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Formulation and *In-vitro* Evaluation of Pantoprazole Sodium Delayed Release Tablets

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A B S T R A C T

Pantoprazole is a category of proton pump inhibitor, belongs to group of benzimidazole derivative used for the treatment of gastric and duodenal ulcers. Pantoprazole is undergoes degradation in acidic media of stomach. In the present study was attempted to formulate and evaluate pantoprazole sodium as enteric coated tablet. The pre-compression parameter of blend was performed includes FT-IR studies, DSC and constructs the calibration curve of pantoprazole sodium. The delayed release tablets of pantoprazole sodium were prepared by dry granulation method using PVPk30 as binder, Mannitol as diluent, and HPMC as a sub-coating material. The prepared sub coated tablets were evaluated for Weight variation, thickness, hardness, friability, disintegration time and it was found that obtaining results was comply with official standards. The prepared tablets were coated by using enteric coating polymers such as Eudragit L30D55 and HPMCP HP55 by using pan coater (spray technique). The prepared enteric coated tablets were subjected for the physical and chemical evaluation. The *in-vitro* drug release studies were performed by using acidic buffer (pH 1.2) and phosphate buffer (pH 6.8). The *in-vitro* drug release study there is no loss during acidic phase (2 hrs). In phosphate buffer the *in-vitro* drug release was observed and it gives highest % drug release (96.81) in F7 (60 min) and also it reaches the innovator product (92.78). Accelarated stability studies were indicated that the prepared enteric coated tablets were stable and maintain their pharmaceutical properties at 40^0C/75% RH for a period of 3 months.

Keywords: Pantoprazole sodium, HPMC, EudragitL30D55, HPMCP HP55, Dry granulation, *in-vitro* drug release.

A R T I C L E I N F O

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1. Introduction

A drug delivery system (DDS) is defined as a formulation or a pattern that enables to introduction of therapeutic substances in the body and develops its efficacy and safety by controlling the rate, time and place of release of drugs in the body. [**Jain N.K & Sharma S.N**] Conventional drug therapy involves periodic doses of therapeutic substance, these are formulated to develop maximum stability, activity and bioavailability. A conventional method of drug administration is efficient in most of the cases, but some drugs are not stable or toxic in nature and having narrow therapeutic window. [**James swarbrick**].

Delayed drug Release Systems (DDDS) (or) Gastro Resistant Drug Delivery Systems:

The contriving of delayed or enteric-coated delivery systems is to improve the acid sensitive drugs and reduce the gastric irritation. If one were to conceive of the ideal drug delivery system, two major things would be required. It should deliver the drug directly to the site of action, thereby minimizing or avoiding side effects. [**Ansel C.H & Patel Harshna**].

Mechanism of drug release from enteric coating:

All enteric polymers have ionizable acid groups, generally a free carboxylic acid from a phthalyl moiety. The equilibrium between unionized insoluble polymer and ionized soluble polymer will be determined by the pH of the medium and the pKa of the polymer. The Henderson-Hasselbach equation can be used to promising the ratio of ionized to unionized polymer based on these two parameters. [**Hogan J**]

$$\mathrm{pH} - \mathrm{pka} = \log \frac{\text{concentration of ionized form}}{\text{concentration of unionized form}}$$

2. Materials and Methods

Pantoprazole sodium sesquihydrate, Mannitol, Sodium lauryl sulphate, Povidone(PVP K-30), Sodium carbonate, Cross povidone, Calcium stearate, HPMC(Methocel,5CPs), Sicovit yellow, Propylene glycol, Titanium dioxide, methacrylic acid copolymer(Eudragit L30D55), Hypromellose phthalate(HPMCPHP55), Triethyl citrate, Polysorbate 80, Acetone, Dehydrated alcohol, Purified water.

Methodology:

Formulation of core tablet:

Pantoprazole sodium sesquihydrate delayed release tablets were prepared by dry granulation technique using different excipients as well as with varying concentrations of polymer proportions using methacrylate copolymer (Eudragit L30D55) and Hydroxy Propyl Methyl Cellulose Phthalate/Hypromellose phthalate as enteric coating materials [Mishra C.K].

Weigh the all ingredients, sifted through 30# and subjecting for the blending by using octagonal blender for 15 min. The blend was placed in roller compactor, passed the compacted materials through 30# again performing the blending and lubrication and finally the granules punched into a tablet using rotary tablet compression machine (16 station, clit, CMP210). To prepare a sub-coating solution and coated on the prepared core tablet by using coating pan (spray technique). Eudragit L30D55 and HPMCP HP55 used as an enteric coating material [Viral patel, Ajit Patil & Singh Deep Hussan].

Table 1: Formula for preparation of pantoprazole sodium core tablets

S. No	Ingredients (mg)	Formulation code									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Pantoprazole sodium	45.11	45.11	45.11	45.11	45.11	45.11	45.11	45.11	45.11	45.11
2.	Mannitol	90	85.09	85.09	85.09	85.09	85.09	85.09	85.09	85.09	85.09
3.	$PVPK_{30}$	15.4	15.4	15.4	15.4	15.4	10	8	8	8	8
4.	Ca. stearate	1	1	1	1	1	1	1	1	1	1
5.	Mannitol	----	10	10	10	10	10	10	10	10	10
6.	Sodium carbonate	10.30	10.30	10.30	10.30	10.30	10.30	10.30	10.30	10.30	10.30
7	Crosspovidone	1.5	1.5	1.5	3.0	3.0	3.0	3.0	3.0	3.0	3.0
8	SLS	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55
9	Ca.stearate	----	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
10.	Total weight	164.86	171.45	171.45	172.95	172.95	167.55	165.55	165.55	165.55	165.55

Table 2: Formula for pantoprazole sodium sesquihydrate sub coated tablets

S. No	Ingredients (mg)	Formulation code								
		F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	HPMC	17.48	17.48	17.48	17.48	17.48	17.48	17.48	17.48	17.48
2.	Sicovit yellow (gms)	0.77	0.77	0.77	0.57	0.57	0.57	0.57	0.57	0.57
3.	Propylene glycol (gms)	1.50	1.50	1.50	1.0	1.0	1.0	1.0	1.0	1.0
4.	Titanium dioxide (gms)	0.40	0.40	0.40	0.28	0.28	0.28	0.28	0.28	0.28
5.	Purified water	175.67	175.67	175.67	175.67	175.67	175.67	175.67	175.67	175.67

Table 3: Formula for pantoprazole sodium sesquihydrate enteric coated tablets

S. No	Ingredients (mg)	Formulation code F2, F3, F4, F5, F6, F7, F8, F9								
		F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Eudragit L30D55	27.0	33.12	33.12	33.12	33.12	33.12	33.12	----	----
2.	HPMCP HP55	----	----	----	----	----	----	----	31.89	31.89
3.	TEC	1.0	1.73	1.73	1.73	1.73	1.73	1.73	2.68	2.68
4.	Polysorbate 80	0.3	0.48	0.48	0.48	0.48	0.48	0.48	0.76	0.76
5.	Acetone	----	----	----	----	----	----	----	190	190
6.	Dehydrated alcohol	----	----	----	----	----	----	----	190	190
7.	Purified Water	59.67	59.67	59.67	59.67	59.67	59.67	59.67	----	----
8.	Total weight	219.9	226.93	228.43	223	217.6	215	215	215	215

3. Results and Discussions

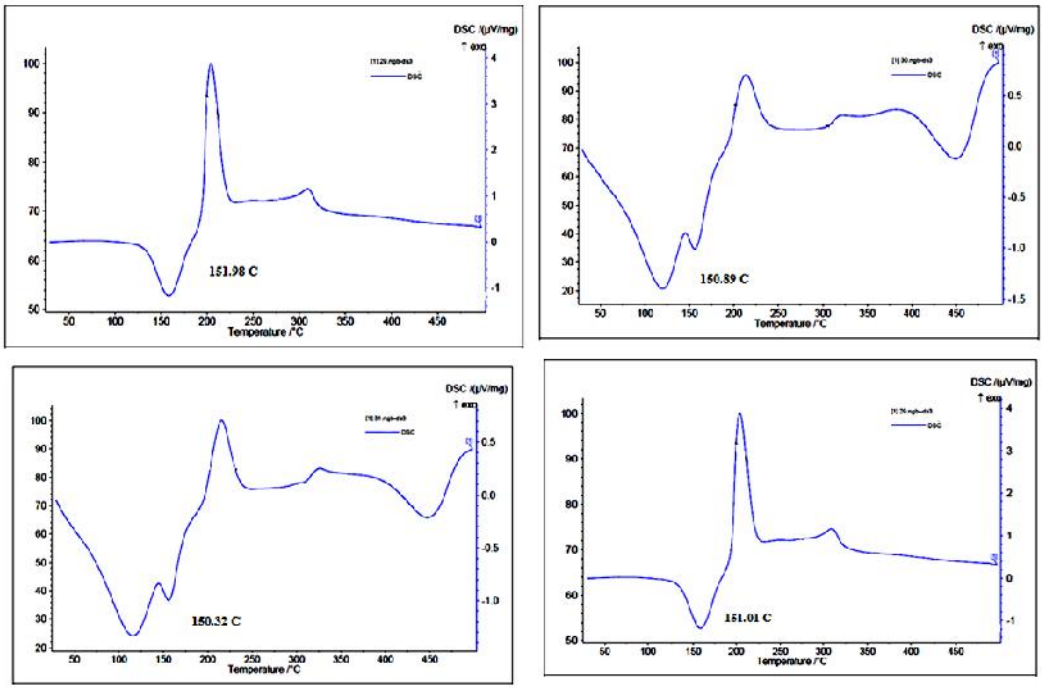

Figure 1: DSC of Pantoprazole sodium, pan: crospovidone, pan: pvpk30, pan: mannitol

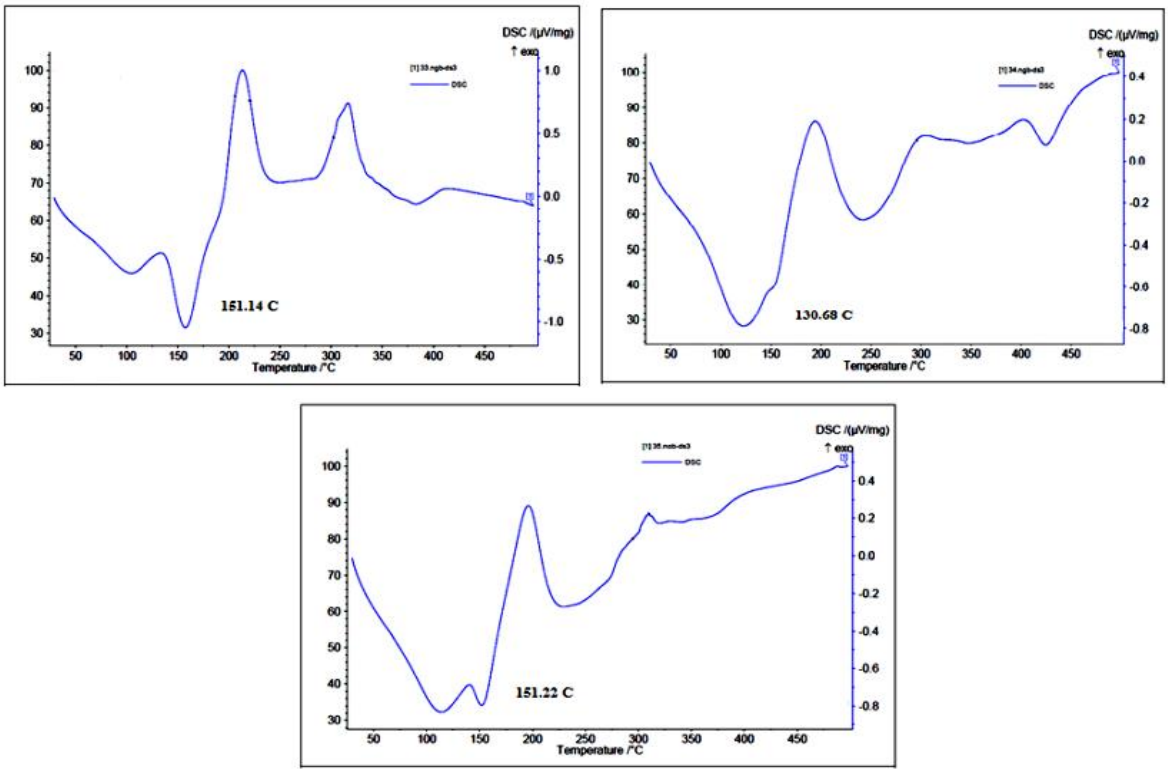

Figure 2: DSC of pan: HPMC, pan: EudragitL30D55, pan: HPMCP HP55

FT-IR Studies:

Table 4: FT-IR interpretations of Pantoprazole and excipients

Functional group	Pantoprazole	Pan: HPMC	Pan: Eudragit	Pan: HPMCP
S=O stretching	1114.92 cm^{-1}	1122.63 cm^{-1}	1118.77 cm^{-1}	1118.66 cm^{-1}
C-O stretching	1041.62 cm^{-1}	1172.78 cm^{-1}	1168.93 cm^{-1}	1037.76 cm^{-1}
CH3 bending	1377.25 cm^{-1}	1373.39 cm^{-1}	1377.25 cm^{-1}	1361.82 cm^{-1}
C-O-C stretching	1230.65 cm^{-1}	1276.95 cm^{-1}	1303.95 cm^{-1}	1307.81 cm^{-1}
C=C stretching	1651.16 cm^{-1}	1593.29 cm^{-1}	1589.43 cm^{-1}	1589.40 cm^{-1}
N-H bending	1589.43 cm^{-1}	1658.87 cm^{-1}	1489.13 cm^{-1}	1647.30 cm^{-1}

Pre-compression studies:

Table 5: Pre-compression parameters

S. No	Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	%Friability	DT time
1	F2	1.70	2.39±0.07	6.47±0.19	0.92±0.06	6.31±0.12
2	F3	1.70	2.34±0.04	7.38±0.192	0.94±0.07	6.56±0.07
3	F4	1.71	2.34±0.04	6.73±0.07	0.62±0.05	5.69±0.39
4	F5	1.71	2.36±0.05	7.14±0.13	0.55±0.041	5.67±0.24
5	F6	1.66	2.37±0.01	6.63±0.037	0.77±0.04	5.41±0.24
6	F7	1.65	2.35±0.2	5.7±0.02	0.5±0.07	6.2±0.27
7	F8	1.65	2.357±0.06	5.82±0.06	0.74±0.06	6.22±0.122
8	F9	1.65	2.34±0.05	5.94±0.04	0.72±0.09	7.40±0.17
9	F10	1.65	2.33±0.18	5.95±0.03	0.74±0.03	7.33±0.249

Particle size distribution (PSD):

Table 6: % Cumulative retained particles

S. No	Sieve No	Empty sieve	Sample sieve(gm)	Difference	% Retained	%Cumulative Retained(CR)
1.	#20	321.4	321.4	0	0	0
2.	#30	328.6	328.8	0.2	0.2	0.2
3.	#40	299.0	300.0	1.0	1.0	1.2
4.	#60	287.2	297.4	10.2	10.2	11.4
5.	#100	255.0	275.0	20.0	20.0	31.4
6.	#120	274.0	299.0	25.0	25.0	56.4
7.	#200	270.0	303.2	33.2	33.2	89.6
8.	Receiver	348.8	359.0	10.2	10.2	99.8

Post compression parameters:

Table 7: Evaluation parameters of Pantoprazole core tablets

S.No	Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	%Friability	DT time
1	F2	1.70	2.39±0.07	6.47±0.19	0.92±0.06	6.31±0.12
2	F3	1.70	2.34±0.04	7.38±0.192	0.94±0.07	6.56±0.07
3	F4	1.71	2.34±0.04	6.73±0.07	0.62±0.05	5.69±0.39
4	F5	1.71	2.36±0.05	7.14±0.13	0.55±0.041	5.67±0.24
5	F6	1.66	2.37±0.01	6.63±0.037	0.77±0.04	5.41±0.24
6	F7	1.65	2.35±0.2	5.7±0.02	0.5±0.07	6.2±0.27
7	F8	1.65	2.357±0.06	5.82±0.06	0.74±0.06	6.22±0.122
8	F9	1.65	2.34±0.05	5.94±0.04	0.72±0.09	7.40±0.17
9	F10	1.65	2.33±0.18	5.95±0.03	0.74±0.03	7.33±0.249

Mean±S.D, n=3

Table 8: Physical evaluation tests of Pantoprazole Enteric coated tablets

S.No	Formulation code	Weight variation (mg)	Thickness (nm)	Hardness (Kg/cm^2)	% Friability	DT time	% Weight gain	%LOD
1	F2	0.21	2.50±0.05	10.46±0.18	0.84±0.035	7.30±0.18	14.77	-
2	F3	0.22	2.4±0.12	10.23±0.09	0.81±0.03	7.19±0.04	18.43	-
3	F4	0.22	2.65±0.29	10.61±0.13	0.40±0.10	6.38±0.14	18.29	-
4	F5	0.22	2.44±0.26	9.48±0.07	0.36±0.04	6.23±0.07	18.82	-
5	F6	0.21	2.54±0.03	9.72±0.11	0.45±0.05	6.32±0.22	19.38	-
6	F7	0.21	2.76±0.06	9.12±0.10	0.56±0.12	9.19±0.08	19.66	0.42±0.17
7	F8	0.21	2.81±0.036	9.19±0.04	0.93±0.043	9.42±0.09	19.66	0.76±0.04
8	F9	0.21	2.88±0.02	9.39±0.05	0.32±0.08	10.34±0.10	19.69	1.0±0.09
9	F10	0.21	2.8±0.07	9.49±0.16	0.36±0.06	10.3±0.24	19.66	0.83±0.25

Mean ± S.D, n=3

Chemical evaluation of Pantoprazole Enteric coated tablets:

Table 9: % acid uptake of Pantoprazole enteric coated tablets

S. No	Formulation code	%Acid uptake
1	F2	13.37± 0.19
2	F3	2.91± 0.05
3	F4	3.51± 0.13
4	F5	1.31± 0.196
5	F6	1.32± 0.18
6	F7	1.52± 0.41
7	F8	1.37± 0.14
8	F9	1.92± 0.09
9	F10	1.97± 0.02

Table 9: Percentage Drug content of Pantoprazole enteric coated tablets

S. No	Formulation code	%Drug content
1	F3	98.26±0.12
2	F4	97.28±0.68
3	F5	99.09±0.45
4	F6	98.41±0.22
5	F7	99.47±0.25
6	F8	99.54±0.225
7	F9	98.86±0.45
8	F10	99.54±0.226

Table 10: Dissolution data of Pantoprazole enteric coated tablet containing Eudragit L30D55 HPMCP HP55.

S.No	Time min	Percent cumulative drug release (mean±S.D.)								Innovator
		Eudragit L30D55						HPMCP HP55		
		F3	F4	F5	F6	F7	F8	F9	F10	
1.	10	9.10±0.57	13.42±0.44	18.38±0.22	24.26±0.442	36.78±0.15	31.45±0.56	33.09±0.31	26.16±0.316	29.75±1.03
2.	20	18.87±0.59	25.52±0.88	33.62±1.46	36.95±0.58	61.15±1.19	53.69±1.40	56.74±0.63	48.30±1.58	51.39±0.51
3.	30	33.53±0.66	39.17±0.25	44.15±1.40	49.86±0.662	75.60±0.79	71.21±0.38	70.25±0.63	62.17±0.38	73.03±1.00
4.	45	41.97±0.66	48.63±0.77	52.67±0.44	61.44±0.12	85.30±0.63	80.87±1.12	83.76±0.15	78.72±0.157	80.15±0.15
5.	60	51.08±1.17	55.01±0.33	59.84±0.22	70.79±1.02	96.81±0.63	93.00±0.67	92.76±0.47	91.24±0.313	92.78±0.58

Mean±S.D, n=3

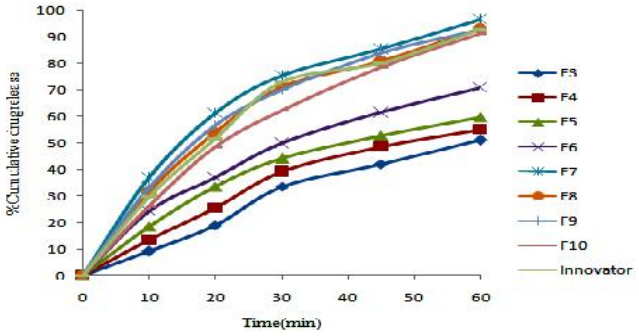

Figure 3: Dissolution profile of Pantoprazole enteric coated tablets

Chemical stability studies:
%acid uptake & %Drug content of F7 and F9 with different stability conditions

Table 11: Percentage acid uptake of F7 and F9

S. No	Stability condition	F7	F9
1	Initial	1.31±0.08	1.82±0.018
2	40^0/75%RH/1month	1.51±0.011	1.87±0.09
3	40^0/75%RH/3month	1.77±0.02	1.96±0.01

Stability studies:
Physical evaluation tests:

Table 11: Physical evaluation tests of F7 and F9 with different stability conditions

Evaluation parameters	Observation in month					
	Initial (F7)	1st month	3rd month	Initial (F9)	1st month	3rd month
Physical appearance	Pale yellow	NC	NC	Pale yellow	NC	NC
Weight variation	0.21	0.21	0.21	0.21	0.21	0.21
Hardness(Kg/cm^2)	9.12±0.10	9.01±0.29	8.87±0.111	9.49±0.16	8.94±0.21	8.85±0.11
Disintegration time	9.19±0.08	9.05±0.17	8.51±0.06	10.34±0.10	10.05±0.07	9.66±0.39
%LOD	0.42±0.13	0.90±0.32	1.40±0.05	1.0±0.16	1.53±0.01	1.96±0.74

Mean±S.D, n=3; NC- No Change

Table 12: Percentage Drug content of F7 and F9

S. No	Stability condition	F7	F9
1	Initial	99.31±0.22	99.61±0.13
2	40^0/75%RH/1month	98.64±0.68	99.09±0.23
3	40^0/75%RH/3month	97.96±0.45	98.83±0.76

***In-vitro* dissolution studies for F7 and F9 with different stability conditions:**

Table 13: Dissolution data of F7 and F9 with initial

S.No	Time (min)	Percent cumulative drug release (mean±S.D.)					
		Initial F7	40^0/75%RH/1mn	40^0/75%RH/3mn	Initial F9	40^0/75%RH/1mn	40^0/75%RH/3mn
1	10	36.78±0.15	35.92±0.30	33.46±1.56	33.09±0.31	32.72±0.56	32.13±2.31
2	20	61.15±1.91	59.13±1.08	57.61±0.47	56.74±0.63	56.03±0.22	55.11±0.22
3	30	75.60±0.79	74.74±0.47	73.79±0.31	70.25±0.63	69.26±2.24	68.27±1.33
4	45	85.30±0.63	84.56±0.31	84.21±0.15	83.76±0.15	82.71±0.78	81.88±0.66
5	60	96.81±0.637	96.17±0.56	95.73±2.10	92.76±0.47	92.12±0.46	91.26±2.23

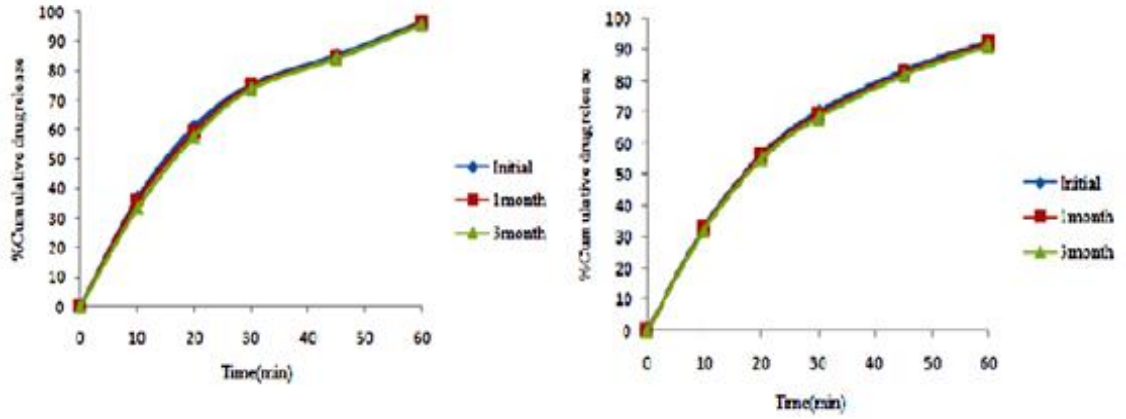

Figure4: Stability studies for Dissolution profile of Pantoprazole sodium enteric coated tablets (F7 and F9).

4. Conclusion

Ten formulations of enteric coated tablets of pantoprazole were developed by preparing core tablets using mannitol as diluent, crospovidone as super disintegrants and povidone (PVPk30) as binder in different proportions and varying compositions of sub coating and enteric coating using Sicovit yellow, titanium dioxide, methacrylic acid copolymer (Eudragit L30D55), Hypromellose phthalate (HPMCP HP55). The core tablets were prepared by dry granulation method. The results indicated that the finished product formulations F7, F8, F9 and F10 fulfilled all specifications of the physical properties and *in-vitro* drug release. Formulation F1 was failed to compress as tablets due to sticking problem. Formulation F2 acid resistance test was failed due to insufficient enteric coating. Formulation 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. The accelerated stability studies performed for F7 and F9 batches of tablets up to 3 months in a humidity chamber at 40^0C and 75 % RH, revealed that the tablets concurred its properties without many differences and the results were found satisfactory. Formulation F7, F8, F9 and F10 fulfilled all the specifications prescribed for pantoprazole gastro release tablets using Eudragit L30D55 and HPMCP HP55 as enteric coating materials. While compared to the above all formulations the F7 showed highest % Cumulative drug release.

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