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FORMULATION AND EVALUATION OF ESOMEPRAZOLE MAGNESIUM TRIHYDRATE DELAYED RELEASE TABLETS

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ABSTRACT

Esomeprazole is a inhibitor of proton pump (PPI) medication used for the managing of gastroesophageal reflux disease (GERD), protection of gastric to arrest regularity of ulcers in the stomach or gastric membrane damage from persistant use of NSAIDs, and for the medication of pathological higher secretory conditions including Zollinger-Ellison (ZE) Syndrome. The strategy of such system explains the release of medicament at a point in the GIT & denotes that the drug is not released instantly but, is being released eventually. Therefore, the formulation is designed in order to increase the stability of drug and optimizing the effect of a medicament by controlling drug release in the body in the lower gastrointestinal tract part. The Present project is to design and evaluate of Esomeprazole Mg trihydrate delayed released tablets using enteric coating. Various tablets are manufactured and proper formulation has selected for enteric coating procedure. Tablet coating was done, fulfil 3% increase in weight. Coating was done by using various polymers like hydroxyl propyl methyl cellulose phthalate to fulfil 5% weight gain. Disintegration test observed, formulations failed in 0.1 N HCl solution. So, the amount of enteric coating was raised to 8% w/w. *In vitro* evaluation of the manufactured tablets was carried out. Evaluation tests were done for tablets and show the result as good quality and as desirable as per enteric coated tablets appearance.

Keywords: Gastroesophageal, Coating technique, Reflux disease, Zollinger-Ellison Syndrome

INTRODUCTION

The design of such system involves release of drugs only at a site in the gastrointestinal tract. The drugs contained in such a system are those that are: a) Destroyed in the stomach or by intestinal enzymes. b) Known to cause gastric distress. c) Absorbed from a specific intestinal site or. d) Meant to exert local effect at a specific gastrointestinal site **[1, 2]**. The two types of delayed release systems are Intestinal release systems A drug may be enteric coated for intestinal release for several known reasons such as to prevent gastric irritation, prevent destabilization in gastric Ph etc. Colonic release systems Drugs are poorly absorbed through colon but may be delivered to such a site for two reasons. a) Local action in the treatment of ulcerative colitis. b) Systemic absorption of protein and peptide drug. The correct selection and balance of excipients and processes in solid dosage formulations are designed either for improving the micrometric or macrometric properties of materials during manufacture and for providing a desired drug delivery system29. The most commonly used pharmaceutical delayed release solid dosage forms today include tablets, capsules, granules, pellets **[3, 4]**.

Delayed release solid oral dosage forms are available either as single unit (non-divided formulations–tablets, capsules) or as multiple unit (divide formulations-pellets, mini - tablets) forms. The single-unit dosage forms usually refer to diffusion-controlled systems which include monolithic systems **[5, 6]**. Where the diffusion of a drug through a matrix is the rate limiting step reservoir or multilayered matrix systems 30. Where the diffusion of the drug through polymer coating or layer of the system is the rate limiting step. However, generally, release of drugs will occur by a mixture of these two mechanisms. Types of multi-unit dosage forms comprises of Granules, Pellets, Microparticles (microspheres or microcapsules) and Nanoparticles, Mini tablets and mini depots (dispersed and distributed throughout the gastro intestinal tract when the capsule or tablet disintegrates), Multi -unit tablets (divided at ingestion without loss of the depot effect as the sub unit act as a self-contained depots) **[7, 8]**.

MATERIALS AND METHODS

Authentication studies:

Preparation method of calibration curve:

6.8 pH Phosphate buffer preparation:

Dissolve 6.8 gms, Pot Dihydrogen ortho Phosphate (KH_2PO_4) in 1000 milli Litres of Water (H_20) and stir rapidly and add 0.9 g of Sodium Hydroxide (NaOH) and Mix

Well till it completely dissolves. Then check for the pH of the mix which shows 6.8 **[9-12]**.

Preparation of stock solution:

Solution is procedured by dispersing accurately weighed amount (10mg) of the esomeprazole drug in previously 10 ml of 6.8pH phosphate buffer medium to get 1000 µg/ml. Then 10ml of 1000 µg/ml solution were added into a 100ml volumetric flask and volume made with 6.8pH phosphate buffer solution, sample was scanned at UV at 275nm.

Preparation of esomeprazole calibration:

The series of standard concentrated solutions of 2, 4, 6, 8….20 µg/ml was formed using medium such as phosphate buffer pH 6.8. The absorbances of prepared concentrations of pure drug were measured at 301 λ_{max} and a calibration plot was made between concentrations of drug solutions (µg/ml) on x-axis v/s absorbances values on y-axis.

Fourier transforms infra-red spectra (FTIR):

The Esomeprazole was placed in FTIR sample holder. The esomeprazole was scanned over the range of 4000-400 cm^{-1} using FTIR (Shimadzu). The FTIR spectra of is recorded. Repeat the procedure by dispersing a drug and polymer of 1:1 as well as combination of drug and polymer in the ratio of 1:1:1:1.

To carry out the chemical reactivity b/w drug and excipient, drug and excipient compatability studies were performed by selected FTIR. FTIR spectra of selected esomeprazole and optimised formulation were analysed in the range of 4000 to 600cm^{-1}.

Preparation of delayed release tablets of esomeprazole megnesium trihydrate

- Esomeprazole tablets core tablets were formulated by selection of wet granulation technique.
- The selected all components were weighed as per formula and sieved as per procedure. All the ingredients are mixed in increasing order of weighs and dry blend was performed for granulation procedure and slowly added to solution of PVP K-3, to form dough like appearent mass.
- Granules were then sifted through the sieve (18 #). Passed powder granules dried in tray drier or hot air oven at temp of 45ºC for 1 hr.
- Properly dried granules were then mixed along with lubricating material as selected in formula, Again passed through sieve excluding Magnesium stearate for about 10 minutes.
- After mixing uniformly, now mix the granules with pre-sieved Magnesium stearate granules for about 5 minutes.

- Finally compression of the dried granules was done on Tablet compression machine to get a tablet form

Coating approach:

- Coating to prepared tablet is added to protect drug from pre-release and to maintain the stability of a drug, also strength and hardness of the tablet are increased.
- Enteric coating was done using variations in the quantities of selected all ingredients as displayed in the table below.
- Mix all together as per their respective quantities and to be made as a solution form and applied coating by spray method and dried.

Table 1: Formulation of esomeprazole delayed tablets (pre-coating approach)

S. No.	Ingredient's	F1	F2	F3	F4	F5	F6	F7
1.	Esomeprazole	40mg	40mg	40mg	40mg	40mg	40mg	40mg
2	HPMC	15	20	25	30	35	40	45
3.	Mannitol	32	32	32	32	32	32	32
4.	PVP K-30	45	40	35	30	25	20	15
5.	Mg.Stearate(mg)	3mg	3mg	3mg	3mg	3mg	3mg	3mg
6.	Talc(mg)	5mg	5mg	5mg	5mg	5mg	5mg	5mg
7.	IPA.	qs	qs	qs	qs	qs	qs	qs

Table 2: Formula of Coating Approach

S. No.	Ingredient's	F1	F2	F3	F4	F5	F6	F7
1.	EUDRAGID L 100(gms)	1.0	1.2	1.5	2.0	2.2	2.5	3.0
2	ISOPROPONOLOL(m)	30	28	26	24	26	28	20
3.	ACETONE (ml)	10	12	14	16	14	12	20
4.	PEG 4000 (%)	8	9	10	11	12	13	14
5.	TALC (%)	12	11	10	9	8	7	6

RESULTS AND DISCUSSION

Calibration curve: The absorbance of Drug was found to be linear from 0µg/ml to 20µg/ml bearing slope of 0.0288 and R^2 of 0.9998 **(Table 3)**.

Pre-compressional studies: The angle of repose was falls in the ranges from 24.0 ± 0.2 and 25.9 ± 0.3. It shows all the values are within the limits. The bulk densities of all formulated tablets were measured by help of bulk density apparatus. Bulk density falls in the average of 0.42 to 0.55 g/cm^3. The tap. density was falls in the range of 0.58 to 0.32 g/cm^3. The Carr's Index is between 17.38 to 14.20. Hence all the Formulations are with good flow Properties **(Table 4)**.

Post compressional studies: (Table 5)

General Appearance: Formulated tablets of all formulations are evaluated for their appearance. All the tablets are round in shape. All tablets showed uniformity in appearance.

Thickness Test: Thickness of all the tablets was found to be in the ranges from 3.25mm ± 0.050 mm to 4.20 ± 0.02 mm.

Hardness: Hardness of all the formulations in the series of 9.00 ± 0.47 to 7.00 ± 0.14kg/cm^2. It indicates all the tablets have optimum mechanical strength.

Wt. variation test: Twenty tablets of each formulation were selected randomly for weight variation evaluation test. The results showed that weight variation was from 151 ± 1.39 to 155 ± 0.19mg. All the formulations passed the evaluation test.

Drug content: The drug content of esomeprazole magnesium trihydrate delayed release tablets were found in the average range between 90.20±0.25 and 96.20±0.25.

***In vitro* Dissolution studies of esomeprazole magnesium trihydrate delayed release tablets: (Table 6) (Figure 2)**

RELEASE KINETICS STUDIES: (Figure 3-6)

Table 3: Calibration curve of esomeprazole magnesium trihydrate

S No	Concentrations	Absorbances
1	0	0.000
2	2	0.065
3	4	0.114
4	6	0.177
5	8	0.233
6	10	0.290
7	12	0.343
8	14	0.408
9	16	0.465
10	18	0.523
11	20	0.566

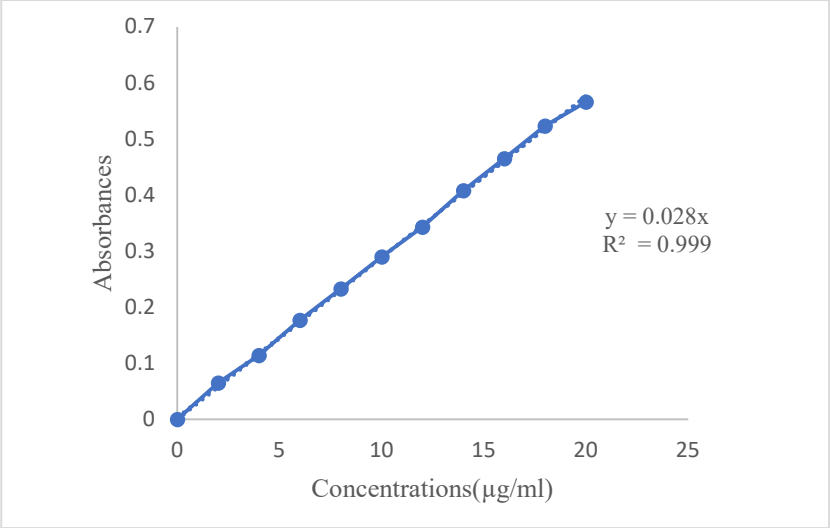

Figure 1: Calibration curve of esomeprazole magnesium trihydrate

Table 4: Pre compressional studies of esomeprazole magnesium trihydrate

Formulation code	Angle of repose	Bulk density	Tapped density	Carr's index
F1	24.21	0.423	0.512	17.38
F2	24.62	0.397	0.465	14.62
F3	25.73	0.425	0.496	14.31
F4	24.02	0.274	0.325	15.69
F5	24.45	0.358	0.458	15.42
F6	25.29	0.547	0.578	14.25
F7	24.53	0.463	0.412	14.58

Table 5: Post compressional studies of esomeprazole magnesium trihydrate

Formulation code	Hardness (kg)	Thickness (mm)	Wt.variation (mg)	Disintegration	Drug content (%)
F1	7.00±0.57	4.20±0.36	155	FAIL	90.20±0.25
F2	7.00±0.24	4.10±0.57	152	FAIL	91.20±0.25
F3	7.00±0.14	4.20±0.35	153	FAIL	92.20±0.25
F4	8.00±0.47	3.98±0.02	153	FAIL	93.20±0.25
F5	8.00±0.52	3.50±0.01	152	PASS	92.20±0.25
F6	8.00±0.47	3.25±0.05	151	PASS	90.20±0.25
F7	9.00±0.47	3.30±0.25	151	PASS	96.20±0.25

Table 6: *In vitro* Cumulative % Drug Release of esomeprazole magnesium trihydrate

Time (mins)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
30	14.84+0.32	15.78 +0.52	16.75 +0.67	17.45 +0.53	18.45 +0.05	19.45 +0.27	20.45 +0.19
60	21.45 +0.28	22.45 +0.56	21.65 +0.42	23.19 +0.63	24.45 +0.43	24.45 +0.28	30.45 +0.58
120	43.42 +0.18	42.20 +0.56	42.20 +0.52	47.17+0.23	48.53 +0.38	42.20 +0.46	60.45 +0.19
240	88.23+0.56	84.44+0.12	82.31+0.25	83.63+0.58	85.55+0.57	87.45+0.54	98.46+0.74

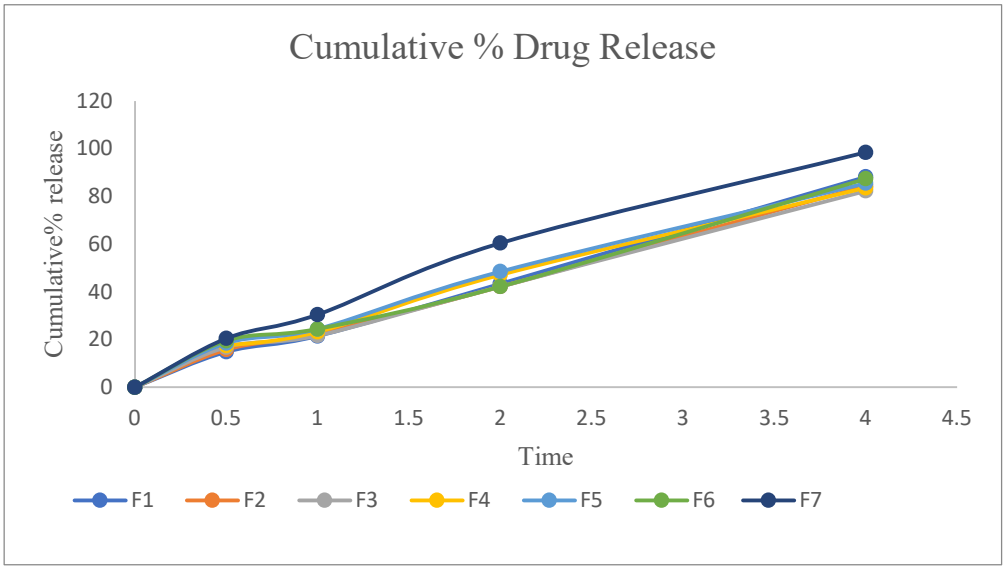

Figure 2: *In vitro* Cumulative % Drug Release profile of esomeprazole magnesium trihydrate

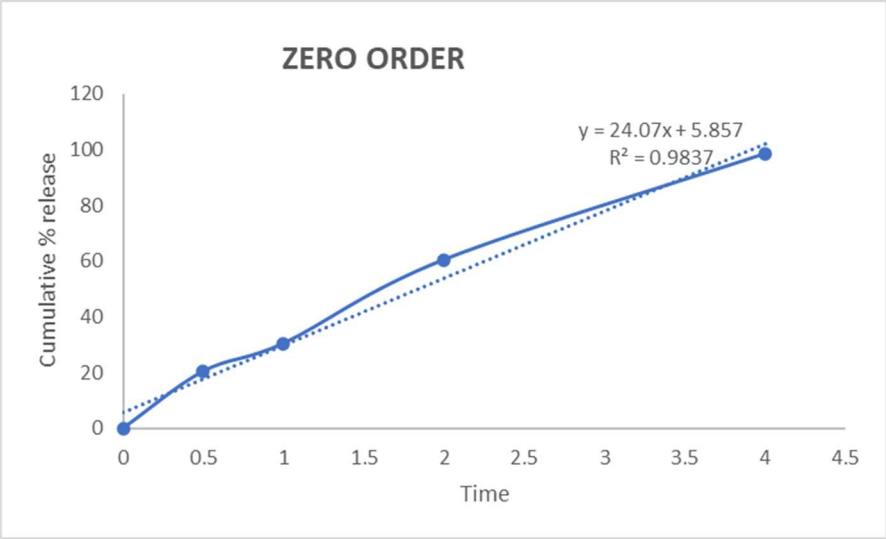

Figure 3: Zero order kinetics study of formulation F7

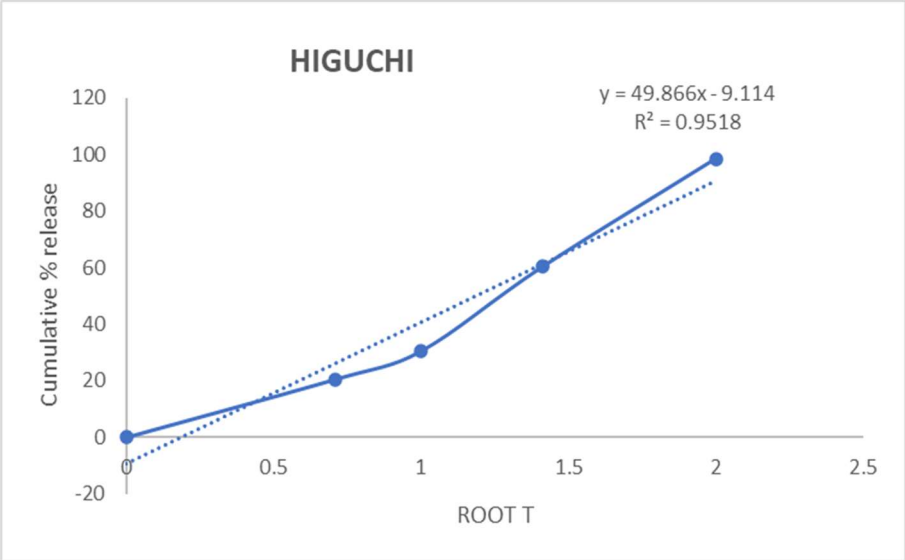

Figure 3: Higuchi plot of kinetics study of formulation F7

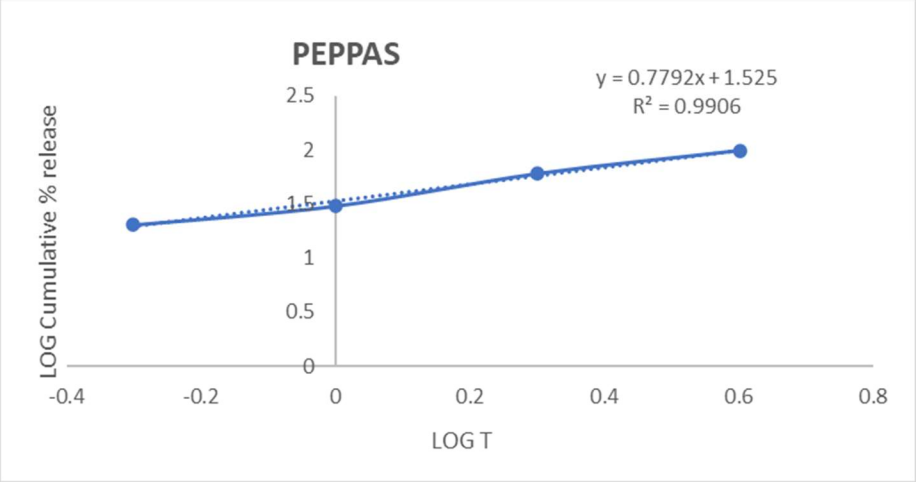

Figure 4: Peppas plot of kinetics study of formulation F7

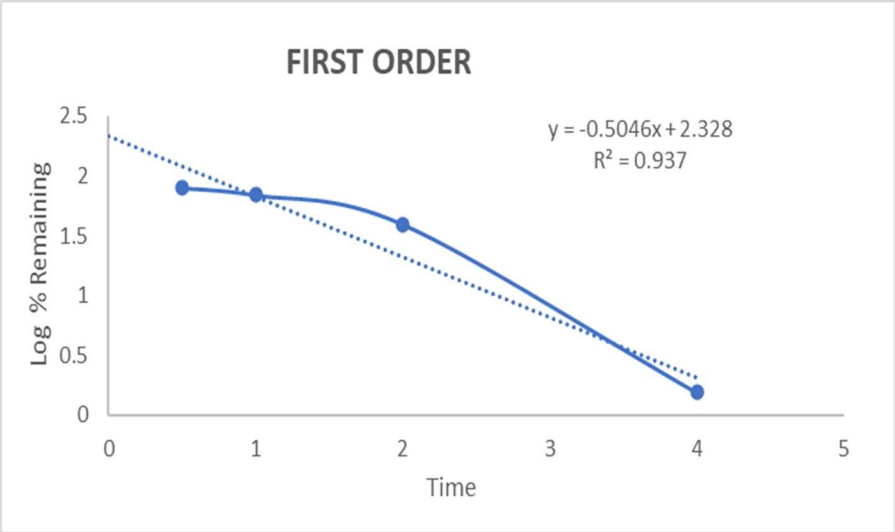

Figure 5: First order of kinetics study of formulation F7

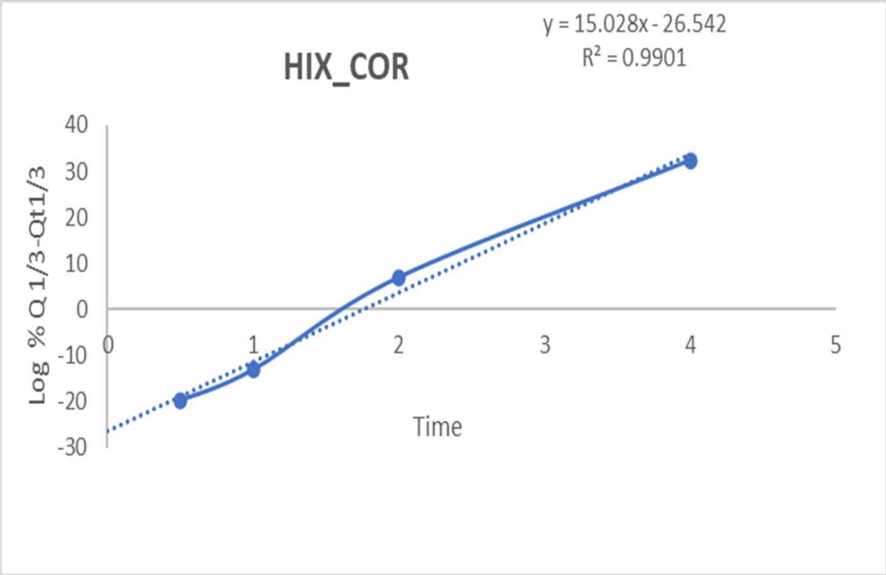

Figure 6: Hixcon cor of kinetics study of formulation F7

CONCLUSION

The Present study aims at developing esomeprazole magnesium trihydrate delayed release tablets adopting enteric coating technique. Esomeprazole Magnesium Trihydrate delayed release tablets were formulated by direct compression procedure and coated using concentrations of coating polymer.

FTIR of drug with excipients was done, drug and excipients were compatible in combination.

The prepared powders mixture was evaluated for precompressional properties such as Hausner's ratio compressibility index (%)

bulk density angle of repose. Results obtained indicate that powder bears good flow property for next procedures.

Tablets were evaluated for tests like Hardness thickness weight variation drug content friability and dissolution studies, parameters were found to be within the limits.

In vitro cumulative release was conducted for all formulations. Highest drug release was found to be 98.46+0.74%.

Hence the studies and results concluded that esomeprazole magnesium trihydrate delayed release tablets manufactured by adopting direct compression method.

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