Research Article

Formulation and Evaluation of Sustained Release Tablets of Esomeprazole Using Natural and Synthetic Polymers

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ABSTRACT

The aim of the present study was to develop Sustained release formulation of Esomeprazole to maintain constant therapeutic levels of the drug for over 12 hrs. Here different types of polymers (HPMC K 15M, Xanthan Gum, Carbopol 934) were used. Esomeprazole dose was fixed as 20 mg. Total weight of the tablet was considered as 400 mg. Polymers were used in the concentration of 10, 20 and 30 mg concentration. Whereas from the dissolution studies it was evident that Among all formulations F2 formulation was considered as optimised formulation. It was shown 99.65% drug release at 12hrs. The optimised formulation F2 was followed Higuchi release kinetics.

Keywords: Esomeprazole, HPMC K 15M, Xanthan Gum, Carbopol 934, Sustained release tablets, Natural Polymers, Synthetic Polymers.

1. INTRODUCTION[1-9]

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 first sustained release tablets were made by Howard Press in New Jersy 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

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 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.

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 effect.

1.1. RATIONALE FOR SUSTAINED RELEASE DOSAGE FORMS[10-12]

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.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).

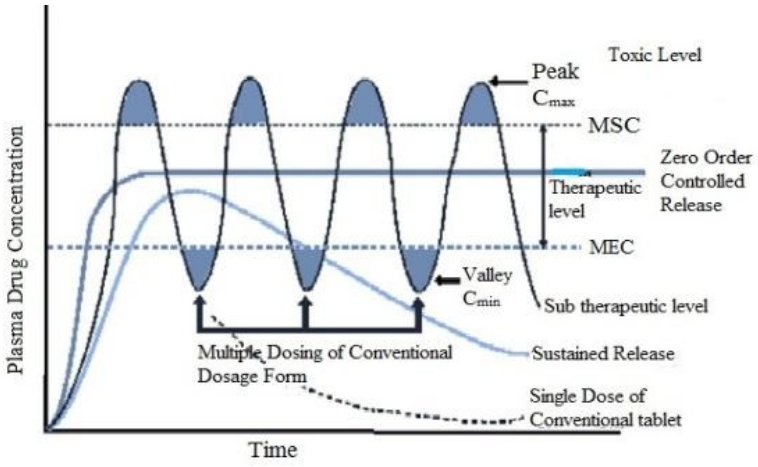

Fig. 1: Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations

1.2. DESIGN AND FORMULATION OF ORAL SUATAINED RELEASE DRUG DELIVERY SYSTEM[14-19]

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance.Sustained (zero-order) drug release has been attempted to be achieved with various classes of sustained drug delivery system:

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.

1.2.1. 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.

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

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.

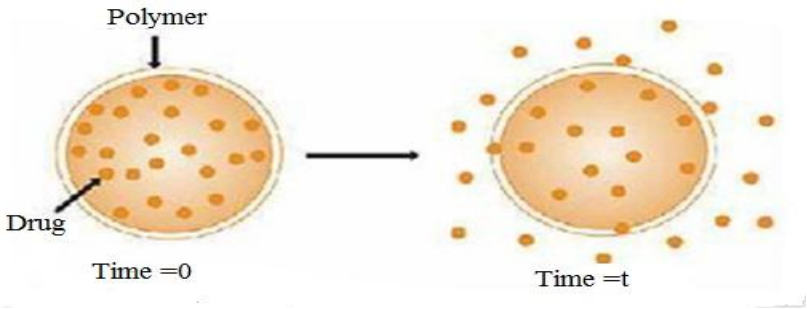

Fig. 2: Schematic representation of diffusion sustained drug release: reservoir system

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:

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

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.
Cs = Solubility of drug in release medium.
T= Tortuosity of the matrix.
A = Concentration of drug in the tablet, as gm/ ml.

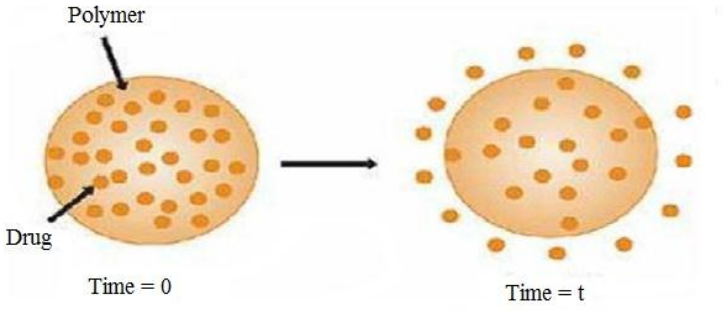

Fig. 3: Schematic representation of diffusion sustained drug release: matrix system

The release rate can be given by following equation.

$$\text{Release rate} = AD / L = [C1 - C2]$$

Where;
A = Area.
D = Diffusion coefficient.
C1 = Drug concentration in the core.
C2 = Drug concentration in the surrounding medium.
L = Diffusional path length.

1.2.2. DISSOLUTION SUSTAINED SYSTEMS: 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. An alternative method is to administer the drug as group of beads that have coating of different thickness. 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.

1.2.3. 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: Resin+ - Drug- + Cl- goes to Resin+- Cl-+ Drug-

Cation Exchangers: Resin-- Drug+ + Na+ goes to Resin- - Na+ + 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.

1.2.4. 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.

1.2.5. pH– Independent Formulations

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. 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.

1.2.6. 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.

1.3. MATRIX TABLETS[9]

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: 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

1.4. 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. DRUG RELEASE FROM MATRIX[23,24]

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 .

2. AIM AND OBJECTIVE

Aim of the Work

Aim of the study is to formulate and evaluate Esomeprazole sustained release tablets using natural and synthetic polymers.

Objective of the Study To improve the bioavailability, reduce the number of doses and to increase patient compliance it was formulated as sustained release tablets.

3.METHODOLOGY

3.1. Analytical method development

a) Determination of absorption maxima

100mg of Esomeprazole pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

(b)Preparation calibration curve

100mg of Esomeprazole pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5,10,15,20 and 25 µg/ml of Esomeprazole per ml of solution. The absorbance of the above dilutions was measured at 266nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

3.2. Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any

spectrum changes.

3.3. Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends.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. The angle of repose was calculated using the following formula:

$$\tan \theta = h / r$$

$\tan \theta$ = Angle of repose

h = Height of the cone , r = Radius of the cone base

Table: 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/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. 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 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. 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: 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

3.4. Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table. 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 400mg

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: Formulation composition for tablets

Formulation No.	Esomeprazole	Xanthan gum	HPMC K 15	Carbopol 934	PVA	Mg. Stearate	Talc	MCC pH 102
F1	20	10	-	-	10	4	4	QS
F2	20	20	-	-	10	4	4	QS
F3	20	30	-	-	10	4	4	QS
F4	20	-	10	-	10	4	4	QS
F5	20	-	20	-	10	4	4	QS
F6	20	-	30	-	10	4	4	QS
F7	20	-	-	10	10	4	4	QS
F8	20	-	-	20	10	4	4	QS
F9	20	-	-	30	10	4	4	QS

All the quantities were in mg

3.5. Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties likeweight 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.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Table: 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
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	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. Preweighed 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 reweighed, loss in the weight of tablet is the measure of friability and is expressed in percentage .

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

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 Phophate buffer
RPM	--	50
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	--	37°c $\pm$ 0.5°c

Procedure

900ml 0f 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°c $\pm$ 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from upto 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 respective 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 ar e fitted to the following equation.

$$F = K_o\, t$$

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

First order release rate kinetics: 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.

$$F = k\, t1/2$$

Where, 'k' is the Higuchi constant.
In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model

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 I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell release model

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

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).

4. RESULTS AND DISCUSSION

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

4.1. Analytical Method

Graphs of Esomeprazole was taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 301 nm and 304 nm respectively.

Table: Observations for graph of Esomeprazole in 0.1N HCl (301nm)

Concentration [µg/ml]	Absorbance
0	0
5	0.12
10	0.248
15	0.361
20	0.482
25	0.61

It was found that the estimation of Esomeprazole by UV spectrophotometric method at λ_{max} 301 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5-25µg/ml. The regression equation generated was y = 0.024x+0.00

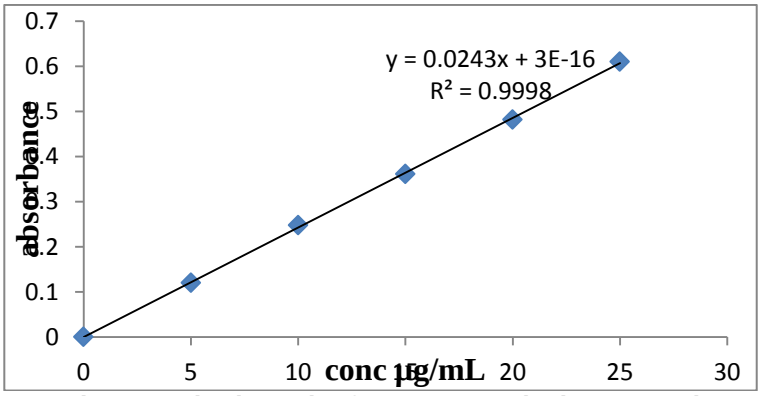

Fig.: Standard graph of Esomeprazole in 0.1N HCl

Table: Observations for graph of Esomeprazole in p H 6.8 phosphate buffer (304nm)

Concentration [µg/ml]	Absorbance
0	0
5	0.181
10	0.362
15	0.543
20	0.712
25	0.867

It was found that the estimation of Esomeprazole by UV spectrophotometric method at λ_{max}304 nm in pH 6.8 Phosphate buffer. had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5-25µg/ml. The regression equation generated was y = 0.035x + 0.007.

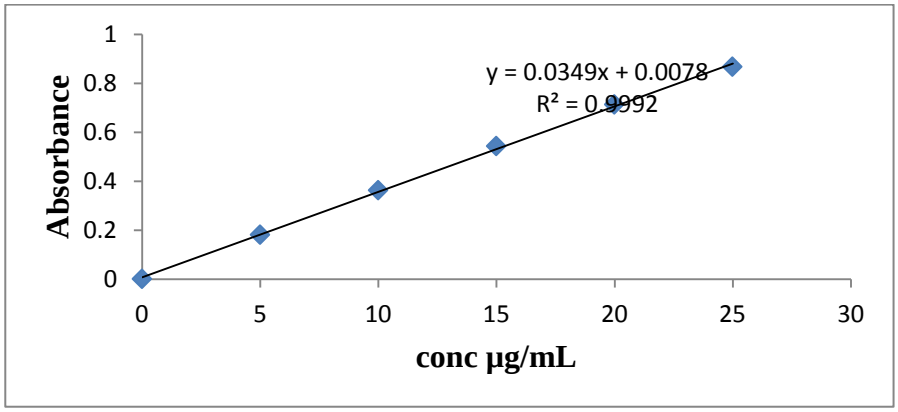

Fig.: Standard graph of Esomeprazole pH 6.8 phosphate buffer (304nm)

4.2. Drug – Excipient compatability studies
Fourier Transform-Infrared Spectroscopy:

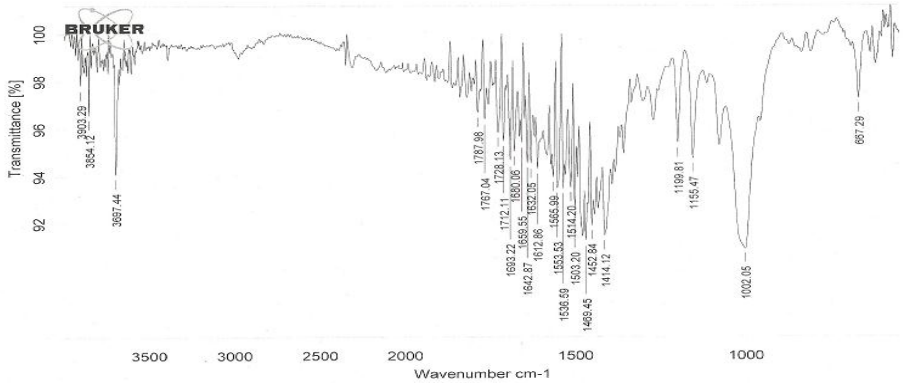

Fig.: FT-IR Spectrum of Esomeprazole pure drug

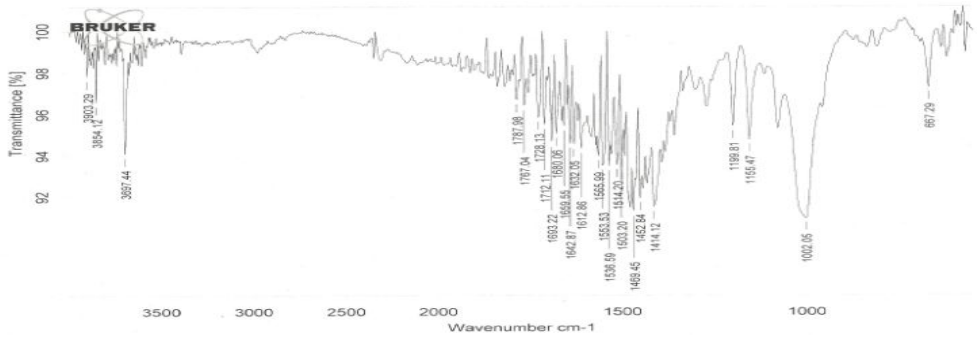

Fig.: FT-IR Spectrum of Optimised Formulation

4.3. Preformulation parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.01±0.21	0.49±0.05	0.57±0.06	14.03±0.01	1.16±0.02
F2	26.8±0.35	0.56±0.04	0.67±0.08	16.41±0.00	1.19±0.05
F3	27.7±0.42	0.52±0.09	0.64±0.02	18.75±0.09	1.23±0.06
F4	25.33±0.48	0.54±0.05	0.64±0.04	15.62±0.05	1.18±0.08
F5	25.24±0.52	0.53±0.02	0.65±0.05	18.46±0.09	1.22±0.07
F6	28.12±0.35	0.56±0.03	0.66±0.02	15.15±0.02	1.17±0.05
F7	27.08±0.47	0.58±0.01	0.69±0.05	15.94±0.01	1.18±0.04
F8	25.12±0.51	0.48±0.09	0.57±0.05	15.78±0.05	1.18±0.06
F9	26.45±0.65	0.54±0.02	0.65±0.04	16.92±0.04	1.2±0.07

Table: Pre-formulation parameters of Core blend

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 of 0.48±0.09 to 0.58±0.01 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57±0.06 to 0.69±0.05 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 14 to 18 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.25 indicating the powder has good flow properties.

4.4. Quality Control Parameters For tablets:

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

Formulation codes	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	399.5	4.5	0.50	3.8	99.8
F2	401.2	4.5	0.51	3.9	99.1
F3	399.5	4.4	0.51	3.9	99.8
F4	400.6	4.5	0.55	3.9	99.7
F5	401	4.4	0.56	3.7	99.3
F6	400	4.5	0.45	3.7	99.5
F7	399.5	4.1	0.51	3.4	99.8
F8	399.5	4.3	0.49	3.7	99.8
F9	400	4.5	0.55	3.6	99.4

Table: *In vitro* quality control parameters for tablets

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

4.5. *In Vitro* Drug Release Studies

Table 4.5: Dissolution Data of Esomeprazole Tablets Prepared With Xanthan gum Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F1	F2	F3
0	0	0	0
0.5	28.18	23.93	18.4
1	34.47	31.68	22.3
2	50.38	39.77	29.5
3	79.33	44.51	32.3
4	84.38	52.97	41.3
5	89.45	59.84	52.6
6	93.4	65.81	59.4
7	96.8	70.91	65.2
8	99.2	78.29	72.3
9		83.94	79.5
10		89.88	82.5
11		93.82	89.1
12		99.65	91.2

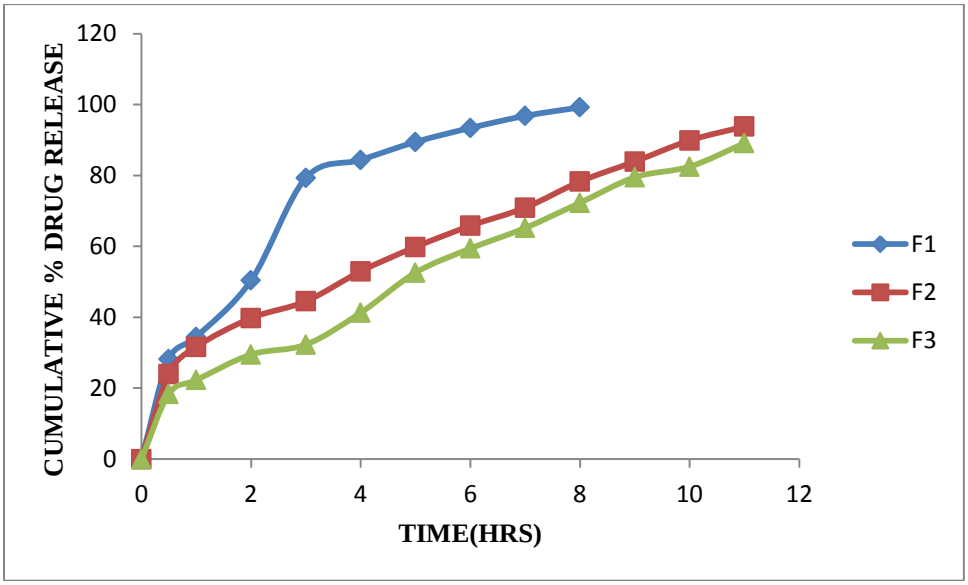

Fig: Dissolution profile of Esomeprazole (F1, F2, F3 formulations).

Table 4.6: Dissolution Data of Esomeprazole Tablets Prepared With HPMC K 15 In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F4	F5	F6
0	0	0	0
0.5	37.25	34.24	30.62
1	48.26	43.37	34.86
2	54.16	48.63	40.35
3	71.01	65.04	48.45
4	88.26	70.25	54.80
5	99.10	87.33	59.25
6		94.41	65.24
7		98.56	70.73
8			78.34
9			85.52
10			99.17

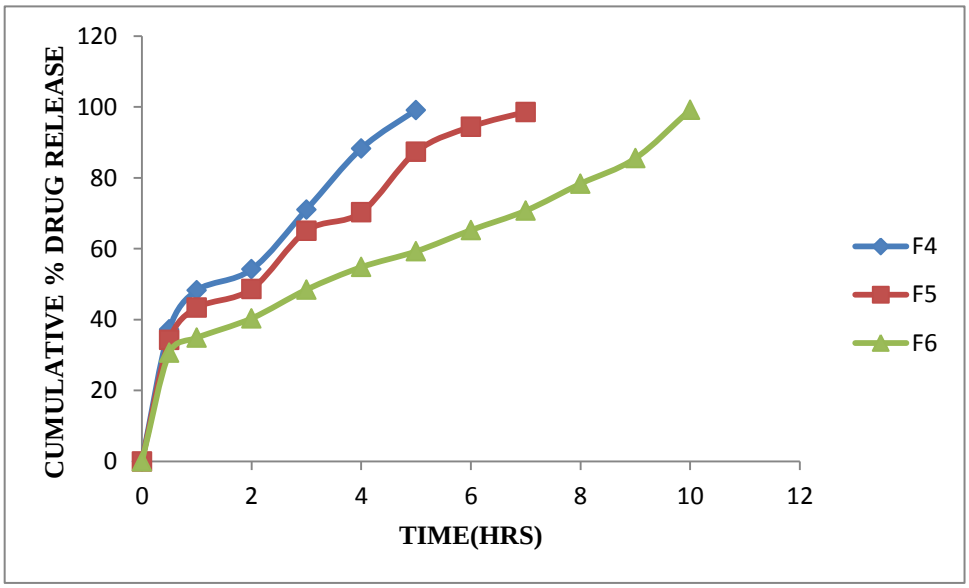

Fig: Dissolution profile of Esomeprazole (F4, F5, F6 formulations)

Table: Dissolution Data of Esomeprazole Tablets Prepared With carbopol 934 In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F7	F8	F9
0	0	0	0
0.5	8.2	3.2	1.9
1	13.2	8.9	2.2
2	16.3	12.3	8.3
3	22.4	17.4	12.3
4	26.3	19.3	17.4
5	29.5	22.4	19.3
6	32.8	25.6	22.4
7	38.4	32.3	25.6
8	42.5	37.6	32.9
9	48.15	42.8	37.5
10	56.36	52.6	42.7
11	73.46	62.3	52.3
12	85.51	72.3	62.8

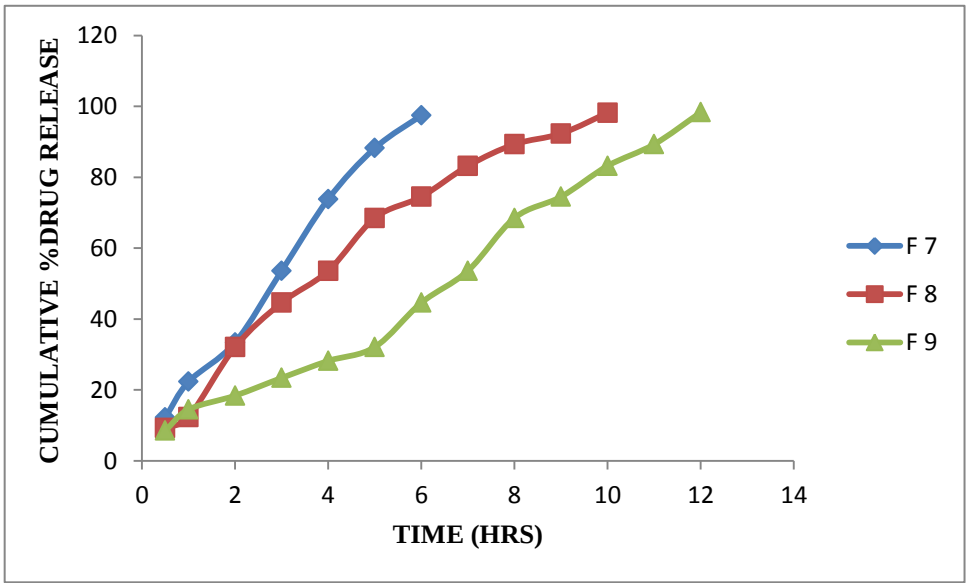

Fig: Dissolution profile of Esomeprazole (F7, F8, F9 formulations)

From the dissolution data, it was revealed that formulations prepared with HPMC K 15 M did not retard the drug release up to 12 hrs. Hence those formulations did not take into consideration.
Formulations prepared with Carbopol 934 retard the drug release more than 12hrs. These formulations also did not take into consideration.
Formulations prepared with xanthan gum were revealed that increase in the concentration retards the drug release. Among all formulations F2 formulation was considered as optimised formulation. It was shown 99.65% drug release at 12hrs

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.

Table 4.8: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining
0	0	0			2.000				100
23.93	0.5	0.707	1.379	-0.301	1.881	47.860	0.0418	-0.621	76.07
31.68	1	1.000	1.501	0.000	1.835	31.680	0.0316	-0.499	68.32
39.77	2	1.414	1.600	0.301	1.780	19.885	0.0251	-0.400	60.23
44.51	3	1.732	1.648	0.477	1.744	14.837	0.0225	-0.352	55.49
52.97	4	2.000	1.724	0.602	1.672	13.243	0.0189	-0.276	47.03
59.84	5	2.236	1.777	0.699	1.604	11.968	0.0167	-0.223	40.16
65.81	6	2.449	1.818	0.778	1.534	10.968	0.0152	-0.182	34.19
70.91	7	2.646	1.851	0.845	1.464	10.130	0.0141	-0.149	29.09
78.29	8	2.828	1.894	0.903	1.337	9.786	0.0128	-0.106	21.71
83.94	9	3.000	1.924	0.954	1.206	9.327	0.0119	-0.076	16.06
89.88	10	3.162	1.954	1.000	1.005	8.988	0.0111	-0.046	10.12
93.82	11	3.317	1.972	1.041	0.791	8.529	0.0107	-0.028	6.18
99.65	12	3.464	1.998	1.079	-0.456	8.304	0.0100	-0.002	0.35

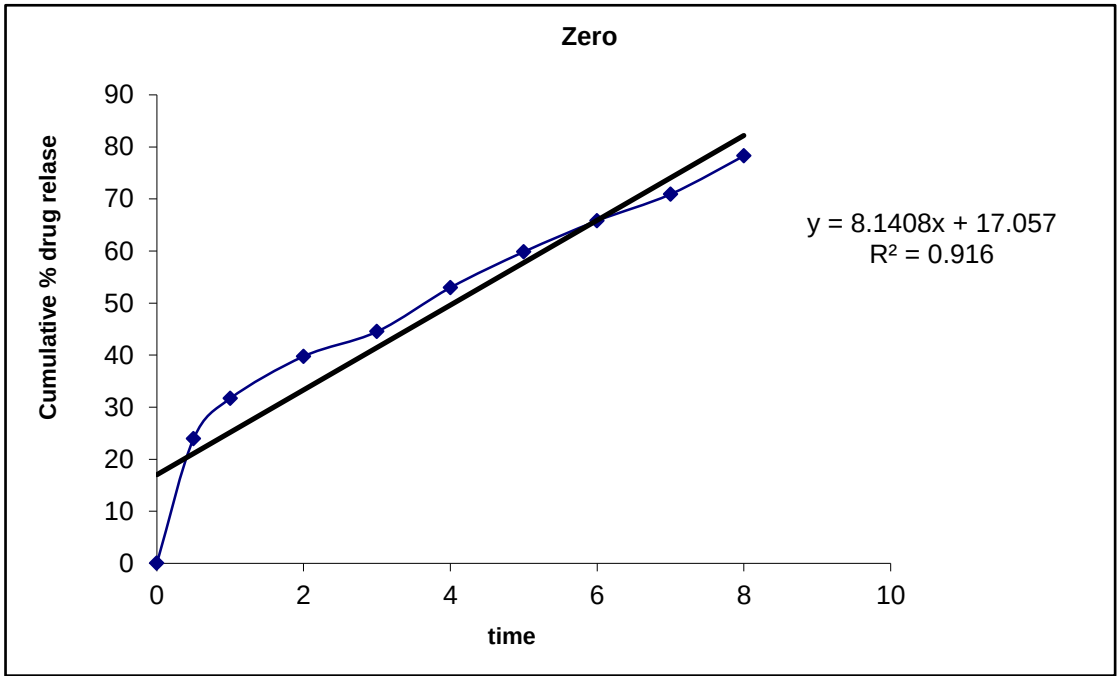

Fig: Zero order release kinetics graph

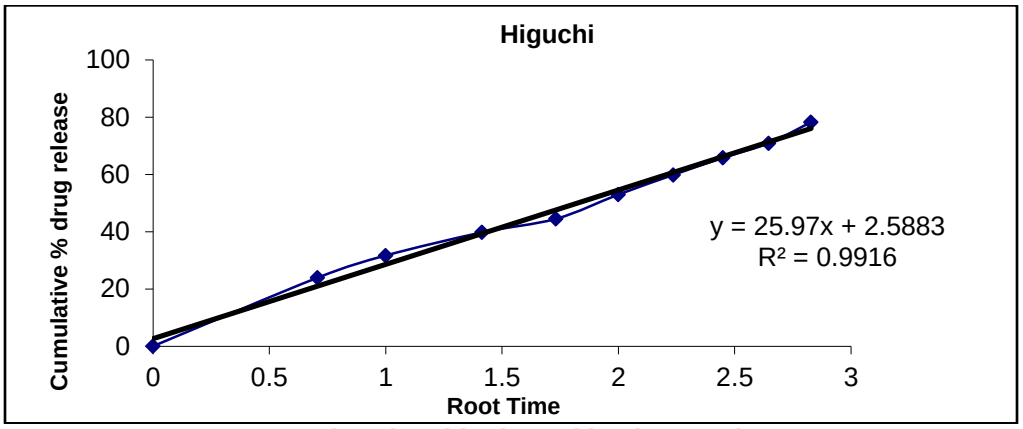

Fig: Higuchi release kinetics graph

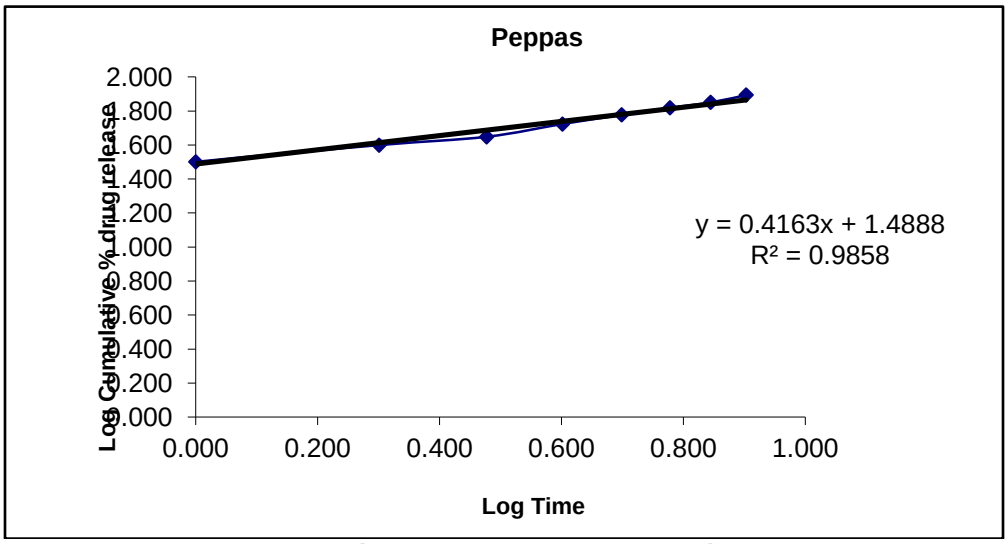

Fig: Kars mayer peppas graph

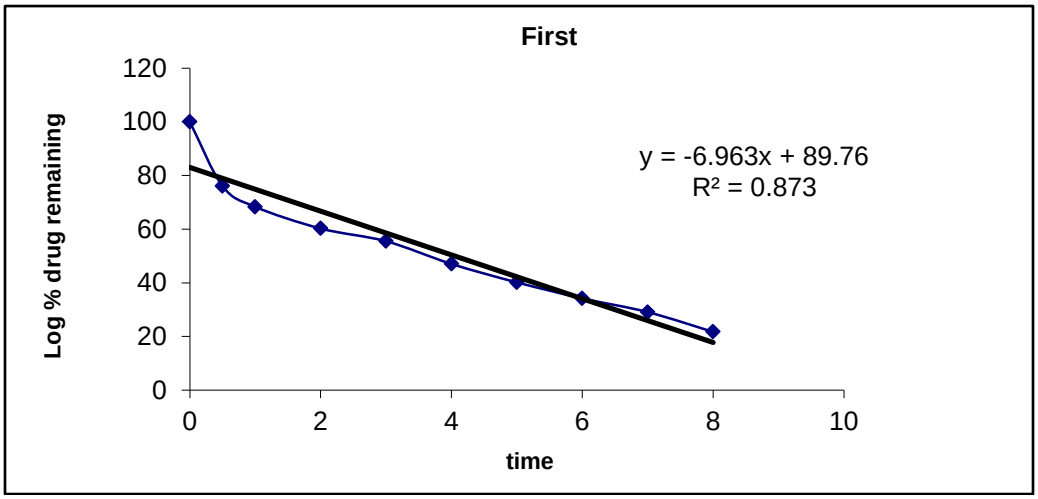

Fig: First order release kinetics graph

From the above graphs it was evident that the formulation F2 was followed Higuchi release kinetics.

CONCLUSION

In the present research work the sustained release matrix formulation of Esomeprazole by using various polymers. Initially analytical method development was done for the drug molecule. Absorption maxima were determined and calibration curve was developed by using different concentrations.

The formulation was developed by using various polymers such as HPMC K 15 M and Xanthan gum, Carbopol 934. The formulation blend was subjected to various preformulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations prepared by using HPMC K 15 M were unable retard drug release up to 12 hours. Hence those formulations did not take into consideration. Formulations prepared with Carbopol 934 retard the drug release more than 12hrs. These formulations also did not take into consideration. Formulations prepared with xanthan gum were revealed that increase in the concentration retards the drug release. Among all formulations F2 formulation was considered as optimised formulation. It was shown 99.65% drug release at 12hrs. The optimised 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.

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