Pantoprazole delayed release tablets using novel co processed excipient DICOM-DC® SP 204 containing an alkaline agent

Purpose:

Direct compression is a well-known, cost effective and convenient process of manufacturing tablets used by formulators all over the world. Pantoprazole delayed release tablets have been formulated worldwide using this technique. Many a times it happens that provided enteric coating is unable to protect acid labile drug under acidic conditions leading to premature drug release and impurity generation. The stability of pantoprazole is depending on pH and it rapidly degrades in acid medium of the stomach (notable decomposition in aqueos media more acidic than pH 4), but stable in alkaline conditions. Also, Pantoprazole is a moisture and light sensitive API, therefore wet granulation (aqueous and non-aqueous) becomes critical. During commercial production of pantoprazole tablets, sometime issues do occur at hold time of the wet blend which may impact certain CQAs of the product. Hence, aqueous based granulation are more problematic with respect to stability issue of Pantoprazole, while non-aqueous based involved cost and also not preferred with respect to the environment. Direct compression reduces the process time, steps and related criticality. The present study highlights uses of DICOM SP 204 containing an alkaline agent to overcome pertaining issues with Pantoprazole sodium.

DICOM-DC® SP204 is a proprietary coprocessed excipient containing Microcrystalline Cellulose, Light Magnesium Oxide, Sodium Starch glycolate, Pregelatinised starch and Maize starch. The presence of alkaline microenvironment is quintessential in case of acid labile drugs like Pantoprazole. Large surface area of Magnesium Oxide in DICOM-DC® SP204 gives enhanced protection by forming a 360° alkaline microenvironment (pH 9.5-11.0). The product also has high bulk density making it suitable to formulate high tablet weight.

Objective: To overcome the stability and processing issues of Pantoprazole sodium using novel co processed excipient DICOM-DC® Sp204

Methods:

Table 1. Manufacturing formula for Pantoprazole sodium delayed release tablets

	Name of the ingredients	Per Tablet
	Core Formula	mg
1	Pantoprazole sodium equivalent to Pantoprazole 40 mg	46
2	DiCOM-DC SP204	96.5
3	Sodium Starch glycolate	10.5
4	Purified Talc	3
5	Magnesium stearate	4
	Total (A)	160
1	HPMC 6 cps	6
2	PEG 6000	0.6
3	Purified Talc	0.6
4	Magnesium Oxide	0.8
5	Purified water	q.s.
	Total (B)	8
	Seal Coated Tablet weight (C=A+B)	168
Enteric Coat (15% of Seal coated tablets weight = 25.2 mg) Enteric Coat dispersion = 20% w/w		
1	Polyquid PA-30 (30% dispersion)	18.9
2	Triethyl Citrate	1.89
3	Purified Talc	4.284
4	Yellow Iron Oxide	0.126
5	Purified water	q.s.
	Total (D)	25.2
	Enteric Coated Tablet weight (E = C+D)	193.2

Manufacturing:

- Core tablets-Pantoprazole sodium and equal quantity of DICOM-DC® SP204 was cosifted through 30 # two times. This was further co-sifted with remaining quantity of DICOM-DC® SP204 and Sodium starch glycolate through 30# sieve.
- Sifted purified talc and magnesium stearate through 40# sieve was kept aside
- Blending-Step 1 mixture was blended in Octagonal Blender at 10 RPM for 10 min and further with mixture from step 2 for 3 min at 10 RPM. Sampling was done from identified locations
- Compression was done using a Round standard concave 8.0 mm punch at a machine speed of 15 RPM
- Characterization- Tablets were evaluated for Blend properties, core tablet evaluation, Content uniformity , related substances and dissolution in acidic media (0.1 N HCL for 2 hrs) followed by pH 6.8 Phosphate buffer for 1 hr.

Table 2 Powder properties of DICOM-DC® SP 204

Tests	Observations	
pH (2% aq. suspension)	9.5 – 11.0	
Bulk Density (g/mL)	0.59	
Tap Density (g/mL)	0.68	
Hausner's ratio	1.16	
Compressibility index (%)	14.07	
Angle of repose (°)	30.73	
Particle size distribution	20 #	NMT 5% retained
	100#	NLT 65% retained

Table 3 Process Parameters

Seal coating parameters		Enteric coating parameters
Tablet bed weight (gm)	700	735
Pan speed (RPM)	8-10	8-10
Spray rate (gm/min)	8-10	8-10
Atomization pressure (bar)	2.4	2.4
Product temperature (OC)	37-39	37-39

Results:

Table 4 Evaluation of Blend and core tablet properties

Bulk density	0.49 gm/ml	Core tablet weight (mg)	160 mg
Tapped Density	0.70 gm/ml	Hardness (N)	60 – 80
Hausner Ratio	1.43	Thickness (mm)	2.71 – 2.78
Carr' s Index	30	Disintegration time (min& sec)	5min 48 sec t o 6 min 54 sec
		Friability (%)	0.048

The blend and core tablet properties were found to be satisfactory for Pantoprazole indicating it to be suitable for direct compression

Table 5 Blend uniformity results

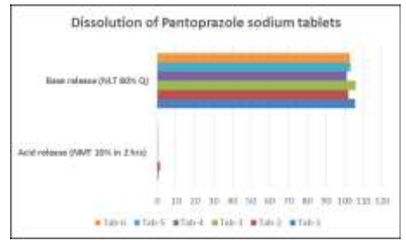
Blend uniformity by HPLC						
Position	R 1	R 2	L 1	L 2	Centre	Composite
R 1	100.4	104.6	100.7	105.3	102.1	100.7
Minimum	100.4					
Maximum	105.3					
Average	102.3					
Content Uniformity by UV						
Minimum	96					
Maximum	104					
% RSD	1.64					
Assay (90-110%)	99.6					

The blend and Content uniformity was found to be well within limits thus attaining uniform weight and quality attributes

Table 6 Organic Impurities by HPLC

Pantoprazole Related Compound A	0.16 % (NMT 0.5 %)
Pantoprazole Related Compound B	Not Detected (NMT 0.3 %)
Pantoprazole Related Compound D & F	0.05 % (NMT 0.5 %)
Any Other Individual Impurity	0.08 % (NMT 0.2 %)
Total Impurities	0.35 (NMT 1.0 %)

The impurity results were found to be stable owing to the microenvironment created by DICOM-DC® SP 204



Dissolution results clearly indicate good acid resistance followed by immediate release

Fig 1 Dissolution properties

Conclusion:

The present study concluded that DICOM-DC® SP 204 was found to be effective in formulating an stable formulation of delayed release tablet of Pantoprazole sodium using fewer excipients. The blend, core tablet properties and dissolution characteristics were found to be quite satisfactory for acid labile pantoprazole. The impurity and dissolution data clearly indicate that the presence of an alkaline ingredient in DICOM-DC® SP 204 facilitated protection of the acid labile drug from generation of impurities owing to the drug being in alkaline condition throughout. The use of DICOM-DC® SP 204 for such acid labile drugs having multiple processing issues can further help in overcoming the same with ease. The formulation will be further evaluated for its stability studies.

References:

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