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Preparation and Evaluation of Esomeprazole Enteric Coated Tablets

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ABSTRACT

Esomeprazole sodium is a proton pump inhibitor used to treat peptic ulcer, duodenal ulcer, gastro oesophageal reflux disease by inhibiting the enzyme H^+ /K^+ATPase. The objective of the revision is to formulate and evaluate the Delayed Release tablets & parallel with that of innovator product. The principal intension is to delay the release of drug which is incapacitated by the stomach contents. Methacrylicacid copolymer (EudragitL30D55) was used as an enteric coating material in the formulation. Eight formulations of enteric coated tablets of Esomeprazole was advanced by preparing core tablets using mannitol as diluent, Crospovidone as super disintegrant, povidone (PVP K-30) as binder in diverse extents and variable the compositions of sub coating and enteric coating using sicovit yellow ,titanium dioxide and eudragit .The core tablets were prepared by dry granulation method. Formulation F7 was institute to be acid resistant and *invitro* drug release was also insightful and akin to the innovator product. Stability study is conceded out for 2 months at 25°C; 60% RH: and 40°C; 75%RH, bestowing to ICH guidelines. The tablets were tested for acid release through the stability period and inveterate that results were institute within the limits. H+ /K+ATPase, inhibition by the Esomeprazole effect the gastric acid formation progression and is dose-dependent and delivers for exceedingly operative inhibition of both basal acid secretion and stimulated acid secretion, irrespective of the stimulus.

INTRODUCTION

For utmost drugs, conventional methods of drug administration are operational, but some drugs are wobbly or toxic and have narrow therapeutic window. Some drugs also retain solubility complications. In such cases, a scheme of unceasing administration of therapeutic agent is anticipated to sustain fixed plasma levels. [1] To incredulous these complications, controlled drug delivery systems were familiarized into the market. These delivery classifications have a number of benefits above traditional classifications such as amended efficiency, abridged toxicity and enhanced patient convenience. The foremost goal of controlled drug delivery systems is to expand the effectiveness of drug therapies. [2]

An ulcer is the consequence of a disproportion among aggressive and defensive factors. [3] Peptic ulcer disease is a collective clinical illness, once supposed to be instigated by over secretion of acid and pepsin, an enzyme of the stomach that indorses digestion by contravention down proteins. [4] Researchers have instituted, however, that although the injury initiated by acid and pepsin is obligatory for the formation of ulcers, acid secretion levels of the preponderance of patients with gastric or duodenal ulcers are normal. An ulcer is now known to be the result of a discrepancy between aggressive and defensive mechanisms in the stomach and duodenum. Part of that imbalance can be attributed to infection by H.pylori. [5] An ulcer forms when there is a discrepancy between aggressive factors, i.e. the digestive power of acid and pepsin and defensive factors, i.e. the facility of the gastric and duodenal mucosa to fight this power. This mucosal resistance creates the gastric mucosal barrier. [6]

Proton pump inhibitors (PPI's) are exceedingly operative in the executive of acid related diseases. [7] There are currently five diverse proton pump inhibitors accessible comprising Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole and Esomeprazole. [8] In the extant study Esomeprazole was designated as the payload model drug to treat the peptic ulcer. Esomeprazole is a proton pump inhibitor. Its metabolism is mainly by liver and excretion by renal and fecal. Esomeprazole spectacles a further rapid onset of acid-suppression consequence & vintages sophisticated erosive esophagitis healing rates and affords sustained resolution of heartburn in more patients than any other. [9]

MATERIALS AND METHODS

MATERIALS

Esomeprazole sodium, Mannitol (perlitol SD200), Sodium lauryl sulphate, Povidone (PVP K-30), Sodium carbonate, Cross povidone (Kollidone CL), Calcium stearate, HPMC(Methocel, 5CPs), Sicovit yellow, Propylene glycol, Titanium dioxide, Methacrylicacid copolymer (Eudragit L30 D55), Triethyl citrate, Polysorbate 80. All the chemicals and solvents used are of analytical reagent grade and were supplied by M/s SARC Research Labs, Hyderabad.

METHODS

1. Solubility studies: The solubility of esomeprazole sodium was indomitable in distilled water, different buffers, viz., pH 1.2, pH 4.0, pH 9.0 and anhydrous ethanol, n-hexane. Triplicate readings were taken and average was calculated.

2. Melting point determination: Melting point of the drugs was indomitable by taking a small extent of drug in a capillary tube closed at one end and was placed in theil's melting point apparatus and the temperature at which the drug melts was noted. Average of triplicate readings was noted.

3. Analytical method development:

Preparation of calibration curve of Esomeprazole in phosphate buffer of pH 6.8: 50mg of Esomeprazole was taken in 50ml volumetric flask and dissolved with few drops of methanol and made up the volume to 50ml with phosphate buffer pH6.8 to give the concentration of 1000µg/ml. 1ml of SS1 was diluted to 10ml with phosphate buffer to give concentration of 100µg/ml. From the above stock solution, aliquots of 0.5, 1, 1.5, 2, 2.5, and 3 ml were transferred to 10 ml volumetric flasks and made up to the mark with phosphate buffer pH 6.8. The absorbance of these solutions was measured at 289 nm and a graph of concentration versus absorbance was plotted.

4. Pre Compression Parameters for pure drug [10,11]

Bulk Density (BD):

Bulk density = Weight of powder / Bulk volume

Tapped density (TD):

Tapped Density = Weight of powder / Tapped volume

Carr's Index: It is a simple test to evaluate the BD and TD of a powder and the rate at which it is packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) x100]/TD

Hausner's Ratio: The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material and their standard values are given in table 2.

Hausner's Ratio = TD / BD

Table 1: Effect of Carr's Index and Hausner's Ratio and Angle of repose on flow property

Flow Character	Carr's Index (%)	Hausner's Ratio	Angle of repose
Excellent	≤10	1.00-1.11	<20
Good	11-15	1.12-1.18	20-30
Fair	16-20	1.19-1.25	-----
Passable	21-25	1.26-1.34	30-34
Poor	26-31	1.35-1.45	-------
Very poor	32-27	1.46-1.59	>35
Very very poor	>38	>1.6	-------

Formulation of Esomeprazole Sodium Delayed Release Tablets

Esomeprazole sodium delayed release tablets were prepared by dry granulation technique using different excipients as well as with varying concentrations of polymer proportions using methacrylate copolymer (EudragitL30D55) as enteric coating materials as shown in table 3. [10]

Procedure:

Weighing→ Sifting→ Blending→ Tablet compression→ Sub coating→ Enteric coating→ Packaging [11]

Formulation Development of Esomeprazole sodium Enteric coated tablets:

Based on preformulation data various excipients were selected and their compilation was shown in table 2. [12-15]

Table 2: Compilation of Esomeprazole Enteric Coated Tablets

S.No.	Ingredients	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8
	Drug loading stage	Q/mg	Q/mg	Q/mg	Q/mg	Q/mg	Q/mg	Q/mg	Q/mg
1.	Esomeprazole sodium	45	45	45	45	45	45	45	45
2.	Mannitol (PerlitolSD 200)	90	45	45	45	45	45	45	45
3.	Mannitol (PerlitolSD 200)	-	44	44	43	43	48	50	50
4.	Kollidon CL	1.5	1.5	1.5	3.0	3.0	3.0	3.0	3.0
5.	Sodium lauryl sulphate	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55
6.	povidone (PVPK-30)	15	15	15	15	15	10	8	8
7.	Sodium carbonate	10	10	10	10	10	10	10	10
8.	Calcium stearate	1	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Subcoating Stage								
9.	HPMC (5CPs)	-	17.5	17.5	17.5	13	13	13	13
10.	Sicovit yellow	-	0.8	0.8	0.8	0.6	0.6	0.6	0.6
11.	Propylene glycol	-	1.5	1.5	1.5	1.0	1.0	1.0	1.0
12.	Titanium dioxide	-	0.4	0.4	0.4	0.3	0.3	0.3	0.3
13.	Purified water	-	175	175	175	130	130	130	130
	Enteric coating stage								
14.	Eudragit L30D55	-	27.0	33.12	33.12	33.12	33.12	33.12	33.12
15.	Triethyl citrate	-	1.0	1.73	1.73	1.73	1.73	1.73	1.73
16.	Polysorbate 80	-	0.3	0.5	0.5	0.5	0.5	0.5	0.5
17.	Purified water	-	60	60	60	60	60	60	60

F=Formulation Batches

5. Post-compressional Studies:

Shape and appearance: Tablets were scrutinized underneath a lens for the shape of the tablet, and color was perceived by keeping the tablets in light. [16]

Uniformity of thickness: Thickness and diameter of both core tablets and coated tablets were restrained expending a calibrated dial calipers. Three tablets of each formulation were chosen arbitrarily and dimensions resolute. It is articulated in mm and standard deviation was also premeditated. [17, 18]

Weight variation test: To study weight variation 20 tablets of each pulse dose formulation were weighed discretely using a Sartorius electronic balance and the test was executed bestowing to the official method. The average weight was prominent and standard deviation designed. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet diverges by more than double the percentage limit. [18]

Hardness test: Hardness designates the ability of a tablet to withstand mechanical shocks while handling. Hardness of core tablets was resolute using a validated dial type hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated. [17]

Friability test: For each pulse dose tablet formulation, the friability of 6 tablets was indomitable using the Roche friabilator. [19] Friability can be dogged by following equation:

$$F = [wt_{initial} - wt_{final} / wt_{initial}] \times 100$$

Disintegration time: The *in-vitro* disintegration time was indomitable by using disintegration test apparatus. The tablets were placed in each of the six tubes of the apparatus. The conditions for enteric-coated tablets are:

a) All the six tablets tested should not disintegrate in 2 hour in 0.1N HCl and should not show any sign of cracks or swelling.

b) All the six tablets tested in 0.1N HCl for 2 hour should disintegrate within 30 min in phosphate buffer pH 6.8.

***6. In vitro* dissolution studies:** Dissolution was carried out in phosphate buffer pH 6.8 for 60 min. in 900ml volume of type 2 paddle apparatus with rotation Speed 75 rpm and at

temperature: $37^0C \pm 0.5^0C$. [20] The percentage drug release can be calculated by following equation;

$$\textbf{\% drug content} = \frac{AT \times WS \times DT \times P \times 100}{AS \times DS \times 1 \times 100 \times LC}$$

7. Stability Studies: the stability studies were conceded out as per ICH guidelines at refrigerator & work bench for the ensuing designated formulation for 2 months. After indicated time intervals, parameters like physical appearance, Assay, Acid release in 0.1N HCl and dissolution study in pH 6.8 buffer were evaluated according to the procedure described as earlier[20].

RESULTS

1. Solubility: It is freely soluble in water and in anhydrous ethanol, practically insoluble in n-hexane and was shown in table 4.

2. Melting Point: melting point was found within the range 150-155°c and was represented in table 4.

3. Analytical method development:

Table 3: Standard graphs for Esomeprazole sodium

S.no	Conc. (µg/ml)	Absorbance (λ-max at 289 nm)
1.	2	0.081
2.	4	0.173
3.	6	0.260
4.	8	0.352
5.	10	0.442
6.	12	0.534

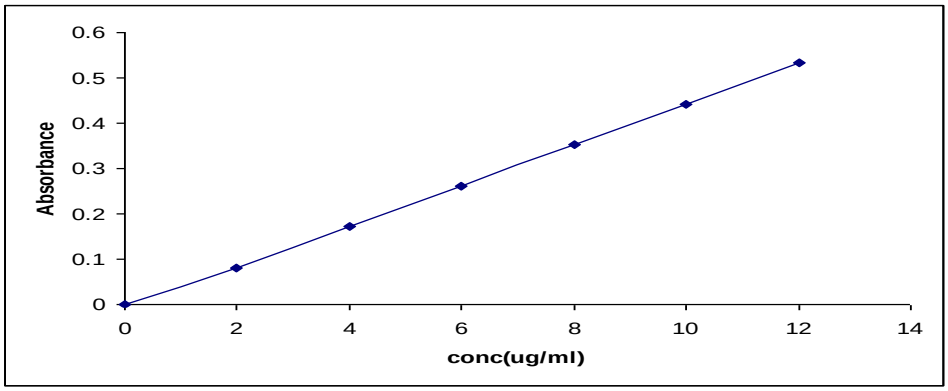


Figure-1 Calibration Curve of Esomeprazole

4. Pre Compression Parameters for pure drug: Preformulation is a group of studies that focus on the physicochemical properties of a drug candidate that could affect the drug performance and the development of a dosage form. This could afford imperative information for formulation design or sustenance the need for molecular modification. Every drug has intrinsic chemical and physical properties which has been deliberate before development of pharmaceutical formulation. This property affords the framework for drugs combination with pharmaceutical components in the fabrication of dosage form.

Table 4: Preformulation studies of Esomeprazole

S.No.	Characteristics	Results
1.	Physical appearance	A white powder
2.	Solubility	Drug was freely soluble in water and in anhydrous ethanol, practically insoluble in n-hexane
3.	Bulk density	0.55gm/ml
4.	Tap density	0.69gm/ml
5.	Compressibility index	20.0%
6.	Hausner's ratio	1.25
7.	Melting point	150°C
8.	Molecular weight	432.4

5. Post-compressional Studies:

Evaluation of Delayed Release Tablets:

Table 5: Physical Evaluation (Core tablet)

S. No	Physical parameter	F1	F2	F3	F4	F5	F6	F7	F8
1	Hardness (Kg/Square inch)	-	6.5	7.2	6.8	7.1	6.8	5.8	5.5
2	WT. variation	-	1.62	1.65	1.63	1.61	1.62	1.64	1.63
3	Friability	-	0.49	0.51	0.56	0.58	0.57	0.66	0.68
4	Disintegration time	-	6min 31sec	6min 49sec	5min 45sec	5min 30sec	5min 56sec	6min 03sec	6min 11sec
5	Thickness (mm)	-	2.34	2.32	2.31	2.33	2.32	2.35	2.30

Table 6: Physical Evaluations (After Sub Coating and Enteric Coating)

Parameters		F 2	F 3	F 4	F 5	F 6	F 7	F 8
After Sub Coating	**Hardness**	8.1	8.4	8.2	8.6	8.1	6.5	6.1
	Thickness	2.41	2.44	2.43	2.46	2.48	2.44	2.39
After Enteric Coating	**Hardness**	10.3	10.6	10.9	11.1	10.5	7.9	7.9
	Thickness	2.54	2.58	2.55	2.56	2.55	2.51	2.53

Table 7: Chemical Evaluations

S.No	Parameters	F 1	F2	F 3	F 4	F 5	F 6	F 7	F 8
1	Acid resistant analysis	-	-	Within the limit	Within the limit	Within the limit	Within the limit	Within the limit	Within the limit
2	Assay	-	-	-	-	-	Within the limit	Within the limit	Within the limit
3	Dissolution study	-	-	-	-	-	Within the limit	Within the limit	Within the limit

6. *In vitro* dissolution studies: Dissolution was carried out in phosphate buffer pH 6.8 for 60 min. in 900ml volume of type 2 paddle apparatus with rotation Speed 75 rpm and at temperature: 370 C + 0.50 C.

Table 8: In-vitro drug release of Esomeprazole sodium DR tablets formulations from F3 to F8 and marketed product (Nexium) in 6.8 ph buffer

S.No.	Time (min)	Percentage release of Esomeprazole sodium DR tablets						
		F3	F4	F5	F6	F7	F8	M
1.	10.	10.21±0.04	13.17±0.71	17.85±0.13	26.30±1.06	33.63±0.60	34.94±1.33	34.75±1.03
2.	20.	22.25±0.33	29.40±1.25	36.73±0.78	54.64±1.88	70.20±0.80	71.02±0.80	68.39±1.00
3.	30.	39.64±0.50	41.27±0.91	45.20±0.76	63.16±0.30	78.47±0.75	80.64±0.97	74.03±0.15
4.	45.	43.40±1.07	47.93±0.58	51.67±0.66	72.81±1.19	86.14±0.30	87.57±0.86	83.73±0.51
5.	60.	49.94±1.37	53.18±1.48	58.28±1.10	81.40±0.86	93.06±0.51	96.29±0.73	92.70±0.58

Symbols F= Formulation batch M= Marketed product (Nexium)

***** Each value is the mean ± SD (n=3)

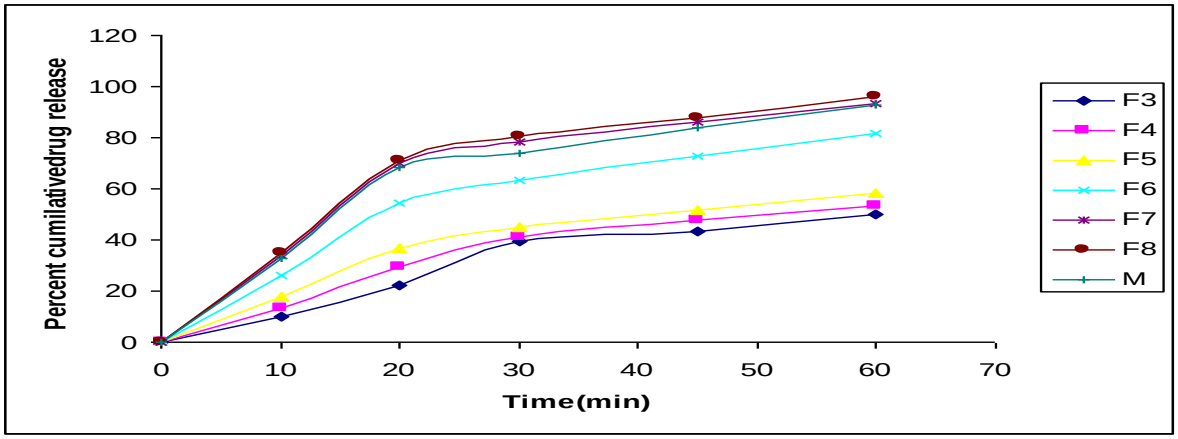


Figure-2 In-vitro drug release of Esomeprazole sodium DR tablets formulations from F3 to F8 and marketed product (Nexium) in 6.8 ph buffer

7. Stability Studies: stability studies were conducted for optimized formulations F7 and F8.

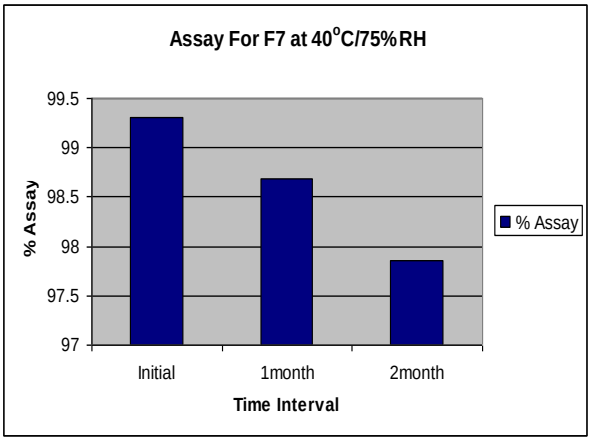
Table 9: Stability Data for F 7

Batch number and stability condition	Description	Assay (%)	Acid release in 0.1N HCl (%)	Dissolution study in pH 6.8 buffer
F 7 (Initial)	Off White colored enteric coated tablets with embossing of 'H' on one side and '126' on another side.	99.30%	1.93%	92.38%
40° C / 75% RH (1month)	Off White colored enteric coated tablets with embossing of 'H' on one side and '126' on another side.	98.69%	2.04%	92.235
40° C / 75% RH (2months)	Off White colored Enteric coated tablets with embossing of 'H' on one side and '126' on another side.	97.86%	2.17%	92.01%
25°C/60% RH (1month)	Off White colored Enteric coated tablets with embossing of 'H' on one side and '126' on another side.	98.85%	2.01%	91.98%
25°C/60% RH (2months)	Off White colored enteric coated tablets with embossing of 'H' on one side and '126' on another side.	98.19%	2.13%	91.92%

Table 10: Stability Data for F8

Batch number and stability condition	Description	Assay (%)	Acid release in 0.1N HCl (%)	Dissolution study in pH 6.8 buffer
F 8 (Initial)	Off White colored Enteric coated tablets with embossing of 'H' on one side and '126' on another side.	99.42%	1.88%	92.4%
40° C / 75% RH (1month)	Off White colored Enteric coated tablets with embossing of 'H' on one side and '126' on another side.	98.53%	1.95%	92.36%
40° C / 75% RH (2months)	Off White colored Enteric coated tablets with embossing of 'H' on one side and '126' on another side.	97.93%	2.06%	92.31%
25°C/60% RH (1month)	Off White colored Enteric coated tablets with embossing of 'H' on one side and '126' on another side.	98.74%	1.92%	91.97%
25°C/60% RH (2months)	Off White colored Enteric coated tablets with embossing of 'H' on one side and '126' on another side.	98.01%	2.00%	91.96%

ASSAY:



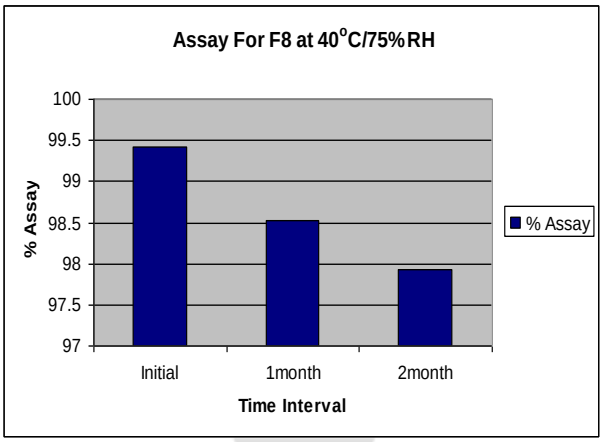
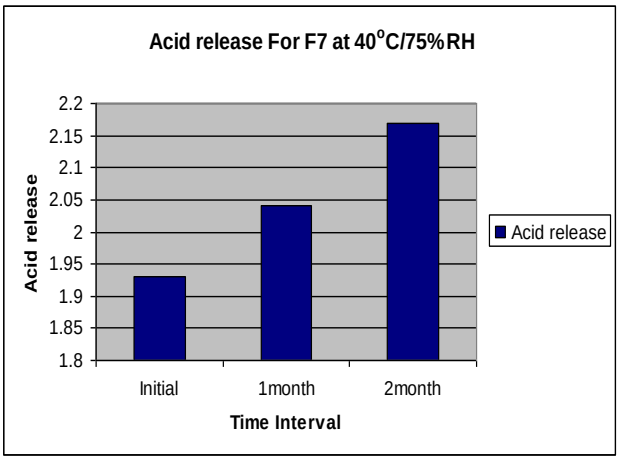


Figure-3 Assay for F7 and F8

Acid Release:



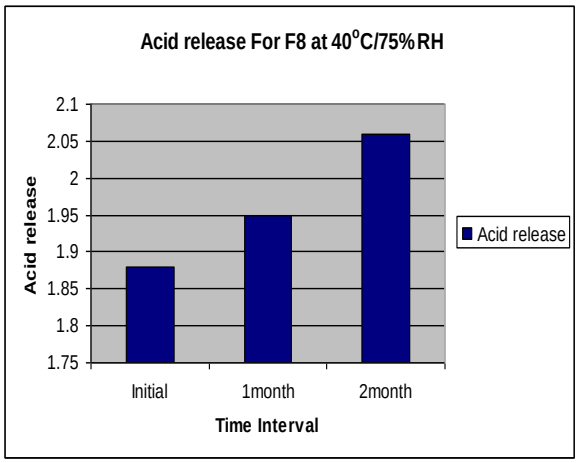


Figure-4 Assay for F7 and F8 at Acid release

DISCUSSION

The objective of the manuscript is to formulate and evaluate Esomeprazole sodium Delayed Release tablets paralleled to the innovator product. Eight formulations of enteric coated tablets of Esomeprazole were developed by preparing core tablets using mannitol as diluent and Crospovidone as super disintegrant and povidone (PVP K-30) as binder in diverse proportions and erratic the compositions of sub coating and enteric coating using sicovit yellow, titanium dioxide and eudragit. The core tablets were prepared by dry granulation method.

The results signposted that the finished product formulations F7, F8, contented all the provisions of the physical properties and *in vitro* release and are similar to the innovator product. Formulation F1 was failed to compress as tablets due to sticking problem. Formulation F2 acid resistance test was failed due to inadequate enteric coating. Formulations F3 to F5 Acid resistance test was passed but in vitro release was quite less. Formulation F6 in vitro release was within the limits but not comparable to the innovator product.

Formulation F7, F8 contented all the provisions approved for Esomeprazole delayed release tablets and comparable to the innovator product. From the results it was evident that, among the two formulations F8 was best formulation.

CONCLUSION

The Esomeprazole sodium is a proton pump-inhibitor which is used in the treatment of peptic

ulcer. In this study Esomeprazole enteric coated tablets were prepared by using methacrylate co-polymers (Eudragit L30D55). Eight formulations of enteric coated tablets of Esomeprazole were developed by preparing core tablets using mannitol as diluent and Crospovidone as super disintegrant and povidone (PVP K-30) as binder in different proportions and varying the compositions of sub coating and enteric coating using sicovit yellow, titanium dioxide and Eudragit (L30D55). The core tablets were prepared by dry granulation method. F8 was found to be best of all the trials showing drug release matching the innovator product. This formulation has the following composition.

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