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1. INTRODUCTION

With many drugs, the basic goal of therapy is to achieve a steady-state blood or tissue level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal[1].

The idealized objective points to the two aspects most important to drug delivery, namely, spatial placement and temporal delivery of a drug. Spatial placement relates to targeting a drug to a specific organ of tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue.

An appropriately designed sustained release drug delivery system can be a major advance toward solving these two problems. The bulk of research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery, but many of the newer approaches under investigation may allow for spatial placement as well.

1.1 Conventional drug therapy

There are several potential problems inherent in multiple dosage therapy:

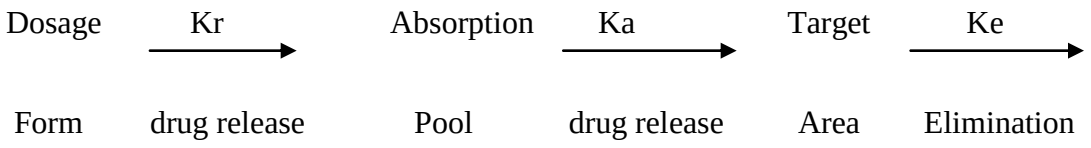
- If the dosing is not appropriate for the biological half-life of the drug, large "Peaks" and "Valleys" in the drug blood level may result. For example, drugs with short half-lives require frequent dosing to maintain constant therapeutic levels.
- The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.

- Patient noncompliance with the multiple-dosing regimen can result in failure of this approach.

Frequently these problems are significant enough to make drug therapy with conventional dosage forms less desirable than sustained release drug therapy. This fact, coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling motive for investigation of sustained-release drug delivery systems.

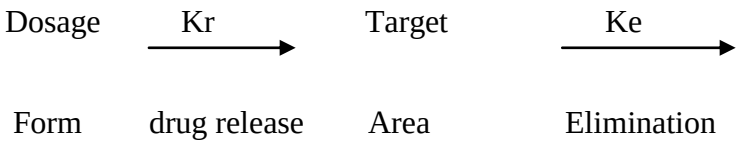
1.2. Sustained Release Drug Therapy

Conventional dosage forms include solutions, suspensions, capsules, tablets, emulsions, aerosols, foams, ointments and suppositories. For this discuss, these dosage forms can be considered to release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme[2]:



The absorption pool represents a solution of the drug at the site of absorption, and the terms Kr, Ka and Ke are first – order rate constants for drug release, absorption and overall elimination, respectively. Immediate release from a conventional dosage form implies that Kr>>>Ka or that observation of drug across a biological membrane, such as the intestinal epithelium, is the rate-limiting step in delivery of the drug to its target area.

For non immediate – release dosage forms, Kr<<<Ka, that is, release of drug from the dosage form the rate-limiting step. This causes the above kinetic to reduce to the following:



Non-immediate-release delivery systems may be divided conveniently into four categories[3]:

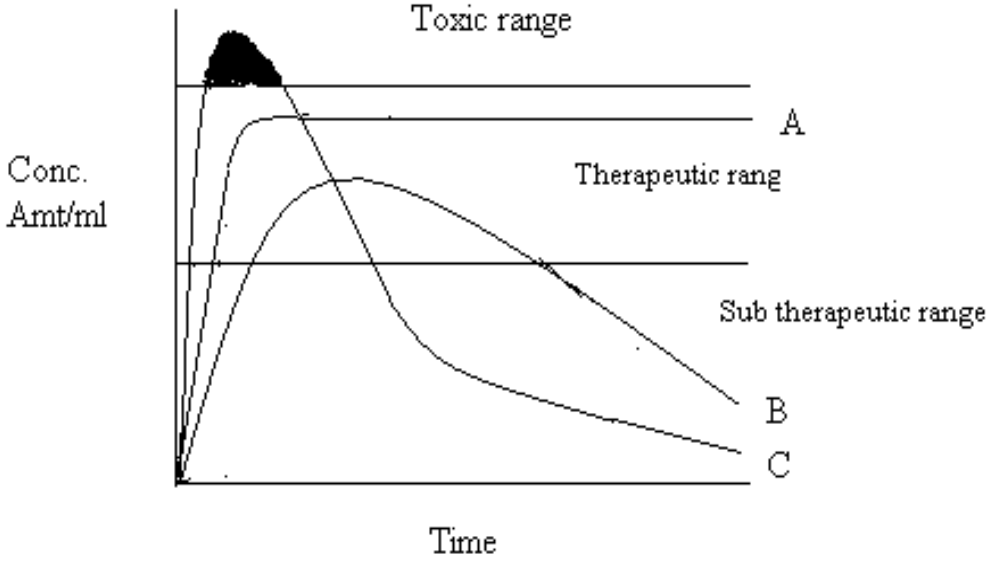
1. Delayed release

2. Sustained release

    a. Controlled release

    b. Prolonged release

3. Site-specific release



4. Receptor release

A-Control Release Formulation

B-Sustain Release Formulation

C-Conventional Release formulation

Figure: 1.1 A Hypothetical plasma concentration-time profile from conventional Sustained and control delivery formulations

In the case of new drug delivery systems, which are based on controlled of programmed drug delivery methods in the vicinity of target tissue, this undeniable fluctuation of drug levels (concentration) between toxic level and sub-therapeutic level can be greatly reduced. This

controlled drug-therapy offers a method for which therapeutic action is enhanced and the dangerous toxic level eliminated.

Digital computers have become integral components of modem methods of analysis. Applications of these devices to analytical instrumentation have increase with advances in computer technology. Initially computers were used to automate conventional calculations and existing instruments. Later new measurement methods were developed which were possible only through the use of computerized instruments and high-speed data processing techniques.

In many cases, identification can be made on a fraction of a milligram, or even on several micrograms, of sample. Identification on the milligram scale is routine, of course, not all molecules yield so easily.

Chemical manipulations may be necessary information obtained from the spectra will permit intelligent selection of chemical treatment, and energy probe methodology can be applied to the resulting products.

1.2.1 Potential Advantages of Sustained Drug Therapy

- Avoid patient compliance problems. [4]
- Employ less total drug.
    - Minimize or eliminate local side effects.
    - Minimize or eliminate systemic side effects.
    - Obtain less potentiating or reduction in drug activity with chronic use.
    - Minimize drug accumulation with chronic dosing.
- .Improve efficiency in treatment

- Cure of control condition more promptly
- Improve control of condition, i.e. reduce fluctuation in drug level
- Improve bioavailability of some drugs
- Make use of special effects, e.g. sustained-release aspirin for relief of arthritis by dosing before bedtime.

1.3. Drug Properties Relevant to Sustained – release Formulation

Discovery, testing and marketing of new chemical entities, the so – called medicinal agents, is what differentiates the pharmaceutical industry from many other enterprises.

The primary objective is to determine the impact of various factors that have forced the drug industry to direct efforts towards development of modified – release or so – called specialized drug delivery systems.

In developing a formulation, product of process, pharmaceutical of otherwise, is rarely known right from the start. Out own past experience, scientific theory, and the contents of the scientific and technical literature may all be of help, but we will still need to do experiments, whether to answer our questions or to conform what we already believe to be the case. And before starting the experimentation, we will need to decide what the experiment is actually going to be. We require an experimental strategy.

The sustained-release products are often designed with an initial dose intended to establish rapidly therapeutic drug blood levels and additional drug intended to maintain those levels for prolonged periods. Those products providing only the slow-release Component and lacking the immediate-release component have sometimes been termed prolonged release.

Product formulation if often considered an art, the formulator's experience and creativity providing the "raw material" for the creation of a new product. Given the same active ingredient and a description of the final marketed producer, two different scientists will very likely concoct different formulations. Certainly, human input is an essential ingredient of the creative process.

The term "sustained release" is known to have existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration.

Initial progress in product development rests heavily on a thorough understanding of the absorption distribution and elimination characteristics of a drug. Absorption, distribution and elimination processes begin when a dose is administered, and may govern the appearance of any therapeutic effect. Pharmacokinetics is used to quantitate these processes.

1.3.1 Physicochemical Properties

A more is an important tool in the development[5] of the "best" formulation, in the understanding of the drug's biopharmaceutical characteristics, and in interpretation of possible risks, such as potential food effect on bioavailability or interaction with other drugs.

Methods for the determination of solubility have been thoroughly reviewed. Solubility is normally highly dependent on temperature, and so the temperature must be recorded for each solubility measurement. Plots of solubility against temperature are commonly used for characterizing pharmaceutical solids.

The historical evolution of this approach to predicting solubility and to predicting the deviations from ideal solubility based on theoretical considerations of the interaction between solute and solvent has been reviewed.

1.3.1.1 Aqueous solubility and pKa

The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and hence the driving force for diffusion across membranes. Dissolution rate is related to aqueous solubility as shown by the Noyes – Whitney equation which, under sink condition, is

$$d_c / d_t = KDACs$$

d_c/d_t= dissolution rate

KD = dissolution rate constant

A = total surface area of the drug particles and

Cs = aqueous saturation solubility of the drug

The dissolution rate is constant only if surface area, A, remains constant, but the important point to note is that initial rate is proportional directly to aqueous solubility Cs. Therefore, the aqueous solubility of a drug can be used as a first approximation of its Dissolution rate. Low solubility limits the dissolution rate and hence the absorption of many drugs.

In general, extreme in the aqueous solubility of a drug are undesirable for formulation into a sustained release product. A drug with very low solubility and a slow dissolution rate will exhibit dissolution-limited absorption and yield an inherently sustained blood level. In most instances, formulation of such a drug into a sustained released system is redundant.

1.3.1.2 Partition coefficient

Between the time that a drug is administered and the time it is eliminated from the body, it must diffuse through a variety of biological membranes which act primarily as Lipid-like barriers.

A major criterion in evaluation of the ability of a drug to penetrate these lipid membranes is its apparent oil/water partition coefficient, defined as

$$K = C_o/C_w$$

C_o = total concentration of all forms of the drug. E.g. ionized and unionized, in some organic phased at equilibrium, and C_w = total concentration of all forms in an aqueous phase at equilibrium

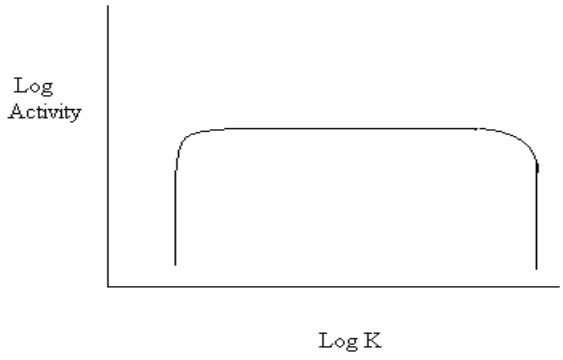


Figure: 1.2 Typical relationship between drug activity and partition coefficient, K, Generally known as the Hansch correlation

Drugs with a partition coefficient that either is extremely higher of lower that the optimum are, in general, poorer candidates for formulation into sustained release dosage forms.

1.3.1.3 Drug Stability

Of importance for oral dosage forms is the loss of drug through acid hydrolysis and/or metabolism in the GI tract. Since a drug in the solid state undergoes degradation at a much slower rate than a drug in suspension or solution, it would be seen possible to improve significantly the bioavailability of a drug, which is unstable in the GI tract by placing it in a slowly available sustained release form. For those drugs that are unstable in the stomach, the appropriate sustaining unit would be one that releases its contents only in the intestine.

However, most sustained-release systems currently in use release their contents over the entire length of the GI tract. Delivery systems that remains localized in a certain area of the GI tract and a act as reservoir for drug release are much advantageous for drug that not suffer from stability problems but have other bioavailability problems as well.

1.3.1.4 Protein Binding

Distribution of the drug into the extra vascular space is governed by the equilibrium process of dissociation of the drug from the protein. The drug-protein complex can serve therefore as a reservoir in the vascular space for sustained drug release to extra vascular tissues, but only for those drugs that exhibit a high degree of binding.

Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug, and such drugs generally do not require a sustained-release dosage form. However, drugs that exhibit a high degree of binding to plasmas proteins also might bind to biopolymer in the GI tract, which could have an influence on sustained drug delivery.

The main forces of attraction responsible for bindings are Vanderwaals forces, hydrogen bonding and electrostatic forces. In general, charged compounds have a greater tendency to bind a protein than uncharged compounds, due to electrostatic effects. The presence of a hydrophobic

moiety of the drug molecule also increases its binding potential. Some drugs that exhibit greater than 95% binding at therapeutic levels are Amitriptyline, Bischydroxycoumarin, Diazepam, Diazoxide, Dicumarol, and Novobioocin.

1.3.1.5 Molecular Size and Diffusivity

In addition to diffusion through these biological membranes, drugs in many sustained-release systems must diffuse through a polymeric membrane or matrix that is used to control their release kinetics. The ability of a drug to diffuse through polymeric membrane or matrix that is used to control their release kinetics membranes is a function of its diffusivity (diffusion coefficient).

An important influence upon the value of the diffusivity, D, in polymers is the molecular size (or molecular weight) of the diffusing species. In most polymers, it is possible to relate log D empirically to some function of molecular size. The value of D thus is related to the size and shape of the cavities as well as size and shape of drugs.

1.3.2 Biological Properties

1.3.2.1 Absorption

The rate, extent and uniformity of absorption of a drug are important factors when considering its formulation into a sustained-release system; since the rate limiting step in drug delivery from a sustained-release system is its release from the dosage form, rather than absorption, a rapid rate of absorption of the drug relative to its release is essential if the system is to be successful. The extent and uniformity of the absorption of a drug, as reflected by its bioavailability and the fraction of the total dose absorbed, may be quite low for a variety of reasons. This usually is not a prohibitive factor in its formulation into a sustained-release system.

Some possible reasons for a low extent of absorption are poor water solubility, small coefficient, acid hydrolysis and metabolism, or site-specific absorption. The latter reason also is responsible for non-uniformity of absorption. Many of these problems can be overcome by an appropriately designed sustained-release system, as exemplified by the discussion under the potential advantages of sustained drug therapy[5].

1.3.2.2 Distribution

The distribution of a drug into vascular and extravascular spaces in the body is an important factor in its overall elimination kinetics. This, in turn, influences the formulation of that drug into a sustained-release system, primarily by restricting the magnitude of the release rate and the dose size which can be employed. The apparent volume of distribution is merely proportionality constant which relates drug concentration in the blood or plasma to the total amount of drug in the body.

The magnitude of the apparent volume of distribution can be used as a guide for additional studies and as a predictor for drug dosing regimen and hence the need to employ sustained-release system.

1.3.2.3 Metabolism

The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained-release system for that drug. As long as the location, rate and extent of metabolism are known and the rate constant(s) for the process (es) are not too large, successful sustained-release products can be developed.

There are two factors associated with the metabolism of some drugs; however that present problems of their use in sustained-release systems. One is the ability of the drug to induce or inhibit enzyme synthesis; this may result in a fluctuating drug blood level with chronic

dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect. Examples of drugs that are subject to intestinal metabolism upon oral dosing are Hydralazine, Salicylamide, Nitroglycerine, Isoproterenol, Chlorpromazine and Levodopa. Examples of drugs that undergo extensive first-pass hepatic metabolism are Propoxyphene, Nortriptyline, Phenacetine, Propranolol and Lidocaine.

`1.3.2.4 Elimination and Biological Half-life

The rate of elimination of a drug is quantitatively described by its biological half-life, t1/2- The half-life of a drug is related to large release rates and large doses. At the other extreme, a drug with a half-life of greater than 8 hours also probably should not be used; in most instances, formulation of such a drug into a sustained-release system its apparent volume of distribution V_d and its systemic clearance may affected. A drug with a short half-life requires frequent dosing and this makes it a desirable candidate for a sustained-release formulation.

In general, however, a drug with a half-life, if less than 2 hours probably should not be used since such systems will require unacceptably large release rates and large doses. At the other extreme, a drug with a half-life of greater than 8 hours also probably should not be used; in most instances, formulation of such a drug into a sustained-release system is unnecessary.

Some examples of drug with half-lives of less than 2 hours are Ampicillin, Cephalexin, Cloxacillin, Furosemide, Levodopa, Penicillin G and Propylthiouracil. Examples of those with half-lives of greater than 8 hours are Dicumarol, Diazepam, Digitoxin, Digoxin, Guanethidine, Phenytoin and Warfarin.

1.3.2.5 Side effects and Safety Considerations

For some drugs, the incidence of side effects, in addition to toxicity, is believed to be related to their plasma concentration. As mentioned in the discussion on the potential advantages of sustained drug therapy, a sustained-release system can at times, minimize side effects for a particular drug by controlling its plasma concentration and using less total drug over the time course of therapy.

The most widely used measure of the margin of safety of a drug is its therapeutic index, TI, defined in the following equation:

$$\mathbf{TI = TD_{50}/ED_{50}}$$

TD_{50} is the median toxic dose

ED_{50} is the median effective dose.

The value of TI varies from as little as unity, where the effective dose is also producing toxic symptoms, to several thousand. For very "potent" drugs, whose therapeutic concentration range is narrow, the value of TI is small. In general, the larger the value of TI, the safer is the drug. Drugs with very small values of TI usually are poor candidates for formulation into sustained-release products primarily due to technological limitations of precise control over release rates. Examples of drugs with values of TK_{10} are Aprobarbital, Digitoxin, Phenobarbital and Digoxin.

1.3.2.6 Dose Size

Since a sustained-release is designed to alleviate repetitive dosing, it naturally will contain a greater amount of drug than a corresponding conventional form. The typical administered dose of a drug in the conventional dosage form will give some indication ofthe total amount needed in the sustained-release preparation. For those drugs requiring-large conventional

doses, the volume of the sustained dose may be so large as that to be Impractical or unacceptable, depending on the route of administration. The same may be true of drugs, which require a large release rate from the sustained-release system, e.g. drugs with short half-lives.

Two geometric systems can be considered, in involving unidirectional leaching of extraction from a simple planar surface and a second involving three-dimensional leaching of extraction from a spherical dosage form, such as a pellet. This corresponds most closely to the release process from an insoluble matrix (tablet) or certain sustained or controlled-release pellets. The mechanisms of release from these systems can be treated in two ways: (a) Extraction of the medicament by a simple diffusion process through enveloping homogeneous matrix, (b) Leaching of the medicament by the bathing fluid, which is able to enter the drug-matrix phase through pores, cracks and intergranular spaces.

When tablet ingredients are sensitive to moisture and are unable to withstand elevated temperature during drying and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is known as dry granulation of pre-compression method or the double compression method.

A matrix is a uniform mixture of drug, excipients, and (e.g.) polymer that is homogeneously fixed in a solid dosage form.

1.4. Selection of drug for Sustained-release drug delivery systems

Judicious choice of the drug substance is the most important decision in the successful development of a sustained-release product,

Several categories of drug have potential for their therapeutics improvement of efficacy

via sustained-release oral routes e.g. Anti-anginal, Anti-inflammatory, Antihistaminic, Anti-gastric resistant agents, Antipsychotic agents and Anti-diabetic drugs of agents.

The common goal for increased duration is twice a day, or when feasible, once a day. Several properties of the drug itself can lead to the achievement of a 12 to 24 hours oral prolonged release dosage form. Some of the characteristics mitigating against success are the following:

1. Very short half-life and/or a relatively large single dose.
2. Long half-life.
3. Potent drug with a low margin safety.
4. Poorly soluble and/or poorly absorbed.
5. Biological activity not a function of core in blend.
6. Absorption primarily active through a 'window'.
7. Large first-pass metabolism.

The selection of both the drug and retardant polymers along with the filler excipients will impact on the mechanism and rates of drug release from monolithic systems. Cellulose derivatives and acrylic resin polymers comprise the group of polymers that are presently available as aqueous coatings for pharmaceutical dosage forms. These polymers in the dry state have been utilized in matrix type tablet formulations by directly compressing.

1.5 Matrix systems

A polymer and active agent have been mixed to form a homogeneous system referred to as a matrix system. [7]:

To control the release of the drug, which are having different solubility properties hydrophobic, and hydrophilic matrices have been used.

For water-soluble drugs, the hydrophobic and hydrophilic polymeric matrices are mixed. The following physicochemical properties of the drug are influence the design of oral controlled drug matrix systems.

- Solubility
- Partition coefficient and molecules weight.
- Drug stability
- Protein binding.

Release from this matrix system occurs based on successive processes of:

- Hydration of the cellulosic polymer.
- Gel formation on the polymer's surface.
- Tablet erosion, & the subsequent & continuous release of drug.

After ingestion, the tablet is wetted by gastric fluid and the polymer begins to hydrate. A gel layer forms around surface of the tablet and an initial quantity of drug is exposed and released. As water penetrates further into the tablet the thickness of the gel layer is increased and soluble drug diffuses through the gel layer. As the outer layer becomes fully hydrated it erodes

from the tablet core.

If the drug is insoluble, it is released as such with the eroding gel layer. Thus, the rate of drug release is controlled by the processes of diffusion and tablet erosion.

2. AIM AND OBJECTIVE

The objective of the study is to design and evaluated of Esomeprazole oral sustained release tablets using natural polymers.

Esomeprazole is a proton pump inhibitor which reduces acid secretion through inhibition of the H+ / K+ ATPase in gastric parietal cells. By inhibiting the functioning of this transporter, the drug prevents formation of gastric acid.

It is used in the treatment of dyspepsia and peptic ulcer disease

Since Esomeprazole is a potent drug used in the treatment of Peptic ulcer its dosing intervals generally varies based on the intensity of the ulcers. Hence to decrease the number of dosing intervals and to sustain the drug Esomeprazole sustain release dosage forms are being designed.The main objective of the work is to develop a simple, cost effective oral sustained release dosage form of Esomeprazole using natural polymers, which shows good stability and sustainability of the drug thus decreasing the number of dosing intervals and increasing the patient compliance.

The preparation of Esomeprazole tables is done by direct compression method. The evaluation of the formulated tablets was to be carried out on the parameters such as hardness, weight variation, drug content, friability and dissolution.

2.1 PLAN OF WORK

The work was planned to carryout study in the sequences below:

1. Formulation of Esomeprazole Sustain Release tablets using guar gum, xanthan gum and pectin.
2. Evaluation of blend characteristics / Pre compression Characteristics of Esomeprazole Sustain Release tablet blends.
    - Angle of repose
    - Bulk density
    - Tapped density
3. Evaluation of Post compression Characteristics of Esomeprazole Sustain Release tablets.
    - Hardness
    - Friability
    - Uniformity
    - Weight variation
3. Selection of best formulation on the basis of *in-vitro* drug release.
4. Stability study on formulations as ICH guideline.

3. LITERATURE REVIEW

- **Uttam mandal *et.al,* (**2008**)**[8] design and studied an oral sustained release matrix tablet of metformin HCl and to optimize the drug release profile using response surface methodology. Tablets were prepared by non-aqueous wet granulation method using HPMC K15M as matrix forming polymer.

- **Syed Nisar Hussain Shah *et.al,* (**2009**)**[9] carried their research work on to design oral sustained release matrix tablets of water-insoluble drug, flurbifrofen, using natural gums as the matrixs polymers and to evaluate the drug release characteristics using response surface methodology. Matrix tablets were prepared by direct compression technique. Xanthan and acacia gums were taken as the independent variables. The formulated matrix tablets followed zero-order kinetics with negligible drug release. The objective of study to produce a formulation avoiding the gastric effects of flurbiprofen.

- **Vinayak Dhopeshwarkar *et.al, (***1994***)**[10] prepared and evaluated sustained release cephalexin tablet formulation containing xanthan gum and sodium alginate in human volunteers. The formulation based on response surface analysis and computer simulation of cephalexin plasma levels Vs time curves. The SR matrix formulation is an alternative delivery method to produce prolonged concentration.

- **John W.Skoug *et.al, (***1993***)**[11] developed a method to evaluate the drug release mechanism of matrix sustained release (SR) tablets by comparison of the drug and polymer release profiles. The method was applied to SR dosage forms of flurbiprofen, adinazolam mesylate and alprazolam, which encompass a wide range of drug solubility and formulation composition. The measurement of polymer release is a simple and rapid method of estimating the relative contributions of erosion and diffusion to the overall release mechanism.

- **Ayhan Savaser *et.al,* (**2004**)**[12]studied the effects of formulation variables on the release profile of diclofenac sodium (DS) from hydroxypropylmethyl cellulose (HPMC) and chitosan matrix tablets prepared by wet granulation and direct compression methods and different ratios of HPMC and chitosan were used.

- **P.G. Yeole *et.al, (***2006***)**[13] developed sustained release matrix tablets of diclofenac sodium by using different drug: polymer ratios. Xanthan gum was used as matrix former, and microcrystalline cellulose as diluent. All the lubricated formulations were compressed using 8 mm flat faced punches. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness, *in vitro* dissolution using basket method, and swelling index. All the formulations showed compliance with pharmacopoeial standards.

- **D.M. Morkhade *et.al,* (**2006**)**[14] evaluated natural gum copal and gum damar as novel sustained release matrix forming materials in tablet formulation using Diclofenac sodium as a model drug and concluded that both gums possess substantial matrix forming property that could be used for sustained drug delivery

- **Umit Gonullu *et al* (**2006***)***[15] were developed 100 mg Opipramol 2-HCl (OP) matrix tablets by direct compression method in order to use once a day to provide patient compliance and constant blood level, consequently to decrease side effects. Two concentrations of polymers (10% and 20%): hydroxypropylcellulose (HPC) and hydroxypropyl methylcellulose (HPMC), sodium alginate (NaAlg), xanthan gum (XG) and Carbopol®941 (C941) were used in preparation of matrix tablets.is used for therapy of general somatoform and anxiety disorders. OP

- **A.K.Srivastava *et.al, (***2005***)***[16] floating matrix tablets of atenolol were developed to prolong gastric residence time and increase drug bio availability. Atenolol was chosen as a model

drug because it is poorly absorbed from lower gastrointestinal tract. The tablets were prepared by direct compression technique. Tablets evaluated by hardness, swelling index, floating capacity, thickness and weight variation. The tablets exhibited controlled drug and prolong drug release profiles while floating over the dissolution meadium.

- **Phaechamud T *et.al, (***2005***)**[17] designed and studied coated valproic acid and sodium valproate sustained-release matrix tablets by wet granulation technique. Colloidal silicon dioxide effectively adsorbed liquid valproic acid during wet granulation and granule preparation. The amounts of colloidal silicon dioxide and hydroxy propyl methyl cellulose employed in tablet formulations affected drug release from the tablets. The drug release was prominently sustained for over 12 h using hydroxy propyl methyl cellulose-based hydrophilic matrix system. Eudragit L 30 D-55 was used as effective subcoating material for core matrix tablets before over coating with hydroxy propyl methyl cellulose film with organic base solvent.

- **Singh Brahma N. et.al,(2000)**[18], Floating drug delivery system; an approach to oral controlled drug delivery via gastric retention have been made for rate- controlled drug delivery by overcoming physiological properties, such as gastric residence times (GRT) and unpredictable gastric emptying time (GET).

- **Xiao Qiang Xu et.al,(2006)**[19] floating matrix dosage form for phenoporlamine HCL based on gas forming agent; In this work the in-vitro an in-vivo evaluation of formulation was done. Formulation showed increased bioavailability with good floating properties.

- **Sunthongjeen Srisagul et.al,(2008)**[20] designed and evaluated of floating multi-layer tablets based on gas formation were developed. In this work gas generating agent (sodium

bicarbonate), protective layer (HPMC) and acrylic polymers (eudragit RL 30 D, NE 30 D) were used. Formulation showed good floating properties and sustained drug release was achieved.

- **Baumgartner Sasa et.al,(2000)**[21] Optimization of floating matrix tablets and evaluation of their gastric residence time. In this work tablet containing hydroxyl propyl methyl cellulose (HPMC), drug and different additives were compressed, and incorporation of gas generating agent together with microcrystalline cellulose. Formulated tablet didn't adhere tablet to the stomach mucus and that the mean gastric residence time was prolonged.
- **Streuble A. et.al,(2003)**[22] Floating matrix tablets based on low density foam powder; effects of formulation and processing parameters on drug release. In this work different types of matrix polymers were studied; hydroxypropyl methylcellulose, polycrylates, sodium alginate, corn starch, carrageenan, guar gum and gum Arabic. Formulation of floating behaviour of low density drug delivery showed accurate control of the drug release patterns.

- **Talwar Naresh et.al,(2009)**[23], Orally administered controlled drug delivery system providing temporal and spatial control. In this work various gas generating component, a swelling agent, viscolyzing agent, and optionally a gel forms polymer were used, causing the tablet or capsule to be retained in the stomach or upper part of the small intestine (spatial control).

- **Jaimini M. et.al,(2007)**[24]Formulation and Evaluation of Famotidine floating tablets was reported. Different grades of Methocel K100 and Methocel K15M were used for gel forming properties, sodium bicarbonate was incorporated as gas generating agent. The drug release

from the tablet was sufficiently sustained and non-Fickian transport of drug from tablets was confirmed.

- **Khalil et.al, (2014)**[25] developed different formulas of 500 mg amoxicillin as sustained release layer by wet granulation method; similarly, different formulas of 20 mg esomeprazole in form of enteric coated pellets was prepared as extended release matrix layer by direct compression technique, using pH-independed hydrophilic Eudragit polymers (ERL100 and E-RSPM type) as matrix forming agent.The physical characteristics and release properties for compressed amoxicillin and esomeprazole matrix tablets were studied in addition the effect of polymer type, polymer concentration,polymer combination and ratio, effect of diluent type, binder type and method of preparation on the release of amoxicillin and esomeprazole from compressed matrix tablets. And results showed that amoxicillin can be prepared as a sustained release tablets using HPMC K100 and Xg. as matrix forming polymers in a polymer-polymer ratio of 4:1, respectively. Also, esomeprazole can be prepared as extended release multi particulate tablets using pH-independed hydrophilic Eudragit polymers (E-RSPM type) as matrix forming agentwith EC.

- **A.K.L. Kabir et.al, (2009)**[26] were made attempt to develop esomeprazole sustained release matrix tablet using hydroxypropyl methylcellulose (HPMC) polymer such as Methocel K4M CR by direct compression method. Various amount of Methocel K4M CR was used to develop matrix builder in the seven proposed formulations (F1-F7) for the study of release rate retardant effect at 20%, 25%, 30%, 35%, 40%, 45% and 50% of total weight of tablet matrix respectively. From in vitro dissolution study, the formulation F-5 (40%) and F-6 (45%) met the official release pattern of esomeprazole for 10h period. The release mechanisms were explored and explained by Zero order, Higuchi, First order and Korsmeyer-Peppas equations. The release kinetics of formulation F-5 and F-6 very closely followed Higuchi kinetic order than

first order and zero order kinetics. From Korsmeyer- Peppas equation it was found that the drug release followed both diffusion and erosion mechanism in all cases.

- **Muthadi Radhika Reddy et.al, (2017)**[27] were prepared sustained release tablets by direct compression method usingcarbopol 934 and xanthan gums, hydroxylpropylmethylcellulose as polymers.The tablets were evaluated for their micromeritic properties and invitro 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 formulationsF2 showed the most suitable sustained release properties with99.65% of drug releaseattheendof12h.Theresults 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 Zeroorder toe valuate the kinetics and mechanism of the drug release. From this studies it s 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.

4.DRUGS AND EXCIPIENTS PROFILE

4.1 ESOMEPRAZOLE[28-29]

Name

Esomeprazole

Struture

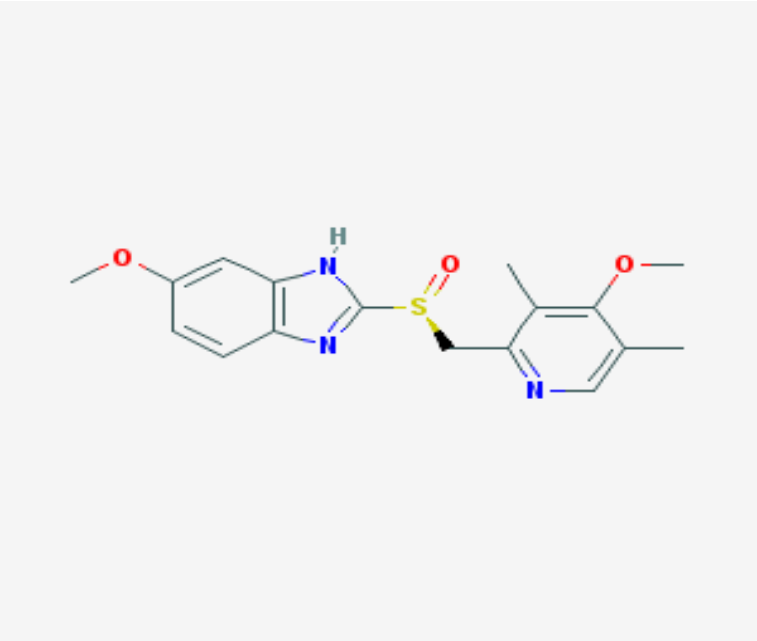


Fig 4.1 structure of esomeprazole

Categories

- Anti-Ulcer Agents

- Enzyme Inhibitors
- Proton-pump Inhibitors
- Antihistamines

Chemical Formula

$C_{17}H_{19}N_3O_3S$

IUPAC Name

5-methoxy-2-[(R)-[(4-methoxy-3,5-dimethylpyridin-2-yl)methane]sulfinyl]-1H-1,3-benzodiazole

PharmacologyIndication

For the treatment of acid-reflux disorders (GERD), peptic ulcer disease, H. pylori eradication, and prevention of gastroinetestinal bleeds with NSAID use.

Pharmacodynamic

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 gsatric 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 is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Esomeprazole blocks the final step in acid production, thus reducing gastric acidity.

Absorption

90%

Volume of distribution

16 L [healthy volunteers]

Protein binding

97%

Metabolism

Mainly hepatic. Esomeprazole is completely metabolized by the cytochrome P450 system via CYP2C19 and CYP3A4. Metabolism produces inactive hydroxy and desmethyl metabolites, which have no effect on gastric. Less than 1% of the parent drug is excreted in urine.

Route of elimination:

Approximately 80% of the administered dose of esomeprazole is excreted as metabolites in urine and the remaining 20% is excreted in feces.

Half life

1-1.5 hours

Toxicity

Blurred vision, confusion, drowsiness, dry mouth, flushing headache, nausea, rapid heartbeat, sweating

4.2 XANTHAN GUM[30]

Synonym:

Corn sugar gum; polysaccharide B-1459; Rhodigel;Vanzan NF; Xantural.

Description:

Xanthan gum occurs as a cream- or white-colored, odorless, free-flowing, fine powder.

Molecular Formula:

$(C35H49O29)_n$

Solubility:

Practically insoluble in ethanol and ether; soluble incold or warm water

Viscosity:

1200–1600 mPa s (1200–1600 cP) for a 1% w/vaqueous solution at 258°C

Functional category:

Gelling agent; stabilizing agent; suspending agent; sustained-release agent; viscosity-increasing agent

Grade:

Keltrol CG, Grindsted Xanthan 80, Vanzan NF

Stability and storage condition:

Aqueous solutions are stable over a wide pH range (pH 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–608°C

Incompatibilities:

Xanthan gum is an ionic material and is not usually compactable with cationic surfactance polymers or preservatives as precipitation occurs

Application:

Xanthan gum is used to prepare sustained-release matrix. Xanthan gum has also been used to produce directly compressed matrices that display a high degree of swelling due to water uptake, and a small amount of erosion due to polymer relaxation.

Safety:

The estimated acceptable daily intake for xanthan gum has been set by WHO at upto 10mg/kg body weight

4.3 GUAR GUM[30]

Guar gum is a naturally occurring galactomannan polysaccharide; consists of chiefly high molecular weight hydro colloidal polysaccharide, composed of galactan and mannan units combined through glycoside linkages and shows degradation in the large intestine due to the presence of microbial enzymes. It contains about 80% galactomannan, 12% water, 5% protein, 2% acid soluble ash, and 0.7% fat. Guar gum has a molecular weight of approximately 1 million, giving it a high viscosity in solution. The high viscosity of guar gum results from its high molecular weight and long chain.

Chemistry of Guar Gum:

A guar gum molecule is made up of about 10,000 residues, which are non-ionic polydisperse rod-shaped polymers. The structure of guar gum is a linear chain of β-Dmannopyranosyl

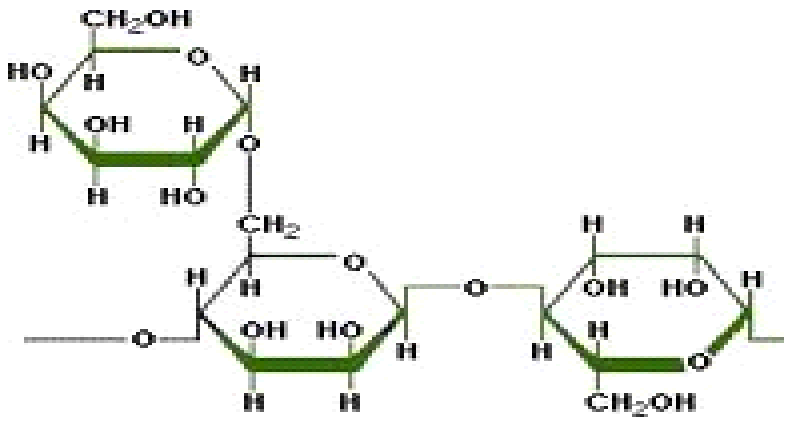


Fig.no:4.2: Structure of guar gum

Properties of Guar Gum

The most important property of guar gum is its ability to hydrate rapidly in cold water to attain uniform and very high viscosity at relatively low concentrations. Apart from being the most cost-effective stabilizer and emulsifier it provides texture improvement and water binding, enhances mouth feel and controls crystal formation.

The main properties of guar gum are:

- It is soluble in hot & cold water but insoluble in most organic solvents and has strong hydrogen bonding properties.
- It has excellent thickening, emulsion, stabilizing and film forming properties, excellent ability to control rheology by water phase management.
- The viscosity of guar gum is influenced by temperature, pH, presence of salts and other solids.

4.4 PECTIN[30]

Pectin is a naturally occurring biopolymer that is finding increasing applications in the pharmaceutical and biotechnology industry. It has been used successfully for many years in the food and beverage industry as a thickening agent, a gelling agent and a colloidal stabilizer. Pectin also has several unique properties that have enabled it to be used as a matrix for the entrapment and/or delivery of a variety of drugs, proteins and cells. This review will first describe the source and production, chemical structure and general properties of pectin. The methods of gel formation and properties of the gels will then be discussed. Finally, some examples of the pharmaceutical uses of pectin will be given.

Chemistry of pectin

Pectin is an essentially linear polysaccharide. Like most other plant polysaccharides, it is both polydisperse and polymolecular and its composition varies with the source and the conditions applied during isolation. In any sample of pectin, parameters such as the molecular weight or the content of particular subunits will differ from molecule to molecule. The composition and structure of pectin are still not completely understood although pectin was discovered over 200 years ago.

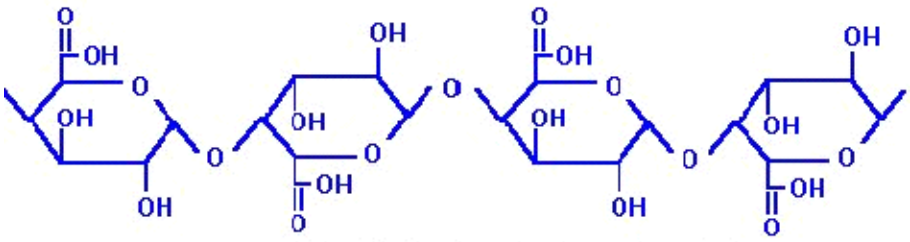


Fig.no: 4.3: Structure of Pectin

Pharmaceutical uses of pectin:

- Pectin has applications in the pharmaceutical industry. Pectin favorably influences cholesterol levels in blood. It has been reported to help reduce blood cholesterol in a wide variety of subjects and experimental conditions.
- Pectin acts as a natural prophylactic substance against poisoning with toxic cations. It has been shown to be effective in removing lead and mercury from the gastrointestinal tract and respiratory organs.
- Pectin reduces rate of digestion by immobilizing food components in the intestine. This results in less absorption of food.
- The thickness of the pectin layer influences the absorption by prohibiting contact between the intestinal enzyme and the food, thus reducing the latter's availability.
- Pectin hydro gels have been used in tablet formulations as a binding agent (Slaney et al., 1981a,b) and have been used in controlled-release matrix tablet formulations.
- Pectin has a promising pharmaceutical uses and is presently considered as a carrier material in colon-specific drug delivery systems.
- Pectin is an interesting candidate for pharmaceutical use, e.g. as a carrier of a variety of drugs for controlled release applications. Many techniques have been used to manufacture the pectin-based
- delivery systems, especially ionotropic gelation and gel coating. These simple techniques, together with the very safe toxicity profile, make pectin an exciting and promising excipient for the pharmaceutical industry for present and future applications.

4.5 POVIDONE[30]

Chemical name:

1-Ethenyl-2-pyrrolidinone homopolymer

Synonym:

E1201, Kollidon, Plasdone, poly [1-(2-oxo-1-pyrrolidinyl)ethylene], polyvidone, Polyvinylpyrrolidone, PVP, 1-vinyl-2-pyrrolidinone polymer.

Description:

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with *K*-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher *K*-value povidones are manufactured by drum drying and occur as plates.

The USP 28 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a *K*-value, in the range 10–120. The *K*-value is calculated using fikentscher's equation

$$\log z = c\left[\frac{75k^2}{1 + 1.5kc}\right] + k$$

Where *z* is the relative viscosity of the solution of concentration *c* (in % w/v), and *k* is the *K* value× 10^{-3}.

Alternatively, the *K*-value may be determined from the following equation,

$$K\text{-value} = \sqrt{\frac{300c \log z \, (c + 1.5c \log z)^2 + 1.5}{0.15c + 0.003c^2}}$$

Where z is the relative viscosity of the solution of concentration c (in % w/v).

Solubility:

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the *K*-value

Table.no:4.1. Approximate molecular weights for different grades of povidone

***K*-value**	**Approximate molecular weight**
12	2,500
15	8,000
17	10,000
25	30,000
30	50,000
60	400,000
90	1 000,000
120	3 000,000

pH: 3.0–7.0

Bulk density: 0.29–0.39 g/cm^3

Tapped density: 0.39–0.54 g/cm^3

Specific surface area: 0.24 m^2/g

Melting point: Softens at 150°C

Incompatibilities; Sodium starch glycolate is incompatible with ascorbic acid.

Pharmaceutical uses: Disintegrant, dissolution aid, suspending agent, tablet binder.

4.6 MICRO CRYSTALLINE CELLULOSE[30]:

Synonyms:

Avicel PH, Celex, cellulose gel, celphere.

Empirical formula and molecular weight:

$(C_6H_{10}O_5)_n$ = 36000W ,Where, n = 220.

Structure:

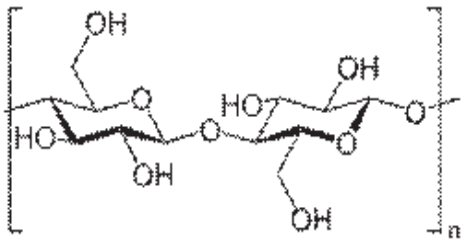


Fig.no:4.4: Structure of Micro crystalline cellulose

Functional category:

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

Description:

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

pH: 5.0 -7.5

Melting point: 260 - 270^{0}C

Stability: It is stable though hygroscopic material.

Storage: Should be stored in well closed container in a cool, dry place.

Safety : Non- toxic and non-irritant material. Consumption of large quantities of cellulose may have a laxative effect

Handling precautions: It may be irritant to eyes Gloves, eye protection and a dust mask is recommended

Applications in pharmaceutical formulation or technology:

- 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 binder/diluents, 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.

4.7 MAGNESIUM STEARATE[30]:

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

Chemical Name: Octadecanoic acid magnesium salt.

Empirical Formula: $C_{36}H_{70}MgO_4$

Description: Magnesium stearate is a very fine, light 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.

Molecular Weight: 591.34

Functional category: Tablet and capsule lubricant.

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

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 produce a laxative effect or mucosal irritation.

Applications in Pharmaceutical Formulation or Technology:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as an lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

4.8 PURIFIED TALC[30]

Synonyms: Hydrous magnesium calcium silicate; hydrous magnesium silicate; powdered talc; purified French chalk; Pure talc; soapstone; steatite; Superiore.

Empirical formula and molecular weight: Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6 (Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

Functional category: Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications: Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties. Talc was once widely used in oral solid dosage formulations as a lubricant and diluent.

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

Incompatibilities: Incompatible with quaternary ammonium compounds.

5. MATERIALS AND METHODS

5.1 MATERIALS USED

Tab 5.1 shows list of material used for this proposed work

Sno	**Name of the material**	**Source from**
1	Esomeprazole	Mylan, Hyderabad.
2	Xanthum gum	Serin Formulations pvt.ltd
3	Guar gum	Mylan, Hyderabad.
4	Pectin	(Standard chemicals
5	Microcrystalline cellulose	Standard chemicals
6	PVP K30	Standard chemicals
7	Talc	Standard chemicals
8	Magnesium stearate – Lubricant	Standard chemicals

Table 5.2 List of Instruments/equipments used.

Equipments	Modified/Manufacturer
Double rotary tablet compression machine	Karunavati Pvt Ltd., Rajasthan (RIMEK minipress)
Hardness tester, Pfizer	Mitutoyo South Asia Pvt Ltd., New Delhi
Friabilator	Roche Friabilator
pH meter	Shankar Scientific, Chennai
Dissolution Apparatus	Lab india disso-2000
Double beam spectrophotometer	Shimadzu Scientific Instruments, Japan
FT-IR Spectrophotometer	Shimadzu Scientific Instruments, Japan

5.2 Formulation table for design of Sustained release tablets of Esomeprazole:

Table no: 5.3 : Design of Sustained release tablets of Esomeprazole

Formulation code / compositions	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**	**F8 (mg)**	**F9 (mg)**	**F10 (mg)**	**F11 (mg)**	**F12 (mg)**
Esomeprazole	20	20	20	20	20	20	20	20	20	20	20	20
Xanthum gum	10	20	40	60	-	-	-	-	-	-	-	-
Guargum	-	-	-	-	10	20	40	60	-	-	-	-
Pectin	-	-	-	-	-	-	-	-	10	20	40	60
Microcrystalline cellulose	63.8	53.8	33.8	13.8	63.8	53.8	33.8	13.8	63.8	53.8	33.8	13.8
PVP K30	5	5	5	5	5	5	5	5	5	5	5	5
Talc	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Magnesium stearate	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Total	100	100	100	100	100	100	100	100	100	100	100	100

5.2.1 Formulation of Esomeprazole matrix tablets:

The matrix tablets were prepared by following the General Methodology as given below:

- The procedure followed was direct compression.
- The drug and all the excipients except magnesium stearate and talc were weighed appropriately and were passed through sieve no.30.
- Magnesium stearate and talc were passed through mesh no.60.
- All the ingredients were mixed thoroughly in a polythene bag and compressed to a tablet.

5.3 EVALUATION OF BLEND CHARECTERISTICS

5.3.1 Pre compression characteristics of Esomeprazole matrix tablets

5.3.1.1 Drug and excipients compatibility studies

FTIR spectroscopy was carried for pure drug and polymers to know any chemical interactions between polymers and drug. The samples of pure drug, polymers and physical mixture of drug and polymers were dispersed in 200 mg of KBr powder and compressed into pellets at a pressure of 6000 kg/cm^2 and analyzed. Spectral measurements were obtained by powder diffuse reflectance on a FT-infrared spectrophotometer (Shimadzu, FT-IR, Japan) in the range 4000 – 400 cm-1.

5.3.1.2 ANGLE OF REPOSE:

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal plane.

$$\theta = \tan^{-1} (h/r)$$

Where, h = height

r = radius

θ = angle of repose

Procedure:

- 20gms of the sample was taken
- The sample was passed through the funnel slowly to form a heap.
- The height of the power heap formed was measured
- The circumference formed was drawn with a pencil on the graph paper.
- The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

5.3.1.3. COMPRESSIBILITY INDEX:

The flow property was also determined by measuring the compressibility index (I) (flowability). A simple indication of the case with which a material can be induced to flow is given by application of a compressibility index (I) given by equation.

$$I = [1 – (V/V_0)] \times 100$$

Where 'V' the volume occupied by a sample of the power after being subjected to a standardized tapping procedure (after 500 vibrations) and 'V_0' in the volume before tapping.

Procedure:

1. 10gms of the final blend was taken in a 50 ml – measuring cylinder.
2. Measured the initial volume before tapping of the three measuring cylinder.
3. After 500 tapings, occupied volume was determined for the measuring cylinder.
4. The compressibility index (I) was determined by using above equation.

5.3.2 Evaluation of post compression characteristics:

The following evaluation of tablets was performed.

- Weight variation
- Hardness
- Friability
- Content uniformity

5.3.2.1 WEIGHT VARIATION

The USP weight variation test was run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets met the USP test that was no more than 2 tablets were outside the percentage limit and no tablets differed by more than 2 times the percentage limit.

5.3.2.2 HARDNESS

Hardness of the tablets was determined by breaking it between the second and third fingers with thumb being as a fulcrum. There was a sharp snap the tablet was deemedto have acceptable strength.

Hardness of the tablets are also determined by Stokes Monsanto Hardness Tester and the hardness should be found within the range of 3.5-5.5 kg/cm².

5.3.2.3 FRIABILITY

The friability of tablets was determined by Roche friabilator. 20 tablets were taken and weighed. After weighing the tablets were placed in the Roche friabilator and subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25RPM /100 revolutions by dropping the from a distance of six inches with each revolution .after operation the tablets were deducted and reweighed .

Friability is determined by

$$F=100(1-W_o/Wt)$$

Where,

W_o= wt. of tablets before friability test.

Wt= wt. of tablets after friability test.

5.3.2.4 CONTENT UNIFORMITY

Five tablets were weighed and powdered, 10 mg of equivalent of Esomeprazole was weighed and dissolved in suitable quantity of methanol, the solution was filtered suitably diluted and the drug content was analyzed using UV spectrometer at 300nm.

Table no 5.4: WEIGHT VARIATION TOLERANCE FOR UNCOATED TABLETS

S.No.	Average weight of tablets (mg)	Maximum percentage difference allowed
1	130 or less	10
2	130 to 324	7.5
3	More than 324	5

5.4.1 IN -VITRO DISSOLUTION STUDIES OF ESOMEPRAZOLE SUSTAINED RELEASED TABLETS:

- **Apparatus II (Paddle Method)**

The same equipment as in apparatus I was used, expected that a paddle replaced the basket, formed from a blade and a shaft as a stirring element. The dosage form was allowed to sink to the bottom of the flask before stirring. A constant temperature of 37±0.5 ºC was maintained. The motor was adjusted to turn at the specified speed of 50rpm, and the samples of the fluid were withdrawn at intervals to determine the amount of drug in solution.

- **DISSOLUTION OF ESOMEPRAZOLE SUSTAINED RELEASE TABLETS**.

The dissolution test was carried out using USP apparatus II (Lab india disso-2000).Stirring speed was maintained at 50rpm. 6.8 pH phosphate buffers were used as dissolution medium (900ml) and were maintained at 37±0.5c. Samples of specified volume were withdrawn at predetermined time intervals, filtered, dilute suitably and assayed spectrophotometrically. An equal volume of fresh medium was immediately replaced to maintain the dissolution volume. The sample was analyzed spectrophotometrically at 300 nm. Using spectrophotometer to assay the amount of Esomeprazole released at each time interval.

5.5 KINETIC MODELS

Release Kinetics

To analyses the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted in to Zero order and First order model. In this by comparing the R-values obtained, the best-fit model was selected.

Zero Order Kinetics

This model describes the system where the release rate is independent of the concentration of the dissolved species.

This following relation can in a simply express this model.

$$Qt = Qo + Kot$$

Where, Qt= Amount of drug dissolved in time t,

Qo = Initial amount of drug in the solution and

Ko = Zero order release constant.

First Order Kinetics

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

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

$$\log Q_t = \log Q_o + K_1 t / 2.303$$

Where,

Q_t = Amount of drug released in time t,

Q_o = Initial amount of drug in the solution and

K_1 = First order release constant.

Higuchi Model

A large number of modified release dosage form contain some sort of matrix system. In such instances, the drug dissolves from the matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled) and thus the following relationship applies as formula:

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

Where Q is the percent of drug release at time t, and k_2 is the diffusion rate constant

In higuchi model, a plot of % drug released versus square root of time is linear.

5.6 STABILITY STUDIES

Short term stability studies were carried out the optimized (F8) formulation Adequate number of tablets were filled in amber colored rubber Stoppard bottles and reserve in stability compartment maintained at temperature at 40 ± 2ºC / 75 ± 5% RH for three months were analyzed regularly, for their physical appearance, friability, drug content, and *in-vitro* drug release.

6. RESULTS AND DISCUSSION

PREFORMULATION STUDIES

Table no: 6.1 pre-formulation study results of Esomeprazole

S.No.	Test	Specification	Results
1.	Organoleptic properties		
	Color	White to off-white	White to off-white
	Odor	Odorless	Odorless
	Nature	Amorphous	Amorphous
2.	Solubility	slightly soluble in water	Slightly soluble in water
3.	LOD	NMT 0.5% of its weight	0.25%
4.	Melting Point	155° C	155° C
5.	Assay	NLT 98.0% and NMT 102.0%	99.86%
6.	Particle size analysis	3-5mm	4mm

DISCUSSION:

The description of the drug was observed visually. The solubility data reveals that the drug is freely soluble and is a member of class III drugs according to the BCS classification.

The LOD data was observed indicating that the API is non-hygroscopic. The melting point of the Esomeprazole was performed using melting point apparatus. The particle size analysis was performed by microscopic method.

Flow properties of Esomeprazole:

Table no: 6.2 Flow properties of Esomeprazole

S.No.	Parameter	Results
1.	Bulk density (gm/cc)	0.55 gm/cc
2.	Tapped Density (gm/cc)	0.64 gm/cc
3.	Compressibility Index(%)	16.36%
4.	Hausner's Ratio	1.16

DISCUSSION:

The Flow indices Hausners ratio and Compressibility index shows that API has good flow. Consequently direct compression was followed for the manufacture of Matrix release tablets.

Drug and excipients compatibility studies

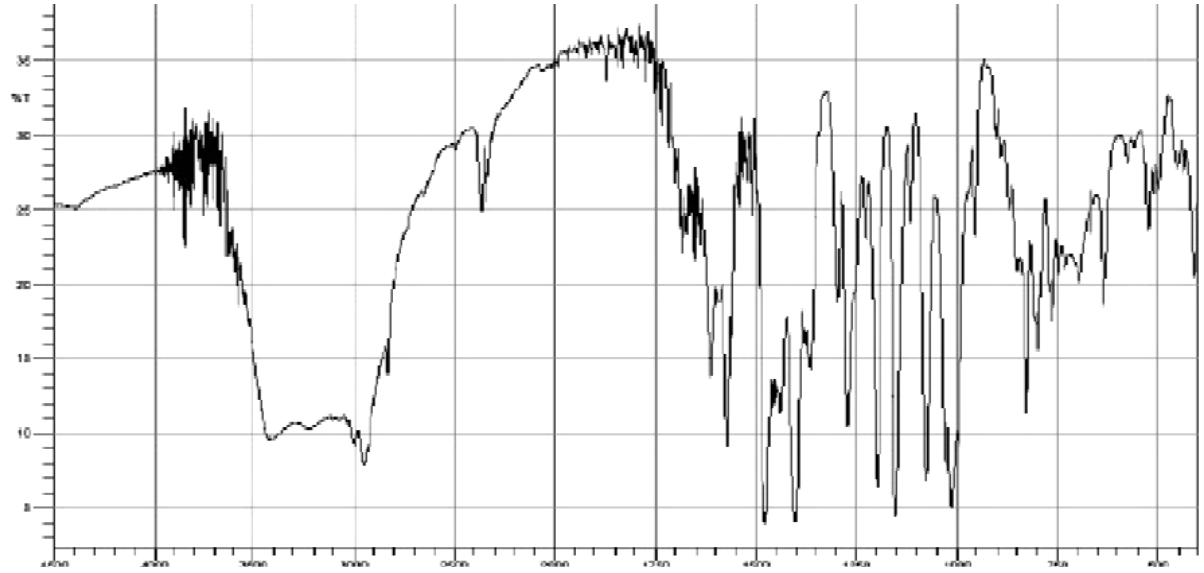


Figure 6.1 FTIR spectra of pure Esomeprazole

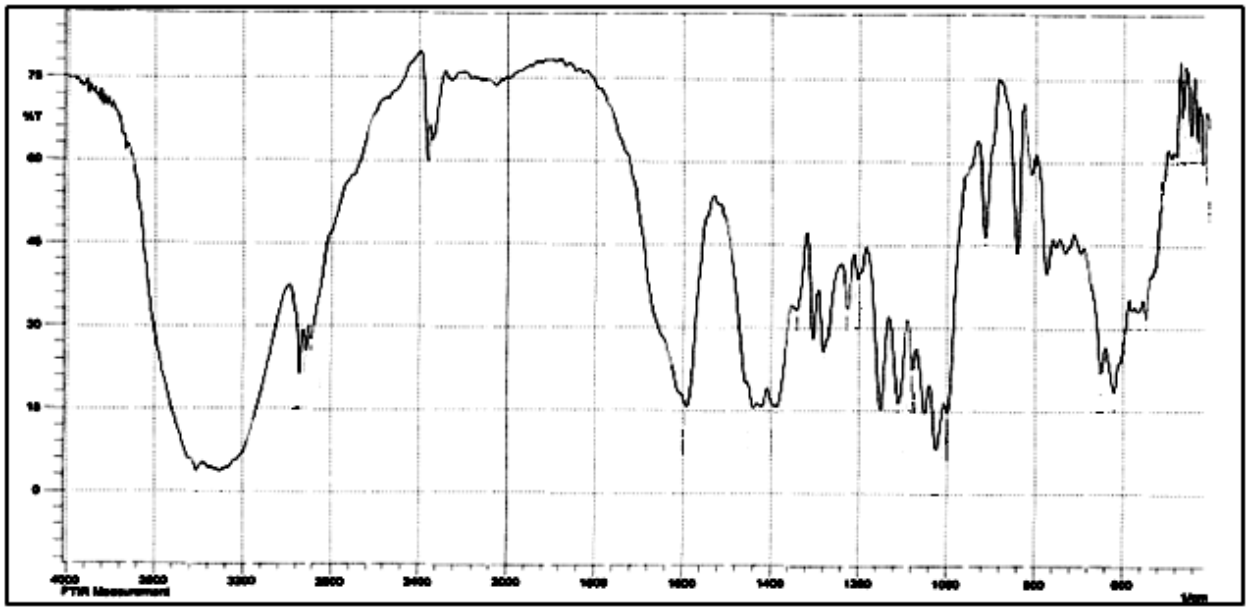


Figure 6.2 FTIR spectra of pectin

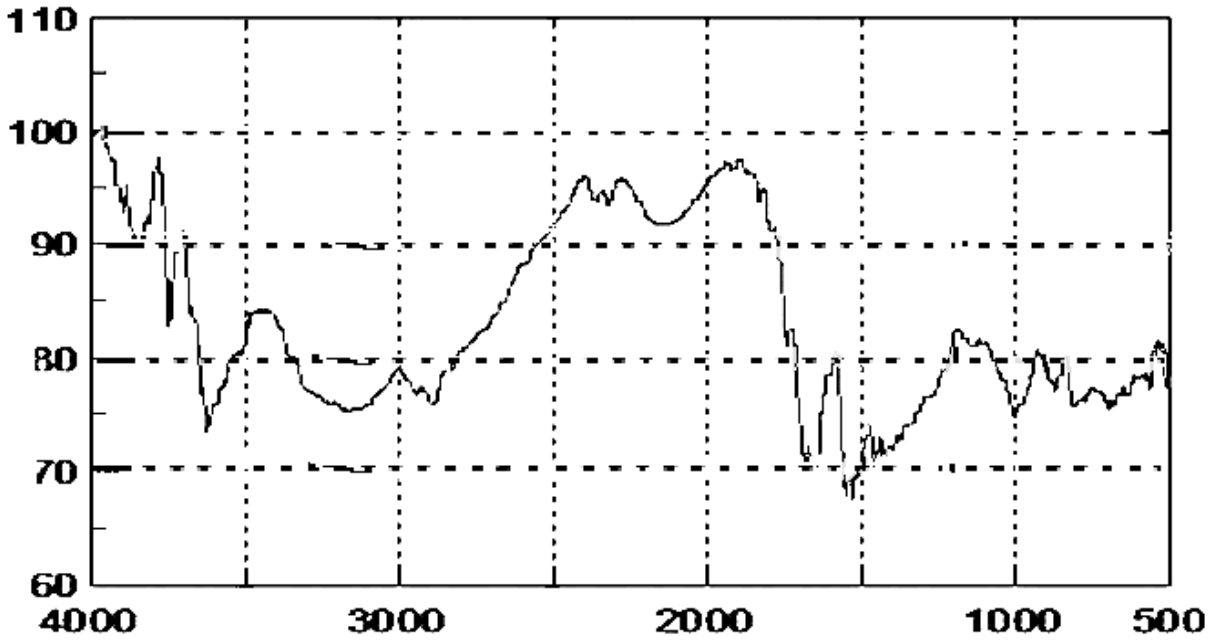


Figure: 6.3 FTIR spectra of guar gum

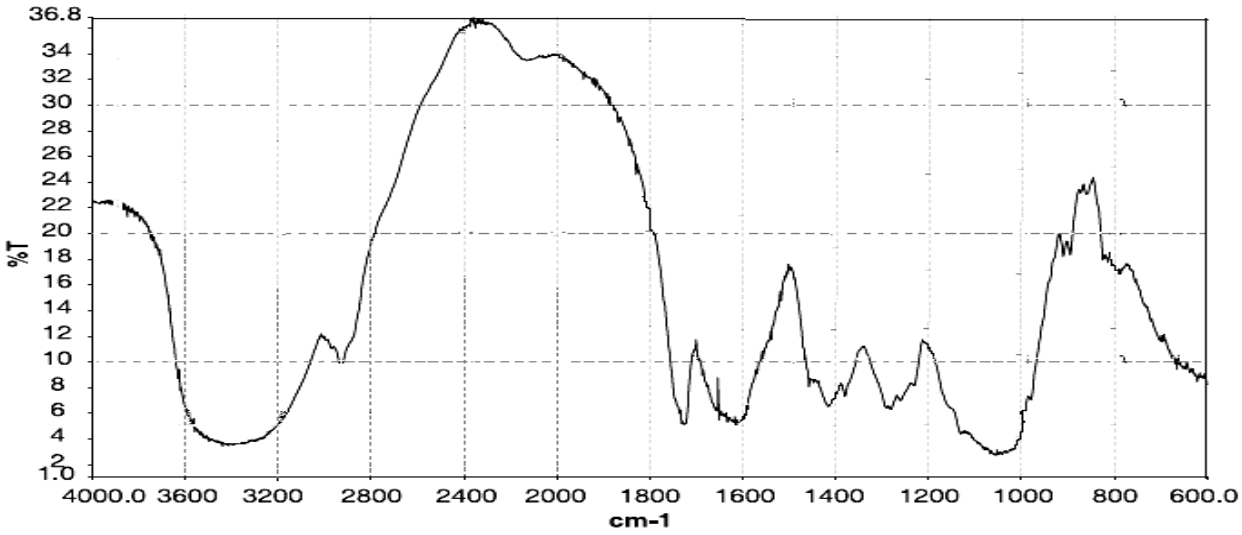


Figure:6.4 FTIR spectra of xanthan gum

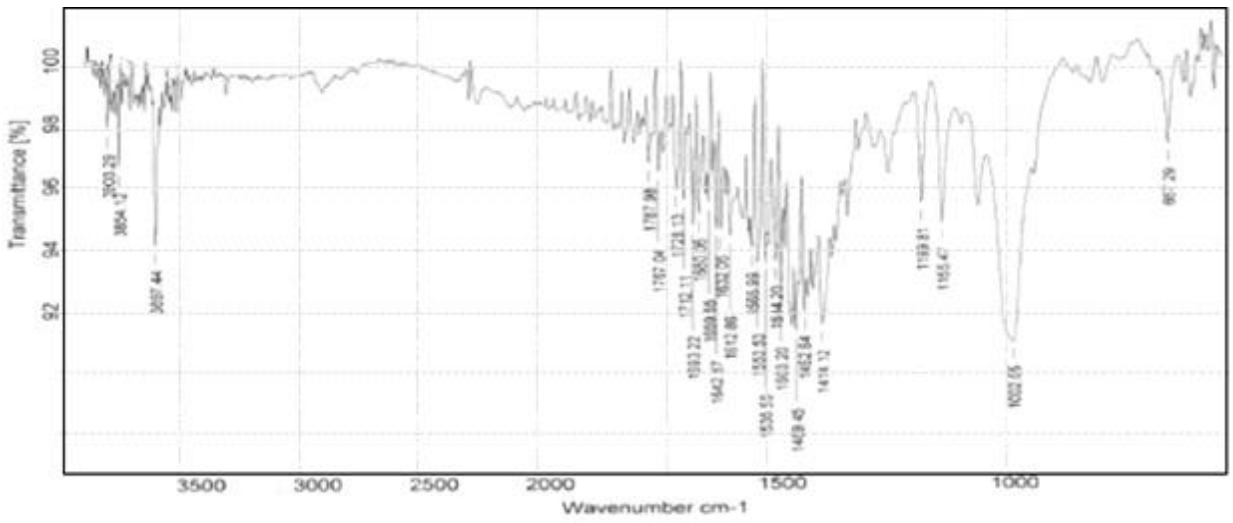


Figure:6.5 FTIR spectra of physical mixture of Esomeprazole and polymers

DISCUSSION

FT-IR spectra of the pure drug shown in figure 6.1. The broad peak at 3897.44cm^{-1}in the spectra of the pure drug corresponds to N-H (stretching). The peak at 1002.05 cm^{-1}corresponds to S=0 (stretching), the peak at 1155.47cm^{-1} for C-O-C (stretching). The drug and polymers employed were found to be compatible as similar peaks were observed with minor differences shown in figure 6.5

Preparation of calibration curve for Esomeprazole:

1 gm of Esomeprazole was dissolved in 100 ml of pH 6.8 buffer by slight shaking (1000 mcg/ml). From the stock solution, suitable serial dilutions were made to get the concentrations of 1, 3, 5, 7 and 9 μg/ml in pH 6.8 phosphate buffer solutions.

The absorbance of these solutions were measured at 300 nm and standard plot was drawn using the data obtained.

Table no 6.3: Calibration curve of Esomeprazole

Sl.No.	Concentration (µg/ml)	Absorbance (λ_{max} =300nm)
1.	1	0.035
2.	3	0.110
3.	5	0.191
4.	7	0.280
5.	9	0.367

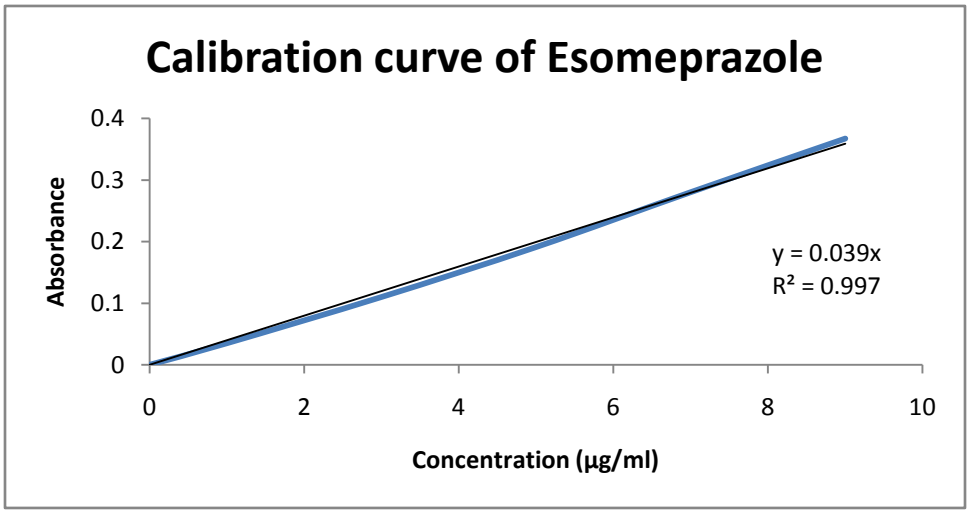


Fig.no:6. 6 : Calibration curve of Esomeprazole

Tab 6.4: Results of pre formulation evaluation

Formulation code/Parameter	Bulk density	Tapped density	Angle of repose	Compressibility index	Hausners ratio
F1	0.462 ±0.01	0.591±0.06	26.06±0.12	21.8	1.25
F2	0.469±0.01	0.561±0.02	25.42±0.98	21.39	1.19
F3	0.46±0.02	0.55±0.01	22.62±0.28	16.36	1.19
F4	0.59±0.05	0.68±0.04	29.19±1.20	13.04	1.15
F5	0.49±0.06	0.57±0.07	27.40±1.21	14.04	1.16
F6	0.48±0.02	0.55±0.06	26.06±0.90	12.72	1.14
F7	0.46±0.02	0.53±0.06	24.38±1.21	13.20	1.15
F8	0.43±0.04	0.49±0.04	23.72±1.23	12.24	1.14
F9	0.41±0.03	0.47±0.01	21.94±2.12	12.76	1.14
F10	0.39±0.02	0.44±0.02	20.48±1.33	11.36	1.12
F11	0.55±0.21	0.64±0,02	26.21±1.78	14.06	1.16
F12	0.53±0.02	0.61±0.02	25.74±1.23	13.11	1.15

All values are expressed as Mean±SD

DISCUSSION

The λ max of Esomeprazole in 6.8 pH phosphate buffer was scanned and found to have the maximum absorbance at 300 nm. Standard graph of Esomeprazole in 6.8pH phosphate buffer was plotted and regression was 0.997.

The formulations were prepared with natural polymers like xanthum gum, guar gum and pectin and then evaluated.

The angle of repose values obtained for the formulations ranged from 20.48 to 27.40 this indicates good flow property of the powder blends.

The compressibility index values for the formulations ranged from 11.36 to 21.8. This also indicates the powder blend have good flow property.

Tab 6.5: Results of post compression evolution

Formulation code/Parameter	**Hardness(units)**	**Weight variation**	**Friability (%)**	**Content uniformity**
F1	3.0±0.02	Pass	0.18±0.02	99.17±1.5
F2	3.1±0.03	Pass	0.22±0.02	99.44±1.2
F3	3.0±0.71	Pass	0.43±0.04	98.64±2.8
F4	3.2±0.03	Pass	0.20±0.02	99.42±3.1
F5	3.0±0.06	Pass	0.19±0.08	99.17±2.8
F6	3.0±0.04	Pass	0.22±0.06	99.44±2.0
F7	3.0±0.03	Pass	0.45±0.04	99.64±2.6
F8	3.1±0.02	Pass	0.24±0.02	100.2±3.2
F9	3.2±0.01	Pass	0.38±0.04	99.89±4.2
F10	3.2±0.03	Pass	0.12±0.04	99.97±3.2
F11	3.1±0.04	Pass	0.24±0.02	99.24±2.1
F12	3.0±0.04	Pass	0.16±0.03	99.62±1.2

All values are expressed as Mean±SD

DISCUSSION

The total weight of each formulation was not maintained uniformly however the weight variation of the tablets within the limits of 5%.

The measured hardness of tablets in all batches was ranged from 3.0 – 3.2 kg/cm^2.

Friability values were found to be less than1% in all prepared formulations and considered to be satisfactory.

Tab 6.6: *in vitro* evaluation percentage of drug results

Time (hr)	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)	F6(%)	F7(%)	F8(%)	F9(%)	F10(%)	F11(%)	F12(%)
1	42±1.2	43±2.2	31±1.1	32±1.8	42±2.4	33±2.1	26±1.5	22±1.8	46±1.9	44±1.0	36±2.4	32±2.6
2	54±1.0	54±2.8	43±1.2	38±1.4	56±3.3	43±2.0	38±1.7	32±4.3	57±2.2	58±1.1	43±1.7	41±2.2
4	65±3.1	61±2.2	52±1.4	46±1.7	61±3.4	57±4.8	46±1.1	41±2.2	67±3.3	66±1.3	55±1.3	51±2.0
6	72±2.9	69±2.6	64±1.0	58±2.1	68±3.3	65±3.2	52±1.2	48±1.2	76±2.1	72±2.2	67±2.4	63±2.8
8	86±2.2	76±2.4	67±1.9	66±2.2	75±3.9	72±2.1	64±2.1	56±3.1	93±1.8	86±2.8	74±3.2	69±1.8
10	92±1.1	84±2.9	82±1.1	72±2.8	86±3.5	83±2.2	76±2.9	62±3.4	98±1.2	95±3.1	85±3.8	82±1.4
12	97±3.2	93±3.0	89±1.3	85±2.2	93±2.2	89±3.5	83±2.7	69±2.8		98±2.1	92±2.1	89±3.1
14		98±3.8	93±1.8	92±2.3	98±0.1	94±3.3	88±2.2	74±1.2			94±0.8	93±3.3
16			98±1.8	94±2.9		98±3.2	92±2.1	82±1.1			98±1.8	95±2.3

18				97±1.1			95±0.2	90±0.4				97±2.1
20							98±1.1	93±1.9				
22								97±0.9				
24								99±1.0				

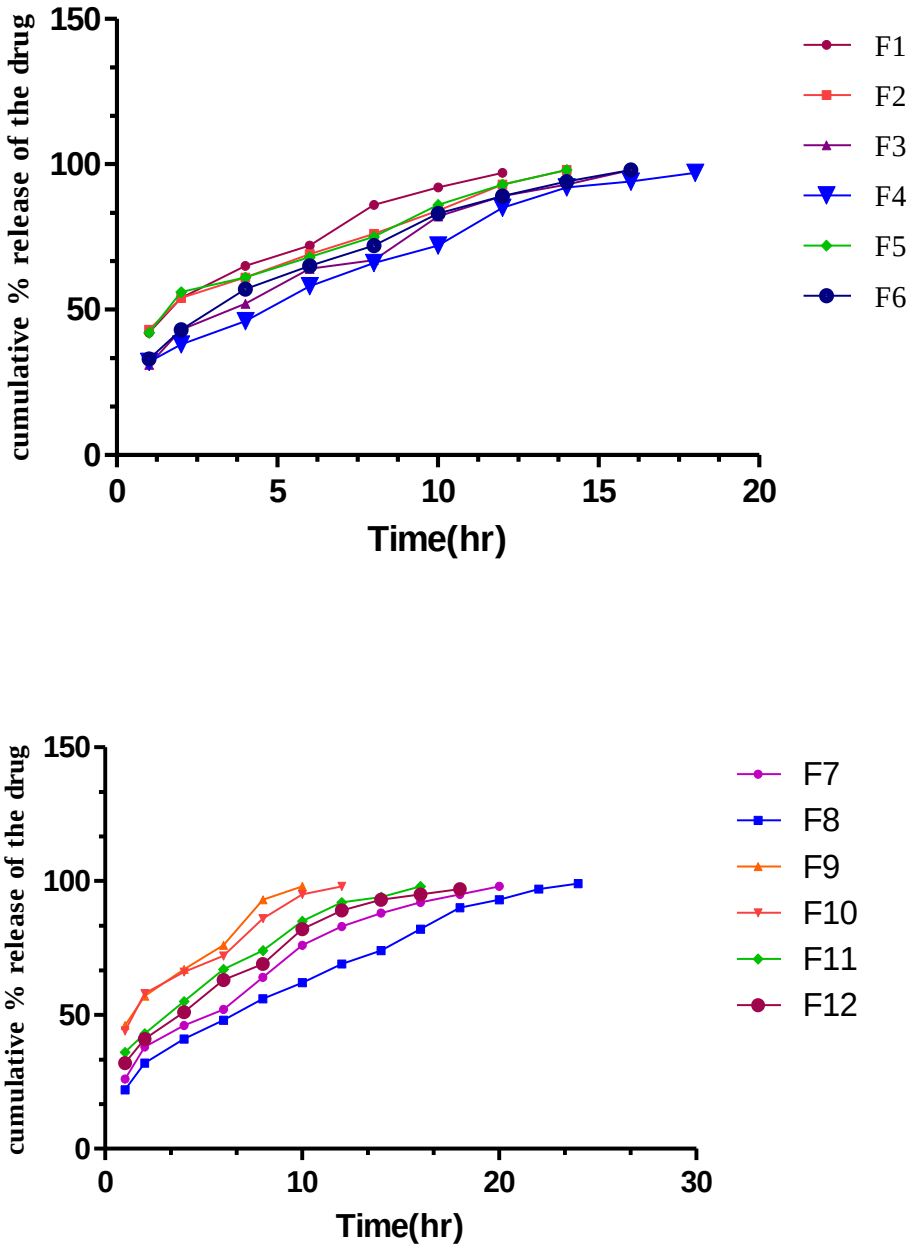


Fig.no:6. 7 : *invitro* cumulative percentage of drug release

Tab 6.7 shows release kinetic pattern of formulations

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Zero-order (R^2)	0.496	0.417	0.667	0.698	0.417	0.609	0.705	0.775	0.529	0.449	0.589	0.612
First order (R^2)	0.959	0.9	0.966	0.939	0.905	0.973	0.975	0.981	0.925	0.94	0.977	0.983
Higuchi order (R^2)	0.949	0.924	0.984	0.983	0.921	0.982	0.989	0.995	0.948	0.931	0.979	0.988

DISCUSSION

In vitro drug release profiles for all formulations were carried out by using 6.8pH phosphate buffer as dissolution medium for about 24 hrs.

From the above results it was found that the release of drug from formulation F8 which was composed of Guargum at 60 mg gave the better release, drug content, friability, hardness than other formulations.

The drug release from all the formulations were followed Higuchi model (Table 6.7). The Correlation Coefficients (r2) for the Higuchi model of drug release for the formulations are in the range of 0.921 to 0.995. The Higuchi plot between amounts of drug released as a function of the square root of time. The amount of drug released from the formulation F6, F7 and F8

increased linearly with the square root of time indicating that the diffusion of drug from the tablets, which is affected by the porosity and tortuosity of the matrix may be the rate-limiting step in the release of Esomeprazole from SR tablets.

Tab 6.8 Stability studies of optimized formulation(F8)

Parameters	**1st month**	**2nd month**	**3rd month**
Physical appearance	No Change	No Change	No Change
Friability	0.25±0.04	0.33±0.09	0.34±0.07
Drug content	101.70±0.47	99.63±0.116	99.13±0.101
In-vitro drug release	99.57±0.53	100.49±0.55	99.43±0.79

All values are expressed as Mean±SD

DISCUSSION

The stability study results of optimized formulation F8 reflect that there is no significant change in physical appearance, friability, drug content and dissolution profile of the formulation. Hence, it concludes that the tablets from this formulation are stable for the period 3 months at 40 ±2°C.

7. SUMMARY AND CONCLUSION

Esomeprazole is a proton pump inhibitor used in dyspepsia. The approach of the present study was to make a comparative evaluation among concentration of Natural polymers like xanthum gum, guar-gum and pectin and to assess the effect of physico-chemical nature of the active ingredients on the drug release profile.

The angle of repose, compressibility index and sieve analysis results shown that the formulation is suitable for direct compression.

This study have been showed that Esomeprazole could be used in sustained release drug delivery system by formulating it has sustained drug delivery system, provides extended duration of action in therapeutic range without reaching toxic levels as in the case of conventional dosage forms. These dosage forms have the ability to reduce the dosing frequency and increasing.

The technique employed in the preparation of matrix system i.e. direct compression, is highly practical and economical from the industry point of view.

The sustainability of the drug with Guar gum as a sustaining polymer at a concentration of 60 mg was found to show good sustainability when compared to the all other formulation, as it showed 99% drug release for 24 hrs.

The optimized formulation dissolution data was subjected to release kinetics; from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release

Success of the *In vitro* drug release studies recommends the product for further *In vivo* studies, it may improve patient compliance.

8. REFERENCES

1. Yie.W.Chien, "Novel Drug Delivery System, 2nd ed., revised and expanded,Pg. 89-129

2. Robinson JR, and Lee, 22nd Ed., New York Controlled Drug Delivery Fundamentals and Applications Pg.67-108

3. D.M.Brahmankar and Sunil B.Jaiswal, Biopharmaceutics and Pharmacokinetics A Treatise", Pg.335-350

4. Robert E. Nortari, "Biopharmaceutics and pharmacokinetics An Introduction" 4th edn revised and expanded, Pg. 208

5.S.P Vyas, Roop K.Khar, Controlled Drug Delivary Concepts and Advances",Pg 155-158

6.Milo Gibaldi and Donald Perzier, Pharmacokinetics, 2nd edn, revised and expanded, Pg.15,185

7.Lisa Brannan-Peppas,Polymers in Controlled Drug Delivary",Pg.1-9

8. Uttam Mandal, Veeran Gowda, Animesh Ghosh, Senthamil Selvan, Sam Solomon And Tapan Kumar Pal, Bioequivalence Study Centre, Department of Pharmaceutical Technology, Jadavpur University.Pg. 342-7.

9. Syed Nisar Hussain Shah, Sajid Asghar, Muhammad Akram Choudhry, Muhammad Sajid Hamid Akash , **"**Formulation and evaluation of natural gum-based sustained release matrix tablets of flurbiprofen using response surface methodology" Drug Development and Industrial Pharmacy 2009, Pg.1470-1478.

10.Vinayak Dhopeshwarkar, Janet C. O'Keeffe, Joel L. Zatz, Robert Deete and And Michael Horton, Development of An Oral Sustained-Release Antibiotic Matrix Tablet Using In-Vitro/In-Vivo Correlations, Drug Development and Industrial Pharmacy, 1994,Pg.1851-1867.

11. John W. Skoug, Martin V. Mikelsons, Cynthia N. Vigneron and Nick L. Stemm "Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms by measurement of polymer release" Control Development, April-1993, Pg.185-189

12. Ayhan Savaşer, Yalçın Özkan and Aşkın Işımer, **"**Preparation and in vitro evaluation of sustained release tablet formulations of diclofenac sodium" Department of Pharmaceutical Technology, Gülhane Military Medical Academy, Etlik, 06018 Ankara, Turkey. October-2008,

13. P.G.Yeole, U.C.Galgatte, I.B.Babla, "Design and evaluation of xanthan gum based sustained release matrix tablets of diclofenac sodium" International Journal of pharmaceutical sciences.2006.

14. D.M. Morkhade, S.V. Fulzele, "Gum Copal and Gum Damar: Novel Matrix forming Materials for Sustained Drug delivery", International Journal of pharmaceutical sciences.2006,Pg. 53-58.

15. Umit Gonullu, Melike Uner, Gulgun Yener, "introduction of sustained release Opipramol Di hydrochloride matrix tablets as a new approach in the treatment of depressive disorders", International Journal of Biomedical science,Pg.337-343.

16. A.K.Srivastava, Saurabh wadhwa, B.mishra, "Oral sustained delivery of Atenolol from floating matrix tablets - formulation and in vitro evaluation." Drug development and industrial pharmacy,Pg. 337-343.

17. Phaechamud T, Mohammad Siahi, Mohammad Barzegar-Jalali, Farnaz Monajjemzadeh, Fatemeh Ghaffari Shirzad Azarmi , "Design and evaluation of 1- and 3-layer matrices of verapamil hydrochloride for sustaining its release", AAPS PharmSciTech, Pg.925-34.

18. Singh Brahma N, Kim Kwon H. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *Journal of Controlled release.* 2000; Pg.63:235-259.

19. Xiao Qiang Xu, Minije Sun, Feng Zhi, Yiqiao Hu. Floating matrix dosage form for phenoporlamine HCL based on gas forming agent: *In vitro* and *in vivo* evaluation in healthy volunteers. *Int J Pharm.* 2006; Pg.310:139-145.

20. Sunthongjeen Srisagul, Sriamornsak Pornsak, Puttipipatkhachorn Satit. Design and evaluation of floating multi-layer tablets based on gas formation. *Eur. J Pharm and Biopharm* 2008; Pg.69:255-263.

21. Baumgartner Sasa, Kristl Julijana, Vrecer Franc, Vodopivec Polona, Zorko Bojan. Optimization of floating matrix tablets and evaluation of their gastric residence time. *Int J Pharm.* 2000; Pg.195:125-135.

22. Streuble A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder; effects of formulation and processing parameters on drug release. *Euro. J Pharm Sci.* 2003;Pg. 18:37-45.

23. Talwar Naresh, Sen Himardi,Staniforth John N. Orally Administered controlled drug delivery system providing temporal and spatial control. 1998.

24. Jaimini M, Rana A.C, Tanwar Y.S. Formulation and Evaluation of Famotidine floating tablets. *Current Drug delivery,* 2007; Pg.4:51-55.

25. Khalil et al formulation and evaluation of bilayer matrix tablets of amoxicillin and esomeprazole as an oral modified release dosage form for treatment of peptic ulcer Int J Pharm Pharm Sci, 2014 Vol 6, Issue 3, Pg.134-142

26. A K L Kabir ,T Jesmeen, B K Biswas ,A S S Rouf. et al Formulation and in vitro evaluation of esomeprazole magnesium hydrophilic matrix SR tablet Turk J Pharm Sci 2009;Pg.6(1):1-10

27. 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) 2017;Pg. 6 (2):1246-53.

28. Padmaja udaya Shankar, Text book of medical Pharmacology, CBS publishers,2nd edn Pg.196-209.

29. R.S.Satoskhar. Pharmacology and pharmacotherapeutics, popular prakashan, revised 18th edn Pg.629.

30. Raymond, C.; Rowe.; Paul J Sheskey.; Mariue E Quinn.; Handbook of Pharmaceutical Excipients. Pharmaceutical press: London. 6th ed. **2006, Pg.**782-785 (Xanthan gum),Pg. 478-481(Pectin), Pg.404-407 (Magnesium Stearate).

31. Andersson T, Hassan-Alin M, Hasselgren G, *et al*. 2001. Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. *Clin Pharmacokinet.* 40 (6): 411-26.

32. Augsburger LL, Shangraw RF, Giannini RP, Shah VP, Prasad VK, Brown D. 1983. Thiazides VIII: Dissolu-tion Survey of marketed Hydrochlorothiazide tab-lets. *J. Pharm. Sci*. 72(8): 876-881.

33.Aulton ME. 1988. Pharmaceutics: The Science of Dosage Form Design, 1st edition, LBS/Churchill Living-stone, Edinburgh. pp. 171.

34.Ayres JW, Huang H, Albert K. 1984. Effect of polymer in sustained release matrix tablet. J. Pharm. Sci. 73: 1629.

35.Fitton A, Wiseman L. 1996. Pantoprazole: a review of its pharmacological properties and clinical efficacy in the management of acid-related disorders. *Drugs.* 51 (3): 460-82.

36.Goodman and Gilman's 2001. The Pharmacological Basis of Therapeutics. 10th edition. McGraw-Hill Medi-cal Publishing Division, pp.644-646.

37.Haider SS, Ahsan GM. 2001. Dissolution profiles of commercially available enteric coated tablets of non steroidal anti inflammatory drugs. J. Bangladesh Acad. Sci. 25(2): 149-155.

38.Longer MA, Robinson JR. 1990. Sustained Release Drug Delivery System, Martindale, 32nd Edition, the 'Complete Drug Reference' 2002. p.1225

39.Remington's Pharmaceutical Science, Chapter 91, 18th edition, pp.1676-1690. Sungthongjeen S, Pitaksuteepong T, Somsiri A, Sria-mornsak P. 1999.

40.Studies on pectins as potential hydrogel matrices for controlled-release drug deli-very. Drug. Dev. Ind. Pharm. 25(12): 1271-1276.

41.United States Pharmacopeia XXIII and National Formulary XVII. 1995. United States Pharmacopeia Convention, Inc., Rand McNally, Taunton, p.1950.

42.Vakil N, Fennerty MB, 2003 Direct comparative trials of the efficacy of proton pump inhibitors in the man-agement of gastro-oesophageal reflux disease and peptic ulcer disease *Aliment Pharmacol Ther,* 18 :559–68.

43.Jantzen GM, Robinson JR, Sustained and controlled-release drug delivery systems, inBanker GS, Rhodes CT (Eds.) Modern Pharmaceutics, 3rd Ed, Revised andExpanded, Drugs and the Pharmaceutical Sciences., Marcell Dekker, Inc. NewYork. 1995; 72: 575-609.

44.Jantzen GM, Robinson JR. Sustained and Controlled- Release Drug Delivery systems Modern Pharmaceutics, 4thed; 2003; 121: 501-502

45.Gwen MJ, Joseph RR, In Banker GS and Rhodes CT, Ed. Modern Pharmaceutics, 3rdEd Marcel Dekker Inc. New York. 1996; 72: 575.

46.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.

47.Kumar KP et al. Innovations in Sustained Release Drug Delivery System and Its Market Opportunities. J Chem Pharm Res. 2010; 2 1: 349-360.

48.ieberman HA, Lachman L, Schwartz JB., Pharmaceutical Dosage Forms: Tablets, 2011; 3 (2): 199-287.

49.Gilard M, Arnuad B, Cornily JC, et al "Influence of Omeprazole on the Antiplatelet Action of Clopidogrel *Journal of the American College of Cardiology.* 2008;51(3) 256-260.

50.Jantzen GM, Robinson JR. Sustained and Controlled- Release Drug Delivery systems Modern Pharmaceutics, 4thed; 2011; 121: 501-502.

51.Laine L, Ahnen D, McClain C, et al "Review Article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors." *Alimentary Pharmacology and Therapeutics.*2000;14:651-668.

52.V. R. Sirisha. K, K. Vijaya Sri, N. Devanna and K. Suresh, Formulation and in vitro evaluation of esomeprazole delayed release beadlets. Indo American Journal of Pharmaceutical Research. 2014; 4(6), 2753-2760.

53.Putta Rajesh Kumar, Hiremath Doddayya and S. Rajendra Reddy. Enteric coated tablets of novel proton pump inhibitor with super disintegrants design, in-vitro evaluation and stability studies. Journal of Applied Pharmaceutical Science. 2011; 1 (6), 106-111.

54.Bhargava.A et al. Oral sustained release dosage form: an opportunity to prolong the release of drug.IntJ ARPB. 2013; 3: 7-14.

55.AstraZeneca Pharmaceuticals LP. Esomeprazole Labeling approved June 2011. Warnings and Precautions Mohammed AD et al. Release of propranolol hydrochloride from matrix tablets containing sodium carboxymethylcellulose and Hydroxypropyl methyl cellulose. Pharm Dev Tech.1999; 4: 313-324.

56.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.

57.Kumar KP et al. Innovations in Sustained Release Drug Delivery System and Its Market Opportunities. J Chem Pharm Res. 2010; 2 1: 349-360.

58.Shimul Halder, Madhabi Lata Shuma, Abul Kalam Lutful Kabir, Abu Shara Shamsur Rouf. In vitro release kinetics study of Esomeprazole Magnesium Trihydrate tablet available in Bangladesh and comparison with the originator brand (Nexium®). S. J. Pharm. Sci. 2011; 4(1): 79-83.

59.Irin Dewan, Sadiya Afrose Jahan, Mahjabeen Gazi, Joydeb Nath, Md. Asaduzzaman, Maksud Al- Hasan. Design, Preparation, Evaluation, Compatibility and Invitro studies of Naproxen and Esomeprazole multilayer tablets: Layer by layer tablet technology. World Journal of Pharmaceutical Research. 2015; 4(6): 472-492.

60.Lakshmi Parvathi, Senthil Kumar Krishnan, Gulzar Ahmed Md, Abdul Naser K, Ramesh B. Formulation and Evaluation of Oral Controlled Release dosage form of Anti-Hypertensive Agent. Journal of Pharmaceutical and Scientific innovation. 2012; 1(6): 31-34.

61.Srinivasulu M, Hindusthan Abdul Ahad, Venupriya R. Formulation and Evaluation of Natural Gum Based Esomeprazole Sustained Released Tablets. 2013; 3(2): 78-83

62.Rajesh Kumar P, Doddayya H, Rajendra Reddy S. Enteric coated tablets of novel proton pump inhibitor with super disintegrants design, in-vitro evaluation and stability studies. Journal of Applied Pharmaceutical Science. 2011; 01 (06); 106-111.

63.Tushar G. Rukari, Ganesh V. Ahire. Formulation and Evaluation of Esomeprazole Delayed Release Tablets. Asian J Pharm Clin Res. 2013; 6 (1), 121-125.

64.Kinam Park.Controlled drug delivery systems: Past forward and future back. Journal of Controlled Release. 2014; 190: 3-8.

65.Kushal M, Monali M, Durgavati M, Mittal P, Umesh S, Pragna S. Oral Controlled Release Drug Delivery System: An Overview. International Research Journal of Pharmacy.2013; 4(3): 70-76.

66.Nagarjuna Naik.R, Laksmano Rao Potti, Rama Kotaiah Mogali, Prasad Rao.M, Sivasankar.R, Beera valli. Formulation and evaluation of esomeprazole magnesium dihydrate multiple unit particulate system (pellets) as a delayed release dosage form. International Journal of Research and Development in Pharmacy and Life Sciences. 2014; 3(2), 935-942