INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

DOI: https://dx.doi.org/10.33289/IJRPC.17.1.2023.13(9)

FORMULATION AND EVALUATION OF EXTENDED RELEASE PELLETS OF ESOMEPRAZOLE

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ABSTRACT

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 *in vitro* release behavior than other dosage forms. Esomeprazole possess higher bioavailability among all Proton pump inhibitors. The main aim of the present study was to formulate Esomeprazole magnesium trihydrate multiple unit particulate system (pellets) as a delayed release dosage form and study the *in vitro* release pattern. The results show that the formulation (E5) was stable. From all the above observations it was concluded that the formulation E5 with enteric coating delays the drug release in acid environment and showing maximum drug release in intestine and complies with the innovator product.

Keywords: Esomeprazole magnesium trihydrate, Hypromellose, Hydoxy propyl cellulose,

INTRODUCTION

The treatment of chronic diseases or acute illness has been achieved by the delivery of drugs to patients for many years. These drug delivery systems include tablets, suspensions, ointments, creams, Injectables, Aerosols and Capsules. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body [1-4].

An ideal drug delivery should fulfill following requirements:

1. The first is to deliver the drug at Rate dictated by the needs of the body over the period of treatment.
2. Spatial targeting to the specific sites.

These prerequisites provide a need for modified drug release technologies, which can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size and number of doses required.[5-8]

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum bioavailability, activity and stability. For most drugs conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic window. Some drugs also possess solubility problems. In such cases a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels. To overcome these problems, modified drug delivery systems were introduced. These delivery systems have number of advantages over the traditional systems such as improved efficacy, reduced toxicity and improved patient compliance. The main goal of modified drug delivery systems is to improve the effectiveness of drug therapies [9-12].

Modified release dosage forms can be defined as the one for which the release characteristics of time course and location are chosen to accomplish therapeutic or convenience objectives which are not offered by conventional dosage forms. Most modified release dosage forms are administered orally as tablets and capsules. Several types of

modified release dosage forms are available.

MANUFACTURING PROCESS
SUSPENSION LAYERING TECHNIQUE
SCREENING
Required quantity of microcrystalline cellulose spheres (Celphere spheres CP-203) were sifted through mesh #60.
Mesh #60 passed MCC spheres were sifted through mesh #80 and retain were collected.

Seal coating
Preparation of seal coating solution

- Required quantity of purified water was taken into stainless steel (SS) vessel and the purified water was heated to 60°C - 70°C.
- HPMC was added slowly to the hot water under continuous stirring for 15 minutes (or) till to get clear solution.

Seal coating

- MCC spheres after screening were loaded into FBP and warmed the microcrystalline cellulose spheres till product temperature of 40-45°C.
- Seal coating was started using the seal coating solution, with following parameters (after reaching the MCC spheres to the temperature of 33 – 35°C).The coating of pellets was continued till target weight.
- The fluidization air flow was reduced to suitable level and the seal coated pellets were dried at the product temperature of 33°C – 35°C.The pellets after drying were collected and sifted through mesh #50 and the mesh #50 passed pellets were collected.

Drug Coating
Preparation of Drug Suspension

- Purified water was kept for heating until it reached 60°C- 70°C and HPMC was added under continuous stirring for 30minutes (or) till clear solution was formed. Now add meglumine under continuous stirring.
- Polysorbate 80 was also added to the above solution under continuous stirring.
- Esomeprazole magnesium trihydrate was slowly added to the above solution and the stirring was continued for 45 minutes (or) till to form clear solution.

Coating of Drug Suspension

- The seal coated pellets were loaded into FBP and the pellets were warmed till the product temperature of 35 ± 3°C.
- Spraying of the prepared drug suspension was started with following parameters. The solution was kept under continuous stirring during the coating process. The coating was continued till the target weight build up was obtained.
- The fluidization air flow was reduced to suitable level and the coated pellets were dried at the temperature of 32°C – 38°C.

SUB COATING
Preparation of Sub coating dispersion
Purified water was taken into beaker and HPMC was added under continuous stirring. Tri ethyl citrate and Talc were added slowly under continuous stirring.

Coating of Sub coating dispersion:

- Drug loaded pellets were loaded into FBP and the pellets were warmed till the product temperature of 30 – 35°C was obtained.
- The sub coating dispersion prepared 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.
- The fluidization air flow was reduced to suitable level and the sub coated pellets were dried at the product temperature of 33°C–35°C for 10 minutes.

ENTERIC COATING
Preparation of Enteric coating Dispersion

- Purified water was taken in a stainless steel vessel. Methacrylic acid copolymer was slowly added to the purified water and the contents were mixed for 15 minutes under continuous stirring.
- Poly ethylene glycol 400 or Tri ethyl citrate was taken in to a beaker and purified water was added and mixed for 5 minutes.
- The Poly ethylene glycol 400 or Tri ethyl citrate solution was added to the polymer solution under continuous stirring and mixed for about 10 minutes.
- Polysorbate 80 was added to above mixture under continuous stirring.

- Talc was added to the above solution under continuous stirring and mixed for about 20 minutes.
- The total dispersion prepared was sifted through mesh #100 and collected in a stainless steel vessel.

Coating of Enteric dispersion

- The sub coated pellets were loaded into fluidized bed processer and the pellets were warmed till product temperature 28°C – 35°C.
- The enteric coating 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.

FORMULATION OF DELAYED RELEASE ESOMEPRAZOLE PELLETS

Table 1: Optimization of Seal Coating

S. No.	Ingredients	mg/unit		
1.	SEAL COATING	F1	F2	F3
2.	MCC Pellets (Celphere cp-203)	38	38	38
3.	Hypromellose 3cps	1	2	3
4.	Purified Water	35	35	35
	Total	39	40	41
	% Yield	65	95	95

Table 2: Optimization of Drug Coating

S. No.	Drug Coating	D1	D2	D3	D4	D5
1.	SEAL COATED PELLETS F2	40	40	40	40	40
2.	Esomeprazole magnesium trihydrate	43	43	43	43	43
3.	Hypromellose 3cps		10	15	17.5	22
4.	Povidone(pvp k17)	10	-	-	-	-
5.	Megulmine	2	2	2	2	2
6.	Polysorbate 80	1	1	1.5	2	2
7.	Purified water	200	200	220	240	240
	Total	96	96	101.5	104.5	109
	% Drug coated	69	80	91	99	98

Table 3: Optimization of sub coating

S. No.	Sub coating	S1	S2	S3
1.	Drug coated pellets(D4)	104.5	104.5	104.5
2.	Hydroxypropyl methyl cellulose 3cps	**3**	4	6
3.	Tri ethyl citrate		0.4	1
4.	Talc	1	1.5	1.5
5.	Purified water	50	60	75
	Total	108.5	110.4	113
	% Yield	85%	91%	96%

Table 4: Optimization of Enteric Coating

S. No.	Enteric Coating	E1	E2	E3	E4	E5	E6
1.	**S**ub coated pellets (S3)	113	113	113	113	113	113
2.	Methacrylic acid co polymer(Type3)	30	-	-	-	-	-
3.	Methacrylic acid co polymer(Type3) 30% Aqueous dispersion	-	134(40.2)	167(50.1)	217(65.1)	234(70.2)	250(75)
4.	Tri ethyl citrate	-	-	5	6.5	7	7.5
5.	polyethylene glycol 400	3	4	-	-	-	-
6.	Talc	6	8	10	13	14	15
7.	Polysorbate 80	0.45	0.6	0.75	0.97	1.05	1.13
	Total	152.45	165.8	178.85	198.57	205.25	211.63

Table: 5 Optimized Formulation

S.No.	Ingredients	mg/unit
1	MCC pellets(Celphere cp-203)	38
2	Hypromellose 3cps	2
3	Purified water	35
	Total	**40**
II	**DRUG COATING(D4)**	
4	Seal Coated Pellets	40
5	Esomeprazole magnesium Trihydrate	43
6	Hypromellose 3cps	17.5
7	Megulmine	2
8	Polysorbate 80	2
9	Purified water	240
	Total	**104.5**
	%drug coated	99
III	**SUB COATING(S3)**	
10	Drug coated pellets	104.5
11	Hydroxypropyl methyl cellulose	6
13	Tri ethyl citrate	1
14	Talc	1.5
15	Purified water	75
	Total	**113**
IV	**ENTERIC COATING(E5)**	
16	Sub coated pellets	113
17	Methacrylic acid copolymer(type c)30% aqueous dispersion	234(70.2)
18	Triethyl citrate	7
19	Talc	14
20	Polysorbate 80	1.05
21	Purified water	180
	Total	**205.25**

Flow properties

Angle of repose

Angle of repose is determined as the maximum angle possible between the surface of the pile of the powder and horizontal plane.

Fixed funnel method was used to determine the angle of repose of powder or granules. pile and diameter (d) of was noted from the diameter, radius (r) was calculated. The angle of repose (Θ) can determined by following equation

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

Where,

Θ= Angle of repose

h = Height of pile

r = Radius of base of the pile

Bulk Density

Weighed amount of the powder blend was taken and transferred to a measuring cylinder. Bulk volume of the blend is noted as per the reading on the measuring cylinder.

Bulk density is calculated using following formula;

Bulk density = Mass of the blend / Bulk volume of the blend

Tapped density

Tapped density is determined by the weighed quantity of powder blend is poured into the graduated cylinder, which is then tapped for 100 taps.

Tapped density is calculated by using following formula,

Tapped density = Mass of blend/ Tapped volume of the blend

Compressibility Index

Compressibility index is important to measure the tendency of powder formulation.

It indicates the flow properties of the blend. Low percentage of compressibility index indicates free flowing powder, whereas high compressibility index indicates poor flowing powder. Compressibility index was calculated from the readings of bulk density and tapped density. The results were shown in Table 3 and Fig. 1.

$$CI = (TD-BD) \times 100/TD$$

Where,

CI = Compressibility index

TD = Tapped density

FTIR STUDIES

The IR spectrum of pure drug was found to be similar to the standard spectrum of Esomoprazole. The spectrum of vshows the following functional groups at their frequencies from the spectra of Esomoprazole, combination of Esomoprazole with polymers, it was observed that all characteristic peaks of Esomoprazole were not altered and present without alteration in the combination spectrum, thus indicating compatibility of the drug and polymers. FTIR spectra and Optimized formulation are shown in Figure 2 and 3 respectively.

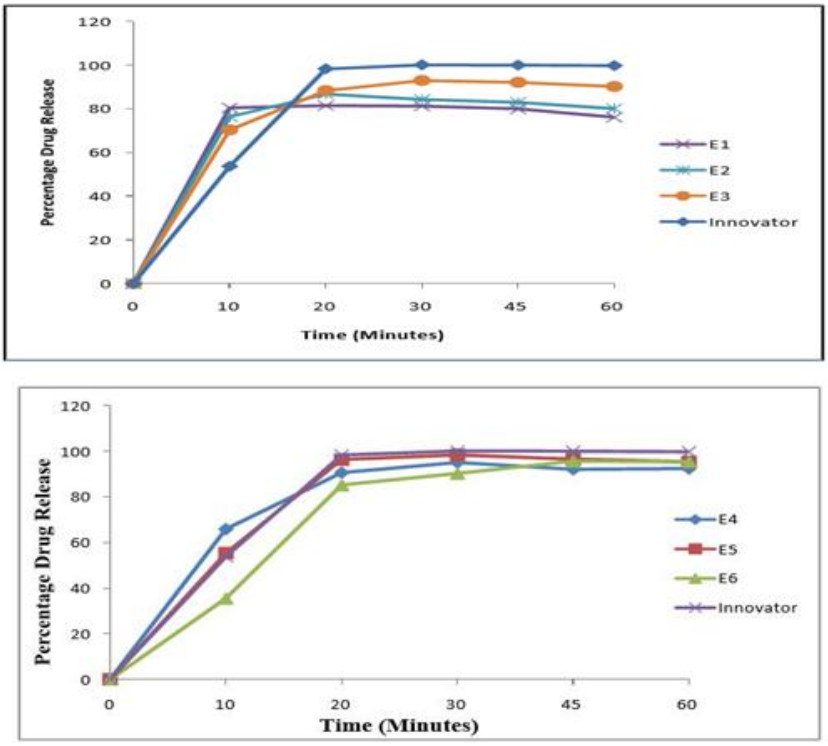

Fig. 1: *In-vitro* dissolution data of formulations

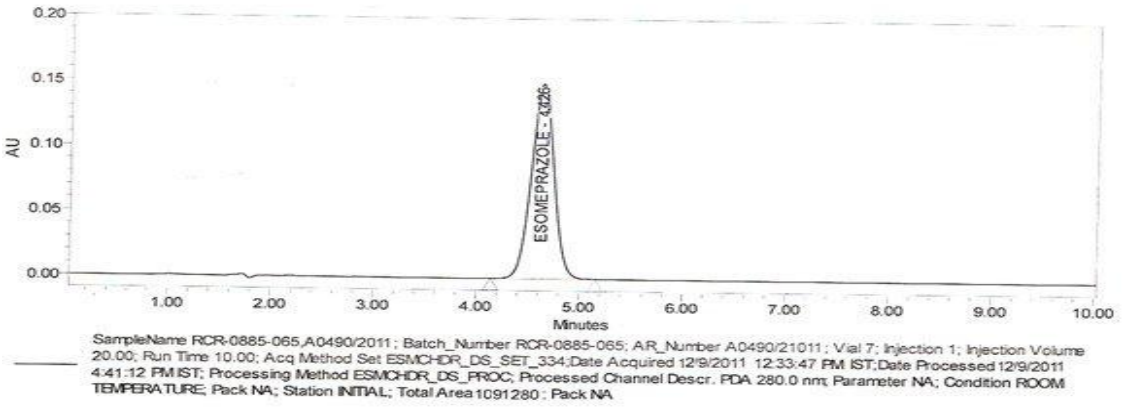

Fig. 2: FTIR spectrum of Esomeprazole

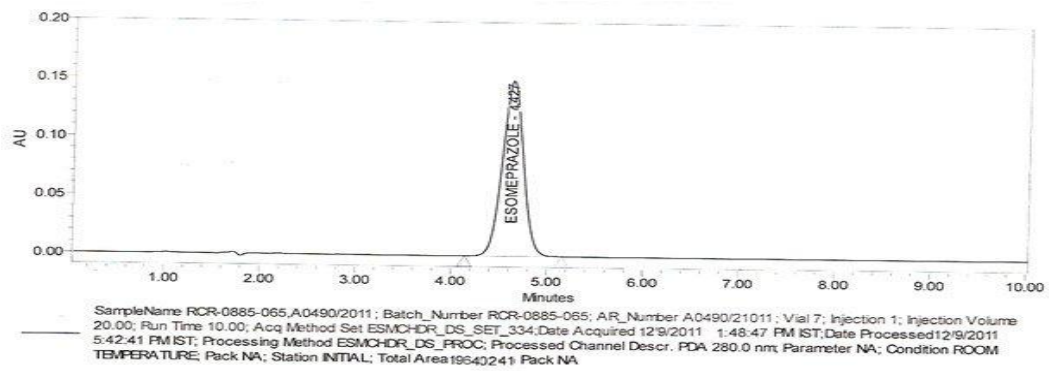

Fig. 3: FTIR spectrum of Optimized Formulation

RESULTS AND DISCUSSION

Esomeprazole belongs to a class of compounds called proton pump inhibitors (PPI), substituted bezimidazole, which inhibit the final common step in gastric acid secretion. The present study was to formulate and evaluate delayed release pellets of Esomeprazole magnesium trihydrate. The formulation process was carried out in Fluidized bed dryer by suspension layering technique. Esomeprazole magnesium trihydrate is an acid labile drug, degrades at acidic pH of stomach. To bypass stomach, the formulation has to delay the release and give the release in proximal small intestine. This can be achieved by enteric coating. The work was carried out to delay the release of Esomeprazole magnesium trihydrate by using enteric polymer Methacrylic acid copolymer (type C). The study includes Prefomulation of drug and excipients, formulation and evaluation, and stability studies of pellets. The inert core material (i.e. Celphere CP-203) was given Seal coating, Drug coating, Sub coating and Enteric coating. Seal coating was given to Celphere CP-203 with Hypromellose 3cps to provide mechanical strength to the pellets. Drug coating was given to seal coated pellets by using different binders i.e., Hydroxy propyl methyl cellulose 3cps and Povidone (k-17) with different concentrations. The amount of drug bound to seal coated pellets increases with an increased concentration of Hydroxy propyl methyl cellulose (17% and 22%). But at high concentration of Hydroxy propyl methyl cellulose (22%), lumps were observed. Finally 17% w/w Hydroxy propyl methyl cellulose was optimized as binder for drug coating. Sub coating was given to drug loaded pellets to avoid direct contact with enteric coating. Sub coating was given with Hydroxy propyl methyl cellulose and Tri ethyl citrate combination at an average weight build up of 4.13% w/w of sub coated pellets Enteric coating was given to Esomeprazole magnesium trihydrate pellets by Meth acrylic acid copolymer type C and Methacrylic acid copolymer type C(30% aqueous dispersion). Six formulations E1, E2, E3, E4, E5, E6 were formulated. For E1 formulation solid enteric polymer coating polymer was given, but due to high viscosity of the polymer 30% aqueous dispersion of enteric polymer was used for further formulations. In enteric coating, plasticizer plays major role in film formation. Among Tri ethyl citrate and Polyethylene glycol 400, Triethylcitrate was found to have good film forming capacity. Plasticizer concentration was optimized at 10% of dry polymer weight.

Evaluation studies were conducted for all formulations E1, E2, E3, E4, E5, E6 i.e, assay acid resistance and dissolution in buffer stage. The results obtained are compared with the USP limits and compared with the innovator product. Out of six formulations. the formulation E5 results were within limits and shows similar drug release profiles with innovator product. E5 formulation showed assay 99.7 %(±0.42)and acid resistance 99.5%(±0.06) were within limits. Comparative in vitro dissolution study of formulation E5, and innovator product shows that the percentage drug release in acid stage at end of two hours was 0.2±0.05 and 0.3±0.01 respectively, and in buffer stage 98.37±0.58 and 100.12±0.63 respectively after 30 minutes.

IR spectroscopic analysis of drug with polymers shows that the drug was compatible with polymers which were used in the formulation. The accelerated stability studies of optimized formulation (E5) AT 40^{o}C/75% RH for a period of 3 months indicated that there were no significant changes in color, assay, acid resistance and in vitro dissolution profiles. The results show that the formulation (E5) was stable. From all the above observations it was concluded that the formulation E5 with enteric coating delays the drug release in acid environment and showing maximum drug release in intestine and complies with the innovator product.

CONCLUSION

Comparative in vitro dissolution study of formulation E5, and innovator product shows that the percentage drug release in acid stage at end of two hours was 0.2±0.05 and 0.3±0.01 respectively, and in buffer stage 98.37±0.58 and 100.12±0.63 respectively after 30 minutes. From all the above observations it was concluded that the formulation E5 with enteric coating delays the drug release in acid environment and showing maximum drug release in intestine and complies with the innovator product.

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