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FORMULATION DEVELOPMENT OF CONTROLLED RELEASE FORMULATION OF ESOMEPRAZOLE SODIUM TABLETS

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Abstract:
The main aim of this work is Esomeprazole sodium is formulated as controlled release tablets to provide desired effect at certain time in maintained drug concentration without any unwanted effect with patient compliance also to improve it bioavailability by decreasing its expose to gastric acid. A controlled release dosage form is designed to release the drug from the dosage form at a time other than promptly after administration. UV Spectrophotometric method has been developed for the estimation of Esomeprazole in pharmaceutical formulations. Then the tablets were prepared by dry granulation method rather than direct compression because of cohesive property of the drug. Optimized core tablet then subjected for enteric coating by selected base coat polymer cellulose derivative for preventing core tablet from moisture. The coated formulations were compared with marketed sample (ESOZ) for optimization. Dissolution results of tablets with enteric coating have shown release of Esomeprazole in simulated gastrointestinal fluid pH 1.2, but most of the drug released in pH 6.8 Phosphate buffer. At the end it was found that prepared formulation gave satisfactory results compared with marketed sample dissolution profile. Hence prepared formulation by-pass the degradation of Esomeprazole by enteric coating approach and can be used as single unit dosage for the treatment of acid-related diseases. Thus a pharmaceutically equivalent, robust formulation of Esomeprazole controlled release tablet was developed.
Keywords: *Esomeprazole, UV spectrophotometric method, Enteric coating, Controlled release tablets, In vitro drug release.*

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INTRODUCTION:

Oral solid dosage form was the preferred route of many drugs. Today, the oral dosage form is still the old and new controlled release products the most widely used forms. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages. Controlled release (CR) tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high potency drugs.

Controlled release dosage form is the best formulations which are used for drugs that are destroyed in gastric fluids, or cause gastric irritation or absorbed preferentially in the intestine. Such preparations contain an alkaline core material comprising the active substance, a separating layer and enteric coating layer [1, 2]. Esomeprazole, the new S-isomer of omeprazole, is introduced to reduce gastric acid secretion more efficiently. esomeprazole exhibits significantly higher bioavailability, leading to the greater inhibition of gastric acid secretion compared to Omeprazole [2]. Esomeprazole, the stereospecific S-isomer of Omeprazole, is the first proton pump inhibitor (PPI) to be developed as a single isomer for use in the treatment of acid-related diseases [3]. The intragastric pH-monitoring data for esomeprazole, 20 mg once daily, show improvement over omeprazole, 20 mg once daily, but the esomeprazole, 40 mg once daily, intragastric pH data show a further convincing gain in control of gastric pH.1 Early studies have shown Esomeprazole achieves greater and more sustained acid control than Omeprazole, with a similar tolerability and safety profile. Furthermore, Esomeprazole shows a more rapid onset of acid-suppression effect than Omeprazole, and less interindividual variation in acid control. Additionally, a recent crossover study demonstrated that Esomeprazole at a standard dose of 40 mg once daily provides more effective control of gastric acid at steady state [5, 6].

MATERIALS AND METHODS:

Materials Esomeprazole Sodium, Eudragit L & S, PVPK-30, Sodium carbonate, Mannitol, Crosspovidone, calcium stearate, HPMC and Propylene glycol. All the chemicals and solvents used are of analytical reagent grade.

Preparation of Tablets Preparation of Core Esomeprazole Tablets Initially core tablets were formulated by using Dry granulation method. Esomeprazole and mannitol were compacted and milled the compacted blend and pass through mesh, blend all the ingredients then compressed. In maintained room condition, relative humidity 65 % and with minimum expose to the light all the ingredients were weighed and sieved. These are the lubricated granules ready for compression. Compression of the granules is done on Tablet compression machine. The detailed compositions of Esomeprazole core tablets and coated materials are given in Tables 1 &2.

Table 1: Composition of core Esomeprazole Tablets

S.No	Ingredients	F 1	F2	F3	F 4	F 5	F 6	F 7	F 8
	Drug loading stage	Qmg	Q/mg	Q/mg	Q/mg	Q/mg	Q/mg	Q/mg	Q/mg
1	Esomeprazole sodium	40	40	40	40	40	40	40	40
2	Mannitol	90	45.11	45.11	45.11	45.11	45.11	45.11	45.11
3	Mannitol	-	44.39	44.39	42.89.	42.89	48.29	50.29	50.29
4	Kollidon CL	1.5	1.5	1.5	3.0	3.0	3.0	3.0	3.0
5	SLS	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55
6	Povidone (PVP K-30)	15.4	15.4	15.4	15.4	15.4	10	8	8
7	Sodium Carbonate	10.30	10.30	10.30	10.30	10.30	10.30	10.30	10.30
8	Calcium stearate	1	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Table 2: Coating Approach for Core Esomeprazole Tablets

Subcoating Stage	Q/mg	Q/mg	Q/mg	Q/mg	Q/mg	Q/mg	Q/mg	Q/mg
HPMC (5CPs)	-	17.48	17.48	17.48	12.87	12.87	12.27	12.27
Sicovit yellow	-	0.77	0.77	0.77	0.57	0.57	0.57	0.57
Propylene glycol	-	1.50	1.50	1.50	1.0	1.0	1.0	1.0
Titanium dioxide	-	0.40	0.40	0.40	0.283	0.283	0.283	0.283
Purified water	-	175.67	175.67	175.67	129.3	129.3	129.3	129.3
Enteric coating stage								
Eudragit	-	27.0	33.12	33.12	33.12	33.12	33.12	33.12
Triethyl citrate	-	1.0	1.73	1.73	1.73	1.73	1.73	1.73
Polysorbate 80	-	0.3	0.48	0.48	0.48	0.48	0.48	0.48
Purified water	-	59.67	59.67	59.67	59.67	59.67	59.67	59.67

Pre compression Parameters:

Angle of repose Static angle of repose was determined according to the fixed funnel method reported by Patel et al.1 The mean diameter of the base for the powder cone was measured and the angle of repose (θ) was calculated using the following equation. /= θTan H R Different types of flowabiliaty depending upon angle of repose.

Bulk density and tapped density:

The bulk density and tapped density was determined by the method reported by Patel et al.1 The tapping was continued until no further change in volume was noted.

Bulk Density = Weight of the powder / Volume of the packing

Tapped Density = Weight of the powder / Tapped volume of the packing

Hausner's factor:

Housner found that the ratio of tapped density to bulk density was related to interparticle friction and as such, could be used to predict powder flow properties.1

Hausner Ratio = Tapped Density / Bulk density Values less than 1.25 indicate good flow, whereas greater than 1.25 indicates poor flow property.

Compressibility index:

Compressibility index of granules was calculated from the following formula.1 It is also known as Carr's index.

Compressibility%= Dt Db / Dt * 100

Where Dt is tapped density and Db is bulk density.

Characterization of core esomeprazole:

Evaluation of Coated Esomeprazole Tablets:

Weight variation test:

Twenty tablets were selected randomly and weighed. The average weight was compared with individual tablet weight. The percentage weight variation was calculated.

Friability test:

8 Weighed amount of 20 dedusted tablets were subjected to rotating drum of friability test apparatus. The drum was rotated at a speed of 25 rpm for 4 minutes and reweighed the tablets.

% friability was calculated by the following formula.

% friability = {(Initial weight – final weight) / initial weight} X 100 %

friability of tablets less than 1% of their weight are considered acceptable.

Diameter & thickness:

Twenty tablets selected randomly and determined its diameter & thickness by using vernier calliperse and reading were noted.

Disintegration test:

Placed one tablet in each tube of the basket and the apparatus, using purified water maintained at 370 C as immersion fluid for 2 hrs. Noted down the time to complete disintegration.

Infrared Spectroscopy

Fourier transformed infrared (FTIR) spectra of Lamivudine was taken by using the KBr disk method. The scanning range was 400 to 4000 Cm^{-1}.The major peaks in recorded spectra were compared with standard spectra. These assignments are in full support of the given structures of drugs.

In Vitro Dissolution Study:

Prepared delayed release tablets were evaluated for their integrity in the physiological environment of stomach and small intestine. These study were carried out using USP dissolution test apparatus type-II .The tablets were tested for drug release in 0.1N HCl (900 ml) for first 2 h as average gastric emptying time is 2 h, then dissolution media was replaced with 6.8 pH phosphate buffer (900 ml) for 1 h. At the end of respective time periods, each sample of 10 ml were taken at specified intervals (i.e. 5, 10, 15, 30, 45, 60 minutes) and analysed for Esomeprazole content at 300 nm using UV spectrophometer (Shimadzu UV-1600).

RESULTS:

Table 3: Pre compressional Parameters of Blend

Formulations	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Compressibility Index (%)	Angle of repose (^{0})	Hausner ratio
F1	0.4208±0.008	0.4503±0.001	6.551±0.052	22.05±0.015	**0.9344±0.022**
F2	0.4460±0.001	0.4752±0.004	6.144±0.065	19.20±0.020	**0.9385±0.034**
F3	0.4502±0.007	0.4803±0.007	6.685±0.043	21.45±0.019	**0.9373±0.014**
F4	0.4256±0.012	0.4524±0.003	5.923±0.012	18.25±0.025	**0.9407±0.009**
F5	0.3957±0.008	0.4351±0.009	9.055±0.034	21.60±0.030	**0.9094±0.026**
F6	0.3803±0.015	0.4402±0.007	13.607±0.075	24.70±0.050	**0.8639±0.010**
F7	0.4102±0.004	0.4803±0.003	14.595±0.109	21.35±0.040	**0.8540±0.045**
F8	**0.4552±0.011**	**0.4899±0.008**	**7.083±0.023**	**19.50±0.035**	**0.9291±0.008**

Table 4: Post Compressional Parameters of Esomeprazole Core Tablets

S. No	Physical parameter	F1	F2	F3	F 4	F 5	F 6	F 7	F 8
1	**Weight variation**	-	1.62	1.65	1.63	1.61	1.62	1.64	1.63
2	**Hardness**	-	6.5	7.2	6.8	7.1	6.8	5.8	5.5
3	**Thickness**	-	2.34	2.32	2.31	2.33	2.32	2.35	2.30
4	**Friability**	-	0.49	0.51	0.56	0.58	0.57	0.66	0.68
5	**Disintigration time**	-	6min 31sec	6min 49sec	5min 45sec	5min 30sec	5min 56sec	6min 03sec	6min 11sec

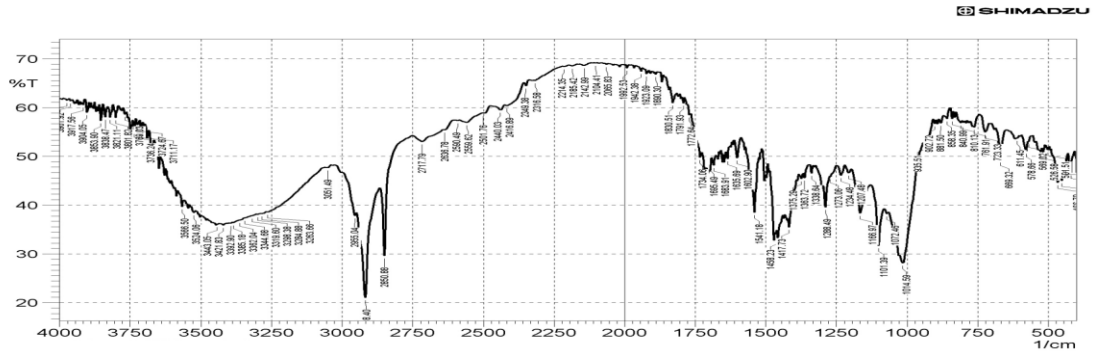

Fig 1: Pure Drug Esomeprazole

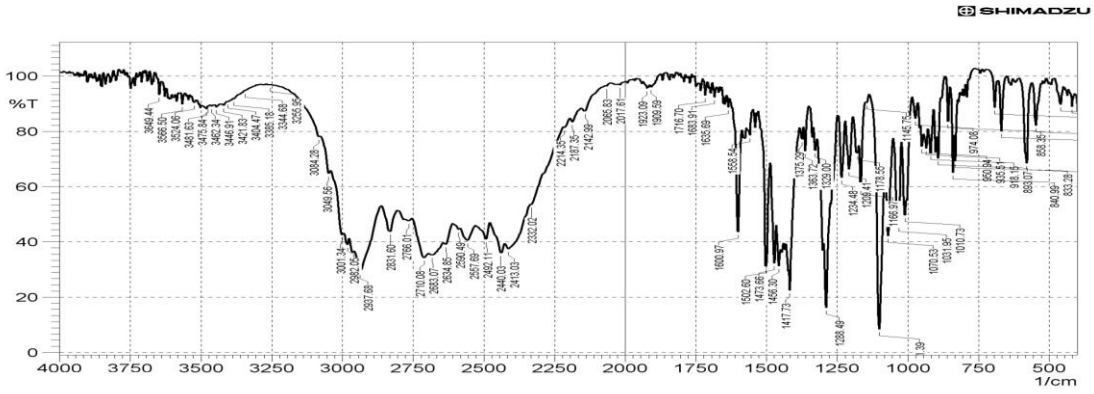

Fig 2: Esomeprazole Physical Mixture

Table 5: Compilation of *In vitro* Release of Esomeprazole sodium CR tablets Prepared Formulations from F3 to F8 and marketed Product (NEXPRO).

Time (min)	Percentage Release Of Esomeprazole Sodium Tablets						
	F3	F4	F5	F6	F7	F8	Marketed Product
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
20	22.25±0.33	29.40±1.24	36.73±0.78	54.64±0.88	70.20±0.8	71.02±0.80	68.39±1.00
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
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±0.52
60	49.94±1.37	53.18±1.48	58.28±1.99	81.40±0.86	93.06±0.51	96.29±0.73	92.70±0.59

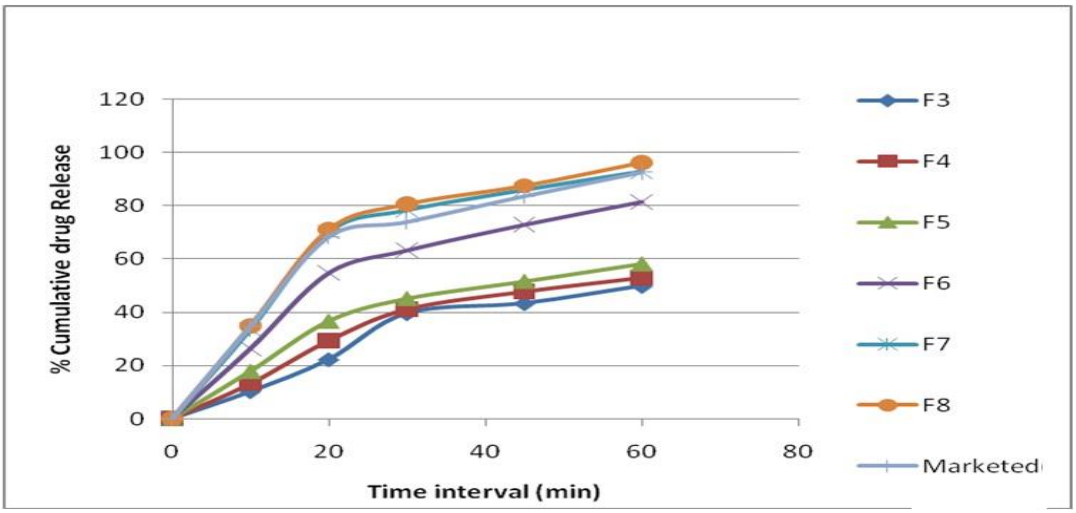

Fig 3: Comparative Dissolution Studies F3-F8&Marketed Product

DISCUSSION:

The objective of the study is to formulate and evaluate Esomeprazole sodium Controlled Release tablets comparable 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 different proportions and varying 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 indicated that the finished product formulations F7, F8, fulfilled all the specifications of the physical properties and invitro release and are comparable to the innovator product results were shown in Tables 3, 4 and 5, and FT-IR results were shown in figures 1&2. Formulation F1 was failed to compress as tablets due to because of improper physical feasibility sticking problem. Formulation F2 acid resistance was failed due to insufficient enteric coating. Formulation F3 to F5 Acid resistance was passed but invitro release was quite less. Formulation F6 *in vitro* release was within the limits but not comparable to the innovator product. Formulation F7, F8 fulfilled all the specifications prescribed for Esomeprazole controlled release tablets and comparable to the innovator product.

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). Eight trail formulations were made with varying levels of mannitol, HPMC, and eudragit coating tablets were done by Dry granulation method. Trail no.7 was found to be best of all the trails showing drug release matching the innovators product. The best formulation- trail no.7 was repeated again for reproducibility. And all the quality control tests were done for conformation. Based on dissolution stability studies trail no.8 better than trail no.7.

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