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PROCESS DEVELOPMENT AND STANDARDIZATION OF CARVEDILOL TABLETS 3.125 mg DURING TECHNOLOGY TRANSFER

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ABSTRACT

The present study is on "Process development and Standardization of carvedilol tablets 3.125 mg during technology transfer." In the study of exhibit batches and stability behavior for generic development of carvedilol tablets 3.125 mg two critical factors, lower side of assay and slight increase in the content of impurities were identified. The trial results of analytical variation were found to be negotiable. The trials of manufacturing process were developed and standardized by making certain modifications to the existing manufacturing process. Individual sifting of carvedilol was avoided. This prevented drug loss during sifting and sifting of all the ingredients together ensured proper mixing. Granulation parameters were also optimized. By the above parameters the higher side of assay was achieved. The slight increase in the content of impurities was arrested by packing tablets in aluminum blisters, which are considered to be adequate water barriers.

KEYWORDS

Carvedilol, granulation parameters, aluminium blisters.

INTRODUCTION

Generic product development aims at the formulation of a product pharmaceutically equivalent to a specific reference product. The formulation and manufacturing process developed at a pilot-scale must be capable of manufacturing large-scale production batches. The process is scaled up to a batch size close to the bio-batch or production batch which has a minimum requirement of 100,000 units as per FDA, after the initial development work. Experimental design may be employed to study and optimize critical parameters. Depending on the complexity of the manufacturing process involved, such as dry blending, wet granulation, roller compacting, tabletting, encapsulation and coating appropriate process parameters are carefully monitored and viable ranges established. The process may be further validated at the extremes of these ranges to set up controls for the manufacturing process. If once a product is identified for generic development, various activities are initiated and a stepwise approach is taken in the development work that includes [1]

Feasibility Studies

The main objective of feasibility studies is to determine whether a certain plan of action is feasible that is., estimating the probability of success and cost effectiveness of the study. In some cases, a feasibility study may help management to determine whether it could achieve the same benefits through easier or cheaper means.[2,3]

Formulation development and Process optimization

Development of a pharmaceutical product is essentially a technique where the physicochemical properties of the active ingredients and the manufacturing processes are manipulated to achieve desired quality in the finished dosage form. Optimization requires statistical skill in addition to an understanding of the physicochemical properties of the materials involved. In today's competitive market, analysis of

data from statistically designed experiments enables one to generate a mathematical model and contour plots to elucidate formulation and process parameters affecting the product properties [4-6]

Scale-Up of Manufacturing Process

Batch sizes are often determined arbitrarily and may require further scale up or scale down. Scale-Up is accomplished by using larger, higher -speed equipment that may require adjustments to the process parameters established during manufacture using small scale equipment.[7]

Process Validation

Process validation for solid dosage forms in the generic industry is required by the Current Good Manufacturing Practices for finished pharmaceuticals.[8]According to the Food Drugs Administration guidelines process validation is defined as "establishing documentary evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics".[9]

Process Demonstration and Technology Transfer

Process demonstration demonstrates that the process utilized in the pilot plant stage is applicable for producing the desired product on a larger scale. All important aspects of the process (mixing time, granulation end point ,drying curves, moisture contents, compression forces and coating parameters),are carefully explored and monitored. Technology transfer involves transferring the product manufacturing technique and responsibilities from development phase to regular production group. The technology transfer process is considered to be completed with the successful completion of three consecutive batches.

Documentation

Documentation is an important aspect of the scale-up, process validation and technology transfer process. Hence it becomes imperative that all relevant documents pertaining to the manufacturing, testing and releasing of Bio/validation batch are compiled and organized prior to a Pre-Approval Inspection.[10]

Scale Up Post Approval Changes

USFDA has issued guidelines for the benefit of Abbreviated New Drugs Application sponsors who, during the post – approval period, intend to change components or compositions, manufacturing site, scale up / scale down of manufacturing process or change equipment used for immediate release and modified release solid oral dosage forms[11-12]. Depending on the scale of change as listed in Scale up Post Approval Changes guideline, the Abbreviated New Drugs Application sponsor may have to perform additional in-vitro testing to establish bioequivalence, stability and similarity to the original bioequivalence-batch[13].By studying the exhibit batches and their stability behavior, a process feasibility plan was prepared by designing of trials to evaluate analytical and manufacturing processes.

Carvedilol is a third generation beta adrenergic blocker used in the treatment of congestive heart failure.[14] It is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25 % to 35% due to a significant degree of first pass metabolism. It is more than 98% bound to plasma proteins, primarily with albumin and is extensively metabolized primarily by aromatic ring oxidation and glucuronidation.The half-life is 7 to 10 hours. Less than 2% is excreted unchanged in urine. Metabolites are excreted via the bile into feces. [15]

MATERIALS AND METHODS

MATERIALS

Carvedilol tablets 3.125 mg was a product transferred from Germany to Hyderabad site for generic development. The excipients included in the study were Lactose monohydrate Ph.Eur (Molikerei Meggle, Wasserburg Gmbh & Co), Ferric oxide NF (BASF South East Asia Pvt.Ltd), Microcrystalline Cellulose Ph.Eur (Ranq Remedies Pvt.Ltd), CrosPovidone Ph.Eur (BASF South East

Asia Pvt.Ltd), Povidone Ph.Eur (BASF South East Asia Pvt.Ltd), Silica Colloidal Anhydrous Ph.Eur (Degussa), Magnesium Stearate Ph.Eur (Ferro Industries, Quimicas) and Purified water Ph.Eur (In house) and Active pharmaceutical ingredient, Carvedilol (Cipla,Kurkumbh). The unit formula is given in **table-1**.

Table-1: UNIT FORMULA

S.No	Name of the Ingredients	Rationale	Quantity(mg)
	Dry mix		
1	Carvedilol Ph.Eur	Active	3.125
2	Lactose monohydrate Ph.Eur	Diluent	65.1
3	Ferric oxide NF	Color	0.025
4	Microcrystalline Cellulose Ph.Eur	Diluent	21.25
5	CrosPovidone Ph.Eur	Disintegrant	5
	Granulating solution		
6	Povidone (K-30) Ph.Eur	Binder	4
7	Purified water Ph.Eur	Vehicle	q.s
	Blending materials		
8	Silica colloidal anhydrous Ph.Eur	Vehicle	0.5
9	Magnesium Stearate Ph.Eur	Lubricant	1
	Total weight		100

The equipments handled during the process were Sifter (Betochem/Sams Techno), Propeller Type Remi Stirrer (Remi/Sams Techno Mech), Rapid mixer granulator(Sams Techno Mech), Fluid Bed Drier (Alliance Engg.Co), Comminuting Mill (Ridhi Pharma Machinery), Octagonal Blender (Saan Engg.Co), Tablet Compression Machine (Sejong), Metal Detection Unit (Auto Control Instruments Rimek), Tablet Dedusting Unit (Chamunda Pharma).

METHODS

Analytical method

Assay was carried by HPLC method (Column: Xterra RP 18, 5 µm, 150*3.9 mm i.d, Mobile phase: Acetonitrile (35 ml), 0.01M Phosphate buffer pH 3.0 (65 ml), Flow rate : Approximately 1.0 ml/minute, Temperature : 40ºC, Detector : U.V 241 nm, Injection volume : 20 µl, Run time: Approximately 6 minutes, Average mass: Determine the average mass of 20 rewrite this in passive voice an past tense. Ex: was weighed tablets. Preparation of mobile phase (0.01M Phosphate buffer pH 3.0): Dissolve 1.36g of potassium dihydrogen phosphate (KH_2PO_4) in 800 ml of purified water. Adjust pH to 3.0 with phosphoric acid (85%) and dilute to 1000 ml with water. Test solution: Powder minimum 20 tablets. Transfer tablet powder equivalent to 25 mg of Carvedilol to a 100 ml volumetric flask, add 50 ml of ethanol 96% and stir for 45 min. Add acidified water to volume , filter and dilute one ml of it to 25 ml with acidified water. **Standard solution:** Transfer 25.0 mg of Carvedilol standard to a 100 ml volumetric flask. Dissolve in 50 ml of ethanol 96% by sonication. Add acidified water to volume and dilute 1 ml of it to 25 ml with acidified water.

Percentage of Carvedilol was calculated by the formula given below.

$$\text{\% of Carvedilol dissolved in declared content 3.125 mg} = \frac{\text{Area (test)} \times \text{Weighed (Std)} \times \text{\% Std} \times 1000 \times 1000}{\text{Area (test)} \times 100 \times 100 \times \text{declared content}}$$

Related substances was carried out by HPLC method (Column: Waters symmetry C18, 5 µm, 150*3.9 mm i.d, Mobile phase: Methanol (42 ml), 0.01M Phosphate buffer pH 4.0: 58 ml, Flow rate: Approximately1.0 ml/minute, Temperature: 40ºC , Detector: U.V 223 nm, Injection volume: 20 µl,Run time: 100 minutes (R_t for Carvedilol 18-20 min).Preparation of mobile phase (0.01M Phosphate buffer pH 4.0): Dissolve 1.36g of potassium dihydrogen phosphate (KH_2PO_4) and 30 ml of heptanesulphonic acid sodium salt (1% in water) in 1000 ml of purified water. Adjust pH to 4.0 with phosphoric acid (85%).Test solution: Transfer tablet powder corresponding to 25 mg of Carvedilol to a volumetric flask. Add 25 ml of methanol and shake for 20 min.Add acidified water to volume and mix. Filter and dilute 5 ml to 100 ml with acidified water. Standard solution: Dilute 2.0 ml of test solution to 100 ml with methanol/ acidified water (50:50). Then dilute 1 ml of it with 10 ml of acidified water).

Dissolution was carried out in paddle apparatus with 50 rpm in 1000 ml of 0.1N Hcl medium at 37± 0.5ºC and samples drawn at interval(10, 30 and 60 min).Method of analysis by HPLC method(Column: Xterra RP 18, 5 µm, 150*3.9 mm i.d,Mobile phase: Acetonitrile (35 ml),0.01M Phosphate buffer pH 3.0(65 ml),Flow rate: Approximately 1.0 ml/minute, Temperature: 40ºC, Detector: U.V(241nm) ,Injection volume: 20µl, Runtime: Approximately six min. Preparation of mobile phase(0.01M Phosphate buffer pH 3.0: Dissolve 1.36g of potassium dihydrogen phosphate (KH_2PO_4) in 800 ml of purified water. Adjust pH to 3.0 with phosphoric acid (85%) and dilute to 1000 ml with water).Preparation of samples (The samples of 10 ml collected after 10, 30 and 60 min were centrifuged for approximately 5 minutes at 3000 rpm and diluted 5 ml to 10 ml with 0.1N Hcl).Standard solution (25.0 mg of Carvedilol standard in a 100 ml volumetric flask was added to 50 ml of ethanol (96%) and dissolved (by sonication, if necessary). Add acidified water to volume. Percentage of Carvedilol dissolved was calculated from the formula given below.

$$\text{\% of Carvedilol dissolved in declared content 3.125 mg} == \frac{\text{Area (test)*Weighed (Std)* \% Std*1000*1000}}{\text{Area (test)*100*100*100*Declared content}}$$

MANUFACTURING METHOD

The existing manufacturing process is wet granulation method and it involves Sifting.: sift Carvedilol through # 30 mesh, Lactose monohydrate (Part-I) and Ferric Oxide through # 40 mesh, the above sifted Carvedilol and Lactose monohydrate (Part-I) with Ferric Oxide through 40 mesh, Lactose monohydrate (Part-II) through # 20 mesh, Microcrystalline Cellulose through # 40 mesh, Crosprovidone through # 40 mesh . Dry mixing: Load the above sifted material in Rapid mixer granulator and mix for 10min with impeller slow speed. Wet granulation: Add binder solution over dry mix material in a period of 10 minutes at impeller slow speed and mix the content in Rapid Mixer Granulator at impeller slow speed and

chopper slow speed for 5 minutes, if suitable wet mass not formed then add additional quantity of purified water.

Drying: Air dry the wet mass for 10 minutes and dry at inlet temperature to reach NMT 80°C., dry the granules till loss on drying reaches to not more than 3.0%w/w at 105°C by IR moisture analyzer.

Sifting and Milling: Sift the dried granules through # 18 mesh and mill retentions through multimill using 1mm screen at medium speed and knives forward configuration. Sifting of extra granular materials: Sift Silica Colloidal Anhydrous and Magnesium Stearate through # 40 mesh. Blending: Mix the materials of dried granules with Silica Colloidal Anhydrous in Octagonal Blender for 15 minutes. Lubrication: Add Magnesium Stearate to the above materials in Octagonal Blender for 5 minutes. Compression: Set the compression machine with punches of 7.0 mm, round, concave scored punches with embossment "C1" in one half and lip cut break line on upper punch and lip cut break line on lower punch and run at a target speed (35 rpm) with parameters of specified limits given in **Table-2**).

Table-2: LIST OF COMPRESSION PARAMETERS AND SPECIFIED LIMITS.

Parameters	Limits
Physical description of Tablet	A light red, round convex tablet with score notch on both side and an embossment "C1"on one side.
Theoretical weight of Tablet	100 mg
Weight of 10 tablets	1.00 g ± 2 % (0.980 g to 1.020 g)
Weight variation	100 mg ± 7.5% (93 mg to 107 mg)
Hardness	3 to 9 Kp (30 to 90 N)
Tablet Thickness	2.0 mm to 2.6 mm
Disintegration Time	NMT 15 minutes
Friability	NMT 1.0%

In study of exhibit batches and stability behavior, the report shows marked decrease in the assay and minor increase in the content of impurities for tablets stored for 6 months at 40^0C/75%RH in blister packs. The trials were designed to evaluate the critical parameters.

Trial - 1

Two samples of 5 dosage units' of samples each taken in two separate 500 ml volumetric flasks, without heating and heating at 40ºC & 75ºC to check analytical process. (In two separate 500 ml volumetric flasks, weighed Carvedilol, Lactose Monohydrate, Ferric Oxide, Microcrystalline Cellulose, Crospovidone and Povidone were added as such and mixed for 5 Min. Purified water with the help of dropper was added and mixed for 5 minutes. The above contents dried in Restch dryer at inlet air temperature of 75^0C till Loss on drying, not more than 3.0% w/w at 105^0C by using Halogen Moisture Balance. Dried granules were sifted through # 18 mesh and the retentions were milled by using mortar & pestle and again sifted through # 18 mesh. Sifted dried granules were loaded in glass bottles, over it Silica Colloidal Anhydrous was added and mixed for 10 min. Magnesium Stearate was added over the contents of above step and blended for 5 min.Two blended samples (one heated at 40ºC & another without heat) of 5 dosage units' were prepared from one of the 500 ml volumetric flask and sent for analysis. Two blended samples (one heated at 75ºC & another without heat) of 5 dosage units' were prepared

from one of the 500 ml volumetric flask and sent for analysis.)

Trial – 2

To develop the existing manufacturing process, 2.0 kg trial batch was done by using direct compression method. (Carvedilol, Lactose monohydrate (part I) and Ferric Oxide through # 40 mesh, Lactose monohydrate (part II) through # 20 mesh, Microcrystalline Cellulose through # 40 mesh, Crospovidone through # 40 mesh, Povidone through # 40 mesh were sifted. The above contents blended in Octagonal Blender for 10 min. Silica Colloidal Anhydrous with some quantity of above step sifted through # 40 mesh. The above contents were transferred to sifted Silica Colloidal Anhydrous and blended in Octagonal Blender for 15 min. Magnesium Stearate with some quantity of above step sifted through # 40 mesh and blended with above contents for 5 min. Lubricated blend samples were sent for analysis.

Trial – 3

To develop the existing manufacturing process, 2.0 kg trial batch was done by using slugging method. (Carvedilol, Lactose monohydrate (part I) and Ferric Oxide through # 40 mesh, Lactose monohydrate (part II) through # 20 mesh, Microcrystalline Cellulose through # 40 mesh,Crospovidone through # 40 mesh, Povidone through # 40 mesh were sifted. The above contents were blended together in Octagonal Blender for 10 min. Soft tablets were prepared by compressing the above blend with low hardness. Soft tablets obtained were milled through multimill using 1 mm screen at medium speed and knives forward configuration. Silica Colloidal Anhydrous with some quantity of above step sifted through # 40 mesh. The milled contents were transferred to the sifted Silica Colloidal Anhydrous into Octagonal Blender and blended for 15 min. Magnesium Stearate with some quantity of above step sifted through # 40 mesh and blended with above contents for 5 min.Lubricated blend samples were sent for analysis.

Trial – 4

To develop the existing manufacturing process, 2.0 kg trial batch was done by using current manufacturing process. (Sifting: Microcrystalline Cellulose through # 40 mesh, Crospovidone through # 40 mesh, Lactose monohydrate (part I) through # 20 mesh, Lactose monohydrate (part II), Carvedilol and ferric oxide through # 40 mesh were sifted. the above contents were blended in Octagonal Blender for 10 min. Preparation of Binder Solution: Povidone added to purified water and stirred continuously until a clear solution was formed.

Granulation: the above blend was loaded into Rapid Mixer Granulator and mixed for 10 min at impeller with slow speed and chopper off. Binder solution was added to the dry mix over a period of 10 min at impeller with slow speed and chopper off. The above contents were mixed at impeller with slow speed and chopper off for 5 min. Additional quantity of 1 kg of purified water added and mixed for 1 minute at impeller with fast speed and chopper with slow speed. The wet granules were unloaded by keeping impeller fast and chopper fast.

Drying: The wet mass was dried in Fluid Bed Drier at inlet temperature of 75±5ºC till Loss on drying reaches to not more than 3.0% w/w at 105ºC; drying was continued for 30 min.

Sifting & Milling: Dried granules sifted through # 18 mesh. The above retentions were milled in a Comminuting Mill fitted with 1 mm screen at medium speed, knives forward configuration. The milled granules were sifted through # 18 mesh. The above contents sifted through # 40 mesh and the retentions could be added to blending stage.

Blending: Silica Colloidal Anhydrous (sifted through # 40 mesh) and # 40 mesh passed granules, both were sifted together through # 40 mesh and blended in Octagonal Blender for 15 min. Magnesiumstearate sifted through # 40 mesh. Sifted Magnesiumstearate was added to above contents and blended for 5 min. The contents were

unloaded into polybags. Lubricated blend samples were sent for analysis. Compression was carried out for the above blend by using 7.0 mm punches with "C1" embossed and lip cut break line on upper punch and lip cut break line on lower punch. Compressed tablets were sent for analysis).

Trial – 5

10.0 kg trial batch was scaled up from the previous batch.(Sifting: Microcrystalline Cellulose through # 40 mesh, Crospovidone through # 40 mesh, Lactose monohydrate (part I of 6.0 kg) through # 20 mesh, Lactose monohydrate (part II of 0.5 kg), Carvedilol and ferric oxide through # 40 mesh were sifted. The above contents were blended in Octagonal Blender for 10 min. Preparation of Binder Solution: Purified water (1.6 kg) taken in S.S Vessel fitted with stirrer, to it Povidone (0.4 kg) was added, and stirring continued till it dissolves completely. Granulation: The above blend loaded into Rapid Mixer Granulator and mixed for 10 min at impeller with slow speed and chopper off. Binder solution added to the dry mix over a period of 10 min at impeller with slow speed and chopper off. The above contents were mixed at impeller with slow speed and chopper off for 5 min. Additional quantity of 1 kg of purified water added and mixed for 1 minute at impeller with fast speed and chopper with slow speed. The wet granules were unloaded by keeping impeller fast and chopper fast.

Drying: The wet mass was dried in Fluid Bed Drier at inlet temperature of 75±5ºC till LOD reaches to NMT 3.0% w/w at 105ºC; drying continued for 30 min.

Sifting & Milling: dried granules sifted through # 18 mesh. The above retentions were milled in a Comminuting Mill fitted with 1 mm screen at medium speed, knives forward configuration. The above milled granules sifted through # 18 mesh. The above contents were sifted through # 40 mesh and the retentions could be added to blending stage.

Blending: Silica Colloidal Anhydrous (sifted through # 40 mesh) and # 40 mesh passed granules, both were sifted together through # 40 mesh and blended in Octagonal Blender for 15 min. Magnesium Stearate sifted through # 40 mesh. Sifted Magnesium Stearate was added to above contents and blended for 5 min. The contents were unloaded into polybags. Lubricated blend samples were sent for analysis. Compression was carried out for the above blend by using 7.0 mm punches with "C1" embossed and lip cut break line on upper punch and lip cut break line on lower punch. Compressed tablets were sent for analysis).

Trial – 6

Reproducibility batch of previous trial was done.

RESULTS AND DISSCUSION

The Trial Results of analytical process were within the accepted limits, hence analytical variation was negotiable. In furthermore trials, existing manufacturing process has been modified, developed and standardized by taking reproducibility trial batch (T-6). The reproducibility trial batch was subjected to stability program at accelerated conditions; 40±2°C & 75±5%RH for 30 days. The product was evaluated for assay and related substances by loading in two types of Blister packs where one type was loaded with PVC-PVDC/ALU Blister pack and are represented as Trial-6.a (T-6.a). Stability Report for Trial-6.a (T-6.a) was shown in Table-3. Another type is loaded with ALU/ALU Blister pack and is represented as Trial-6.b (T-6.b). Stability Report for Trial-6.b (T-6.b) was shown in **Table-4**.

Assay compilation of Exhibit batches (B.No:1, 2 & 3) and Reproducibility batches (Trial-6.a &Trial-6.b) of Carvedilol tablets 3.125 mg was shown in **Table-4** and Graph-1 was plotted. Related substances compilation of Exhibit batches (B.No:1, 2 & 3) and Reproducibility trial batches (Trial-6.a &Trial-6.b) of Carvedilol tablets 3.125 mg was shown in **Table-5** and Graph-2 was plotted. The lower side of the assay during the study of exhibit batches due to

the process losses has been restricted by developing the current manufacturing process and standardizing by means of reproducibility trial batch and loading it to stability. The slight increase in the content of impurities was arrested by packing tablets in aluminum blisters, which are considered to be adequate water barriers.

Table-3: STABILITY REPORT FOR TRIAL-6.A (T-6.a)

Testing Period (in terms of Months)	Assay	Related Substances		Dissolution						Disintegration
	NLT 95.0 % NMT 105.0 %	Single unknown Impurity	Total Impurity	NLT 75% (Q) of the Carvedilol dissolved in 30 Minutes.						All six tablets should disintegrate within 15 mins
				Tablets						
		NMT 0.2%	NMT 1.0%	1	2	3	4	5	6	
Initial	100.4	0.04	0.15	95	97	98	96	99	93	--
1 Month	101.4	0.18	0.80	102	103	98	102	102	101	Within 11 mins

NMT: Not More Than

Table-4: STABILITY REPORT FOR TRIAL-6.B (T-6.b)

Testing Period (in terms of Months)	Assay	Related Substances		Dissolution						Disintegration
	NLT 95.0 % NMT 105.0 %	Single unknown Impurity	Total Impurity	NLT 75% (Q) of the Carvedilol dissolved in 30 Minutes.						All six tablets should disintegrate within 15 mins
				Tablets						
		NMT 0.2%	NMT 1.0%	1	2	3	4	5	6	
Initial	100.4	0.04	0.15	95	97	98	96	99	93	--
1 Month	101.8	0.04	0.26	103	101	103	101	102	103	Within 12 mins

NLT: Not Less Than

Table-5: ASSAY COMPILATION OF EXHIBIT BATCHES (B.NO:1, 2 & 3) AND REPRODUCIBILITY BATCHES (TRIAL-6.a &TRIAL-6.b) OF CARVEDILOL TABLETS 3.125 mg

Batch No	Testing Period	Assay (NLT 95.0 % NMT 105.0 %)
B.No:1	Initial	95.5
	1 Month	94.9
	6 Months	91.8
B.No:2	Initial	96.7
	1 Month	95.6
	6 Months	92.8
B.No:3	Initial	96.9
	1 Month	95.4
	6 Months	92.3
TRIAL-6.a (T-6.a)	Initial	100.4
	1 Month	101.4
TRIAL-6.b(T-6.b)	Initial	100.4
	1 Month	101.8

Table-6: RELATED SUBSTANCES COMPILATION OF EXHIBIT BATCHES (B.NO:1, 2 & 3) AND REPRODUCIBILITY TRIAL BATCHES (TRIAL-6.a &TRIAL-6.b) OF CARVEDILOL TABLETS 3.125 mg

Batch No	Testing Period	Related Substances	
		Single unknown Impurity	**Total Impurities**
		NMT 0.2%	**NMT 1.0%**
B.No:1	Initial	0.04	0.14
	1 Month	0.04	0.21
	6 Months	0.12	0.62
B.No:2	Initial	0.03	0.16
	1 Month	0.05	0.27
	6 Months	0.22	1.02
B.No:3	Initial	0.05	0.19
	1 Month	0.08	0.27
	6 Months	0.24	1.09
Trial-6.a (T-6.a)	Initial	0.04	0.15
	1 Month	0.18	0.8
Trial-6.b(T-6.b)	Initial	0.04	0.15
	1 Month	0.04	0.26

CONCLUSION

Certain modifications were done to the existing manufacturing process, to develop it to satisfactory specifications. Sifting of carvedilol was avoided by co-sifting of sifted Lactose monohydrate Ph.Eur and ferric oxide NF with carvedilol through #40 meshes. Granulation parameters were optimized by adding excess binder solution,, increasing the kneading time from one minute to three minutes and carrying out the wet mixing of granules at impeller with slow speed and chopper off. The

higher side of assay was achieved by preventing drug losses and the slight increase in the content of impurities was arrested by packing tablets in aluminum blisters. Hence the main goal of the present study was achieved, with this standardized manufacturing process. Further commercial scale-up needs to be carried out by executing and monitoring three exhibit batches.

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