PROCESS VALIDATION OF DOMPERIDONE SUSTAINED RELEASE AND PANTOPRAZOLE ENTERIC COATED TABLET IN TABLET FORMULATION

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Abstract: A proton pump inhibitor that is a member of the benzimidazole family, pantoprazole was manufactured using the direct compression method, microcrystalline cellulose as filler, mannitol and dicalcium phosphate as diluents, croscarmellose sodium as a disintegrating agent, magnesium stearate as a glidant, and talc as a lubricant. Since it involves fewer unit operations than wet granulation, direct compression is more cost-effective. As a result, the cost of producing tablets will be lower since there will be less equipment, less power usage, less space, less time, and less labour. The manufactured tablets were tested for uniformity of drug content, weight variation, friability, and hardness, and it was discovered that the results meet official standards. The produced tablets were coated using a dip coating technique and an enteric coating polymer, such as cellulose acetate phthalate. Using an acidic buffer pH of 1.2 and a phosphate buffer pH of 6.8, the in vitro release was investigated. The best batches were those that had been prepared, with the hardness, drug content, time till disintegration, and cumulative drug release % starting after 120 minutes and reaching 99.72 after 180 minutes. Studies on stability showed that the created tablets maintained their medicinal qualities for three months at room temperature and at 40°C and 75 percent relative humidity.

Keywords: **Direct compression, Pantoprazole, Proton pump inhibitor**

1. INTRODUCTION

To raise the standard of pharmaceuticals, two Food and Drug Administration (FDA) employees named Ted Byers and Bud Loftus originally introduced the idea of validation in the middle of the 1970s. The selection of high-quality components and materials, appropriate product and process design, process control, and in-process and end-product testing are just a few of the aspects that contribute to product quality assurance.[1,2,3] Routine end product testing alone is frequently insufficient to ensure product quality due to the complexity of today's medical devices for a number of reasons. Some testing on finished goods is only moderately sensitive. In some instances, final product testing does not account for all possible product changes, which could have an influence on safety.[4,5]

1.1 Process Validation

According to the FDA's 1987 Guideline, process validation is "establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes." Process validation was defined as "The collection and evaluation of data, from the design stage through production, which establishes scientific evidence that a process is capable of consistently delivering quality products" in the FDA's new guidelines.[6,7,8] Tablets contain a mixture of active substances and excipients, typically in the form of powder, pressed or compacted into a solid. Despite the ongoing development of more sophisticated solid drug delivery systems, tablets are still by far the most common solid dosage form. The size of the manufacturing and related facilities will vary according to the scale of production. The fundamental principles of validation will remain the same whether the facility produces thousands or millions of tablets or capsules per day.[9,10,11] The process should run using the extremes of the system at the critical points (worst case), and all of its critical points should be clearly identified. Before approving validation, the area should be conformed for the requirement of validation. Before approving validation, the area should be conformed for the requirement of validation.[12,13,14] Adequate run (data) are required to provide statistical support to demonstrate product consistency. The execution of the protocol should follow the requirements of the validation document, with all deviations from the validation document well recorded and properly followed up.[15,16]

1.2 PHARMACEUTICAL TABLETS:

Oral dosage form is the most popular route for drug therapy and over 80% of the drugs formulated to produce systemic effects are produced as oral dosage forms. The tablet dosage form accounts for approximately 50% of all dosage forms on the market.[17,18] When a new drug is discovered the pharmaceutical company makes all possible efforts to ensure that the drug can be so formulated that it is competent of being administered orally. If it cannot be administered by oral route, and should a more complex parenteral route be the only choice, then the drug is principally demoted for administration in a hospital setting or physician's office. If self-administration of drugs cannot be attained, the sales of the drug may comprise only a small portion of what the market would be otherwise.[19,20]

1.21.1 Advantages of tablets as a dosage form:

• They offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.

• Product identification of potentially the simplest and the cheapest.[21,22]

1.21.2 Disadvantages of tablets as a dosage form

• Irritant effects on the GI mucosa by some solids (e.g., aspirin).

• In emergency cases, intravenous or intramuscular injections are more effective.[23,24]

2. MATERIAL AND METHODS

2.1 Batch Manufacturing of Validation Batch details:

1	Generic name	Pantoprazole (Extended –Release Tablets40mg) and Domperidone (sustained release tablets 30mg).
2	Label Claim	Each film coated tablet contains: Pantoprazole (40mg) and Domperidone (30mg)
3	Description	Bilayered, circular, biconvex uncoated tablet having white coloured layer on one side, orange coloured layer on another side and having plain surface on both sides.
4	Batch Size	150,000 Tablets
5	Storage Condition	Store at 25^0C (77^0F)
6	Shelf Life	24 Months

Table 1. Product Details

2.2 Protocol for concurrent process Validation of the pantoprazole Extended-Release Tablets 40 mg and Domperidone sustained release tablet 30mg

S. No.	Section Title
1.	Objective
2.	Scope
3.	Responsibility
4.	Process Validation Team Members
5.	Number of batches subjected for validation
6.	Equipment Detail
7.	Raw Material & Packing Material
8	Process Flow Chart
9	Manufacturing process risk assessment of process validation batches
10	Process parameter
11	Analytical Results
12	Finished Product Analytical Results

2.3 Number/Details of batches subjected for validation:

Sr. No.	Product Name	Generic Name	Batch No.	Batch Size
1	Pantoprazole Tablets 40mg	Pantoprazole Extended Release Tablets 40mg	E40545	1,50,000 tablets
2	Pantoprazole Tablets 40mg	Pantoprazole Extended Release Tablets 40mg	E40609	1,50,000 tablets
3	Pantoprazole Tablets 40mg	Pantoprazole Extended Release Tablets 40mg	E40638	1,50,000 tablets

Table 2. Details of batches (pantoprazole) subjected for validation

Sr. No.	ProductName	Generic Name	Batch No.	Batch Size
1	Domperidone Tablets30mg	Domperidone sustained-ReleaseTablets30mg.	E40527	1,50,000 tablets
2	Domperidone Tablets30mg	Domperidone sustained-ReleaseTablets30mg.	E40605	1,50,000 tablets
3	Domperidone Tablets30mg	Domperidone sustained-ReleaseTablets30mg.	E40637	1,50,000 tablets

Table 3. Details of batches (Domperidone) subjected for validation

2.4 Granulation Raw Materials Details

Ingredient	SAP item code	Spec	AR. No/batch no			QTY reqd/15,00,00	Qty Dispensed		
			E40527	E40605	E40637		E40527	E40605	E40637
Pantoprazole Part									
Dry mixing									
Pantoprazole sodium	1001112	IP	157772	161513	16153	63.600kg	54.203	67.286	67.286
Mannitol	1000285	IP	157893	157894	157893	23.25kg	18.884	19.56	19.56
Sodium carbonate	1000404	BP	155168	155168	155168	5.25kg	5.250	5.250	5.250
Crospovidone	1000101	USNF	157296	160374	160374	7.50kg	7.5	7.5	7.5
Binder preparation									
HPC (klucel-LF)	1000991	USNF	162232	162232	162232	2.40kg	2.40	2.40	2.40
Isopropyl alcohol	1000248	IP	157955	160109	160109	30.00kg	30.00	30.00	30.00
Lubrication									
Calcium striate	1000923	IP	156381	156381	156381	3.00kg	3.00	3.00	3.00
Seal coating solution									
HPMC E-5	1000200	IP	04948	04948	04948	6.60kg	6.60	6.60	6.60
Isopropyl alchol	1000248	IP	157955	160109	160109	73.95kg	73.95	73.95	73.95
Methylene chloride	1000298	BP	157957	157957	157957	31.95kg	31.95	31.95	31.95
Purified talc	1000452	IP	157271	162619	162619	2.805kg	2.805	2.805	2.805
Polyethylene glycol 6000(laffcol-6000)	1000364	IP	162343	163524	163524	1.155kg	1.155	1.155	1.155
Enteric coating solution									
Methacrylic acid co-polymer type-C(L100-55) {Acrycoat L100D}	1001139	USNF	136893 162645	162645	162645	11.22kg	7.610 3.610	11.220	11.220
Dibutyl Phthalate	1000109	IP	149436	149436	149436	1.815kg	1.815	1.815	1.815
Titanium dioxide	1000464	IP	157276	157276	157276	0.495kg	0.495	0.495	0.495
Sunset yellow lake	1000448	IH	157244	162334	162334	1.65kg	1.650	1.650	1.650
Purified talc	1000452	IP	157271	162619	162619	0.66kg	0.66	0.66	0.66
Isopropyl alcohol	1000248	IP	157955	160109	160109	127.50kg	127.50	127.50	127.50
Acetone	1000003	BP	155357	157781	157781	54.60kg	17.25	54.60	54.60

Table 4. raw material (Pantoprazole)

Ingredient	SAP item code	Spec	AR. No/batch no			QTY reqd/15,00,00	Qty Dispensed		
			E40545	E40609	E40638		E40545	E40609	E40638
Domperidone sustained release									
Dry mixing									
Domperidone	1001109	IP	157754	161510	161510	45.00kg	5.413	45.221	14.461
Microcrystalline cellulose plain	1000310	IP	157345	157345	159345	44.25kg	44.030	44.030	44.030

HPMC K4M	1000197	IP	155540	161849	161849	19.50kg	13.905	19.250	19.250
HPMC K15M	1000196	USP	160394	161847	161847	30.00kg	24.50	30	30
Sunset yellow lake	1000448	IH	157244	162334	162334	01.50kg	1.5	1.5	1.5
Binder preparation									
HPMC E-5	1000200	USNF	04918	04918	04918	7.50kg	7.5	7.5	7.5
Isopropyl alcohol	1000248	IP	157955	160109	160109	105.00kg	105	105	105
Purified water	2002104	IP	0505	3105	0206	30kg	15	15	15
Lubrication									
Sunset yellow lake	1000448	IH	157244	162334	162334	0.75kg	0.75	0.75	0.75
Potassium bi-carbonate	1001204	BP	134900	134900	134900	15kg	15	15	15
Purified talc	1000452	IP	157271	162619	162619	4.50kg	4.5	4.5	4.5
Magnesium stearate	1000277	IP	157838	157838	157838	1.50kg	1.5	1.5	1.5
Granulation addition									
HPMC K4M	1000197	USP	161849	161849	161849	4.50kg	4.5	4.5	4.5
HPMCK15M	1000196	USP	161842	161842	161842	6.00kg	6.00	6.00	6.00

Table 5. raw material (Domperidone)

3. RESULT AND DISCUSSION

3.1 Dry Mixing: (Pantoprazole IP Part)

RMG Parameters	Specification	Observed in Batch Nos.		
		E40527	E40605	E40637
Impeller	ON	ON	ON	ON
Chopper	OFF	OFF	OFF	OFF
Speed	Slow	52RPM	52 RPM	52 RPM
Mixing Time	10minute	10min	10min	10min

Table 6: Dry mixing Parameters

3.2 Analytical Parameters: Assay – Pantoprazole IP Part

Sampling Location	Limit	Observed in Batch Nos.		
		E40527	E40605	E40637
TL	95.0% to 110.0% of Label Claim	101.70	100.20	100.10
BL		101.10	99.10	98.10
M		102.0	99.50	97.20
TR		100.90	99.40	97.30
BR		102.20	98.70	97.50
Mean	(95.00 % - 110.00 %)	101.58	99.38	98.04

Table 7: Assay results of Pantoprazole blend

3.3 Wet Granulation:

5.3.1 Pantoprazole IP Part

Batch Nos.	Step	RMG Parameters	Speed	RPM Observed	Time		
					From	To	Total
E40527	Binder Addition	Impeller	Slow	52	14:01	14:05	04min
		Chopper	Slow	1440			
	Wet Mixing	Impeller	Slow	52	14:06	14:10	04min
		Chopper	Slow	1440			

E40605	Binder Addition	Impeller	Slow	52	12:56	13:00	04min
		Chopper	Slow	1440			
	Wet Mixing	Impeller	Slow	52	13:03	13:05	02min
		Chopper	Slow	1440			
E40637	Binder Addition	Impeller	Slow	52	9:36	9:40	04min
		Chopper	Slow	1440			
	Wet Mixing	Impeller	Slow	52	09:42	09:44	02min
		Chopper	Slow	1440			

Table 8: Wet granulation Parameters

3.4 Air Drying: Pantoprazole IP Part

Parameter	Limit	Observed in Batch Nos.		
		E40527	E40605	E40637
Drying time	10 Min.	15min	15min	15min

3.5 Size Reduction: Pantoprazole IP Part

Sieve & Screen Size		Sieve & Screen Size Observed in Batch Nos.					
		E40527		E40605		E40637	
20#	1.0 mm or1.5 mm	20#	1.0/1.5mm	20#	1.0/1.5mm	20#	1.0/1.5mm

3.6 Final Drying: Pantoprazole IP Part

Parameter	Limit	Observed in Batch Nos.		
		E40527	E40605	E40637
Drying time	2±1min	01min	01min	01min

3.7 Analytical Parameters: Pantoprazole IP Part

3.7.1 Loss on Drying

Loss on Drying	LOD Limit	Observed in Batch Nos.								
		E40527			E40605			E40637		
		Top	Middle	Bottom	Top	Middle	Bottom	Top	Middle	Bottom
Pantoprazole IP Part	NMT 2.5% at 60ºC(byIR/ halogen Moisture balance for 10 Min.)	1.89	1.90	1.92	1.76	1.78	1.77	1.75	1.78	1.76

3.8 Lubrication: Pantoprazole IP Part

Step	Spec. (RPM)	Observed in Batch Nos.			Time (min)	Observed in Batch Nos.		
		E40527	E40605	E40637		E40527	E40605	E40637
Lubrication (Pantoprazole –IP Part)	10 - 12	10	10	10	10 Min	10	10	10

Table 9: Lubrication Parameters for Pantoprazole

3.9 Analytical Parameters: Pantoprazole IP Part

3.9.1 Loss on Drying

Loss on Drying	LOD Limit	Observed in Batch Nos.								
		E40527			E40605			E40637		
		Top	Middle	Bottom	Top	Middle	Bottom	Top	Middle	Bottom
Pantoprazole IP Part	NMT 2.5% at 60ºC (by IR/halogen Moisture balance)	1.90	1.92	1.90	1.81	1.82	1.79	1.80	1.78	1.80

3.9.2 Assay: Pantoprazole –IP Part

Sampling Location	Limit	Observed in Batch Nos.		
		E40527	E40605	E40637
1T	95.0% to 110.0% of Label Claim	98.0	98.9	100.60
2T		100.6	99.1	100.60
3T		99.0	100.7	102.0
1M		98.5	100.4	99.8
2M		97.8	99.2	101.1
3M		98.4	98.9	100.5
1B		100.1	100.7	101.4
2B		98.6	100.4	101.8
3B		98.31	100.4	102.8
4B		98.34	101.7	102.2
Mean	(95.00 % - 110.00 %)	98.31	100.19	101.3
RSD	NMT 5.0%	1.396	1.009	0.904

Table 10: Assay results for Pantoprazole

3.9.3 Assay (Composite sample analysis): Pantoprazole –IP Part

API	Limit	Observed in Batch Nos.		
		E40527	E40605	E40637
Pantoprazole IP	95-110 % of Label Claim	96.2	101.3	101.8

3.9.4 Composite sample analysis

Parameters	Limit	Observed in Batch Nos.		
		E40527	E40605	E40637
		Pantoprazole IP Part	Pantoprazole IP Part	Pantoprazole IP Part
Bulk density	For information	OK	OK	OK
Tapped density		OK	OK	OK
Sieve Analysis		OK	OK	OK

3.9.5 COMPRESSION: Pantoprazole IP Part

3.9.5.1 Physical Parameters:

Parameters	Limit	Observed in Batch Nos.		
		E40527	E40605	E40637
Speed	35±5RPM	38	30	30
Punch Size	5.50 mm	5.50	5.50	5.50
Upper punch	Plain Surface	Plain Surface	Plain Surface	Plain Surface
Lower punch	Plain Surface	Plain Surface	Plain Surface	Plain Surface
Description	White to off white circular, biconvex, uncoated tablet having plain surface on both the sides.	Conforms	Conforms	Conforms
Friability	NMT 1.0 % w/w	0.42%	0.35%	0.39%
Average Wt.	70.0 mg/tab. ±2.5 % (68.25 mg-71.75 mg)	70.25mg	70.31mg	70.25mg
Uniformity of Wt.	± 7.5 % of Av. Wt.	+5.29%,-6.43%	+3.29%,-4.1%	+4.15,-4.25%
Thickness	2.65 mm- 2.95 mm	2.78	2.82	2.79
Diameter	5.50 mm- 5.70 mm	5.51mm	5.53mm	5.52mm
Disintegration Time	NMT 15 minutes	6.04min	6.40min	5.55min
Hardness	20 – 60 Newton	40.628N	50.21N	40.615N

Table 11: Physical Parameters of Pantoprazole compressed tablet

3.9.6 Hopper Study: Physical Parameters

Parameters	Limit	Observed in Batch Nos.		
		E40527	E40605	E40637
Speed	35±5RPM	38	28	32
Punch Size	5.50 mm	5.50 mm	5.50 mm	5.50 mm
Upper punch	Plain Surface	Plain Surface	Plain Surface	Plain Surface
Lower punch	Plain Surface	Plain Surface	Plain Surface	Plain Surface
Description	White to off white circular, biconvex, uncoated tablet having plain surface on both the sides.	Conforms	Conforms	Conforms
Friability	NMT 1.0 % w/w	0.46%	0.41%	0.38%
Average Wt.	70.0 mg/tab. ±2.5 % (68.25 mg-71.75 mg)	71.0mg	70.21mg	70.05mg
Uniformity of Wt.	± 7.5 % of Av. Wt.	Conforms	Conforms	Conforms
Thickness	Between 2.65 mm- 2.95 mm	2.88mm	2.81mm	2.80mm
Diameter	Between 5.50 mm- 5.70 mm	5.52mm	5.52mm	5.54mm
Disintegration Time	NMT 15 minutes	6:08min	6.78min	6.05min
Hardness	20 – 60 Newton	38.86N	39.56N	40.08N

3.9.7 Speed & Hardness challenge Test: Physical Parameters

Min. & Max. Speed	Parameters	Limit	Observed in Batch Nos.		
			E40527	E40605	E40637
Max. Speed	Average Wt.	68.25 mg- 71.75 mg	70.21mg	70.14mg	70.28mg
	Thickness	2.65 mm- 2.95 mm	2.93mm	2.94mm	2.90mm

(40 RPM)	Diameter	5.50 mm- 5.70 mm	5.53mm	5.51mm	5.54mm
	Disintegration	NMT 15 minutes	6.10min	6.20min	6.19min
	Hardness	20 – 60 Newton	41.25N	40.59N	40.12N
Min. Speed (30 RPM)	Average Wt.	68.25 mg- 71.75 mg	69.81mg	69.59mg	68.79mg
	Thickness	2.65 mm- 2.95 mm	2.74mm	2.80mm	2.81mm
	Diameter	5.50 mm- 5.70 mm	5.52mm	5.52mm	5.54mm
	Disintegration	NMT 15 minutes	6.05min	6.15min	6.02min
	Hardness	20 – 60 Newton	40.62N	39.25N	41.06N

3.10 COATING: **Pantoprazole IP Tablet**

3.10.1 Physical **Parameters: Enteric Coating**

Parameters	Limit	Observed in Batch Nos.		
		E40527	**E40605**	**E40637**
Pan Speed	4±2 RPM	6	6	6
Spray Rate	150± 50gm/min	110gm/min	110gm/min	110gm/min
Inlet Temp.	55- 60°C	55°C	55°C	55°C
Exhaust Temp.	40-50°C	37°C	38°C	37°C
Distance b/w Spray Gun & Bed	09.00 inch.	9.0inch	9.0inch	9.0inch
Nozzles in Spray Gun	05 Nos.	03Nos	03 Nos	03 Nos
Diameter. Of Spray Gun Nozzle	01.00 mm	1.0mm	1.0mm	1.0mm
Description	Orange coloured, circular, biconvex, enteric coated delayed release tablet plain on both sides	Conforms	Conforms	Conforms
Average Wt.	86.0 mg. ±2.5%	82.4mg	82.56mg	82.70mg
Thickness	2.90 mm – 3.30mm	3.06mm	3.05mm	6.01mm
LOD (crushed Tablet)	NMT 2.5% by IR/halogen	1.90%	1.81%	1.79%

3.10.2 Dissolution

API	Limit	Observed in Batch Nos.					
		E40527		**E40605**		**E40637**	
Pantoprazole IP (Enteric Coated Tablet)	NMT 10% of the label amount is dissolved in 120 Min. In Acidic Medium	0.0	0.0	0.0	0.0	0.0	0.0
		0.0	0.0	0.0	0.0	0.0	0.0
		0.0	0.0	0.0	0.0	0.0	0.0
	NLT 75 %(Q) of the label amount is dissolve in 60 Min. in Buffer Medium	95.8	95.4	90.3	95.0	99.3	95.2
		91.9	9.7	90.1	95.10	95.5	98.5
		92.9	83.6	92.4	92.4	95.3	98.4

3.11 PROCESS DESCRIPTION: Domperidone IP Part

3.11.1 Dry Mixing

RMG Parameters	Specification	Observed in Batch Nos.		
		E40533	**E40606**	**E40636**
Impeller	ON	ON	ON	ON
Chopper	OFF	OFF	OFF	OFF
Speed	Slow	Slow	Slow	Slow
Mixing Time	20 minute	15min	15min	15min

3.12 Analytical Parameters: Assay – Domperidone IP Part

Sampling Location	Limit	Observed in Batch Nos.		
		E40545	E40609	E40638
T	95.0% to 110.0% of Label Claim	103.9	102.3	100.5
M		104.4	103.3	103.0
B		104.5	102.5	101.2
ML		104.9	102.7	100.6
MR		104.1	104.9	98.6
Mean		104.4	103.1	100.2

Remarks: The assay content of Domperidone is within the limit of 95.0 to110.0%

3.13 Wet Granulation: Domperidone IP Part

Batch Nos.	Step	RMG Parameters	Speed	RPM Observed	Time		
					From	To	Total
E40545	Binder Addition	Impeller	slow	52	14:31	14:43	23min
		Chopper	slow	1440			
	Wet Mixing	Impeller	slow	52	14:44	14.58	14min
		Chopper	slow	1440			
E40609	Binder Addition	Impeller	slow	52	12:36	12:50	14min
		Chopper	slow	1440			
	Wet Mixing	Impeller	slow	52	12:51	13:05	14min
		Chopper	slow	1440			
E40638	Binder Addition	Impeller	slow	52	14:50	15:04	14min
		Chopper	slow	1440			
	Wet Mixing	Impeller	slow	52	15:05	15:17	12min
		Chopper	slow	1440			

3.14 Air Drying: Domperidone IP Part

Parameter	Limit	Observed in Batch Nos.		
		E40545	E40609	E40638
Drying time	20 to 30min.	45min	50min	40min
Shaking time	01min	01min	01min	01min
Shaking interval time	15min	15min	15min	15min

3.15 Size Reduction: Domperidone IP Part

Sieve & Screen Size		Sieve & Screen Size Observed in Batch Nos.					
		E40545		E40609		E40638	
16#	1.0 mm or1.5 mm	**18#**	**1.0/1.5**	**18#**	**1.0/1.5**	**18#**	**1.0/1.5**

3.16 Final Drying: Domperidone IP Part

Parameter	Limit	Observed in Batch Nos.		
		E40545	E40609	E40638
Drying time	50±10min	50min	50min	50min
Shaking time	05± 2sec	05sec	05sec	05sec
Shaking interval time	10min	10min	10min	10min
Inlet Temp.	60º C ± 5º C	60^0C	60^0C	60^0C
Outlet Temp.	40±5^0C	38^0C	38^0C	38^0C
Cooling time	05min	05min	05min	05min

3.17 Extra Granulation: Domperidone - IP Part

Parameters	Specification	Observed in Batch Nos.		
		E40545	E40609	E40638
Mixing Time	10 minute	10min	10min	10min

3.18 Lubrication: Domperidone - IP Part

Step	Spec. (RPM)	Observed in Batch Nos.			Time (minute)	Observed in Batch Nos.		
		E40545	E40609	E40638		E40545	E40609	E40638
	10 - 12	10	10	10	05 Minute	05	05	05

3.19 Analytical Parameters: Domperidone IP Part

3.19.1 Loss on Drying

Loss on Drying	LOD Limit	Observed in Batch Nos.								
		E40545			E40609			E40638		
		Top	Middle	Bottom	Top	Middle	Bottom	Top	Middle	Bottom
Domperidone IP Part	NMT 2.0% at 60ºC (by IR/halogen Moisture balance)	1.20	1.22	1.21	1.21	1.20	1.21	1.23	1.30	1.26

3.19.2 Assay: Domperidone IP Part

Sampling Location	Limit	Observed in Batch Nos.		
		E40545	E40609	E40638
1T	95.0% to 110.0% of Label Claim	103.1	103.6	98.8
2T		104.0	103.6	98.1
3T		103.4	103.4	98.7
1M		103.9	102.4	105.6
2M		102.5	103.6	102.4
3M		102.1	102.0	103.6
1B		102.1	98.3	101.6
2B		102.3	98.1	107.7
3B		103.3	101.5	103.1
4B		102.3	99.7	101.6
Mean (95.00 % - 110.00 %)		102.9	98.2	102.7

3.20 COMPRESSION: Bilayered Part

Parameters	Limit	Observed in Batch Nos.		
		E40545	E40609	E40638
Speed	15±5 RPM	15 RPM	15 RPM	15 RPM
Punch Size	10.10 mm	10.10mm	10.10mm	10.10mm
Upper punch	Plain Surface	Plain Surface	Plain Surface	Plain Surface
Lower punch	Plain Surface	Plain Surface	Plain Surface	Plain Surface
Description	Bilayered, circular, biconvex uncoated tablet having white coloured layer on one side, orange coloured layer on another side and having plain surface on both sides.	Conforms	Conforms	Conforms
Friability	NMT 1.0 % w/w	0.046%	0.023%	0.048%
Average Wt. of Domperidone IP Part	120.00 mg ± 2.0 % (117.6 mg- 122.4 mg)	114.0mg	129.0mg	118.0mg
Average Wt. Bilayered Tablet	426.00 mg ± 3.5 % (411.09 mg- 440.91 mg)	426.33mg	427.13mg	428.6mg
Uniformity of Weight	± 5.0 % of Av. Wt.	Conforms	Conforms	Conforms
Thickness	Between 5.70 mm – 6.10 mm	5.83mm	5.88mm	5.89mm
Diameter	Between 10.10 mm – 10.30 mm	10.14mm	10.13mm	10.14mm
Disintegration Time	NMT 15 Minute in water for Immediate Release Dummy layer part	05sec	06sec	10sec
Hardness	60 – 140 Newton	100.52N	99.22N	79.22N
LOD(Crushed Tablet)	NMT 5.0% by IR/halogen moisture balance at 60°C	3.5%	3.6%	3.5%

3.21 Microbial limit test

Parameters		Observed in Batch Nos.		
		E40545	E40609	E40638
Total Bacterial Count - NMT 1000cfu/gm		20 cfu/gm	25 cfu/gm	35 cfu/gm
Combined yeast and mould count NMT 100cfu/gm		<10 cfu/gm	<10 cfu/gm	<10 cfu/gm
Pathogens should be absent	E.Coli	Absent	Absent	Absent
	Pseudomonas aeruginosa	Absent	Absent	Absent
	Staphylococcus Aureus	Absent	Absent	Absent
	Salmonella species	Absent	Absent	Absent

Remarks: The analytical results for assay. Dissolution & content uniformity along with the microbial limit test are up to the expectations.

3.22 PACKING PROCESS DESCRIPTION:

Parameters	Limit	Observed in Batch Nos.		
		E40545	E40609	E40638
RPM	30 ± 5 Cycle/Min	30 Cycle/Min	32 Cycle/Min	32 Cycle/Min
Sealing temperature	150ºC±10ºC	155 ºC	150 ºC	151 ºC
Leak test	Should Pass	Pass	Pass	Pass
Knurling	Satisfactory	Satisfactory	Satisfactory	Satisfactory
Overprinting	Satisfactory	Satisfactory	Satisfactory	Satisfactory

3.23 Assay -Composite sample analysis:

API	Limit	Observed in Batch Nos.		
		E40545	E40609	E40638
Pantoprazole IP	95-115 % of Label Claim	99.6%	99.2%	103.5%
Domperidone IP	95-115 % of Label Claim	98.4%	98.6%	98.4%

Remarks: The assay content for both API'S are well within the specification.

3.24 YIELD STATUS:

Stage	Limit	Observed in Batch Nos.		
		E40545	E40609	E40638
Lubrication (Pantoprazole IP)	NLT 90%	99.80%	99.80%	99.61%
Lubrication (dummy Granules)		99.57%	99.69%	99.87%
Lubrication (Domperidone IP)		99.88%	98.77%	98.77%
Compression (Pantoprazole IP)		97.62%	97.52%	97.09%
Compression (Domperidone IP)		95.62%	98.14%	91.74%
Coating (Pantoprazole IP)		97.48%	97.81%	96.94%
Packing Domperidone IP		93.0%	93.45%	92.32%

Remarks: The data generated and gathered during the manufacturing process and analysis thereof, conforms with the prescribed acceptance criteria at each stage.

4. SUMMARY AND CONCLUSION

SUMMARY

All the process variables were monitored for manufacturing process of product pantoprazole and domperidone Tablets at different stages of manufacturing as defined in sampling plan of approved Process validation Protocol. The manufacturing process was executed as per approved batch manufacturing and batch packing record.

The process variables such as, Dry mixing time and impeller speed, binder addition, and kneading time,impeller speed, chopper speed, drying inlet temperature, outlet temperature, LOD, Multi-mill speed, mixing time / blending time and blender RPM were monitored at the granulation stage for process validation batch i.e., B. No. E40545, E40609 and E40638. The sample was withdrawn at Lubrication stage, compression stage, coating stage and packing stage as per approved process validation protocol. All theanalytical results were found satisfactory and well within the specification limits.

The process validation protocol was applicable for consecutive process validation batches. However, the interim process validation report is compiled after completion of batch. Further final process validation report shall be compiled after completion of batch as per addendum protocol which was applicable for coating stage.

Compression challenges study i.e., hardness challenges and compression machine speed challenges has been performed in first validation batch.

Hopper depletion Study was performed with start, middle and end of compression operation asstart with full hopper, middle with half-filled hopper and end with near to empty hopper and the test parameter was found with in the specification limit. Pooled sample from compression cycleat start, middle and end stage was collected and analysed, and the results was found within the specification limit.

Packing machine evaluation was performed in validation batch for blister sealing temperature and blister packing machine speed and samples were collected as per protocol and results was found satisfactory and within specification limits.

CONCLUSION:

The validation batches of pantoprazole and domperidone Tablets were manufactured as per approved Batch manufacturing Record.

All required validation activities were completed, and results are compiled in this report. During validation study critical process parameters were monitored as defined in the protocol.

All the In-process test parameters were found well within the specified limit.

There is no change in method of manufacturing followed during manufacturing of all thesevalidation batches.

No anomaly was noted with respect to the testing parameters of all these batches when tested using the approved specification.

This validation report proves that the manufacturing process of pantoprazole and domperidone Tablets and is consistent and meets the predetermined specifications and required quality attributes and based on the interim report this batch can be release for marketing and distribution.

REFERENCES

1. Streubel, A., Siepmann, J., Bodmeier, R. (2006). Gastro retentive drug delivery system. Expert Opin Drug Delivery. 3(2): 217- 33.

2. Iannucelli, V., Coppi, G., Bernabei, M.T., Camerorni, R. (1998). Air compartment multiple-unit system for prolonged gastric residence. Part-I. Formulation study. International Journal of Pharmaceutics. 174: 47-54.

3. Garg, R., Gupta, G.D. (2008). Progress in controlled gastro retentive delivery systems. Tropical Journal of Pharmaceutical Research. 7(3): 1055-66.

4. Chawla, G., Gupta, P., Koradia, V., Bansal, A. (2003). Gastro retention: A means to address regional variability in intestinal drug absorption. Pharmaceutical Technology. 50-58.

5. Hwang, S.J., Park, H., Park, K. (1998). Gastric retentive drug delivery systems. Critical Reviews in Therapeutic Drug Carrier System. 3(15): 243-284.

6. Fell, J.T. (1996). Targeting of drugs and delivery systems to specific sites in the gastrointestinal tract. Journal of Anatomy. 189 (3): 517-519.

7. Streubel, A., Siepmann, J., Bodmeier, R. (2003). Multiple unit gastroretentive drug delivery: a new preparation method for low density micro particles. Journal of Microencapsulation. 20: 329-47.

8. Dave, B., Amin, A., Patel, M.M. (2004). Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *in-vitro* evaluation. American Association of Pharmaceutical Scientists PharmSciTech. 5(2): 77–82.

9. Nayak, A.K., Maji, R., Das, B. (2010). Gastro retentive drug delivery systems: A review. Asian Journal of Pharmaceutical and Clinical Research. 3(1): 2-10.

10. Rouge, N., Allemann, E., Gex, F.M., Balant, L., Cole, E.T, Buri, P., Doelker, E. (1998). Comparative pharmacokinetic study of a floating multiple-unit capsule, a high density multiple unit capsule and an immediate-release tablet containing 25 mg atenolol. Pharmaceutica Acta Helvetiae. 73: 81-7.

11. Streubel, A., Siepmann, J., Bodmeier, R. (2003). Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. European Journal of Pharmaceutical Science. 18: 37-45.

12. Goole, J., Vanderbist, F., Aruighi, K. (2007). Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms. International Journal of Pharmaceutics. 334: 35-41.

13. Sharma, S., Pawar, A. (2006). Low density multiparticulate system for pulsatile release of meloxicam. International Journal of Pharmaceutics. 313:150-58.

14. Santus, G., Lazzarini, G., Bottoni, G., Sandefer, E.P., Page, R.C., Doll, W.J., Ryo, U.Y., Digenis, G.A. (1997). An *in vitro- in vivo* investigation of oral bioadhesive controlled release furosemide formulations. European Journal of Pharmaceutical Biopharmaceutics. 44: 39-52.

15. Klausner, E.A., Lavy, E., Friedman, M., Hoffman, A. (2003). Expandable gastro retentive dosage forms. Journal of Control Release. 90(2): 143-62.

16. Deshpande, A.A., Shah, N., Rhodes, C.T., Malik, W. (1997). Development of a novel controlled-release system for gastric retention. Pharmaceutical Research. 14(6):815-819.

17. Park, K. (1988). Enzyme-digestible swelling as platforms for long term oral drug delivery: synthesis and characterization. Biomaterials. 9: 435.

18. Fujimori, J., Machida, Y., Nagai, T. (1994). Preparation of a magnetically-responsive tablet and configure ration of its gastric residence in beagle dogs. STP Pharma Science. 4: 425-430.

19. Lokendrapal, S., Rajesh, K.S., Deepak, G.U. (2011). Floating effervescent tablet: a review. International Journal of Pharma and Bio Sciences. 5(11):1-6.

20. Debjit, B., Chiranjib, B., Margret, C., Jayakar, B., Sampath, K.P. (2009). Floating drug delivery system- Review. Der Pharmacia Lettre.1 (2):199-218.

21. Vyas, S.P, Khar, R.K. (2006). Gastroretentive systems. In: Controlled drug delivery (pp.197-217) Delhi: Vallabh Prakashan.

22. Desai, S., Bolton, S.A. (1993). Floating controlled release drug delivery system: *invitro- in-vivo* evaluation. Pharmaceutical Research. 10(9): 1321-1325.

23. Singh, B.N., Kim, K.H. (2000). Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Journal of Control Release. 63: 235-259.

24. Nayak, A.K., Maji, R., Das, B. (2010). Gastroretentive drug delivery systems: a review, Asian Journal of Pharmaceutical and Clinical Research. 3(1):1-18.