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Formulation and evaluation of double walled microspheres of esomeprazole

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ABSTRACT

The present study involves the preparation of double walled microspheres of Esomeprazole sodium. Esomeprazole microspheres are mainly designed to achieve constant release of the drug over long periods of time. Preformulation studies were carried out before formulation design. Total seven formulations were prepared using two different polymers viz., Hydroxy Propyl Methyl Cellulose and sodium alginate in various ratios. Microspheres were discrete, spherical, and free-flowing and showed a good percentage of drug entrapment efficiency. FT-IR spectraof the physical mixture revealed that the drug is compatible with the polymers and copolymer used. In-*vitro* dissolution test was carried out. All the formulations showed good dissolution profiles. Among all the formulation F6 showed good dissolution profile with 97.80% of drug release in 12 hours. . *In-vitro* release kinetic data of Esomeprazole microspheres showed that the drug release follows showed that the drug release from the formulations followed the Non fickian diffusion mechanism and follows zero order kinectics.Stability studies were done for the selected formulation which indicates that there is no change in drug content of the formulation. Based on the results of evaluation tests formulation coded F6 was concluded as best formulation. The results of this investigation indicate that Ion gelation method can be successfully employed to fabricate Esomeprazole microspheres

Keywords: Esomeprazole sodium, Hydroxy Propyl Methyl Cellulose, Sodium alginate, Evaluation.

INTRODUCTION

For many decades, medication of an acute disease or a chronic illness has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams, ointments, liquids, aerosols, injectable and suppositories as carriers efficiency. This factor as well as other factors such as repetitive dosing and unpredictable absorption lead to the concept of controlled drug delivery systems.[2,] Controlled release systems includes any drug delivery system that "achieves slow release of the drug over an extended period of time." If the system can provide some control weather this is of a temporal or spatial nature, in other words, if the system is successful in maintaining predictable and reproducible kinetics in the target tissue or cell, it is considered as a controlled release system.The objectives in designing a controlled release system is to deliver the drug at a rate necessary to achieve and maintain a constant drug blood level. This rate should be analogous to that achieved by continuous intravenous infusion where a drug is provided to the patient at a rate just equal to its rate of elimination. This implies that the rate of delivery must

be independent of the amount of drug remaining in the dosage form and constant over time. That is release from the dosage form should follow zero-order kinetics.[4]

MICROENCAPSULATION

Micro-encapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules of many useful properties. In general, it is used to incorporate food ingredients, enzymes, cells or other materials on a micro metric scale. Microencapsulation can also be used to enclose solids, liquids, or gases inside a micrometric wall made of hard or soft soluble film, in order to reduce dosing frequency and prevent the degradation of pharmaceuticals.[1]

MICROENCAPAULATION APPLICATIONS

1. Microencapsulation has been employed to provide protection to the core material against atmospheric effects.
2. The separation of incompatible substances, for example pharmaceutical eutectics, has been achieved by encapsulation.
3. Toxic chemicals such as insecticides may be microencapsulated to reduce hazards.
4. Also the hygroscopic properties of many core materials such as sodium chloride may be reduced by microencapsulation.
5. Many drugs have been microencapsulated to reduce the gastric and other gastrointestinal tract irritation.

DOUBLE WALLED MICROSPHERES

Present microsphere delivery system technology consisting of a single drug dispersed within a polymer matrix has several drawbacks. One is the problem of the so-called “burst effect”. By exploiting the phenomenon of phase separation between two immiscible polymers dissolved in a mutual solvent, a double-walled microsphere could be manufactured with the second polymer coating the polymer/drug matrix.

ADVANTAGES

1. Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.
2. Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.
3. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor.
4. The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles *in vivo.*
5. Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intracellularly.

LIMITATIONS

1. The modified release from the formulations.
2. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
3. Differences in the release rate from one dose to another.
4. Controlled release formulations generally contarin a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
5. Dosage forms of this kind should not be crushed or chewed.

ESOMEPRAZOLE SODIUM

Esomeprazole is a proton pump inhibitor which reduces stomach acid secretion through inhibition of the H+ / K+ ATPase in the parietal cells of the stomach. By inhibiting the functioning of this transporter, the drug prevents formation of stomach acid. The primary uses of esomeprazole are gastro esophageal reflux disease, treatment and maintenance of erosive esophagitis treatment of duodenal ulcers caused by H. pylori, prevention of gastric ulcers in those on chronic NSAID therapy, and treatment of gastrointestinal ulcers associated with Crohn's disease.

METHOLDOLOGY

PREFORMULATION STUDIES

Preformulation testing is the first step in the development of dosage forms of a drug substance

DESCRIPTION / APPEARANCE

Esomeprazole is a white to pale greenish-yellow powder.

DETERMINATION OF MELTING POINT

Melting point of Esomeprazole was determined by capillary method.

SOLUBILTY

Solubility of Esomeprazole was determined in water, 0.1N HCL, 0.1N NaOH, Ethanol, Methylene Chloride Esomeprazole was mixed with all excipients, used in the formulation in different ratios and subjected to Physical observation/FTIR.

DRUG-EXCIPIENT COMPATIBILITY STUDY (FTIR)

Prior to the development of the dosage forms the pre-formulation study was carried out. IR spectral studies lies more in the qualitative identification of substances either in pure form or in combination with polymers and excipients and acts as a tool in establishment of chemical interaction. Since I.R. is related to covalent bonds, the spectra can provide detailed information about the structure of molecular compounds. In order to establish this point, comparisons were made between the spectrum of the substances and the pure compound. The above discussions imply that infrared data is helpful to confirm the identity of the drug and to detect the interaction of the drug with the carriers. FTIR spectra were recorded with a Thermo Nicolet. Japan In the range 400–4000 cm−1 using a resolution of 4 cm−1 and 16 scans. Samples were diluted with KBr mixing Powder, and pressed to obtain self-supporting disks. Liquid samples formulations were analyzed to form a thin liquid film between two KBr disks[23].

ESTIMATION OF ESOMEPRAZOLE

STANDARD GRAPH OF ESOMEPRAZOLE

STANDARD STOCK SOLUTION

100 mg of Esomeprazole was dissolved in small quantity of Methanol and make up to 100 ml 0.1N HCL to give a concentration of (1000 µg/ml)

SCANNING

From the stock solution 100µg/ml was prepared and UV scan was taken between 200 to 400 nm. The absorption maximum was found to be 203.5nm and was used for the further analytical studies.

CALIBRATION CURVE OF ESOMEPRAZOLE IN 0.1 N HCL

The standard solutions were prepared by proper dilutions of the primary stock solution with buffer to obtain working standards in the concentration range of 2-10µg/ml of pure sample of Esomeprazole. The concentration of Esomeprazole present in the microspheres was obtained from the calibrationcurve[30, 31].

CALIBRATION CURVE OF ESOMEPRAZOLE IN PH6.8 PHOSPHATE BUFFER

STANDARD STOCK SOLUTION

100 mg of Esomeprazole was dissolved in small quantity of ethanol and make up to 100 ml of pH6..8 Phosphate buffer to give a concentration of (1000 µg/ml). The standard solutions were prepared by proper dilutions of the primary stock solution with buffer to obtain working standards in the concentration range of 2-10µg/ml of pure sample of Esomeprazole. The concentration of Esomeprazole presenting the microspheres was obtained from the calibrationcurve[30, 31].

FORMULATION

PREPARATION OF DOUBLE WALLED MICROSPHERE OF ESOMEPRAZOLE

The double walled microspheres were prepared by two step process.

FORMULATION OF CORE MICROSPHERES WITH DRUG

Esomeprazole and all other polymers were individually passed through sieve no≠60. The required quantities of Sodium alginate and the polymer were dissolved in purified water to form a homogenous polymer solution. The Drug, Esomeprazole was added to the polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added manually drop wise into calcium chloride (1.5 % w/v) solution through a syringe with a needle of size no. 22. The added droplets were retained in the calcium chloride solution for 15 minutes to complete the curing reaction and to produce the spherical rigid microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with water and dried at 45^0C for12 hours.

FORMULATION OF DOUBLE WALLED MICROSPHERES

The previously formulated microspheres were dispersed in the organic phase. The second polymer 3%HPMC Phthalate was dissolved in the same organic

phase. The resulting organic phase solution was emulsified in liquid paraffin. 1% span 80 solutions were used as emulsifying agent. Above emulsion was stirred for complete evaporation of the organic solution. After complete evaporation of the organic solution the double walled microspheres were collected by vacuum filtration and washed with n-hexane. The resulted double walled microspheres were freeze dried for 24hrs.

Table: 1 Formulation of Microspheres

Ingredients (%)	F1	F2	F3	F4	F5	F6	F7
Esomeprazole(mg)	20	20	20	20	20	20	20
HPMC	1	-	-	1.5	1.5	1.5	1.5
Ethyl cellulose	-	1	-	-	-	-	-
Guar gum	-	-	1	-	-	-	-
Carbopol	0.5	0.5	0.5	0.5	0.5	1	1
Sodium alginate	1	1	1	1	1.5	1.5	1

EVALUATION OF MICROSPHERES

DRUG ENTRAPMENT EFFICIENCY

Microspheres equivalent to 20mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of pH6.8 Phosphate buffer repeatedly. The extract was transferred to a100ml volumetric flask and the volume was made up using pH6.8 Phosphate buffer. The Solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically (UV1700, Shimadzu, Japan) at203.5nmagainstappropriate blank[21, 39]. The amount of drug loaded and entrapped in the microspheres was calculated by the following formulas:

Drug entrapment efficiency (%) = Amount of drug actually present/ Theoretical drug load expected × 100

DETERMINATION OF PERCENTAGE YIELD

The dried microspheres were weighed and percentage yield of the prepared. Microspheres were calculated by using the following formula[37].

Percentage yield = Practical yield (mg)/ Theoretical yield ×100

IN-VITRO RELEASE STUDY

The drug release study was performed for microsphere containing quantity equivalent to 20mg of Esomeprazole Microspheres by using USP dissolution apparatus Type I in 900ml of 0.1 N HCL for first 2hrs then replaced with pH6.8 Phosphate buffer dissolution media at 100rpm and 370C temperature. 10ml of sample was withdrawn at predetermined time interval lor 12h and same volume of fresh medium was replaced to maintained sink condition. Withdrawn samples were assayed spectrophotometrically at 203.5nm. The cumulative% drug release was calculated using standard calibration curve. Details of dissolution testing: Apparatus: Lab India DS 8000,Dissolution media:0.1NHCl(pH-1.2), pH6.8 Phosphate buffer, Speed: 50 rpm, Volume of medium: 900 ml ,Aliquots taken at each time interval: 5ml, Temperature: 37±0.5°C,Wavelength: 203.5nm.

RELEASE KINETICS

The matrix systems were reported to follow the Peppas release rate and the diffusion mechanism for the release of the drug

ZERO ORDER KINETICS

Drug dissolution from Pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation

$Qt = Qo + Ko\ t$

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

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

Log Qt = log Qo + K1t / 2.303

Qt = Amount of drug released in time t,
Qo = Initial amount of drug in the solution and
K1 = First order release constant.

HIGUCHI MODEL

Higuchi developed several theoretical models to study the release of water soluble and low-soluble drugs incorporated in semisolids and or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. The higuchi equation is

Qt = KH x t 1/2

Qt = Amount of drug released in time t and,
KH = Higuchi dissolution constant.

PEPPAS RELEASE MODEL

To study this model the release rate data is fitted to the following equation

Mt / M∞ = K. tn

Mt / M∞ = Fraction of drug release,
K= Release constant,
t = Drug release time and
n = Diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form.

STABILITY STUDIES

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light, and enables recommended storage conditions. Overall observations from different evaluation studies such as drug-polymer interactions, evaluation of prepared formulations and drug release studies were carried out. Based on the obtained results best formulation was subjected for further stability study. The stability study was conducted as per ICH guidelines for the period of six months at various accelerated temperature and humidity conditions of 25°C/60%RH, 40°C/70%RH, 60°C/80%RH.The accelerated stability study of the best formulations was carried out as per the ICH guidelines. The selected formulation was analyzed for the drug entrapment efficiency and in vitro release study at different temperature.

RESULTS AND DISCUSSION

PREFORMULATION STUDIES

Pre-formulation testing is the first step in the development of dosage forms of a drug substance

DESCRIPTION/APPEARANCE

Esomeprazole is a white to pale greenish-yellow powder.

DETERMINATION OF MELTING POINT

Melting point of Esomeprazole was determined by capillary method found to be in the range 171° to 174°C, which complied with USP standards, indicating purity of the drug sample.

SOLUBILTY

Solubility of Esomeprazole was determined and summarized below.

Table 2 Solubility of someorazole

Solvent	Solubility (mg/lit)
Water [a]	133000
0.1 M HCl	86,900
0.1 N NaOH	3,700
Ethanol	4,200
Methylene chloride	300

(a→ P^H not specified).

The solubility data indicate that Esomeprazole is extremely soluble in protic solvents. Since Esomeprazole is a base, the aqueous solubility is expected to be lowest at high P

DRUG AND EXCIPIENT COMPATIBILITY STUDIES

Fig: 1 FTIR Spectra of Esomeprazole

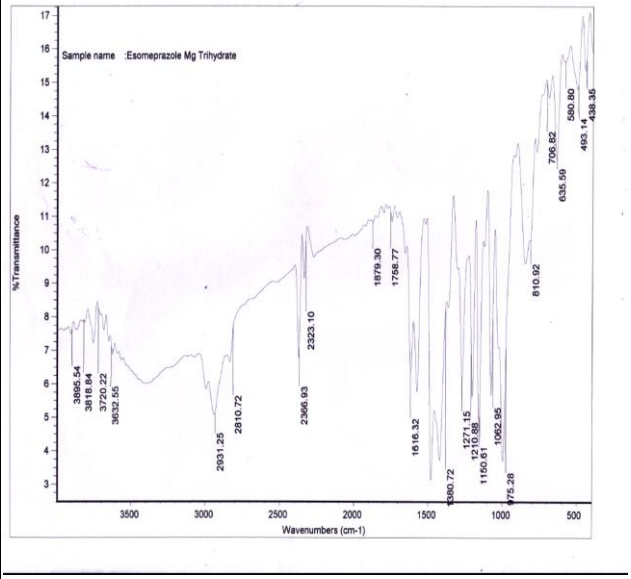
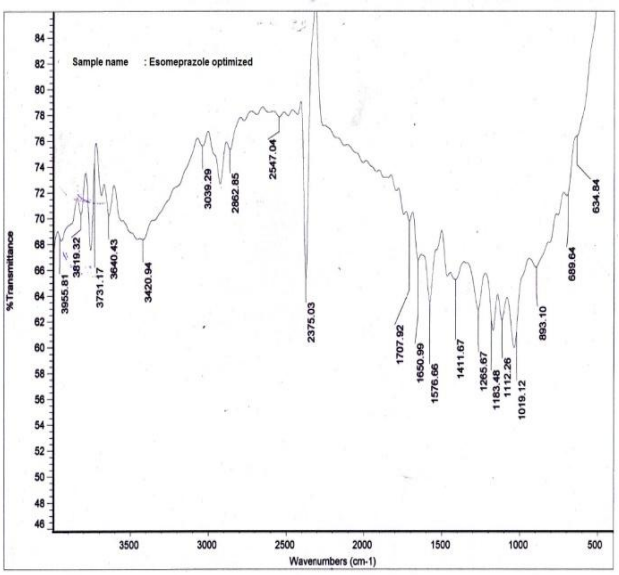


Fig: 2 FTIR Spectra of Esomeprazole optimized formulation



ESTIMATION OF ESOMEPRAZOLE

CALIBRATION CURVE OF ESOMEPRAZOLE IN0.1N HCL

Table 3 shows the calibration curve data of Esomeprazole in 0.1N HCL at 203.5nm. Fig 3 shows the standard calibration curve with a regression value of 0.9978, slope of 0.0291 and intercept of 0.0016. The curve was found to be linear in the concentration range of 2-10µg/ml.

Table:3 Calibration curve data for Esomeprazole in0.1N HCL

CONCENTRATION (µg /ml)	ABSORBANCE
0	0
2	0.067
4	0.112
6	0.178
8	0.23
10	0.297

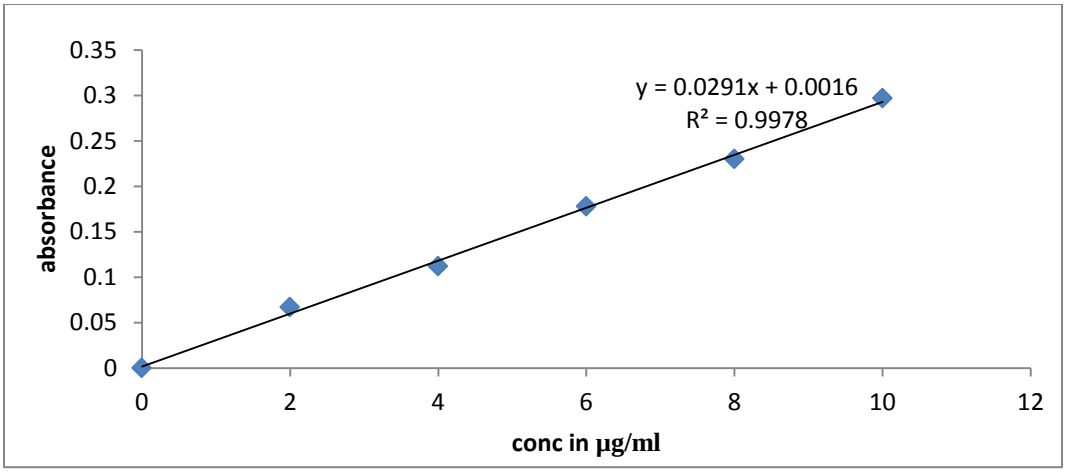


Figure: 3 Standard graph Of Esomeprazolein 0.1 N HCL

CALIBRATION CURVE OF ESOMEPRAZOLE IN6.8 PH PHOSPHATE BUFFER

Table 4 shows the calibration curve data of Esomeprazole in6.8 pH phosphate buffer at 203.5nm. Fig.4 shows the standard calibration curve with a regression value of 0.9996, slope of 0.154 and intercept of 0.004. The curve was found to be linear in the concentration range of 2-10µg/ml.

Table:4 Calibration curve data for Esomeprazole in6.8 pH phosphate buffer

CONCENTRATION (µg /ml)	ABSORBANCE
0	0
2	0.307
4	0.616
6	0.901
8	1.247
10	1.544

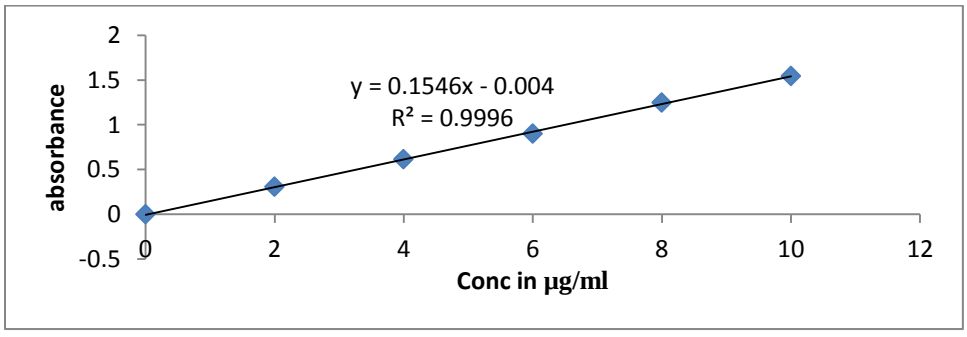


Figure: 4 Standard graph Of Esomeprazolein 6.8 pH phosphate buffer

EVALUATION AND CHARACTERISATION OF MICROSPHERES PERCENTAGE YIELD

The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug-polymer solution, adhesion of polymer solution to the magnetic bead and microspheres lost during the washing process. The percentage yield was found to be in the range of79.9 to 88.8% for microspheres containing sodium alginate along with different ratios of polymers. The percentage yield of the prepared microspheres is recorded in table 5 and displayed in figure 5.

DRUG ENTRAPMENT EFFICIENCY

Percentage Drug entrapment efficiency of Esomeprazole ranged from 75.3 to 88.7% for microspheres containing sodium alginate along with different ratios of polymers. The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared microspheres is displayed in Table 5 and displayed in Figure 6.

Table: 5 Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

S. No.	Formulation code	% yield	%Drug Entrapment Efficiency
1	**F1**	82.1	77.9
2	**F2**	85.4	75.3
3	**F3**	86.2	85.2
4	**F4**	88.8	85.6
5	**F5**	79.9	87.1
6	**F6**	85.2	88.7
7	**F7**	84.6	87.3

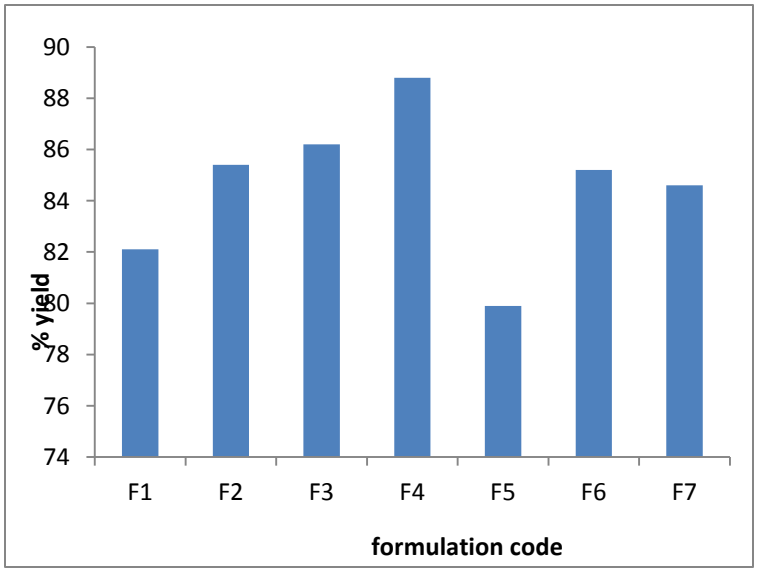


Fig:5 Graphical representation of percentage yield of formulations F1- F7

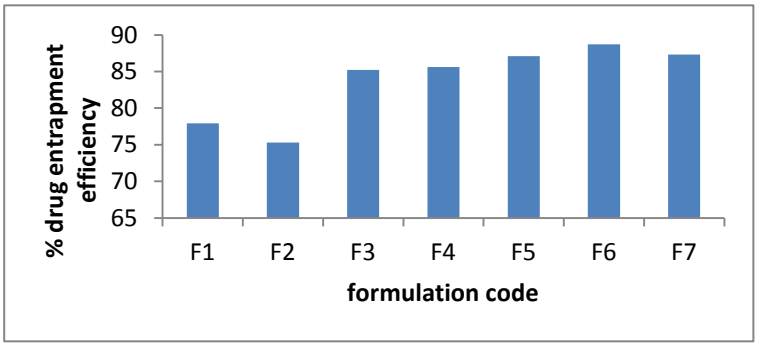


Fig:6 Graphical representation of percentage drug entrapment efficiency of formulations F1- F7

PARTICLE SIZE ANALYSIS

The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. Microspheres containing sodium alginate along with carbopol and HPMC had a least size range of 613µm. The particle size data is presented in Tables 6 and displayed in Figure. The effect of drug to polymer ratio on particle size is displayed in Figure -7. The particle size as well as % drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.

Table: 6 Average Particle Size analyses for formulation F1- F8

Formulation code	Average particle size(µm)
F1	648
F2	754
F3	768
F4	622
F5	625
F6	613
F7	635

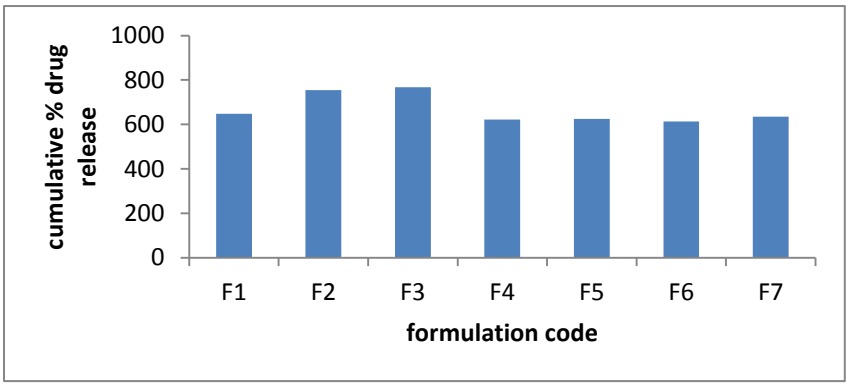


Fig: 7 Graphical representation of average particle size for formulations

IN-VITRO DRUG RELEASE STUDIES

Dissolution studies of all the formulations were carried out using dissolution apparatus USP type I. The dissolution studies were conducted by using dissolution media, 0.1 N HCl for 2hrs and 6.8 pH phosphate buffers for next hours. The results of the in vitro dissolution studies of formulations F1 – F7, shown in table no.9 and 10.The plots of Cumulative

percentage drug release Vs Time, Figure 8 shows the comparison of %CDR for formulations F1 – F7.The formulations F1, F2 showed a maximum release of 98.74, 92.31 % at 8 hours, respectively, While F3 and F4 showed a maximum release of 95.62, 99.21% at 10hrs respectively. The formulations F5 showed a maximum release of 95.51% at 10 hours, F6 and F7 showed 97.80 and 95.4 % at 12 hours respectively. Among all formulations F6 shows Maximum drug release in 12hrs when compared with other formulations. This shows that more sustained release was observed with the increase in percentage. As the polymer to drug ratio was increased the extent of drug released creased. A significant decrease in the rate and extent of drug release is attributed to the increase in density of polymer matrix that results in increased diffusion path length which the drug molecules have to traverse. Additionally, the larger particle size eat higher polymer concentration also restricted the total surface area resulting in slower release. Table: 7 In-Vitro drug release data of Esomeprazole microspheres

Table: 7 In-Vitro drug release data of Esomeprazole microspheres

TIME (hrs)	Cumulative Percent Of Drug Released			
	F1	F2	F3	F4
0	0	0	0	0
1	5.08	2.60	1.82	1.78
2	9.70	8.01	12.62	11.07
3	22.68	24.80	20.96	28.86
4	44.25	40.68	38.84	45.42
5	51.36	47.13	50.80	56.62
6	72.74	53.69	62.26	67.71
7	86.47	76.82	72.18	70.92
8	98.74	92.31	80.11	86.54
10	--	--	95.62	99.21
12	--	--	--	--

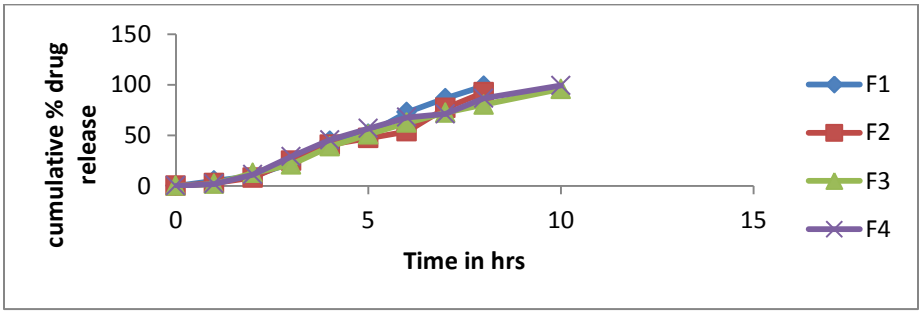


Fig:8 Comparison of In-Vitro drug release profile of Esomeprazole microspheres

Table 8 : In-Vitro drug release data of Esomeprazole microspheres

TIME (hrs)	Cumulative Percent Of Drug Released

	F5	F6	F7
0	0	0	0
1	4.70	5.61	8.20
2	15.62	12.07	12.60
3	22.40	22.46	20.34
4	36.16	38.60	28.00
5	43.80	46.90	34.31
6	50.91	57.22	45.52
7	65.40	75.07	55.61
8	71.82	88.09	70.11
10	95.51	94.58	85.98
12	--	97.80	95.4

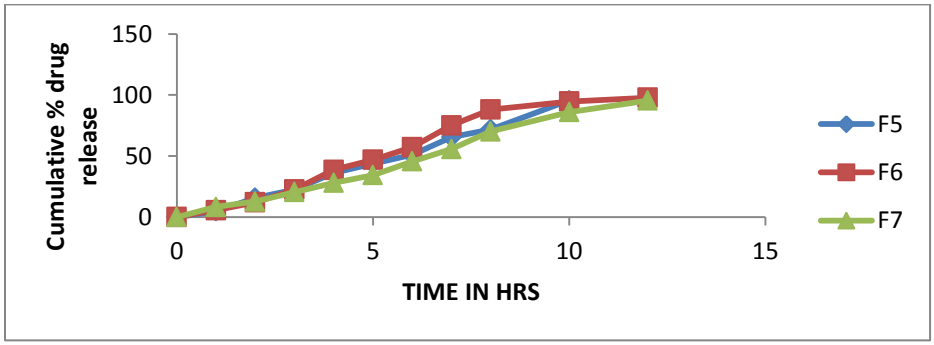


Fig:9 Comparison of In-Vitro drug release profile of Esomeprazole microspheres

IN-VITRO DRUG RELEASE KINETICS

Table: 9 Release kinetics for optimized formulation (F6)

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	9.425421995	-0.15743304	34.05080648	2.257708071
Intercept	-0.75222506	2.299167477	-22.0423660	-0.20820595
Correlation	0.978268756	-0.93952964	0.946195226	0.9097114
R 2	0.957009759	0.882715944	0.895285405	0.827574831

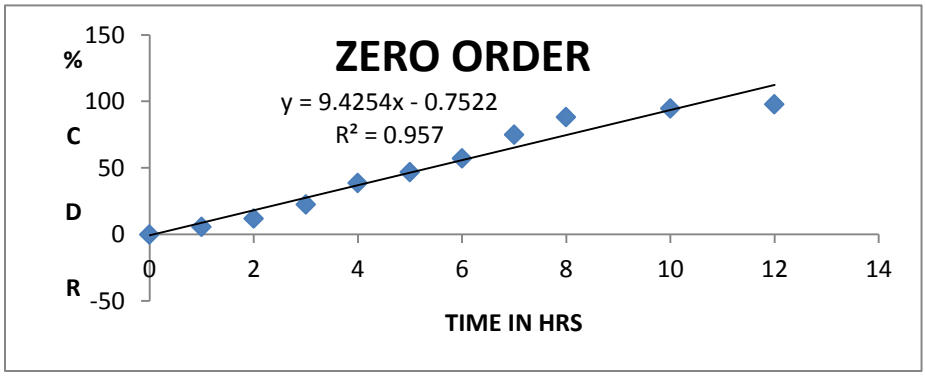


Fig: 10 Zero order kinetics

Fig: 11 first order kinetics

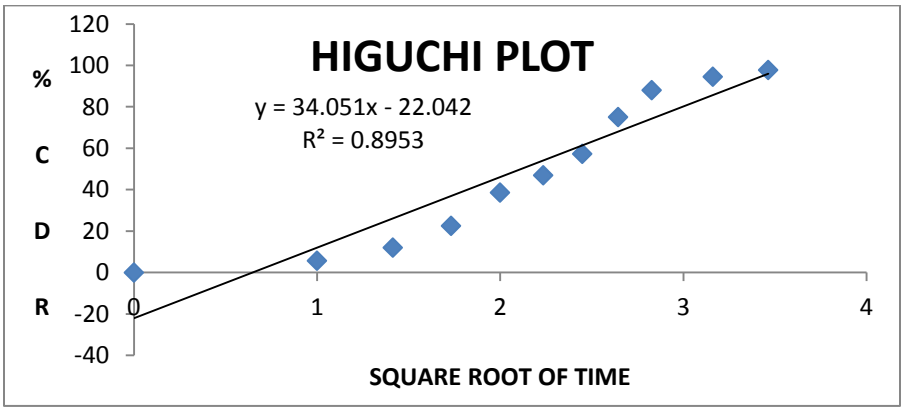


Fig: 12 Higuchis plot

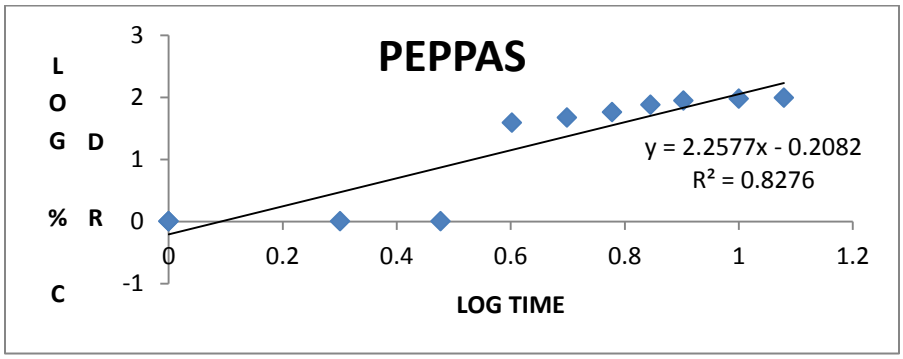


Fig: 13 Peppas plot

For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the in-vitro drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer-Peppas model. The values are compiled. The coefficient of determination (R2) was used as an indicator of the best fitting for each of the models considered. From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Zero order kinetics which is independent on concentration and Peppas model shows Non fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

SUMMARY AND CONCLUSION

Inthepresent work, double walled microspheres of Esomeprazole using Sodium alginate, HPMC K100, Guar gum, Ethyl cellulose ascopolymers and along with Carbopol were formulated to deliver Esomeprazole via oral route. Details regarding the preparation and

evaluation of the formulations have been discussed in the previous chapter. From the study following conclusions could be drawn:-

- FT-IR spectraof the physical mixture revealed thatthedrug is compatible with the polymers and copolymer used.
- Microspheres containing sodium alginate along with carbopol and Guar gum in 1:1.5 ratio had a least size range of 613µm.
- Increase in the polymer concentration led to increase in% Yield, % Drug entrapment efficiency, Particle size.
- The *invitro* drug release decreased with increase in the polymer and copolymer concentration.
- Among all formulations F6 shows Maximum drug release in 12hrs when compared with other formulations.
- Analysis of drug release mechanism showed that the drug release from the formulations followed the Non fickian diffusion mechanism and follows zero order kinectics.
- Based on the results of evaluation tests formulation codedF6 was concluded as best formulation.
- The results of this investigation indicate that Ion gelation method can be successfully employed to fabricate Esomeprazole microspheres.

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