IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
April 2024 Vol.:30, Issue:4

Formulation and Evaluation of Enteric-Coated Tablets of Pantoprazole

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ISSN 2349-7203
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Tejashkumar Patel[1], Jeevan Patel[2], Amulya Singh Solanki[2], Sumit Kapasiya[2], Dr. Rakesh Patel[3]

1PG Scholar, School of Pharmacy, Dr. A.P. J. Abdul Kalam University, Indore. India.

2Assistant Professor, School of Pharmacy, Dr. A.P. J. Abdul Kalam University, Indore. India.

3Professor and Principal, School of Pharmacy. A.P. J. Abdul Kalam University, Indore. India.

Submitted: 25 March 2024
Accepted: 31 March 2024
Published: 30 April 2024

HUMAN JOURNALS
ijppr.humanjournals.com

Keywords: Pantoprazole, Direct compression, Proton pump inhibitor, Cellulose acetate phthalate, Eudragit L100

ABSTRACT

Pantoprazole is a proton pump inhibitor, belongs to group of benzimidazole, Pantoprazole sodium was prepared by direct compression method using different concentration of, microcrystalline cellulose as filler, mannitol and dicalcium phosphate as diluents, crosscarmellose sodium as disintegrating agents, magnesium stearate and talc was used as a glidant and lubricant respectively. Direct compression is economical compared to wet granulation since it requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labor leading to reduced production cost of tablets. The prepared tablets were evaluated for hardness, weight variation, friability and drug content uniformity and it was found that the results comply with official standards. The prepared tablets were coated using enteric coating polymers such as cellulose acetate phthalate, Eudragit L100 and by dip coating method. The *in vitro* release was studied using acidic buffer pH 1.2 and phosphate buffer pH 6.8. Prepared all batch's C2F9 was found best, with hardness 5.60 ± 0.24 (Kg/cm^2), drug content 99.08 ± 0.35(%), disintegration time 7.02± 0.21(min), and percentage cumulative drug released which started after 120 min and reached 99.72 after 180 min. Stability studies indicated that the developed tablets were stable and retained their pharmaceutical properties at room temperature and 40 °C / 75% RH for 3 months.

INTRODUCTION

Pathways activate H^+, K^+-ATPase (the proton pump), which exchanges hydrogen and potassium ions across the parietal cell membrane. This pump generates the largest known ion gradient in vertebrates, with an intracellular pH of about 7.3 and an intracanalicular pH of about 0.8. The most important structures for CNS stimulation of gastric acid secretion are the dorsal motor nucleus of the vagal nerve, the hypothalamus, and the solitary tract nucleus. Efferent fibers originating in the dorsal motor nuclei descend to the stomach *via* the vagus nerve and synapse with ganglion cells of the enteric nervous system. ACh release from postganglionic vagal fibers directly stimulates gastric acid secretion through muscarinic M3 receptors on the basolateral membrane of parietal cells. The CNS predominantly modulates the activity of the enteric nervous system *via* ACh, stimulating gastric acid secretion in response to the sight, smell, taste, or anticipation of food (the "cephalic" phase of acid secretion). ACh also indirectly affects parietal cells by increasing the release of histamine from the enterochromaffin-like (ECL) cells in the fundus of the stomach and of gastrin from G cells in the gastric antrum. ECL cells, the source of gastric histamine secretion, usually are near parietal cells. Histamine acts as a paracrine mediator, diffusing from its site of release to nearby parietal cells, where it activates H2 receptors. The critical role of histamine in gastric acid secretion is dramatically demonstrated by the efficacy of H2-receptor antagonists in decreasing gastric acid secretion. Gastrin, which is produced by antral G cells, is the most potent inducer of acid secretion. Multiple pathways stimulate gastrin release, including CNS activation, local distention, and chemical components of the gastric contents. Gastrin stimulates acid secretion indirectly by inducing the release of histamine by ECL cells; a direct effect on parietal cells also plays a lesser role. Somatostatin (SST), which is produced by antral D cells, inhibits gastric acid secretion. Acidification of the gastric luminal pH to <3 stimulates SST release, suppressing gastrin release in a negative feedback loop. SST-producing cells are decreased in patients with H. pylori infection, and the consequent reduction of SST's inhibitory effect may contribute to excess gastrin production.

Structure and functions of the stomach

The stomach is continuous with the esophagus at the cardiac sphincter and with the duodenum at the pyloric sphincter. It has two curvatures. The stomach is divided into three regions: the fundus, the body, and the antrum. At the distal end of the pyloric antrum is the pyloric sphincter, guarding the opening between the stomach and the duodenum. When the

stomach is inactive the pyloric sphincter is relaxed and open and when the stomach contains food the sphincter is closed.

Temporary storage allowing time for the digestive, chemical digestion, preparation of iron for absorption, production of intrinsic factor needed for absorption of vitamin B12 in the terminal ileum regulation of the passage of gastric contents into the duodenum. When the chyme is sufficiently

-MATERIALS AND METHODS

Preformulation studies

Preparation of standard graph for pantoprazole sodium using acidic buffer (pH 1.2)

Determination of absorption maxima (λmax)

100 mg of pantoprazole sodium sesquihydrate was weighed accurately and dissolved in 100 mL of pH 1.2 acidic buffer in a 100 mL volumetric flask (stock solution). 2 mL was taken from the stock solution and transferred into 100 mL volumetric flask and diluted up to 100 mL with pH 1.2 acidic buffer. The resulting solution was labeled as standard working Solution. 2 mL of the working solution was withdrawn and diluted up to 10 mL with pH 1.2 acidic buffer in 10 mL volumetric flask. The spectrum of this solution was run in 200 to 400 nm range in a UV-visible spectrophotometer. The λ max of the pantoprazole sodium sesquihydrate was found to be 283 nm.

Preparation of standard graph

From the above standard working solution, 1, 2, 3, 4, 5, and 6 mL was withdrawn and diluted up to 10 mL with pH 1.2 acidic buffer in 10 mL volumetric flask to get concentration of 2 µg, 4 µg, 6 µg, 8 µg, 10 µg and 12 µg respectively. The absorbance of each solution was measured by UV-visible spectrophotometer at 283 nm using the pH 1.2 acidic buffer as blank.

Preparation of standard graph for pantoprazole sodium using phosphate buffer (pH 6.8)

Determination of absorption maxima (λmax)

100 mg of pantoprazole sodium sesquihydrate was weighed accurately and dissolved in 100 mL of pH 6.8 phosphate buffer in 100 mL volumetric flask (stock solution). 2 mL was taken

from the stock solution and transferred into 100 mL volumetric flask and diluted up to 100 mL with pH 6.8 phosphate buffer. The resulting solution was labeled as standard working Solution. 2 mL of the working solution was withdrawn and diluted up to 10 mL with pH 6.8 phosphate buffer in 10 mL volumetric flask. The spectrum of this solution was run in 200 to 400 nm range in a UV-visible spectrophotometer. The λ max of the pantoprazole sodium sesquihydrate was found to be 288 nm.

Evaluation

Precompression parameters

Bulk density (Db)

Accurately weighed granules were carefully transferred into graduated measuring cylinder. The granules bed was then made uniform and the volume occupied by the granules was noted as per the graduation marks on the cylinder as mL. It is expressed in gm/mL and is calculated using the following formula[49,50].

Tapped density (Dt)

It is the ratio of total mass of granule to the tapped volume of granule. The graduated measuring cylinder containing accurately weighed granule was manually tapped for 50 times. Volume occupied by the granule was noted. It is expressed in gram/mL and is calculated by following

Preparation of pantoprazole sodium tablets

An ideal mixture of granules was directly punched into tablets weighing about 200 mg containing 40 mg of pantoprazole sodium sesquihydrate, using a rotary tablet compression machine (Riddhi 10 stn mini tablet press RDB4-10, Rimek, Ahmedabad, India), using 8 mm diameter concave punches. The different batches of pantoprazole tablets were collected and stored in air-tight containers.

Table 1. Composition of pantoprazole sodium enteric coated sodium tablets

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pantoprazole sodium (mg)	40	40	40	40	40	40	40	40	40
Croscarmellose sodium (mg)	2	4	6	2	4	6	2	4	6
Microcrystalline cellulose(mg)	27	25	23	27	25	43	80	50	23
Mannitol (mg)	50	75	100	40	85	80	43	50	75
Dicalcium phosphate (mg)	75	50	25	85	40	25	75	50	50
Talc (mg)	2	2	2	2	2	2	2	2	2
Magnesium stearate (mg)	4	4	4	4	4	4	4	4	4
Total weight (mg)	200	200	200	200	200	200	200	200	200

Post compression parameters

Hardness test

The prepared tablets were subjected to hardness test[28,38]. It was carried out by using hardness tester and expressed in kg/cm^2.

Friability test

The friability was determined using friabilator and expressed in percentage (%). 20 tablets from each batch were weighed separately (W initial) and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were reweighed (W final) and the percentage friability (F) was calculated for each batch by using the following formula[28,38].

$$F = \frac{(Winitial) - (Wfinal)}{Winitial} \quad X \quad 100$$

Weight variation test

Twenty tablets were selected at random from the lot, weighed individually and the average weight was determined. The percent deviation of each tablet weight against the average weight was calculated[28,38]. The test requirements are met, if not more than two of the individual weights deviate from the average weight by more than 5% and none deviates more

than 10%. IP limit for weight variation in case of tablets weighing more than 80 mg but less than 250 mg is ± 7.5 %.

Drug content uniformity

The prepared pantoprazole sodium sesquihydrate tablets were tested for their drug content. Three tablets of each formulation were weighed and finely powdered. About 40 mg equivalent of pantoprazole sodium sesquihydrate was accurately weighed and completely dissolved in pH 6.8 phosphate buffer and the solution was filtered. 1 mL of the filtrate was further diluted to 100 mL with pH 6.8 phosphate buffer. Absorbance of the resulting solution was measured by UV spectrophotometer at 288 nm[28].

Disintegration time of Pantoprazole sodium core tablets

Disintegration test was carried out using the tablet disintegration test apparatus (Serve well Instruments Pvt. Ltd., Electrolab ED-2L, India) pH 6.8 phosphate buffer at 37 ± 0.5 ºC was used as the disintegration media and the time in second taken for complete disintegration of the tablet.

Coating of compressed pantoprazole sodium tablets

Preparation of enteric coating solution

The enteric coating solution was prepared by simple solution method. It was prepared by 6% w/w and 8% W/W of Eudragit L100 (E1 and E2)or cellulose acetate phthalate (C1 and C2) as an enteric polymer, PEG 1.5% w/w as plasticizer and acetone and isopropyl acetone was used as solvent. Diethyl phthalate was added and made up the volume with the rest of the solvent mixture; this mixture was constantly stirred for 1h with paddle mechanical stirrer at the rate of 1000 rpm and the stirred coating solution was again filtered through muslin cloth, a coating solution was obtained38,42.

Table 2. Composition of coating solution

Ingredients	**Quantity (%)**
Cellulose Eudragit L100	6.0 / 8.0
PEG	1.5
Acetone	59.4

Enteric coating of pantoprazole sodium compressed tablets by dipping method

Physicochemical evaluation of coating films

The same polymer solution was used to prepare the polymeric films and was subjected for film thickness, and film solubility. The polymeric films were prepared by casting the acetone with PEG the polymer solution was poured on the glass plate. The film was dried for 24 h at room temperature under a special cover with reduced solvent evaporation to obtain smooth homogenous films.

RESULTS AND DISCUSSION.

Preformulation studies

Preparation of standard graphs

The standard graph for the drug pantoprazole sodium was done separately in pH 1.2 acidic buffer and pH 6.8 phosphate buffer. Tables show the concentrations of pantoprazole sodium in pH 1.2 acidic and pH 6.8 phosphate buffers and the respective absorbance. The Figures 1 and 2 show the calibration curves of pantoprazole sodium in pH 1.2 acidic buffer and pH 6.8 phosphate buffer respectively.

Table 3. Calibration data of pantoprazole sodium in 0.1N HCl (pH 1.2)

SL. NO.	Concentration (mg /mL)	Absorbance* (nm)
1	0	0
2	2	0.082+0.0005
3	4	0.145+0.0015
4	6	0.231+0.0101
5	8	0.289+0.0023
6	10	0.361+0.0025
7	12	0.459+0.0047

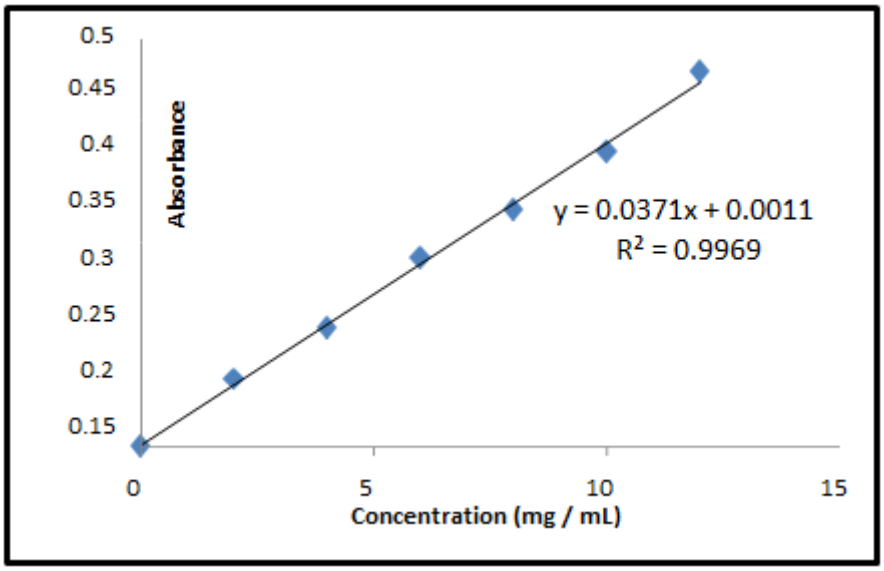

Figure 1. Standard graph of pantoprazole sodium

Table 4. Calibration data of pantoprazole sodium in phosphate buffer (pH 6.8)

SL. NO.	Concentration (mg /mL)	Absorbance* (nm)
1	0	0
2	2	0.085±0.0040
3	4	0.149±0.0036
4	6	0.243±0.0015
5	8	0.305±0.0075
6	10	0.373±0.0051
7	12	0.468±0.0020

*Mean±SD, *n* =

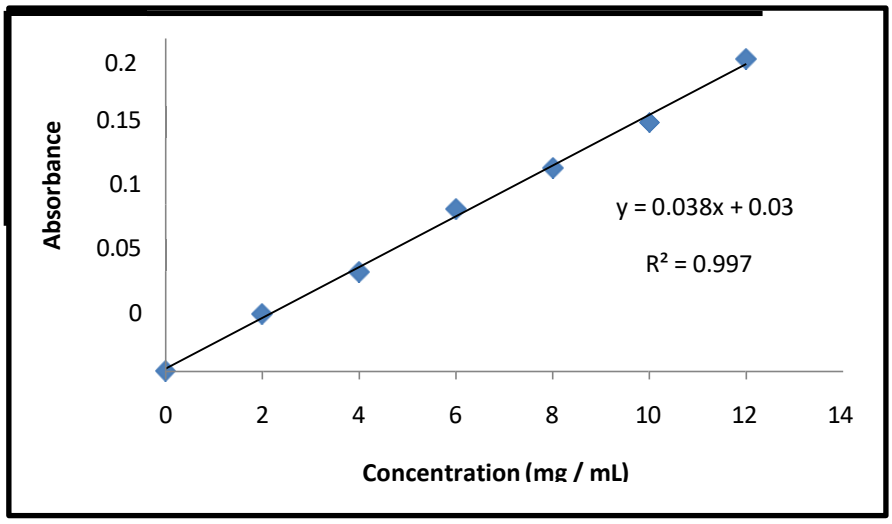

Figure 2. Standard graph of pantoprazole sodium in phosphate buffer (pH 6.8

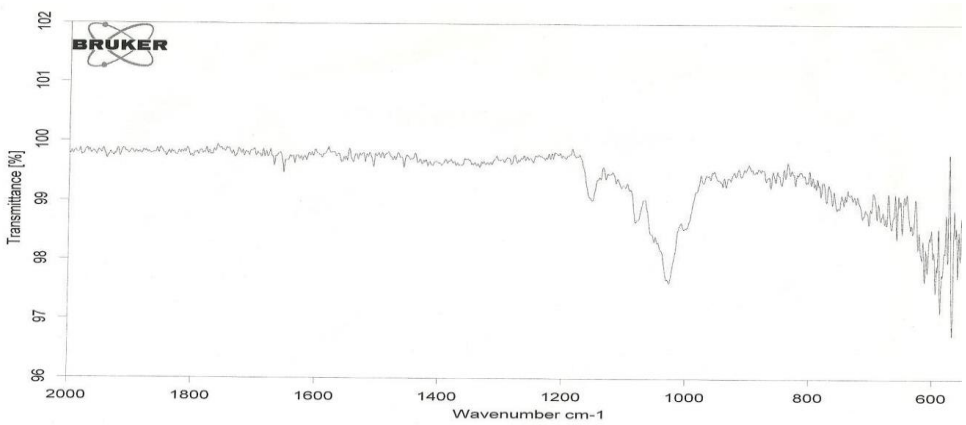

Figure 3. FTIR Spectrum of pantoprazole sodium

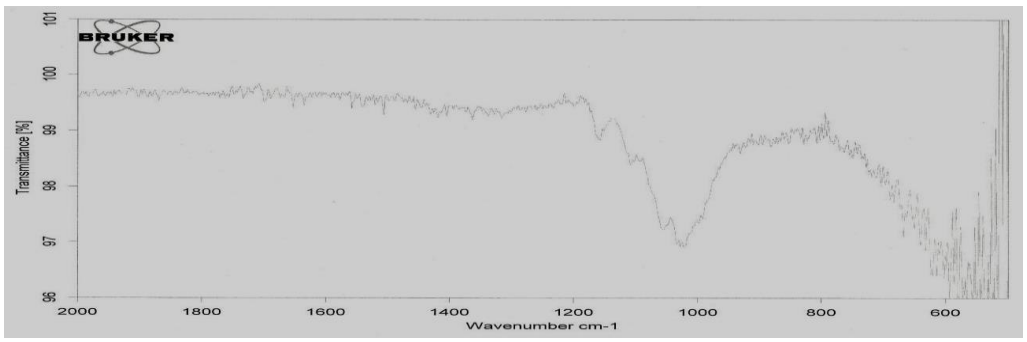

Figure 4. FTIR Spectrum of physical mixture of pantoprazole sodium with mannitol

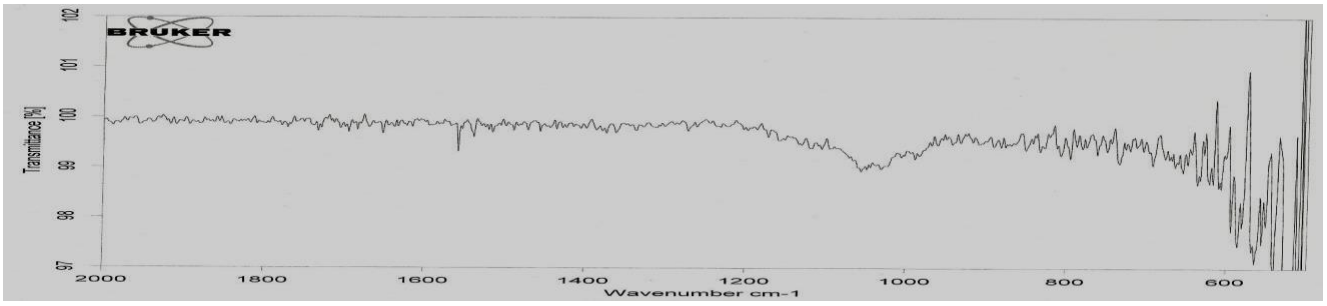

Figure 5. FTIR Spectrum of physical mixture of pantoprazole sodium with dicalcium phosphate

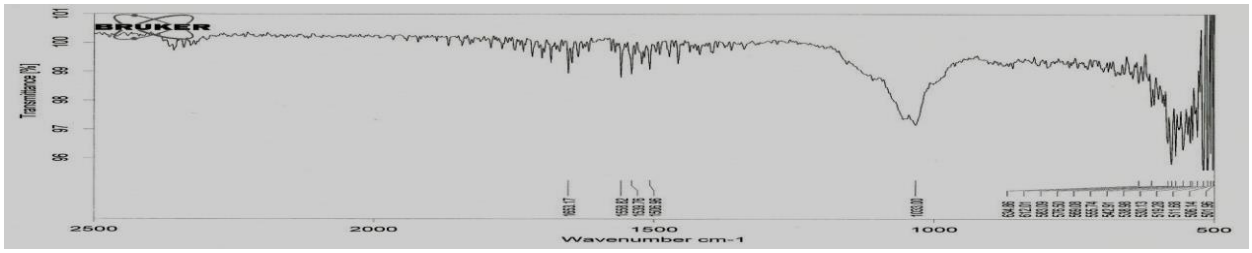

Figure 6. FTIR Spectrum of physical mixture of pantoprazole sodium with Dicalcium phosphate and mannitol

The standard band frequency of the pantoprazole sodium is shown in the Table 5.

Table 5. Standard band frequency of Pantoprazole Sodium

Wave number in cm^{-1}	**Characteristic**
1900	C=H
1650 - 1580	N-H bending
1600 - 1400	Aromatic C=C stretching
1400 - 1000	C-N bending
1373	C-F
1049	S=O

Evaluations

Precompression parameters

The prepared pantoprazole powder blend for tableting was prepared by direct compression method. The prepared pantoprazole powder blend was evaluated by angle of repose, bulk density, tapped density, Hausner's ratio, and compressibility index as given on Table 6. The 3.

Table 6 Pre compression parameters of pantoprazole sodium

Formulation Code	Parameter				
	Bulk density (gm/mL) *	**Tapped density (gm/mL) ***	**Carr's Index (%) ***	**Hausner's ratio***	**Angle of repose (Ɵ)***
F1	0.357±0.03	0.384±0.05	7.03±0.09	1.075±0.04	28.31±0.26
F2	0.312±0.04	0.335±0.02	6.86±0.15	1.073±0.05	27.20±0.14
F3	0.306±0.03	0.326±0.03	6.13±0.12	1.065±0.02	29.13±0.34
F4	0.312±0.03	0.334±0.06	6.58±0.14	1.070±0.06	26.13±0.26
F5	0.306±0.03	0.334±0.05	8.38±0.17	1.091±0.08	26.78±0.18
F6	0.384±0.04	0.429±0.05	10.48±0.20	1.117±0.07	25.79±0.24
F7	0.358±0.05	0.385±0.04	7.01±0.13	1.075±0.03	29.52±0.14
F8	0.286±0.05	0.313±0.04	8.62±0.07	1.094±0.03	26.95 ±0.15
F9	0.348±0.08	0.328±0.05	5.74±0.13	1.06±0.08	26.13±0.26

***Mean ± SD n=3

Table 7 Physicochemical evaluation of different polymer coating films

Formulation Code	Parameter				
	Hardness (Kg/cm^2) *	Friability (%) *	Weight variation (mg) *	Drug content (%) *	Disintegration time(min) *
F1	5.80 ± 0.12	0.69 ± 0.015	199 ± 0.12	96.28 ± 0.15	10.6± 0.62
F2	5.56 ± 0.24	0.51 ± 0.017	206 ± 0.24	97.62 ± 0.27	8.26± 0.56
F3	5.83 ± 0.08	0.48 ± 0.014	201 ± 0.17	99.51 ± 0.36	5.38± 0.23
F4	4.93 ± 0.15	0.64 ± 0.015	208 ± 0.20	98.17 ± 0.16	11.48± 0.15
F5	5.73 ± 0.25	0.71 ± 0.016	203 ± 0.16	98.92 ± 0.42	9.32± 0.18
F6	5.12 ± 0.34	0.68 ± 0.026	206 ± 0.14	100.34 ± 0.13	6.13± 0.25
F7	5.66 ± 0.17	0.54 ± 0.026	199 ± 0.22	98.50 ± 0.48	10.54± 0.43
F8	6.20 ± 0.35	0.49 ± 0.025	204 ± 0.18	98.41 ± 0.34	9.12± 0.71
F9	5.60 ± 0.24	0.42 ± 0.018	198 ± 0.15	99.08 ± 0.35	6.02± 0.21

***** Mean ± SD, n=3

Table 8 Physicochemical evaluation parameters of enteric coated tablets

Polymer	Parameter		
	Film solubility		Film thickness (mm) *
	pH 1.2	pH 6.8	
CAP	Insoluble	Soluble	0.21 ± 0.07
Eudragit L 100	Insoluble	Soluble	0.24 ± 0.08

*****Mean±SD, *n*

Table 9 In vitro drug release studies of enteric-coated tablets

Polymer	Batch Code	Parameter		
		Weight Variation (mg) *	Hardness Kg/cm2*	Drug content (%)*
CAP	C1F3	211 ± 0.035	6.5 ± 0.15	96.75 ± 0.14
	C2F3	214 ± 0.016	5.9 ± 0.24	93.65 ± 0.35
	C1F9	212 ± 0.006	5.4 ± 0.09	94.45 ± 0.26
	C2F9	210 ± 0.024	6.3 ± 0.14	98.54 ± 0.12
Eudragit L 100	E1F3	214 ± 0.021	5.5 ± 0.16	93.47 ± 0.23
	E2F3	213 ± 0.012	6.0 ± 0.06	94.56 ± 0.14
	E1F9	215 ± 0.015	6.5 ± 0.31	98.27 ± 0.45
	E2F9	211 ± 0.024	5.7 ± 0.20	96.35 ± 0.12

*Mean±SD, *n* = 3

Table 10. In vitro drug release of pantoprazole sodium (C1F3)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg /mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0.024	0.6469	5.822	0	0	5.822	14.62+0.52
120	0.06	1.6172	14.555	0.0064	0.0064	14.561	36.58+0.40
135	0.091	2.3884	21.496	0.0161	0.0226	21.518	54.05+0.90
150	0.121	3.1758	28.582	0.0238	0.0465	28.629	71.91+0.39
165	0.142	3.7270	33.543	0.0317	0.0782	33.621	84.46+0.17
180	0.162	4.2519	38.267	0.0372	0.1155	38.383	96.42+0.40

* Mean±SD, *n* = 3

Table 11. *In vitro* drug release of pantoprazole sodium (C2F3)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg / mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0
120	0	0	0	0	0	0	0
135	0.019	0.4986	4.488	0	0	4.488	11.27 ±0.90
150	0.082	2.1522	19.370	0.0049	0.0049	19.375	48.67+0.27
165	0.122	3.2021	28.818	0.0215	0.0265	28.845	72.46+0.18
180	0.149	3.9107	35.196	0.0320	0.0585	35.255	88.56+0.42
195	0.159	4.1732	37.559	0.0391	0.0976	37.656	94.59+0.70

***** Mean±SD, *n* = 3

Table 12. In vitro drug release of pantoprazole sodium (E1F3)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg / mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0.041	1.1051	9.946	0	0	9.946	24.98+0.34
120	0.071	1.9137	17.223	0.0110	0.0110	17.234	43.29+0.62
135	0.116	3.0446	27.401	0.0191	0.0301	27.431	68.91+0.72
150	0.137	3.5958	32.362	0.0304	0.0606	32.422	81.44+0.58
165	0.165	4.3307	38.976	0.0359	0.0965	39.072	98.15+0.40

***** Mean±SD, *n* = 3

Table 13. *In vitro* drug release of pantoprazole sodium (E2F3)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg / mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0
120	0.02	0.5390	4.851	0	0	4.851	12.18+0.82
135	0.07	1.8372	16.535	0.0053	0.0053	16.540	41.55+0.66
150	0.116	3.0446	27.401	0.0183	0.0237	27.425	68.89+0.72
165	0.142	3.7270	33.543	0.0304	0.0542	33.597	84.39+0.48
180	0.164	4.3044	38.740	0.0372	0.0914	38.831	97.54+0.70

***** Mean±SD, *n* = 3

Table 14. *In vitro* drug release of pantoprazole sodium (C1F9)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg / mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0.04	1.0781	9.703	0	0	9.703	24.48+0.18
120	0.079	2.1293	19.164	0.0107	0.0107	19.175	48.38+0.67
135	0.121	3.1758	28.582	0.0212	0.0320	28.614	72.20+0.58
150	0.15	3.9370	35.433	0.0317	0.0638	35.496	89.56+0.42
165	0.167	4.3832	39.448	0.0393	0.1032	39.552	99.79+0.70

***** Mean±SD, *n* = 3

Table 15. *In vitro* drug release of pantoprazole sodium (C2F9)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg / mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0
120	0	0	0	0	0	0	0
135	0.054	1.417	12.755	0	0	12.755	32.18+0.34
150	0.098	2.572	23.149	0.0141	0.0141	23.163	58.44+0.58
165	0.139	3.648	32.834	0.0257	0.0398	32.874	82.94+0.18
180	0.167	0.038	0.043	39.448	0.0364	0.076	99.72+0.46

***** Mean±SD, *n* =

Table 16. *In vitro* drug release of pantoprazole sodium (E1F9)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg / mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0.03	0.8086	7.277	0	0	7.277	18.36+0.42
120	0.063	1.6981	15.283	0.0080	0.0080	15.291	38.58+0.22
135	0.104	2.7296	24.566	0.0169	0.0250	24.592	62.05+0.58
150	0.15	3.9370	35.433	0.0272	0.0523	35.485	89.53+0.39
165	0.164	4.3044	38.740	0.0393	0.0917	38.831	97.97+0.48

***** Mean±SD, *n* = 3

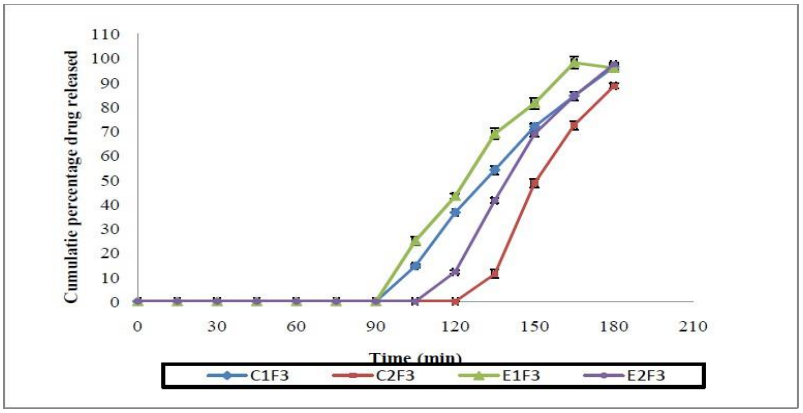

Figure 7. In vitro drug release of pantoprazole sodium (C1F3 to E2F3)

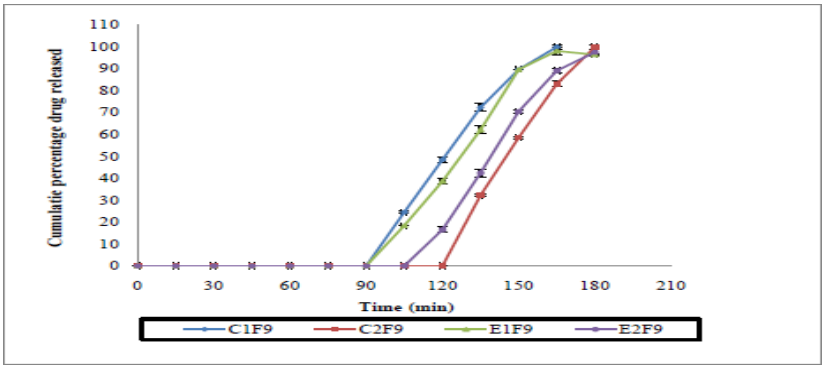

Figure 8. In vitro drug release of pantoprazole sodium (C1F9 to E2F9)

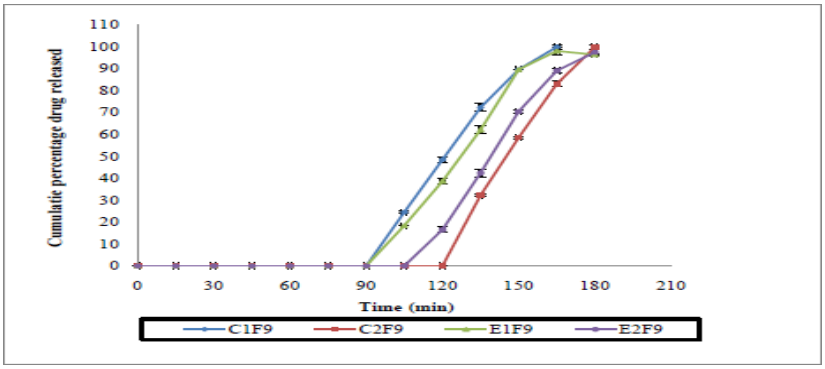

Table 17. Stability studies of cellulose acetate phthalate coated tablet formulation C2F9

Evaluation parameters	Observation in month			
	Initial	1st month	2nd month	3rd month
Physical Appearance	white color tablets	No change	No change	No change
Hardness (Kg / cm2) *	6.3 ± 0.14	6.2 ± 0.56	6.2 ± 0.64	6.2 ± 0.26
Drug Content (%) *	98.54 ± 0.12	98.36 ± 0.52	98.16 ± 0.36	98.07 ± 0.28

*Mean ± SD, n=3

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