuth subcitrate (CBS)
4. **Anti -H.pylori drugs**: Amoxicillin, Clarithromycin, Metronidazole, Tinidazole,Tetracycline

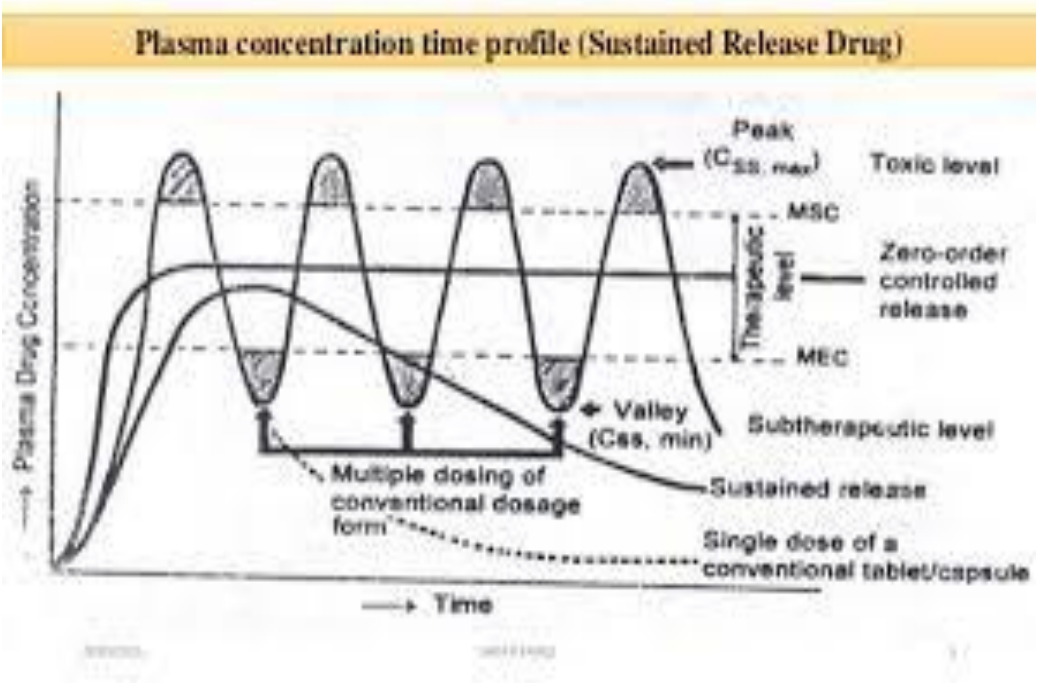
CONTROLLED DRUG DELIVERY SYSTEMS:

The United State Pharmacopoeia (USP) defines the modified release dosage form as,"The one for which the drug release characteristics of time course and location are location are chosen to accomplish therapeutic or convenience objectives not offered by

conventional dosage forms". Oral route is the most popular oral formulation available in the market and prepared by the patients. There are two types of modified release dosage forms. One is delayed release dosage forms and the other one is extended release dosage forms. Delayed release products usually are enteric coated tablets or capsules designed to pass through the stomach unaltered later to release their medication within the intestinal tract. Extended release products are designed to release their medicament a predetermined rate, duration and location to achieve and maintain optimum therapeutic level.







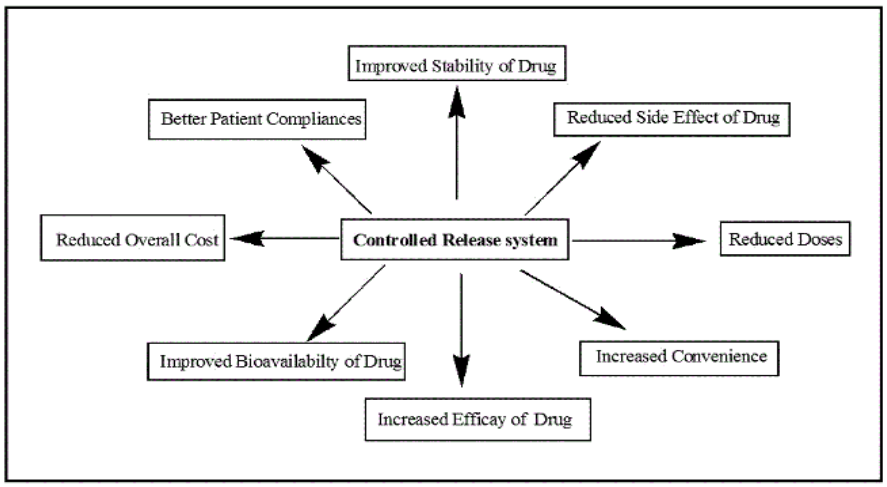


Fig1.9 Advantages of controlled release drug delivery system

Extended release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amount of drug to maintain the effect over a predetermined period.

Potential advantages of modified-release drug therapy[3,33,34]:

1. Avoid patient compliance problem,
2. Employ less total drug
    a .Minimize or eliminate local side effect,
    b .Minimize or eliminate systemic side effect,
    c. Obtain less potentiating or reduction in drug activity with chronic use,
    d. Minimize drug accumulation with chronic dosing.
3. Improve efficiency in treatment
    a. Cure or control condition more promptly,
    b. Improve control of condition (reduce fluctuation in drug level).
    c. Improve bioavailability of some drugs.
    d. Make use of special effects,

e.g. Sustained-Release aspirin for morning relief of arthritis by dosing before bed time.

4. Economic savings lower. Economic saving also may result from a decrease in nursing time/hospitalization, less cost work time etc..

Advantages of a controlled drug delivery system over a conventional dosage form:

- Frequency of drug administration is reduced patient compliance is improved.
- In multiple dosing of conventional dosage forms the blood level of drug shows oscillatory characteristic. In controlled release dosage form the blood level is evenly maintained.
- Safety margin of high potency drugs can be increased and thus side effects or adverse effects can be minimized.
- Total amount of drug administered can be reduced, because of maximum utilization.

- Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients.

Disadvantages of a controlled drug delivery system over a conventional dosage form:

- Decrease in systemic availability in comparison to immediate release conventional dosage forms.**(**incomplete release, increased first pass metabolism, increase instability, insufficient residence) time for complete release site specific absorption, pH dependent solubility etc..
- Poor *Invitro-Invivo* correlation.
- Possibility of dose dumping due to food physiologic or oral formulations by the patient and thus increase risk of toxicity.
- Reduction potential for dosage adjustment of drugs normally administered in varying strength.
- Higher cost of formulation.

  Various physical and chemical approaches can be used to design oral ER dosage forms that extend drug input into gastrointestinal (GI) Tract. Most ER products on the market fall into one of three categories: matrix, reservoir (or membrane controlled) and osmotic systems. Drug release from these ER delivery systems generally involves one or more of the following mechanism: drug diffusion, System Swelling (or) erosion and dissolution (or) osmotic pressure induced release

Matrix systems:

The drug substance is homogeneously mixed with the rate controlling materials and other inactive ingredients in a matrix system. Drug release occurs either by drug diffusion or erosion of the system.

Reservoir systems:

A reservoir systems is normally utilized to control the release rate of water soluble active agents .A typical reservoir system consists of a core containing solid drug surrounded by an insoluble film or membrane. Similar to matrix systems drug release from reservoir system usually varies with pH unless the solubility of the active is pH independent.

Pellets[7,55]:

Pellets can be defined as small free flowing spherical units normally the size various from 0.5 mm to 1.5 mm, intended for oral administration manufactured by the agglomerate of fine powders (or) granules of bulk drugs and excipients using appropriate processing equipments.

Multiple unit pellets[42,45]:

Multiple unit pellets (MUPS) comprises of number of discrete particles that are combined into one dosage unit.

Merits of multiple unit pellets:

- Reduce dosing frequency of drugs.
- Maintain therapeutics concentration.
- Improve the patient compliance and convenience.
- Improvement in treatment efficacy
- Minimize the local and systemic side effects.
- Maximizing absorption.

Development of Novel Drug Delivery Systems for oral controlled release drug administration:

- Drug Delivery refers to approaches, formulations, technologies and system for transporting Pharmaceutical compounds in the body as needed to safely achieve its desired therapeutic effect.
- Controlled Drug Delivery is one which delivers the drug at a predetermined rate, for locally (or) systematically for a specified period of time.
- For the oral controlled administration of drugs several research , new approaches are followed.

Approach to developed oral controlled release drug delivery system:

- Delivering a drug at therapeutically effective rate to desired site.
- Modulation of GI transit time.
- Minimization of first pass elimination.

The controlled / sustained release can be achieved through strategies such as

1. The use of pellets coated with different polymers and different film thickness that allow modulation of the release rate pellets . the polymers used or cellulose derivatives such as HPMC ,Ethyl cellulose etc,
2. The use of uncoated pellets as matrix polymeric system for controlled / sustained release of the drug. In this system cellulose polymer, carbomers , xanthan gums are frequently used.

Pelletization[14,16,57] is referred to as an agglomeration process of size enlargement, that converts fine powders or granules of bulk drugs or excipients into small, free flowing, spherical or Semispherical units of size 0.5-2.0mm, referred to as pellets.

The use of pellets as vehicle for drug delivery at a control rate has recently significant attention. Multiparticulate drug delivery systems provide several all the advantages

including greater flexibility and adaptability of micro particulate dosage forms which gives clinicians and those engaged in product development powerful new tools to optimize therapy.

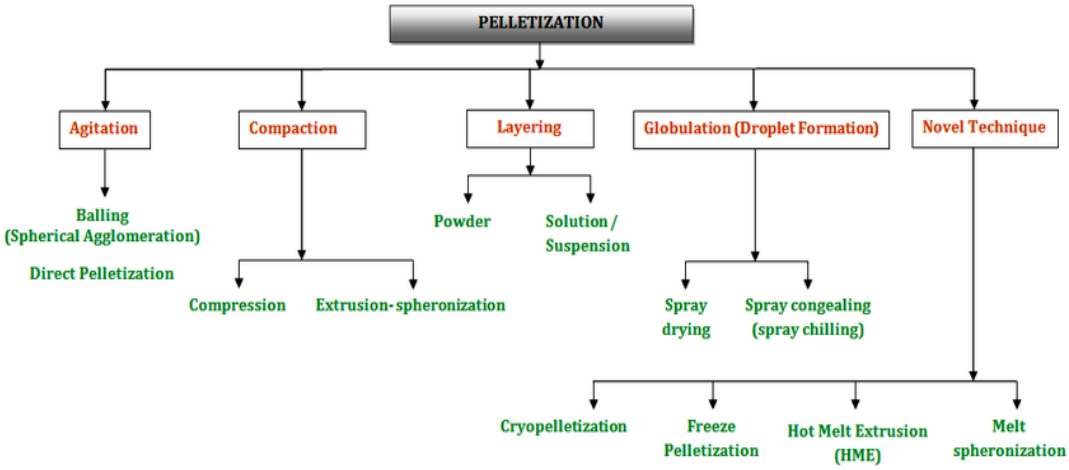


Fig1.10 Pelletization Techniques

1**. Drug Layering**: It includes deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the same material or inert starter seeds. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid. In powder drug layering, a binder solution is first sprayed onto previously prepared inert seeds, followed by the addition of powder.

2. **Extrusion-Spheronization:** Produces pellets with high loading capacity of active ingredient without producing extensively larger particles and particles of uniform size distribution with good flow properties.

Steps involved in Extrusion-spheronization-

Dry Mixing-Dry mixing of ingredients is done to achieve homogenous powder dispersion using Twin shell blender, Planetary mixer, High speed mixer and Tumbler mixer.

Wet massing-It is done to produce a sufficient plastic mass for extrusion, by employing normal equipment and process as employed in wet granulation for compaction.

Extrusion-It produces rod shaped particles of uniform diameter from wet mass. The wet mass is forced through dies and shaped into small cylindrical particles with uniform diameter. Such shaping of wet mass into long rods, commonly termed 'extrudate'. Types of extruder Screw feed extruder Gravity feed extruder Piston feed.

Spheronization-It is also known as 'Merumerizer' consists of a static cylinder and a rotating friction plate where the extrudate is broken up into smaller cylinders with a length equal to their diameter and these plastic cylinders are rounded due to frictional forces. Two geometric patterns are generally used. It includes a cross-hatched pattern with grooves running at right angle to one another, a radial pattern with grooves running radially from the center of the disc.

Drying-A drying stage is required in order to achieve the desired moisture content. An increase in drying rate gives more porous pellets due to decrease pellet densification during drying process. Screening: It is necessary to achieve the desired size distribution, and for this purpose sieves are used.

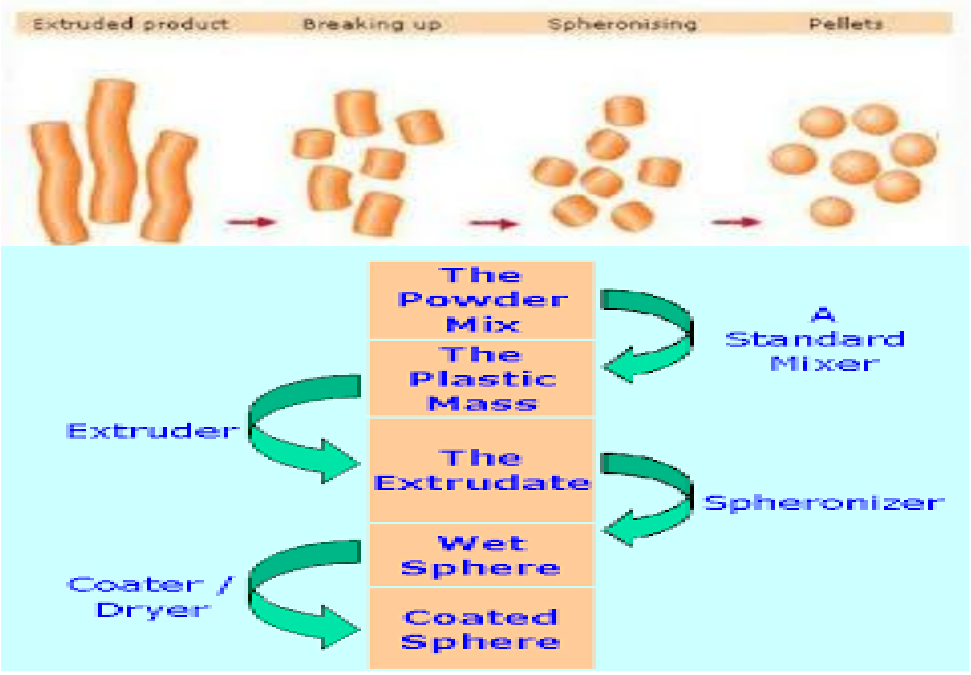


Fig1.11 Steps of pellet formation by Extrusion-spheronization

3. **Cryopelletization** Pellets here can be produced by allowing droplets of liquid formulation such as solution, suspension or emulsion to come in contact with liquid nitrogen at - 160˚C in

which liquid nitrogen used as solidifying medium. The procedure permits freezing of the material being processed due to rapid heat transfer that occurs between the droplets and the liquid nitrogen for manufacturing a given quantity depends on the solid content and temperature of solution or suspension being processed. The pellets are dried in conventional freeze dryers to remove water or organic solvents.

4. **Compression** It is one 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 tablets manufacturing.

5. **Balling I**t is pelletization process in which pellets are formed by a continuous rolling and thumbing motion in pans, discs, drums or mixtures. The process consists of conversion of finely divided particles in to spherical particles upon the addition of appropriate amounts of liquid

6. **Hot-Melt Extrusion technology** (HME) It is process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape. Rotating screw impose mixing and agitation result in the de-aggregation of suspended particles in the molten polymer resulting in the

7. **Spray-drying and Spray-congealing**

1. **Spray-Drying During spray drying**, a drug solution or suspension is sprayed, with or without excipients, into a hot-air stream generating dry and highly spherical particles. Though this technique is suitable for development of controlled release pellets, it is

generally employed to improve the dissolution rates and hence improve the bioavailability of poorly soluble drugs. The spray dried powder particles are homogenous, approximately spherical and nearly uniform in size. The design and operation of spray drier can influence a great number of the characteristics of the final product, such as particle size and size distribution, bulk density, porosity, moisture content, flowability and friability.

2**. Spray-congealing (Spray-chilling)** It is a technique similar to spray-drying. Spray congealing is a process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes, fattyacids or other melting solids. The dispersion is then sprayed into stream of air and other gases with a temperature below the melting point of formulation components. Under appropriate processing conditions, spherical congealed pellets are obtained.

8. **Freeze pelletization** In this technique, a molten-solid carrier/matrix is introduced as droplets into an inert column of liquid in which the molten solid is immiscible. The molten solid moves in the liquid column as droplets and solidifies into spherical pellets. The molten solid droplets can move upward or downward in the liquid column depending on the droplet's density with respect to the liquid in the column. If the density of the molten-solid carrier/matrix is less than that of the liquid in the column, then droplets are introduced from top of the column and pellets solidify in the bottom portion of the column. Conversely, if the density of molten-solid carrier/matrix is less than that of the liquid in the column, then the droplets are introduced from the bottom of the column and pellets solidify at the top portion of column.

MECHANISM OF DRUG RELEASE FROM MULTI-PARTICULATES

The mechanism of drug release from multiparticulates can be occur in the following ways:

Diffusion On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

Osmosis In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

Factors affecting pelletization technique:

1. **Moisture content**: Moisture in the wet mass brings cohesiveness to powder so that the wet mass can be more uniform dispersion extracted and spheronizer to give spherical shape. High moisture contents lead to agglomeration of pellets during the process

2. **Rheological characteristics**: The optimum rheological condition leads to good flow ability in order to extrudate the wet mass. The rheological variations make improper and non-uniform extrudate.

3. **Solubility of excipients and drug in granulating fluid**: Soluble drug get dissolve in a granulating liquid. Thus increasing the volume of liquid phase leads to over wetting of pellets. But increase in wetting liquid increases plasticity but includes sticky mass.

4. **Composition of granulating fluid:**Besides water, alcohol, water/alcohol mixture, ethyl ether, dilute acetic acid, isopropyl alcohol is used as a granulating liquid. Aqueous polymer dispersion containing HPMC, PVP, etc can also be used as granulating fluid.

5. **Physical properties of starting material:** Quality of pellets depend not only composition but also on different grades of the same product. The swelling property of material used in pelletization technique decides the release rate of drug in pellets.

6. **Speed of Spheronizer**: It affects the size, hardness, sphericity and density of pellets. The high speed gives high sphericity, lower friability, smooth surface and higher crushing strength.

7. **Extrusion screen:** The quality of pellets is greatly influenced by the characteristics of orifice of the screen. And increase in orifice dimension resulted in increased mean pellet size. The increase in orifice depth decreased with the presence of water at the extrudate surface.

EVALUATION PARAMETERS :

1. **Particle size distribution** Particle size should be as narrow as possible. This will ensure minimum variation in coating, thickness, facilitate blending process if blending of different types is requires. Sieve analysis using sieve shaker is most widely used method for measuring particle size distribution. 100 gm of pellets are weighed using electronic weighing balance. Pellets are then transferred to set of sieves having different mesh size for particle size analysis. Calculate the % retained on each sieve.

2. Surface Area The characteristics of pellets, those controlling the surface area, are mainly size shape, porosity and surface roughness. There are three methods of measuring the surface area of pellets. It can be calculated from particle-size distribution by measuring the mean diameter, gas adsorption, and air permeability.

Mean diameter- This calculation does not account for the contributions of the surface area arising from other morphologic characteristics such as porosity, surface roughness and shape of pellets.

Air permeability method- It is widely used pharmaceutically for specific surface measurement, for controlling batch to batch variations. The principle for resistance to flow of a fluid such as air through a plug of compacted material is the surface area of material.

Gas adsorption method- In this method the volume of nitrogen that is absorbed by the substrate contained in an evacuated glass blub is measured at different pressures.

3. Porosity The porosity of pellets influences the rate of release of drugs from pellets by affecting the capillary action of the dissolved drug. The porosity of pellets can be measured qualitatively by scanning electron microscopy (SEM) and quantitatively by mercury porosimetry; optical microscopy and scanning electron microscopy together with image.

4. Density The density of pellets can be affected by changes in the formulation or process, which may affects other processes or factors, such as capsule filling, coating and mixing. The bulk density of pellets can be measured by anautomated tapper. True density indicates the extent of densification or compactness of substances.

- **Bulk Density= Weight of powder/ Bulk volume**
- **Tapped density= Weight of powder/ Tapped volume**

5. Hardness and Friability Hardness and friability determination of pellets is necessary because the pellets have to withstand during handling, shipping, storage and other processes such as coating. The instrument such as Kaul pellet hardness tester provide relative hardness values .

Friability of pellets are determined by using Erkewa type tablet friabilator or Turbula mixer for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion.

Although drug treatment for peptic ulceration has improved in the recent past, the need of better therapy is still prevailing. Successful pharmacotherapy is dependent on many factors. Efficacy is obviously important, other factors that are often overlooked include availability of optimal dosage and delivery forms, effect the treatment and reduction of side effect. Proton pump inhibitors (PPI) are substituted benzimidazole and all share a similar core structure and mode of action but differ in substituted group. Rabeprazole sodium is one of the most effective Proton pump inhibitor have 52% bioavailability and have half life 1 to 1.5 hours. Esomeprazole an s-isomer of Omeprazole have plasma elimination half life about 1.3 hours. Exposure of Rabeprazole and Esomeprazole to the acidic content of the stomach would lead to significant degradation of the drug and hence reduced bioavailability

2. AIM AND OBJECTIVES

The main aim of the present study was to formulate and evaluate enteric coated, controlled release multiple unit pellets of Esomprazole magnesium and Rabeprazole sodium using natural and synthetic polymers.

2.1 Objectives

- To formulate Esomeprazole magnesium and Rabeprazole Sodium Controlled release Multiple Unit Pellets using various concentrations of Hydroxy Propyl Methyl Cellulose K15, Hydroxy Propyl Methyl Cellulose K100, Ethyl Cellulose, and Xanthan gum by Extrusion Spheronization process.
- To evaluate the pre - compression parameters like drug excipient interaction study, bulk density, tapped density, compressibility index and angle of repose.
- To evaluate various post compression evaluation parameters like friability, drug content and *in vitro* dissolution studies and Scanning Electron Microscopy (SEM) study
- To formulate gastric protection for the prepared multiple unit pellets using Hydroxy Propyl Methyl Cellulose Phthalate as enteric polymer.
- To carry out the *in vivo* pharmacokinetic studies.
- To determine the mechanism and kinetics of drug release.
- To conduct stability studies on optimized formulation as per ICH guidelines.

2.2. Plan of Work

2.2.1. Review of Literature Collection

2.2. 2Pre formulation studies

- Preparation of calibration curve of Rabeprazole Sodium and Esomeprazole Magnesium dehydrate.
- Drug excipient compatibility study.
- Micromeritics properties of powdered drugs.

2.2.3. Formulation of Rabeprazole Sodium and Esomeprazole Magnesium Multiple Unit Pellets.

2.2.4 Post formulation studies.

- Micromeritics properties of pellets
- Drug content.
- *In vitro* dissolution study.
- Scanning Electron Microscopy (SEM).

2.2.5 Enteric coating of multiple unit pellets.

2.2.6 Evaluation of prepared multiple unit pellets.

2.2.7 *In vitro* Pharmacokinetics study

2.2.8 *In vivo* Pharmacokinetics study

2.2.8 Stability study as per ICH guidelines.

3. LITERATURE REVIEWS

Saad m. Majeed et al[17] formulated bilayer matrix tablets of amoxicillin and Esomeprazole as an oral modified release dosage form for treatment for peptic ulcer. The objective of the present study was to formulate a dual therapy of peptic ulcer containing antimicrobial agent amoxicillin and anti-secretory agent esomeprazole, utilizing the concept of bilayer tablet system for the effective treatment of H. pylori associated gastric/duodenal ulcer, in an attempt to improve bioavailability and to get maximum therapeutic benefits and patient compliance about the treatment. Enteric coated pellets was prepared as extended release matrix layer by direct compression technique, using pH-independent hydrophilic Eudragit polymers (E-RL100 and E-RSPM type) as matrix forming agent.

Muthadi Radhika Reddy et al[64] has studied Sustained Release Tablets of Esomeprazole Using Natural and Synthetic Polymers the main objective of the study to increase the bioavailability, reduce the number of doses and to increase patient compliance for the treatment of Zollinger Ellison syndrome and peptic ulcer disease. The tablets were prepared by direct compression method using carbopol 934 and xanthan gums, hydroxyl propyl methyl cellulose as polymers.The tablet evaluated by FTIR and DSC. The release data was fitted to various mathematical models Higuchi, Korsmeyer, First order, Zero order to evaluate the kinetics and mechanism of the drug release .Finally tablets prepared with xanthan gum was increase the concentration of drug release profile.

Y.Naveen Kumar et al[65] has studied Controlled release formulation of Esomeprazole sodium tablets.The main aim of this work is desired effect at certain time in maintained drug concentration without any unwanted effect and improve its bioavailability by decreasing its expose to gastric acid. Tablets were prepared by dry granulation method

rather than direct compression because of cohesive property of the drug. UV Spectrophotometric method used for the estimation. Dissolution results of tablets with enteric coating have shown release of Esomeprazole in simulated gastrointestinal fluid pH 1.2, but most of the drug released in pH 6.8 Phosphate buffer. At the end it was found that prepared formulation gave satisfactory results compared with marketed sample dissolution profile. Hence prepared formulation by-pass the degradation of Esomeprazole by enteric coating approach and can be used as single unit dosage for the treatment of acid-related diseases.

Dhruv Malik et al[66] has studied press coated tablets of esomeprazole for colonic delivery. Aim to prevent the gastric degradation of drug so as to improve the bioavailability of drug. Various polymers such as pH dependent (Eudragit L100, Eudragit S100), enzyme dependent (Pectin) and time dependent (HPMC K4M) are selected for press coating the drug incorporated core tablets. FTIR analysis was performed to check the compatibility of drug and polymers. Core and coating materials evaluated for pre compression parameters like bulk density, tapped density, angle of repose, Carr's index, and Hauser's ratio. Press coated tablets were evaluated for hardness, thickness, friability, tensile strength, drug content, and *in vitro* drug release.

Suryakanta Swain et al[67] formulated rabeprazole microcapsule using enteric-coated using ethyl cellulose followed by a triple coating with Eudragit L100. FT-IR studies revealed that there was no drug-polymer interaction .*In vitro* drug release data to explain drug release profiles. Analysis of variance (ANOVA) showed significant difference in the release of drug from all formulations .

Taraq A. Attumi et al[68] has studied High-Dose Extended-Release Lansoprazole (Dexlansoprazole) and Amoxicillin Dual Therapy for *Helicobacter pylori* Infections. Amoxicillin 1 g and dexlansoprazole 120 mg each twice a day at approximately 12-hour intervals for 14 days. Success was accessed by urea breath test. An effective therapy was defined as a per-protocol treatment success of 90% or greater; treatment success of 80% or less was pre specified as an unacceptable result. Dual PPI plus amoxicillin should reliably eradicate *H. pylori* provided nearly neutral intra gastric pH can be maintained. Clearly, dexlansoprazole, despite being administered at high dose and twice a day (i.e., total daily dose 240 mg), failed to achieve an intra gastric milieu consistent with dual PPI plus amoxicillin therapy being an effective anti-*H. pylori* regimen.

Wilson Bet al[69] has studied Sustained release enteric coated tablets of pantoprazole formulation, *in vitro* and *in vivo* evaluation. Tablets are prepared by the wet granulation method using HPMC, cassava starch and polyvinyl pyrrolidine as polymers, Avicel PH 102 (MCC) as filler and potato starch as binder and evaluated by hardness, mass variation, friability and drug content uniformity. Tablets are coated by using an enteric coating polymer such as cellulose acetate phthalateThe anti-ulcer activity was evaluated by a water immersion stress induced ulcer model. The enteric coated pantoprazole tablets significantly reduced ulcer formation.

Rajesh et al[48] has studied enteric coated pellets of pantoprazole sodium by extrusion and spheronization method. The present study was focused to formulate delayed release capsule by MUPS Technique. Average pellets size was determined by sieve analysis and found to be 1680-1200 microns (ASTM sieve no. 12-16). Sieve analysis was the essential step before coating.

Because uniform sized pellets undergo effective coating. The result indicates a effective enteric coating and delay the drug release, with 32% acrylezee solution, is possible. The formulation developed can further be worked on. For identifying a best formulation for delayed release pellets of pantoprazole sodium.

Sandeep Choudhary et al[70] has studies stomach specific polymeric low density micro balloons as a vector for extended delivery of Rabeprazole and amoxicillin for treatment of peptic ulcer. Various concentrations of Eudragit S-100 and hydroxyl propyl methyl cellulose, to which varying concentration of drug was added, and formulated by stirring at variable. The formulation variables like concentration and ration of polymers significantly affected the in vitro drug release. In conclusion, greater compatibility, higher gastro-retention and higher anti-ulcer activity of the presently fabricated formulations to improve potential of formulation for redefining ulcer treatment are presented here. These learning exposed a targeted and sustained drug delivery potential of prepared micro balloons in gastric region for ulcer therapeutic intervention as corroborated by in vitro and in vivo findings and, thus, deserves further attention for improved ulcer treatment.

M. El Badry et al[71] has studied comparative study of preparation and characterization of enteric and enhanced release omeprazole micro particles. The preparation of microparticles of omeprazole using spray drying technique and then filling hard gelatin capsules coated with enteric polymer with these particles. The other method is the preparation of enteric microspheres by emulsification/solvent method. Omeprazole micro particles were prepared by spray drying technique using hydroxyl propyl-β-cyclodextrin as a carrier. Omeprazole dissolution rate was enhanced significantly from its spray dried microparticles as compared to the corresponding drug alone ($p<0.05$). In acidic medium, the release in phosphate buffer (pH 7.4) depends on the amount of the hydrophilic

carrier. Omeprazole microspheres were prepared by emulsification/solvent technique using Eudargit S 100 as enteric polymers. The prepared microspheres were characterized by DSC and a scanning electron microscope. The dissolution of microspheres was also attempted. The results showed that, the prepared microspheres are spherical in shape. DSC results showed that the drug dispersed homogenously in the polymer. Also, the dissolution of drug depends on the ration of the drug:Eudargit S 100

Rama Rao Nadendla et al[9] developed sustained release formulation of esomeprazole to maintain constant therapeutic levels of the drug for over 12hrs. Different types of polymers (HPMC K 15M, Xanthan Gum, Carbapol 934) were used. Esomeprazole dose was fixed as 20mg. Total weight of the tablet was considered as 400 mg. polymers were used in the concentration of 10, 20 and 30 mg concentrations. Whereas from the dissolution studies it was evident that among all the formulations F2 formulation was considered as optimised formulation. It was shown 99.65% drug release at 12hrs. The optimised formulation F2 followed Higuchi release kinetics.

N. Rama Rao et al[10] formulated different core tablets of Esomeprazole using starch as a disintegrates and microcrystalline cellulose as a filler. Core tablet of F3 formulation was selected and coated with seal coating of HPMC and with a dispersion of enteric polymer such as hydroxyl propyl methyl cellulose phthalate using a syringe method.Seal coating was applied to achieve 1% weight gain using HPMC dispersion. Enteric coating was carried out using hydroxyl propyl methyl cellulose phthalate dispersion to achieve a 10%, 20% and 30% weight gain. Enteric coated tablets with or without a seal coat, which gained a 30% weight gain after enteric coating with hydroxy propyl methyl cellulose phthalate were found to show a delayed release when tested for dissolution. The results of stability under accelerated conditions indicated the necessity of a seal coat between core and enteric coat in formulation. By utilizing syringe method, a variety of enteric

polymers can be coated on to a seal coated Esomeprazole magnesium trihydrate core tablets, which are stable and exhibit a delayed drug release

Swamykannu Dinesh Mohan et al[11] formulated enteric coated pellets of Omeprazole. Two different groups were prepared, one group consists of drug layer coat, enteric layer coat and another group of pellets consists of drug layer coat, enteric layer coat and over coat as the. The over coat application played a vital role in acid resistance it protects the drug release in stomach environment. Three month accelerated stability studies, showed over coated pellets to be stable.

NagarjunaNaik R et al[12] studied the formulation and evaluation of enteric coated tablets of Esomeprazole magnesium dihydrate delayed release multi-particulate to reduce the gastrointestinal tract side effects. The delayed release multiple units were prepared. These are selected by seal coating, drug coating and enteric coating. These Esomeprazole magnesium dehydrate were evaluated for assay, acid resistance, drug release, dissolution, kinetic studies of innovator and optimized formulation, stability studies of optimized formulation. This study concluded Esomeprazole magnesium dehydratecan be prepared by using combination of polymers studied and we can reduce the GI tract side effects

Shu-Ling Kan et al[13] studied the preparation and in vitro/ in vivo evaluation of esomeprazole magnesium- modified release pellets. The drug loaded pellet was subsequently coated with Eudragit RS30D to achieve sustained release characteristics. Further coated with Eudragit L30D-55 to achieve enteric properties. The optimal formulation achieved good SR feature both in vitro and in vivo with the relative bioavailability of 103.50%. Results manifested esomeprazole modified release pellets had satisfactory sustained release behaviour, a desired pharmacokinetic property, improved in vitro retention and decreased plasma drug concentration fluctuation.

DerarM. Omari et al[14] developed Esomeprazole solid dosage form as minitablets. The effect of coating thickness and percentage of disintegrants on the *in vitro* and *in vivo* performance of minitablets was studied. Two formulae (A1 and B1) of the same core composition with different coat thickness were prepared initially. The in vivo study of A1 and B1 revealed that their rate of dissolution was not enough to achieve bioequivalence with respect to Cmax. Therefore one of the formulas (A1) was formulated to C1, by keeping the same coat thickness and increasing the percentage of disintegrant to enhance drug release. This modification increased in the dissolution rate as indicated by a higher dissolution efficiency (DE) for C1 than A1 and B1. Good correlation between DE and rate of absorption for A1, B1 and C1 was observed. In vivo studies under fasting conditions carried on 22 subjects revealed that the minitablets and Nexium were bioequivalent. Fed study was conducted on 16 subjects, showed that there was a significant delaying effect of food on drug absorption from minitablets.

S. Ramu et al[15] studied the development of pharmaceutically equivalent, stable, cost of effective and quality improved formulation of lansoprazole enteric coated pellets (delayed release). The preparation contains nine formulations by drug loading, sub coating, enteric coating, and lubrication steps. E8 enteric coated pellets were found to be optimum and were filled into capsules. These capsules were evaluated and the results were found to be more similar with innovator.

Joel E Richter et al[16] studied the efficacy and tolerability of esomeprazole relative to that of omeprazole in healing erosive esophagitis and resolving accompanying symptoms of GERD. In patients with gastroesophageal reflux disease (GERD), esomeprazole, the S-isomer of omeprazole, has demonstrated pharmacological and clinical benefits beyond those seen with the racemic parent compound. This study was designed to further

evaluate the efficacy and tolerability of esomeprazole relative to that of omeprazole in healing erosive esophagitis and resolving accompanying symptoms of GERD.

Jiang- Yan Liu et al[18] developed esomeprazole magnesium enteric coated pellets and pellet-based tablets, as well as to investigate the effects of pellet size and compression method on acid tolerance, content uniformity, compressibility and stability of the preparations.Two types of pellet cores, namely, microcrystalline cellulose (MCC) core (particle size 150-300µm) and sucrose core(particle size 600-700µm). The pellets based on MCC core (with smaller particle size) showed a significantly higher acid tolerance compared with the pellets based on sucrose core (larger particle size). Results showed that reduction in pellet size and wet granulation reduced the differences in content uniformity and better protected and pellet coating from damages during compression.

Altay celebi et al[19] compared the acid inhibitory effects of esomeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg on days 1 to 5 of treatments in patients with GERD, who were extensive metabolizers in regard to the CYP2C19 genotype. Results showed the mean percentage of time with intra gastric pH>4 were 54%, 58%, 60% and 35% respectively on day 1 and on day 5 these values were 67%, 60%, 68% and 59% respectively.it was concluded that pantoprazole is less potent PPI than other PPIs tested on the first day of treatment.when the time needed to raise the intra gastric pH to over 4 was evaluated, esomeprazole was found to have the most rapid action, followed by lansoprazole and rabeprazole.

Ruqaiyah Khan et al[20] studied on the attempt to formulate and evaluate Rabeprazole sustained release matrix tablet using wet granulation incorporating various polymers like HPMC-E15, Carbapol934, and sodium carboxy methyl cellulose. It revealed that all the physicochemical parameters comply with the official standards. The in vitro release studies exhibit the release up to 90% over a prolonged period of time which confirms the

extend release profile of formulation, having better bioavailability as well as decreased dosing frequency with reduced doses

Muhammad Tariq Khalil et al[21] developed a reversed- phase HPLC method and validated for the estimation of esomeprazole in bulk and capsules dosage forms. Detection was carried out using a UV detector at 302nm. Validation studies demonstrated that this HPLC method is simple, specific and reproducible. The developed and validated method was successfully applied for quantitative analysis of capsules. The high recovery and low relative standard deviation confirm the suitability of the proposed method for the determination of esomeprazole.

Y.Surekha et al[8] prepared rabeprazole sodium pellets by using HPMC for subcoating based subcoating and methacrylic acid was used for based enteric coating and to target the release of drug in intestine and to avoid stability related problems. They compared the distribution profile of final batch with market product.It showed better stability and could be the good way. To improve the bioavilability of rabeprozolesodium meprazole in capsule dosage form .

Rakesh N. Tirpude et al[22] has studied the effect of polymeric coating on product performance, the pellet core structure and composition was kept constant. Enteric coated drug multi particulates prepared with single polymeric coating (acrylic or cellulogic) were compared with two different polymeric layer coatings to evaluate the effectiveness of latter coatings. The pH dependent, enteric acrylic and cellulogic polymers were used either alone , in combinating or applied one over the other to impat delayed release properties to the core drug pellets.It was demonstrated that dual delayed release coating with two different enteric polymer an inner acrylic polymer an inner acrylic coating yield the best product that provides all the desired physicochemical and drug dissolution characteristics.

Muthuumaran.M et.al[23] investigated delayed release rabeprazole sodium by using hydroxypropyl methyl cellulose baedsubcoating and methacrylic acid co polymer based

entric coating. The different batches of pellets were prepared by drug suspensding layering method. Comparative study of dissolution profile of final batch with marketpreparing wasconducted and it was concluded that the final for batch shows good similarity with market product.

Ruqaiyak khan et al[24] formulated rabeprazole sustained release matrix tablet using wet granulation technique in corprating various polymers like HPMC, Carbopol 943, and sodium carboxy methyl cellulose (CMC) to extends the release rate of drug for a prolong period of time at treat 10hrs and shows to increase the bioavailability and simultaneously decrease the dosing intravel as well as dosing amount.

Arti mohan, et al[25] has formulated Immediate release tablets of rabeprazole sodium by Technology. The tablet was delivered in alkaline environment to enhances in vivo stability of rabeprazole. The drug was present as inner core and buffer as the outer layer.

Ashish Kumar Garg et al[28] has developed and evaluated pulsatile release tablets of rabeprazole sodium contain drug which was further coated by erodible outer layer consisted of HPMC K_4 M, ethyl cellulose and xanthan gum. The developed delivery system holds good promises of benefiting the patients suffering from peptic ulcers.

Niyazs.Mansuri et al[29] developed a delayed release pellets of rabeprazole using various principles of quality by design. Sugar sphere were drug layered seal coated in a fluid bed coater to achieve delayed drug release.

YihongQiu et al[30] and deliangzhou, discuss scientific and technical principles associated with pharmaceutical product development useful to practioner in validation compliance.

Deb Ratul et al[41] discussed various pellatization technique including extrusim, Spheroniczation methods. Every techniques has their own advantages and limitations.

B.Rama et al[43] were developed Rabeprazole sodium. Entric coated tablets using mannitol as diluent and cross carmellose as super disintegration as super disintegrant in

different properties. Further optimized formulation was coated with opadry white and entric yellow.

C.Muraikrisha Goud et al[44] were developed Rabeprazole sodium delayed release entric coated tablet using mannitol as diluents, crospovidone and polyplasdone XL as super disintegrant, sodium carbonate as stabilizer . Prepared core tablet were coated with entricpolumerhypromellosephalate F5,F6 shows highest percentage of drug release. **Karim s** et al[45] prepared spherical pellets of omeprazole by sieving spheronization .An optimized formulation was also prepared by extrusion – spheronization as process to compare the physical properties between these two methods.

S.Ramu et al[47] formulation of capsule of Lasoprazole. The Formulation process was carried out in FBP by solution -suspension layering technique by using entric polymer methacrylic acid co polymertype C.

S.K Singh et al[49] formulation delayed release micropellet dosage form for Lansoprazole using HPMC E5 polymer as release retardant i.e 40%,50%, and 60% and acrylcoat at L30D solution was used for entric coating.

Gulam Irfani et al[50] the studied multiunit particulate system of Rebeprazole using different Percentage is excipients like crospovidone, HPMC, entriccoating material as light MgO, Eudragit L30D and HPMC Phthalate 5% shows better release U6 94.0%.

Krutika sawant,et al[51] formulated Esomeprazole loaded Gastro-resistant microspheres were prepared using hypomellos acetate succinate as Gastro-resistant polimer by non-aqueous solvent evaporation technique.In vivo anti-ulcer activity demonstated that EMT loaded microsphers were able to the solution of EMT.

Diptiphadtare et al[52] has studied the release of a drug in a controlled manner,effectively increasing the duration of release of a drug to prolong its therapeutic effect.The review gives a current in sight into hypromellise and its application in the formulation of extended release.

M.C.Shaema et al[53] developed a simple accurate UV-Visible spectrophotometric methods for the estimation of Esomeprozole in bulk and pharmaceutical dosage forms.A linear response was observed in the range of 5-35 microgram/ml with as regression in co efficient of 0.9997 and0.9989.This method was then validated for different parameters as per the ICH guidances.

A.Badoni et al[54] formulated Rabeprazole enteric coated mucoadhesibe tablet.Delayed release tablerts ofRabeprazole sodium were prepared by wet granulation method using synthetic and natural polymers.

N.Jawahar et al[55] reviewed multi unit particulated system advantages ,disadvantages,desirable properties,equipment Description and pharmaceutical applications,

Mangesh E.Bhad et al[57] reviewed more recent and challenging technologies that combine the advantages ideal involved in their compaction their disintegration and dissolution.

4. MATEIALS AND METHODS

4.1 MATERIALS:

TABLE 4.1: Materials and their sources:

S.No.	Chemical / Excipients	Manufacturer / Suppliers
1.	Esomeprazole magnesium	Mylan Laboratories Limited,Hyderabad
2.	Rabeprazole sodium	Zydus Cadila
3.	HPMC K 15,K100	Triveni chemicals,Gujarat
4.	Xanthan gum	Lobachemie,Mumbai
5.	Ethyl cellulose	Triveni chemicals,Gujarat
6.	Microcrystalline pH 02 cellulose	Triveni chemicals, Gujarat
7.	Polyvinyl pyrrolidone povidone K-30	SD Fine chem Ltd,Mumbai
8.	Talc	SD Fine chem Ltd,Mumbai
9.	Hypromellose phthalate HP 55	Neha life science, Ahmedabad

Table 4.2: List of equipments used:

S.No.	Equipment	Make
1.	FT/IR Spectroscopy	Jasco
2.	UV-Viscible double beam spectrophotometer	Systronics
3.	Bulk and tapped density apparatus	CAMPELL Electronics
4.	Weighing balance	Schimedzu
5.	Friability apparatus	Campbell electronics
6.	Dissolution apparatus	Six stage dissolution rate testapparatus (Tab machine)
7.	Tablet disintegration apparatus	Tab machine
8.	Extruder	R.R ENTERPRISES Machine No. PRE/ EXT-65/037
9.	Spheronizer	R.R ENTERPRISES Machine No: RRE/SPH -5/010.
10.	Capsule hand filling machine	Rinak,kalweka
11.	Conventional coating pan/ spray gun	Rinak ,kalweka HD41UAC

4.2 PREFORMULATION PARAMETERS:

4.2.1. ORGANOLEPTIC EVALUTION:

For the identification of specific drug material organoleptic evaluation is very useful one. The physical properties of API were given in table 5.1.1.

4.2.2 MELTING POINT:

Small quantity of drug molecule was sealed in a capillary tube and was placed in melting point apparatus. The temperature at which the drug molecule melted was noticed and average of triplicate was noted.

4.2.3 IDENTIFICATION OF PURE DRUGS:

Identification of Esomeprazole Magnesium and Rabeprazole sodium was examined by FT-IR and compared with the reference spectrum of drug.

4.2.4.1 CALIBRATION CURVE OF ESOMEPRAZOLE IN PHOSPHATE BUFFER pH 6.8:

100mg of Esomeprazole magnesium was dissolved in 100ml of phosphate buffer pH 6.8. From the primary stock solution (1mg/ml) 10ml solution was transferred to another volumetric flask made up to 100ml with phosphate buffer pH 6.8,0.5,1.0,1.5,2.0 and 2.5 ml was taken separately and made up 1ml with phosphate buffer to produce 5µg,10µg,15µg,20µg and 25µg/ml respectively. The absorbance was measured at 302nm using a UV spectrophotometer.

4.2.4.2 CALIBRATION CURVE OF RABEPRAZOLE MAGNESIUM IN PHOSPHATE BUFFER pH 7.4:

The drug Rabeprazole sodium was dissolved in phosphate buffer 7.2 to set 10 h/ml solution. Further diluted with the same and scanned for maximum absorbance λmax in a double beam UV-Visible spectrophotometer between a UV range from 200 to 400nm against phosphate buffer pH 7.2 as blank and λ max was found to be 287nm.

4.2.5. 1 COMPATABILITY STUDY RESULT FOR ESOMEPRAZOLE MAGNESIUM WITH VARIOUS EXCIPIENTS:

Esomeprazole and excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions. Studies were performed in flint vials at accelerated conditions, 40±2^{o}C /75%RH±5%. The studies were conducted for 4 weeks and compared with control at 2 -8^{o}C. Physical observations of the blend were recorded at for period of one week.

4.2.5.2. COMAPTABILITY STUDY RESULT FOR RABEPRAZOLE MAGNESIUM WITH VARIOUS EXCIPIENTS:

Rabeprazole and excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions. Studies were performed in flint vials at accelerated conditions, 40±2^{o}C /75%RH±5%. The studies were conducted for 4 weeks and compared with control at 2 -8^{o}C. Physical observations of the blend were recorded at for a period of one week.

4.2.6 DRUG-EXCIPIENT COMPATIBILITY STUDIES:

Fourier Transform Infra Red (FT-IR) spectroscopy[10]:

IR spectroscopy studies lies more in the qualitative identification of substance either in pure form (or) in combination with polymers and excipients and acts as a tool in establishment of chemical interaction .Since IR is related to covalent bonds the spectra cam provide detailed information about the structure of molecular compounds. Thus FT IR studies helpful to confirm the identity of the drug with the carriers, samples were diluted with KBr mixing powder, and compacted under vacuum at a pressure of about 12psi for 3minutes. The resultant disc was mounted in holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 400 cm^{-1} in a scan time of 3minutes. The resultant spectrum was compared for any spectral changes.

4.2.7. ANGLE OF REPOSE[11]:

Angle of repose is a characteristic related to interparticulate friction (or) resistance to movement between particles. A variety of angle of repose test methods are describe in the literature.The most common methods for determining the static angle of repose can be classified on the basis of the following important experimental variables.

The height of the funnel through which the powder passes may be fixed relative to the base or the height may be varied as the pile forms.

Angle of repose is used to determine the flow properties of powders, pellets or granules. It is defined as the maximum angle that can be obtained between the free-standing surface of the powder heap and the horizontal plane. An accurately weighed quantity of powder /pellets was allowed to flow through the funnel freely on the surface. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend/pellets. The diameter of the powder concentration was measured and angle of repose was calculated using the following formula.

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

Where h and r are the height and radius of the powder cone.

Table: 4.3 Flow Properties of Corresponding Angles of Repose.

Flow Property	Angle of Repose (Degree)
Excellent	25-30
Good	31-35
Fair aid not needed	36-40
Passable- may hang up	41-45
Poor- must agitate,vibrate	46-55
Very poor	>66

4.2.8. BULK DENSITY[12]: (D_b)

It is the ratio of mass of the powder divided by the bulk volume. It was measured by pouring the weight powder into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. Bulk density of the pellets was determined by pouring pellets into a graduated cylinder via large funnel and measuring the volume and weight.

$$\text{Bulk density} = \frac{mass\ of\ powder}{bulk\ volume\ of\ the\ powder}$$

4.2.9. TAPPED DENSITY[22] (D_t)

It is the ratio of total mass of the powder to the tapped volume of the powder. Tapped density was determined by placing a graduated cylinder containing a known mass of powder/ granules and mechanically tapper apparatus which was operated for a fixed number of taps until the powder bed volume has reached a minimum volume.

$$\text{Tapped density} = \frac{mass\ of\ powder\ (m)}{tapped\ volume\ of\ the\ powder\ (vt)}$$

4.2.10 CARR'S INDEX[51]

Compressibility index is the simple, fast, and popular method of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape; surface area and moisture content, and cohesiveness of materials because of these can influence observed compressibility index.

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index

$$\text{Carr's index} = \frac{Dt-Db}{Dt} \times 100$$

Where,

Dt is the tapped density of the powder

Db is the bulk density of the powder

4.2.11.HAUSNER'S RATIO[64]

Hausener's ratio is a number that is correlated to the following flowability of a powder core granular material. The ratio of tapped density to bulk density of the powder is called the Hausner's ratio. It is calculated by the following equation

$$\text{Hausner's ratio (H)} = \frac{Dt}{Db}$$

Where,

Dt is the tapped density of the powder

Db is the bulk density of the powder

Table: 4.4 Scale of Flowability (U.S Pharmacopeia)

Compressibility Index	Flow Character	Hausner Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

4.2.12. METHODS OF PELLETS PREPARATION:

The pellets were prepared by a promising pelletization technique extrusion spheronization.

Table: 4.5 Excipients used in pellet formulation:

Filler/diluent	Dibasic calcium phosphate, Lactose, starch and sucrose
Binders	HPMC, PVP
Spheronization enhancer	MCC (Avicel pH 101)
Separating agents	Talc
Disintegrants	Croscarmellose sodium, sodium starch glycolate
Release Modifier	HPMC, Ethyl cellulose, shellac etc.

The Process involved the following four steps:

1. a) Dry mixing of ingredients to achieve homogeneous powder dispersion before wetting.
   b) Wet mass was done to produce a sufficient plastic mass for extrusion.
2. Extrusion during this process shaping of the wet mass into long rods of uniform diameter. This long shape product at the end of this stage commonly termed as ‘Extrudate’

3. Breaking up the extrudate and rounding of the particles into spheres (spheronization)
4. Drying of the pellets

Wetting operation brings the material to a state in which porosity is linked to water content. Spheronization is only shaping process which maintain hydro textural state. The drying operation finalizes the textural characteristics of the product by densifying the medium through induced shrinkage.

Advantages of extrusion – spheronization over other techniques:

1. Ability to incorporate higher levels of active components without producing larger particles.
2. Two or more active ingredients can be easily combined in any ratio in the same unit.
3. Particles having high sphericity, dust free, smoother surface can be produced.

4.2.12. FRIABILITY:

The mechanical properties of pellets are important it because it flake off during handling and coating process resulting in formation of dust. Friability of pellets is determined by using Erkewa type tablet Friablator or turbula mixer.

4.2.13. 1.ASSAY OF RABEPRAZOLE SODIUM:

Weighed accurately the quantity equivalent to10mg of Rabeprazole sodium transferred to a100ml volumetric flask. It was made up 100ml with phosphate buffer 7.4 to produce stock solution of concentration 100mcg/ml. The above stock solution of drug was subsequently diluted with phosphate buffer 7.2 to get 2mcg, 4mcg,6mcg,8mcg and 10mcg of drug per ml. The absorbance of these dilute solutions was measured at a λ_{max} of 287nm by using double beam UV spectrophotometer against a blank of phosphate buffer pH7.2

4.2.13.2. ASSAY OF ESOMEPRAZOLE MAGNESIUM:

Drug content was determined by HPLC -Chromatography method. Phosphate buffer pH6.8. Acetonitrile was used as mobile phase in the ratio of 530:470 in an Lichrosorb Rp-18, 25x4.0mm,5µ column maintained at a temperature 30˚C and the flow rate is 1.0m ml/min. The injection volume is 10µl.

4.2.14. 1. *IN VITRO* DRUG RELEASE STUDIES[65]: (ESOMEPRAZOLE MAGNESIUM)

Apparatus : USP -II Basket model

Dissolution medium : 0.1 N Hcl, pH6.8 Phosphate buffer

RPM : 50

Sampling intervals (hrs): 0.5,1,2,3,4,5,6,7,8,10,12

Temperature : 37˚C ± 0.5˚C

The invitro release study of Esomeprazole magnesium pellets was conducted in USP dissolution apparatus (basket model). Pellets (equivalent to 40mg of Esomeprazole) were accurately weighed and filled into hard gelatin capsule in 900ml 0.1N HCl (pH1.2) for the experiment at 37˚C±0.5˚C, the speed of the peddle was 50rpm, under skin condition. Samples of 5ml were withdrawn at specific time intervals, then filtered, diluted and analysed spectrophotometrically at 302nm.

After 2hours and then the media 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from upto 12hrs at 50rpm. At definite interval withdrawn 5ml of sample, filtered and 5ml media was replaced. Suitable dilutions were done with pH buffer and analysed by spectrophotometrically at 302 nm using UV-spectrophotometer.

4.2.14.2. *IN VITRO* DRUG RELEASE STUDIES[24]: (RABEPRAZOLE SODIUM)

Apparatus : USP -II Basket model

Dissolution medium : 0.1 N HCl, pH 7.4 phosphate buffer

RPM : 50

Sampling intervals (hrs) : 0.5,1,2,3,4,5,6,7,8,10,12

Temperature : 37˚C ± 0.5˚C

The invitro release study of rabeprazole sodium pellets was conducted in USP dissolution apparatus (basket model). Pellets (equivalent to 40mg of Esomeprazole) were accurately weighed and filled into hard gelatin capsule in 900ml 0.1N HCl (pH 1.2) for the experiment at 37˚C±0.5˚C, the speed of the peddle was 50rpm, under skin condition. Samples of 5ml were withdrawn at specific time intervals, then filtered, diluted and analysed spectrophotometrically at 287nm.

After 2hours and then the media 0.1 N HCl was removed and pH 7.4 phosphate buffer was added process was continued from upto 12hrs at 50rpm. At definite interval withdrawn 5ml of sample, filtered and 5ml media was replaced. Suitable dilutions were done with pH buffer and analysed by spectrophotometrically at 287 nm using UV-spectrophotometer.

ANALYSIS OF RELEASE DATA:

Difference in the release profiles was evaluated using the similarity factor (f2), a criterion for the different release profiles. This can be compared with recommended the United States Food and Drug Administration. The f2 was calculated by following equation:

$$f_2 = 50 \log \{ [1+1/n \Sigma^{n}_{t=1} (R_t-T_t)^2]^{-0.5} \times 100\}$$

Where n is the number of time points, R_t and T_t are the reference and test dissolution at the predetermine time points respectively. The two formulations release profiles are considered to be similar when the value of f2 is 50 or above.

4.2.15. KINETIC DISSOLUTION DATA[17]:

The results of *in vitro* release profiles obtained for all the formulations were fitted into five models of data treatment as follows:

1. Cumulative percent drug released versus time (zero-order kinetic model).
2. Log cumulative percent drug remaining versus time. (First-order kinetic model).
3. Cumulative percent drug released versus square root of time (Higuchi's model).
4. Log cumulative percent drug released versus log time (Korsmeyer-Peppasequation).
5. Cumulative percent drug released versus cube root of time (Hixson and Crowell's cubic root law of cubic root law of dissolution)

Zero order release rate kinetics[35]

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$\mathbf{F = K_o t}$$

Where, F is the drug release at time t, and K_o is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics[42]:

The release rate data are fitted to the following equation

Log (100-F) = kt

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model[44]**:**

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$

Where, k is the Higuchi constant.

In Higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model[51]

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer-Peppas equation. The exponent,,n indicates the mechanism of drug release calculated through the slope of the straight Line. The release rates from controlled release polymeric matrices can be described by the equation proposed by korsmeyer et al.

$$Q = K_1 t^n$$

Q is the percentage of drug released at time 't', K is a kinetic constant incorporating structural and geometric characteristics of the tablets and 'n' is the diffusion exponent indicative of the release mechanism.

Hixson and Crowell's cubic root law of dissolution[66]**:**

The Noyes-Whitney's equation assumes that surface area of the dissolving solid remains constant during dissolution, which is practically not possible for dissolving particles. Hence, dissolution methods that involve use of constant surface area discs are employed to determine the rate of dissolution.

To account for the particle size decrease and change in surface area accompanying dissolution, Hixson and Crowell's cubic root law of dissolution is used:

$$W_0^{1/3} - W^{1/3} = Kt$$

4.2.16. PHARMACOKINETIC PARAMETERS OF ESOMEPRAZOLE:

Pharmacokinetic parameters, involving Cmax, Tmax, MRT,AUC0–t and AUC0–1 were calculated by non-compartmentalanalyses using the software program PKSolver . All results were expressed as mean±SD(n¼6). Two-tailed Student's t-test (SPSS, version 10.0) wasused for statistically significant differences with p50.05 orp50.01. In order to compare the relative bioavailabilitybetween the test and the reference esomeprazole, the relative bioavailability (Frel%) was calculated (from AUC0–1) as thefollowing equation: F¼AUCtest/AUCreference×100%.

Table: 4.6 Pharmacokinetic property of proton pump inhibitors

PARAMETER	OMEPRAZOLE 20MG	RABEPRAZOLE 20MG	ESOMEPRAZOLE
tmax (hr)	1 - 4	3-5	1.0- 3.5
Cmax (µmol/L)	0.23-23.2	1.14	2.1-2.4 at 20mg, 4.7-5.1 at40mg
AUC (µmol hr/L)	0.58- 3.47	2.22	4.2 at 20mg, 12.6 at 40mg
V (L/kg)	0.13 -0.35		0.22-0.26
CL (mL/min)	400-620		160-330
$t_{1/2}$	0.5-1.2	0.6-1.4	1.3-1.6

t_{max}, time to maximal plasma concentration; C_{max}, maxima plasma concentration;AUC, area under the plasmic concentration curve; V, apparent volume of distribution; CL, clearance; $t_{1/2}$, elimination half-life.

4.2.18. *IN VIVO* ANTI-ULCER ACTIVITY[60]:

In-vivo anti -ulcer activity was carried out using male Wistar rats (180-220g) and protocol **KMCHRET/PH.D/11/2013-14** was approved by the Institutional Animal Ethics Committee. The study was carried out in accordance with the CPCSEA guidelines, Department of animal welfare, Government of India. The rats were left for 2days for acclimatization to animal room conditions (24˚C), exposed to 12h of light and dark cycle and maintained on a standard pellet diet and water ablibitum. The food was, however, withdrawn 48h before the experiment, but water was freely accessible.

Groups of rats for the *in vivo* antiulcer activity:

Group	**Administered samples**
Control 1	42% sodium bicarbonate
Control 2	Esomeprazole MUPS/Rabeprazole MUPS
Control 3	Marketed Product

Ulcer indices (UI) were calculated to equation: UI = 10/X

Where X is the total mucosal area divided by the total ulcerated area.

Indomethacin induced ulcer[60]:

Antiulcer activity was determined in an indomethacin- induced ulcer model, The production of acute gastric ulcer action by indomethacin in the rat. All fasted rats were treated with the vehicle and treated with Esomeprazole pellets (orally). After 1h animals were orally administered 50mg/kg indomethacin (dissolved in 2% $NaHCO_3$). After 4hr, the animals were sacrificed and the stomachs were removed and open for observation.

Pylorus-ligation induced ulcer[61]:

Ulcer were induced by ligating the pylorus according to the method previously reported. Fasted rats were treated orally with the vehicle and Esomeprazole MUPS. Thirty minutes after compound administration the animals were anaesthetized with anaesthetic ether. The abdomen was opened and a stomach was slightly lifted out and ligated with care to any injury or damage to the vein. The stomach was carefully replaced and the wound was closed. The animals were allowed to recover with free access to water. Four hours with free ligation, the animals were sacrificed and stomach was remaining for ulcer observation.

4.2.19. MORPHOLOGY OF PELLETS:

The shape, surface and cross-section morphology of Esomeprazole magnesium were visualized using a SEM (S-3000N, Hitachi, Japan). All samples were coated with a golden layer using an ion-sputter device (E1030; Hitachi, Tokyo, Japan)

4.2.20. ACCELERATED STABILITY STUDIES:

Stability study is used to predict the shelf life of the product by accelerating the rate of decomposition, preferably by increasing the temperature of reaction condition. The pellets were packed in aluminium pouch and charged for accelerated stability study at 40˚C/75 RH for 3 months in accelerated stability chamber. At the end of 1, 2 and 3 months the formulation was evaluated for the drug content.

5. RESULTS AND ANALYSIS

5.1 PREFORMULATION STUDIES

5.1.1. ORGANOLEPTIC EVALUATION OF ESOMEPRAZOLE MAGNESIUM:

Table 5.1.1 Organoleptic Evaluation of Esomeprazole magnesium

PARAMETER	ESOMERAZOLE MAGNESIUM
Organoleptic evaluation	A white to off white powder
Solubility analysis	Very slightly soluble in water solute in methanol Freely soluble in dichloromethane.

5.1.2 ORGANOLEPTIC EVALUATION OF RABEPRAZOLE SODIUM

Table 5.1.2 Organoleptic Evaluation of Rabeprazole Sodium

PARAMETERS	RABEPRAZOLE SODIUM
Organoleptic evaluation	White to slightly yellowish whit solid
Solubility analysis	Very soluble in water and methanol Freely soluble in ethanol, chloroform and ethyl acetate. Insoluble in ether and n-hexane

5.1.3. Melting Point

Table: 5.1.3 The melting point of Esomeprazole magnesium

SAMPLE	REPORTED	OBSERVED
Esomeorazole magnesium	155˚C	158˚C

5.1.4. MELTING POINT

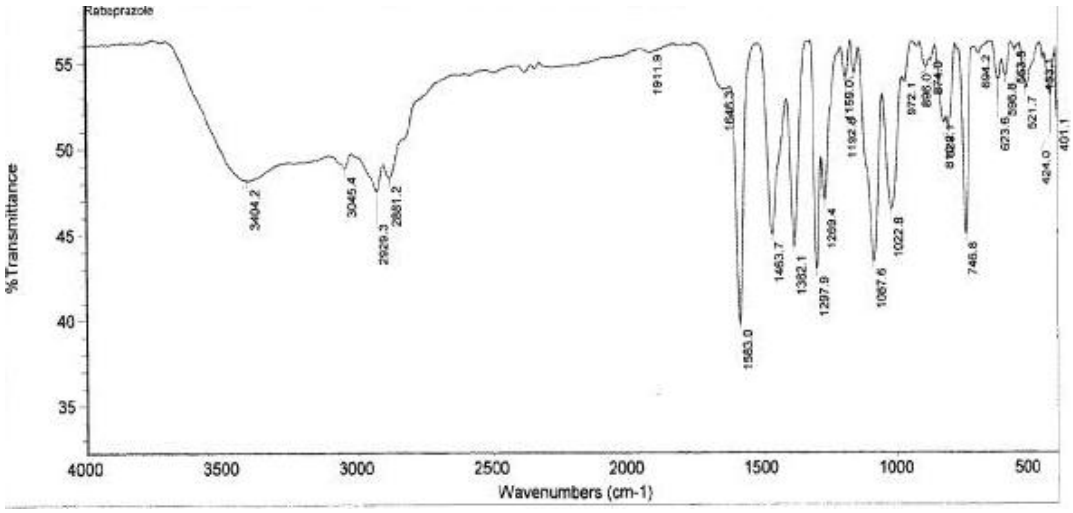
Table: 5.1.4 The melting point of Rabeprazole sodium

SAMPLE	REPORTED	OBSERVED
Rabeprazole sodium	99˚C -100˚C	103˚C

The melting point was one of the supportive data on melting behavior of the drug substance. The melting point of Esomeprazole magnesium and Rabeprazole sodium was 158˚Cand 103˚C respectively shows the sample was pure with no impurities.

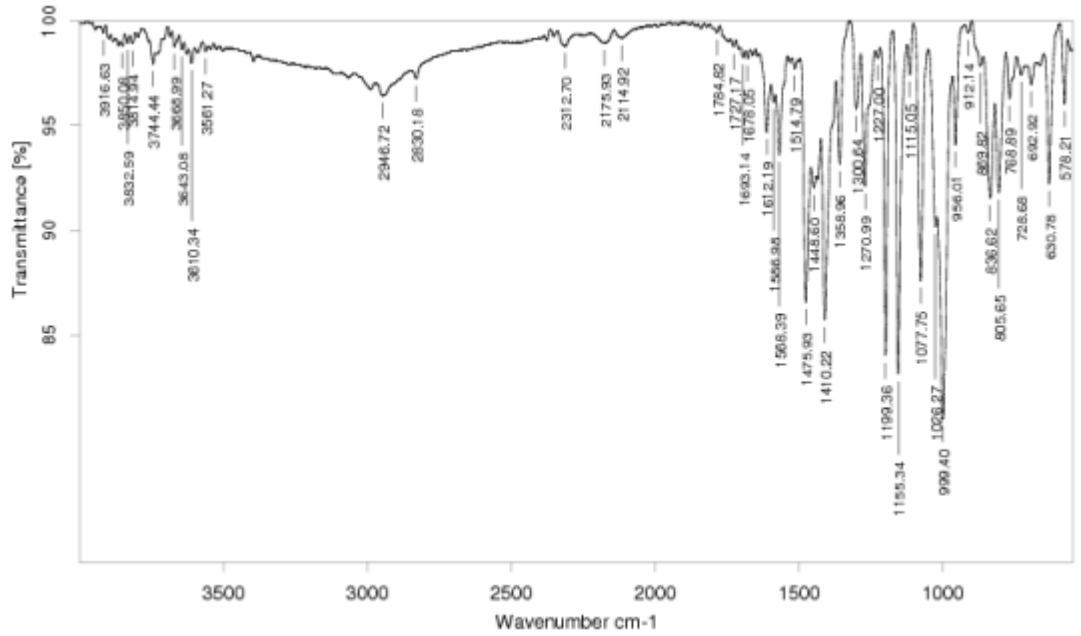
5.1.1 IDENTIFICATION OF PURE DRUGS:ESOMEPRAZOLE MAGNESIUM

Fig 5.1: Identification of Pure Drugs:Esomeprazole Magnesium



5.1.2 IDENTIFICATION OF PURE DRUGS:RABEPRAZOLE SODIUM

Fig 5.2 Identification of Pure Drugs: Rabeprazole Sodium

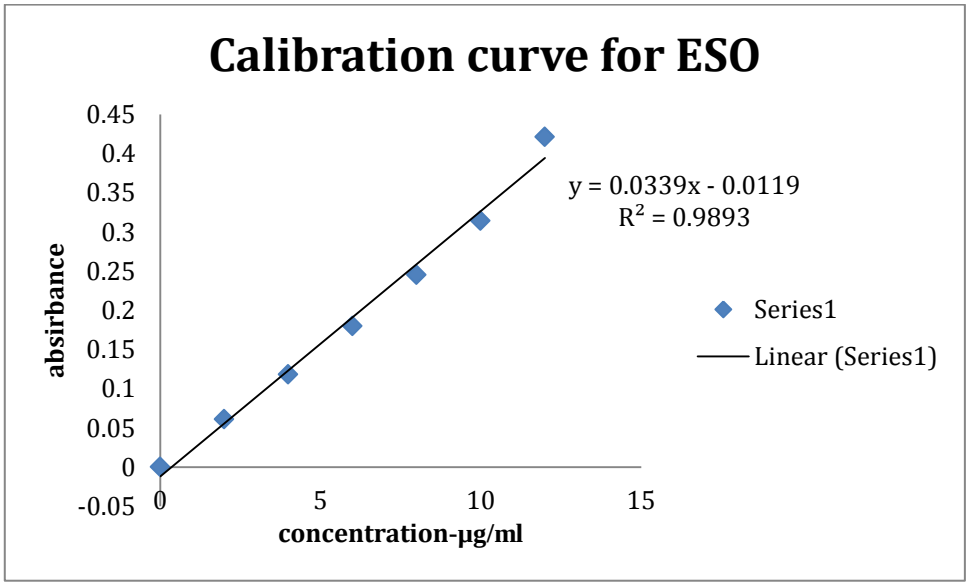


5.1.3. CALIBRATION CURVE OF ESOMEPRAZOLE MAGNESIUM

Table 5.1.3 Calibration curve of esomeprazole magnesium

SL.NO	CONCENTRATION (µG/ML)	ABSORBANCE
1	0	0±0
2	2	0.06 ± 0.001
3	4	0.138 ± 0.001
4	6	0.216 ± 0.004
5	8	0.2995 ± 0.004
6	10	0.3925 ± 0.009
7	12	0.464 ± 0.001

Fig: 5.1.3 Standard calibration curve of Esomeprazole

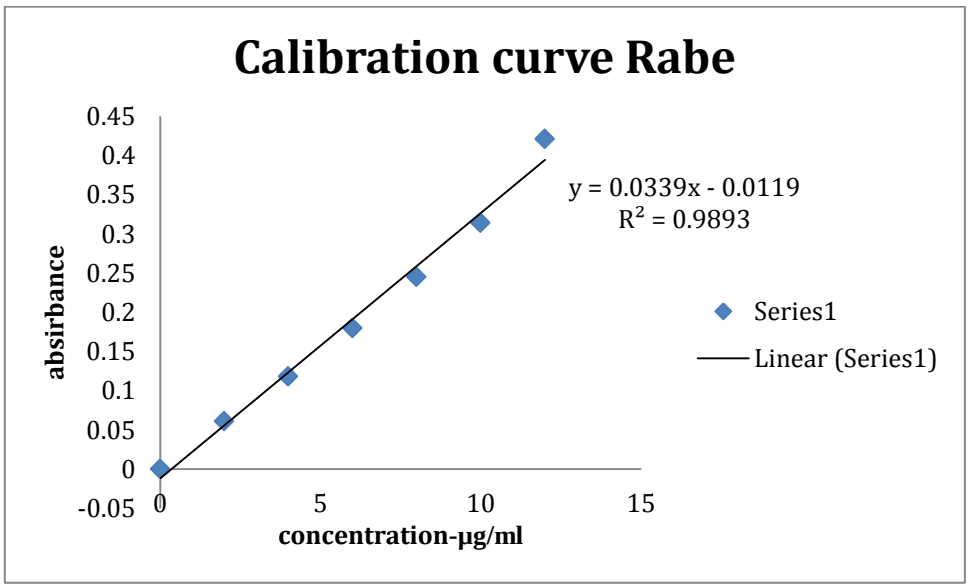


5.1.4. CALIBRATION CURVE OF RABEPRAZOLE MAGNESIUM:

Table: 5.1.4 Calibration Curve of Rabeprazole Magnesium:

S.NO.	CONCENTRATION	ABSORBANCE
1	0	0
2	2	0.061
3	4	0.118
4	6	0.180
5	8	0.245
6	10	0.310

FIG : 5.1.4 Caliberation curve of Rabeprazole magnesium:



5.1.5. COMPATABILITY STUDY RESULT FOR ESOMEPRAZOLE MAGNESIUM WITH VARIOUS EXCIPIENTS:

S.NO.	DRUG EXCIPIENTS COMBINATION	FINAL DESCRIPTION 40˚C/75% RH 7 DAYS
1.	Esomeprazole	No colour change
2.	Esomeprazole+HPMC K15	No colour change
3.	Esomeprazole+ HPMC K 100	No colour change
4.	Esomeprazole+ Xanthangum	No colour change
5.	Esomeprazole+ Ethylcellulose	No colour change
6.	Esomeprazole+ Magnesium stearate	No colour change
7.	Esomeprazole+ Talc	No colour change

5.1.5. COMAPTABILITY STUDY RESULT FOR RABEPRAZOLE MAGNESIUM WITH VARIOUS EXCIPIENTS:

S.NO.	DRUG EXCIPIENTS COMBINATION	FINAL DESCRIPTION 40˚C/75% RH 7 DAYS
1.	Rabeprazole	No colour change
2.	Rabeprazole +HPMC K15	No colour change
3.	Rabeprazole+ HPMC K 100	No colour change
4.	Rabeprazole + Xanthangum	No colour change
5.	Rabeprazole + Ethylcellulose	No colour change
6.	Rabeprazole + Magnesium stearate	No colour change
7.	Rabeprazole + Talc	No colour change

5.1.6. DRUG-EXCIPIENT COMPATIBILITY STUDIES (ESOMEPRAZOLE)

In order to investigate the possible interaction between Rabeprazole and Esomeprazole and distinct polymers FT - IR studies work carried out.

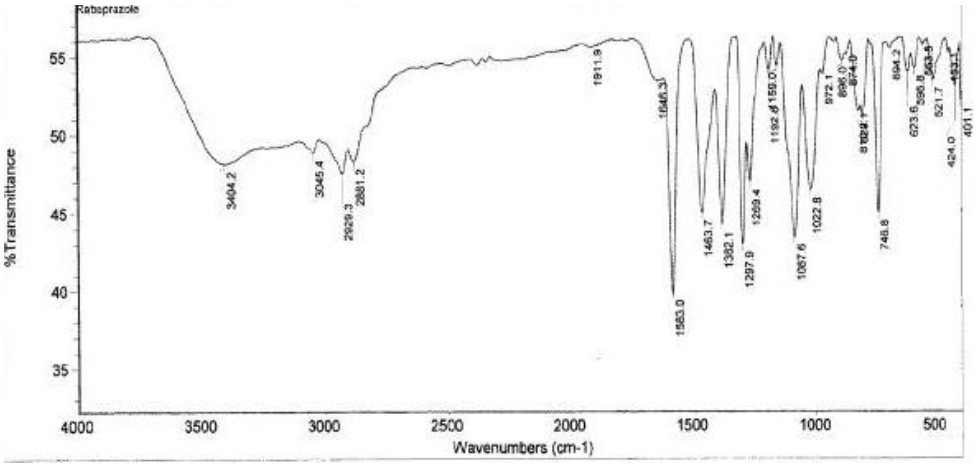


FIG: 5.1.6 FT-IR Spectra of Esomprazole Pure Drug.

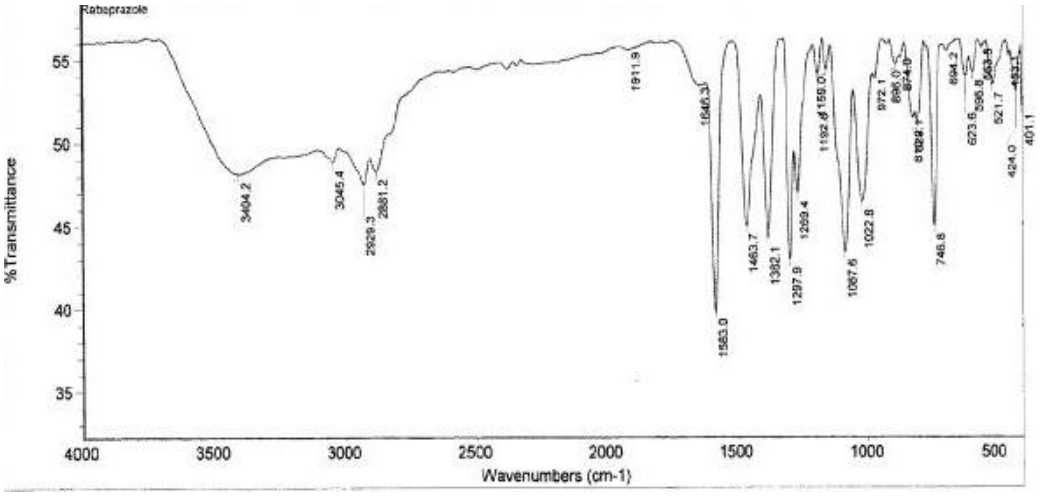


Fig: 5.1.6 FT-IR Spectra of Esomprazole Pure Drug With Excipients

5.1.7. DRUG-EXCIPIENT COMPATIBILITY STUDIES (RABEPRAZOLE)

FIG:5.1.7 FT-IR Spectra of Rabeprazole Pure Drug

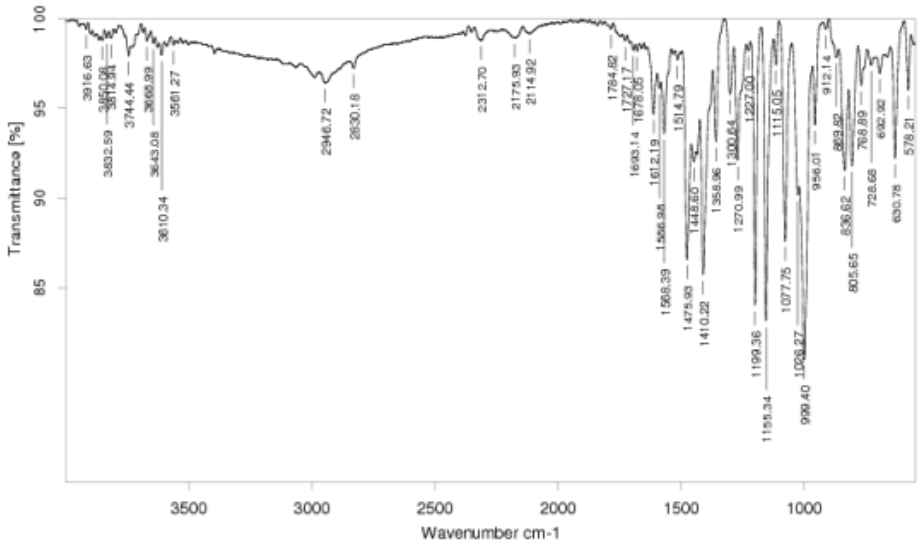
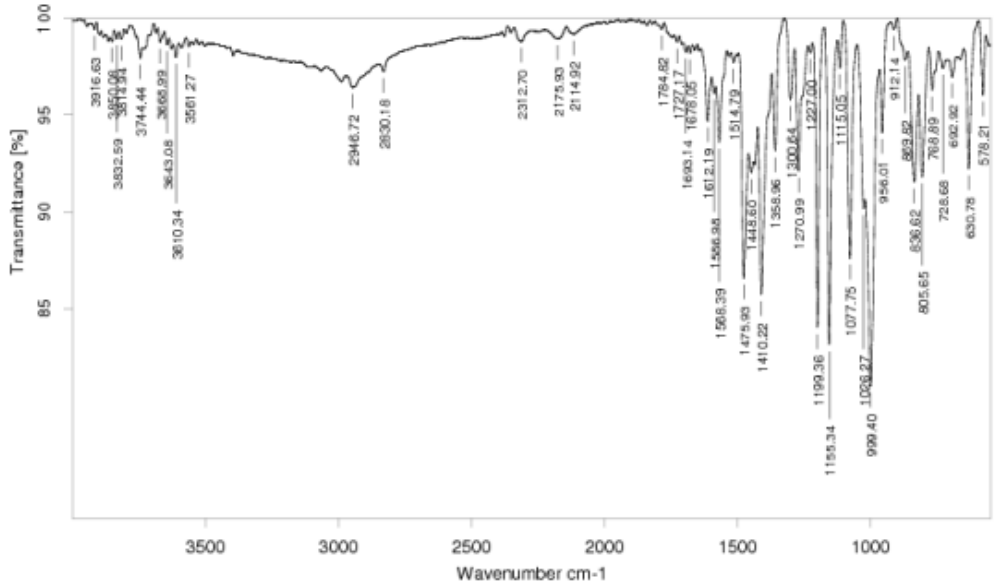


FIG: 5.1.7 FT-IR Spectra of Rabeprazole Pure Drug With Excipients



5.1.8 EVALUATION OF PELLETS FOR ESOMEPRAZOLE MAGNESIUM:

BATCH	BULK DENSITY gm/ml	TAPPED DENSITY gm/ml	HAUSNER'S RATIO	%COMPRESSIBILITY INTEX	ANGLE OF REPOSE Ɵ	FRIABILITY %
F1	0.457	0.543	1.018	15.83	22	Less than 1
F2	0.460	0.580	1.26	20.68	26	Less than 1
F3	0.455	0.536	1.17	15.11	27	Less than 1
F4	0.440	0.544	1.24	20.47	25	Less than 1
F5	0.440	0.508	1.15	13.38	28	Less than 1
F6	0.430	0.501	1.10	14.17	25	Less than 1
F7	0.462	0.521	1.03	11.32	23	Less than 1
F8	0.420	0.536	1.03	21.67	22	Less than 1
F9	0.480	0.571	1.08	15.93	21	Less than 1
F10	0.482	0.595	1.16	22.46	20	Less than 1
F11	0.452	0.598	1.14	24.41	23	Less than 1
F12	0.460	0.586	1.08	21.50	26	Less than 1

5.1.9 EVALUATION OF PELLETS FOR RABEPRAZOLE SODIUM:

BATCH	BULK DENSITY gm/ml	TAPPED DENSITY gm/ml	HAUSNER'S RATIO	%COMPRESSIBILITY INDEX	ANGLE OF REPOSE	FRIABILITY %
F1	0.310	0.37	1.19	16.00	27	Less than 1
F2	0.32	0.38	1.18	15.78	29	Less than 1
F3	0.32	0.37	1.15	13.51	24	Less than 1
F4	0.34	0.38	1.11	10.52	24	Less than 1
F5	0.38	0.42	1.10	09.52	29	Less than 1
F6	0.37	0.43	1.16	13.95	27	Less than 1
F7	0.36	0.41	1.13	12.19	26	Less than 1
F8	0.35	0.39	1.11	10.26	25	Less than 1
F9	0.37	0.42	1.13	11.90	29	Less than 1
F10	0.39	0.44	1.12	11.36	28.	Less than 1
F11	0.38	0.43	1.13	11.62	30	Less than 1
F12	0.37	0.43	1.16	13.95	28	Less than 1

5.2. OPTIMIZATION OF RABEPRAZOLE CONTROLLED RELEASE POLYMERS

5.2.1 OPTIMIZATION OF RABEPRAZOLE CONTROLLED RELEASE POLYMERS

Table 5.2.1: Optimization of Rabeprazole controlled release polymers

S.No.	Ingredients	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12
		mg/pellet unit											
1	Rabeprazole sodium	20	20	20	20	20	20	20	20	20	20	20	20
2	HPMC K 100	20	30	40	-	-	-	-	-	-	-	-	-
3	HPMC K15	-	-	-	20	30	40	-	-	-	-	-	-
4	Ethyl cellulose	-	-	-	-	-	-	20	30	40	-	-	-
5	Xanthan gum	-	-	-	-	-	-	-	-	-	20	30	40
6	Avicel pH 101	12	12	12	11	11	11	12	12	12	11	11	11
7	Povidone k_{30} solution	14	14	14	14	14	14	14	14	14	14	14	14
8	Talc	1	1	1	1	1	1	1	1	1	1	1	1

5.2.2 OPTIMIZATION OF ESOMEPRAZOLE CONTROLLED RELEASE POLYMERS

TABLE 5.2.2: Optimization of Esomeprazole magnesium controlled release polymers

S.No.	Ingredients	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12
		mg/pellet unit											
1	Esomeprazole magnesium	40	40	40	40	40	40	40	40	40	40	40	40
2	HPMC K 100	40	60	80	-	-	-	-	-	-	-	-	-
3	HPMC K15	-	-	-	40	60	80	-	-	-	-	-	-
4	Ethyl cellulose	-	-	-	-	-	-	40	60	80	-	-	-
5	Xanthan gum	-	-	-	-	-	-	-	-	-	40	60	80
6	Avicel pH 101	12	12	12	11	11	11	12	12	12	11	11	11
7	Povidone k_{30} solution	14	14	14	14	14	14	14	14	14	14	14	14
8	Talc	1	1	1	1	1	1	1	1	1	1	1	1

5.3 *IN VITRO* RELEASE OF TRIAL BATCHES E1 TO E 12 (ESOMEPRAZOLE)

5.3.1 *IN VITRO* RELEASE OF TRIAL BATCHES E1 TO E 12 (ESOMEPRAZOLE)

Table 5.3.1 *In Vitro* Release of Trial Batches E1 To E 12(Esomeprazole)

Time	% Cumulative Drug Release					
	E1	**E2**	**E3**	**E4**	**E5**	**E6**
0	0	0	0	0	0	0
0.5	2.47	3.47	2.68	4.47	6.47	3.68
1	4.21	4.21	4.01	9.21	9.21	6.01
1.5	5.54	5.54	6.54	14.54	13.54	8.54
2	8.87	6.25	9.87	20.87	18.87	13.87
4	52.45	41.84	48.83	65.45	41.84	48.83
6	81.77	58.85	59.52	99.77	73.85	62.52
8	95.09	70.86	70.21		98.86	80.21
10		82.87	80.9			99.9
12		97.88	91.59			
Time	**E7**	**E8**	**E9**	**E10**	**E11**	**E12**
0	0	0	0	0	0	0
0.5	4.21	2.21	2.68	3.27	6.16	5.18
1	5.54	5.54	4.01	7.21	7.21	8.01
1.5	8.87	6.25	6.54	28.54	13.54	11.54
2	9.45	44.44	45.87	40.87	28.31	23.87
4	46.77	88.15	71.35	62.45	21.84	48.83
6	63.09	92.26	99.31	97.77	63.85	62.52
8	91.23				99.86	70.21
10						99.23
12						

5.3.2 *VITRO* RELEASE OF TRIAL BATCHES R1 to R 12(RABEPRAZOLE)

Table 5.3.2 *In vitro* Release of Trial Batches R1 To R 12(Rabeprazole)

Time	% Cumulative Drug Release					
	R1	R2	R3	R4	R5	**R6**
0	0	0	0	0	0	0
0.5	2.47	5.47	3.68	7.47	6.47	2.68
1	4.21	6.22	6.01	9.21	7.21	3.01
1.5	5.54	7.50	8.54	24.54	25.54	4.56
2	8.87	8.25	23.87	55.87	38.87	5.23
4	52.45	41.84	38.83	65.29	61.84	38.83
6	81.77	78.85	42.52	99.77	83.85	49.52
8	95.09	80.86	90.21		97.86	62.21
10		96.87	97.95			85.9
12						97.59
Time	R7	R8	R9	R10	R11	R12
0	0	0	0	0	0	0
0.5	5.21	2.21	2.68	3.27	6.16	5.18
1	7.58	5.54	4.01	7.21	7.21	8.01
1.5	9.87	16.25	6.54	28.54	13.54	11.54
2	9.45	24.44	45.87	70.87	58.31	23.87
4	66.77	68.15	61.35	82.45	61.84	48.83
6	83.09	84.28	79.31	97.77	73.85	62.52
8	91.23	97.36	95.32		89.86	80.21
10					97.23	99.23
12						

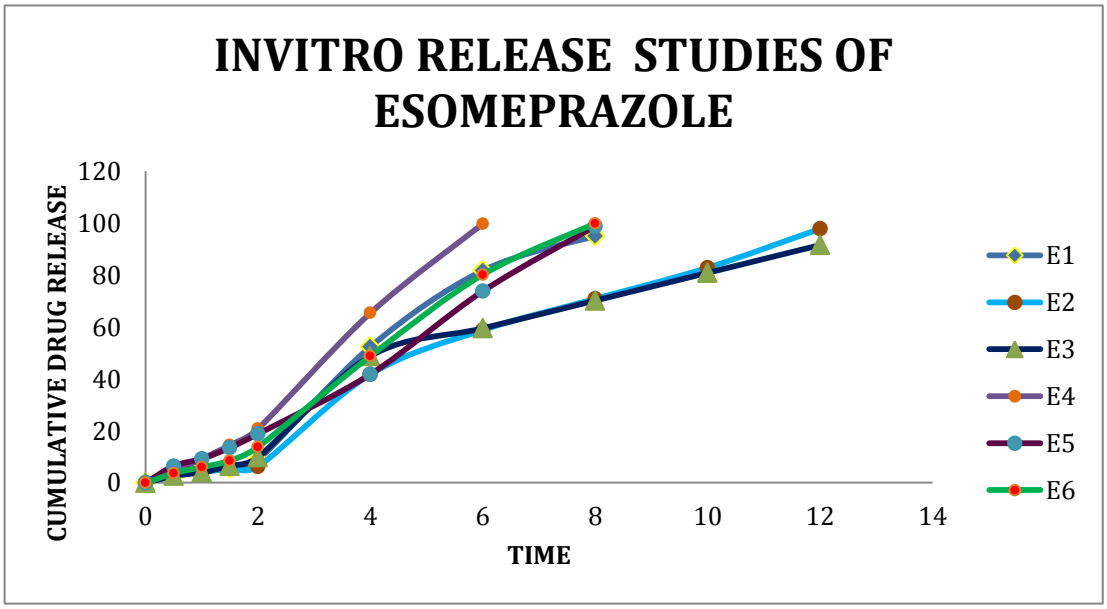


Fig 5.3.1 *invitro* release studies of esomeprazole (E1 - E6)

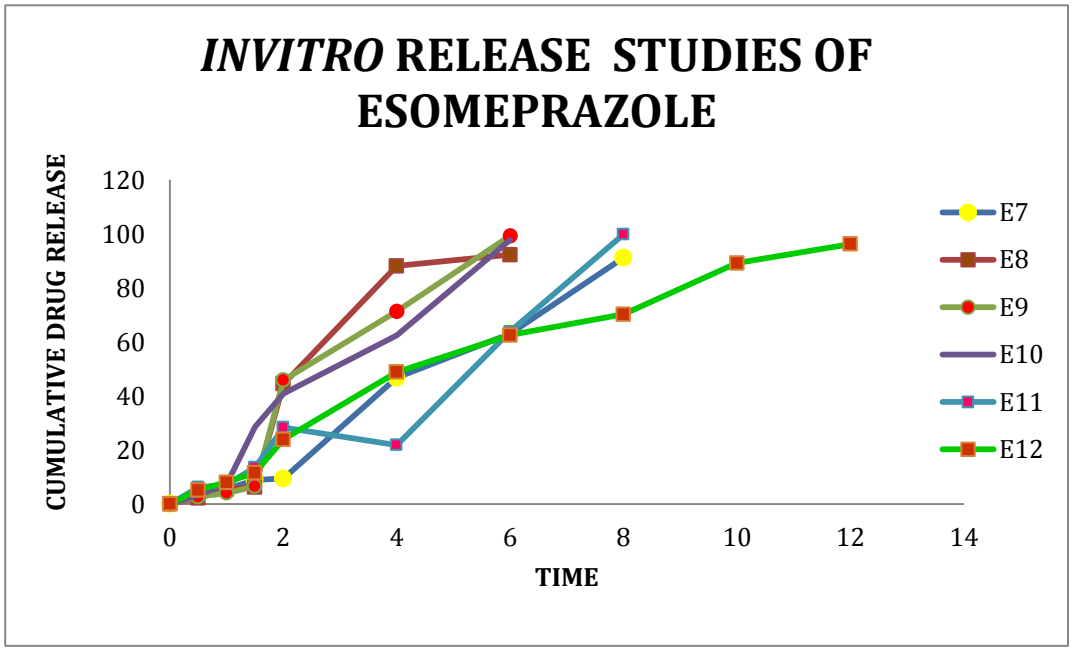


Fig 5.3.1 *invitro* release studies of esomeprazole (E7-E12)

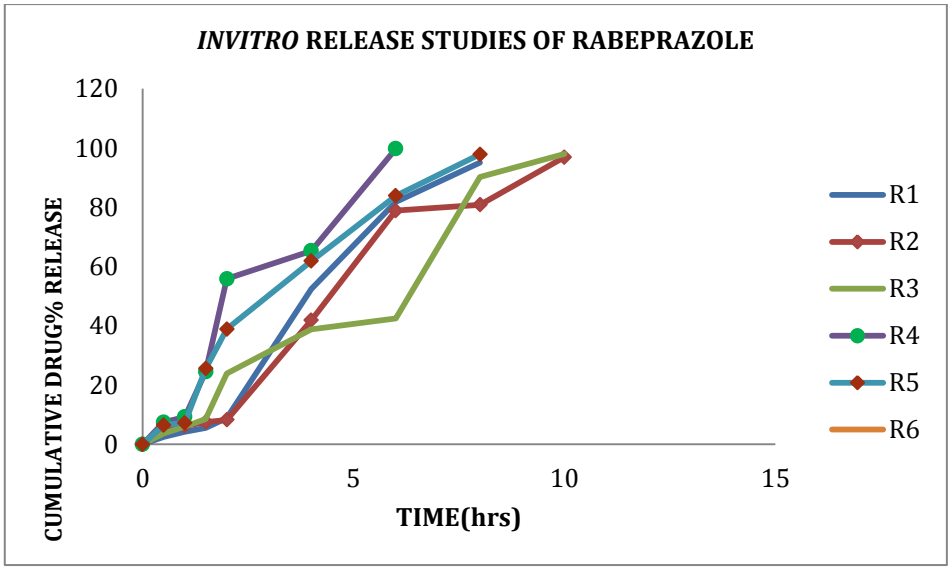


Fig 5.3.2 *Invitro* Release Studies of Rabeprazole (R1-R6)

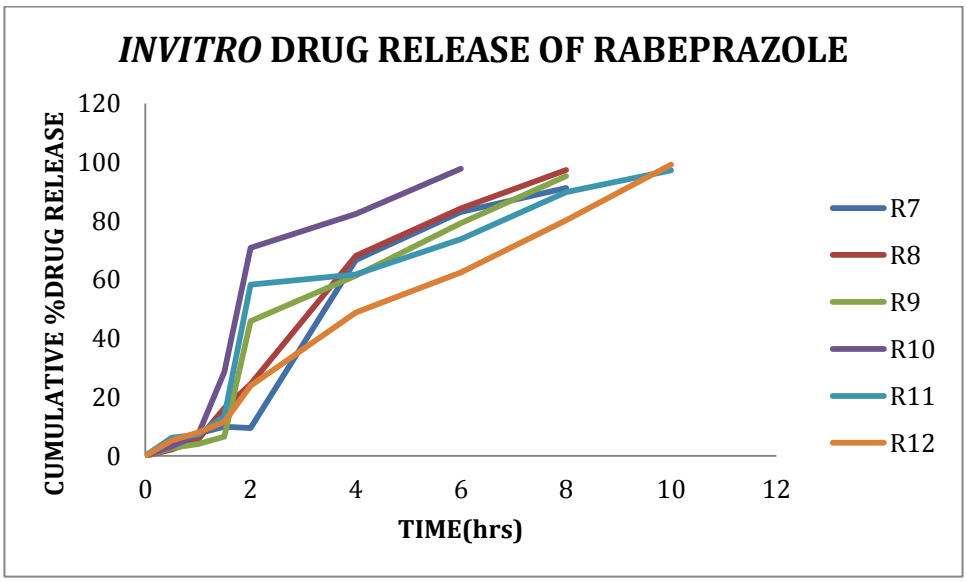


Fig 5.3.2 *Invitro* release studies of Rabeprazole (R7-R12)

5.3.3 *VITRO* RELEASE OF OPTIMIZED FORMULATION

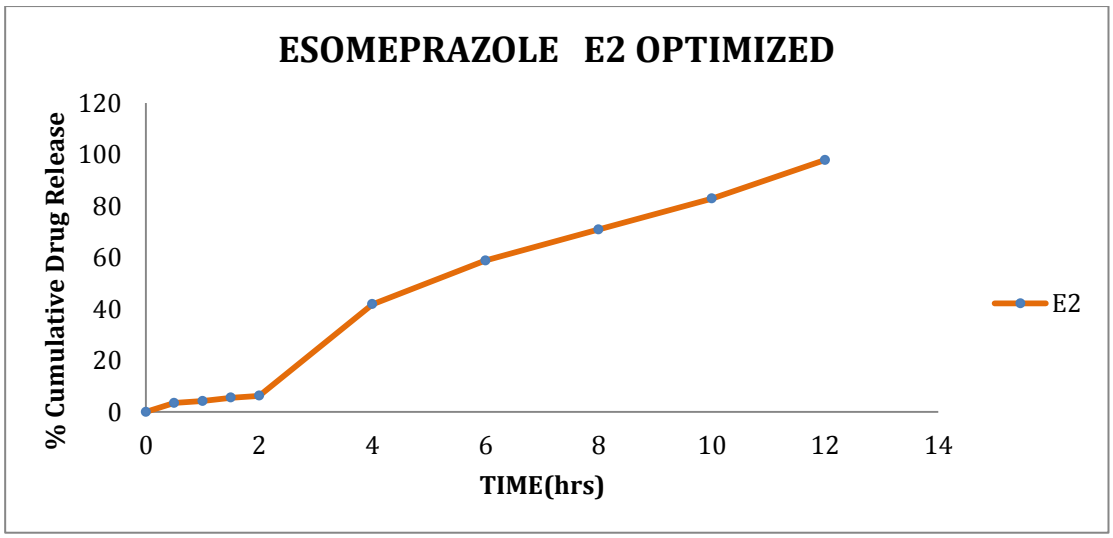


Fig 5.3.3 *Invitro* release studies of esomeprazole

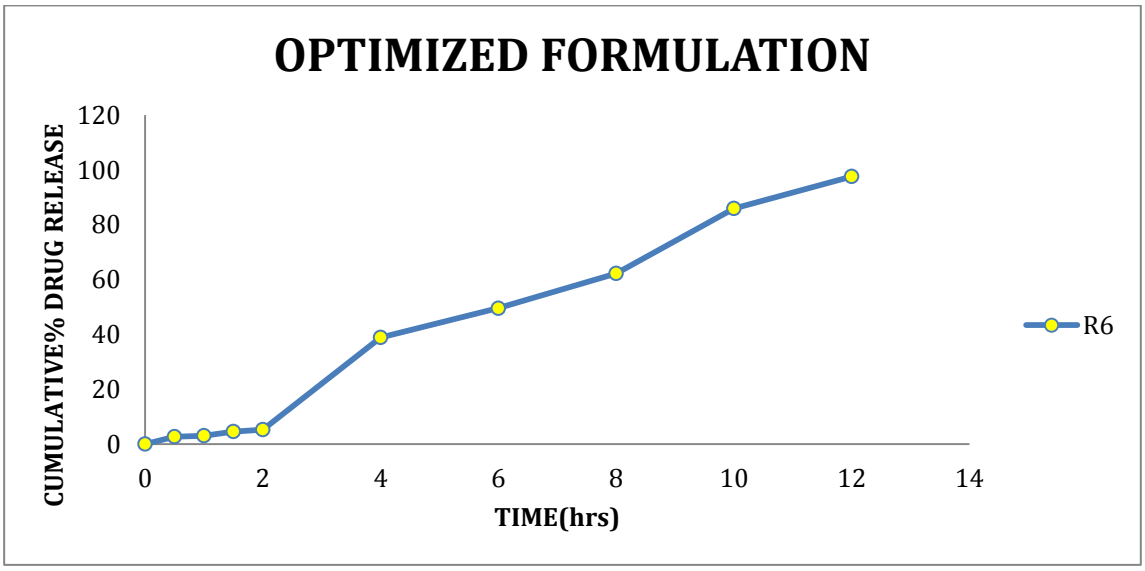
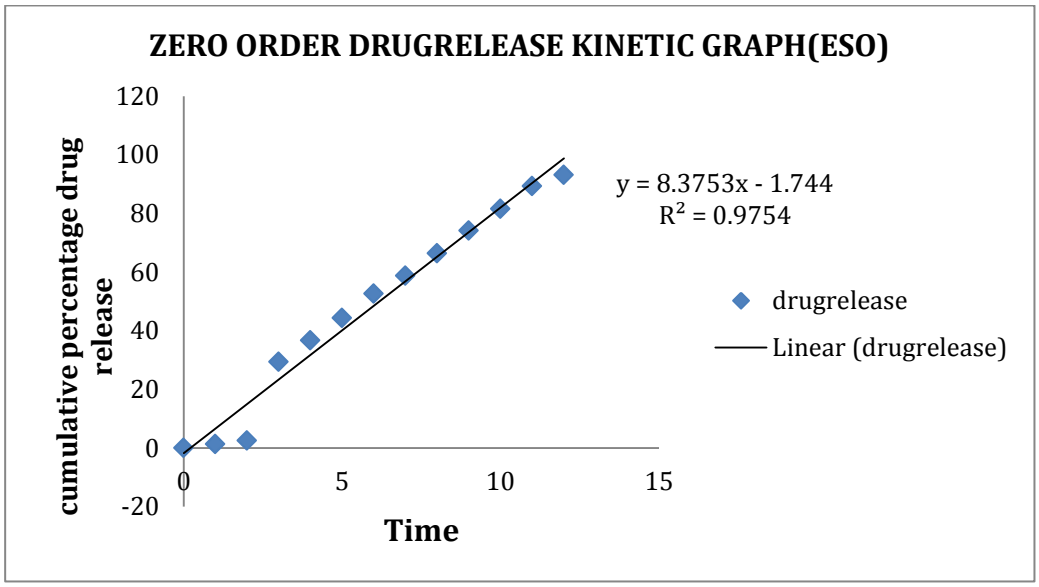
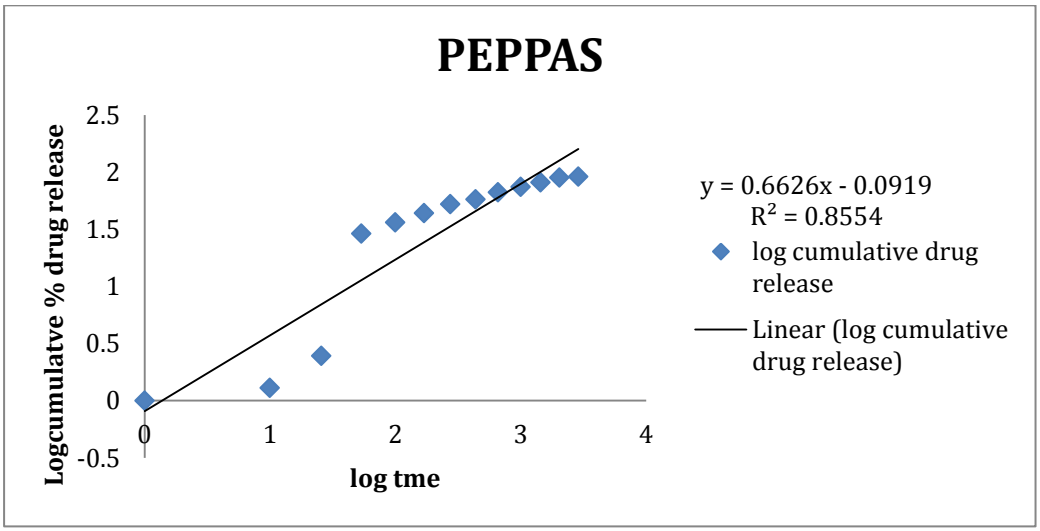
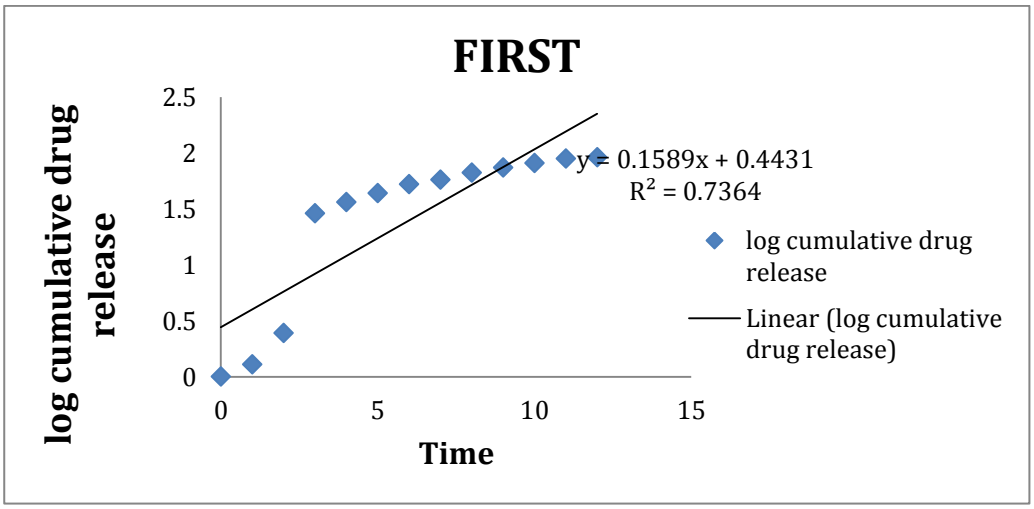


Fig 5.3.3 *Invitro* release of Optimized Formulation (RABEPRAZOLE)

5.4 *IN VITRO* RELEASE KINETICS OF ESOMEPRAZOLE







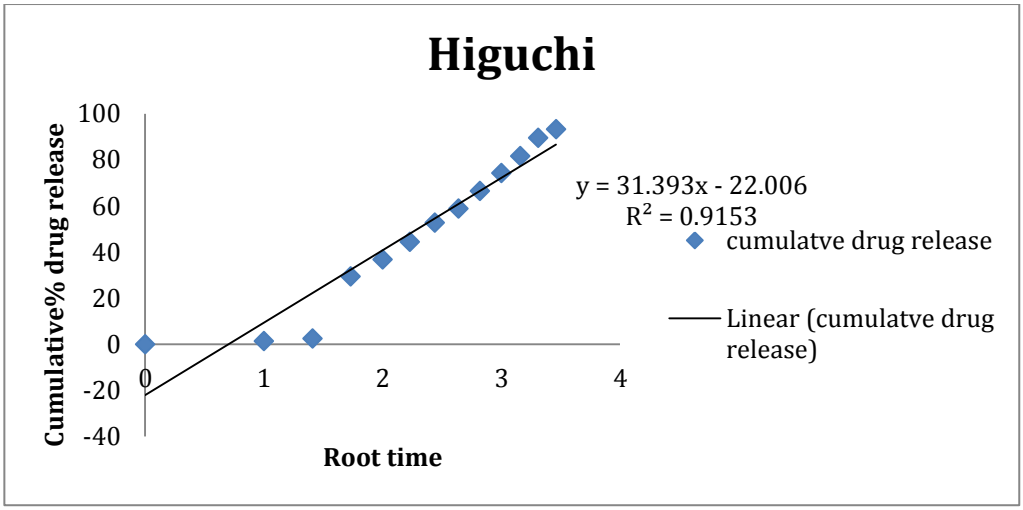
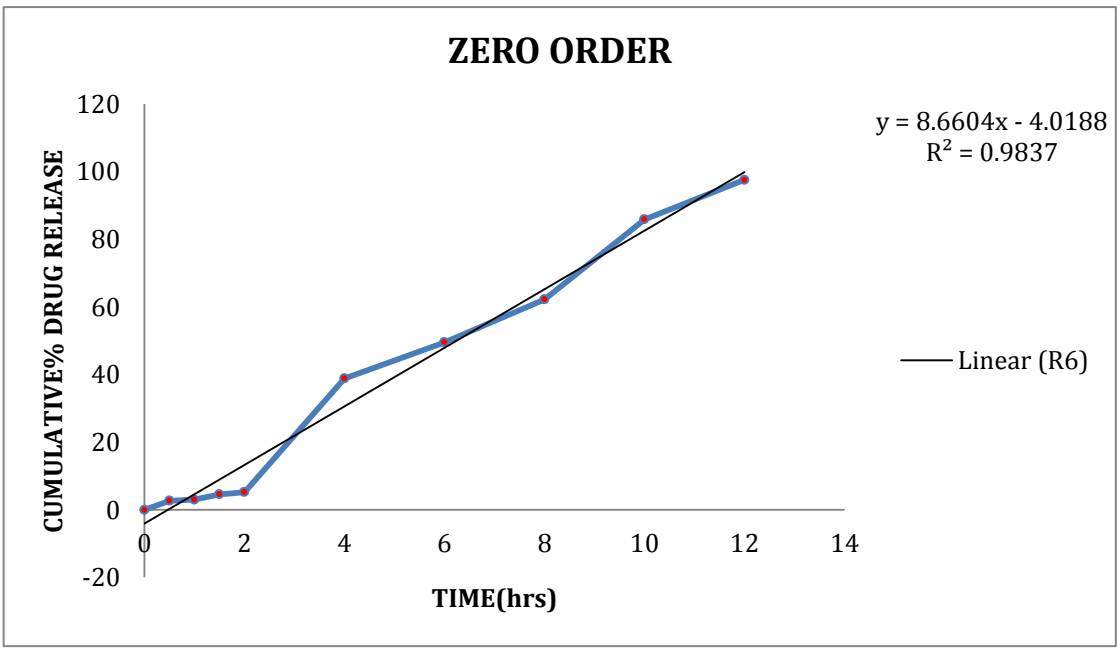
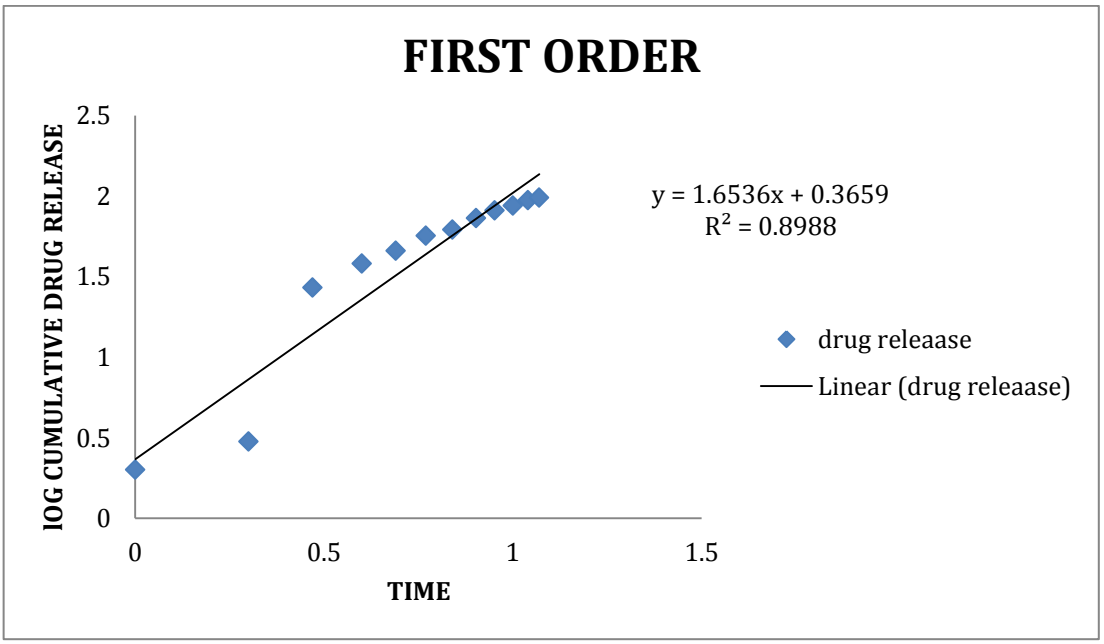
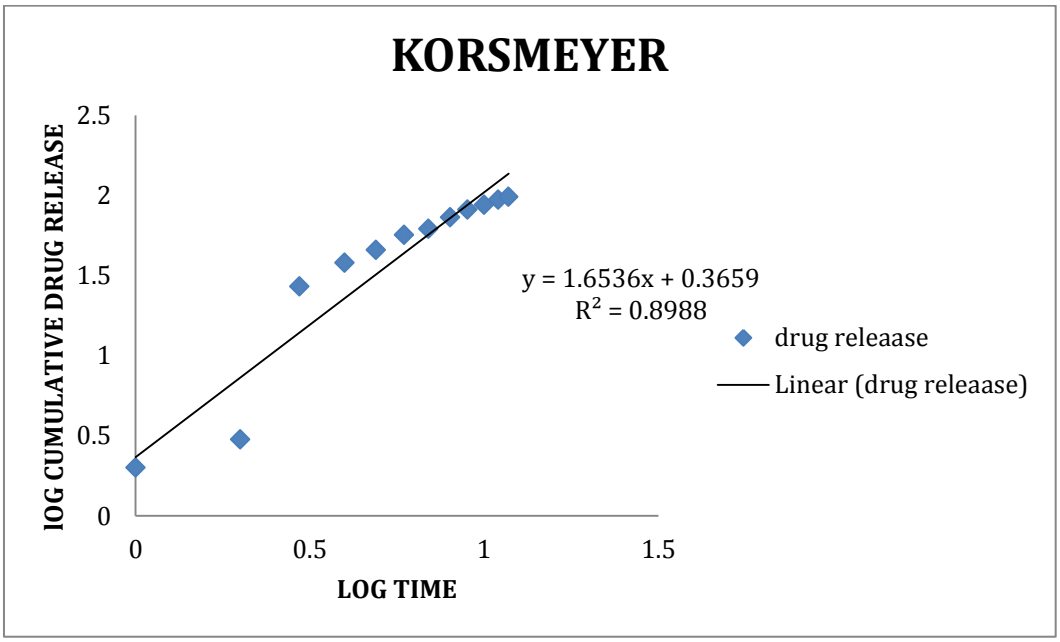


Fig.5.2 In vitro release kinetics of Esomeprazole

5.5 *IN VITRO* RELEASE KINETICS OF RABEPRAZOLE







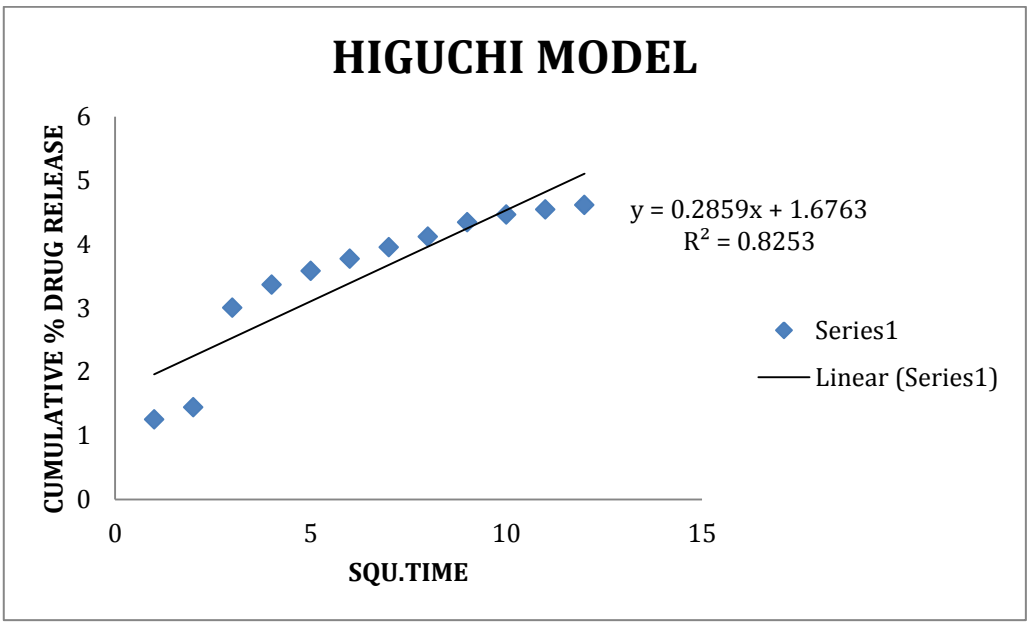


Fig 5.5 *IN VITRO* RELEASE KINETICS OF RABEPRAZOLE

5.6 RESULTS OF KINETIC ANALYSIS OF KINETIC OPTIMIZED FORMULATION

Table 5.6 Results of kinetic analysis of kinetic optimized formulation

Formulation code	Zero order	First order	Higuchi's	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	n
E2	0.9789	0.9181	0.8141	0.9802	1.065
R3	0.9780	0.9101	0.8042	0.9816	1.112

5.7 ESOMEPRAZOLE MUPS PLASMA CONCENTRATION CURVE

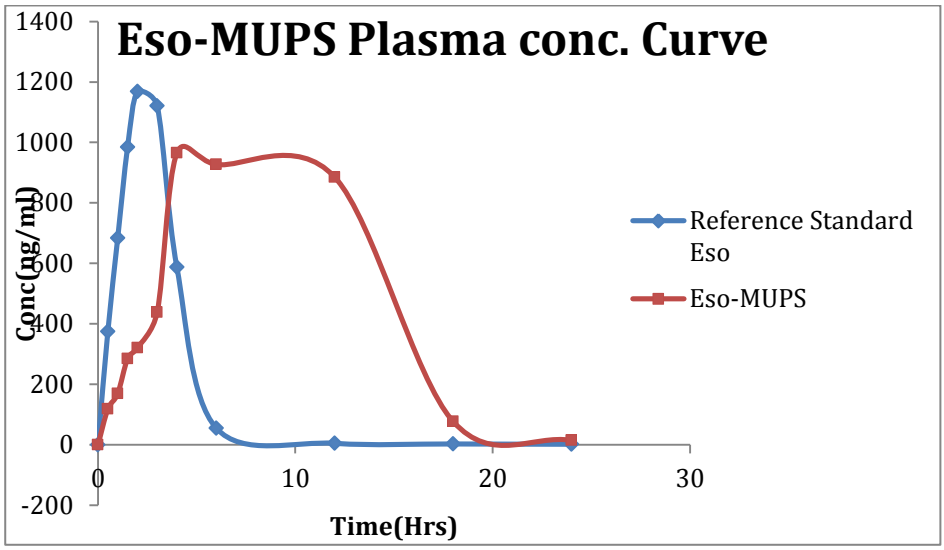


Fig: 5.7.1 Esomeprazole MUPS Plasma Concentration Curve

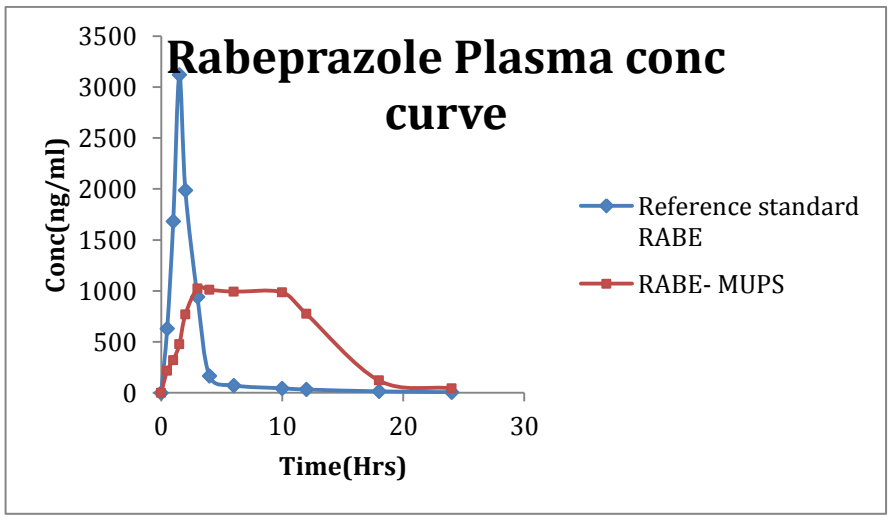
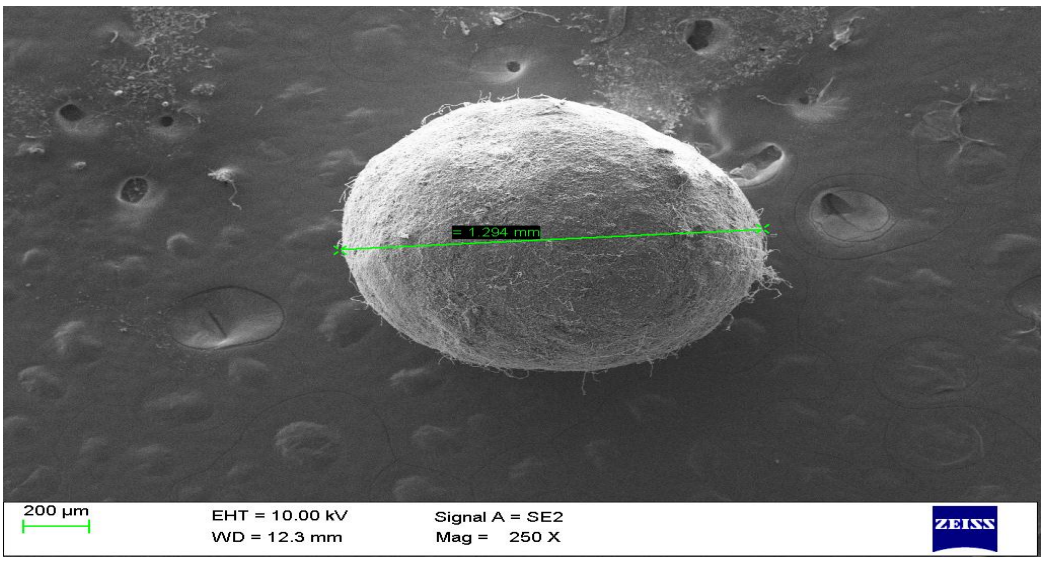


Fig: 5.7.2 Rabeprazole MUPS Plasma Concentration Curve

5.8 SCANNING ELECTRON MICROSCOPY:

Fig:5.8.1 Morphology of Esomeprazole Mups Pellets



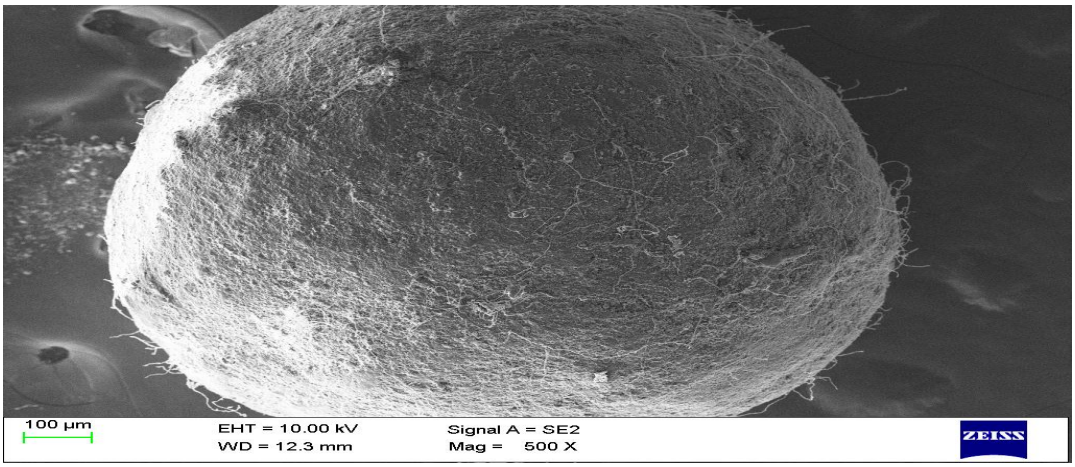


Fig:5.8.2 Morphology of Rabeprazole Mups Pellets

Microscopy figures of Optimized formulation that pellets appeared to exist as spherical discrete units while the surface morphology of the pellets was compact, continuous and is porous in nature SEM demonstrated the spherical nature of the pellets.

5. STABILITY STUDIES:

Stability study of the best fit formulation was conducted as ICH guidelines for both drugs under Accelerated condition at 40° ±2ºC / 75%RH for about 6 months in a stability chamber. Sample were collected and analysed at 1^{st}, 2^{nd}&,3^{rd}, months. There was no significant change in in vitro release profile .All the parameters were within the limit after 60 days.

6. DISUSSION

6.1. PRE FORMULATION STUDIES

6.1.1 Solubility Analysis of Esomeprazole Magnesium

The solubility analysis of Esomeprazole Magnesium shows that it was slightly soluble in water, soluble in methanol and freely soluble in Dichloro methane.

The solubility analysis of Rabeprazole sodium shows that it was very soluble in water and methanol. Freely soluble in ethanol, chloroform and ethyl acetone. Practically it was insoluble in ether and n-hexane.

6.1.2. Melting Point

The melting point of Esomeprazole Magnesium and Rabeprazole Sodium was 158°C and 103°C respectively shows that the sample was pure with no impurities.

6.1.3. Identification of Esomeprazole Pure drug

The FTIR Spectra of the pure drug shown in Fig.5.1.3.1 the 1 broad peak at 3217cm^{-1} in the spectra corresponding to C=N group. The peak at 1613.2cm^{-1} and 1581.2 cm^{-1} indicate the presence of carbonyl group.

6.1.4. Identification of Rabeprazole Sodium Pure drug

The IR spectrum of pure drug shows the characteristic peaks at 1028 cm^{-1} for C-O-C band, 3016cm^{-1} for C-H aliphate stretching as shown in fig. 5.1.3.2.

6.1.5. Calibration Curve of Esomeprazole Magnesium

A calibration curve of Esomeprazole magnesium was constructed in pH 6.8 buffer by measuring the diluted solution at 302nm. The linearity of curve was found in the range of 2-15µg/ml.

6.1.6. Calibration curve of Rabeprazole Sodium

A calibration of Rabeprazole Sodium was constructed in pH 7.2 by measuring the dilute solution at 287nm. The linearity of curve was found in the range of 2-12µg/ml.

6.1.7 Comparability Study of Rabeprazole Sodium and Esomeprazole Magnesium (Physical Observation)

From the compatibility study of Esomeprazole magnesium/ Rabeprazole Sodium mixed with various excipients the Physical Observation shows there is no significant Drug – excipient interaction was noticed. So it was concluded that drug and other excipient were compatible with each other.

6.1.8. Drug-Excipient Compatibility studies (FT-IR Spectral Analysis)

In order to investigate the possible interaction between Esomeprazole magnesium and excipients and Rabeprazole Sodium and excipients, FT-IR studies was carried out. The result proved that the drug was compatible with excipients as the peaks are almost similar seen in pure drug.

6.1.9. Micromeritics Evaluation of Esomeprazole Magnesium Pellets

The Esomeprazole Magnesium Pellets were evaluated for angle of repose, Bulk density, tapped density, carr's index and Hausner's ratio. From the results the bulk density of Esomeprazole pellets was lies in between 0.430 to 0.482 and Tapped density was from 0.501 to 0.598. The angle of repose was found to be in the range of 20.28 to 28.56. The compression index within the range of 11.32 to 24.41. The friability was less than one. The above results indicating the prepared Esomeprazole pellets have good flow characteristics and suitable for handling and filling into capsules.

6.1.10. Micromeritic Evaluation of Rabeprazole Sodium pellets

The Rabeprazole Sodium pellets were evaluation for all micromeritic parameters. The bulk density of the prepared pellets was in between 0.31 to 0.39 and tapped density from 0.37 to 0.44. The angle of repose in the range of 24.01 to 30.03 and compressibility index indicate that the prepared pellets have good flow properties.

6.2. ASSAY OF ESOMEPRAZOLE MAGNESIUM

6.2.1 Assay of Esomeprazole Magnesium

Esomeprazole	E_1	E_2	E_3	E_4	E_5	E_6	E_7	E_8	E_9	E_{10}	E_{11}	E_{12}
% Drug	96	98	98	88	87	89	91	92	93	95	95	91

6.2.2 Assay of Rabeprazole Sodium

Rabeprazole	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	R_{11}	R_{12}
% Drug	92	95	98	94	90	91	86	85	85	85	89	89

The observation shows the percent drug content in each formulations within the limit (not less than 85% and not more than 105%)

6.3. INVITRO DISSOLUTION STUDIES

From the dissolution profile of Esomeprazole Magnesium all the formulation had better resistance to 0.1N HCl and formulation F_2(Esomeprazole) has better cumulative percent drug release as compared to other formulation. After 12 hours F_2 shows 98% cumulative percent drug release, as compared to other formulations. So E_2 (Esomeprazole Magnesium) was selected as optimized formulation.

From the dissolution profile of Rabeprazole sodium pellets had better resistant to 0.1N HCl and formulation F_3(Rabeprazole) has better cumulative percent drug release as

compared to other formulation. After 12 hours F_2 shows 97% cumulative percent drug release as compared to other formulation. So R_6 (Rabeprazole Sodium) was selected as optimized formulation.

6.4. SCANNING ELECTRON MICROSCOPY (SEM) STUDY

Microscopy figures of optimized formulations of Esomeprazole and Rabeprazole appeared to exist as spherical discrete unit and the surface morphology of the pellets was compact, and porous in nature.

6.5. ACCELERATED STABILITY STUDIES

Stability study of the best fit formulation were conducted as ICH guidelines for both drugs under accelerated conditions at 40°C ± 2°C/75% RH for 3 months in a stability chamber. Samples were collected and analysed at 1^{st}, 2^{nd} and 3^{rd} months. There was no significant change in *invitro* and percent of drug release.

7. SUMMARY

In the modern era of Pharmaceutical research much attention has been focussed on patient's health in terms of therapeutic efficacy and safety. Modified Dosage Form (MRDF) has always been more effective therapeutic alternative to conventional or immediate release. The term modified release drug product is used to describe product that alter the timing and /or the rate of release of the drug substances. There are two types of MRDF .i) Delayed release ii) Extended release. The terms Controlled release (CR), Sustained release (SR) Prolong release (PR) has been used synonymously with extended release dosage forms. Controlled release drug delivery is one which delivers the drug at a predetermined rate for locally (or) systemically for a specified period of time. Controlled release drug delivery system aim to maintain plasma concentration of drugs within the therapeutic window for a longer period of time. Delayed release products are formulated with acid resistance (or) enteric coating protects acid labile drug substance from the gastric environment (or) to prevent adverse events such as irritation.

A peptic ulcer is an open sore on the lining of the stomach or duodenum. Gastric and duodenal ulcer is produced by an imbalance between mucosal defences particularly gastric acid and pepsin. In addition, H.pylori infection is a major factor in the pathogenic of peptic ulcer. Proton pump inhibitors (PPI) rank among the top 10 prescribed classes of drugs and are commonly used to treat acid reflux, indigestion and peptic ulcers. PPIs are among the most widely sold drugs in the world and the first one in antiulcer medicine is omeprazole(WHO model list of essential medicines). Among seven available PPI drugs Esomeprazole magnesium and Rabeprazole sodium are classical examples of proton pump inhibitors and are approved by FDA for the treatment of GERD, Peptic ulcer and maintains of erosive esophagites. These drugs will degrading in acidic environment of

stomach and will lead to therapeutic in efficacy so it is necessary to bypass the acidic pH of the stomach which can be achieved by formulating delayed release dosage forms by using different enteric polymers.

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. Many marketed Esomeprazole and Rabeprazole tablets/pellets are available as enteric coated formulation only. The main aim of the present study was to develop and evaluate enteric coated, controlled release tablets of Esomeprazole magnesium and Rabeprazole sodium using natural and synthetic polymers gives better and more uniform drug absorption and greater bioavailability.

To design the multiple unit pellets, we have developed two different spheroid unit of uniform drug content with varying in polymer concentration to achieve rate controlled drug release as per our specification. The first group spheroid unit which contain only drug with spheroidizing polymers was prepared to achieve the minimum effective concentration. The second group of spheroid unit was prepared by using the controlled release polymers HPMC K100, HPMC K15, Ethyl cellulose and Xanthan gum. Among the four polymers HPMC K100 the drug Polymer ratio 1:1.5 shows good controlled release characters in Esomeprazole magnesium and HPMC K 15 the drug and polymer ratio 1:2 shows good controlled release profile in Rabeprazole sodium. The MUPS were prepared by Extrusion -Spheronization a promising pelletization technique. In this process the pellets were prepared by mixing the drug with excipient along with binder solution the resultant mass was extruded through extruder followed by spheronizer and finally dried.

The possible interactions between drugs and distinct polymers were investigated via FT-IR Studies. Results proved that Rabeprazole sodium and Esomeprazole

magnesium was found to be compatible with excipient as no disappearance of the peaks or shift of the peaks indicating that the drugs are compatible with ingredients. The micromeritics evaluation like Bulk density, Tapped density, Angle of repose, Carr's index and Hauser's ratio of the prepared pellets shows good flow property. The post formulation parameters like friability, drug content were carried out and found to be within acceptable limit. SEM study shows the surface morphology of the optimized formulations E2 and R6 the pellets was compact, continuous and was porous in nature, demonstrated the spherical nature of the pellets.

Based on in vitro dissolution profile the enteric coated, controlled release multiple unit pellets of Esomeprazole magnesium and Rabeprazole sodium was developed using HPMCK100 in the ratio 1:1.5 (drug :polymer) and HPMC K15 in the ratio 1:1.5 (drug :polymer) respectively as controlled release polymer and Hypromellose phthalate HP55 as enteric coated polymer. The optimized formulations E2 (Esomeprazole) and R6 (Rabeprazole) had better resistant to 0.1N HCl and better cumulative percent drug release as compared to other formulation. After 12 hours E2 shows 97.88% and R6 shows 97.59 % cumulative percent drug release as compared to other formulation. So E2 (Esomeprazole) R6 (Rabeprazole) was selected as optimized formulation from the trail batches.

The in vivo pharmacokinetic plasma concentration and time curve parameters shows that less plasma concentration fluctuation, lower $C_{max,}$ prolonged t_{max} and MRT of formulated MUPS than that of marketed enteric coated formulations. Stability study revealed there was no significant change in *in vitro* release profile. All the parameters were within limit after 90 days.

8. CONCLUSION

From the above research finding it can be concluded that controlled release of Esomeprazole Magnesium and Rabeprazole Sodium Multiple Unit Pellets could be developed by using HPMC K100 the drug Polymer ratio 1:1.5 and HPMC K 15 the drug and polymer ratio 1:2 prepared by Extrusion -Spheronization to achieve better bioavailability and extended drug release. Further, the first group spheroid unit could maintain the minimum effective concentration and the second group spheroid unit could release the medicament in control release manner. Hence the prepared Multiple Unit Pellets could achieve both enteric coating and controlled release approach for the potential delivery of Antiulcerants.

9. IMPACT OF THE STUDY

Compaction of multiple particulates, commonly called Multiple Unit Pellets (MUPS), is one of the more recent and challenging technologies that combine the advantages of both tablets and pellets filled capsules in one dosage forms.

MUPS a novel drug delivery platform may improve acid suppression and offer benefits over conventional single release oral dose.

Rapid and uniform transit from the stomach into small intestine owing to their small size gives better and more uniform drug absorption and greater bioavailability.

There will be drug dissolution of Esomeprazole magnesium MUPS, Rabeprazole sodium MUPS results in consistent and controlled pharmacological action.

It is a flexible technology help to prepare different release pattern like immediate, sustained and controlled release of drug.

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