JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

STUDIES OF ESOMEPRAZOLE DELAYED RELEASE FORMULATION

Correspondence author's: [1]Mr. Harish Kumar Singh, [1]Mr. Krishna Prasad Mehta, [1]Ms. Shweta Kumari, [2]Dr. Anurag Jain, [2]Dr. Prabhakar Budholiya

[1]Government Pharmacy, College Rohtas, Bihar
[2]Government Medical College Ratlam (M.P.)

In this study Esomeprazole enteric coated tablets were prepared by using Eudragit(L30D) to provide desired effect at certain time in maintained drug concentration without any side effect with patient compliance also to improve it bioavailability by decreasing its expose to gastric acid. Esomeprazole is used in the treatment of peptic ulcer disease, gastroesophageal reflux disease and Zollinger-Ellison syndrome and Crohn's disease. PPIs such as Nexium reduce stomach acid secretion. The tablets which are prepared by compaction of coated pellets are called as Multiple Unit Pellet Systemstablets. Pellets are produced for the purpose of oral controlled release dosage form having gastro resistant or sustained release properties. For such purpose, coated pellets are administered in the form of MUPS tablets. A delayed release dosage form is designed to release the drug from the dosage form at a time other than promptly after administration. Thus a pharmaceutically equivalent, robust formulation of Esomeprazole delayed release tablet was developed.

Keywords: Esomeprazole, Enteric coating, Delayed release tablets, In vitro drug releas

1. INTRODUCTION

Multiple Unit Pellet Systems (MUPS) tablets are widely used in solid dosage form design. MUPS is considered to provide pharmacokinetic advantages compared to monolithic dosage forms. Pellets are produced primarily for the purpose of oral modified release forms having gastro resistant, sustained-release properties and the capability of Pulsatile Drug Delivery Systems. Coated pellets are administered in the form of hard gelatin capsules or disintegrating tablets that quickly disperse in the stomach. The safety and efficacy of the formulation is higher than that of other dosage forms. Pellets provide high degree of flexibility during the design and development of oral dosage forms. They can be divided into desired dose without formulation or process changes, and can also be blended to deliver incompatible agents simultaneously or particles with different release profiles at the same site or at different sites within the gastrointestinal tract.

Orally administered pellets generally disperse freely in the gastrointestinal tract and maximize the drug absorption, minimize local irritation of the mucosa for certain irritant drugs. The most widely used processes are extrusion and spheronization, solution or suspension layering, and powder layering. Other processes with limited application in the development of pharmaceutical pelletized products include globulation, balling,

and compression. The compression of pelletsinto tablets is a novel technology and is much more ideal than filling them into capsule.

1.1 MUPS tablets

MUPS tablets are widely used in solid dosage form design. MUPS is advantageous in comparison to monolithic dosage forms. Combination of drug substances and release profiles can be provided by formulating the MUPS tablets with different pellet qualities or combining pellets with drugs in powder or granulated form. MUPS tablet contains several hundred of coated pelletsof active pharmaceutical ingredients which delivered the drug at predetermined rate and absorption to provide constant blood profile. MUPS are easily administered as disintegratable tablet which disperse into their subunits across the stomach and the small intestine, leading to predictable oral transition and constant bioavailability.

1.2 Advantages of MUPS tablets:

1.Easy handling.

2.Smaller volume/size of tablet leads to Better patient compliance than capsules.

3. Lower tendency of adhering to esophagus during swallowing.

4. Lower production costs.

5. Reduced risk of tampering.

6. Ability to incorporate large dose of drug in controlled release form in comparison to capsules.

7. Greater stability of drug and the formulation owing to small size and absence of gelatin shell.

1.3 DISADVANTAGES

The drawback of multiple-unit modified -release dosage forms are that their manufacture istechnically more complicated, time – consuming and expensive.

1. Compaction of pellets into tablets is a complex technology.

2. For disintegration into their subunits within short time, they should retain the dissolutionprofile of the original subunits.

3. The transit time in the colon for the multiple units was longer compared to the monolithicsystem.

4. The multiple-unit systems may well be longer than for monolithic systems.

5. Process development and scale-up is more challenging /time consuming.

1.4 APPLICATION OF MUPS:

1. To protect drugs that are unstable in acid from disintegrating in the gastric juice e.g.antibiotics enzymes, peptides proton pump inhibitors.

2. PH Dependent controlled release of drugs for optimal absorption.

3. GI targeting of different sections of small intestine or of the colon (absorption window, targeting

localized effects).

4. Combination of drug substances and release profiles can be provided by formulating the MUPS tablets with different pellet qualities or combining pellets with APIs in powder orgranulated form.

2. PREFORMULATION STUDIES

2.1 Pre-compression evaluation parameters

A. Solubility study

According to the Biopharmaceutical Classification System (BCS) drug substances of esomeprazole is absorption is limited by the permeation rate but the drug is solvated very fast. Solubility class boundaries are based on the highest dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1 to 7.5.

B. Angle of repose

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\tan\theta = \frac{h}{r}$$

$$\theta = \tan^{-1}\frac{h}{r}$$

Where, **θ** = angle of repose,

h = height,

r = is the radius.

Table 2.1 Relationship between angle of repose (θ) and flow properties

S.NO.	Flow ability	Angle of repose
1	Excellent	<25
2	Good	25-30
3	Moderate flow	30-40
4	Poor flow	>40

C. Bulk Density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve #20) into a measuring cylinder and initisl weight was noted. This initial volume is called the bulk volume.

It is expressed in g/ml and given by

$$D_b = M/Vb$$

Where,

M is the mass of powder

Vb is the bulk volume of the powder

D. Tapped density

It is the ratio of the total mass powder to the tapped volume of the powder. It was determined by placing a graduated cylinder, containing a known mass of drug and expedients. The cylinder wasallowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second interval. The tapping was continued until no further change in the volume was noted.

$$D_t = M/Vt$$

Where,

M = is the mass of powder

V = is the tapped volume of the powder.

D. Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the followingformula,

$$\text{Hausner's ratio} = t/d$$

Where,
t is the tapped density

d is bulk density

Lower H (<1.25) indicates better flow properties than higher ones (>1.25)

Table 2.2 Hausner's index

Sr. No.	Hausner's Ratio	Type of flow
1	1-1.11	Excellent
2	1.12-1.18	Good
3	1.19-1.25	Fair
4	1.26-1.34	Passable
5	1.35-1.45	Poor
6	1.46-1.59	Very poor
7	>1.60	Extremely poor

E. Compressibility index

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of material because all of these can influence the observed compressibility index.

$$\text{Carr's Index \%} = D_t - D_b \times 100 / D_t$$

Where,

D_b = Loose Bulk Density D_t = Tapped Bulk Density

Table 2.3 Compressibility index

Carr's index %	Type of flow
5-15	Excellent
12-18	Good
18-23	Satisfactory
23-35	Poor
35-38	Very poor
>40	Extremely poor

F. Compression of coated pellets

Compaction of coated multi-particulates into tablets could result either in disintegrating tablets providing a multi-particulates system during GI transit or in intact tablet due to the fusion of the multi-particulates in a larger compact. Ideally, the compacted pellets should disintegrate rapidly in the individual pellets in gastrointestinal fluids. The pellets should not fuse into a non- disintegrating matrix during compaction. The drug release should not be affected by the compaction process.

2.2 FORMULATION DEVELOPMENT

Formulation studies Esomeprazole Delayed Release Pellets:

Formulation studies Esomeprazole GR Delayed release Pellets is based on Pre-formulation dataof various excipients selected and their compilation was shown in the following Table.

Table 2.4 Formulas and their quantities as per percentage w/w

ESOMEPRAZOLE GR PELLETS 22.5% W/W						
S.NO.	**INGREDIENTS**	**F1**	**F2**	**F3**	**F4**	**F5**
I	**Pre-Coating(4%w/w)**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**
1.	Sugar Spheres 45#60	21.87	22.00	23.44	20.12	29.62
2.	Hypromellose E5	2.00	2.00	1.00	2.00	2.00
3.	Talc	0.50	0.375	0.50	0.50	0.50
4.	Purified Water	Qs	Qs	Qs	Qs	Qs
II	**Drug loading (10%w/w)**					
5.	Esomeprazole Mg. Trihydrate	25.06	25.06	25.06	25.06	25.06
6.	Hypromellose E5	6.27	6.27	4.70	6.27	6.27
7.	Purified Water	Qs	Qs	Qs	Qs	Qs
III	**Seal Coating (8% w/w)**					
8.	Hypromellose E5	8.00	8.00	8.00	7.50	8.00
9.	PEG 6000	0.80	0.80	0.80	0.80	0.80

10.	Magnesium stearate	1.00	1.00	1.00	0.75	1.00
11.	Purified Water	Qs	Qs	Qs	Qs	Qs
IV	**Enteric Coating (15%w/w)**					
12.	Eudragit L 30D	30.00	30.00	30.00	30.00	22.50
13.	PEG 6000	3.00	3.00	3.00	3.00	3.00
14.	Talc	1.00	1.00	1.00	1.00	0.75
15.	Titanium dioxide	0.50	0.50	0.50	0.50	0.50
16.	Purified Water	Qs	Qs	Qs	Qs	Qs
	Pellets weight	**100**	**100**	**99**	**97.5**	**100**

2.5 Tabletting (for 40mg strength)

Esomeprazole MUPS Tablet 40 mg							
S.N.	**INGREDIENTS**	**F1 mg**	**F2 mg**	**F3 mg**	**F4 mg**	**F5 mg**	**F6 mg**
1	Esomeprazole pellets	177.78	177.78	177.78	177.78	177.78	177.78
2	MCC PH 102	308.22	297.72	309.76	314.52	317.6	311.9
3	PEG 6000	48.00	58.50	48.00	48.00	48.00	48.00
4	Aerosil	3.00	3.00	1.46	3.00	3.00	3.00
5	L-HPC-LH 11	18.00	18.00	18.00	11.70	18.00	18.00
6	Crosspovidone	24.00	24.00	24.00	24.00	14.62	14.62
7	Magnesium stearate	6.00	6.00	6.00	6.00	6.00	11.70
	Core Tablet Weight	**585**	**585**	**585**	**585**	**585**	**585**
VI	**Film coating(12%w/w)**						
8	Opadry Red	15.00	15.00	15.00	15.00	15.00	15.00
9	Purified Water	Qs	Qs	Qs	Qs	Qs	Qs
	TOTAL TABLET WEIGHT	**600**	**600**	**600**	**600**	**600**	**600**

2.3 MANUFACTURING PROCESS:

2.3.1 PRE-COATING

Preparation of Pre-Coating Solution

a. Take the Purified Water.

b. Dissolve the Hypromellose E5 in Purified Water with continuous stirring.

c. Disperse the Talc in Purified Water with continuous stirring.

d. Finally pass the above solution through (#200) Nylon cloth and collect the solutionseparately.

COATING

a. Load the Sugar Spheres pellets into FBC bowl.

b. Set the Inlet temperature to 55-60°C, Bed temperature 40-45°C.

c. Dry the pellets in FBC for about 10 min before unloading.

d. Sift the dried pellets through # 35 and collect # 35 retains and passing separately.

e. Now pass # 35 passing pellets through # 40 and collect retains and passing separately.

2.3.2 DRUG LOADING

Preparation of Drug Loading Solution

a. Take the Purified Water.

b. Dissolve the Hypromellose E5 in purified water with continuous stirring.

c. Then dissolve the Esomeprazole Mg. stearate in purified water with continuous stirring.

d. Finally pass the above solution through (#200) Nylon cloth and collect the solutionseparately.

COATING

a. Load the Pre-Coating pellets into FBC bowl.

b. Set the Inlet temperature to 55-60°C, Bed temperature 40-45°C.

c. Sift the dried pellets through # 35 and collect # 35 retains and passing separately.

d. Now pass # 35 passing pellets through # 40 and collect retains and passing separately.

2.3.3 SEAL COATING

Preparation of Seal Coating Solution

a. Take the Purified Water.

b. Dissolve the Hypromellose E5 in purified water with continuous stirring.

c. Then dissolve the PEG 6000 in purified water with continuous stirring.

d. Disperse the Mg. stearate in purified water with continuous stirring.

e. Finally pass the above solution through (#200) Nylon cloth and collect the solutionseparately.

COATING:

a. Load the Pre-Coating pellets into FBC bowl.

b. Set the Inlet temperature to 55-60°C, Bed temperature 40-45°C.

2.3.4 SIFTING

a. Sift the dried pellets through # 35 and collect # 35 retains and passing separately.

b. Now pass # 35 passing pellets through # 40 and collect retains and passing separately.

2.3 .4 ENTERIC COATING

Preparation of enteric Coating Solution

a. Take the Purified Water.

b. Dissolve the Eudragit L 30D in purified water with continuous stirring.

c. Then dissolve the PEG 6000 in purified water with continuous stirring.

d. Disperse the Talc in purified water with continuous stirring.

e. Finally pass the above solution through (#200) Nylon cloth and collect the

f. Solution separately.

COATING

a. Load the Pre-Coating pellets into FBC bowl.

b. Set the Inlet temperature to 55-60°C, Bed temperature 40-45°C.

c. Coat the Enteric coated pellets by bottom spray wurster at peristaltic pump rpm of 2-3 and atomizing air pressure of 0.8-1.4 Kg/cm² with pre-coating solution till the coating solution is completed.

d.Dry the pellets in FBC for about 10 min before unloading.

SIFTING

a. Sift the dried pellets through # 35 and collect # 35 retains and passing separately.

b. Now pass # 35 passing pellets through # 40 and collect retains and passing separately.

2.3.5 DIRECT COMPRESSION

a. Granulation of excipients

b. Compression process was performed using prosolve, Colloidal Silicone Dioxide, Polyethylene Glycol 6000, L-HPC-LH 11, and Crospovidone in order to compare the particle size of excipients with the pellets. The blend was sifted #40 through a Vibro sifter.

c. Blended the above mixture through the Double Cone Blender. After then # 60 sifted Mg. Stearate was added to the step0000 mixtures and added Esomeprazole ER Lubricated Pellets.

d. With the help of laboratory size Double Cone blender, the components of coated pellets; granular excipients and lubricant were blended uniformly.

2.3.6 Tabletting

Esomeprazole coated pellets were compressed into tablets with a thickness of 6.5 mm using 11 ×

8.5 mm punch. Compression of tablets in an industrial type machine was performed using 24 station rotary tablet press (Cadmach, Mumbai).

3. EVALUATION OF TABLETS

3.1 Post-compression parameters

A. Shape and color of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and color was observed by keeping the tablets in light.

B. Uniformity of thickness

Three tablets were picked from each formulation randomly and thickness was measured individually. It is

expressed in mm and standard deviation was also calculated.

C. Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in Newton(N). Three tablets were randomly picked and hardness of the same tablets from each formulation was determined. The mean and standard deviation values were also calculated.

D. Friability Test

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W initial) and transferred into Friabilator. The Friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W final). The % friability was then calculated by,

$$F = W_{initial} - W_{final} \times 100 / W_{initial}$$

% Friability of tablets less than 1% are considered acceptable.

E. Weight Variation Test

20 tablets were selected randomly from each formulation and weighed individually to check for weight variation. The US Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed:

$$\% \text{ of Weightt Variation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Table 3.1 Percentage deviation in weight variation

Average weight of a tablet	Percentage deviation
130 mg or less	10%
130 mg to 324 mg	7.5%
More than 324 mg	5%

F. In vitro Disintegration Test

The process of breakdown of a tablet into smaller particles is called as disintegration. The in vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 phosphate buffer maintained at 37±2 C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 phosphate buffer maintained at 37±2C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

In vitro release studies were carried out using tablet dissolution test apparatus USP II. Two objectives in the development of in vitro dissolution tests are to show:

1. That the release of the drug from the tablet is as close as possible to 100% and
2. That the rate of drug release is uniform batch to batch and is the same as the release ratefrom those batches proven to be bio-available and clinically effective.

Table 3.2 In-vitro drug release studies

Apparatus used	USP 1 dissolution test apparatus
Dissolution medium	pH 6.8 phosphate buffer/ pH 0.1N HCl
Dissolution medium volume	900 ml
Temperature	37±0.5°C
Speed of basket paddle	100 rpm
Sampling intervals	5 min
Amount of sample withdrawn	5 ml
Absorbance measured	274, 243.5 nm

G. Excipients Compatibility Studies

Compatibility studies were carried out to study the possible interactions between Esomeprazole Mg. Trihydrate and other inactive ingredients in the formula.

Accelerated Compatibility Studies

The physical compatibility of Esomeprazole mg. trihydrate drug substance with various excipients was carried out with an aim to select suitable excipients for a stable and robust formulation. A blend of drug with the excipients in suitable ratios(1:5) was filled in double linedpoly bag (for exposing to 40° C /75% RH) and filled in glass vials to keep at 60° C. They were observed for any physical change against control samples kept at refrigerated condition (4°C).

Calibration curve of Esomeprazole mg. trihydrate Calibration Curve of Esomeprazole mg. trihydrate method **Preparations of drug stoke solution**

Accurately weigh about 10 mg of ESOMEPRAZOLE and transferred to 100 ml volumetric flask.To it 40 ml of ethanol was added to the dissolve the drug completely with vigorous shaking then the volume was made up with distilled water up to the mark to give the drug stoke solution of concentration 100 µ/ml.

Preparation of standard drug dilution

Stoke solution of ESOMEPRAZOLE appropriate volume were pipette out and transfer to 10 ml volumetric flask. The volume was made up to the mark with glass distilled water to give the sample of desired concentration.

H. STABILITY STUDIES

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This includes storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behavior and properties of the drug substance and formal stability studies on the drug substance.

Storage Conditions

In general, a drug product should be evaluated under storage condition that tests its stability and if applicable, its sensitivity to moisture or potential for solvent loss. The long term testing should cover a minimum of 12 months study or at least three batches at the time of submission and should be continued for a period of sufficient time till it covers the proposed shelf life. Accelerated, intermediate storage conditions for drug products are given below.

Storage Conditions in Stability Study: Stability samples are stored at:

A. Accelerated= 40±2°C/75±5% RH.
B. Intermediate =30±2°C/65±5% RH.
C. Long term= 25±2°C/60±5% RH.

4. RESULT OF PRE-FORMULATION STUDIES

A. Solubility studies

Table 4.1 Solubility study

Sr. No.	SOLVENTS	RESULT
1	Water	Slightly soluble in water
2	Methanol	Soluble
3	Heptane	Insoluble
4	Acetone	Insoluble

B. Angle of repose

The angle of repose for various powder blends are show in table below:

Table 4.2 Angle of repose

S.No.	Formulation	Angle of repose(^{0})	Type of flow
1	F1	44.66	Very poor
2	F2	47.43	Very poor
3	F3	34.38	Moderate flow
4	F4	28.52	Good
5	F5	24.7	Very good

Discussion-

- The values of angle of repose of formulations F1and F2 indicating very poor flow properties.
- F3 indicating moderate flow properties
- F4 indicating good flow properties
- F5formulation shows very good flow properties

C. Bulk Density and Tapped Density Studies

Table 4.3 Bulk density and Tapped density studies of Esomeprazole

Sr. No.	Formulation	Bulk density (g/ml)	Tapped density (g/ml)
1	F1	0.923±0.26	0.989±0.21
2	F2	0.937±0.29	1.0048±0.34
3	F3	0.921±0.17	0.988±0.26
4	F4	0.934±0.14	0.991±0.35
5	F5	0.915±0.36	0.959±0.15

D. Hausner's Ratio and Compressibility Index Studies

Table 4.4 Hausner's ratio and compressibility index studies

Sr. No.	Formulation	Hausner's ratio	Carr' s Index
1	F1	1.07±0.25	5.47±0.31
2	F2	1.07±0.26	5.71±0.37
3	F3	1.07±0.24	4.38±0.41
4	F4	1.06±0.26	4.96±0.27
5	F5	1.04±0.13	5.21±0.26

4.2 EVALUATION OF MULTIPLE UNIT PELLET SYSTEMS TABLETS:

a. Post compression parameter

Shape and Color of tablets

- Shape of the tablets: Capsule-shaped
- Color of the tablets: Off-white.

b. Weight variation

Ten tablets are individually weighed of the formulation.

Table 4.5 Weight variation values of all formulation F1-F5

S.NO.	Formulation	Average Weight of tablet (mg)	Weight variation (%)
1	F1	595.2	1.6
2	F2	592.1	1.3
3	F3	591.6	1.42
4	F4	595.9	0.688
5	F5	598.4	0.267

c. Uniformity of thickness

Table 4.6 Thickness values of all formulation F1-F5

S.NO	Formulation	Tablet thickness mm(SD±Mean)
1	F1	6.21±0.03
2	F2	6.18±0.04
3	F3	6.22±0.05
4	F4	6.15±0.02
5	F5	6.14±0.02

d. Hardness

Table 4.7 Hardness test values of all formulation F1-F5

S.NO	Formulation	Hardness
1	F1	175
2	F2	180
3	F3	187
4	F4	193
5	F5	195

e. Friability

Table 4.8 Friability values of all formulation F1-F5

S.NO	Formulation	Friability
1	F1	0.48±0.16
2	F2	0.40±0.25
3	F3	0.39±0.27
4	F4	0.31±0.19
5	F5	0.30±0.29

f. Disintegration test

Table 4.9 Disintegration values of all formulation F1-F5

S.NO	Formulation	Disintegrations Time inmin.
1	F1	3 min 35 sec
2	F2	3 min 58 sec
3	F3	3 min 38 sec
4	F4	3 min 55 sec
5	F5	3 min 49 sec

g. Compatibility studies

Table 4.10 Drug- Excipients Compatibility studies at (25±2^0 C/60±5% RH)

S. No.	Material	Ratio (D:E)	Physical appearance	(25±2^0 C/60±5% RH) & (40±20C/75±5% RH)		
				Week 1	Week 2	Week 3
1	Esomeprazole	1:00	#	√	√	√
2	API + Hypromellose E5	1:05	#	√	√	√
3	API + Talc	1:05	#	√	√	√
4	API + PEG 6000	1:05	#	√	√	√
5	API + Magnesium stearate	1:05	#	√	√	√
6	API + Eudragit L 30D	1:05	#	√	√	√
7	API + Titanium Dioxide	1:05	#	√	√	√
8	API +Hypromellose E5	1:05	#	√	√	√
19	API + Magnesium stearate	1:05	#	√	√	√

10	API + Eudragit L 30D	1:05	#	√	√	√
11	API + MCC PH 102	1:05	#	√	√	√
12	Silicon Dioxide	1:05	#	√	√	√
13	API + L-HPC-LH11	1:05	#	√	√	√
14	API + Crospovidone	1:05	#	√	√	√

is Light yellow color powder

√ No color change

h. Dissolution study

Table 4.11: Dissolution study

Apparatus	USP Type-II (Paddle)
Volume	900 ml
RPM	100
Medium	pH 6.8 phosphate buffer/ pH 0.1N HCL
Drug release time	5min,10min,15min,20min,30min,45min,60 min.
Temperature	37± 0.5°C

Table 4.12 Compilation of *In vitro* Release of Esomeprazole sodium DR tablets PreparedFormulations from F1 to F5 and Innovator Product

Times	**CUMULATIVE % DRUG RELEASE**					
	INNOVATOR (NEXIUM 40MG)	**FORMULATION**				
		F1	**F2**	**F3**	**F4**	**F5**
5	17.4	49±0.2	58±0.5	60±0.5	32±0.2	25±0.6
10	60.4	50±0.6	60±0.5	46±0.1	74±0.8	50±0.9
15	81.2	52±0.8	64±0.8	34±0.9	86±0.4	74±0.5
20	90.2	46±0.7	50±0.3	33±0.5	88±0.9	85±0.1
30	94.6	46±0.2	48±0.4	30±0.6	89±0.8	90±0.4
45	96.4	42±0.1	46±0.3	29±0.5	92±0.7	93±0.6
60	98.6	40±0.3	46±0.4	28±0.6	93±0.8	97±0.3
Difference factor (f1)		51.41	46.03	67.56	9.43	7.42
Similarity factor (f2)		18.55	20.05	12.95	53.33	59.68

5. SUMMARY AND CONCLUSION

Esomeprazole is used in the treatment of peptic ulcer disease (PUD), gastroesophageal reflux disease(GERD) and Zollinger-Ellison syndrome and Crohn's disease. PPIs such as Nexium reduce stomach acid secretion. The

tablets which are prepared by compaction of coated pellets are called as MUPStablets. Pellets are produced for the purpose of oral controlled release dosage form having gastro resistant or sustained release properties. For such purpose, coated pellets are administered in the form of MUPS tablets. Different release profile can be achieved at same time at same site in GIT. The Esomeprazole sodium is a proton pump-inhibitor which is used in the treatment ofpeptic ulcer. Five formulations of enteric coated tablets of Esomeprazole were developed by preparing core tablets using microcrystalline cellulose (MCC PH 102) as diluent and Crospovidone as disintegrant and Hypromellose E5 as binder in different proportions and varying the compositions of Pre coating, seal coating and enteric coating using titanium dioxide and Eudragit (L 30D).

In this study Esomeprazole enteric coated tablets were prepared by using Eudragit(L30D). Formulation F1 was failed to compress as tablets due to because of improper physical practicability sticking problem. Formulation F2 acid resistance was failed due to insufficient enteric coating. Formulation F3 in vitro release was within the limits but not comparable to the innovatorproduct. Formulation F4 was passed but in-vitro releases was quite less. Formulation F5 fulfilled all the specifications prescribed for Esomeprazole delayed release tablets and comparable to the innovator product. Formulation 5 was found to be best of all the trails showing drug release matching the innovators product. The best formulation 5 was repeated again for reproducibility. Based on dissolution stability studies formulation 5 is better than formulation 4.

REFERENCES

1. Grover JK, Vats V. Proton pump inhibitors. Trop Gastroenterol. 1999; 20:16-28.
2. Horn J. The proton-pump inhibitors: similarities and differences. Clin Ther. 2000; 22:266-80.
3. Nexium (esomeprazole magnesium) delayed-release capsules package insert. Wilmington, DE: AstraZeneca; 2001.
4. Prevacid (lansoprazole) delayed-release capsules package insert. Lake Forest, IL: TAP Pharmaceuticals; 2000.
5. Prilosec (omeprazole) delayed-release capsules package insert. Wilmington, DE: AstraZeneca;2000.
6. Protonix (pantoprazole sodium) delayedrelease tablets package insert. Philadelphia: Wyeth Laboratories; 2000.
7. Aciphex (rabeprazole sodium) delayedrelease tablets package insert. Teaneck, NJ: Eisai; 1999.
8. Sachs G. Proton pump inhibitors and acid-related diseases. Pharmacotherapy. 1997; 17:22-37.
9. Thitiphuree S, Talley NJ. Esomeprazole, a new proton pump inhibitor: pharmacological characteristics and clinical efficacy. Int J Clin Pract. 2000; 54:537-41.
10. Spencer CM, Faulds D. Esomeprazole. Drugs. 2000; 60:321-9.
11. Junghard O, Hassan-Alin M, Hasselgren G. The effect of AUC and Cmax of esome 1339Am J Health-Syst Pharm—Vol 59 Jul 15, 2002 Esomeprazole CLINICAL REVIEW prazole on acid secretion and intragastric pH. Gastroenterology. 2000; 118(suppl 2, pt. 1):A17. Abstract.
12. Andersson T, Röhss K, Hassan-Alin M et al. Pharmacokinetics (PK) and doseresponse relationship of esomeprazole (E). Gastroenterology. 2000; 118(suppl 2, pt. 2):A1210. Abstract.
13. Andersson T, Bredberg E, Sunzel M et al. Pharmacokinetics (PK) and effect on pentagastrin stimulated peak acid output (PAO) of omeprazole (O) and its 2 optical isomers, S- omeprazole/esomeprazole (E) and R-omeprazole (R-O). Gastroenterology. 2000; 118(suppl 2, pt.2):A1210. Abstract.
14. Langtry HD, Wilde MI. Omeprazole: a review of its use in Helicobacter pylori infection, gastro-oesophageal reflux disease and peptic ulcers induced by nonsteroidal anti-inflammatory drugs. Drugs.

1998; 56:447-86.
15. The American Society of Health-System Pharmacists. Retrieved 3 April 2011.
16. Li J, Zhao J, Hamer-Maansson JE, Andersson T, Fulmer R, Illueca M, Lundborg P (March 2006). "Pharmacokinetic properties of esomeprazole in adolescent patients aged 12 to 17 years with symptoms of gastroesophageal reflux disease: A randomized, open-label study". Clin Ther. 28 (3): 419–27.
17. Laine L, Fennerty MB, Osato M et al. Esomeprazole- based Helicobacter pylori eradication therapy and the effect of antibiotic resistance: results of three US multicenter, double-blind trials.Am J Gastroenterol. 2000; 95:3393-8.
18. Lind T, Rydberg L, Kylebäck A et al. Esomeprazole provides improved acid control vs. omeprazole in patients with symptoms of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2000; 14:861-7.
19. Talley NJ, Lauritsen K, Tunturi-Hihnala H et al. Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastro-oesophageal reflux disease: a controlled trial of ‘on- demand’ therapy for 6 months. Aliment Pharmacol Ther. 2001; 15:347-54.
20. Yang YX, Lewis JD, Epstein S, Metz DC (2006). "Long-term proton pump inhibitor therapy and risk of hip fracture". JAMA. 296 (24): 2947–53.