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Process validation of Azithromycin Film Coated Tablets

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ABSTRACT

The purpose of research was to study process validation of Azithromycin 250 mg tablet dosage formulation. Tablets were manufactured by wet granulation method. The critical parameters involved in sifting, dry mixing, wet granulation, drying, dry milling, lubrication, compression and coating stages were identified and evaluated as per validation master plan. Uniformity of dry mixing was found to be satisfactory in 15min. For suitable wet mass consistency, slow speed of impeller was maintained during the addition of binder solution for 10 min which was followed by high speed of impeller for 20 min. Drying time of 1 hour was sufficient to achieve % Loss on drying up to 1.5-2%w/w. Uncoated azithromycin tablets were collected at different speeds and different stages and evaluated for their appearance, average weight, diameter, thickness, disintegration time, hardness, friability and assay. Film coating was performed in auto coater and film coated tablets were evaluated for appearance, average weight, diameter, thickness, disintegration time, hardness, friability, dissolution test and assay. Based on results, it can be concluded that Azithromycin tablets can be effectively prepared with the desired specifications and reproducible quality standards. The outcome indicated that process validation data provides high degree of assurance that manufacturing process produces product meeting its predetermined specifications and quality attributes.

Keywords: Process validation, Azithromycin film coated tablet, Control variables

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INTRODUCTION

The validation concept came in mid 1970's in order to improve the quality of pharmaceuticals. Due to the complexity of today's medical products, routine end product testing alone often is not sufficient to assure product quality for several reasons. Also, some end-products tests have limited sensitivity. The pharmaceutical industry uses expensive materials, sophisticated facilities and equipments. The efficient use of these resources is necessary for the continued success of the industry and also for maintaining quality of the product. The cost of product failures, rejects, reworks, recalls, complaints are the significant parts of the total production cost. So process validation is necessary for reducing these types of costs. [1-8]

Validation is defined as follows by different agencies:

Food and Drug Administration (FDA)

Establishing documentation evidence, which provides a high degree of assurance that specific process will consistently produce a product meeting its predetermined specification and quality attributes.

World Health Organization (WHO)

Action of providing that any procedure, process, equipment, activity, material or system actually leads to the expected results.

Benefits of process validation

- Only fewer batch failures and may operate more efficiently with greater output.
- Timely and appropriate validation studies will transmit a commitment to product quality, which may facilitate pre-approval inspection & expedite the granting of marketing authorization.
- Validation makes good business sense.
- Enhanced data and evaluation capabilities and increase confidence about process reproducibility and product quality.
- Improved ability to set target parameters and control limits for routine production.
- It may reduce utility cost and product recall.

MATERIALS AND METHODS:

Azithromycin dihydrate (Century Pharmaceuticals Ltd, Vadodara), Cross carmellose sodium (Ascot PharmaChem Ltd, Nandesari), Doshion P44DB (Doshion Limited, Ahmedabad), Isopropyl alcohol (IPA) (Deepak Fertilizers, Pune), Magnesium stearate (Komal Pharmaceuticals, Vadodara), Microcrystalline cellulose (MCC) (Gujarat Microwax Pvt Ltd,

Ahmedabad), Poly vinyl povidone K30 (PVP K30) (BoaiNky Pharmaceuticals Ltd, China), Sodium benzoate (Navyug Pharma Chem Pvt Ltd, Bhavnagar), Talcum (Gangotri Inorganic Pvt Ltd, Ahmedabad), Ezy white (Colourcon Asia Pvt Ltd, Goa), Yellow oxide of iron (Narmada Colours Pvt Ltd, Bhavnagar), Methylene chloride (GACL Ltd, Vadodara) were used in this formulation. All raw materials used were of IP grade and chemicals used in the analysis were of analytical reagent grade.

Machineries:

Machineries and equipments used were Multi mill (Ganson Ltd, Bombay), Mass mixer (Universal Mechanical Works Pvt Ltd, Bombay), Tray dryer (Veldon Engineers, Bombay), Compression machine 16 station single rotary (Cadmach, Ahmedabad), Auto coater (36'' , Hishore& Co Office, Delhi), UV visible spectrophotometer (Shimadzu Analytical Pvt Ltd, India), Dissolution test apparatus (SP Automatics, Bombay), Monsanto hardness tester (Advance Technology, Mumbai), Disintegration test apparatus(Tab Machines, Bombay) , Friability test apparatus (Campbell Electronics, Bombay), Vernier caliperse (Mitutoyo, Japan), Weighing balance (Jalaram Electronics, Bombay), IR Moisture balance(Rajdhani Scientific Instts Co, New Delhi).

Manufacturing process

Tablets were manufactured by wet granulation method. During manufacturing, temperature should not be more than 30^{o}C and Relative humidity(RH)should not be more than 50% which was maintained by using air conditioner and dehumidifier. Azithromycin dihydrate IP, Microcrystalline cellulose, Crosscarmellose sodium, Sodium benzoate, Doshion P544DB, Polyvinyl povidone(PVP) K30, Magnesium stearate and Talcum were sifted through mechanical sifter from 40 mesh sieve. Dry mix was prepared by mixing Azithromycin and MCC at slow speed in mass mixer for 15 min. Granulating fluid was prepared by mixing PVP K30 and IPA using mechanical stirrer. Granulating fluid was added into the prepared dry mix for 10 min at slow speed of impeller which is followed by mixing for 20 min at high speed of impeller for obtaining desired consistency of dough mass. This mass was passed through multi mill, using 8 mm screen for wet milling. It was then dried in tray dryer at inlet temperature of about 55°C and % Loss on drying of NMT 2% w/w was ensured. Sizing was done by passing dried mass through 30 mesh sieve using multi mill. Magnesium stearate and talcum were added as lubricant into the granules. Tablets were compressed on 16 station single rotary machine, such that each 305 mg tablet contains 250 mg Azithromycin. The specifications for uncoated tablets were average

weight 305 mg (±5%), hardness NLT 2 kg/cm^2, thickness 4.65 mm (±0.05 mm), diameter 9.6 mm (±0.05 mm), friability NMT 1%, disintegration time NMT 15 Min, Assay (100%± 10%).

Film coating of tablets:

Tablets were coated by using Ezy white, colour yellow oxide iron, IPA and methylene chloride. Samples were collected at the end of coating stage. The specifications for film coated tablets were average weight 310 mg (±5%), hardness Not less than (NLT) 2 kg/cm^2, thickness 4.75 mm (±0.05 mm), diameter 9.66 mm (±0.05 mm), friability NMT 1%, DT Not more than (NMT) 30 Min, Assay 100%(± 10%) and dissolution NLT 75% in 45 min.

Process validation stage, control variables and measuring justification

Process validation was carried out using three batches of Azithromycin tablets each of 50,000 batch size. In sifting, sieve integrity was checked before and after sifting. For dry mixing uniformity, the samples were withdrawn at 5, 10 and 15min intervals and analyzed for drug content. In wet mixing, dough mass consistency was evaluated by studying speed of impeller and time of mixing. At drying stage, composite sample was selected for evaluation of % Loss on drying. Moreover, inlet air temperature and total drying time were recorded. In dry screening process, sieve integrity was checked. At lubrication stage, uniformity of mixing was checked for the samples withdrawn from 9 different locations from mass mixer. At compression stage, samples were collected at different speeds (16, 20, 24 RPM) and different stages (Initial, Middle, End)for each batch. These uncoated tablets were evaluated for appearance, weight variation, thickness, diameter, hardness, DT, friability and assay. In case of film coating process, inlet air temperature, outlet air temperature, speed of pan, fanning air pressure and spraying rate were recorded. Film coated tablets were then evaluated for appearance, weight variation, thickness, diameter, hardness, DT, friability, assay and dissolution.

RESULTS AND DISCUSSION

Azithromycin film coated tablets were prepared using wet granulation technique and process validation was carried out for three batches each having batch size of 50,000 tablets at Kaptab Pharmaceuticals, vadodara. Azithromycin film coated tablets were evaluated for process validation parameters like sifting, dry mixing, wet granulation, drying, dry milling, lubrication, compression and coating.

Sifting

The sieve size of 40 mesh was selected for sifting the materials. Integrity of sieve before and after sifting of the materials was found to be satisfactory for all 3 batches.

Dry mixing

Uniformity of mixing was checked by performing assay at 3 different locations at the interval of 5, 10 &15 min. The results shown in Table 1 clearly indicate that the blend uniformity was found between 98.15-98.89 % at 15 min & hence the dry mixing process is satisfactory at 15 min.

Table 1: % Assay during dry mixing

Time (min)	% Assay Batch PVB1			% Assay Batch PVB2			% Assay Batch PVB3		
	T	M	B	T	M	B	T	M	B
05	92.93	93.10	92.98	91.89	92.90	92.87	92.35	92.31	92.46
10	95.54	95.62	96.10	95.78	96.11	95.67	96.12	96.10	95.58
15	98.83	98.56	98.29	98.15	98.66	98.54	98.89	98.25	98.47

PVB1=Process validation batch 1, **PVB2=**Process validation batch 2, **PVB3=**Process validation batch 3 **T=**Top, **M=**Middle, **B=**Bottom

Wet granulation

For suitable dough mass consistency, slow speed of impeller was maintained during the addition of binder solution for 10 min which was followed by high speed for 20 min as shown in Table 2.

Table 2: Critical process parameters (CPPs) during granulation process for all batches

Sr. No.	Process Parameter		Batch PVB1 Batch PVB2 Batch PVB3
1.	Speed of Impeller	At binder addition	Slow speed for 10 minutes
		At mixing	Fast speed for 20 minutes.
2.	Quantity of Granulating fluid		5.4 Kg
3.	Total Granulation time (Granulation)		30 min.

Drying

The drying is critical step as high moisture content may lead to poor flow and sticking problem while low moisture content may lead to capping, high friability and chipping. At drying stage, the %Loss on drying obtained in the sample was 1.6-1.8 % w/w which was found to be within the limit as shown in Table 3.

Table 3: CPP's and Critical quality attributes (CQA's) during Drying process

Sr. No.	Process Parameter	Batch PVB1	Batch PVB2	Batch PVB3
1	Inlet air temperature (55°C to 60°C)	59°C	57°C	57°C
2	Total drying time	1 Hour	1 Hour	1 Hour
3	LOD at 65°C (NMT2% w/w)	1.8%	1.6%	1.6%

Blending and lubrication

At blending and lubrication stage, the samples were drawn at 9 different locations for determining the content uniformity of Azithromycin. The % Relative standard deviation (RSD) values were found between 0.95-1.08 % as shown in Table 4which are well within the limits.

Table 4: % Assay results of Blending and Lubrication stage

Locations	Batch PVB1	Batch PVB2	Batch PVB3	Acceptance Criteria
1.	96.43%	96.35%	96.27%	Assay results should be
2.	96.51%	96.49%	97.32%	between 90.00 % to
3.	95.93%	97.12%	97.96%	110.00% of the labeled
4.	97.10%	98.23%	97.98%	claim.
5.	98.82%	99.10%	98.91%	RSD: NMT 5 %
6.	98.23%	98.54%	98.62%	
7.	97.98%	98.57%	98.85%	
8.	98.16%	97.95%	99.10%	
9.	95.98%	97.99%	99.18%	
Min.	95.93%	96.35%	96.27%	
Max.	98.82%	99.10%	99.18%	
Average	97.23%	97.82%	98.24%	
SD	1.08	0.9587	0.9657	
%RSD	1.11%	0.9800%	0.9830%	

Compression

The compression for all the three batches was validated at different speeds (16, 20, 24 RPM) and different stages of compression (Initial, Middle and end stage). The results for uncoated tablets for appearance, weight variation, thickness, diameter, hardness, disintegration time, friability and assay as shown in Table 5 and 6 were found well within the limits.

Table 5: Results for uncoated tablets at different speed

Speed	Parameter	Batch PVB1	Batch PVB2	Batch PVB3
16 RPM	Avg. Wt.	0.3042 gm	0.3052 gm	0.3043gm
	Diameter*	9.631 mm	9.621 mm	9.630 mm
	Thickness*	4.665 mm	4.666 mm	4.668 mm
	Disintegration time	2 min 30 sec	2 min 45 sec	2 min 36 sec
	Hardness *	5.0 Kg/ cm^2	5.0 Kg/ cm^2	5.0 Kg/ cm^2
	Friability	0.45 %	0.37 %	0.59%
	Assay	98.23 %	98.26 %	98.56%
20 RPM	Avg. Wt.	0.3049gm	0.3039gm	0.3050gm
	Diameter*	9.627 mm	9.622 mm	9.629 mm
	Thickness*	4.661 mm	4.667 mm	4.666 mm
	Disintegration time	2 min 26 sec	2 min 48 sec	2 min 41 sec
	Hardness *	5.0 Kg/ cm^2	5.0 Kg/ cm^2	5.0 Kg/ cm^2
	Friability	0.48 %	0.35 %	0.45%
	Assay	97.98 %	98.52 %	98.72%
24 RPM	Avg. Wt.	0.3045gm	0.3041gm	0.3021gm
	Diameter*	9.632 mm	9.619 mm	9.623 mm
	Thickness*	4.663 mm	4.656 mm	4.666 mm
	Disintegration time	2 min 27 sec	2 min 44 sec	2 min 38 sec
	Hardness *	4.0 Kg/ cm^2	4.5 Kg/ cm^2	4.5 Kg/ cm^2
	Friability	0.46 %	0.38 %	0.51%
	Assay	98.16 %	99.03 %	98.81%

***Average of 10 tablets**

Table 6: Results for uncoated tablets at different stages

Stages	Parameter	Batch PVB1	Batch PVB2	Batch PVB3
Initial	Avg. Wt.	0.3019 gm	0.3035gm	0.3044gm
	Diameter*	9.628 mm	9.633 mm	9.629 mm
	Thickness*	4.668 mm	4.674 mm	4.663 mm
	Disintegration time	2 min 25 sec	2 min 43 sec	2 min 36 sec
	Hardness *	5.0 Kg/ cm^2	5.0 Kg/ cm^2	5.0 Kg/ cm^2
	Friability	0.46 %	0.38 %	0.41%
	Assay	98.26 %	97.82 %	97.36%
Middle	Avg. Wt.	0.3068gm	0.3066 gm	0.3039 gm
	Diameter*	9.618 mm	9.626 mm	9.628 mm
	Thickness*	4.669 mm	4.678 mm	4.664 mm
	Disintegration time	2 min 26 sec	2 min 46 sec	2 min 43 sec
	Hardness *	5.0 Kg/ cm^2	5.0 Kg/ cm^2	5.0 Kg/ cm^2
	Friability	0.48 %	0.39 %	0.47%
	Assay	98.45 %	98.23 %	98.54%
End	Avg. Wt.	0.3075 gm	0.3032gm	0.3019gm
	Diameter*	9.631 mm	9.630 mm	9.623 mm
	Thickness*	4.659 mm	4.665 mm	4.666 mm
	Disintegration time	2 min 23 sec	2 min 42 sec	2 min 39 sec
	Hardness*	4.0 Kg/ cm^2	4.0 Kg/ cm^2	4.5 Kg/ cm^2
	Friability	0.45 %	0.38 %	0.46%
	Assay	98.56 %	99.10 %	98.68%

***Average of 10 tablets**

Film coating

The coating process of all three batches has been validated for inlet air temperature, outlet air temperature, speed of pan, fanning air pressure and spraying rate. Speed of pan was maintained 9 RPM for effective coating. Spraying rate was maintained to between 33 to 35 ml/min/gun. Fanning air pressure 1.5 Kg/$cm^2$was constantly maintained otherwise at lower pressure sticking and picking was observed. The results for all the critical parameters observed during film coating process were shown in Table 7 reveals that all the parameters are within the acceptable limit.

Table 7: Validation of film coating process

Sr. No.	Parameter	Limit	Batch PVB1	Batch PVB2	Batch PVB3
1.	Speed of pan	8-10 RPM	9 RPM	9RPM	9 RPM
2.	Inlet air temperature	70ºC ± 10ºC	73ºC	75 ºC	76ºC
3.	Outlet air temperature	50ºC ± 10ºC	48 ºC	47 ºC	47ºC
4.	Fanning air Pressure	1.0 – 3.0 Kg/cm^2	1.5	1.5	1.5
5.	Spray rate	25-40 ml/min/gun	33	35	35
6.	Total Coating time	To be recorded	5 Hr	5 Hr	5 Hr

Finished product

The film coated tablets were evaluated for appearance, weight variation, thickness, diameter, hardness, disintegration time, friability, dissolution test and assay. The results shown in Table 8 were found well within the specifications.

Table 8: Results for finished product (film coated tablet)

Sr. No.	Parameter	Batch PVB1	Batch PVB2	Batch PVB3
1	Description	Yellow coloured round shaped biconvex, film coated tablet	Yellow coloured round shaped biconvex, film coated tablet	Yellow coloured round shaped biconvex, film coated tablet
2	Wt of 20 tablets	6.2237 gm	6.2169 gm	6.2260 gm
3	Avg. Wt.	0.3112 gm	0.3120 gm	0.3113 gm
4	Diameter	9.69 mm	9.67 mm	9.68 mm
5	Thickness	4.76 mm	4.77 mm	4.77 mm
6	Disintegration time	3 min 23 sec	3 min 33 sec	3 min 21 sec
7	Hardness	5.0 Kg/ cm^2	5.0 Kg/ cm^2	5.0 Kg/ cm^2
8	Friability	0.04 %	0.06%	0.07%
9	Assay	98.12 %	97.98 %	98.63%
10	Dissolution	92.36 %	93.13 %	93.39%

CONCLUSION

Quality cannot be adequately assured by in-process and finished inspections and testing but it should be built in to the manufacturing process. These processes should be controlled in order that the finished product meets all quality specifications. Three batches of Azithromycin viz.,PVB1, PVB2 and PVB3 were taken for performing concurrent process validation. All the critical process parameters, in process results, quality Attributes of intermediate and finished product were well within the approved standard parameters and limits. Therefore, the process for manufacturing Azithromycin film coated tablets can considered to be validated. Thus it provides high degree of assurance that manufacturing process of Azithromycin film coated tablets produces product meeting its predetermined specifications and quality attributes.

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