OPTIMIZATION & VALIDATION OF BILAYER TABLET FABRICATED BY ANTIHYPERTENSIVE DRUGS

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Abstract

The objective of this study was to systematically conduct the process validation studies pertaining to the manufacturing activities of Bilayer tablet. The optimization of critical process steps and acceptance criteria at various stages of the process is referred in the validation report. The specifications of raw materials used in the manufacturing of Bilayer tablets of antihypertensive drugs have been derived from the monograph or previous history. The tolerance limits for the process parameters and the acceptance criteria for the various tests performed on in-process samples are derived from the FRND inputs. The physical characteristics of the final product are based on actual production scale, as some of these processes cannot be simulated in the laboratory. This research was carried out to produce a Bilayer tablet of antihypertensive drug. The immediate release Bilayer tablet of Telmisartan, Amlodipine besylate & Hydrochlorothiazide (40+5+12.5 mg) was successfully prepared. This combination Therapy indicated for the treatment of severe hypertension & coronary heart disease. Therefore, the purpose of performing optimization study for Antihypertensive drug form facility to provide necessary assurance for consistent quality product has been fulfilled.

Keywords: Telmisartan, Amlodipine besylate, Bilayer tablet, Hydrochlorothiazide, optimization and validation.

Introduction

Tablets are solid dosage forms containing medicinal substance with or without suitable diluents [1]. A tablet formulation contains several ingredients and the active ingredient is the most important among them. The remaining ingredients are necessary because a suitable tablet cannot compress of active ingredient alone. In pharmaceutical industry many methods are involved in the formulation of tablets i.e. direct compression or granulation. In granulation most products are manufactured by either dry granulation or wet granulation process [2-4].

When two or more active pharmaceutical ingredients are needed to be administered simultaneously and they are incompatible, the best option for the formulation pharmacist would be to formulate multilayer tablet. Bilayer tablets require fewer material than compression coated tablets, weight, and may be thinner. Monograms and other distinctive marking may be compressed in the surface of the bilayer tablets [5].

Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide successful drug delivery system [6]. Now a day's developed and developing countries move towards combination therapy (Bilayer tablet) for treatment of various diseases and disorders requiring long term therapy

such hypertension and diabetes [7]. In addition, if the compacted layers are too soft or too hard, they will not bond securely with each other [8]. Bilayer tablets are composed of two layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed [9,10].

Validation is a concept that has been evolving continuously since its first formal appearance in the United States in 1978. The concept of validation has expanded through the years to encompass a wide range of activities from analytical methods used for the quality control of the drug substances and drug products to computerized systems for clinical trials [11]. Validation is therefore one element of quality assurance associated with a particular process, as the process differs so widely, there is no universal approach to validation and regulatory bodies such as FDA and EC who have developed general non-mandatory guidelines [12]. The word validation simply means, 'assessment of validity' or 'action of proving effectiveness'. According to European community for medicinal products, validation is 'action of proving', in accordance with the principles of GMP that any procedures, process, requirement, material, activity or system actually leads to expected results [13]. Process validation is "A documented program which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes"[14-17].

Telmisartan prevents the constriction (narrowing) of blood vessels (veins and arteries). Telmisartan is practically insoluble in water; sparingly soluble in strong acid; soluble in strong bases. Absolute bioavailability depends on dosage. Food slightly decreases the bioavailability (a decrease of about 6% is seen when the 40-mg dose is administered with food). Oral administration peak concentrations of telmisartan are reached in 0.5-1.5h after dosing. Following either intravenous or oral administration of 14 C labelled telmisartan most of the administered dose (>97%) was eliminated in faeces via biliary excretion. Only minute amount found in urine [18].

Amlodipine besylate (AML) is in a class of drugs Calcium channel blockers. Calcium channel blocker affects the heart and circulatory system (arteries and veins). It is used to lower blood pressure, lower heart rate, reduce chest pain (angina), and to reduce the risk of recurrent heart attacks. Amlodipine besylate is a white or almost white powder. It is freely soluble in methanol, sparingly soluble in ethanol; slightly soluble in 2-propanol. Peak plasma concentrations are reached within 6-12h after administration. The absolute bioavailability of unchanged active substance is approximately 64-68%. Amlodipine is extensively converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine [19].

Hydrochlorothiazide (H) is a thiazide diuretic (water pill) that decreases the amount of fluid in the body by increasing the amount of salt and water lost in the urine. Hydrochlorothiazide is used to lower blood pressure and to decrease oedema (swelling). It is soluble in acetone, sparingly soluble in ethanol, very slightly soluble in water. It belongs to diuretics category. Oral administration peak concentrations of Hydrochlorothiazide are reached in 1.0-3.0 h after dosing. Based on cumulative renal excretion of hydrochlorothiazide the absolute bioavailability was about 60% [20].

The aim of this work was on process validation, which was to reduce product recalls and troubleshooting assignments which results in more economical manufacturing process and Quality products. The objectives of the present investigation were to ensure drug product quality and the consistency of the manufacturing operation and reproducibility of the process. Also to demonstrate the robustness of the process and to ensure that there is no Lot to Lot variation in the three validation lots i.e., PVR A, PVR B and PVR C. This work actually based on manufacturing of bilayer Tablets of Antihypertensive drugs and carry out Process validation of critical parameters involved, to ensure the existence of all necessary quality assurance systems within the organization and that personnel producing the drug product are properly trained and qualified to produce the product.

The Process of manufacturing of bilayer tablets of antihypertensive drugs was developed by the R&D of the CGC, PVT.LTD. Rationale for the selection of the combination telmisartan, amlodipine besylate and hydrochlorothiazide bilayer tablet was to treat the hypertension with a combination of TAH has multiple rationale and advantages and might offer the possibility to reduce the number of non-responders. Triple drug combination TAH (Telmisartan, amlodipine & hydrochlorothiazide) serve a potential role in achieving desired BP goal in patients with essential hypertension, which are otherwise not well managed by either monotherapy or dual therapy.

Materials & Method

Materials

Details of the source of telmisartan, amlodipine & hydrochlorothiazide are mentioned in table 6. All others chemicals, reagents and solvents used in the present investigation were analytical grades.

Methods

Processing steps

For telmisartan first layer

Dispensing

Dispense of Raw material.

Dispense the materials into double polyethylene HDPE container.

Sifting

Set up the sifter.

Sift the material through the specified mesh and collect them separately in clean HDPE container lined with double polythene bags and label them.

Table 1: Granulation material and mesh size

Granulation material	Mesh size
Mannitol	# 40
Lubrication material	Mesh size
Mannitol IP (300 DC)	#30
Magnesium Stearate IP	#60

Drug Binder Solution Preparation

Take purified water IP in SS vessel.

Add sodium hydroxide IP and stir slowly until vortex is formed.

Add meglumine to the vortex followed by the addition of Povidone IP, while stirring continuously till a clear dispersion is formed.

Add Telmisartan IP to the dispersion, while stirring continuously till a clear dispersion is formed.

Add polysorbate 80 IP to the solution, while stirring continuously till a clear solution is formed.

Fluid Bed Granulation (Top Spray Granulation)

Load the sifted material into the top spray bowl of fluid bed processor.

Pre warm the materials keeping product in between 40°C at fluidization air.

Spray the drug binder solution on the materials of above step.

Drying

Dry the wet granules at 50 ±5 °C till LOD reaches NMT 2.0% w/w at 105°C.

Sifting and milling

Set up the Quadro co mill.

Set the desired granules through # 30 mesh, collect retentions and % 30 mesh granules separately into polythene bags.

Mill the retention of above step and transfer it to double lined polythene HDPE container.

Repeat the sifting and milling till all the materials passes through #30 mesh.

Blending and lubrication

Load # 30 mesh passed granules with sifted materials except Magnesium Stearate. Ensure that all granules are fully transferred into Bin blender.

Start the blender & check the leakage of materials. Blend the loaded material for a specified time in a blender at specified rpm.

Mix Magnesium stearate with equal quantity of blend from blender in double polythene bag for appropriate time and add this back to the blender & blend for specified time at specified rpm.

Unload the lubricated granules into tared HDPE container with double polythene bags.

Figure 1: Process flow chart

For amlodipine besylate and hydrochloro-thiazide second layer

Dispensing

Dispensing of raw material.

Dispense the materials into double polyethylene HDPE container.

Sifting

Set up the sifter.

Sift the material through the specified mesh and collect them separately in clean HDPE container lined with double polythene bags and label them.

Table 2: Granulation material and mesh size

Granulation material	Mesh size
Hydrochlorothiazide IP	# 30
Microcrystalline Cellulose IP	#30
Amlodipine Besylate IP	#30
Mannitol IP	#30
Iron Oxide Red	# 30
Lubrication material	Mesh size
Magnesium Stearate IP	#60

Binder Solution Preparation

Take purified water IP in SS vessel and prepare binder solution using Povidone under stirring.

Dry mixing and granulation

Set up shear mixture granulator.

Load sifted dry mixed material into shear granulator and ensure all the materials are fully transferred into shear mixture granulator bowl.

After addition of sifted materials close the lid of shear mixture then start the impeller at appropriate speed and continue dry mixing for required duration.

Add binder solution in him stream to the dried mixed powder in a granulator while mixing at specified speed of impeller and chopper for appropriate time.

Open the lid and scraped the material adhere to the lid and wall.

Mix the material with impeller and chopper at specified speed for appropriate time.

Open the lid and observe the granules for appearance, if end point is reached then close the lid and start discharge and unload the granules to FBD bowl.

Subject it for drying.

Drying

Set up the FBD.

Place the FBD bowl containing wet mass under the retarding chamber.

Air dry the material for appropriate time and rakes the material.

Dry the material uniformly by raking as and when required at inlet temperature of 60°C till the LOD of granules reaches NMT 2.0% w/w.

Check the LOD of dried granules.

Air dry the material for appropriate time after achieving required LOD.

Sifting and milling

Set up Quadro co Mill.

Sift the dried granules through #30 mesh, collect retention and #30 mesh granules separately into polythene bags.

Mill the retention of above step and transfer it to double lined polythene HDPE container.

Repeat the Sifting and milling till all the materials passes through #30 mesh.

Blending

Set up the blender.

Load the # 30 mesh passed granules.

Start the blender and check the leakage of material.

Sift Magnesium stearate IP with equal quantity of blend from blender in double polythene bag for appropriate time and add this back to the blender for specified time at specified rpm.

Unload the granules into tared HDPE container lined with double polythene bags.

Fig. 2: Process flow chart

Compression

Set up the tablet compression machine, Deduster machine and metal detector.

Check the lower and upper punch before starting the machine.

Table 3: Standard of punches

Material	Standards
Upper Punch	14 mm x 7 mm oval shaped punch
Lower Punch	14 mm x 7 mm oval shaped punch
Dies	m x 7 mm oval shaped punch

Ensure that the blend of Telmisartan layer (87.00 kg) for compression. Load white layer blend in first station compression hopper and set the tablet press with the following parameters.

Table 4: Physical parameters

Parameter	Theoretical limits
Target weight	290.00 mg
Weight of 20 tablets	5.800 gm $\pm$ 3%
Weight variation	290 mg $\pm$ 5 %
Hardness	Kp

Ensure that the blend of Amlodipine besylate and hydrochlorothiazide (60.00 kg). Load the pink layer blend in second station compression hopper and set the tablet press with following parameters.

Table 5: Physical parameter

Parameter	Theoretical limits
Weight variation	490.00 mg $\pm$ 5.0 %
Weight of 20 tablets	9.800 gm $\pm$ 3%
Thickness	5.6 $\pm$ 0.3 mm
Hardness	10-17 Kp
Disintegration time	NMT 5 min.
Friability	NMT 0.8%

Perform start up single layer tablet in process parameter to be noted down for single layer. Perform start up for double layer tablet.

If the tablet parameters are within the limits, start the compression machine at 10-20 rpm and collect the tablet through tablet dedusting unit and metal detector into container lined with polythene bags.

Check the ejection of any tablet due to initial particle and destroy the rejected tablets.

Check the individual weight variation and thickness of 50 tablets. Check the group weight variation (20 tablets), thickness and hardness every 30 minutes and friability and DT parameter every 60 minutes and record inspection.

Figure 3: Process flow chart of compression

Table 6: Material and Quantity of formulation

Sr. No.	Materials	Quantity kg/batch	Function	Manufacturer
Materials used in first layer (white layer)				
1.	Telmisartan	6.18kg	Active pharmaceutical ingredient	Dr. Reddy's CTO unit 2
2.	Meglumine Ph. Eur	1.45 kg	Alkalizer	Merck
3.	Sodium Hydroxide IP	0.47 kg	Alkalizer	Canton
4.	Povidone IP	1.02 kg	Binder	ISP
5.	Polysorbate 80 IP	0.09 kg	Solubilizer	Viswant
6.	Mannitol IP (Pearlitol SD 200)	24.39 kg	Diluent	Roquette
7.	Purified Water	40 kg	Aqueous solvent	NA
8.	Mannitol (300 DC) IP	12.11 kg	Diluent	Roquette
9.	Mannitol IP (Pearlitol SD 200)	6.31 kg	Diluent	Roquette
10.	Magnesium Stearate IP	1.74	Lubricant	Sunshine
	Weight of first layer	87 kg		
Materials used in Second layer (Pink layer)				
1.	Amlodipine Besylate	1.04 kg	Active pharmaceutical ingredient	Dr. Reddy's CTO unit 2
2.	Hydrochlorothiazide	1.875 kg	Active pharmaceutical ingredient	Dr. Reddy's CTO unit 2
3.	Mannitol IP	16.36 kg	Diluent	Roquette
4.	Microcrystalline Cellulose (Avicel PH 101)	9.78 kg	Diluent	RAN – Q
5.	Iron oxide Red IH	0.045 kg	Colorants	ROHA
6.	Povidone IP	0.150 kg	Binder	ISP
7.	Purified Water	6.315 kg	Aqueous solvent	NA
8.	Magnesium stearate	1.50 kg	Lubricant	Sunshine
	Weight of second layer	60 kg		

Optimization studies

The scope of this study is applicable to the trial batch that is taken for checking the feasibility of process and facility. Studies are performed on the basis of this sampling and testing plan:

Table 7: Sampling and testing plan

Stage	Process variables	Sampling frequency	Tests to be performed	Acceptance criteria
Telmisartan (White layer)				
Drying	Inlet, Outlet temperature, & Drying time	At regular intervals	Loss on Drying	NMT 2.0 %
		At the end		
Blending	Pre-Blending Time	5, 10 &15 minutes with extra granular materials	Content uniformity & RSD	For Information
	Blending Time	3, 5 & 7 minutes with lubricant	Content uniformity & RSD	100.0 ± 15% RSD NMT 6.0%
		Pooled samples after Blending	Bulk density, Angle of repose, Sieve analysis, Compressibility Index	For Information
			Water content & Assay	As per In-process Specification.
Amlodipine Besilate and Hydrochlorothiazide (Pink layer)				
Dry Mixing	Mixing time	10, 15 & 20 minutes	Drug Homogeneity & RSD	For Information
Drying	Inlet, Outlet temperature & Drying time	At regular intervals	Loss on Drying	NMT 2.0 %
		At the end		
Blending	Pre-Blending Time	5, 10 &15 minutes with extra granular materials	Content uniformity & RSD	For Information
	Blending Time	3, 5 & 7 minutes with lubricant	Content uniformity & RSD	100.0 ± 15% RSD NMT 6.0%
		Pooled samples after Blending	Bulk density, Angle of repose, Sieve analysis, Compressibility Index, Water content & Assay	For Information
			Water content & Assay	As per In-process Specification.
Compression				
Compression	Hardness	Optimum speed	Physical Parameters at low & high hardness	For information
			Dissolution At low hardness & high hardness	For information
	Machine speeds (different speed).	At different speeds	UOD & RSD	100.0 ± 15 % RSD NMT 6.0%
			Dissolution	For information
			Group weight variation	9.800 ± 2% (9.604g – 9.996 g)
			Individual weight variation	490.0 mg ± 5 % (466 mg – 514mg)
			Hardness	10-17 KP (100-170 N)
			Thickness	5.60 ± 0.3 mm (5.3 mm - 5.9mm)
			Disintegration time	NMT 15 min.
			Friability	NMT 0.8 % w/w

Process validation studies

Three batches of Bilayer a tablet of Antihypertensive drugs was manufactured as described in the batch manufacturing record.

Objective: To establish documented evidence which provide high degree of assurance that the specific process will consistently produce Antihypertensive drug meeting its predetermined acceptance criteria and quality attributes.

Sampling procedures at different stages:

Telmisartan (White) layer: Blending: Load sifted materials into the Bin Blender except Magnesium stearate as per BMR. Start the blender in inch mode and check for any leakage of material. On ensuring that there is no leakage, blended for 10 minutes. The sample quantity shall be between x to 3x mg. Blend Magnesium stearate along with equal quantity of blend from Bin Blender in double polythene bags as

per BMR and load into Bin Blender and blend for 5 minutes and collect the sample from 10 locations. The sample size after lubrication shall be between x to 3x mg.

Note: Collect samples for Content Uniformity in three sets. One set of samples to be taken for analysis and other two sets are to be kept as a reserve sample. In case of failure of results of one set use the reserve sample set for analysis, otherwise, discard the reserve sample set.

Hydrochlorothiazide and Amlodipine (Pink) layer

Dry mixing:

Samples are collected at 15 minutes of time interval from 10 different locations as shown in the diagram. The acceptance criteria for the content uniformity of Amlodipine Besilate IP and Hydrochlorothiazide IP are $100 \pm 10\%$ of the theoretical quantity, whereas the limit for Relative Standard Deviation (RSD) should be NMT 6.0%. The sample quantity shall be between 222.78 mg to 668.34 mg. Sampling should be done with sampling rod.

Granulation:

The granulation to be performed using RMG. The granulation step involves converting the powder into wet dough mass. Mixing time influences the granule strength, bulk density of blend, dissolution, hardness of tablets etc. Aqueous binder solution is being used for granulation. The granulation end point is a critical process and the end point

of granulation determined by physical observation and amperage readings of Impeller is recorded to co-relate the same.

Drying:

Drying of granules in FBE controls the moisture content. Inlet of FBE is most critical variable for the same. LOD is checked periodically to establish this. Carryout drying as per the batch manufacturing record at an inlet temperature NMT 60°C till the LOD in granules comes to 2.0 – 2.5 % w/w outlet temperature is recorded to co-relate the same. After drying, withdraw samples from five places of the FBE bowl and check LOD to confirm uniform drying.

Blending:

Load sifted materials into the Bin Blender except Magnesium stearate as per BMR. Start the blender in inch mode and check for any leakage of material. On ensuring that there is no leakage, blended for 10 minutes. Blend Magnesium stearate along with equal quantity of blend from Bin Blender in double polythene bags as per BMR and load into Blender and blend for 5 minutes and collect the sample from 10 locations. The sample size after lubrication shall be between 200.00 to 600.00 mg.

Sampling and Testing Plan:

Following process parameter was listed for monitoring during the Trail batch for optimization of process paramet

Table 8: Sampling and testing plan of telmisartan

Stage	Process variables	Time	Tests to be performed	Acceptance criteria
Blending	Blending Time	5 minutes (Pre-lubrication)	Blend uniformity & RSD	For information
		5 minutes (Lubrication)	Blend uniformity & RSD	$100.0 \pm 15\%$ RSD NMT 6.0
		Pooled sample	Description, Assay, LOD Bulk density, Angle of repose, Particle size distribution.	As per In-process Specification.

Table 9: Sampling and testing plan of Amlodipine besylate and Hydrochlorothiazide

Stage	Process Variable	Time	Tests to be performed	Approximate Sample Size	Acceptance criteria
Dry Mixing	Mixing time	15 minutes	Blend uniformity&its RSD	3×10 Samples each size194.0-582.0 mg (Die capacity: Approximate die)	For Information
Granulation	Kneading & Binder addition time, Impeller& chopper speed, impeller amperage		Physical observation	NA	NA
Drying	Inlet, Outlet temperature & Drying time	At every 10 min intervals	Loss on Drying	Pooled sample (10g)	2.0 %w/w at 105°C
		At the end of drying		Approx. 5 gm pool from 5 different places of bowl	
Blending	Blending Time	10 minutes (Prelubrication)	Blend uniformity& RSD	3×10 Samples each size195.0-585.0 mg (Die capacity: Approximate die)	For Information
		5 (lubricant)	Blend uniformity & RSD	3×10 Samples each size 200.0-600.0 mg (Die capacity: Approximate die)	$100.0 \pm 15\%$ RSD NMT 6.0%
		Pooled samples	Description, Assay,LOD	25 g	As per In-process Specification.
			Bulk density, tapped density, Angle of repose, Particle size distribution	300 g	

Formulation aspects and optimization

Formulation studies are here divided into two specific areas viz., preformulation studies and formulation aspects and process parameters optimization.

Formulation aspects and process parameter optimization

Solvent aspects

Aqueous Solvents

Telmisartan has poor and pH dependent water solubility in order to enhance its dissolution different alkalizers like Meglumine and sodium hydroxide were used in an appropriate ratio.

Use of excipients

Alkalizers is a substance that serves to reduce acidity in water, then taking it slightly to the other side of the scale, making it a little on the base side. Different alkalizers used are Meglumine and sodium hydroxide. Here sodium hydroxide is strong base which is used to dissolve the drug as the drug is soluble in strong base. Meglumine is used as a basic agent who also helps for dissolving the drug so the desired solubility of the formulation can be achieved.

Binders are widely used for binding. The preferred binder is Povidone.

Diluents are fillers designed to make up the required bulk of the tablet when the drug dosage itself is inadequate to produce this bulk. Commonly used diluents are Lactose, Spray dried lactose, Mannitol, Sorbitol, Sucrose and Microcrystalline cellulose.

Lubricants are agents added in small quantities to tablet and capsule formulations to improve certain processing characteristics. The various lubricants are Magnesium stearate, Steric acid, sodium lauryl phosphate, polyethylene glycol 4000-6000, mineral oil, sodium benzoate.

Process parameters optimization

Air velocity

Minimum fluidization velocity is the air velocity required to produce incipient fluidisation, the transition of the bed from the fixed to the fluidisation state occurs at the point where the pressure drop across the bed is equal to the weight of the bed per unit of the cross sectional area. When solid particles are small in size and of relatively low density then the air velocity should be low so that bed will be fluidized in smooth and even manner. If the solid particles are larger in diameter and higher in density, higher air velocity is required for the fluidization

Temperature

The temperature of inlet air should be kept as low as possible to keep the temperature of the core around room temperature and to increase the amount of drying air to maximum consistent with the capability of the apparatus. Under such conditions, stickiness is reduced.

Spray rate

The spray rate of a binder solution depends on several parameters: (i) the drying air capacity of the machinery, (ii) the mixing intensity of cores, and (iii) the spray area. To get fine spray droplets of approximately 20 μm , an atomization air pressure of about 2.0 to 2.5 bar is sufficient, and the spray rate can be regulated with spray nozzles approximately 1.8 mm in diameter. The binder solution can be fed to the nozzle by a peristaltic pump. The spray rate must be reduced if the level of stickiness is so high that more agglomerates are formed than destroyed in the normal cycle of the movement of the particles in the machinery. If it is not possible to overcome the sticking effects by increasing the drying air capacity or by intensifying the movement of the particles in the machinery, the binder solution should be diluted. Diluted binder solutions can be sprayed at a much higher rate, Diluted coating solutions also give smoother, more uniform spray.

Drying

In Top Spray granulation thin layer of binder solution is atomized on to the surface of the solid particle because of the elevated temperature large volume of air passing over the particles solvent is rapidly removed and drying occurs under the steady state condition. The exhaust temperature should remain relatively constant during the coating process. If during the coating process the exhaust below that set temperature the binder solution rate will increase and the particles may become too wet and aggregation will occur. Conversely if the exhaust temperature from the set exhaust temperature then the chamber condition is dryer then desire and particle attrition may occur.

Formulation consideration

Blending

Blending involves the uniform distribution of Granules. This is followed by mixing of blend with Magnesium stearate (Lubrication) to get good flow and adhesion property of the blend. Mixing speed and time are critical process variables to optimize. If less blending will result in non-uniform granules distribution and poor flow and more blending will result in de-mixing leading to non-uniform granules distribution. To prevent such effects proper blending should be done for uniform distribution of granules.

Compression

- Layer separation
- Layer mixing

Layer Separation:

Separation of the two individual layers is the consequence of insufficient bonding between the two layers during final compression of the bi-layer tablet. Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression of the tablet. Bonding is severely restricted if the first layer is compressed at a too-high compression force.

This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the consequence of lower tablet output. Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed.

Layer mixing:

Machine should be equipped with several blow and suction nozzles, located at carefully determined points around the die table. The combined action of blowing and extracting air allows for very specific powder removal, which is vital to the elimination of cross-contamination or layer mixing.

Table 10: Yield Reconciliation Summary of Trial Batches:

For Trial batch					
Batches	Batch yield		Blending		Compression
Standard Limits	Limit of Batch yield		TEL	AML+HCTZ	96 % - 100 %
			99 % - 100 %	99 % - 100 %	
Trail 1	Actual Yield	Percentage	99.0	96.78	98.61
	Yield		87.30	60.36	147.66
	Theoretical Yield		86.49	58.42	1465.62
	Actual Yield		810g	1.94 kg	2.04 kg
	Non-Recoverable Residues				

Table 11: Yield Reconciliation Summary of Validation Batches:

For Process validation batches					
Batches	Batch yield		Blending		Compression
Standard Limits	Limit of Batch yield		TEL	AML+HCTZ	96 % - 100 %
			99 % - 100 %	99 % - 100 %	
PVR A	Actual Percentage Yield		99.11	96.91	98.73
	Theoretical Yield		87.65	60.68	148.34
	Actual Yield		86.87	58.69	146.34
	Non-Recoverable Residues		780g	1.87kg	1.87kg
PVR B	Actual Percentage Yield		98.91	96.60	97.98
	Theoretical Yield		87.87	60.68	148.55
	Actual Yield		86.92	58.62	145.66
	Non-Recoverable Residues		950g	2.06 kg	2.99kg
PVR C	Actual Percentage Yield		99.09	96.97	97.83
	Theoretical Yield		87.77	60.55	148.42
	Actual Yield		86.98	58.72	145.21
	Non-Recoverable Residues		790g	1.83kg	3.21kg

Process validation

- Three batches of Bilayer tablets of Antihypertensive drugs will be manufactured as described in the batch manufacturing record.

- Current version of standard operating procedures to be followed.

Aim

This is a Prospective validation being performed to establish the efficiency of the new process. Validation will be performed on three consecutive lots or three repetitive process steps.

Objective

To establish documented evidence which provide high degree of assurance that the specific process will consistently produce Antihypertensive drug meeting its predetermined acceptance criteria and quality attributes.

Scope

If any batch fails due to process extrinsic causes or deviation from the batch manufacturing record the batch will be disqualified for validation and next three consecutive batches shall be considered.

Responsibility

Table 12: Data for responsibilities of different departments:

Department	Responsibility
Formulation & Development	Review & approval of Process Validation Protocol. Monitoring of Validation activities.
Production	Execution of Manufacturing & Packing Process.
Quality Assurance	Prepare Review & approval of Process Validation Protocol. Monitoring of Validation activities. Sampling as per the sampling plan of validation protocol.
Quality Control	Carrying out analysis of the sampled samples as per Specification.

Details of lot no. Of validation

Table 13: Details of Validation Lot no. Taken:

S.No.	Validation lots
1	PVR A
2	PVR B
3	PVR C

RATIONALE FOR SELECTION OF CRITICAL STEPS AND ITS PROCESS PARAMETERS FOR VALIDATION

Telmisartan (White) layer

Granulation: The granulation step involves converting the fine powder into free flowing granular mass. The amount of granulating solution added, Inlet & outlet temperature, Atomization, Spray rate are critical variables.

These variables affect the

- Granule strength (fines)
- Bulk density of blend
- Flow characteristics of granules

These in turn affects the quality attributes of tablets like Weight Variation, Hardness, Disintegration Time and Dissolution.

Drying: The drying step involves drying of wet mass. Moisture content in granules, which determines in terms of LOD, is important factor. If moisture content is more in granules, it will lead to poor flow and sticking problem. If moisture is less it will lead to capping, high friability and chipping. Drying is carried out till the desired LOD is achieved. Inlet temperature and Outlet temperature of FBP is most critical variable for the same. LOD is checked periodically at to establish the same.

Blending: This step involves mixing of granules with other excipients and lubricants. The purpose of blending is to get a uniform distribution of Telmisartan. This is followed by mixing of the blend with Magnesium stearate (Lubrication) to get good flow and anti-adhesion property of the blend. Mixing speed and time are critical variables in this process.

Since speed of the blender is constant, time required for proper mixing shall be determined. Mixing time is critical as less blending will result in non-uniform distribution of drug and poor flow whereas more blending will result in de-mixing leading to non-uniform distribution of drug and increase in disintegration time.

Proper blending shall be established by checking content uniformity of drug at predefined time intervals mentioned in protocol.

In addition to this following test shall be carried out for information purpose. This shall be carried out on final time interval samples only.

- a) Water content
- b) Compressibility Index
- c) Bulk Density
- d) Assay
- e) Content uniformity

Hydrochlorothiazide and Amlodipine (Pink) layer

Dry mixing: The dry-mixing step involves mixing of active ingredient with other additives using Rapid Mixer Granulator (RMG). The content uniformity of Amlodipine Besilate and Hydrochlorothiazide established during validation of dry mixing process. The mixing of the active ingredient depends on the mixing time and speed of RMG, which affect the uniform distribution of drug during mixing. Hence it is a critical step to be validated.

Note: The critical steps i.e. Granulation, Drying and Blending are same as Telmisartan layer.

Compression: This step involves conversion of blended material into tablets as per specifications. Speed of machine is major variable. Following physical parameters

are to be checked to establish the above-mentioned variables at regular intervals

- a) Appearance b) Individual Weight variation c) Group Weight variation d) Hardness
- e) Thickness f) Friability g) Disintegration time
- h) Dissolution i) Assay.

Pre-requisites of Process validation:

- The batch shall be manufactured as per current approved respective Master Production document (MPD).
- The equipment utilized for manufacturing & processing of these batches shall be as per list of equipment in MPD & all the equipment shall be qualified.
- Different lots of Active Pharmaceutical Ingredients (API) where possible shall be used for the manufacturing of validation batches. The raw material & packing material used for manufacturing shall be from approved vendors & shall be approved by quality control.
- The critical process parameters of the process shall be evaluated with respect to quality attributes of the product.
- Sampling for in-process control samples shall be carried as per sampling plan.
- Critical in-process control shall confirm to the specification.

Results and Discussion

Processing steps

For telmisartan first layer

Dispensing

- Dispense of Raw material.
- Dispense the materials into double polyethylene HDPE container.

Sifting

- Set up the sifter.
- Sift the material through the specified mesh and collect them separately in clean HDPE container lined with double polythene bags and label them.

Table 14: Granulation material and mesh size

Granulation material	Mesh size
Mannitol	# 40
Lubrication material	Mesh size
Mannitol IP (300 DC)	#30
Magnesium Stearate IP	#60

Drug Binder Solution Preparation

- Take purified water IP in SS vessel.
- Add sodium hydroxide IP and stir slowly until vortex is formed.
- Add meglumine to the vortex followed by the addition of Povidone IP, while stirring continuously till a clear dispersion is formed.
- Add Telmisartan IP to the dispersion, while stirring continuously till a clear dispersion is formed.

- Add polysorbate 80 IP to the solution, while stirring continuously till a clear solution is formed.

Fluid Bed Granulation (Top Spray Granulation)

- Load the sifted material into the top spray bowl of fluid bed processor.
- Pre warm the materials keeping product in between 40°C at fluidization air of 300-750m.
- Spray the drug binder solution on the materials of above step.

Drying

- Dry the wet granules at 50 ±5 °C till LOD reaches NMT 2.0% w/w at 105°C.

Sifting and milling

- Set up the Quadro co mill.
- Set the desired granules through # 30 mesh, collect retentions and # 30 mesh granules separately into polythene bags.
- Mill the retention of above step and transfer it to double lined polythene HDPE container.
- Repeat the sifting and milling till all the materials passes through #30 mesh.

Blending and lubrication

- Load # 30 mesh passed granules with sifted materials except Magnesium Stearate. Ensure that all granules are fully transferred into Bin blender.
- Start the blender & check the leakage of materials. Blend the loaded material for a specified time in a blender at specified rpm.
- Mix Magnesium stearate with equal quantity of blend from blender in double polythene bag for appropriate time and add this back to the blender & blend or specified time at specified rpm.
- Unload the lubricated granules into tarred HDPE container with double polythene bags.

For amlodipine besylate and hydrochlorothiazide second layer

Dispensing

- Dispensing of Raw material.
- Dispense the materials into double polyethylene HDPE container.

Sifting

- Set up the sifter.
- Sift the material through the specified mesh and collect them separately in clean HDPE container lined with double polythene bags and label them.

Table 15: Granulation material and mesh size

Granulation material	Mesh size
Hydrochlorothiazide IP	# 30
Microcrystalline Cellulose IP	#30
Amlodipine Besylate IP	#30
Mannitol IP	#30
Iron Oxide Red	# 30
Lubrication material	Mesh size
Magnesium Stearate IP	#60

Binder Solution Preparation

- Take purified water IP in SS vessel and prepare binder solution using Povidone under stirring.

Dry mixing and granulation

- Set up shear mixture granulator.
- Load sifted dry mixed material into shear granulator and ensure all the materials are fully transferred into shear mixture granulator bowl.
- After addition of sifted materials close the lid of shear mixture then start the impeller at appropriate speed and continue dry mixing for required duration.
- Add binder solution in him stream to the dried mixed powder in a granulator while mixing at specified speed of impeller and chopper for appropriate time.
- Open the lid and scraped the material adhere to the lid and wall.
- Mix the material with impeller and chopper at specified speed for appropriate time.
- Open the lid and observe the granules for appearance, if end point is reached then close the lid and start discharge and unload the granules to FBD bowl.
- Subject it for drying.

Drying

- Set up the FBD.
- Place the FBD bowl containing wet mass under the retarding chamber.
- Air dry the material for appropriate time and rakes the material.
- Dry the material uniformly by raking as and when required at inlet temperature of 60°C till the LOD of granules reaches NMT 2.0% w/w.
- Check the LOD of dried granules.
- Air dry the material for appropriate time after achieving required LOD.

Sifting and milling

- Set up Quadro co Mill.
- Sift the dried granules through #30 mesh, collect retention and #30 mesh granules separately into polythene bags.
- Mill the retention of above step and transfer it to double lined polythene HDPE container.
- Repeat the Sifting and milling till all the materials passes through #30 mesh.

Blending

- Set up the blender.
- Load the # 30 mesh passed granules.
- Start the blender and check the leakage of material.
- Sift Magnesium stearate IP with equal quantity of blend from blender in double polythene bag for appropriate time and add this back to the blender for specified time at specified rpm.
- Unload the granules into tared HDPE container lined with double polythene bags.

Conclusion

The quality system regulation defines Validation by establishing objective, evidence that a critical process control parameter was established and capable to consistently produce a result or product meeting its predetermined specifications.

Validation study was carried out for Antihypertensive drug "Telmisartan, Amlodipine besylate & Hydrochlorothiazide" in Bilayer tablet form and critical process parameters were optimized and established for each unit operations.

The tablets thus formulated were characterized by weight variation, hardness, thickness, disintegration time, friability and in-vitro release studies. Weight variation test was conducted and was calculated 9.712 g (limit 9.800 g $\pm$ 3.0) while hardness was calculated 15kp (limit -10-17 Kp). Thickness was also measured and calculated as 5.50-5.61mm (limit 5.6 $\pm$ 0.3 mm). Disintegration test was conducted, and the time was to be 12 min 05 sec (NMT 15 minutes), while the result of friability test was calculated to be 0.29 (NMT 0.8% w/w). *In vitro* drug release experiments were performed on optimized formulation using IP apparatus 2 (Basket) at 100 rpm in 900 ml of phosphate buffer (pH 7.5) with methanol as dissolution media, maintained at 37 $\pm$ 0.5° C for first layer telmisartan and IP apparatus 1(Paddle) at 75 rpm in 0.01N HCl with methanol as a dissolution media for second layer amlodipine besylate and hydrochlorothiazide. The drug release was calculated to be 101.7% (Limit: NLT 70% of labeled amount is dissolved in 60 minutes) for telmisartan, 93.7 % (NLT 75% of labeled amount is dissolved in 30 minutes) for amlodipine and 99 % (NLT 60 % of labeled amount is dissolved in 60 minutes) for hydrochlorothiazide. The drug release was found within the specification. Stability study was conducted on the optimized formulation at accelerated condition (40 $\pm$ 2°C/75% $\pm$ 5% RH). The tablets were analyzed for weight variation, hardness, friability, disintegration time, drug content and drug release at different time interval for period of 90 days. The assay for telmisartan (NLT 90.0% & NMT 110%) was calculated to be 97.1%-99.8%, for amlodipine besylate (NLT 90.0% & NMT 110%) the assay was calculated 97.00%-104.0% while for Hydrochlorothiazide (NLT 90.0% & NMT 110%) it was calculated 95.00%-101.8%. Results indicated no significant difference. Further there was no change in physical appearance at the end of 90 days storage period at accelerated conditions.

Hypertension or high blood pressure is a chronic medical condition in which the blood pressure in the arteries is elevated. The purpose of this research work was to develop a stable and immediate release bilayer tablet formulation of antihypertensive drugs (Telmisartan,

Amlodipine besylate and Hydrochlorothiazide) and further to study the process optimization studies at different process variables. Telmisartan is one of the components of Angiotensin Receptor Blocker (ARB) and shows high affinity for the angiotensin II type 1 (AT1) receptors. The drug is used to treat high blood pressure (hypertension) by blocking the hormone angiotensin, thereby relaxing blood vessels and causing them to widen. Moreover, telmisartan is a poorly water-soluble drug. Therefore, to improve the solubility and drug release, the drug was converted to its sodium salt form by dissolving it in aqueous solution of sodium hydroxide. Amlodipine is one of the components of dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Hydrochlorothiazide is one of the diuretics of the benzothiadiazine group and has proved very important in the management of mild to moderate hypertension. It inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions. Hydrochlorothiazide is also a poorly water-soluble drug having plasma half-life of 6-8 hrs. Therefore, we have formulated antihypertensive drugs using bilayer technique, which includes top spray granulation (Telmisartan first layer) and wet granulation (Amlodipine besylate and hydrochlorothiazide second layer). Meglumine and Sodium hydroxide were used as an alkalizer, microcrystalline cellulose as diluent while magnesium stearate was used as the lubricant. The prepared granules were compressed into double layer compression machine. In process Optimization, one trial and three validation batches of antihypertensive drugs were manufactured and validated for the parameters of FBE (inlet air temperature, bed temperature, atomization air pressure, peristaltic pump RPM, drive speed/ exhaust blower, air flow {CFM} and spray rate, compression machine (compression speed and compression force).

This research was carried out to produce a Bilayer tablet of antihypertensive drug. The immediate release Bilayer tablet of Telmisartan, Amlodipine besylate & Hydrochlorothiazide (40+5+12.5 mg) was successfully prepared. This combination Therapy indicated for the treatment of severe hypertension & coronary heart disease. Therefore, the purpose of performing optimization study for Antihypertensive drug form facility to provide necessary assurance for consistent quality product has been fulfilled.

The optimization of process showed that there was no significant variation observed during the process variables studied. Therefore, it can be concluded that the process stands optimized and the data can be used to take Commercial batches for regulatory submission to get marketing authorization.

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