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Research Article

Formulation and Process Validation of Clopidogrel Bisulfate 300mg Tablet

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ABSTRACT
The purpose of study is to formulate and process validation is to create a robust formulation and to validate all the critical parameters challenged in manufacturing process like dry mixing, blending, lubrication, compression, coating and packing. By comparing the results of above challenged parameters, it shown that all the results of three batch's had met the pre determine specification and FDA requirement. Finally by seeing the results we can say that the process followed was correct and are as per c GMP requirements.

KEY WORDS: Clopidogrel bisulfate, Blending, Lubrication, Mannitol, formulating, Process validation.

INTRODUCTION:
Process validation is nothing but giving an assurance to the quality of product in a document form. The process validation establishes the flexibility and constraints in the manufacturing process controls in the attainment of desirable attributes in the drug product which preventing undesirable properties. So, it is an important concept to support the underlying definition of validation with a systemic approach for identifying, measuring, evaluating, documenting and re-evaluating series critical steps in the manufacturing process and require control to ensure a reproducible final product.

Need of validation:
Quality, safety and effectiveness must be designed and built into the product. Quality its self cannot be inspected or tested into the finished product. Each step of the manufacturing process must be controlled to maximize the probability that the finished product meet all quality and design specification.

Type of validation

Prospective validation (pre marketing validation):
Prospective validation is nothing but need of qualification for completion of experimental trails before the process is put into commercial use.

Retrospective validation:
The retrospective validation is an establishment processes that are stable and in routine use have not under gone a formally documented validation process. In this retrospective validation the manufacturing method has to remain in unchanged for period of time. Historical data is also useful for documentary evidence that the processes are validated.

Concurrent validation:
This validation involves in process monitoring of critical processing steps and product testing, this helps to generate the document evidence to show that the production process is in a state control.

Revalidation:
It is the repetition of a validation process or a part of it. This is carried out when there is any change or replacement in formulation, equipment plan or site location, batch size and in the case of sequential batches that do not meet product specifications and is also carried out at specific time intervals in case of no changes**.**

Process validation protocol
General information
- Objective
- Background/revalidation activities
- Summary of development and technology transfer (for R & D or another site) activities to justify in process testing and controls any previous validations.
- List of equipment and qualification status
- Facilities qualification
- Process validation

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- Manufacturing procedure narrative
- List critical processing parameters and critical excipients
- Sampling, tests and specifications
- Acceptance criteria [1 to 11]

TABLE -1.DRY MIXING

Sample taken	Sample no	Content of clopidogrel bisulphate		
		Batch -1	**Batch -2**	**Batch -3**
After 3 mints	Location-1	99.2	103.1	98.2
	Location-2	102.7	95.7	100.7
	Location-3	100.7	96.8	101.7
	Location-4	101.4	102.7	103.4
	Location-5	100.2	100.2	104.2
	Location-6	103.5	102.3	100.5
	Average	101.3	100.1	101.45
	Percentage of RSD	1.6	3.1	2.1
After 5 mints	Location-1	96.8	94.7	97.8
	Location-2	98.8	98.7	98.8
	Location-3	96.7	98.1	99.7
	Location-4	101.4	95.7	100.4
	Location-5	102.3	100.4	105.3
	Location-6	99.4	99.0	99.4
	Average	99.2	97.7	100.2
	Percentage of RSD	2.3	2.1	2.6
After 7 mints	Location-1	99.6	95.4	99.6
	Location-2	101.0	92.1	101.8
	Location-3	96.5	99.5	100.5
	Location-4	101.1	96.8	95.6
	Location-5	100.4	99.4	98.4
	Location-6	100.8	100.3	102.8
	Average	99.9	97.2	99.78
	Percentage of RSD	1.8	3.2	2.5

MATERIALS AND METHODS

Materials

Clopidogrel bisulfate powder drug was given by the Orchid chemical labs, Mannitol, hydroxyl propyl cellulose,microcrystalline cellulose was given by the Signet chemicals, poly ethylene glycol 6000 was given by the Clariant chemicals,hydrogenated castor oil by Cosph care chemicals, colloidal silicon dioxide was given by Gem corporation,Opadry pink was gifted by Colorcon, India**.**

Equipments

The powdered ingredients were blend and granulated in Double cone blender and Rapid mixing granulator manufacture by Sam Techno PVT.LTD, Roller compaction and Oscillating granulator using model PRC 100/25 and manufacture by Prism machinery, coating the table by using Neo cota manufacture by Neomachine. Finally packing of tablet by Elmach packer. Dissolution test was carried out by using Disso 2000 model of Labindia dissolution apparatuses. Aligent 1200 series integrated high performance liquid chromatographic system was used for assay, Disintigration test was done by TD20S model of tab machines, Friability test was carried by FTA20 of Thermonik.

Method of manufacturing:

Sifting: Sifted Clopidogrel bisulfate and mannitol together through mesh # 20. Microcrystalline cellulose and low substituted hydroxy propyl cellulose and lactose monohydrate , together passed through mesh # 20.The Polyethylene glycol and Hydrogenated castor oil through mesh # 20.

Dry mixing: Loaded the materials of Clopidogrel bisulfate, mannitol, hydroxyl propyl Cellulose, lactose monohydrate in rapid mixing granulator. Rapid mixing granulator is used for dry mixing of ingredients at 100 RPM for 5mints.In this processes challenges were take such as like at different times points 3, 5, 7 mints sample were collected and it determines the uniformity of mixing of ingredients.

Pre compaction lubrication: Transfer the dry mixing material in double cone blender and add hydrogenated castor oil (cutina HR). Lubricated for 5 mints and samples were collected and uniformity of mixing has been seen.

Slugging or compaction: Transfer the pre lubrication material in to roller compactor to form slugs. In this processes challenges were taken such as like roller speed, vertical and horizontal feed of screw and roller pressure and they were

TABLE -2 PRE COMPACTION LUBRICATION (BLEND UNIFORMITY)

Sample taken	Sample n0	Content of clopidogrel bisulphate		
		Batch -1	**Batch -2**	**Batch -3**
After 3 mints	Location-1	98.6	98.5	99.5
	Location-2	99.5	97.2	100.2
	Location-3	99.7	98.2	98.2
	Location-4	98.2	99.5	99.5
	Location-5	100.2	100.8	100.8
	Location-6	101.2	101.2	101.2
	Location-7	100.3	99.2	101.2
	Location-8	100.8	99.6	99.6
	Location-9	101.3	101.5	101.5
	Location-10	100.4	101.6	101.6
	Average	100.02	99.73	100.3
	Percentage of RSD	1.3	1.5	1.1
After 5 mints	Location-1	97.3	99.3	99.3
	Location-2	99.6	99.9	99.9
	Location-3	99.8	105.4	105.4
	Location-4	100.5	103.7	103.7
	Location-5	100.2	101.0	101.7
	Location-6	100.8	100.8	98.6
	Location-7	101.2	102.8	97.8
	Location-8	101.8	104.8	103.8
	Location-9	100.2	101.1	101.1
	Location-10	100.1	100.7	100.7
	Average	100.15	101.9	101.2
	Percentage of RSD	1.19	2.05	2.4
After 7 mints	Location-1	99.3	99.8	100.8
	Location-2	99.9	99.6	99.6
	Location-3	105.4	99.1	99.1
	Location-4	103.7	97.5	97.5
	Location-5	101.0	96.5	98.5
	Location-6	100.8	100.2	100.2
	Location-7	102.8	100.8	100.8
	Location-8	104.8	101.6	101.6
	Location-9	101.1	101.5	101.5
	Location-10	100.7	100.2	100.2
	Average	101.95	99.68	99.8
	Percentage of RSD	2.05	1.6	1.3

kept constant over the process and the slugs were passed over1.0mm screen mesh which was fixed on oscillating granulator and the granules were collected. passé the granules through # 60 meshes.

Blending: Microcrystalline cellulose and colloidal silicon dioxide were taken and added to the granules and Blend the material for 20 mints. In this stage challenges were taken at different time point such as like 10, 15, 20 mints sample were collected to know the blend uniformity.

Lubrication: Load the above material, polyethylene glycol and hydrogenated castor oil were added and it was lubricated for 5 mints. Samples were drawn for 5 mints and pooled sample 100mg was also collected to check the water content.

Compression: Finally the lubricated blend was transfer into mini tablet compression machine with 18*8 oblong punch embossed with 'SN' on upper side and '08' on lower punch, compression was done at speed of 15±2 RPM.

Coating: The uncoated tablet was coated with opadry solution till the average tablet weight gains 2.5±0.5%w/w of core tablet weight. After coating, the tablets were collected and sent for analysis to check whether they are meeting the specifications.[12-13]

Assay by HPLC :

Preparation of buffer:

Dissolved 1.36gms of potassium dihydrogen phosphate in 1000ml of demineralised water.

Preparation of mobile phase:

Prepared a mixture of buffer and acetonitrile in the ratio of 750:250, filtered and degassed.

Chromatographic conditions:

Column: ULTRON, ES-OVEN, 150 x 4.9mm, 5µ

TABLE -3 BLENDING(PRE LUBRICATION)

Sample taken	Sample no	Blend uniformity of clopidogrel bisulphate		
		Batch -1	**Batch -2**	**Batch -3**
After 10 mints	Location-1	99.8	100.8	99.8
	Location-2	98.9	100.9	100.9
	Location-3	98.8	98.8	98.8
	Location-4	99.6	100.6	100.6
	Location-5	103.6	103.6	97.6
	Location-6	106.1	102.1	102.1
	Location-7	102.9	102.9	101.9
	Location-8	100.5	99.6	99.6
	Location-9	103.7	103.7	103.7
	Location-10	99.2	99.2	99.2
	Average	101.3	101.2	100.42
	Percentage of RSD	2.5	1.7	1.7
After 15 mints	Location-1	104.6	104.6	100.6
	Location-2	100.2	100.2	100.2
	Location-3	102.1	102.1	98.1
	Location-4	101.0	101.0	101.0
	Location-5	98.4	98.4	98.4
	Location-6	99.7	99.7	99.7
	Location-7	102.9	102.9	102.9
	Location-8	103.4	103.4	100.4
	Location-9	101.1	101.1	101.1
	Location-10	100.6	100.6	100.6
	Average	100.9	100.4	100.3
	Percentage of RSD	3.1	1.8	1.3
After 20 mints	Location-1	99.1	99.1	102.1
	Location-2	98.9	100.9	99.9
	Location-3	95.0	98.8	98.8
	Location-4	101.0	100.6	100.6
	Location-5	96.6	101.6	101.6
	Location-6	100.3	95.5	95.5
	Location-7	101.3	101.3	101.3
	Location-8	97.5	97.5	97.5
	Location-9	93.3	105.3	100.3
	Location-10	99.4	99.4	99.4
	Average	98.24	100.4	99.7
	Percentage of RSD	2.6	2.1	2.0

Flow rate: 1.0 ml/ min
Wave length: 220 nm
Injection volume: 10 µL
Column Temperature: 25°C
Run time: 12 min

Standard preparation: Weighed accurately about 50.39 mg of Clopidogrel bisulfate working standard into 50 ml volumetric flask, added 20ml of methanol, sonicated to dissolve and diluted to volume with mobile phase. Mixed well for 5 minutes, transferred 5ml of this solution into 50ml volumetric flask and diluted to volume with mobile phase.

Sample preparation: Finely powered Clopidogrel bisulfate into a 100ml volumetric flask. Added 60ml of methanol, sonicated to dissolve and dilute to volume with mobile phase. Mixed well and transfer 5ml of this solution into 50ml volumetric flask and diluted to volume with mobile phase.

Procedure: Separately injected the standard preparation and the sample preparation into the liquid chromatography and recorded the area due to major peaks fig 4 to fig 7.

Calculation: Calculated the amount of clopidogrel bisulfate present in tablets, in % using the following equation.

$$\frac{A}{B} \times \frac{S_w}{100} \times \frac{5}{50} \times \frac{100}{Tw} \times \frac{5}{50} \times \frac{At}{L} \times P \times 100$$

A = principal peak area due to sample preparation,B =principal peak area due to standard preparation,
S_w= weight of clopidogrel bisulate standard taken in mg, T_w= weight of sample taken in mg,

P= Potency of the standard. L= Label claim, A_t= Average weigh.[14-15]

TABLE-4. LUBRICATION (POST LUBRICATION)

Sample taken	Sample no	Blend uniformity of clopidogrel bisulphate		
		Batch -1	**Batch -2**	**Batch -3**
After 3 mints	Location-1	99.4	101.2	100.2
	Location-2	99.6	102.8	99.8
	Location-3	99.8	99.8	101.8
	Location-4	98.5	99.5	99.5
	Location-5	100.2	101.3	100.3
	Location-6	100.5	99.2	99.2
	Location-7	100.8	100.8	103.8
	Location-8	101.2	99.5	100.5
	Location-9	101.8	98.6	103.6
	Location-10	100.2	100.4	100.4
	Average	100.2	100.31	100.9
	Percentage of RSD	1.04	1.2	1.6
After 5 mints	Location-1	99.6	100.3	100.3
	Location-2	99.5	98.5	98.5
	Location-3	98.7	101.2	101.2
	Location-4	98.6	101.7	101.7
	Location-5	100.6	100.2	100.2
	Location-6	100.8	99.8	100.8
	Location-7	100.2	99.6	99.6
	Location-8	100.3	99.8	99.8
	Location-9	101.6	99.2	100.2
	Location-10	101.8	101.3	101.3
	Average	100.17	100.1	100.3
	Percentage of RSD	1.09	1.0	1.04
After 7 mints	Location-1	100.3	100.3	100.3
	Location-2	100.9	100.9	98.5
	Location-3	103.0	103.0	103.0
	Location-4	104.5	98.5	100.9
	Location-5	102.8	102.8	103.3
	Location-6	103.3	103.3	98.6
	Location-7	102.5	99.5	103.5
	Location-8	106.6	98.6	101.4
	Location-9	103.5	103.5	102.8
	Location-10	101.4	101.4	99.5
	Average	102.8	101.18	101.18
	Percentage of RSD	1.7	1.9	1.9

RESULTS AND DISCUSSION

Validation results:

Dry mixing: In this processes challenges were take such as like at different times points 3, 5, 7 mints sample were collected and it determines the uniformity of mixing of ingredients.

Critical parameters: Mixingtime, ImpellerRPM, ChopperRPM

Fixing of parameter: Time interval studies: 3, 5 & 7 minutes

Acceptance criteria: Not less than 90.0%- Not more than110.0% & RSD NMT -5.0%

Test: uniformity of mixing.

Discussion

In dry mixing process the results of three batchs at different time intervals show that the % RSD was with the limit that NMT 5%.So, that the proper mixing was done. Comparing to the other time interval dry mixing at 5 mints is optimum.

Pre compaction lubrication: In this processes challenges were take such as like at different times points 3, 5, 7 mints sample were collected and it determines the uniformity of mixing of ingredients

Critical parameters: Blender RPM, Lubrication time

Fixing of parameter: Time interval studies: 3, 5 & 7 minutes

Acceptance criteria: Not less than 90.0%- Not more than110.0% & RSD NMT -5.0%

Test: uniformity of mixing.

TABLE-5. POOLED SAMPLE

Sample taken	**Tests**	**Content of clopidogrel bisulphate**		
		Batch -1	**Batch -2**	**Batch -3**
100gms of pooled sample was taken (for 10 mints)	Assay	100.4	100.6	102.6
	Water content	1.84%	1.9	2.1
100gms of pooled sample was taken (for 15 mints)	Assay	100.6	101.2	100.2
	Water content	1.78%	2.2	1.9
100gms of pooled sample was taken (for 20 mints)	Assay	100.2	98.9	100.9
	Water content	1.8	2.0	2.2

Discussion

In Precompaction lubrication process the results of three batchs at different time intervals show that the % RSD was with the limit that NMT 5%.So, that the proper mixing was done. Comparing to the other time interval dry mixing at 5 mints is optimum.

Blending: In this stage challenges were taken at different time point such as like 10, 15, 20 mints sample were collected to know the blend uniformity.
Critical parameters: Blender RPM, Blending time
Fixing of parameter: Time interval studies: 10, 15 & 20 minutes
Acceptance criteria: Not less than 90.0%- Not more than110.0% & RSD NMT -5.0%
Test: Blend uniformity

TABLE – 6 COMPRESSION RESULTS AT DIFFERENT SPEED

Stage	**Tests**	**Batch-I**	**Batch-II**	**Batch-III**
Low speed (10RPM)	Uniformity of weight (mg)	complies	complies	complies
	Weight of 10 tablets(g)	9.11	9.08	9.10
	Friability (%)	NMT 0.36	NMT 0.43	NMT 0.46
	Disintegration	9mins20sec	9mins28sec	9mins24sec
	Thickness(mm)	7.54	7.58	7.57
	Content uniformity (Assay)	99.85	100.12	100.03
Target speed (15RPM)	Uniformity of weight (mg)	complies	complies	Complies
	Weight of 10 tablets	9.08	9.15	9.10
	Friability (%)	NMT 0.37	NMT 0.46	NMT 0.47
	Disintegration	9mins35sec	9mins39sec	9mins29sec
	Thickness(mm)	7.57	7.53	7.56
	Content uniformity (Assay)	100.3	100.7	99.7
Higher speed (20RPM)	Uniformity of weight (mg)	complies	complies	Complies
	Weight of 10 tablets	9.20	9.08	9.09
	Friability (%)	NMT 0.56	NMT 0.21	NMT 0.46
	Disintegration	9mins44sec	9mins44sec	9mins44sec
	Thickness(mm)	7.54	7.58	7.53
	Content uniformity (Assay)	100.04	99.37	100.24

TABLE– 7 COMPRESSION RESULTS AT DIFFERENT HARDNESS

Stage	Tests	Batch-I	Batch-II	Batch-III
Lower Hardness (6-8Kg/cm2)	Dissolution	87 86 94 90 97 89	89 85 87 94 96 97	84 98 87 90 96 95
Target Hardness (9-13kg/cm2)		88 85 87 90 99 95	86 86 85 94 92 98	85 84 82 98 97 97
Higher Hardness (13-16Kg/cm2)		85 84 96 90 96 98	91 89 85 82 94 89	91 89 89 85 94 89

TABLE- 8 COMPRESSIONS AT DIFFERENT HOPPER LEVELS

Stage	Sample n0	Hopper level (content uniformity)		
		Batch-I	Batch-II	Batch-III
INITAL OF HOPPER	Tablet-1	100.5	102.5	102.5
	Tablet-2	100.7	100.7	100.7
	Tablet -3	97.4	97.4	97.4
	Tablet-4	94.1	100.1	100.1
	Tablet-5	99.0	99.0	99.2
	Tablet-6	98.7	98.7	98.7
	Tablet-7	99.0	99.0	100.3
	Tablet-8	95.7	95.7	95.7
	Tablet-9	95.5	100.5	100.5
	Tablet-10	98.6	98.6	98.6
	Average	97.92	99.2	99.35
	% RSD	2.2	1.8	1.9
MIDDLE OF HOPPER	Tablet-1	94.2	101.2	101.2
	Tablet-2	97.6	97.6	97.6
	Tablet -3	95.1	95.1	95.1
	Tablet-4	94.5	100.5	100.5
	Tablet-5	97.9	97.9	97.9
	Tablet-6	95.9	95.9	95.9
	Tablet-7	101.9	101.9	101.9
	Tablet-8	93.3	101.3	101.3
	Tablet-9	96.9	96.9	96.9
	Tablet-10	95.4	95.4	100.4
	Average	96.2	98.37	98.87
	% RSD	2.5	2.6	2.4
END OF HOPPER	Tablet-1	95.0	95.0	100.2
	Tablet-2	94.1	94.1	100.9
	Tablet -3	100.9	100.9	94.1
	Tablet-4	96.7	96.7	96.7
	Tablet-5	95.0	95.0	98.2
	Tablet-6	100.6	100.6	94.8
	Tablet-7	94.8	94.8	96.6
	Tablet-8	96.6	96.6	97.6
	Tablet-9	97.6	97.6	100.4
	Tablet-10	100.4	100.4	100.6
	Average	97.1	97.1	98.0
	% RSD	2.7	2.7	2.4

TABLE-9 END PROCESS CHECKING

S.NO	Parameters	Specification	Batch numbers					
			I		**II**		**II**	
1	Description	Pink oblong tablet	Complies		Complies		Complies	
2	Identification	The retention time of major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay	Complies		Complies		Complies	
3	Dissolution	Not less than 80.0% (Q) of the stated amount of clopidogrel bisulphate at 30 mints	96	94	101	91	89	90
			85	89	90	87	94	88
			87	96	97	95	85	94
4	Uniformity of dosage Units(assay)	NLT-85%-NMT-115%	100.6		99.6		100.5	
5	Assay	NA	99.6		99.8		99.2	
6	Disintegration	Not more than 15 minutes	9min15sec		9min1sec		9min34sec	
7	Water content (By KFmethod)	NMT 5% W/W	1.8029		2.5		1.8	
8	**Related impurities (BY HPLC)**							
	Individual know impurities							
	IMP A	NMT-1.2%	0.06%		0.07%		0.09%	
	IMP B	NMT0-0.3%	0.03%		0.02%		0.05%	
	IMP C	NMT-1.5%	0.37%		0.27%		0.32%	
	Total impurities	NMT-1.0%	0.47%		0.56%		0.40%	

Discussion

In blending process the results of three batchs at different time intervals show that the % RSD was with the limit that NMT 5%.So, that the blend was uniformly mixed. Comparing to the other time interval blending at 20 mints is optimum.

Lubrication : In this stage challenges were taken at different time point such as like 3,5,& 7mints sample were collected to know the blend uniformity.

Critical parameters: Blender RPM, lubrication time

Fixing of parameter: Time interval studies: 3,5,& 7mints

Acceptance criteria: Not less than 90.0%- Not more than110.0% & RSD NMT -5.0%

Test: Blend uniformity, Water content, Assay

TABLE : 10 DISSOLUTION PROFILE OF CLOPIDOGREL BISUFATE TABLE

S.No.	Time(mins)	Cumulative %drug Release
1	5	16
2	10	36
3	15	52
4	30	88
5	45	92
6	60	99

Discussion

In lubrication process the results of three batch's at different time intervals show that the % RSD was with the limit that NMT 5%.So, that the blend was uniformly lubricated. Comparing to the other time interval dry mixing at 5 mints is optimum. The pooled sample was draw to conduct assay and water content test and results were shown that assay NMT 105% and water content NMT 5%.

Compression: In this stage the challenges are

Hardness challenges

Target speed (15RPM) – higher hardness (13-16Kg/cm2)

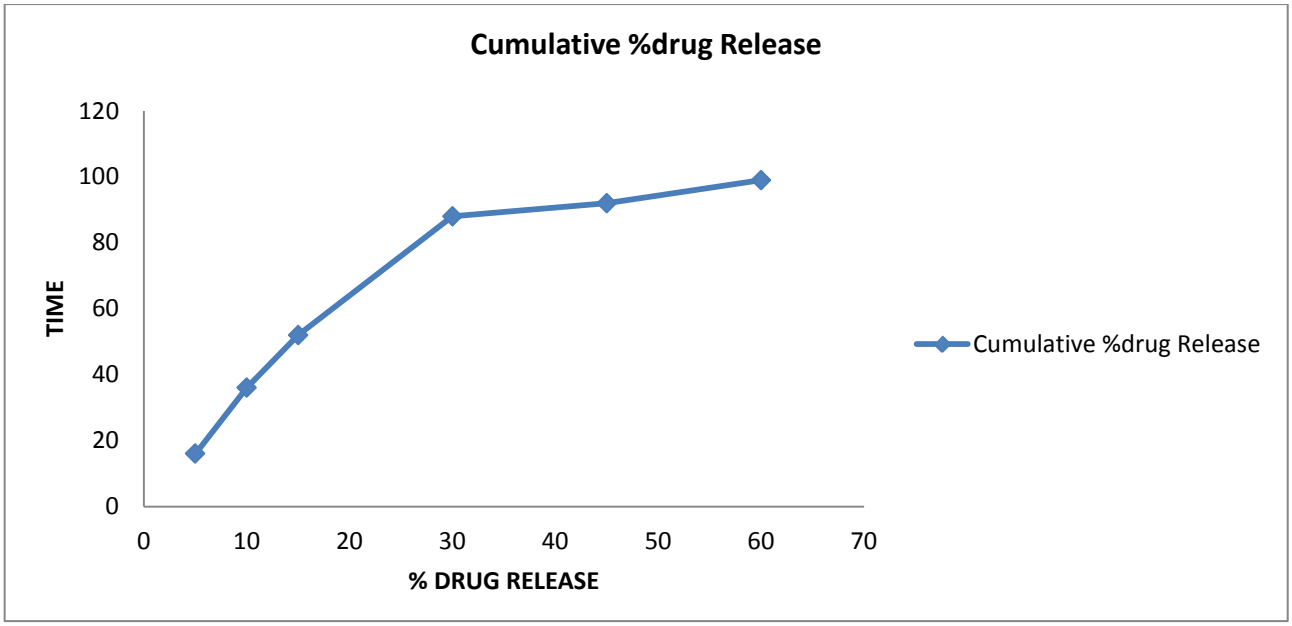

FIG:1 DISSOLUTION RELEASE PROFILE OF CLOPIDOGREL BISULFATE TABLET

Target speed (15RPM) – lower hardness (6-8Kg/cm2)
Speed challenges
Low speed (10RPM) -target hardness (9-13kg/cm2)
Higher speed (20RPM) - target hardness (9-13kg/cm2)
Flow of granule at hopper levels
Initial of hopper level (0-1/3rd)
Middle of hopper level (1/3-2/3$^{rd)}$ &
End of hopper level (2/3-3/3rd)
Critical parameters: Different speed of machine, different speed of force feeder, different Compression force, flow of powder/granules at hopper levels.
Fixing of parameter: Initial , Middle , End of Hopper
Acceptance criteria: Content uniformity, Uniformity of dose and Assay: Not less than 90.0%- Not more than110.0% & RSD NMT -5.0%.
Dissolution: NLT 80% at Q point-30.
Disintegration: within 15mins.
Friability: NMT 1%.
Weight variation: In between 900mg-945mg.
Test: Hardness, friability, disintegration dissolution, uniformity of weight, uniformity of content.

Discussion
In the compression process at the different hardness stages the dissolution of each tablet at Q point 30 shows NLT 80% and the target hardness (9-13 kg/cm^2) results were optimum**.** At the different speed levels the tablets were under go different test and results of the test were within the limit and at target speed results were optimum. Among the different levels of the hopper the middle of hopper have content uniformity drug was present compare to initial and end of the hopper.
Coating: The tablets were collected and checked for purity, Dissolution, water content, uniformity of dosage related impurities Assay.

ISCUSSION: The drug profile of clopidogrel bisulfate tablet was released 16% of drug in 5 mins, 36% of drug in 10mins, 52%of drug in 15 mins, 88%of drug in 30 mins, 92% of drug in 45 mins, 99% of drug in 60 mins.

Assay chromatogram:

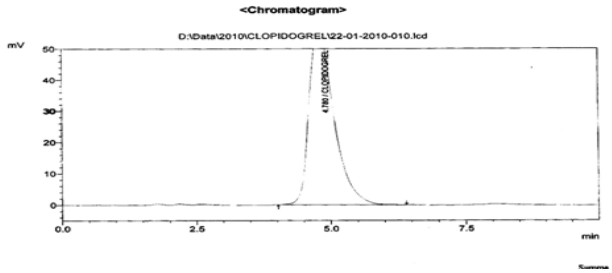

FIG: 2STANDARD

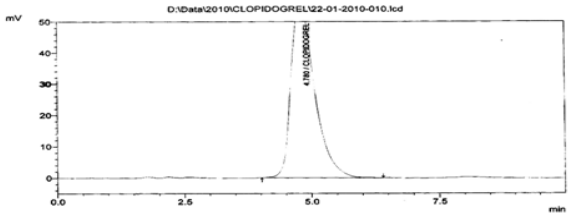

FIG: 4BATCH-II

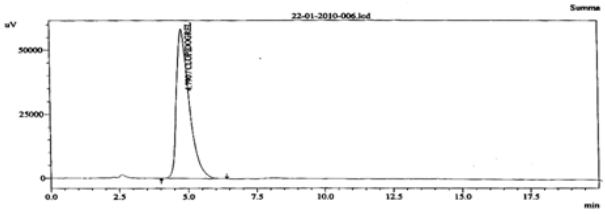

FIG: 3 BATCH-I

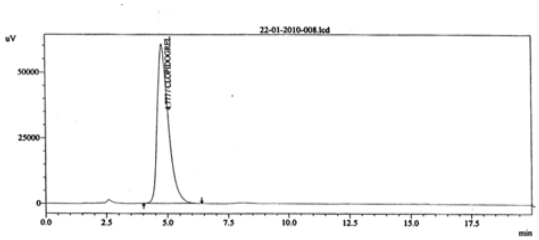

FIG-5 BATCH-III

Discussion: The coated tablets were tested and results of three batch s are within the limit and no deviations were found**.** The peak elution of all three batch's was found to at same point.

EVALUATION OF TABLETS

The critical parameters considered during the process validation of Clopidogrel bisulfate 300mg tablets were Weight variation, Hardness Test, Friability, Assay, and Dissolution Study.

Weight variation:

Twenty tablets were randomly selected from each batch and their average weight was calculated. The individual weights were compared with the average weight. The % difference in the weight variation should be within the permissible limits. The results are shown in table-10 and fig-5.

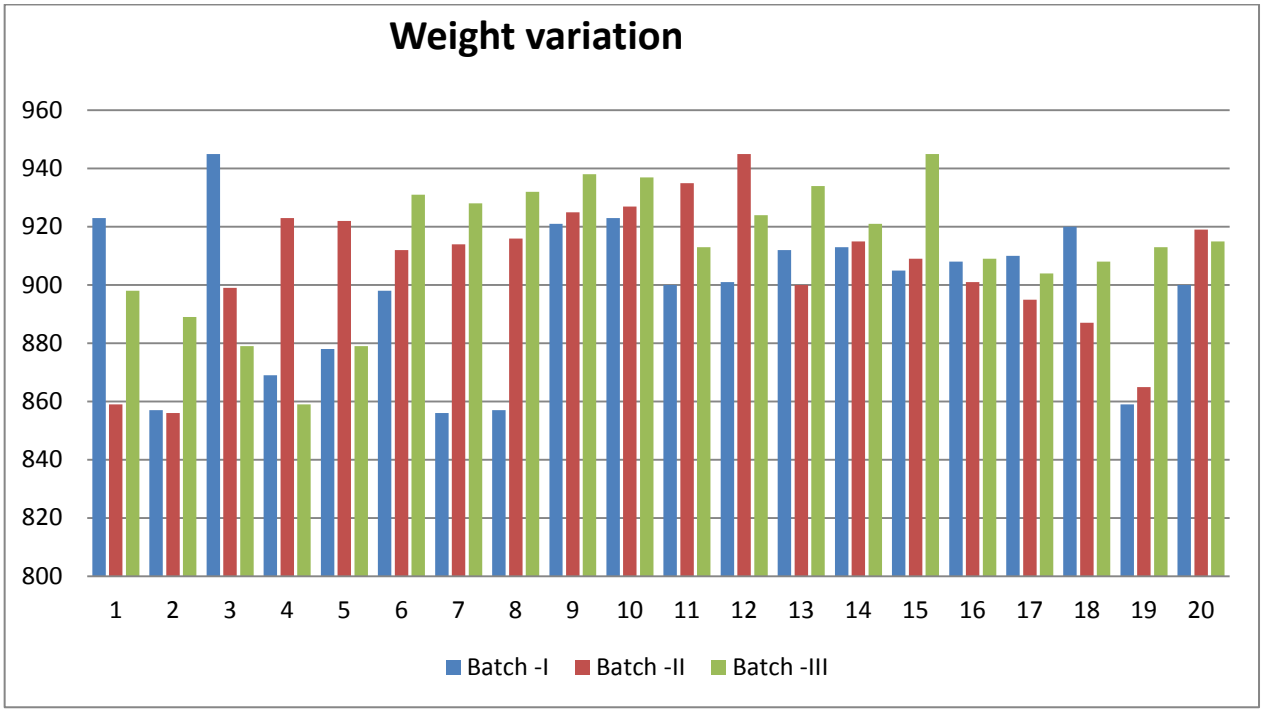

Fig 6 WEIGTH VARIATION

TABLE-11 WEIGHT VARIATION

S.NO	Group of weight variation(mg)		
	Batch -I	**Batch-II**	**Batch-III**
1	923	859	898
2	857	856	889
3	945	899	879
4	869	923	859
5	878	922	879
6	898	912	931
7	856	914	928
8	857	916	932
9	921	925	938
10	923	927	937
11	900	935	913
12	901	945	924
13	912	900	934
14	913	915	921
15	905	909	945
16	908	901	909
17	910	895	904
18	920	887	908
19	859	865	913
20	900	919	915
Minimum	855	855	855
Maximum	945	945	945
Average	897.75	906.2	912.8

Thickness:

The thickness and diameter of 10 tablets were recorded during the process of compression using vernier calliper .The results are shown in table -12 and fig -7

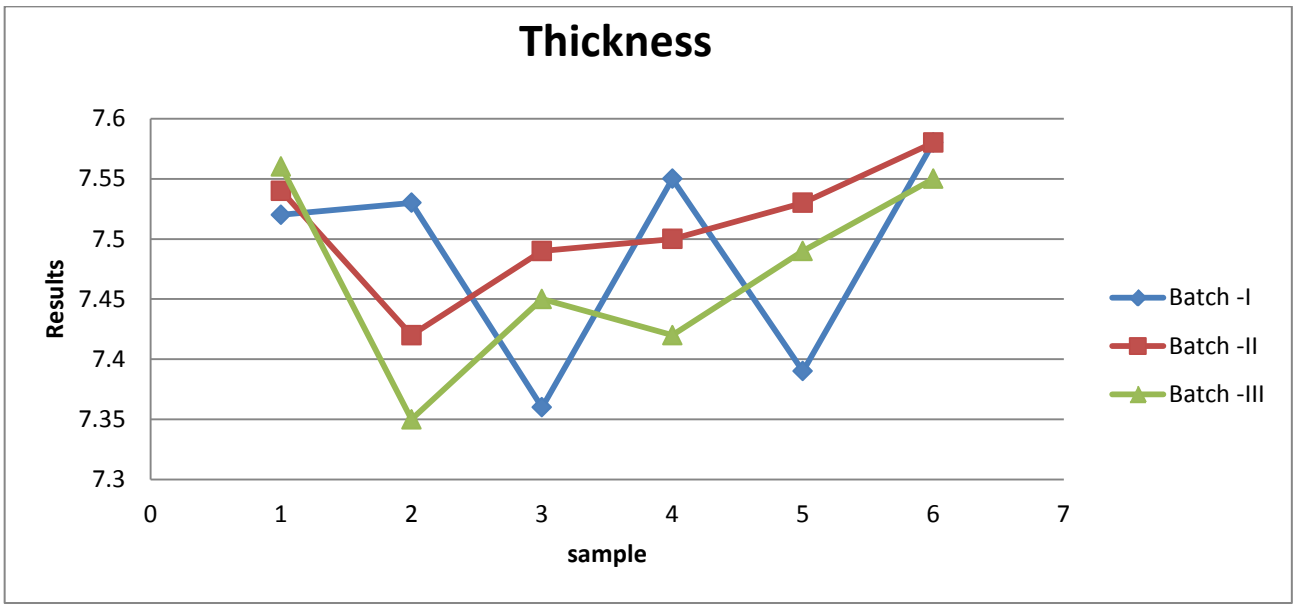

FIG: 7 THICKNESS

TABLE-12 THICKNESS & HARDNESS

S.NO	Thickness(7.5±0.2mm)			Hardness(9-13 kg/cm^2)		
	Batch number			Batch number		
	I	II	III	I	II	III
1	7.52	7.54	7.56	10.02	9.54	10.67
2	7.53	7.42	7.35	9.46	10	11.21
3	7.36	7.49	7.45	9.52	11	9.59
4	7.55	7.5	7.42	10.7	9.09	9.89
5	7.39	7.53	7.49	10	9.8	10.58
6	7.58	7.58	7.55	11	10.02	11.07
Average	7.51	7.51	7.50	10.11	9.90	10.50
Minimum	7.3	7.3	7.3	9	9	9
Maximum	7.8	7.8	7.8	13	13	13

Hardness

The crushing strength Kg/cm^2 of prepared tablets was determined for 10 tablets of each batch by using Monsanto tablet hardness tester. The average hardness and standard deviation was determined. The results are shown in Table-12 and fig-8.

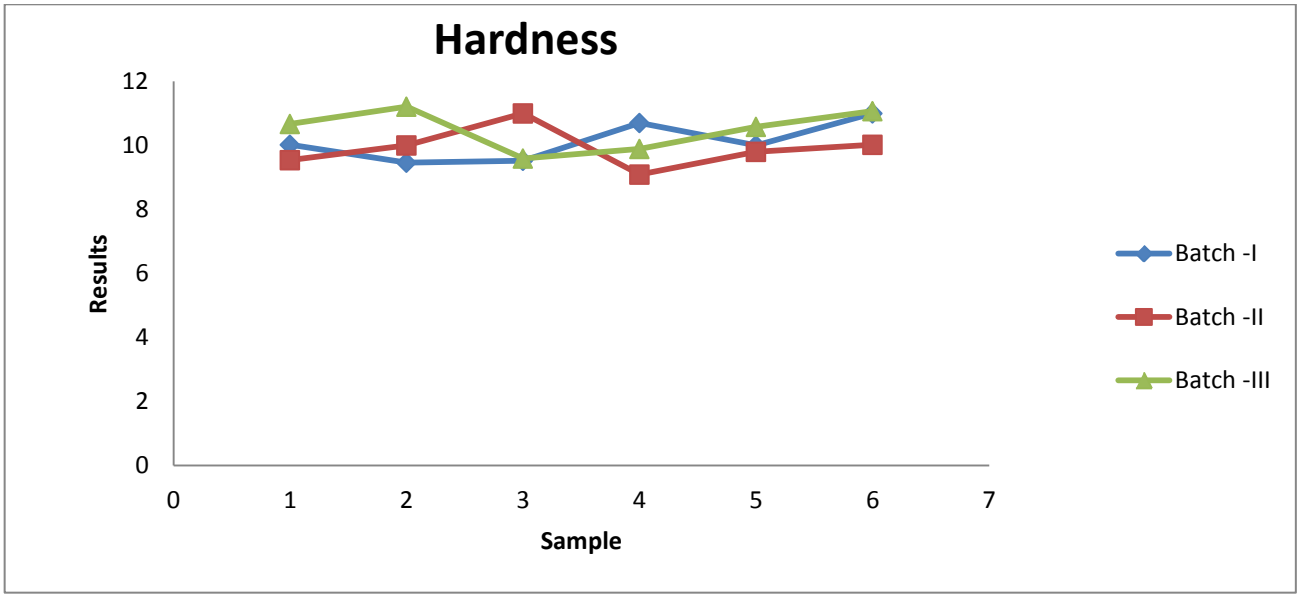

FIG: 8 HARDNESS

Friability:

Twenty tablets were placed in the friabilator and subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula

F % =(1-W_0 /W)×100

Where, W_0 is weight of the tablets before the test and W is the weight of the tablets after test.The results are shown in table -13 .

TABLE-13 FRIABILITY

S.NO	Batch number	Results
1	Batch –I	0.67
2	Batch-II	0.68
3	Batch -III	0.45

In vitro dissolution studies:

Six tablets were placed in each of 6 dissolution flasks containing 900 ml of pH 2.0 HCl, previously maintained at 37±0.5°C and the basket was set at 50 rpm the apparatus was run for 60 minutes. A suitable volume of sample was withdrawn at regular intervals of time and filtered through 0.45 µm membrane filter. The absorbance of the sample preparations were measured at 249 nm, using pH 2.0 HCl as blank.

TABLE-14 IN VITRO DISSOLUTION PROFILE OF THREE BATCH'S

S.NO	Product		Clopidogrel bisulFate (NLT 80% in 30min)					
			5	**10**	**15**	**30**	**45**	**60**
1	Batch-I	Tablet -1	10	28	45	82	89	95
		Tablet-2	12	31	48	83	90	96
		Tablet-3	14	33	50	85	92	98
		Tablet-4	16	35	51	88	93	97
		Tablet-5	15	32	50	84	90	94
		Tablet-6	18	30	56	89	95	98
2	Batch-II	Tablet -1	12	25	40	86	90	93
		Tablet-2	18	32	48	84	95	96
		Tablet-3	14	36	42	82	91	94
		Tablet-4	16	38	52	87	96	97
		Tablet-5	15	34	58	86	94	95
		Tablet-6	19	39	54	85	96	98
3	Batch-III	Tablet -1	11	24	41	82	89	91
		Tablet-2	15	30	42	85	91	95
		Tablet-3	16	32	45	84	90	92
		Tablet-4	12	34	53	86	94	96
		Tablet-5	15	38	57	87	93	98
		Tablet-6	19	35	52	84	90	97

Discussion: The results of evaluation of table were found to within the limit, the weight variation was found to be between the range of 855-945, thickness of tablet was found to be within the 7.3-7.5, hardness was found to be within the 9-13 kg/cm^2 friability was found to be Not more than 1% and dissolution release profile of all the three batch's were not less 80% at Q 30.

CONCLUSION

The clopidogrel bisulfate tablet was formulated and its drug release profile at Q point was greater than 80%.so, the formulated product was optimum**.** The Dry mixing and Precompaction Lubrication at 5mins, Blending at 15 mins, Lubrication at 5 mins, Compression at Optimum Hardness (9-13kg/cm^2) and Optimum Speed (20 RPM) were compiled and all the results were in pre determine specification.

During in process checking of three batch's (compression) Thickness, Hardness, Friability, weight variation, Disintegration and Dissolution parameters were observed and all are in within the specification limits. The graph was plotted for weight variation, thickness and hardness of tablet it say that the three batch's of validation are within the limit. The peak retention time of batch's were compare with standard and the peak was eluted as same that of standard one .

The coating of all three batches has been validated for Pan Load, Pan RPM, Inlet & outlet temperature, gun distance, atomization and spray rate and the results are comparable among all the three batches. The packing was done.

SUMMARY

The quality system regulation defines process validation by establishing objective evidence that a process consistently produces a result or product meeting its predetermined specifications. The goal of quality system is to consistently produce products that are suitable for their intended use. Process validation is a key element in assuring that these principles and goals are met.

In this study concurrent process validation was carried out for one product. In tablet dosage form, critical parameters were taken up for validation studies and the results shown that the process was validated.

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