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Research Article

FORMULATION AND EVALUATION OF ESOMEPRAZOLE MAGNESIUM DIHYDRATE MULTIPLE UNIT PARTICULATE SYSTEM (PELLETS) AS A DELAYED RELEASE DOSAGE FORM

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ABSTRACT

The present study was an attempt to formulate and evaluate enteric coated tablets for Esomeprazole magnesium dihydrate delayed release multi-particulate to reduce the Gastrointestinal tract side effects.The delayed release multiple units were prepared by using fluid-bed werster technology.These multiple units are selected by seal coating, drug coating and enteric coating.These Esomeprazole magnesium dehydrate were evaluated for assay, acid resistence, drug release,dissolution, Kinetic studies of Innovator and Optimized formulation, Stability studies of Optimized formulation. This study concluded Esomeprazole magnesium dihydrate can be prepared by using combination of polymers studied and we can reduce the GI tract side effects.

Keywords: Esomeprazole magnesium dehydrates, proton pump inhibitor, fluid-bed technique.

INTRODUCTION

Proton pump inhibitors are acid labile drugs. These drugs will degrade in acidic environment of stomach and will lead to therapeutic inefficacy. It is necessary to bypass the acidic pH of the stomach which can be achieved by formulating delayed release dosage forms (single unit or multiple units) by using different enteric polymers. Multiple unit particulate system offers better *invitro* release behavior than other dosage forms.

Delayed release coatings consist of pH sensitive polymers, which means the coating remains intact in the acidic environment of the stomach and then solubilizes in the more alkaline environment of the small intestine. Enteric protection for solid oral dosage forms is required to prevent gastric mucosal irritation, to protect a drug which is unstable in gastric fluids or to delay release for local delivery in the intestine. Colorcon's coating systems are based on a range of enteric polymers to suit the needs of the pharmaceutical formulator.

MATERIALS AND METHODS

Esomeprazole magnesium dihydrate(Hetero drugs) MCC (#60/#80) / celephere cp-2039Asakesi) Hypromellose (The Dow chemical company) Hydroxypropyl cellulose 3cp Meglumine(Merck) Polyvinylpyrrolidon(Basf) Methacrylic acid copolymer typeC(Degessa) Triethyl citrate(Morflex) Polyethylene glycol 400(Clariant) Polysorbate 80(Aqualon) Talc(Luzanac pharma) Purified water (Heterodrugs).

Formulations Trials (table no.1)

S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
DRUG COATING									
1.	Esomeprazole Mg	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5
2.	Sugarspheres 25/30	143.2	143.2	143.2	143.2	143.2	143.2	143.2	143.2
3.	Povidone K29/32	14	14	14	14	14	14	14	14
4.	Hydroxypropyl cellulose (HPC SSL)	3	3	3	3	3	3	3	3
5.	Talc	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
6.	Cross Povidone	-	-	-	-	-	-	-	7
7.	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
BARRIER COATING.									
8.	HPMC 5 CPS	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
9.	Sucrose	7	7	7	7	7	7	7	7
10.	Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
11	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
ENTERIC COATING									
12	Eudragit L30 -D55	-	57	-	57	60	60	60	60
13	Sodium Hydroxide	-	-	-	-	0.18	0.18	0.18	0.18
14	Triethylcitrate	6	5.7	6	5.7	7.5	7.5	6	9
15	Talc	6	6	6	6	6	6	6	6
16	Povidone K29/32	-	-	-	-	-	4.5	4.5	4.5
17	HPMC pathalate	50	-	50	-	-	-	-	-

was then scanned in UV range. This showed an absorption maximum at -- nm (Figure 2).

plotted. The concentration of the unknown was read from the calibration graph or computed from the regression equation.

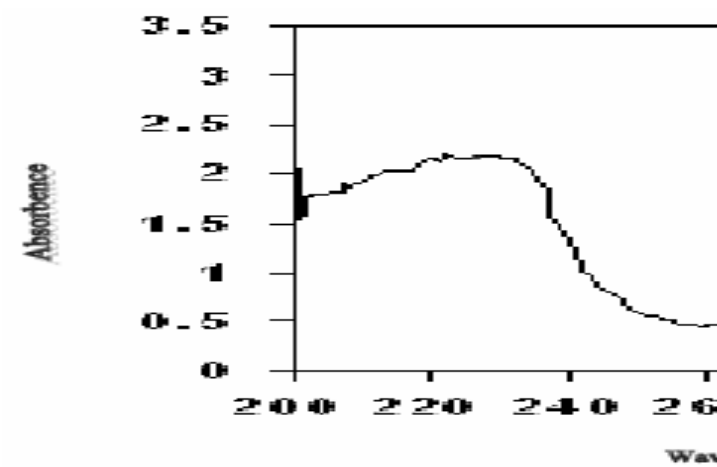

Fig.1 Esomeprazole Mg scanned in

METHODS

1. DRUG COATING:

a) Preparation of Drug suspension:

- Dispensed all the ingredients (Sugar spheres, Esomeprazole Mg, Povidone k29/32, HPC-SSL, Talc, Cross povidone and Purified water.

- Dissolve 14gms of Povidone k 29/32 in 240gms of purified water using lab stirrer (800r.p.m)
- Add Esomeprazole Mg and HPC-SSL to Step 2 under continuous stirring, stirred for 15 minutes and kept aside.
- Cross povidone and Talc were sifted through mesh 40# ASTM & dispersed in 408 g of purified water using lab stirrer.
- Step 3 was kept for stirring to this add Step 4 & stirred for 30 minutes (or) till it forms a homogenous suspension and kept under continuous agitation.

b) Coating of Drug suspension:

- Loaded 20/25 # Sugar spheres into fluid bed processor warmed for 10 minutes using the following process parameters.
- Sugar Spheres of Step 6 were coated with the drug suspension of Step 5 till a weight Gain of 99 % w/w.
- Drug loaded pellets of Step 7 were collected at 233gms.
- Drug loaded pellets of Step 8 were submitted to AR&D for Assay.

2) BARRIER COATING:

- a) PREPARATION OF BARRIER SUSPENSION:
- 1. Purified water was taken into beaker and HPMC 5CPS was added under continuous stirring.
- 2. Sucrose and Talc were added slowly to the step no.1 under continuous stirring.
- b) COATING OF BARRIER SUSPENSION:
- 1. Drug loaded pellets of step no 9 were loaded into FBP and the pellets were
- Warmed till the product temperature of 30-35˚c was obtained.
- 2. The sub coating dispersion of step A.1 was sprayed with following parameters.
- The dispersion was kept under continuous stirring during the coating process.
- The coating was continued till target weight build up was obtained.
- 3. The fluidization air flow was reduced to suitable level and the sub coated pellets
- Where dried at the product temperature of 33˚c-35˚c for 10 minutes.

3) ENTERIC COATING:

I. POLYMER USED HERE WAS HPMCP HP-55:

a) PREPARATION OF ENTERIC COATING SUSPENSION:

- IPA & dichloromethane was taken in 1:1 ratio in a stainless steel vessel.HPMCP-55 was slowly added to this solvent and the contents were mixed for 15 minutes under continuous stirring.
- TEC was taken into a beaker and purified water was added and mixed for 5 minutes.
- Solution of 2.A was added to Step 1.A under continuous stirring and mixed for about 10 minutes.
- Talc was added to solution of step 3.A, under continuous stirring and mixed for about 20 minutes.
- The dispersion of the above step was sifted through mesh # 100 and collected in a stainless steel vessel.

b) COATING OF ENTERIC SUSPENSION:

- The sub coated pellets of step no II .b.3., were loaded into FBP and the pellets were Warmed till product temperature 28˚c-35˚c.
- The enteric coating dispersion of step III .a.5 was started spraying with following Parameters. The dispersion was kept under continuous stirring, during the coating Process. The coating was continued till target weight build up was obtained.

II. POLYMER USED HERE WAS EUDRAGIT L30-D55:

a) PREPARATION OF ENTERIC COATING SUSPENSION:

- Purified water was taken in a stainless steel vessel Eudragit L30-D55 was slowly added to the purified water and the contents were mixed for 15 minutes under Continuous stirring.

- Added 4 % w/w solution of NAOH to step a.1.
- TEC was taken into a beaker and purified water was added and mixed for 5 minutes.
- Solution of step 3.A was added to step 2.A, under continuous stirring and mixed for About 10 minutes.
- Talc was added to solution of step 4.A, under continuous stirring and mixed for About 20 minutes.
- Povidone k 29/32 was added to step 5.A under continuous stirring.
- The dispersion of the above step was sifted through mesh # 100 and collected in a Stainless steel vessel.

b) COATING OF ENTERIC SUSPENSION:

- The sub coated pellets of step no II .B.3, were loaded into FBP and the pellets were Warmed till product temperature 28˚c-35˚c.
- The enteric coating dispersion of step III.A.7 was started spraying with following Parameters. The dispersion was kept under continuous stirring, during the coating Process. The coating was continued till target weight build up was obtained.

NOTE: In case, if lumps formation was observed during coating, unload the pellets and Sift through #18 or # 20 mesh.

- The fluidization air flow was reduced to suitable level and the pellets were warmed at the product temperature 28˚c-35˚c for 30 minutes.
- The enteric coated pellets were sifted through mesh # 18 and passed pellets were collected into a container.

EVALUATION OF DELAYED RELEASE FORMULATIONS AND COMPARISION WITH INNOVATOR

Delayed release formulations include enteric coated pellets and capsule formulations are evaluate for:

- Assay
- Acid resistance
- Drug Release
- Dissolution (acid stage followed by buffer stage)

ASSAY PROCEDURE

Assay procedure of standard solution

Weigh 10mg of Esomeprazole Mg and transfer into 50ml volumetric flask. The contents were ultrasonicated for 15min with 50ml of HPLC methanol and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with mobile phase. The solution was filtered using 0.45µm membrane filter. To calculate the percentage purity of drug.

Twenty capsule contents were weighed accurately. The average weight was determined and then ground to a fine powder. A quantity equivalent to 20mg was transferred to a 100ml volumetric flask. The contents were ultrasonicated for 15min with 50ml of HPLC methanol and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with mobile phase. The solution was filtered using 0.45µm membrane filter. The drug content per capsule (on an average weight basis) was calculated.

CHROMATOGRAPHIC CONDITIONS:

Apparatus	: WATERS
Pump	: LC28 model
Detectors	: SPD 20a
Injection Port	: Reodyne Injection
Software	: Spincron
Column	: symmetry c, 250×4.6, Mm, 5 µ
Flow rate	: 1.0 ml/min
Loop Capacity	: 20µg/ml
Column Temp	: Ambient
Mobile Phase	: Mixture of A&B (55:45% v/v)
pH	: *6.8*

- PREPARATION OF MOBILE PHASE :

  Prepare degassed mixture solution A & Solution B in the ratio of 55:45% v/v.

- PREPARATION OF SOLUTION A:

Transfer 2 ml of Trifluoroacetic acid into a beaker containing 1000 ml of water and mix. Filter through 0.45 µm membrane filter.

- PREPARATION OF SOLUTION B:

Transfer 2 ml of Trifluoroacetic acid into a beaker containing 1000 ml of acetonitrile and mix. Filter through 0.45 µm membrane filter.

Description of Dissolution test:

Acid Stage: 0.1NHCL, 1000ml, Basket, 100rpm, 2hrs

Sampling points: 30, 60, 120mins

Cumulative percentage of ESO release in 0.1N HCL

Time	F1	F2	F3	F4	F5	F6	F7	F8	Marketed product
30	0.5	0.9	0.7	0.5	0.9	0.8	0.6	0.1	0.3
60	1.2	1.3	1.1	2.3	1.4	1.4	0.8	0.4	0.8
120	1.6	1.7	1.3	3.1	1.6	2.5	1.3	0.8	1.4

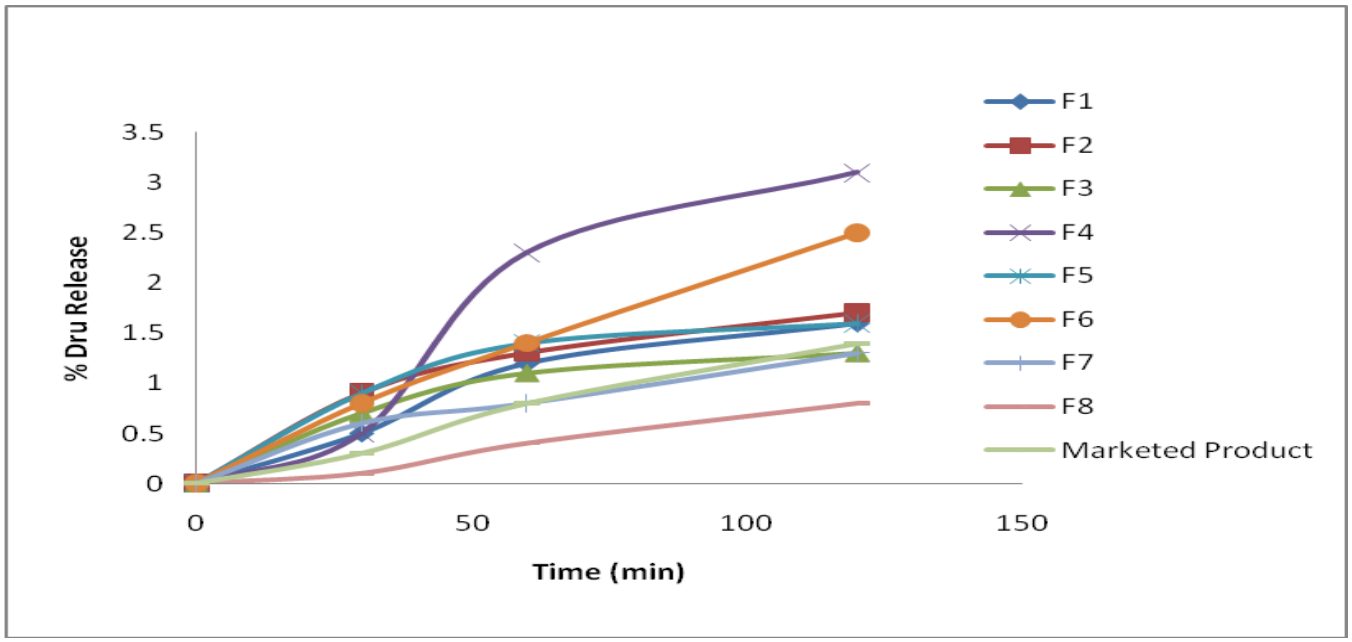

Fig.3 Cumulative percentage of ESO release in 0.1N HCL

Dissolution :

Buffer Stage: P^H 6.8 phosphate buffer, 1000 ml, and Basket 100 rpm

Sampling Points: 130, 150, 165, 180, 210 (minutes).

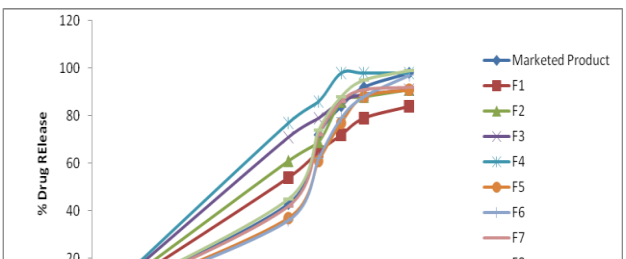

Table: Dissolution of Esomeprazole Magnesium dihydate in Phosphate

Time (min)	Marketed Product	F1	F2	F3
130	43	54±0.2	61±0.6	71±0.2
150	72	65±0.3	69±0.3	79±0.9
165	84	72±0.8	86±0.2	86±0.6
180	92	79±0.5	88±0.7	89±0.2
210	98	84±0.5	91±0.5	91±0.1

Acid Resistance: % Acid release= %Assay - % of Assay after acid treatment (Acid resistance)

FORMULATIONS	% ACID RESISTANCE
F1	98.4±0.12
F2	98.1±0.08
F3	98.4±0.04
F4	97.9±0.06
F5	98.2±0.10
F6	98.5±0.09
F7	98.9±0.07
F8	99.6±0.11

Assay Studies: By the above results, the F8 batch was selected. The retention time of F8 batch is 6.797minutes.

Invitro Studies

Acid Stage: Dissolution study of Esomeprazole Mg was carried out using 0.1N HCl. There was a slow release in the acidic medium, which has shown 0.8% of drug release in 120minutes. It was observed that the formulation showed Delayed release of the drug.

Buffer Stage: Dissolution study of Esomeprazole Mg was carried out using 6.8 pH phosphate buffer. There was maximum release in the buffer phase, which has shown 99% of drug release in 210minutes.

Acid Resistance: By the above results, the F8 batch was selected. The Percentage acid resistance of F8 was found to be 99.6%.

CONCLUSION

The present study was to formulate and evaluate delayed release Capsules of Esomeprazole magnesium dihydrate. The formulation process was carried out in FBW by suspension layering technique. The work was carried out to delay the release of Esomeprazole magnesium dihydrate by using enteric polymer Methacrylic acid copolymer (type C). The study includes preformulation of drug and excipients, formulation and evaluation, release kinetics and stability studies of capsules.

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