

FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF ESOMEPRAZOLE USING NATURAL AND SYNTHETIC POLYMERS

Authors:

- 1. Janakathotty Bharathi, Associate Professor, Krishna Teja Pharmacy College, Tirupati**
- 2. C.Reddy Kumari, Assistant Professor, Gautham College of Pharmacy, Bengaluru**
- 3. Dr.K.Umasankar, Professor, HOD Department of Pharmaceutics, Krishna Teja Pharmacy College, Tirupati**

ABSTRACT

The objective of this study was to formulate and evaluate sustained-release tablets of Esomeprazole, a proton pump inhibitor, using a combination of natural and synthetic polymers. Esomeprazole is commonly used for the treatment of gastroesophageal reflux disease (GERD), but its short half-life necessitates the development of controlled-release formulations for improved therapeutic efficacy and patient compliance. In this study, various natural (e.g., hydroxypropyl methylcellulose, Amla extract, Ginger extract) and synthetic polymers (e.g., polyvinylpyrrolidone) were employed to prepare sustained-release tablets of Esomeprazole via direct compression. The prepared tablets were evaluated for various physicochemical properties, including weight uniformity, hardness, friability, drug content, and in vitro drug release profiles. The release data were analyzed using kinetic models to determine the release mechanism. The formulations demonstrated a controlled release of Esomeprazole over an extended period, with significant improvement in the drug's bioavailability and therapeutic performance compared to immediate-release formulations. The results indicate that the combination of natural and synthetic polymers can be effectively used to develop sustained-release Esomeprazole tablets, offering a promising approach for the treatment of acid-related disorders.

Keywords: Esomeprazole, Amla extract, Ginger extract and HPMC

LIST OF CONTENTS

CHAPTER	TITLE	PAGE NO
1	INTRODUCTION	1 – 29
2	LITERATURE REVIEW	30 - 35
3	AIM & OBJECTIVE	36
4	PLAN OF WORK	37
5	DRUG PROFILE	38 - 41
6	EXCIPIENT PROFILE	42 - 50
7	METHODOLOGY	51 – 60
8	RESULTS & DISCUSSION	61 – 73
9	CONCLUSION	74
	REFERENCES	75 - 77

1.INTRODUCTION

Drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action. The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use[1-6]

The first sustained release tablets were made by Howard Press in New Jersey in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.

Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ[7-8].

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- ✓ If the active compound has a long half-life, it is sustained on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and
- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed[9].

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

1.1. Rationale for extended release dosage forms:

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen[10-11]. When conventional immediate-

release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose. However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. 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 amounts of drug to maintain this effect over a predetermined period (Fig.1).

The sustained plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well[12].

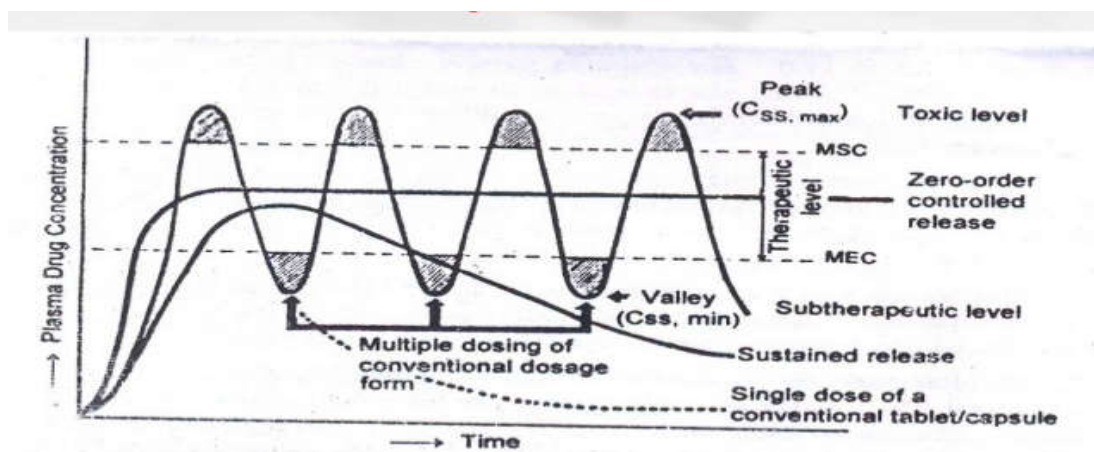


Figure 1.1: Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

1.2. Advantages of sustained release dosage forms

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient as well.
- The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.
- The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
- The total amount of drug administered can be reduced, thus:
 - Maximizing availability with minimum dose;
 - Minimize or eliminate local side effects;
 - Minimize or eliminate systemic side effects;
 - Minimize drug accumulation with chronic dosing.

- Safety margins of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
- Improve efficiency in treatment.
 - Cure or control condition more promptly
 - Improve control of condition
 - Improve bioavailability of some drugs
 - Make use of special effects; e.g. sustain release aspirin for morning relief of arthritis by dosing before bed-time.

Disadvantages of sustained release dosage forms

- Probability of dose dumping.
- Reduced potential for dose adjustment.
- Cost of single unit higher than conventional dosage forms.
- Increase potential for first pass metabolism.
- Requirement for additional patient education for proper medication.
- Decreased systemic availability in comparison to immediate release conventional dosage forms.
- Poor *invitro* and *invivo* correlations.

Terminology:

Modified release delivery systems may be divided conveniently into four categories.

A) Delayed release

B) Sustained release

✓ Controlled release

✓ Extended release

C) Site specific targeting

D) Receptor targeting

A) Delayed Release:

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating[13-14].

B) Sustained release:

During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of sustained release is also being applied to veterinary products. These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells[15].

1. Controlled Release:

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

2. Extended Release:

Pharmaceutical dosage forms release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

C) Site specific targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

D) Receptor targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific

targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.

1.4. Design and formulation of oral sustained release drug delivery system:

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood level time profile similar to that after intravenous constant rate infusion.

Sustained (zero-order) drug release has been attempted to be achieved with various classes of sustained drug delivery system[16]:

A) Diffusion sustained system.

i) Reservoir type.

ii) Matrix type

B) Dissolution sustained system.

i) Reservoir type.

ii) Matrix type

C) Methods using Ion-exchange.

D) Methods using osmotic pressure.

E) pH independent formulations.

F) Altered density formulations.

1.4.1. Diffusion sustained system:

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug J (in amount / area - time), across a membrane in the direction of decreasing concentration is given by Fick's law[17].

$$J = -D \frac{dc}{dx}$$

D = diffusion coefficient in area/ time

dc/dx = change of concentration 'c' with distance 'x'

In common form, when a water insoluble membrane encloses a core of drug, it must diffuse through the membrane.

The drug release rate dm/dt is given by

$$\frac{dm}{dt} = \frac{ADK\Delta C}{L}$$

Where;

A = Area.

K = Partition coefficient of drug between the membrane and drug core.

L = Diffusion path length (i.e. thickness of coat).

ΔC = Concentration difference across the membrane.

i) Reservoir Type:

In the system, a water insoluble polymeric material encases a core of drug (Figure 4.). Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media.

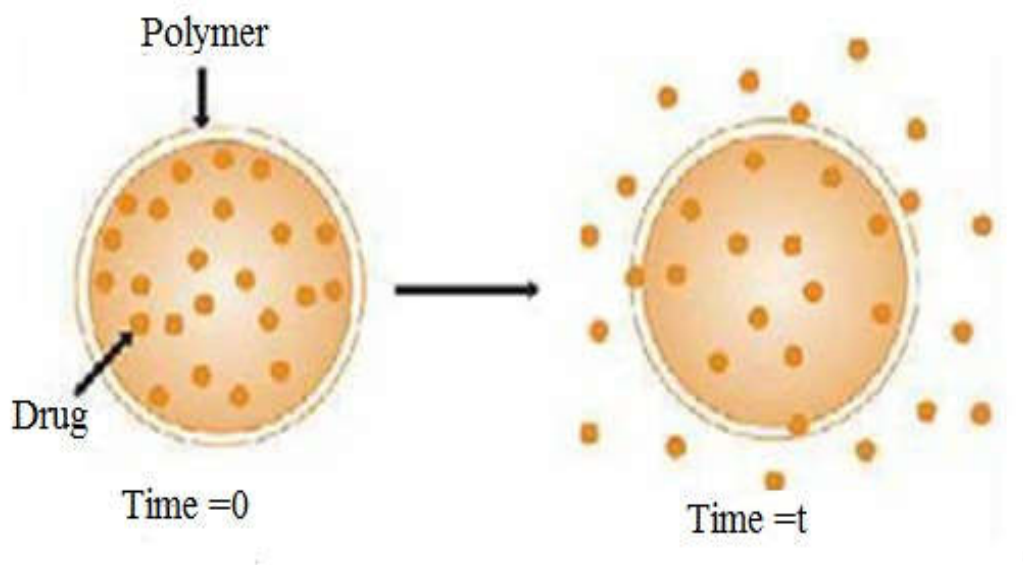


Figure 1.2: Schematic representation of diffusion sustained drug release: reservoir system

Characterization:

Description: Drug core surrounded by polymer membrane which controls release rate.

Advantages: Zero order delivery is possible, release rates variable with polymer type.

Disadvantages: System must be physically removed from implant sites. Difficult to deliver high molecular weight compound, generally increased cost per dosage unit, potential toxicity if system fails.

ii) Matrix Type:

A solid drug is dispersed in an insoluble matrix (Figure 5.) and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution. Higuchi has derived the appropriate equation for drug release for this system:

$$Q = D\varepsilon / T [2A - \varepsilon C_s] Cst^{1/2}$$

Where;

Q = Weight in gms of drug released per unit area of surface at time t.

D = Diffusion coefficient of drug in the release medium.

ε = Porosity of the matrix.

C_s = Solubility of drug in release medium.

T = Tortuosity of the matrix.

A = Concentration of drug in the tablet, as gm/ ml.

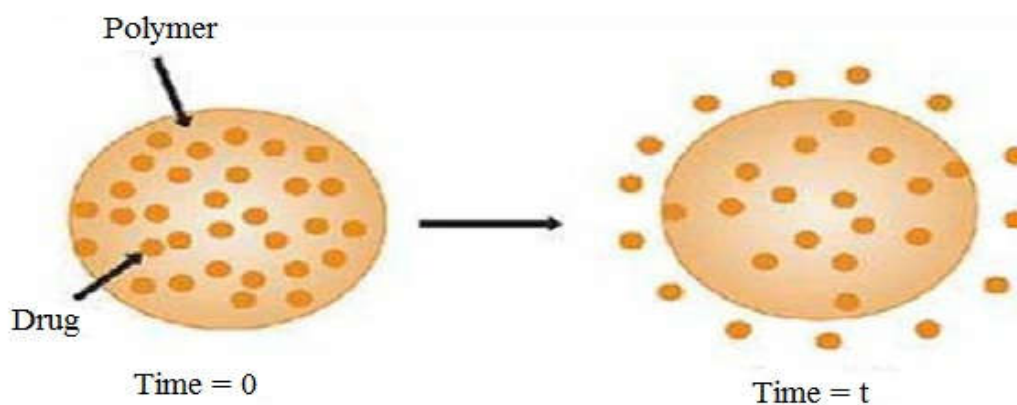


Figure 1.3: Schematic representation of diffusion sustained drug release: matrix system

Characterization:

Description: Homogenous dispersion of solid drug in a polymer mixture.

Advantages: Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.

Disadvantages: Cannot provide zero order release, removal of remaining matrix is necessary for implanted system.

A third possible diffusional mechanism is the system where a partially soluble membrane encloses a drug core. Dissolution of part of membrane allows for diffusion of the constrained drug through pores in the polymer coat.

The release rate can be given by following equation.

$$\text{Release rate} = AD / L = [C_1 - C_2]$$

Where;

A = Area.

D = Diffusion coefficient.

C₁ = Drug concentration in the core.

C₂ = Drug concentration in the surrounding medium.

L = Diffusional path length.

Thus diffusion sustained products are based on two approaches the first approach entails placement of the drug in an insoluble matrix of some sort. The eluting medium penetrates the matrix and drug diffuses out of the matrix to the surrounding pool for ultimate absorption. The second approach involves enclosing the drug particle with a polymer coat. In this case the portion of the drug which has dissolved in the polymer coat diffuses through an unstirred film of liquid into the surrounding fluid.[18]

1.4.2. Dissolution sustained systems:

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation.

These systems are most commonly employed in the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the device until it reaches the higher pH of the intestine. In most cases, enteric coated dosage forms are not truly sustaining in nature, but serve as a useful function in directing release of the drug to a special site. The same approach can be employed for compounds that are degraded by the harsh conditions found in the gastric region.

i) Reservoir Type:

Drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract. By alternating layers of drug with the rate controlling coats as shown in figure, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals. Although this is not a true sustained release system, the biological effects can be similar. An alternative method is to administer the drug as group of beads that have coating of different thickness. This is shown in figure. Since the beads have different coating thickness, their release occurs in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at late times will be achieved from those with thicker coating. This is the principle of the spansule capsule. Cellulose nitrate phthalate was synthesized and used as an enteric coating agent for acetyl salicylic acid tablets.

ii) Matrix Type:

The more common type of dissolution sustained dosage form (as shown in figure 4). It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion

Two types of dissolution sustained pulsed delivery systems

- ✓ Single bead type device with alternating drug and rate-controlling layer.
- ✓ Beads containing drug with differing thickness of dissolving coats.

Amongst sustained release formulations, hydrophilic matrix technology is the most widely used drug delivery system due to following advantages

- ✓ Provide desired release profiles for a wide therapeutic drug category, dose and solubility.

- ✓ Simple and cost effective manufacturing using existing tableting unit operation equipment
- ✓ Robust formulation.
- ✓ Broad regulatory and patient acceptance.
- ✓ Ease of drug release modulation through level and choice of polymeric systems and function coatings.

1.4.3. Methods Using Ion Exchange:

It is based on the formation of drug resin complex formed when anionic solution is kept in contact with ionic resins. The drug from these complexes gets exchanged in gastro intestinal tract and released with excess of Na^+ and Cl^- present in gastrointestinal tract.

Anion Exchangers: $\text{Resin}^+ - \text{Drug}^- + \text{Cl}^-$ goes to $\text{Resin}^+ - \text{Cl}^- + \text{Drug}^-$

Cation Exchangers: $\text{Resin}^- - \text{Drug}^+ + \text{Na}^+$ goes to $\text{Resin}^- - \text{Na}^+ + \text{Drug}^+$

These systems generally utilize resin compounds of water insoluble cross linked polymer. They contain salt forming functional group in repeating positions on the polymer chain. The rate of drug diffusion out of the resin is sustained by the area of diffusion, diffusional path length and rigidity of therein which is function of the amount of cross linking agent used to prepare resins. The release rate can be further sustained by coating the drug resin complex by microencapsulation process.

1.4.4. Methods Using Osmotic Pressure:

A semi permeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating.

Two types of osmotically sustained systems are

- ✓ Type A contains an osmotic core with drug.
- ✓ Type B contains the drug in flexible bag with osmotic core surrounding.

1.4.5. pH– Independent Formulations:

The gastrointestinal tract present some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which constraint the length

of prolongation, further the chemical environment throughout the length of gastrointestinal tract is constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH independent drug release. A buffered sustained release formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release e.g. propoxyphene in a buffered sustained release formulation, which significantly increase reproducibility.

1.4.6. Altered Density Formulations:

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug content is released, it would have limited utility. To this end, several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

1.4.7. High Density Approach:

In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4gm/cm.

1.4.8. Low Density Approach:

Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose.

1.5. Matrix tablets:

One of the least complicated approaches to the manufacture of controlled release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression. Examples of Retardant.

Table 1. 1: Materials used to formulate matrix tablet

S. No	Matrix Characteristics	Material
1	Insoluble, Inert	Polyethylene, Polyvinyl chloride, Ethyl Cellulose
2	Insoluble, Erodible	Carnauba wax, Stearic acid, Polyethylene glycol

1.5.1 Classification of matrix tablets:

1.5.1.1 On the basis of polymer used:

A) Hydrophilic matrix tablet:

Hydrophilic matrix can be utilized as a means to control the drug release rate. The matrix may be tabulated by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. The hydrophilic matrix requires water to activate the release mechanism and explore several advantages, including ease of manufacture and excellent uniformity of matrix tablets. Upon immersion in drug release is controlled by a gel diffusion barrier that is formed and tablet erosion. The effect of formulation and processing variables on drug release behaviour from compressed hydrophilic matrices has been studied by number of investigators. The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablet formulation. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is particularly true for formulation of water soluble drug. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups as follow,

Cellulose derivatives:

- ✓ Hydroxyethylcellulose,
- ✓ Hydroxypropyl methylcellulose (HPMC) 25, 100, 4000 and 15000 cps,
- ✓ Sodium carboxy methyl cellulose and
- ✓ Methyl cellulose 400 and 4000 cps.

Non-cellulose natural or semi synthetic polymers:

- ✓ Agar-agar, Carob Gum, Alginates,
- ✓ Molasses, Polysaccharides of mannose and
- ✓ Galactose, Chitosan and Modified starches.

Polymers of acrylic acid:

- ✓ Polymer which is used in acrylic acid category is Carbopol 934.

Other hydrophilic materials

- ✓ Alginic acid,
- ✓ Gelatin and
- ✓ Natural gums.

B) Fat-wax matrix tablet:

The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. In the bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and is then comminute for controlled-release granulations. The mixture of active ingredients, waxy materials and fillers also can be converted into granules by compacting with roller compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material or other binders. The drug embedded into a melt of fats and waxes is released by leaching and/ or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the GIT. The addition of surfactants to the formulation can also influence both the drug release rate and the proportion of total drug that can be incorporated into a matrix.

C) Plastic matrix tablet (hydrophobic matrices):

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. Controlled release tablets based upon an inert compressed plastic matrix have been used extensively. Release is usually delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic materials provided the plastic

material can be comminute or granulated to desired particle size to facilitate mixing with the drug particle. In order to granulate for compression into tablets, the embedding process may be accomplished by.

- ❖ The solid drug and the plastic powder can be mixed and kneaded with a solution of the same plastic material or other binding agent in an organic solvent and then granulated.
- ❖ The drug can be dissolved in the plastic by using an organic solvent and granulated upon evaporation of the solvent.
- ❖ Using latex or pseudo latex as granulating fluid to granulate the drug and plastic masses. For example: Polyvinyl chloride, Ethyl cellulose, Cellulose acetate and Polystyrene.

D) Bio-degradable matrices:

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. It is biologically degraded or eroded by enzymes generated by surrounding living cells or by non-enzymatic process into oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins, polysaccharides and modified natural polymers, synthetic polymers such as aliphatic poly (esters) and poly anhydrides. v) Mineral matrices: These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaeophyceae) by the use of dilute alkali.

1.5.1.2. Classification according to their porosity:

A) Macro porous systems:

In such systems, the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm . This pore size is larger than diffusing molecule size.

B) Micro porous system:

Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50-200 $\text{\AA}$, which is slightly larger than diffusing molecules size.

C) Non-porous system:

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.[19]

1.5.2 Polymers used in the matrix:

The polymers most widely used in preparing matrix system include both hydrophilic and hydrophobic polymers.

A) Hydrophilic Polymers:

Hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose (HPC), hydroxyl ethyl cellulose (HEC), Xanthan gum, Sodium alginate, poly(ethylene oxide), and cross linked homo polymers and co-polymers of acrylic acid.

B) Hydrophobic Polymers:

This usually includes waxes and water insoluble polymers in their formulation Waxes: carnauba wax, bees wax, candelilla wax, micro crystalline wax, ozokerite wax, paraffin waxes and low molecular weight polyethylene. Insoluble polymers: Ammoniomethacrylate co-polymers (Eudragit RL100, PO, RS100, PO), ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate and latex dispersion of meth acrylic ester copolymers.

1.5.3 Drug release from matrix:

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the following assumptions:

- ❖ A pseudo-steady state is maintained during drug release;
- ❖ The diameter of the drug particles is less than the average distance of drug diffusion through the matrix;
- ❖ The bathing solution provides sink conditions at all times.

The release behaviour for the system can be mathematically described by the following equation:

$$DM/Dh = C_o. Dh - C_s/2 \quad (1)$$

Where

DM = Change in the amount of drug released per unit area

Dh = Change in the thickness of the zone of matrix that has been depleted of drug

Co = Total amount of drug in a unit volume of matrix

Cs = Saturated concentration of the drug within the matrix. Additionally, according to diffusion theory:

$$\mathbf{DM = (Dm. Cs / h).Dt \text{ (2)}}$$

Where:

Dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix

Dt = Change in time

By combining equation 1 and equation 2 and integrating:

$$\mathbf{M = [Cs. Dm. (2Co - Cs). t]^{1/2} \text{ (3)}}$$

When the amount of drug is in excess of the saturation concentration, then:

$$\mathbf{M = [2Cs. Dm. Co. t]^{1/2} \text{ (4)}}$$

Equation 3 and equation 4 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

$$\mathbf{M = [Ds.Ca.p/T. (2Co - p.Ca) t]^{1/2} \text{ (5)}}$$

Where:

p = Porosity of the matrix

t = Tortuosity

Ca = solubility of the drug in the release medium

D_s = Diffusion coefficient in the release medium.

T = Diffusion path length

For pseudo steady state, the equation can be written as:

$$M = [2D.C_a .C_o (p/T) t]^{1/2} \quad (6)$$

The total porosity of the matrix can be calculated with the following equation:

$$p = p_a + C_a / \rho + C_{ex} / p_{ex} \quad (7)$$

Where: p = Porosity

ρ = Drug density

p_a = Porosity due to air pockets in the matrix

p_{ex} = Density of the water soluble excipients

C_{ex} = Concentration of water soluble excipients

For the purpose of data treatment, equation 7 can be reduced to:

$$M = k. t^{1/2} \quad (8)$$

Where k is a constant.

So that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:

- ✓ Initial concentration of drug in the matrix
- ✓ Porosity
- ✓ Tortuosity
- ✓ Polymer system forming the matrix
- ✓ Solubility of the drug.

1.5.4 Components of matrix tablets:

These include:

- ✓ Active drug
- ✓ Release controlling agent(s): matrix formers
- ✓ Matrix Modifiers, such as channelling agents and wicking agents
- ✓ Solubilizers and pH modifiers
- ✓ Lubricants and flow aid
- ✓ Supplementary coatings to extend lag time further reduce drug release etc.
- ✓ Density modifiers (if required)

A) Matrix formers:

Hydrophobic materials that are solid at room temperature and do not melt at body temperature are used as matrix formers. These include hydrogenated vegetable oils, cotton seed oil, soya oil, microcrystalline wax and carnauba wax. In general such waxes form 20- 40% of the formulation.

B) Channelling agents:

These are chosen to be soluble in gastrointestinal tract and to leach from the formulation, so leaving tortuous capillaries through which the dissolved drug may diffuse in order to be released. The drug itself can be a channelling agent but a water soluble pharmaceutical acceptable solid material is more likely to be used. Typical examples include sodium chloride, sugars and polyols. This choice will depend on the drug and desired released characteristics. These agents can be 20-30% of the formulation.

C) Solubilizers and pH modifiers:

It is often necessary to enhance the dissolution of drug. This may be achieved by the inclusion of solubilising agents such as PEGs, polyols and surfactants. If the drug is ionisable then the inclusion of buffers or counter ions may be appropriate. On occasions the dissolution enhancer may also be the channelling agent.

D) Anti-adherent or glidant:

Heat is generated during compaction of the matrix can cause melting of the wax matrix forming compounds and sticking to the punches. Something is needed to cope with the sticking; suitable anti adherents include talc and colloidal silicon dioxide. These materials also can act as glidants and improve the flow of formulations on the tablet machine. The typical amounts used will depend on the anti adherent used, for example 0.5-1% for colloidal silicon dioxide and 4-6% for talc. Magnesium stearate, if added, can also act as an anti-adherent.[20]

1.6. Basic principle of drug release:

In solution, drug diffusion will occur from a region of high concentration to the region of low concentration. This concentration gradient is the driving force for the drug diffusion, out of a system. Water diffuses into the system in analogous manner. There is an abundance of water in the surrounding medium and system should allow water penetration. The inside of the system has low water content initially than the surrounding medium.

1.7. Effect of release limiting factor on drug release:

The mechanistic analysis of controlled release of drug reveals that partition coefficient; diffusivity; diffusional path thickness and other system parameters play various rate determining roles in the controlled release of drugs from either capsules, matrix or sandwich type drug delivery systems.

A) Polymer hydration:

It is important to study polymer hydration/swelling process for the maximum number of polymers and polymeric combinations. The more important step in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

B) Drug solubility:

Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

C) Solution solubility:

In view of in vivo (biological) sink condition maintained actively by hem perfusion, it is logical that all the in vitro drug release studies should also be conducted under perfect sink condition. In this way a better simulation and correlation of in vitro drug release profile with in vivo drug administration can be achieved. It is necessary to maintain a sink condition so that the release of drug is controlled solely by the delivery system and is not affected or complicated by solubility factor.

D) Polymer diffusivity:

The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion E_d has been acquired by the diffusant is dependent on length of polymer chain segment, cross linking and crystallinity of polymer.

The release of drug may be attributed to the three factors viz,

- i. Polymer particle size
- ii. Polymer viscosity
- iii. Polymer concentration.

i. Polymer particle size:

Malamataris stated that when the content of hydroxyl propyl methylcellulose is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable more important when the content of polymer is low. He also justified these results by considering that in certain areas of matrix containing low levels of hydroxyl propyl methylcellulose led to the burst release.

ii. Polymer viscosity:

With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution.

iii. Polymer concentration:

An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.[21]

E) Thickness of polymer diffusional path:

The controlled release of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion:

$$JD = D \, dc/dx$$

Where,

JD is flux of diffusion across a plane surface of unit area

D is diffusibility of drug molecule; dc/dx is concentration gradient of drug molecule across a diffusion path with thickness dx .

F) Thickness of hydrodynamic diffusion layer:

It was observed that the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. The magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer δd .

G) Drug loading dose:

The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water soluble drugs, with increasing initial drug loading the relative release rate first decreases and then increases, whereas, absolute release rate monotonically increases. In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute drug transfer rate. But in case of poorly water soluble drugs another phenomenon also has to be taken in to account. When the amount of drug present at certain position within the matrix,

exceeds the amount of drug soluble under given conditions, the excess of drug has to be considered as non-dissolved and thus not available for diffusion. The solid drug remains within tablet, on increasing the initial drug loading of poorly water soluble drugs, the excess of drug remaining within matrix increases.

H) Surface area and volume:

The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretically and experimentally. Both the in vitro and in vivo rate of the drug release, are observed to be dependent upon surface area of dosage form. Siepmann et al. found that release from small tablet is faster than large cylindrical tablets.

I) Diluent's effect:

The effect of diluent or filler depends upon the nature of diluent. Water soluble diluents like lactose cause marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of matrix. The reason behind this is that water soluble filler in matrices stimulate the water penetration into inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of drug, leads to increased drug release rate.

J) Additives:

The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydrosoluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less important if the excipients are insoluble like tricalcium phosphate.

1.8 Biological factors influencing drug release from matrix tablet:

- ✓ Biological half-life.
- ✓ Absorption.
- ✓ Metabolism
- ✓ Distribution
- ✓ Protein binding
- ✓ Margin of safety

A) Biological half-life:

The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life ($t_{1/2}$). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with half-life shorter than 2 hours such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples.

B) Absorption:

Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of $0.17\text{--}0.23\text{h}^{-1}$ to give 80-95% over this time period. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, SR preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds tries to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-administration results in sustaining effect. One such attempt is to formulate low density pellet or capsule. Another approach is that of bio adhesive materials.[22]

C) Metabolism:

Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Hence criteria for the drug to be used for formulating Sustained-Release dosage form is,

- ✓ Drug should have low half-life (<5 hrs.)
- ✓ Drug should be freely soluble in water.
- ✓ Drug should have larger therapeutic window.
- ✓ Drug should be absorbed throughout the GIT

Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

D) Distribution:

Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral SR drug delivery system e.g. Chloroquine.

E) Protein Binding:

The Pharmacological response of drug depends on unbound drug concentration rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Protein binding of drug play a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes SR drug delivery system is not required for this type of drug.

F) Margin of safety:

As we know larger the value of therapeutic index safer is the drug. Drugs with less therapeutic index usually poor candidate for formulation of oral SR drug delivery system due to technological limitation of control over release rates.

1.9. Physicochemical factors influencing drug release from matrix tablet:

A) Dose size:

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form. Compounds that require large

dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

B) Ionization, pKa and aqueous solubility:

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKa of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of the release process must be defined. Compounds with very low solubility ($<0.01\text{mg/ml}$) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility of the compound will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.

C) Partition Coefficient:

When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

D) Stability:

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this

is the preferred composition of delivery for problem cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation. Propentheline and probanthine are representative example of such drug[23-25].

2. LITERATURE REVIEW

Kathane Sudhir et al.,(2024) Formulation and Evaluation of Indomethacin Sustained Release Tablet By Using Natural Polymers. Arthritis is most prevalent disorder and Indomethacin is choice of drug for arthritis. Oral route is most preferred route of drug administration and tablets are the more convenient dosage form. In present research natural polymers guar gum and xanthan gum were used to make sustained release tablet of Indomethacin. Indomethacin release from the tablets was studied in phosphate buffer pH 7.2. The drug release pattern of six different formulations in which xanthan gum and guar gum were used as a retarding material in different proportions was shown in table no. 6. The formulation F1 releases (75.20%) upto 12 hrs whereas the formulation F2 releases the drug (98.81%) in same time. The formulations F3, F4, F5 and F6 release 98.32%, 99.29%, 98.79% and 82.40% respectively. The dissolution pattern of both gums was similar i.e. with drug to polymer ratio (1:1). In present work F1 shows best sustained release upto 12 hrs in which Drug to Polymer ratio was 1:1:0 (Drug : Xanthan gum : Guar gum). In formulation F2 drug release was not sustained and complete release occurs in 12 hrs where the Drug to Polymer ratio was 1:1.67:0 (Drug: Xanthan gum : Guar gum). It was found that on the concentration of xanthan gum decreases the release rate of the drug also decreases. For sustain release there is not much role of Guar Gum reported. Indomethacin drug has been selected which has half-life 4.5 hrs. Hence the present work, an attempt has been made to provide sustained release drug delivery using polymers with Indomethacin as the model drug. Xanthan gum was best able to retard Indomethacin release mechanism even in the presence of a polymer. Polymer can be used to formulate successful sustained release Indomethacin matrix tablets that have desirable characteristics.²⁶

Avinash V. Dhobale et al., (2023) Formulation, Evaluation and Comparison of Sustained Release Matrix Tablet of Losartan Potassium Using Natural Polymers. The aim of this research work was to Evaluation of Some Natural Polymer used as Sustained Release Matrix Tablet, any pharmaceutical formulation contains two ingredients one is the active ingredient and other is an excipients. An excipients help in the manufacturing of dosage form and it also improves physicochemical parameters of the dosage form. Polymers play an important role as excipients in any dosage form. They influence drug release and should be compatible, nontoxic, stable, economic etc. and develop a fixed Dose Combination product in a two different strength using same blend for both the strengths of tablet as a SR tablet formulation. In the tablet, Extended Release layer consist of Antihypertensive Drug belonging to class β -selective adrenergic blocking agent without partial agonist or membrane stabilizing properties. Extended release preparation provides sustained release and reduces the chances of tough related side effects. In selected cases of extended release preparation of this drug used in treatment of hypertension and congestive heart failure. The clinical studies have shown beneficial role of this drug as an extended release preparation. The main objective of the present study was to develop, formulate and evaluate a matrix tablet by using hydrophilic natural retardant polymers which would retard drug release in upper GI tract and should start releasing the drug when it reaches the alkaline environment of small intestine. Okara and Tramarind Gum Mucilage were investigated as the model hydrophilic retardant polymers. Wet granulation method was and nine batches of tablets were prepared. The prepared tablets were subjected for pharmacopoeial and non-pharmacopoeial evaluation parameters including loose and tapped bulk density, compressibility index, hausner ratio, angle of repose, friability, hardness, thickness, weight variation, % drug content and in-vitro drug release studies. It can be concluded that the combination of hydrophilic polymers that are retardant in nature are better suited for sustained and controlled drug delivery system than the hydrophilic polymer alone.²⁷

Dr. Y. Krishna Reddy et al.,(2020) Formulation and Evaluation of Sustained release matrix tablets of Atomoxetine HCl by using Natural and Synthetic Polymers. The primary benefit of a sustained release dosage form compared to a conventional dosage form, is the uniform drug plasma concentration and therefore uniform therapeutic effect. Matrix system are favored because of their simplicity, patient compliance etc, than traditional drug delivery which have many drawbacks like repeated administration, fluctuation in blood concentration level etc. The objective of the present study was to develop, evaluate and compare once-daily sustained release matrix tablets of Atomoxetine HCL using Xanthan gum, Karaya gum, Ethyl cellulose

and HPMC K 100 polymers. The matrix tablet formulations were prepared by using different drug: polymer ratios (1:1, 1:2, and 1:3). The prepared matrix tablets were evaluated for various parameters like hardness, thickness, weight variation, friability, percent drug content and *in vitro* drug release studies as per IP guidelines. Out of 12 formulations, the formulation F5 is selected as best formulation which shows 98.56 % drug release in 12 hrs.²⁸

M. Kaleemullah et al., (2017) Development and evaluation of Ketoprofen sustained release matrix tablet using Hibiscus rosa-sinensis leaves mucilage. Currently, the use of natural gums and mucilage is of increasing importance in pharmaceutical formulations as valuable drug excipient. Natural plant-based materials are economic, free of side effects, biocompatible and biodegradable. Therefore, Ketoprofen matrix tablets were formulated by employing Hibiscus rosa-sinensis leaves mucilage as natural polymer and HPMC (K100M) as a synthetic polymer to sustain the drug release from matrix system. Direct compression method was used to develop sustained released matrix tablets. The formulated matrix tablets were evaluated in terms of physical appearance, weight variation, thickness, diameter, hardness, friability and *in vitro* drug release. The difference between the natural and synthetic polymers was investigated concurrently. Matrix tablets developed from each formulation passed all standard physical evaluation tests. The dissolution studies of formulated tablets revealed sustained drug release up to 24 h compared to the reference drug Apo Keto® SR tablets. The dissolution data later were fitted into kinetic models such as zero order equation, first order equation, Higuchi equation, Hixson Crowell equation and Korsmeyer-Peppas equation to study the release of drugs from each formulation. The best formulations were selected based on the similarity factor (f_2) value of 50% and more. Through the research, it is found that by increasing the polymers concentration, the rate of drug release decreased for both natural and synthetic polymers. The best formulation was found to be F3 which contained 40% *Hibiscus rosa-sinensis* mucilage polymer and showed comparable dissolution profile to the reference drug with f_2 value of 78.03%. The release kinetics of this formulation has shown to follow non-Fickian type which involved both diffusion and erosion mechanism. Additionally, the statistical results indicated that there was no significant difference ($p > 0.05$) between the F3 and reference drug in terms of MDT and T50% with p-values of 1.00 and 0.995 respectively.²⁹

B. Ramu et al., (2016) Formulation and Evaluation of Sustained Release Verapamil Hydrochloride Using Natural Polymers. The aim of the present study was to develop sustained

release formulation of Verapamil Hydrochloride to maintain constant therapeutic levels of the drug for over 12 hrs. Various grades of HPMC polymers, Guar gum, and Xanthum gum were employed as polymers. Verapamil Hydrochloride dose was fixed as 120 mg. Total weight of the tablet was considered as 400 mg. Polymers were used in the concentration of 60, 120 and 180 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e., 96.10 % in 12 hours containing Guar gum polymer in the concentration of 180mg. It followed zero order release kinetics. For the optimized formulation alcohol effect has been studied by using various concentrations of alcohol in dissolution medium. As the concentration of alcohol increased the sustained action of polymer was decreased. Hence it was concluded that alcohol has significant effect on drug release pattern.³⁰

Basavaraja et al., (2015) Formulation and Evaluation of Sustained Release Matrix Tablets of Flurbiprofen by Using Natural and Synthetic Polymers. The objective of the present work is to design of novel sustained release matrix tablets of Flurbiprofen influence of natural, synthetic polymers, on the release rate and in vitro evaluation. Flurbiprofen is NSAID drug used extensively in the treatment of rheumatoid arthritis, degenerative joint disease, osteoarthritis, Ankylosing Spondylitis, acute musculoskeletal disorders, low back pain and allied conditions. The natural polymers are Xanthan gum, Karaya gum, and synthetic polymers like HPMC K-100, Ethyl cellulose were utilized in the formulation of matrix tablets containing Flurbiprofen by wet granulation technique and evaluated for its in-vitro drug release. Natural polymer is hydrophilic in nature and rate controlling polymers. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. Formulation was optimized on the basis of acceptable tablet properties (hardness, friability, drug content and weight variations), in vitro drug release and stability studies. All the formulations showed compliance with Pharmacopeial standards. The in vitro release study of matrix tablets were carried out in pH 1.2 HCl for 2 hours and pH 7.4 phosphate buffer for the remaining 10 hours as dissolution medium. Among all the formulation, F12 shows 97.23% of drug which was better controlled release at the end of 12 hrs. It has been found that the optimized formulation F-12 containing 500 mg of ethyl cellulose better sustained effect for 12 hr, The results indicated that a decrease in release kinetics of the drug was observed by increasing the polymer concentration. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order and Zero order to evaluate the kinetics

and mechanism of the drug release. The stability studies were carried out according to ICH guideline which indicates that the selected formulations were stable.³¹

Muthadi Radhika Reddy et al., (2015) Formulation and Evaluation of Sustained Release Tablets of Esomeprazole Using Natural and Synthetic Polymers. The main objective of the present study is to prepare and evaluate in vitro sustained release tablets to improve 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 tablets were evaluated for their micromeritic properties and in vitro release as well as by Fourier transform infrared (FTIR). The data showed FTIR and DSC results indicate that the drug was compatible with the polymers used. Among all formulations F2 showed the most suitable sustained release properties with 99.65% of drug release at the end of 12 h. The results indicated that a decrease in release kinetics of the drug was observed by increasing the polymer concentration. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer- Peppas, First-order, and Zero order to evaluate the kinetics and mechanism of the drug release. From this studies it is concluded that the Tablets prepared with xanthan gum were revealed that increase in the concentration retards the drug release and can be used as a sustained release delivery system for Esmoprazole.³²

Y Ganesh Kumar et al., (2015) Formulation Development and Evaluation of Sustained Release Matrix Tablets of Vildagliptin - Synthetic and Natural Polymers. Aim: The present research work was to design and develop the sustained release matrix tablets of vildagliptin. It is having a short biological half-life (1.5 h) so it is considered as a suitable drug for the formulation of sustained release tablets to prolong its therapeutic action. Vildagliptin is an oral antihyperglycemic agent of the new dipeptidyl peptidase-4 inhibitor class of drug. Materials and Methods: Matrix tablets were prepared by wet granulation technique, using synthetic and natural polymers at different ratios. Granules were prepared and evaluated for bulk density, tapped density, Hausner's ratio, compressibility index. Statistical Analysis Used: The Fourier-transform infrared spectra of the vildagliptin and different polymers alone and in a combination show the compatibility of the drug with excipients. Results: The physicochemical properties of tablets were found within the limits. The prepared tablets were evaluated for weight variation, thickness, hardness, % friability, % drug contents, and in vitro release. In vitro dissolution studies (USP dissolution rate test apparatus II, 50 rpm, 37°C $\pm$ 0.5°C) was carried out for the first 2 h in 0.1 N HCl (1.2 pH) and followed 6.8 phosphate buffer for

10 h as a dissolution medium. Conclusion: The optimized formulation F-8 was shown maximum drug release $97.56 \pm 0.72\%$ in 12 h of dissolution. The release kinetic data of formulation F-8 shown zero order ($R^2 = 9902$).³³

Ahmad Khan et al., (2015) Formulation Development and In Vitro Characterization of Sustained Release Matrix Tablets of Verapamil HCl Using Synthetic and Natural Polymers. The pharmaceutical attributes of sustained release (SR) oral tablets containing verapamil hydrochloride prepared by using synthetic polymers (HPMC K4M and Na carboxymethylcellulose) and natural hydrophilic matrix formers (xanthan gum and Acacia) were observed in the present work. Direct compression method was used for the preparation of sustained release matrix tablet using the polymers in different ratios. Compressed tablets were evaluated for hardness, friability, weight variation and in vitro dissolution using USP dissolution apparatus-II. Dissolution profiles of test formulations were obtained in 900 mL distilled water for 12 h at 37 °C. The data was then kinetically evaluated with different mathematical models i.e., Zero Order, First Order, Higuchi, Hixson-Crowell, Baker & Lonsdale, Korsmeyer and Peppas, Weibull, Hoffenberg and Peppas Sahi. Different verapamil hydrochloride matrix tablet formulations have shown different dissolution behavior and it was concluded that the synthetic polymers HPMC K4M and Na carboxymethylcellulose in combination is a better choice for sustained release formulation development for verapamil hydrochloride. Furthermore, the results of similarity factor f_2 between the compressed formulations and Calan SR® have verified formulation F4 (having synthetic polymers) as optimized formulation due to greatest similarity.³⁴

3. AIM & OBJECTIVES

Aim:

The aim of this study is to formulate and evaluate sustained-release (SR) tablets of Esomeprazole using both natural and synthetic polymers to improve the therapeutic efficacy, reduce the frequency of dosing, and enhance patient compliance. The formulation aims to provide a controlled release of Esomeprazole over an extended period to maintain effective plasma drug concentrations for prolonged therapeutic action.

Objectives:

1. **Formulation Development:** To develop Esomeprazole sustained-release tablets using a combination of natural (e.g., HPMC K 15 ,Amla extract Ginger extract) and synthetic (polyvinyl alcohol) polymers.
2. **Characterization of Polymers:** To assess and compare the properties of the natural and synthetic polymers, including their swelling behaviour, viscosity, and release control capabilities.
3. **Evaluation of Physicochemical Properties:** To evaluate the formulation for key tablet characteristics such as weight uniformity, hardness, friability, thickness, and drug content.
4. **In-vitro Drug Release Studies:** To conduct in-vitro drug release studies using USP dissolution apparatus to determine the release profile of Esomeprazole from the sustained-release tablets.
5. **Optimization of Release Kinetics:** To evaluate the release mechanisms of the formulated tablets and apply mathematical models (Zero-order, First-order, Higuchi, and Korsmeyer-Peppas) to analyze the release kinetics and ensure sustained drug release.

4. PLAN OF WORK

1. Literature survey
2. Selection and procurement of suitable drug candidate and excipients
3. Construction of standard graph
4. Pre-formulation studies
5. Preparation of powders
6. Characterization of Powdered blend
 - ✓ Angle of repose
 - ✓ Bulk density
 - ✓ Tapped density
 - ✓ Carr's index
 - ✓ Hausner's ratio
7. Formulation of Sustained release matrix tablet of Esomeprazole
8. Evaluation of Sustained release matrix tablet of Esomeprazole

- ✓ Thickness
 - ✓ Hardness
 - ✓ Friability
 - ✓ Uniformity of weight
 - ✓ Drug content
 - ✓ *In vitro* dissolution
9. Drug polymer interaction study
- ✓ Fourier transform Infra-Red (FTIR) spectroscopy

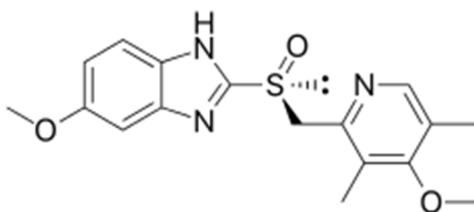
5. DRUG PROFILE:

Drug : Esomeprazole

Synonym : (-)-omeprazole

Drug category : Proton Pump Inhibitors

Structure :



Chemical name/ Nomenclature / IUPAC Name : 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethylpyridin-2-yl)methanesulfinyl]-1H-1,3-benzodiazole

Molecular Formula : C₁₇H₁₉N₃O₃S

Molecular Weight : 345.416 gm/mole.

Official Pharmacopoeia : EP,USP

PHYSICOCHEMICAL PROPERTIES:

Description(Physical State): Solid

Solubility: water solubility Very slightly soluble in water

Dosage: Kit, Capsule, Injection powder

Melting point: 155 °C

pKa(strongest acidic):9.68

Log P:2.43

PHARMACOKINETIC PROPERTIES:

Bioavailability : 50-90 %

Half-life :1-1.5 hrs

Absorption : After oral administration, peak plasma levels (C_{max}) occur at approximately 1.5 hours (T_{max}).

Volume of Distribution : 16 L

Protein binding : 97 %

Metabolism : Liver

Excretion : 80% Kidney, 20% Faecal

Adverse effects/Side effects : Common side effects include headache, diarrhea, nausea, flatulence, decreased appetite, constipation, dry mouth, and abdominal pain. More severe side effects are severe allergic reactions, chest pain, dark urine, fast heartbeat, fever, paresthesia, persistent sore throat, severe stomach pain, unusual bruising or bleeding, unusual tiredness, and yellowing of the eyes or skin.

PHARMACODYNAMICS: Esomeprazole is a compound that inhibits gastric acid secretion and is indicated in the treatment of gastroesophageal reflux disease (GERD), the healing of erosive esophagitis, and H. pylori eradication to reduce the risk of duodenal ulcer recurrence. Esomeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H₂ histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H⁺/K⁺ ATPase at the secretory surface of the gastric parietal cell. By doing so, it inhibits acid secretion into the gastric lumen. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

Mechanism of action:

Esomeprazole exerts its stomach acid-suppressing effects by preventing the final step in gastric acid production by covalently binding to sulfhydryl groups of cysteines found on the (H⁺, K⁺)-ATPase enzyme at the secretory surface of gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. As the binding of esomeprazole to the (H⁺, K⁺)-ATPase enzyme is irreversible and new enzyme needs to be expressed in order to resume acid secretion, esomeprazole's duration of antisecretory effect that persists longer than 24 hours

Therapeutic efficacy/ Indications:

Esomeprazole is indicated for the treatment of acid-reflux disorders including healing and maintenance of erosive esophagitis, and symptomatic gastroesophageal reflux disease (GERD), peptic ulcer disease, H. pylori eradication, prevention of gastrointestinal bleeds with NSAID use, and for the long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome.

Contraindications:

Conditions:

- Clostridium difficile infection
- Inadequate vitamin b12
- Low amount of magnesium in the blood
- Severe liver disease

- Interstitial nephritis
- Subacute cutaneous lupus erythematosus
- Systemic lupus erythematosus
- Osteoporosis
- Broken bone
- Cyp2c19 poor metabolizer

Allergies:

- Proton pump inhibitors

INTERACTIONS:**Drug interactions:**

- The serum concentration of Acetylsalicylic acid can be increased when it is combined with Esomeprazole.
- Acyclovir may decrease the excretion rate of Esomeprazole which could result in a higher serum level.
- The serum concentration of Betamethasone can be increased when it is combined with Esomeprazole.
- The serum concentration of Carbamazepine can be increased when it is combined with Esomeprazole.
- Cefpodoxime may decrease the excretion rate of Esomeprazole which could result in a higher serum level.

Food interactions:

- Take without regard to meals.

DRUG FORMULATION:

S.No	Drug name	Label Claim	Brand name	Company
1	Esomeprazole	40 mg	Actipraz	Invision Medie Science Pvt Ltd

6. EXCIPIENTS PROFILE

HYDROXY PROPYL METHYL CELLULOSE

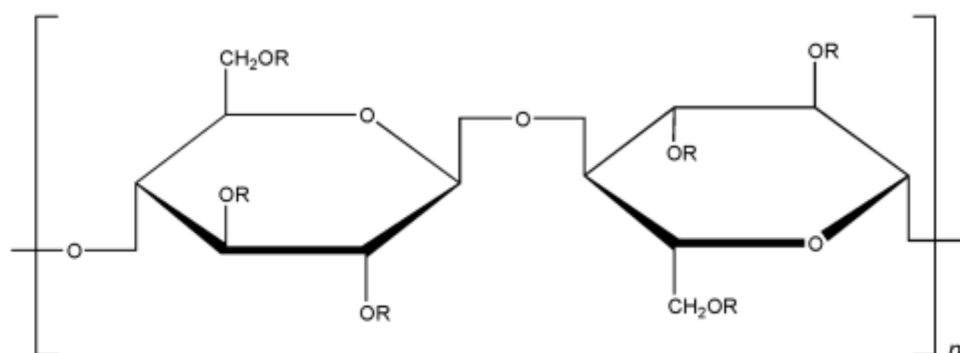
General Descriptions

Nonpropriety Names : BP: Hypromellose, USP : Hypromellose

Synonyms : Methocel, HPMC2208, Benecal MHPC, Pharmacoat.

Description : It is odorless & tasteless, white or creamy white colored Fibrous or granular powder.

Structural Formula :



Structure of HPMC

Functional categories : Tablet binder, Coating agent, Film former stabilizing agent, Suspending agent, Viscosity increasing agent.

Solubility : It is soluble in cold water but insoluble in Chloroform, ethanol (95%) & ether but Soluble in mixture of ethanol & dichloromethane mixture of methanol & dichloromethane, mixture of alcohol.

Viscosity (dynamic) : A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous Hypromellose

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

Melting point : Brown at 190- 200⁰C; chars at 225-230⁰C.

Specific gravity	: 1.26
Loss on drying	: < 5.0 %
Density (bulk)	: 0.341 gm / cm³
Density (tapped)	: 0.557 gm / cm³

Stability and storage Conditions: Hypromellose powder is a stable material although it is hygroscopic after drying. Solutions are stable at pH 3. Upon heating and cooling hypromellose undergoes a reversible gel transformation. Viscosity of solutions is reduced by increasing the temperature. Depending upon the grade and concentration of material, the gel point is 50-90°C. It is stable material although it is hygroscopic after drying. It should be stored in a well -closed container in a cool dry place.

Incompatibilities : Incompatible with some oxidizing Agents.

Applications : It is widely used oral & topical pharmaceutical formulations primarily used in film-coating, binder in tablets in concentrations of 2 – 5 %.

AMLA EXTRACT

SCIENTIFIC CLASSIFICATION

BOTONICAL NAME : Emblica officinalis and
Phyllanthus emblica

Kingdom :

Family : Euphorbiaceae

Common Name : **English** : Emblic Myrobalan,

Hindi: Amla

Bengali : Amla, Dhatri

Gujrati : Ambala

Marathi : Anvala

Telugu : Usirika

Urdu : Amla, Amlaj

Chemical Constituents: Amla is the richest known source of vitamin 'C'. The fruit contains Ascorbic acid and tannins. It contains Gallic acid, tannic acid, albumin, cellulose and other minerals. It contains moisture 81.2 %, proteins 0.5%, fats 0.1 %, carbohydrates 14.1 %, calcium 0.05 %, phosphorus 0.02 %, iron 1.2 mg and nicotinic acid 0.2 mg per 100 gram. A seed contains the stable oil which is 16 %. Main active constituents of amla, emblicanin A&B, Punigluconin, Pedunculagin, 2-keto- gluconolactone (Vitamin-C equivalents). Ellagic acid, Hexahydroxy-diphenic acid and conjugates.

GINGER EXTRACT

BOTANICAL NAME : *Zingiber officinale*

Kingdom : Plantae

Family : Zingiberaceae

Genus : Zingiber

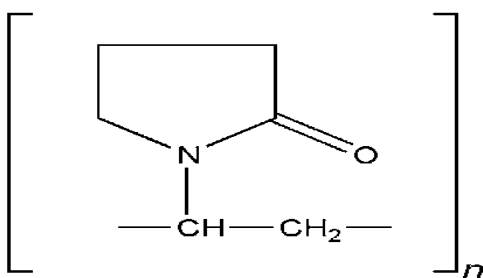
Species : Z. officinale

Chemical Constituents: Numerous active ingredients are present in ginger including terpenes and oleoresin which called ginger oil. Ginger also constitutes volatile oils approximately 1% to 3% and non-volatile pungent components oleoresin [7]. The major identified components from terpene are sesquiterpene hydrocarbons and phenolic compounds which are gingerol and shogaol [8] and lipophilic rhizome extracts, yielded potentially active gingerols, which can be converted to shogaols, zingerone, and paradol.

POLY VINYL PYRROLIDINE K30 :

Synonyms : E1201, Kollidon, Plasdone, polyvidone, povidonum, Poviphar, PVP.

Structural formula :



Chemical name	:	1-Ethenyl-2-pyrrolidinone homopolymer
Empirical formula	:	(C ₆ H ₉ NO) _n
Molecular weight	:	2500–30,00,000 daltons
Functional category	:	Disintegrant, dissolution enhancer, suspending agent, tablet binder.
Description	:	Povidone occurs as a fine, white to creamy- white colored, odorless or almost odorless, hygroscopic powder.
Physicochemical properties:		
a. Solubility	:	Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil.
b. Melting point	:	1508°C.
Stability and Storage	:	Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in cool, dry place.
Safety	:	Povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.
Incompatibilities	:	The efficacy of some preservatives, e.g. thiomersal may be adversely affected by the

formation of complexes with povidone.

Applications : Povidone is used in a variety of pharmaceutical formulations. It is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is used as a solubilizer in oral and parenteral formulations.

MAGNESIUM STEARATE

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

Molecular weight: 591.34.

Structural formula: $[\text{CH}_3(\text{CH}_2)_{16}\text{COO}]_2\text{Mg}$

Functional category: Tablet and capsule lubricant

Applications in pharmaceutical formulation technology : It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25 % and 5.0 % w/w.

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

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

Flowability: Poorly flowing, cohesive powder.

Melting range: 117-150°C (commercial samples) 126-130°C (high purity magnesium stearate).

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

Specific surface area: 1.6-14.8 m² /g

Density (bulk): 0.159 g/cm³

Density (tapped): 0.286 g/cm³

Density (true): 1.092 g/cm³

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

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

Safety : Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may result in some laxative effect or mucosal irritation.

TALC:

Synonyms: Altalco; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Functional category: Anticaking agent; Tablet and Capsule diluent; Tablet and Capsule lubricant.

Applications in pharmaceutical formulations: Used in oral solid dosage formulations as a lubricant and glidant (1-10%), Dissolution retardant in the development of controlled release products. Used as dusting powder (90.0-99.0), Lubricant properties in cosmetics and food properties, Talc is widely used in oral solid dosage formulations as lubricant and diluents.

Description: Talc is a very fine, white to greyish-white coloured, odorless, impalpable crystalline powder. It adheres to the skin readily. Insoluble in water, dilute acids, alkalis and organic solvents.

Moisture content: Talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%.

Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.

Specific gravity: 2.7–2.8

Specific surface area: 2.41–2.42 m²/g

Stability and storage conditions: Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hr. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Talc is incompatible with quaternary ammonium compounds.

Method of manufacture: Talc is a naturally occurring hydropolysilicate mineral found in many parts of the world including: Australia; China; Italy and the US. Naturally occurring talc is mined and pulverized before being subjected to flotation processes to remove various impurities such as: asbestos (tremolite), carbon, dolomite, iron oxide and various other magnesium and carbonate minerals. Following this process the talc is finely powdered, treated with dilute Hydrochloric acid, washed with water and then dried. It is the processing variables of agglomerated talc that strongly influence its physical characteristics.

Safety: Talc is mainly used in tablet and capsule formulations. Following oral ingestion talc is not absorbed systemically and may thus be regarded as an essentially nontoxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs. Contamination of wounds or body cavities with talc may also cause granulomas, hence it should not be used to dust surgical gloves. Inhalation of talc causes irritation and may cause severe respiratory distress in infants. Although talc has been extensively investigated for its carcinogenic potential with some suggestion that there is an increased risk of ovarian cancer in women using talc, the evidence is inconclusive. However, talc contaminated with asbestos has been concluded to be carcinogenic in humans and asbestos-free grades should therefore be used in pharmaceutical products. Also, long-term toxic effects of talc contaminated with large quantities of Hexachlorophene caused serious irreversible neurotoxicity in infants accidentally exposed.

Handling precautions: Observe normal precautions appropriate to the circumstances and quantity of material. Talc is irritant if handled and prolonged excessive exposure may cause pneumoconiosis. Eye protection, gloves and a respirator are recommended.

MICROCRYSTALLINE CELLULOSE

Synonyms : Avicel PH; Cellex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres;

Chemical Name : Cellulose

Empirical Formula : $(C_6H_{10}O_5)_n$ where $n \approx 220$.

Molecular Weight: $\approx 36\,000$

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

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

Table 6.1: Uses of Microcrystalline Cellulose

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

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

Angle of repose (θ): 34.4°

Density (bulk): 0.337 g/cm³ for Avicel P^H 200,
0.32 g/cm³ for Avicel P^H 101

Density (tapped): 0.478 g/cm³ for Avicel 200
0.45 g/cm³ for Avicel P^H-101

Density (true): 1.512–1.668 g/cm³

Flowability: 1.41 g/s

Melting point: 260–270°C.

Moisture content: Typically less than 5% w/w. microcrystalline cellulose is hygroscopic.

Particle size distribution: Typical mean particle size is 20–200 µm.

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

Specific surface area : 1.21–1.30 m²/g for Avicel P^H-101
0.78–1.18 m²/g for Avicel P^H-200.

Stability: Microcrystalline cellulose is a stable though hygroscopic material.

Storage Conditions: The bulk material should be stored in a well-closed container in a cool, dry place.

Safety: It is widely used in oral pharmaceutical formulations is generally regarded as a relatively nontoxic and nonirritant material. Deliberate abuse of formulations containing

cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.

List of Materials Used

Name of the material	Source
Esomeprazole	Procured From Neon Laboratories Ltd, Provided by SURA LABS, Dilsukhnagar, Hyderabad.
HPMC K 15	Merck Specialities Pvt Ltd, Mumbai, India
Amla extract	Merck Specialities Pvt Ltd, Mumbai, India
Ginger extract	Merck Specialities Pvt Ltd, Mumbai, India
PVP K30	Merck Specialities Pvt Ltd, Mumbai, India
Mg Stearate	Merck Specialities Pvt Ltd, Mumbai, India
Talc	Merck Specialities Pvt Ltd, Mumbai, India
MCC	Merck Specialities Pvt Ltd, Mumbai, India

List of Equipments used

Name of the Equipment	Manufacturer
Weighing Balance	Sartorius
Tablet Compression Machine (Multistation)	Lab Press Limited, India.
Hardness tester	Monsanto, Mumbai, India.
Vernier callipers	Mitutoyo, Japan.
Roche Friabilator	Labindia, Mumbai, India
Dissolution Apparatus	Labindia, Mumbai, India
UV-Visible Spectrophotometer	Labindia, Mumbai, India
pH meter	Labindia, Mumbai, India
FT-IR Spectrophotometer	Bruker, Germany

7. METHODOLOGY**Analytical method development:****Determination of Wavelength:**

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution, 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From the secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with

media (working solution - 10µg/ml). The working solution was taken to determine the wavelength.

Determination of Calibration Curve:

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution, 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 7.1 and 7.2) and those concentrations absorbance were found out at required wavelength.

Pre formulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

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

Tan θ = Angle of repose

h = Height of the cone ,

r = Radius of the cone base

Table 7.1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm³. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, V_o , was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density

M = Weight of sample

V = Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density

Tap = Tapped Density

Table 7.2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of Tablets:

All the formulations were prepared by direct compression method. The compositions of different formulations are given in Table 7.3. The tablets were prepared as per the procedure given below and aim is to prolong the release of Esomeprazole. Total weight of the tablet was considered as 200mg.

Procedure:

- 1) Esomeprazole and all other ingredients were individually passed through sieve no ≠ 60.
- 2) All the ingredients were mixed thoroughly by triturating up to 15 min.
- 3) The powder mixture was lubricated with talc.
- 4) The tablets were prepared by using direct compression method.

Table 7.3: Formulation composition for tablets

INGREDIENTS	FORMULATION CODES								
	E1	E2	E3	E4	E5	E6	E7	E8	E9
Esomeprazole	40	40	40	40	40	40	40	40	40
HPMC K 15	20	40	60	-	-	-	-	-	-
Amla extract	-	-	-	20	40	60	-	-	-
Ginger extract	-	-	-	-	-	-	20	40	60
PVP K30	10	10	10	10	10	10	10	10	10
Mg Stearate	6	6	6	6	6	6	6	6	6
Talc	5	5	5	5	5	5	5	5	5
MCC	119	99	79	119	99	79	119	99	79
Total weight	200	200	200	200	200	200	200	200	200

All the quantities were in mg

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = (\text{Individual weight} - \text{Average weight} / \text{Average weight}) \times 100$$

Table 7.4: Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
≤ 80 mg	≤ 130 mg	$\pm 10\%$
≥ 80 mg to ≤ 250 mg	≥ 130 mg to ≤ 324 mg	$\pm 7.5\%$
≥ 250 mg	≥ 324 mg	$\pm 5\%$

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = [(W1 - W2) / W] \times 100$$

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content:

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV–Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro* drug release studies*Dissolution parameters:**

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCl, p H 6.8 Phosphate buffer
RPM	--	50
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	--	37°C ± 0.5°C

Procedure:

900ml of 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl were removed and pH 6.8 phosphate buffer was added process was continued up to 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at required wavelength using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics:

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

$$F = K_0 t$$

Where, ‘F’ is the drug release at time ‘t’, and ‘K₀’ is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$\text{Log } (100-F) = kt$$

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

$$F = k t^{1/2}$$

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:

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.

$$M_t / M_{\infty} = K t^n$$

Where, M_t / M_{∞} is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, $n = 0.5$; for zero-order release (case I transport), $n=1$; and for supercase II transport, $n > 1$. In this model, a plot of $\log (M_t / M_{\infty})$ versus $\log (time)$ is linear.

Hixson-Crowell release model:

$$(100-Q_t)^{1/3} = 100^{1/3} - K_{HC} \cdot t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 400 cm^{-1} .

8. RESULTS & DISCUSSION

The present study was aimed to develop sustained-release tablets of Esomeprazole using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Graphs of Esomeprazole were taken in 0.1N HCL and in pH 6.8 phosphate buffer at 305 nm and 310 nm respectively.

Table 8.1: Observations for the graph of Esomeprazole in 0.1N HCL

Concentration ($\mu\text{g/ml}$)	Absorbance
0	0
5	0.111
10	0.214
15	0.318
20	0.425
25	0.527

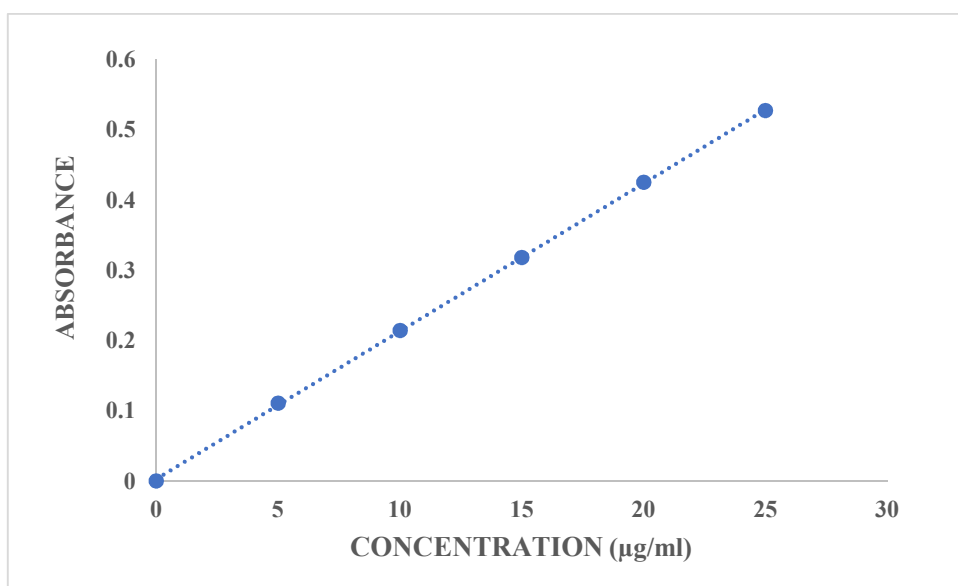
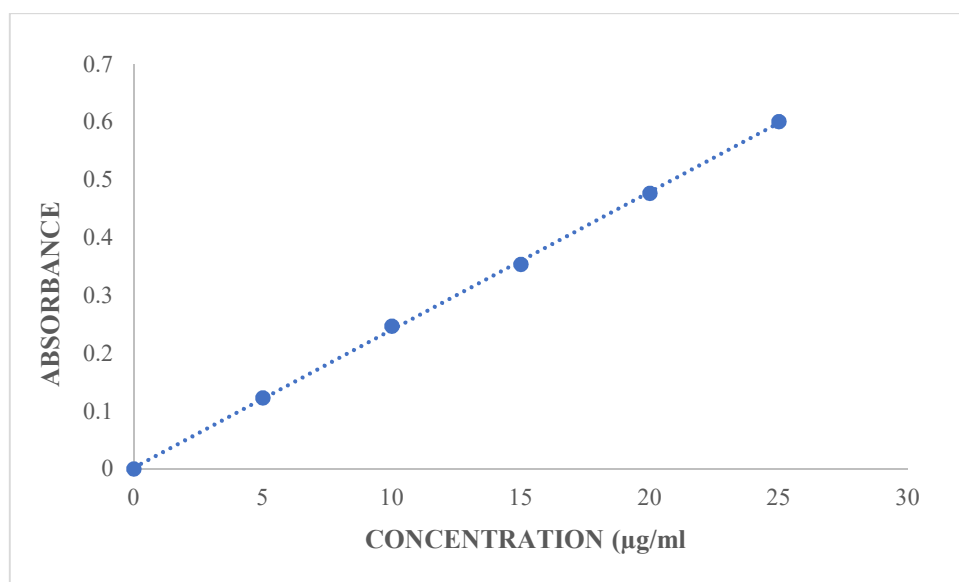


Fig 8.1: Standard curve of Esomeprazole

Table 8.2: Standard graph values of Esomeprazole at 310 nm in pH 6.8 phosphate buffer

Concentration ($\mu\text{g/ml}$)	Absorbance
0	0
5	0.123
10	0.247
15	0.354
20	0.477
25	0.601

**Fig 8.2: Standard curve of Esomeprazole**

Pre-formulation parameters of powder blend**Table 8.3: Pre-formulation parameters of Core blend**

Formulation code	Angle of repose (Θ)	Bulk density (gm/cm³)	Tapped density(gm/cm³)	Carr's index (%)	Hausner's ratio
E1	26.45±0.65	0.54±0.02	0.65±0.04	16.92±0.04	1.2±0.07
E2	25.12±0.51	0.48±0.09	0.57±0.05	15.78±0.05	1.18±0.06
E3	27.08±0.47	0.58±0.01	0.69±0.05	15.94±0.01	1.18±0.04
E4	28.12±0.35	0.56±0.03	0.66±0.02	15.15±0.02	1.17±0.05
E5	25.24±0.52	0.53±0.02	0.65±0.05	18.46±0.09	1.22±0.07
E6	25.33±0.48	0.54±0.05	0.64±0.04	15.62±0.05	1.18±0.08
E7	27.7±0.42	0.52±0.09	0.64±0.02	18.75±0.09	1.23±0.06
E8	26.8±0.35	0.56±0.04	0.67±0.08 1	16.41±0.00	1.19±0.05
E9	25.01±0.21	0.49±0.05	0.57±0.06	14.03±0.01 1	1.16±0.02

All the values represent n=3

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range showing that the powder has good flow properties. The tapped density of all the formulations powders has good flow properties. The compressibility index of all the formulations was found to be below 16.19 which show that the powder has good flow properties. All the formulations has shown the hausner ratio below 1.19 indicating the powder has good flow properties.

Quality Control Parameters for tablets:

Tablet quality control tests such as weight variation, hardness, friability, thickness and drug release studies in different media were performed on the compression tablet.

Table 8.4: *In vitro* quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm²)	Friability (%loss)	Thickness (mm)	Drug content (%)
E1	198.35	2.57	0.68	1.87	98.12
E2	199.22	2.83	0.71	1.98	99.22
E3	201.12	2.66	0.57	1.75	97.08
E4	205.08	2.79	0.44	1.79	99.71
E5	199.67	2.49	0.61	1.81	99.05
E6	200.44	2.64	0.68	1.93	98.51
E7	204.83	2.71	0.51	1.88	97.67
E8	200.37	2.88	0.61	1.79	99.28
E9	195.18	2.54	0.77	1.92	98.73

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 195.18 to 205.08 mg, so the permissible limit is $\pm 7.5\%$ (>200 mg). The results of the test showed that, the tablet weights were within limit.

Hardness test:

The hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 2.49 to 2.88 kg/cm², which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-8.4. The result showed that thickness of the tablet is ranging from 1.75 to 1.98mm.

Friability:

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content:

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 97.08 – 99.71 %.

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In Vitro* Drug Release Studies**

Table 8.5: Dissolution Data of Esomeprazole Tablets

TIME	CUMULATIVE % OF DRUG RELEASE								
	E1	E2	E3	E4	E5	E6	E7	E8	E9
0	0	0	0	0	0	0	0	0	0
0.5	17.89	14.08	21.01	13.61	11.64	19.39	12.73	13.76	16.58
1	21.24	19.11	25.32	19.26	18.58	24.96	16.23	18.05	21.43
2	24.68	26.12	29.67	27.37	28.24	29.57	25.96	28.29	25.16
3	31.07	33.68	42.35	35.52	39.21	34.41	31.47	37.11	28.27
4	39.41	37.27	48.29	38.19	44.64	41.93	37.51	41.67	37.15
5	42.95	44.56	57.68	49.46	51.12	48.66	44.27	48.53	43.03
6	56.52	47.91	65.09	54.11	58.39	51.19	49.32	52.98	48.88
7	59.37	63.45	72.68	59.03	68.57	59.17	55.71	57.43	57.11
8	63.41	74.98	79.54	63.84	75.92	67.75	61.87	68.12	64.22
9	74.25	79.23	84.21	68.96	79.19	71.97	66.21	73.42	71.08
10	81.94	85.89	91.52	74.12	87.52	87.15	72.95	77.79	79.12
11	84.02	89.23	95.26	79.07	94.44	92.51	76.01	82.07	84.62
12	88.08	98.21	96.21	86.71	98.28	99.82	81.19	89.41	98.24

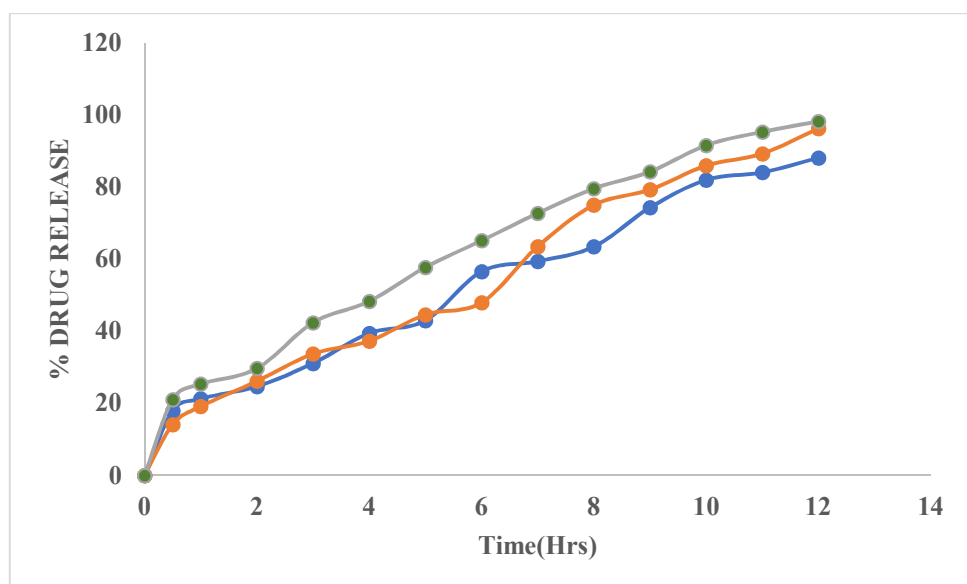


Fig 8.3: Dissolution profile of Esomeprazole (E1, E2, E3 formulations)

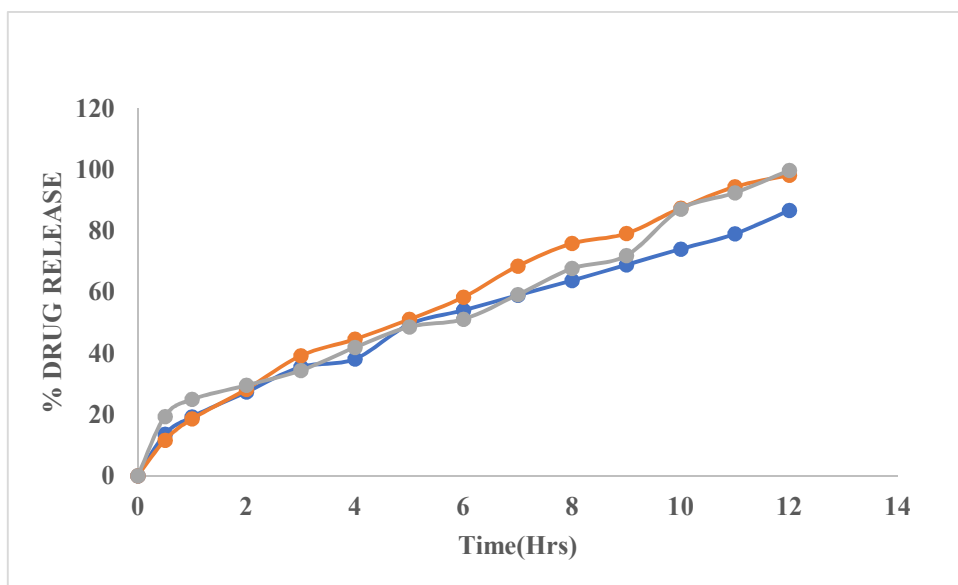


Fig 8.4: Dissolution profile of Esomeprazole (E4, E5, E6 formulations)

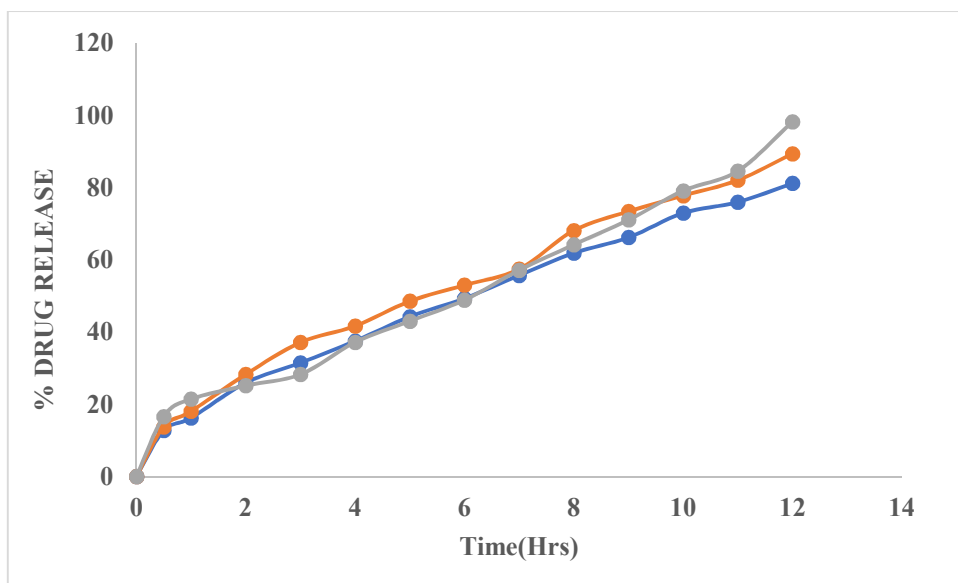


Fig 8.5: Dissolution profile of Esomeprazole (E7, E8, E9 formulations)

The formulations prepared with HPMC K 15 extract showed good retardation capacity of drug release (98.21 %) up to 12 hours in concentration 40 mg whereas high concentrations retard the drug release up to 12 hours.

The formulations prepared with Amla extract showed good retardation capacity of drug release (99.82 %) up to 12 hours in concentration 60 mg whereas high concentrations retard the drug release up to 12 hours.

The formulations prepared with Ginger extract showed good retardation capacity of drug release (98.24%) up to 12 hours in concentration 60 mg whereas high concentrations retard the drug release up to 12 hours.

Hence from the above dissolution data it was concluded that E6 formulation was considered as optimised formulation because good drug release (99.82 %) in 12 hours.

Table 8.6: Release Kinetics:

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEAS E	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3- Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
19.39	0.5	0.707	1.288	-0.301	1.906	38.780	0.0516	-0.712	80.61	4.642	4.320	0.322
24.96	1	1.000	1.397	0.000	1.875	24.960	0.0401	-0.603	75.04	4.642	4.218	0.424
29.57	2	1.414	1.471	0.301	1.848	14.785	0.0338	-0.529	70.43	4.642	4.130	0.512
34.41	3	1.732	1.537	0.477	1.817	11.470	0.0291	-0.463	65.59	4.642	4.033	0.609
41.93	4	2.000	1.623	0.602	1.764	10.483	0.0238	-0.377	58.07	4.642	3.872	0.769
48.66	5	2.236	1.687	0.699	1.710	9.732	0.0206	-0.313	51.34	4.642	3.717	0.925
51.19	6	2.449	1.709	0.778	1.689	8.532	0.0195	-0.291	48.81	4.642	3.655	0.987
59.17	7	2.646	1.772	0.845	1.611	8.453	0.0169	-0.228	40.83	4.642	3.443	1.198
67.75	8	2.828	1.831	0.903	1.509	8.469	0.0148	-0.169	32.25	4.642	3.183	1.459
71.97	9	3.000	1.857	0.954	1.448	7.997	0.0139	-0.143	28.03	4.642	3.038	1.604
87.15	10	3.162	1.940	1.000	1.109	8.715	0.0115	-0.060	12.85	4.642	2.342	2.299
92.51	11	3.317	1.966	1.041	0.874	8.410	0.0108	-0.034	7.49	4.642	1.957	2.685
99.82	12	3.464	1.999	1.079	-0.745	8.318	0.0100	-0.001	0.18	4.642	0.565	4.077

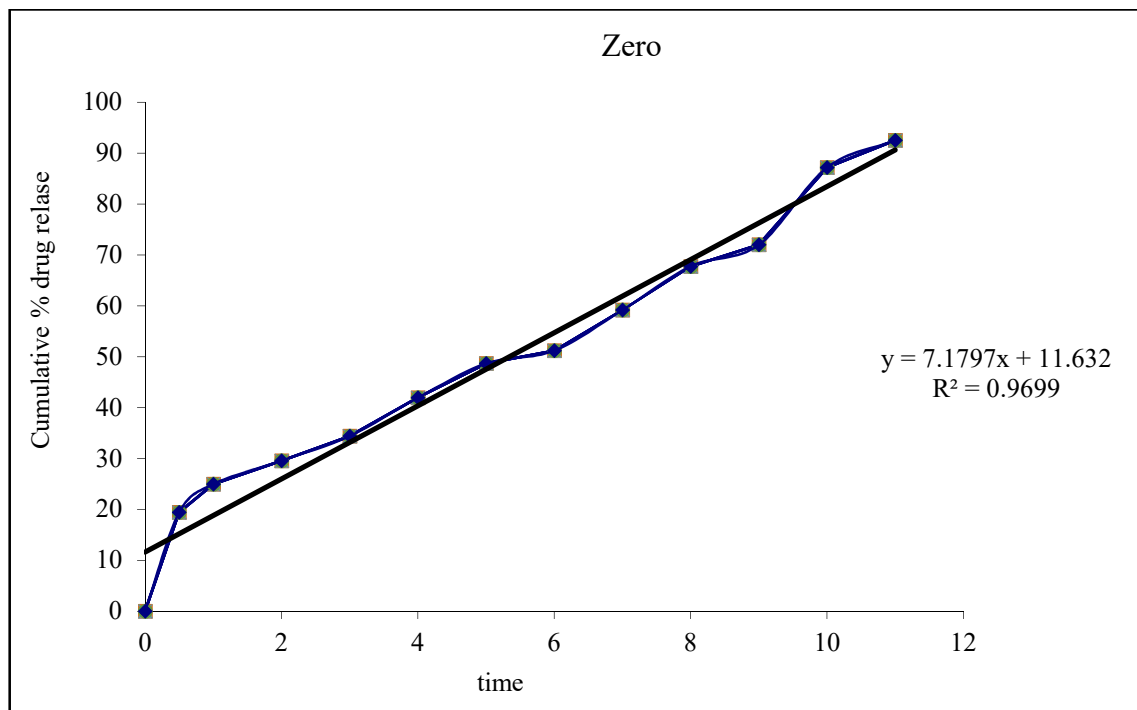


Figure 8.6: Zero order release kinetics graph

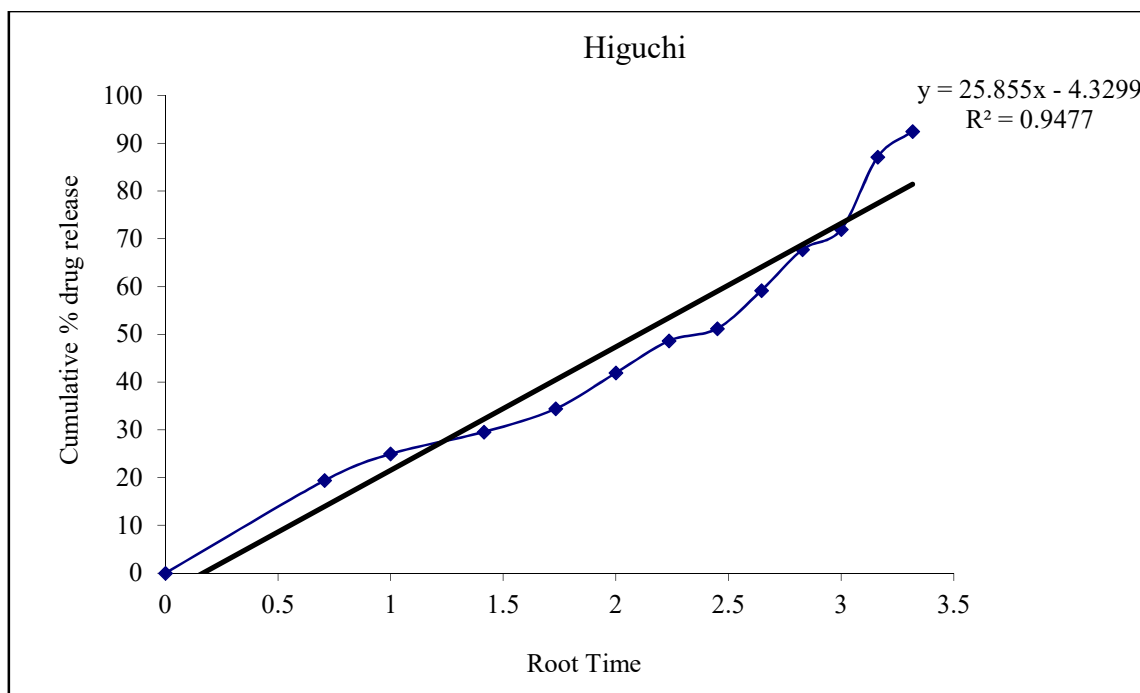


Figure 8.7: Higuchi release kinetics graph

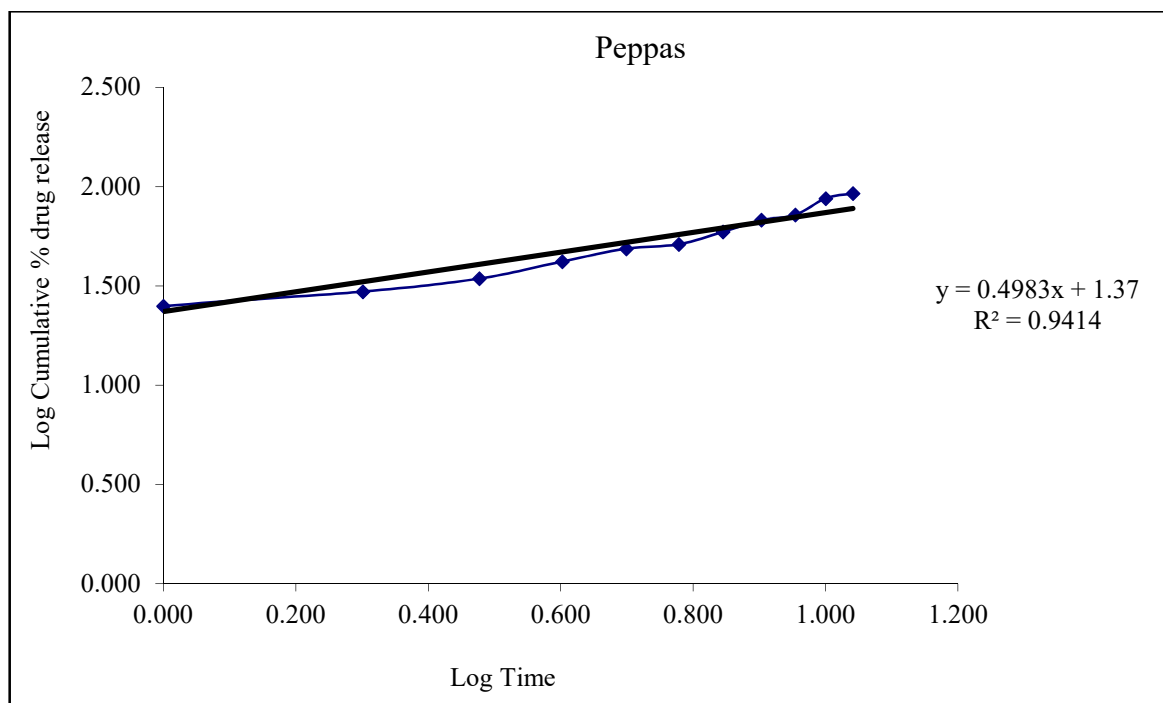


Figure 8.8: Peppas release kinetics graph

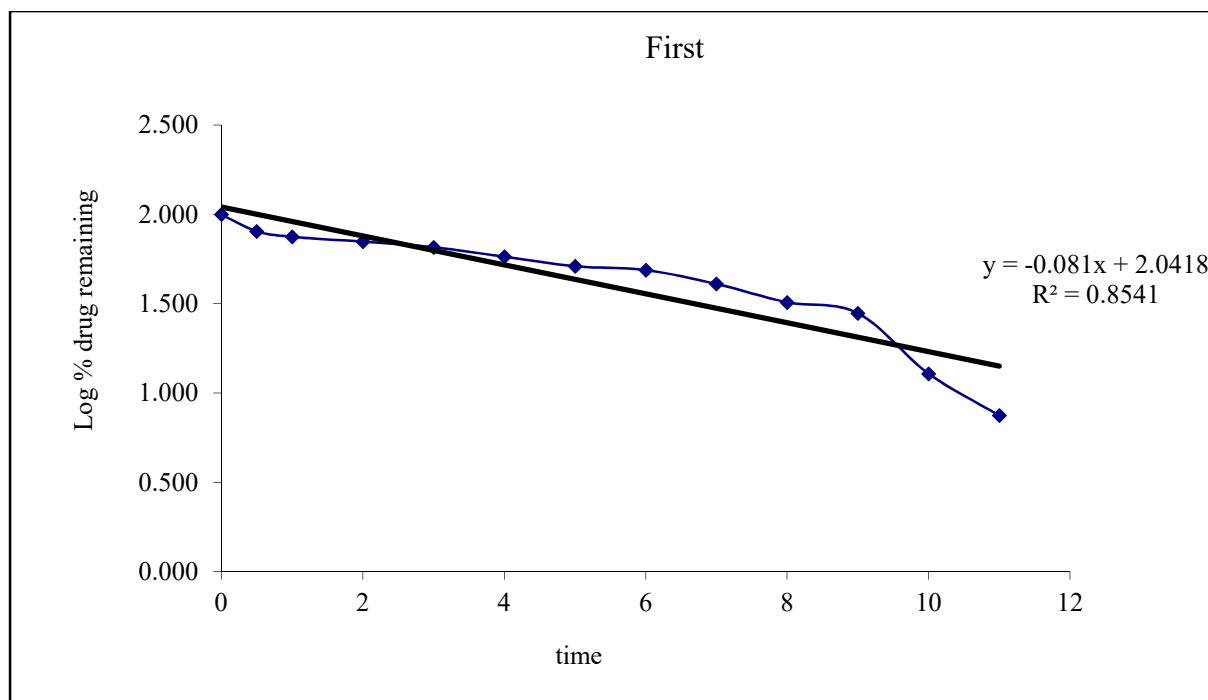


Figure 8.9: First order release kinetics graph

Optimised formulation E9 was kept for release kinetic studies. From the above graphs it was evident that the formulation E9 was followed Higuchi release kinetics mechanism.

Drug – Excipient compatibility studies

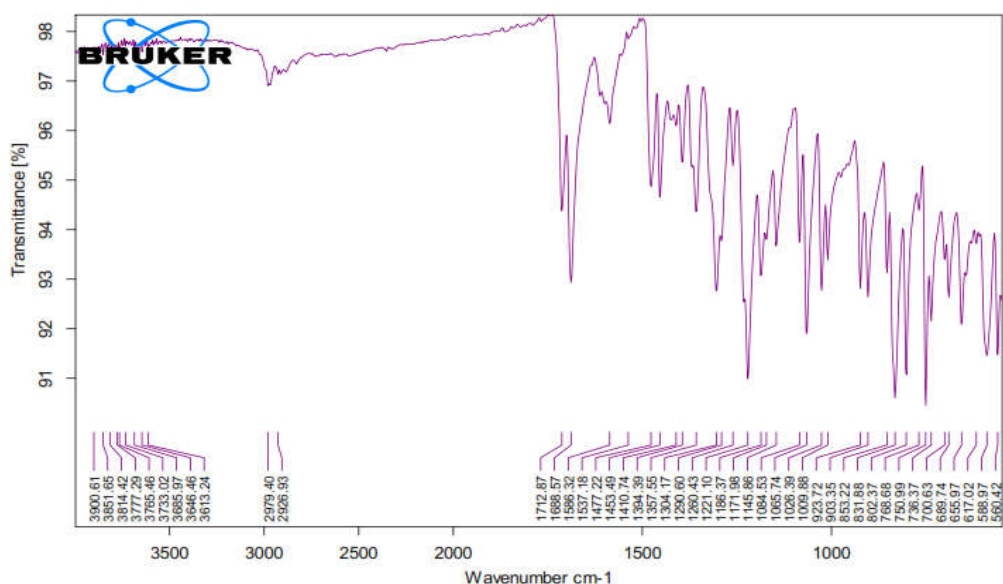


Figure 8.10: FT-TR Spectrum of Esomeprazole pure drug

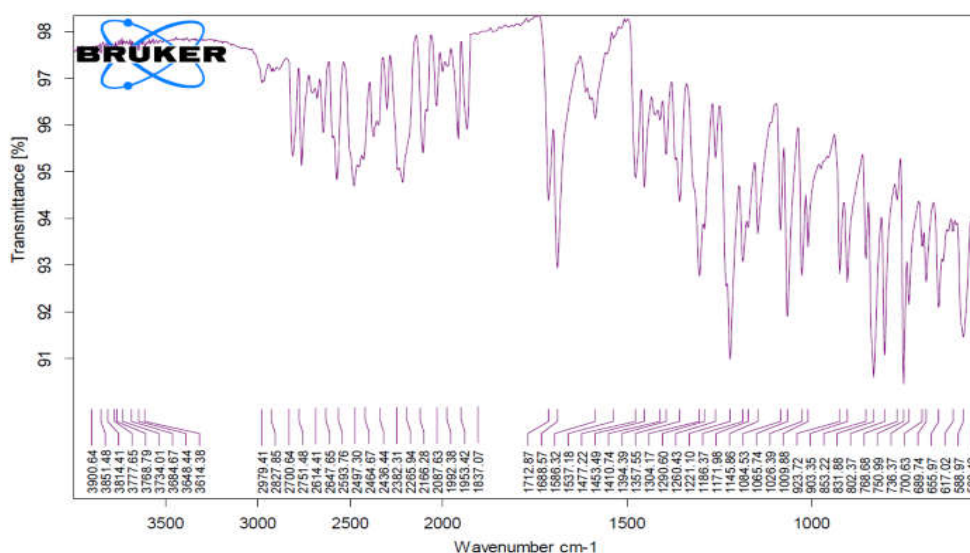


Figure 8.11: FT-IR Spectrum of Optimized Formulation

There was no disappearance of any characteristic peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Pefloxacin is also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

9. CONCLUSION

From current research work the formulation and evaluation of sustained release tablets of Esomeprazole by using both natural and synthetic polymers. Initially Analytical studies are done for the drug molecule to determine Wavelength, Calibration curve at various dosage concentrations. Then followed by pre formulation studies i.e.: Angle of repose, Bulk and Tapped densities, Compressibility studies to formulate the tablets. The tablets of Esomeprazole were formulated using polymers like HPMC K 15, Amla extract, Ginger extract and other excipients. Then post compression evaluation studies tests like Hardness, Weight variation, Thickness, Friability of Drug content are done and results conclude that the formulation prepared with Amla extract showed good retardation capacity of drug release (99.82 %) up to 12 hours in concentration 60 mg whereas high concentrations retard the drug release up to 12 hours. Hence from the above dissolution data it was concluded that E6 formulation with concentration of 60 mg of Amla extract was considered as optimised formulation because good drug release (99.82 %) in 12 hours. Overall, the study supports the potential of using these

polymer blends for the development of efficient sustained release dosage forms of Esomeprazole, offering an effective solution for chronic treatments while minimizing side effects associated with fluctuating drug levels.

ABBREVIATIONS

Conc.	=	Concentration
°C	=	Degree centigrade
%	=	Percentage
hrs	=	Hours
mg	=	Milligram
gm	=	Gram
µg/mL	=	Microgram per millileter
min	=	Minute
mL	=	Milliliter
mM	=	Millimolar
cm	=	Centimeter
mm	=	Millimeter
nm	=	Nanometer
rpm	=	Revolution per minute
Sec	=	Second
S.D	=	Standard deviation
R ²	=	Regression coefficient
n	=	Diffusion coefficient
pH	=	Negative logarithm of hydrogen ion concentration
USP	=	United States Pharmacopoeia
IP	=	Indian Pharmacopoeia
UV	=	Ultraviolet
F	=	Formulation
FTIR	=	Fourier transmission infrared spectroscopy
Fig	=	Figure

REFERENCES:

1. Jain KK. Drug delivery systems. 1st edition. Switzerland: Humana Press; 2008. P. 1-51.
2. Reddy KR., Mutalik S, Reddy S. AAPS Pharm. Sci. Tech. 2003; 4: 19. 121-125.
3. Chien YW. Novel drug delivery system. 2nd edition revised and expanded. New York: Informa health care; 2009. P. 1-50.
4. Jantzen GM, Robinson JR. Sustained and Controlled- Release Drug Delivery systems Modern Pharmaceutics, 4th ed; 2003; 121: 501-502.
5. Salsa T, Veiga F. Drug Develop. Ind Pharm. 1997; 23: 931.
6. Gwen MJ, Joseph RR, In Banker GS and Rhodes CT, Ed. Modern Pharmaceutics, 3rd Ed Marcel Dekker Inc. New York. 1996; 72: 575.
7. Jantzen GM, Robinson JR, Sustained and controlled-release drug delivery systems, in Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, 3rd Ed, Revised and Expanded, Drugs and the Pharmaceutical Sciences., Marcell Dekker, Inc. New York. 1995; 72: 575-609.
8. Lee BJ, Ryu SG, Cui JH, Drug Dev. Ind. Pharm. 1999; 25: 493-501.
9. Vidyadhara S, Rao PR, Prasad JA. Indian J Pharm Sci. 2004; 66: 188-192.
10. Bogner RH. Bioavailability and bioequivalence of extended-release oral dosage forms. US Pharmacist. 1997; 22: 3-12.
11. Rogers JD, Kwan KC. Pharmacokinetic requirements for controlled-release dosage forms. In: John Urquhart, ed. Controlled-release Pharmaceuticals. Academy of Pharmaceutical Sciences. American Pharmaceutical Association. 1979: 95-119.
12. Madan PL. Sustained-release drug delivery systems, part II: Preformulation considerations. Pharm Manu fact. 1985; 2: 41-45.
13. Wani MS, Controlled Release System-A Review, 2008; 6 1: 56-62.
14. Banker GS, Anderson NR. The Theory and Practice of Industrial Pharmacy: Tablet, Lachman, (3rd ed) Varghese Publishing House, Bombay. 1990; 3: 293-303.

14. Manish R, Jayesh P, Siahboomi AR. Hydrophilic Matrices for Oral Extended Release: Influence of Fillers on Drug Release from HPMC Matrices. *Pharma Times*. 2010; 42(04): 67-73.
15. Lee VHL, *Controlled Drug Delivery Fundamentals and Applications: Influence of drug properties on design*, Marcel Dekker, INC, and New York. 1987; 2: 16-29.
16. Kumar KP et al. Innovations in Sustained Release Drug Delivery System and Its Market Opportunities. *J Chem Pharm Res*. 2010; 2 1: 349-360.
17. Brahmkar DM, Sunil B. Jaishwal. "Controlled release medication" chapter 15th in "Bio pharmaceuticals and Pharmacokinetics – A Treatise, 1st ed, 2010; 1: 347- 353.
18. Mallikarjunarao p, mohan kumar y, kiran kumar m, prathyusha s, lavanya d. Formulation and invitro evaluation of nevirapine extended release matrix tablets. *International journal of research and development in pharmacy and life sciences*. 2014;3(4)1054-1065.
19. Stanley S. Davis, *Formulation strategies for abs windows*. *Drug Discovery Today*, 2005; 10: 249-257.
20. Lieberman HA, Lachman L, Schwartz JB., *Pharmaceutical Dosage Forms: Tablets*, 2011; 3 (2): 199-287.
21. Modi SA et al. Sustained Release Drug Delivery System: A Review. *Int J Pharma. Res Dev*. 2011; 2 (12): 147-160.
22. Aulton ME. *Pharmaceutics: The Science of Dosage Form Design*. 2005; 2: 296-298.
23. Wise DL. *Handbook of Pharmaceutical Controlled Release Technology*. Inc. 2005; 2: 5-24
24. Jantzen GM, Robinson JR. Sustained and Controlled- Release Drug Delivery systems *Modern Pharmaceutics*, 4th ed; 2011; 121: 501-502.
25. Bhargava.A et al. Oral sustained release dosage form: an opportunity to prolong the release of drug. *IntJ ARPB*. 2013; 3: 7-14.
26. Kathane Sudhir, Rathore Shruti, Chandrakar Shashikant. Formulation and evaluation of indomethacin sustained release tablet by using natural polymers. *Indian Journal*, Volume : 16, Issue : 1, 2024.
27. Shukla M et al., *A Detailed Review On Artificial Intelligence In Pharmacy*. *American Journal of PharmTech Research* 2023.

28. Dr. Y. Krishna Reddy, Fathima Umera. Formulation and Evaluation of Sustained release matrix tablets of Atomoxetine HCl by using Natural and Synthetic Polymers. Asian Journal of Pharmacy. 2020-10-1-9.
29. M. Kaleemullah, K. Jiyaiddin, E. Thiban, S. Rasha, S. Al-Dhalli, S. Budiasih, O.E. Gamal, A. Fadli, Y. Eddy, Development and evaluation of Ketoprofen sustained release matrix tablet using Hibiscus rosa-sinensis leaves mucilage, Saudi Pharmaceutical Journal, Volume 25, Issue 5, 2017,
30. Ramu B, Kumar S, Srikanth G, Rajkamal B. Formulation and Evaluation of Sustained Release Verapamil Hydrochloride Using Natural Polymers. IJAPSR. 13 Jun.2016.
31. Basavaraja, Kirankumar Navade, B.Someswara Rao, Suresh V. Kulkarni. Formulation and Evaluation of Sustained Release Matrix Tablets of Flurbiprofen by Using Natural and Synthetic Polymers. /J. Pharm. Sci. & Res. Vol. 7(6), 2015.
32. Muthadi Radhika Reddy, Pola Kranthi Kumar. Formulation and Evaluation of Sustained Release Tablets of Esomeprazole Using Natural and Synthetic Polymers. International Journal of Science and Research (IJSR) 2015.
- 33.Y Ganesh Kumar, Formulation Development and Evaluation of Sustained Release Matrix Tablets of Vildagliptin - Synthetic and Natural Polymers. Vol. 9 No. 4: Asian Journal of Pharmaceutics Oct-Dec 2015.
34. Ahmad Khan, Muhammad Iqbal Ch, Jallat Khan, Gul Majid Khan, Muhammad Hanif & Amjad Khan. Formulation Development and In Vitro Characterization of Sustained Release Matrix Tablets of Verapamil HCl Using Synthetic and Natural Polymers. Latin American Journal of Pharmacy, 34 (2): 277-82 (2015).0