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Formulation and Evaluation of Delayed Release Enteric Coated Tablets of Tenatoprazole, by Optimizing the Plymers

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Abstract

The present study was undertaken with an aim to formulate enteric coated tablets of Tenatoprazole (a novel proton pump inhibitor with an imidazopyridine ring) to improve bioavailability by avoiding degradation. Different core tablets were prepared using approved excipients by direct compression method and evaluated for different parameters like hardness, thickness, friability and disintegration time. Sub-coating was done for optimized formulation (F5) by using HPMC 5 cps with buildup of 3% w/w and finally enteric coating was done by using HPMCP, Eudragit L30 D55 and HPMC Acetate succinate (HPMCAS) with an average weight buildup of 5%, 8% and 10% w/w. all formulations were evaluated for different parameters like hardness, friability, thickness, disintegration time, drug content and dissolution studies and compared with marketed sample. Results indicated that, methacrylic acid polymers exhibited better dissolution rate than cellulose polymers. The optimized formulation was subjected to stability studies as per ICH guidelines for 3 months and was observed that no significant change was observed.

Keywords: Sub-coating, Enteric Coating Tablets, HPMCP, Eudragit L30 D55, HPMCAS, Stability studies.

1. Introduction

Delivery of therapeutic agent into the intestinal region could be accomplished by the application of an enteric coating on a solid dosage form. Several approaches have been attempted and reported during the last decade to develop new methodologies for site-specific drug release, including time-controlled drug release and pH-sensitive drug release, such as enteric-coated dosage forms offer a simple and practical means for intestinal drug delivery (1).

Tenatoprazole is a proton pump inhibitor drug candidate that was undergoing clinical testing as a potential treatment for reflux oesophagitis and peptic ulcer with a half-life of 4.8 to 7.7 hours. The stability of Tenatoprazole Sodium decreases with a corresponding decrease in the pH of the media. Hence, the exposure of Tenatoprazole sodium to the acidic contents of the stomach would lead to significant degradation of the drug and would result in reduced bioavailability (2).

A number of enteric coating polymers are available and capable of protecting the drug core from the aggressive environments of the stomach. Being soluble at higher pH values, these polymers dissolve in the intestine and release the core for ready action. These polymers include several synthetic polymers like polymethacrylates (Eudragits), cellulose acetate phthalate (CAP), hydroxy propyl methyl cellulose phthalate (HPMCP). The aim of the present study was to compare the suitability of these renowned polymers to develop enteric coated tablets of a very sensitive proton pump inhibitor, Tenataprazole (3-7). *In vitro* analysis of the prepared tablets was carried out as

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Table 1. Core tablet formulation.

Ingredients	Quantity (mg)					
	F1	F2	F3	F4	F5	F6
Tenatoprazole	**60**	**60**	**60**	**60**	**60**	**60**
Microcrystalline Cellulose	175	---	28.4	113.2	141.6	56.8
Lactose		175	141.6	56.8	28.4	113.2
Sodium Starch Glycolate	10	---	15	---	15	---
Crosscarmellose	---	10	---	15	---	15
Magnesium stearate	5	5	5	5	5	5
Total weight	250	250	250	250	250	250

per the requirements of enteric coated tablets as specified in official pharmacopoeia (8).

2. Materials and methods

2.1. Materials

Tenatoprazole sodium (Lara Drugs Pvt. Ltd.), HPMCAS, Eudragit L30 D 55 and HPMCP (Evonik Industries), Crosscarmellose and sodium starch Glycolate from (Aqualon Inc) all other chemicals were purchased from SD Fine chemicals.

2.2. Preparation of Core tablets

Accurately weighed quantity of Tenatoprazole, lactose anhydrous, microcrystalline cellulose, sodium starch Glycolate/cross caremellose were sifted through sieve no. 30 and mixed thoroughly for 10 minutes in blender to ensure uniform mixing. Then accurately weighed magnesium stearate was sifted through sieve no. 40 and added to above blend and mixed properly for 5 minutes. The tablets were prepared by direct compression technique using sixteen station rotary machines. The detailed compositions of Tenatoprazole core tablet formulations are given in Table 1. Further, the optimized core tablet formulation was enteric coated with different enteric coating polymers namely, Hydroxy propyl methyl cellulose phthalate, Eudragit L30 D55 and Hypromellose acetate succinate, at different concentrations and combination as shown in the Table 2.

2.3. Evaluation of Granules

2.3.1. UV Scanning & calibration curve for Tenatoprazole

GUV Scanning and Calibration curve for Tenatoprazole sodium was carried out by taking phosphate buffer of pH 6.8 as dissolution medium. The λmax of the drug was determined by scanning one of the dilutions between 400 to 200 nm using a UV-visible spectrophotometer (9-11).

2.4. Compatibility Studies

A physical mixture (1:1) of drug and polymers was prepared and mixed with suitable quantity of IR grade potassium bromide and prepared transparent pellets. They were scanned from 4000 to 400 cm-1 in a Perkin Elmer FTIR spectrophotometer.

Table 2. Enteric coated tablet formulation.

Ingredients	Quantity/ tablet (mg)								
	5%			10 %			8%		
	F5 a	F5 b	F5 c	F5 d	F5 e	F5 f	F5 g	F5 h	F5i
HPMCP	12.9	---	---	25.8	---	---	20.64	---	---
Eudragit L30 D55	---	12.9	---	---	25.8	---	---	20.64	---
HPMCAS	---	---	12.9	---	---	25.8	---	---	20.64
Dibutyl phthalate	1.28	1.28	1.28	1.28	1.28	1.28	1.28	1.28	1.28
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Dichloro methane	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

2.5. Bulk density, tapped density and Carr's index

Ten grams of granules were introduced into a clean, dry 100 ml measuring cylinder and the volume was recorded. The cylinder was then tapped 25 times from a constant height and the tapped volume was read. The bulk density and tapped density were calculated as the ratio of the granules mass and the respective volumes. Carr's index (I) was calculated using the equation:

$$I=D_t-D_b/D_t\times100$$

Where, D_t is the tapped density of the powder and

D_b is the bulk density of the powder.

2.6. Angle of repose

The fixed funnel method was employed for determining the angle of repose. The granules were poured carefully until the apex of the conical pile just touches the tip of the stem of the funnel. The angle of repose was calculated using the equation : $\tan\alpha= H/R$

Where H is the height of the pile and R is the radius of the base of the conical pile.

2.7. Evaluation of prepared tablets

2.7.1. Hardness

The tablet crushing strength was tested by commonly used Monsanto type tablet hardness tester (IEC, Mumbai, India). A tablet is placed between the anvils and the crushing strength, which causes the tablet to break, is recorded (7, 12-13).

2.8. Friability Test

Tablet strength was tested by Roche friabilator (Electrolab, Bangalore, India). Pre weighed tablets were given 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets (8).

2.9. Uniformity of weight

Randomly selected twenty tablets were weighed individually and together in a single pan balance (Shimadzu, AX200, Japan). The average weight was noted and standard deviation calculated.

2.10. Disintegration time

Disintegration time was determined using the disintegration apparatus USP (Electrolab, Bangalore, India) in 0.1N HCl for 2 h and then in phosphate buffer pH 6.8 maintaining the temperature at 37±2 °C .

2.11. In vitro Dissolution tests

Drug release profile was evaluated in vitro using a dissolution test apparatus (Electro Lab, TDT-08L, Mumbai, India). The USP XIII Type II (paddle type) method was selected to perform the dissolution profile of Tenatoprazole. The dissolution for all the formulations was carried out according to US Pharmacopoeia for 2 h in 0.1 N HCl and then media was changed into phosphate buffer pH 6.8. The temperature was maintained at 37±0.5 °C and a constant paddle rotation speed of 75 rpm. Samples (5 ml) were withdrawn at regular intervals and filtered through membrane filter (pore size 0.22 µm). The samples were analyzed by UV Spectrophotometer at 270 nm.

2.12. Accelerated stability studies

Accelerated stability studies were performed as per the ICH guidelines. Selected formulations of Tenatoprazole sodium tablet were sealed in aluminum foil cover and stored at (40±2 °C / 75±5 % R.H) for a period of 3 months and evaluated for physical appearance, hardness and drug content.

3. Results and Discussion

3.1. Pre- compression Parameters

3.1.1. UV Scanning & Calibration curve studies for Tenatoprazole sodium

The scanning of the drug solution in the UV range 400 to 200 nm showed λ_{max} at 314 nm and hence, the calibration curve was developed at this wavelength. Calibration curve was plotted with concentrations vs. absorbance and the equation for the calibration curve was obtained as y=0.0125x+0.003 with R2 value obtained as 0.9991.

3.2. Compatibility Studies

The compatibility between the drug and the selected polymers was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the polymer-drug

Table 3. Bulk density, tapped density and Carr's index and Angle of repose for core tablets.

Parameters	F1	F2	F3	F4	F5	F6
Angle of repose	33.93	36.75	37.89	34.09	28.15	34.55
Bulk Density (g/cc)	0.48± 0.01	0.45±0.01	0.46±0.02	0.46±0.05	50.46± 0.01	0.45± 0.01
Tapped Density (g/cc)	0.59±0.016	0.55±0.015	0.54±0.015	0.52±0.014	0.53±0.02	0.56±0.02
Carr's Index (%)	14.78±2.0	18.41±3.82	16.53±1.38	14.09±1.6	9.2±0.73	16.4±0.6
Hausner's Ratio	1.15±0.05	1.22±0.05	1.19±0.02	1.17±0.05	1.1±0.01	1.16±0.03
Flow property	Good	Fair	Fair	Good	Excellent	Good

mean±SD (n=3).

mixture, which confirmed the absence of any chemical interaction between the drug and the polymers.

The results of evaluation on flow properties of the prepared granules are shown in table 3. Angle of repose, bulk density, tapped density, compressibility index and Hausners ratio were found to indicate overall good flow properties for all the formulations. It suggests that the quantity ratio of all ingredients to that of the lubricant is suitable to possess fair- good- excellent flow properties.

The results of the post compression evaluation of tablet formulations are given in table 4 for all batches of core tablets. The average weight of tablets was found to be within 249.6-252.5 mg. Drug content was found to be between 98.76-100.12 %. The hardness of tablets was found to be from 3.5-7.0 (kg/cm^2). Friability was found to be less than 1% for all the core tablet formulations. Disintegration studies showed time range for 3 min 26 seconds-7 min 12 seconds, optimum for core tablets.

Table 4. Post compression evaluation of Tablet formulations F1-F6.

Parameters	F1	F2	F3	F4	F5	F6
Average weight (mg)	251.6	251.2	250.8	249.6	251.5	252.5
Hardness	3.5 ±1.6	4.5±1.4	4.5±0.9	5.5±1.8	7.0±2.1	6.0±0.8
Thickness (mm)	4.32±0.3	4.26±0.2	4.28±0.2	4.30±0.2	4.25±0.3	4.29±0.3
Drug Content (%)	98.66	97.81	100.12	100.01	99.89	99.28
Friability (%)	0.33	0.28	0.25	0.23	0.17	0.21
Disintegration time (min)	6′47″	7′ 12″	6′ 05″	4′ 34″	3′ 26″	5′ 50″

mean±SD (n=3).

The enteric coated tablets were prepared and evaluated for Average wt, Thickness, Disintegration time in 0.1N HCL, Disintegration time in pH 6.8 phosphate buffer, Drug content studies. The studies revealed that the 5% enteric coating is not

Table 5. Physical properties of Enteric coated Tablet formulations by comparing with innovator drug product.

Parameters	F5 a	F5 b	F5 c	F5 d	F5 e	F5 f	F5 g	F5 h	F5 i	Innovator
Average wt. (g)	270.6	271.4	270.8	282.9	283.4	283.1	284.1	278.7	278.1	275.9
Thickness	4.37± 0.05	4.39± 0.01	4.36± 0.03	4.37± 0.05	4.35± 0.04	4.38± 0.03	4.36± 0.02	4.38± 0.01	4.36± 0.02	4.37± 0.02
Disintegration time in 0.1N HCL (min)	Failed	Failed	Failed	Passed	Passed	Passed	Passed	Passed	Passed	Passed
Disintegration time in pH 6.8 phosphate buffer (min)	---	---	---	16′ 18″	12′ 1″	11′ 31″	9′ 51″	7′ 23″	8′ 12″	10′ 28″
Drug content (%)	97.56	97.65	98.75	98.64	98.74	97.45	98.89	99.76	98.96	99.62

mean±SD (n=3).

Table 6. *In Vitro* Dissolution Studies with innovator drug product.

Time (Hrs)	F5a	F5b	F5c	F5 d	F5 e	F5 f	F5 g	F5 h	F5i	Innova-tor
In-vitro dissolution studies in 0.1N HCl										
1	0.65 ±0.23	0.69 ±0.25	0.83 ±0.89	0.27 ±0.24	0.57 ±0.25	0.23 ±0.58	0.59 ±0.29	0.87 ±0.89	0.58 ±0.23	0.57 ±0.36
2	6.61 ±0.25	5.32 ±0.23	4.63 ±0.28	2.57 ±0.28	2.41 ±0.47	2.56 ±1.02	7.89 ±0.48	6.23 ±0.54	8.96 ±0.14	2.41 ±0.98
In-vitro dissolution studies in pH 6.8 phosphate buffer										
3	41.56 ±0.23	39.26 ±0.32	37.87 ±0.23	35.89 ±0.65	8.57 ±0.89	24.58 ±0.56	36.89 ±0.23	7.46 ±0.27	32.56 ±0.59	8.89 ±0.39
4	65.31 ±0.99	62.35 ±0.28	59.86 ±0.56	52.38 ±0.89	21.52 ±0.21	36.89 ±0.48	47.74 ±0.98	22.27 ±1.03	44.89 ±0.25	24.24 ±0.28
6	89.63 ±0.23	81.36 ±1.02	79.68 ±0.87	74.59 ±0.21	45.61 ±0.59	45.69 ±1.06	57.59 ±0.47	64.61 ±0.98	54.78 ±0.69	42.47 ±0.58
8	96.36 ±0.12	90.36 ±0.27	89.63 ±0.29	84.66 ±0.39	65.85 ±0.48	58.79 ±0.87	66.58 ±0.25	65.85 ±0.75	69.35 ±0.14	66.42 ±0.89
10			98.56 ±0.47	99.79 ±0.99	82.21 ±0.98	66.58 ±0.36	88.79 ±0.12	80.78 ±0.23	88.74 ±0.29	81.89 ±1.03
12					98.69 ±0.54	78.96 ±0.89	91.87 ±0.47	97.28 ±0.14	89.75 ±1.03	96.48 ±0.68
f1=	6.5	5.94	5.87	5.02	3.15	4.78	4.66	4.22	4.32	
f2=	10.467	13.88	13.53	16.55	67.52	25.08	26.87	35.57	29.12	

mean±SD (n=3).

appropriate for achieving sufficient resistance to disintegration in 0.1 N HCl. Comparing the enteric coated tablet formulations with that of the Innovator drug product it was observed that, formulations F5e, F5f, F5g and F5i were acceptably similar to that of the Innovator in terms of Disintegration time. The results have been given in the table 5.

The enteric coated tablets were evaluated and compared to that of the innovator drug product for *in vitro* dissolution studies and kinetics of drug release. The percentage cummulative drug release data and their graph (% CDR vs time) has been exhibited in Table 6 and Figure 1 respectively. The enteric coated tablet formulation F5e, coated with Eudragit L30 D55 (at 10% weight percentage) showed highest similarity and lowest dissimilarity when compared to the conventional enteric coated innovator drug product.

The tablet formulation F5e was observed to release the drug slowly at the initial hours and a sutained release further for more than 12 hours. By fitting to the drug release kinetic modeling, its was found to release the drug at zero order, with highest linearity for percentage cummulative drug release vs time plot.

The optimized enteric coated tablet formulation F5e was examined for any change in disintegration time as well as dissolution or drug release during different accelearated stability conditions. Negligible differences were observed during the entire period of stability studies and different stability testing conditions. The results of stability studies for disintegration time as well as drug release can be found in the table 7 and 8 re-

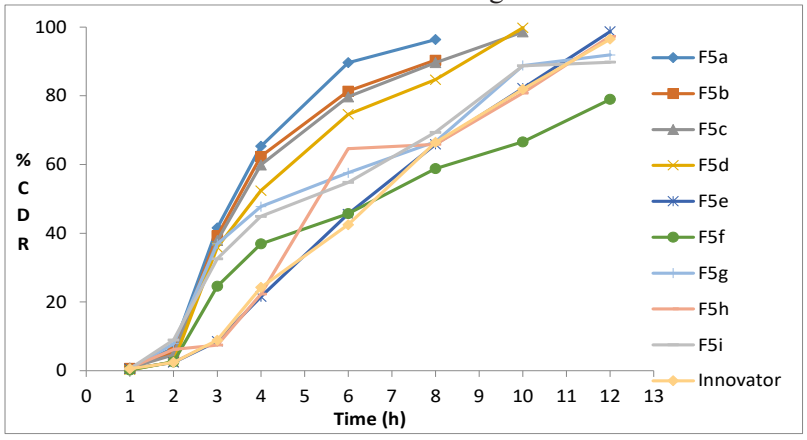

Figure 1. % CDR vs time plots for enteric coated tablet formulations F5a to F5i.

Table 7. Disintegration time of optimized formulation under different Stability Studies.

Stability testing conditions	25OC±2 OC / 60%± 5 % RH		30OC± 2OC / 65%± 5 % RH		40OC±2 OC / 75%± 5 % RH	
Time (min)	Disintegration time in 0.1N HCL	Disintegration time in pH 6.8 phosphate buffer	Disintegration time in 0.1N HCL	Disintegration time in pH 6.8 phosphate buffer	Disintegration time in 0.1N HCL	Disintegration time in pH 6.8 phosphate buffer
0	Passed	7′23″	Passed	7′30″	Passed	7′32″
1	Passed	7′33″	Passed	7′40″	Passed	7′44″
2	Passed	7′44″	Passed	7′48″	Passed	7′50″
3	Passed	8′10″	Passed	8′15″	Passed	8′20″
3	Passed	8′10″	Passed	8′15″	Passed	8′20″

spectively.

4. Conclusion

The enteric coated tablets of Tenatoprazole is a right option for the drug as it gets degraded at lower pH condition. The enteric coating not only avoids degradation of the drug but also favors in increasing drug absorption in the intestine. Here, different enteric coating polymers, HPMCP, Eudragit L30 D55 and HPMC Acetate succinate (HPMCAS) were studied, all were found to be effective in this regard.

The suitable enteric coating was observed in case of polymer Eudragit L30 D55 at 10% weight percentage. The disintegration study, dissolution studies, comparision with that of the innovator drug product and stability study results favored the findings.Thereby, methacrylic acid polymers exhibited better dissolution rate than cellulose polymers.

Conflict of Interest

None declared.

Table 8. Dissolution studies of optimized formulation under different Stability Studies.

Stabiliy testing conditions	25 °C±2 °C /60%±5% RH		30 °C± 2 °C /65%±5% RH		40 °C±2 °C /75%±5% RH	
Time in months coating (%)	dissolution 0.1N HCL	dissolution pH 6.8 phosphate buffer	dissolution 0.1N HCL	dissolution pH 6.8 phosphate buffer	dissolution 0.1N HCL	dissolution pH 6.8 phosphate buffer
0 (8%)	0.59±0.36	98.69±0.62	0.59±0.23	98.79±0.59	0.62±0.98	98.87±0.23
1(8%)	2.41±0.25	98.87±0.78	2.55±0.45	98.99±0.74	2.78±0.47	99.66±0.58
2(8%)	3.53±0.45	99.12±0.58	3.89±0.58	99.65±0.98	3.77±0.21	99.78±0.69
3(8%)	3.98±0.53	99.88±0.79	4.12±0.39	99.96±0.51	4.23±0.58	99.81±0.12

mean±SD (n=3).

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