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Process Validation of Amoxicillin and Clavulanic Acid Immediate Release Tablets by Wet Granulation Method

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Abstract: **The current aim is to study and validate the manufacturing process of amoxicillin trihydrate and potassium clavulanate tablets immediate release tablets. Amoxicillin trihydrate and potassium clavulanate are antibiotic and bet- lactimase inhibitor used in the treatment of pharyngitis/tonsillitis, respiratory tract infections and some microbial infections. The present work was undertaken with a goal to carry out a study on concurrent process validation of antibiotic solid dosage forms for three consecutive batches to prove that system remains in control and the process is capable of consistently produce tablets meeting the predetermined process variables, acceptance criteria and quality attributes. Based on the results of the validation data for three consecutive batches, it is concluded that the manufacturing process used for Amoxicillin Trihydrate and Potassium Clavulanate Immediate Release tablets 625 mg consistently producing the stable product meeting its predetermined specifications and quality attributes. Hence the method employed in the manufacture of Amoxicillin Trihydrate and Potassium Clavulanate immediate release tablets is considered to be validated and can be routinely followed.**

Keywords: **Immediate release tablets, amoxicillin trihydrate, validation.**

I. INTRODUCTION TO VALIDATION

WHO[10] defines Good Manufacturing Practices (GMP) as "that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization." GMP covers all aspects of the manufacturing process: validated critical manufacturing steps; approved written procedures and instructions; records to show all steps of defined procedures have been taken. The guiding principle of GMP is that quality is built into a product, and not just tested into a product. Therefore, the assurance is that the product not only meets the final specifications, but that it has been made by the same procedures under the same conditions each and every time it is made. [1]

Validation is the process of evaluating products or analytical methods to ensure compliance with products or cleaning method requirements. It is a concept that has been evolving continuously since its first formal appearance in 1978 in USA.

Validation (USFDA) is defined as the establishing of documented evidence which provides a high degree of assurance that a planned process will consistently perform according to the intended specified outcomes.

The validity of systems/equipment/tests/processes can be established by prospective, concurrent or retrospective studies.

Types of Validations: Process validation (21CFR211.220) and method validation (21CFR211.222) are two major types recognized. But Cleaning method and utility validations are also another type to be considered for validations.

Process Validation is the establishment and performance of activities required to obtain documented assurance that a manufacturing process or a part thereof- during routine use are correct so that specified requirements on process variables and product properties are compiled.

Qualification: A phase of validation that provide documented verification that any system or equipment works correctly leads to the expected results. Qualifications are divided into four parts. These are:

I. Design Qualifications (DQ). II. Installation Qualifications (IQ).
III. Operational Qualifications (OQ). IV. Performance Qualifications (PQ).

Validation Lifecycle*:* Steps involved in Validation Process are:

1. Validation master plan. 2. Validation protocol. 3. Execution of validation. 4. Validation report
5. Preparation of SOPs

Master Validation Plan*:* It is a document pertaining to the whole facility that describe which will be validated by whom and when. It also provides standards. It also indicates why and when it should be revalidated.

A. PROCESS VALIDATION PROTOCOL OR PLAN

Validation of the individual steps of the manufacturing processes is called Process validation. Different dosage forms have different validation protocols. Process validation establishes the flexibility and constraints in the manufacturing process controls in the attainment of desirable attributes in the drug product while preventing undesirable properties. It is a systematic approach to identify measure, evaluate, document and re-evaluate a series of critical steps in the manufacturing process to ensure a reproducible final product. [2]

USFDA defined process validation as establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality.

Regulatory basis for process validation

There are several important reasons for validating a product or a process.

1) Manufacturers are required to conform to cGMP (current Good Manufacturing Practices) regulations.
2) Good business dictates that a manufacturer avoids the possibility of rejected batches.

It provides a synopsis of what is hoped to be accomplished.

It should list,

1) Selected process. 2) Control parameters. 3) State the no. of batches to be included in the study. 4) Specify how the data, once assembled, will be treated for relevance. 5) Date of approval by the validation team should also be noted.

Validation report

A document in which the records, results and evaluation of a completed validation programs are assembled. It may also contain the proposals for the improvement of process or equipment

B. TYPES OF PROCESS VALIDATION

1. Prospective validation: Validation conducted prior to the distribution of either a new product or product made under a revised manufacturing process. This form of validation is necessary in order to limit the risk of errors.

2. Retrospective validation: Validation of a process for a product already in distribution based upon accumulated production, testing and control data. In the approach based on the analysis of the historical data, no experiments are performed in retrospective validation, but instead all available historic data concerning a no of batches are combined and jointly analyzed.

3. Concurrent validation: In process monitoring of critical processing steps and end product testing of current production is involved in concurrent validation. It is similar to prospective validation except the operating firm will sell the product during the qualification runs, to the public at its market price.

4. Revalidation: It is the repetition of a validation process or a part of it. It is carried out when there is any change or replacement in formulation, equipment plan or site location, batch size and in case of sequential batches that do not meet product specifications and is also carried out at specific time intervals in case of no changes. Revalidation is needed to ensure that changes in the process or in the process environment, whether intentional or unintentional, do not adversely affect the process characteristics and product quality. [3]

Revalidation may be divided into two broad categories:

1) Revalidation after any change having a bearing on the product quality.
2) Periodic revalidation carried out at scheduled intervals.

Prerequisites for process validation

Before process validation can be started, manufacturing equipment and control instruments as well as formulation must be qualified. This involves pre-formulation studies, incompatibility of active ingredients and excipients and of final drug products and packaging material, stability studies.

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Approaches: The experimental approach, which is applicable to both prospective and concurrent validation may involve:
Extensive product testing: One of the most practical forms of process validation, mainly for non-sterile products is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling. Several hundreds of tablets may be weighed to determine unit content uniformity. The results are then treated statistically to verify the normality of the distribution and to determine the standard deviation from the average weight.
Challenge/worst case trials: Challenge experiments are performed to determine the robustness of the process. It makes possible to estimate the extent to which the process is still capable of producing an end product that meet the specifications.
Controls of process parameters: The physical parameters of the process are monitored in the normal production process to obtain additional information on the process and its reliability. A tabletting press equipped with pressure sensitive cells will be helpful in collecting statistical data on the uniformity of the die-fill and therefore on mass uniformity.

C. VALIDATION OF MIXING PROCESS

Materials that have similar physical properties will be easier to form a uniform mix or blend and will not segregate as early as materials with large differences.
Parameters:
Mixing technique*:* Diffusion or pneumatic or convection techniques can be used. The technique may be different depending upon whether you are mixing the drug and excipient for a direct compression or adding the lubricant (magnesium stearate) to the granulation.
Mixing speed: Determine the intensity (low/high shear/optimal shear) (RPM) of mixing or blending. Mixing the drug and excipient requires more intense mixing than adding the lubricant to the final blend.
Mixing time: It should be known how much mixing or blending is required to get uniform mix. It depends on the mixing technique and time. Experiments should be done to determine if the materials can be over mixed, resulting in demixing or segregation of the materials. For example, demixing can occur in a direct compression formulation in which the drug substance is micronized and the excipients are granular.
Drug uniformity: Content uniformity is usually performed to determine the uniformity of the drug throughout the mix or blend. To determine the uniformity of the drug throughout the mix, representative samples should be taken throughout the mix. The sampling techniques and handling of materials are key in obtaining valid content uniformity results. For the final blend (blend prior to compression), the sample taken should be equivalent to the weight of the single tablet.
Excipient uniformity: Besides drug uniformity, excipients need to be uniform in the granulation or blend.
2 key excipients are:
1. Lubricant: The lubricant need to be distributed uniformly in the mixture for the high speed compression operation. The uneven distribution of the lubricant results in picking and sticking problems during compression.
2.Colour: Need to be uniformly distributed to have uniform appearance to avoid speckling or shading of the colour. The colouring agent may need to be pre-screened or more uniformly dispersed in the blend prior to compression. [4]

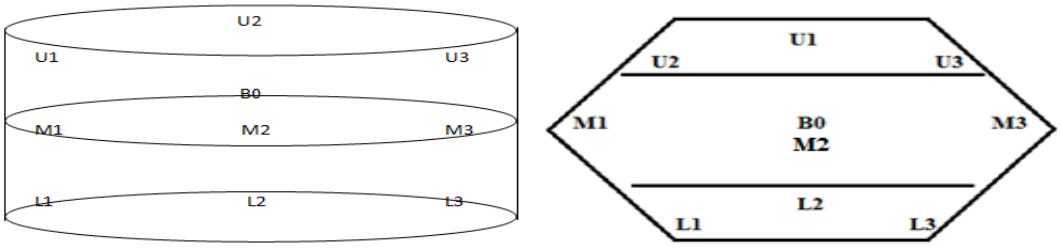

Fig 1 : Sampling ponts of simple mixer and octagonal blender

D. VALIDATION OF WET GRANULATION PROCESS

Granulation may be of low shear or high shear or fluid bed. Each technique will produce granules of different physical properties and will require monitoring of different processing parameters.
Parameters:

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Binder addition: It should be validated for the binder to be added as a either in solution or dry form. Adding the binder dry avoids the need to determine the optimal binder concentration and a separate manufacture for the binder concentration.

Binder concentration: The optimal binder concentration will need to determine for the formulation. If the binder is to be sprayed the binder solution need to be diluted enough so that it can be pumped through the spray nozzle. It should be sufficiently concentrated to form granules without over wetting the materials.

Amount of binder solution: The amount of binder required to granulate the material is validated. Too much binder will over wet the materials and prolong the drying time. The amount of binder solution is related to the binder concentration.

Binder solution addition rate: It should be defined the rate range at which the binder solution can be added to the materials and if the granulating solvent be dumped into the mixer or does it have to be metered in at a specific rate.

Mixing time: The material has to be mixed to ensure the proper formation of the granules. It should be validated if the mixing can be stopped after the addition of the binder or should additional mixing be required. Granulations that are not mixed long enough form incomplete granules that have poor flow and compression properties. Over mixing the granulation can lead to harder granules and lower dissolution rate.

Granulation end point: Whether it is controlled by granulation end point equipment (ammeter or wattmeter) or if it is controlled by specifying critical process parameters has to be validated. The granulation is completed after mixing for a set time after the water has been added. [5]

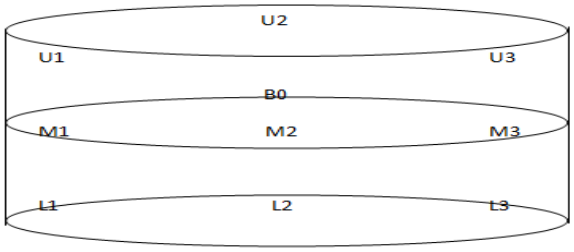

Fig : 2 Sampling Points

E. VALIDATION OF DRYING PROCESS

Type of drying technique (tray, fluid bed, and microwave) required for the formulation need to be determined and justified. The technique is dependent on drug or formulation properties and equipment availability. Changing dryer techniques could affect such tablet properties as hardness, disintegration, dissolution or stability. The optimal moisture content of the dried granulation needs to be determined.

High moisture content can result in

1) Picking and sticking to tablet punch surfaces.
2) Poor chemical stability as a result of hydrolysis.

An over dried granulation can lead to poor hardness and friability.

Parameters:

Inlet/outlet temperatures: Inlet temperature is the temperature of the incoming air to the dryer, outlet temperature is the temperature leaving the unit. Inlet temperature is critical to the drying efficiency of the granulation and should be set high enough to maximize drying without affecting the physical and chemical stability of the granulation. The outlet temperature is the indicator of the granulation temperature and will increase toward the inlet temperature as the moisture content of the granulation decreases.

Airflow: There should be sufficient airflow to ensure removal of moisture laden air from the wet granulation. Insufficient air flow could prolong the drying and affect the chemical stability of the drug.

Moisture uniformity: Heat uniformity of the dryer, amount of granulation of the tray and incomplete fluidization of the tray are the factors that could affect the moisture uniformity of the drug.

Equipment capability/capacity: A larger load will require more moisture to be removed from drying and will affect the drying time. In case of fluid bed drying, a maximum dryer load is that load above which the dryer will not fluidize the material. [6]

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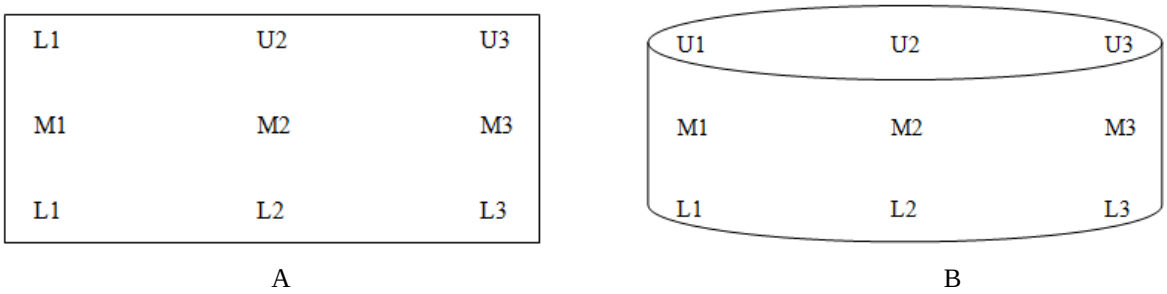

Fig : 3 Sampling Points In A: Vaccum Tray Drier And B: Fluid Bed Drier

F. VALIDATION OF COMPRESSION PROCESS

The materials being compressed will need to have adequate flow and compression properties. The material should readily flow from the hopper onto the feed frame and into the dies. Inadequate flow can result in rat holing in the hopper or segregation of the blend in the hopper /feed frame. This causes tablet weight and content uniformity problems.
Tooling: Shape, size and concavity of the tooling should be examined based on the formulation properties and commercial specifications.

Compression speed: Compression ejection force and the compression profile for the table formulation will need to be determined to establish the optimal compression force to obtain the desired tablet hardness. [7]

II. MATERIALS AND METHOD

TABLE I: MATERIALS AND SOURCE

INGREDIENT	BRAND NAME	MANUFACTURER
Amoxicillin Trihydrate	Powder grade	Aurobindo pharma
Potassium Clavulanate	Powder grade	Aurobindo pharma
Crosspovidone USNF	Polyplasdone XL10	ISP technologies
Sodium Starch Glycolate	Primojel	DMV international
Hydroxy propyl cellulose	Klucel	Colorcon Asia
Micro crystalline cellulose	Avicel PH101	FMC Biopolymer
Collidal silicon dioxide	Aerosil	Degusser
Magnesium sterate USNF	-	Ferro industrial chemicals
Hypromellose USP	Methocel E5LV	Colorcon asia
Polyethylene glycol USNF	Polyglycol 4000 PF	Clariant
Titanium dioxide	-	Kronos internation

TABLE II: MANUFACTURING FORMULA

S.NO	RAW MATERIAL	UNITY QUNTITY
1	AMOXICILLIN USP	573.920
2	MICROCRYSTALLINE CELLULOSE	189.3
3	CROSSPOVIDINE	18.589
4	SODIUM STARCH GLYCOLATE	8.400
5.	HYDROXY PROPYL CELLULOSE	10.570
6	CLAVUNATE POTASSIUM	145.8
7	AEROSIL	10.189
8	MAGNESUIM STERATE	10.189
9	PURIFIED WATER	Q.S

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TABLE III: MANUFACTURING EQUIPMENTS

S.NO	EQUIPMENT NAME	COMPANY NAME	CAPACITY
1	VIBRATORY SIFTER	----	BECTOCHEM
2	RAPID MIXER GRANULATOR	1200 LTRS	GANSONS
3	FLUID BED DRYER	450 KG	GANSONS
4	OSILLATING GRANULATOR	--------	SRUTHI
5	VACCUM TRAY DRYER	48 TRAYS	GROOVERS
6	OCTAGONAL BLENDER	2250 LTRS	BECTOCHEM

A. PROTOCOL FOR BLEND

BRIEF MANUFACTURING PROCEDURE:

1. SIFTING :

- Sift amoxicillin through # 14 sieve (1400 microns) on vibratory sifter and collect in a clean preloaded in process container.
- Sift microcrystalline cellulose through # 40 sieve (425 micrns) on vibratory sifter and collect in a pre labelled in – process container
- Sift crosspovidine through # 40 sieve (425 microns) on vibratory sifter and collect in clean pre labelled in process container
- Sift sodium starch glycolate through # 40 sieve (425 microns) on vibratory sifter and collect in clean pre labelled in process container

2. DRY MIXING :

- Load the sifted amoxicillin ,microcrystalline cellulose , crosspovidone and sodium starch glycolate in rapid mixer granulator and mix for ten minutes with impeller at slow speed .

3.GRANULATION :

- Dilute the hydropropyl cellulose in 73.728 kg of purified water and stir continuously to form uniform solution
- Add the diluted hydropropyl cellulose to dry mixer over a period of 2-3 minutes with impeller to form a uniform solution
- Knead the wet mass for not more the 12 minutes with both impeller and chopper at fast speed
- Knead the wet mass for 1 min or more with impeller and chopper at slow speed
- Check and record the amperage reading of impeller and chopper at the granulation and point .

4.DRYING :

- Air dry the wet granular mass for 5 minutes to ensure proper fluidization in fluid bed drier and dry the wet mass at an inlet temperature of 50 ± 5^0 C in fluid bed drier. Continue the drying with intermittent raking NMT 15 mins of drying till the LOD is achieved between 11.0-13.5 % w/w on IR moisture balance in auto mode at 105 ^{0}C

5.SCREENING AND SIFTING THE DRIED GRANULES :

- Screen the dried granules using Oscillating granulator with 1.00mm screen at medium speed .
- Sift the screened materials of above through #18 sieve and ensure all the material through #18 sieve . check the water activity of screened & sifted granules .

6.DRYING OF SCREENED AND SIFTED GRANULES :

- Load the material in to the separate tray drier . load the filled trays into vaccum trat drier and dry for 30 mins or more at 50 ± 5 C to get the water activity of the tray dried materials less than 0.10 using water activity analyzer .
- Unload the material from Vaccum tray drier and collect the material in double polythene laminated bag with 20gm molecular sieve desiccant in every bag and seal.

7.DRYING OF EXTRA GRNULAR MATERIAL :

- Load the material of the crosspovidone , colloidal silicon dioxide and magnesium striate on to the separate trays of vaccum tray drier .
- Load the filled trays into vaccum tray drier and dry for 30 mins or more at 55±5^0C of the cabinet temperature to get the water activity of dried materials less the .010 using water activity anlalyzer .
- Unload the material from vaccum tray drier and collect the material in double polythylene lined ,triple laminated bag with 20 gm of molecular sieve desiccant every bag and heat seal.

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8.SIFTING OF EXTRA GRANULAR MATERIAL :

- Sift the clavulanate potassium + microcrystalline cellulose (1:1) ,dried crosspovidone and dried colloidal silicon Dioxide through #40 sieve (ASTM 425) and collect in double polythene lined , triple laminated bag and heat seal .
- Sift together the sifted material of above material and about 50% of screened and sifted granules of step 6 through #18 sieve (ASTM, 1000 microns) and collect in double pollythene lined, triple laminated bag and heat seal .
- Sift together the sifted material of above step and remaining granules of dried and screened of step 6 through #18 sieve (ASTM 1000 microns) and collect in double polythene lined triple laminated bag and heat seal.
- Resift the sifted materials of above step through #18 sieves (ASTM 1000 microns) and collect in double polythene triple laminated bag and heat seal.
- Sift the Dried Magnesium stearete through #60 sieve (ASTM 250) and collect in double polythene triple laminated bag and heat seal.

9.BLENDING AND LUBRICATION :

- Load the sifted granules of step 8 into the octagonal Blender and blend for 10, 15, 20 mins at 6 RPM.
- And magnesium stearate material to the above granules and mix for 2, 5 mins at 6 RPM.
- Check the AW (water activity) of blend it should be less than 0.1.
- Unload the lubricated granules into double lined poly bag in triple laminated aluminium bag in containers. First tie the inner polybag and outer tightly laminated aluminium bag in containers.

10. BLEND SAMPLE ANALYSIS:

- Send the samples for analysis.

TABLE IV: PROTOCOL FOR TABLET AND COATING

SNO	EQUIPMENT NAME	CAPACITY	MAKE
1	Compression machine	51 stn	Sejong
2	Metal detector & de duster	-	sejong
3	Colloid mill	-	Unipharma
4	Coating machine	66”	Sejong
5	Tablet thickness sorter	--	Pam
6	Tablet sorter	--	Pam

B. PROTOCOL FOR COMPRESSION AND COATING:

The process validation report Amoxicillin and Clavulanate potassium blend 500/125 mg presents the results of process validation study performed on the three consecutive batches due to additional compression machine sejong 51 station double rotary tablet press and coating machine sejong 66” was used for the compression and coating of tablets . Which were manufactured as per batch processing record, batch number 1, 2, 3 with batch size of 950000 tablets 921.500 kg. These report asses the data obtained during this process validation study.

Samples were collected and analyzed as per process validated protocol. The analytical results of compressed and coated were meeting the specified limits. Coated tablets dissolution profile was compared in three batches. Finished product was analyzed as per product release specification and found to be complex with specification and assure that the manufacturing process is reproducible, yielding a considered product, which meets specification.

Based on data generated and presented quality of subsequent batches can be predicted with a higher degree of assurance to consistently meet the desire quality attributes.

III.RESULTS

TABLE V: WATER ACTIVITY OF BLEND AFTER DRYING USING WATER ACTIVITY ANALYZER

S.NO	BATCH 1	BATCH 2	BATCH 3
1	0.03	0.09	0.02
2	0.02	0.05	0.06
3	0.04	0.02	0.03

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TABLE VI: BLEND UNIFORMITY DATA : FOR 20 MINS (6RPM)

BATCH NO LOCATION	BATCH 1		BATCH 2		BATCH 3	
	AMOXICILLIN	CLAVULANIC ACID	AMOXICILLIN	CLAVULANIC ACID	AMOXICILLIN	CLAVULANIC ACID
U1	101	91.2	92.2	105.5	93.2	94.3
U2	102.2	95.5	96.5	100.2	95.2	93.2
U3	102.1	95.5	92.0	102.3	99.2	101.3
M1	99.5	96.3	93.5	94.2	95.5	98.3
M2	96.3	98.3	95.3	95.1	93.3	94.6
M3	100.5	98.2	97.5	91.3	98.3	94.2
L1	97.5	96.3	97.1	94.3	91.8	98.6
L2	95.6	94.5	93.6	97.5	95.5	93.3
L3	97.3	95.4	96.3	93.2	96.8	94.2
B0	99.3	94.3	92.3	94.6	98.1	101.2
MEAN	99.13	95.55	94.63	96.82	95.6	96.32
MINIMUM	95.6	91.2	92.0	91.3	91.8	93.2
MAXIMUM	102.2	98.3	97.5	105.5	99.2	101.3

ACCEPTENCE LIMIT : Blend uniformity 90.0 – 110.0 %

TABLE VII: DATA/ OBSERVATIONS OF PROCESS CAPABILITY RESULTS OF BLEND UNIFORMITY AFTER ADDITION OF LUBRICANT

BATCH NO LOCATION	BATCH 1		BATCH 2		BATCH 3	
	AMOXICILLIN	CLAVULANIC ACID	AMOXICILLIN	CLAVULANIC ACID	AMOXICILLIN	CLAVULANIC ACID
U1	109.3	93.3	94.5	108.8	95.6	96.3
U2	104.5	98.5	98.5	102.5	99.6	97.6
U3	103.9	100.0	96.6	108.5	97.3	102.5
M1	104	99.5	96.3	96.5	97.5	99.6
M2	101.7	98.6	97.6	97.5	96.3	98.2
M3	102	99.5	98	96	99.2	96.5
L1	98.5	97.3	99.3	96.3	98.4	99.1
L2	98.2	99.6	98.6	99.2	97.2	96.3
L3	99.1	97.2	98.3	94.2	99.6	97.2
B0	101	105	98.3	98.5	99.2	103.2
MEAN	102.2	98.8	97.6	99.8	97.99	98.65
MINIMUM	98.2	93.3	94.5	94.2	95.6	96.3
MAXIMUM	109	105	99.3	10.8	99.6	103.2

ACCEPTENCE LIMIT : Blend uniformity 90.0 – 110.0 %

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TABLE VIII: WATER ACTIVITY OF BLEND AFTER LUBRICATION USING ANALYZER

S.NO	BATCH 1	BATCH 2	BATCH 3
1	0.02	0.04	0.03
2	0.01	0.03	0.05
3	0.04	0.02	0.04

ACCEPTANCE LIMIT: water activity (A_w) shoulb less than 0.1

TABLE IX: ACCEPTANCE CRITERIA FOR COMPRESSION

PARAMETERS	SPECIFICATION
Appearance	White to off white oval shaped tablets , debossed with X on side and 33 on the other side
Average weight	970.00 mg ± 2 % (950-989.40mg)
Thickness	6.90±0.30 (6.60-7.20mm)
Hardness	16.0-22.0 kp
Disintegration	NMT 10 mnts
Friability (%w/w)	NMT 1.0 %
Uniformity of weight	970.00±5% (921.50-1018.50 mg)
Uniformity of dosage units for amoxicillin For clavulanic acid	Not more than 15.0 % Not more than 15.0 %
Water activity	Not more than 0.10
Dissolution profile	Not more than 30 mins

TABLE X: COMPRESSION PARAMETERS : BATCH I

PARAMETERS		INTIAL
Speed		10
Appearance		Complies
Average weight (mg) (950.60-989.40)		975.31
Thickness (mm) (6.60 – 7.20)		6.77-6.86
Disintegration time NMT 10 MINS		9 MINS 21 SECONDS
Friability (% w/w) (NMT 1.0 %)		0.1
Uniformity of weight (mg) (921-1018.50)		948 to 985.87
Water activity (NMT 0.10)		0.083
Uniformity of dosage units (NMT 15.0 %)	For amoxicillin	4.0
	For clavulanic acid	2.3

TABLE X1: BATCH II

PARAMETERS		INTIAL
Speed		20
Appearance		Complies
Average weight (mg) (950.60-989.40)		970.8
Thickness (mm) (6.60 – 7.20)		6.73-6.81
Disintegration time NMT 10 MINS		09 MINS 24 SECONDS
Fraiability (% w/w) (NMT 1.0 %)		0.1
Uniformity of weight (mg) (921-1018.50)		948.39 to 990.44
Water activity (NMT 0.10)		0.080
Uniformity of dosage	For amoxicillin	4.2

units (NMT 15.0 %)	For clavulanic acid	1.9

TABLE XII: BATCH III

PARAMETERS		INTIAL
Speed		15
Appearance		Complies
Average weight (mg) (950.60-989.40)		97011
Thickness (mm) (6.60 – 7.20)		6.70-6.80
Disintegration time NMT 10 MINS		09 MINS 32 SECONDS
Fraiability (% w/w) (NMT 1.0 %)		0.1
Uniformity of weight (mg) (921-1018.50)		946.68 to 1001.99
Water activity (NMT 0.10)		0.083
Uniformity of dosage units (NMT 15.0 %)	For amoxicillin	3.9
	For clavulanic acid	2.8

TABLE XIII: DISSOLUTION PROFILE FOR SPEED TRAILS DURING COMPRESSION

Batch number	**Batch I**		**Batch II**		**Batch III**	
	Amoxicillin	**Clavlanic acid**	**Amoxicillin**	**Clavulanic acid**	**Amoxicillin**	**Clavlanic acid**
5	43.2	41.3	42.5	40.5	44.7	43.5
10	61.4	65.5	63.4	62.5	65.3	62.5
15	81.6	83.7	80.5	82.5	82.4	83.5
20	99.5	101.4	98.7	99.5	101.2	98.7

DATA / OBSERVATION OF COATING OPERATION :

BATCH NUMBER : BATCH I , BATCH II, BATCH III

TABLE XIV: ACCEPTANCE CRITERIA

PARAMETER	**SPECIFICATION**
Appearance	White coloured , oval shaped , film coated tablets debosed with ' **X** ' on one side and '**33**' on the other side
Average weight	991.825 mg ± 2 % (971.989 mg – 1011.662 mg)
Thickness	7.00 ± 0.30 mm (6.70 – 7.30 mm)
Uniformity of weight	991.825 mg ± 5 % (942.234 – 1041.416)
Water activity	Not more than 0.10
Dissolution profile For amoxicillin For clavulanic acid	Not more than 30 mins

TABLE XV: DATA / OBSERVATION OF COATING

Parameters	**Batch I**	**Batch II**	**BATCH III**
Inlet temperature [55 ± 5C]	58.2 – 58.6	554.8 – 58.9	54.5 – 58.6
Outlet temperature [45 – 49 C]	46.1 – 47.6	46.3 – 47.6	46.6 -47.5
Exhaust air RH [<10 %]	6.5 – 7.8	6.3 – 7.7	6.2 – 7.4
Pan rpm	1.5 – 2.3	1.6 – 2.2	1.5 – 2.3
Atomizing air pressure [MPA]	0.3	0.3	0.3
Spray rate [gm/min]	45	45	45
Distance between bed and spray gun	9 inch	9 inch	9 inch
No of guns used	4	4	4
% weight build up	2.41	2.32	2.40

Quantity of suspension prepared[kg]	65	65	65

TABLE XVI: DATA OBSERVATION AFTER COATING

PARAMETER	BATCH I	BATCH II	BATCH III
Appearance	Complies	Complies	Complies
Average weight	1001.43	1001.21	995.16
Uniformity of weight	964.63 – 1023.33	969.15 – 1032	977.15 – 1027
Thickness	6.81 – 6.89	6.79 – 6.84	6.74 – 6.82
Water activity	0.081	0.081	0.082

TABLE XVII: DISSOLUTION PROFILE: COATED TABLETS

Dissolution time	**Batch I**		**Batch II**		**Batch III**	
	Amoxicillin	Clavulanic acid	Amoxicillin	Clavulanic acid	Amoxicillin	Clavulanic acid
10 mins	Avg 65.2% [63 - 71]	Avg 67.5% [64.5-72.5]	Avg 61.5% [53.1-72.3]	Avg 63.7% [55.7-71.4]	Avg 62.4% [54.2-72.3]	Avg 62.4% [57.5-71.8]
15 mins	Avg 84.3% [81-86.2]%	Avg 86.2% [82.1-87.1]	Avg 81.4% [79.5-84.5]	Avg 83.2% [80.1-83.5]	Avg 82.5% [81-84.2]	Avg 83.2% [80.5-84.7]
20 mins	Avg 98.3 [93.2-100.3]	Avg 97.7 [94.6-98.5]	Avg 97.5 [94.2-98.2]	Avg 97.6 [94.4-98.3]	Avg 98.7 [94.3-99.5]	Avg 98.2 [96.2-103.2]

TABLE XIX: DISSOLUTION PROFILE COMPARISION

Time	Amoxicillin				Clavulanic acid			
	Batch X	Batch I	Batch II	Batch III	Batch X	Batch I	Batch II	Batch III
10 mins	63.4	65.2	61.5	62.4	64.2	67.5	63.7	62.4
15 mins	83.5	84.3	81.4	82.5	85.5	86.2	83.2	82.5
20 mins	98.5	98.3	97.5	98.7	97.2	97.7	97.6	98.2

TABLE XX: YIELD RATE

Batch no	**After compression**		**After coating**	
I	98.83	97-100 %	98.7	97.0-100 %
II	98.03	98.0-100%	97.00	97-100 %
III	98.28	98.0-100 %	97.13	97.0-100 %

TABLE XXI: FINISHED PRODUCT ANALYTICAL DATA

S.No	**Test**	**Finished product specification**	**Batch number**		
			I	**II**	**III**
1	Description	White off white oval shaped,film coated tablets,debossed with X on side	Compiles	Compiles	Compiles
2	Identification By TLC By HPLC	The Rf value of principal spots in the chromatogram obtained from test solution should correspond to that obtained from standard solution The retention time of major peak in the chromatogram of the sample solution should correspond to that in the	Compiles	Compiles	Compiles

		chromatogram of the standard solution as obtained in assay	Compiles	Compiles	Compiles
3	Average wt	991.83 ± 3.0% [962.08 – 1021.56 mg]	996.57	995.6	994.5
4	Dissolution (by HPLC) Amoxicillin Clavulanic acid	Not less than 85% of the labeled claim dissolved in 20 mins Not less than the 80% of labeled amount ofclavulanic acid dissolved in 20 mins	93.1-99.4% 96.3-100.4	97.7-100.4 100-102.5	92.8-100.2 94.1-97.3
5	Uniformity of dosage for Amoxicillin Clavulanic acid	 Not more than 15% Not more than 15%	 6 1.8	 4.8 5.4	 6.8 1.8
6	Water activity	Not more than 10 %	8.45	8.56	8.42
7	Assay (hplc) Amoxicillin trihydrate Clavlanic acid	450 – 550 mg 90.0 % - 110 % 112.5 mg – 137 mg 90.0 % - 110 %	504.7 mg 100.9 % 125 mg 100.0 %	501.0 mg 100.2 % 124.5 mg 99.5 %	502.0mg 100.3% 122.2 mg 97.8 %
8	Thickness	7.00 mm ± 0.30 mm (6.70 – 7.30 mm)	Min 6.7 Max 6.9	Min 6.8 Max 6.9	Min 6.7 Max 6.9

IV. DISCUSSION

The results of blend uniformity at 6 RPM for 20 mins meets the acceptance criteria for all the three batches . So the blending of material in octagonal blender for 20 mins at 6 RPM produces a product which meets acceptance criteria. The addition of lubricant to the material and blending for 5 mins at 6 RPM produces a product which meets acceptance criteria. Water activity results after blending and lubrication stage found to be well within the specification limit in three batches. The compression done at 10 and 20 RPM about half an hour at each speed and the remaining blend was compressed at optimum speed (15 RPM). Second and third batches were compressed at optimum speed (15 RPM). The samples were collected as per protocol and analyzed. Physical and chemical/analytical parameters were found complying with the specified limits. Dissolution profile was comparable at compression stage in all three batches. Coating was performed as per procedure. The percentage mass build up was found to be 2.20-2.42 % w/w in all the three batches. Physical and analytical parameters of coated tablets comply with the specification limit. Coated tablets dissolution profile was comparable in all the three batches. The percentage amount dissolved at 30 mins time point was found meeting the finished product specification requirement of NLT 85 % (Q) of amoxicillin and NLT 80 % (Q) of LA for clavulanic acid in all three batches.

V. CONCLUSION

Process validation of Amoxicillin Trihydrate and Potassium Clavulanate tablets 625 mg, batch No. 1,2and 3 has been carried out as per approved validation protocol and sampling plan and no deviations were found. Hence the method employed in the manufacture of the given product is considered to be validated and can be followed.

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