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PROCESS VALIDATION OF THE AZITHROMYCIN TABLETS 500 MG

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ABSTRACT
Azithromycin achieves prolonged, high tissue concentrations in spite of low serum levels and obviously must be active at tissue sites of infection to be effective. Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an ever increasing interest in validation owing to their industry's greater emphasis in recent years on quality assurance program and is fundamental to an efficient production operation. The angle of repose was calculated by using the equation. it ranged from 21-30. The compressibility index of all ingredients were determined by equation. It ranged from 1-20. The Hausner's Ratio of all ingredients were determined by equation. It ranged from 1 – 1.50. Prepared tablets ware evaluated for post compression parameters like thickness and diameter, hardness, friability, disintegration time, drug content. Thickness and diameter of tablets were accurately measured by using digital Vernier caliper for desired uniformity in size and shape. Active concentration and prolonged retention of azithromycin by phagocytic cells should allow delivery and subsequent release of accumulated drug at sites of infection. Process Validation of batches has been completed. The results of batches was found well within the defined limits.

KEYWORDS: Pharmaceutical Drug, Azithromycin, Validation, Process Validation.

INTRODUCTION
Drug is a medication or substance used to treat or forestall illness. "Any medication or planning that is utilized to treat and fix illness," "a substance used in treating a sickness or facilitating torment," as depicted by Britannica, as per the Pharmaceutical dictionary.[1]

Public Cancer Institute's definition Tablets, cases, fluids, salves, and fixes that contain at least one dynamic or latent substances are instances of measurements structures. Medications can be directed in various ways, including orally, intravenously, or topically through drops in the ear or eye. A fake treatment is a medication that is utilized in research tests yet doesn't have a functioning part. otherwise called a medication item.

BDS Medication Administration Curriculum, Section II cases that "A prescription is a synthetic that is ingested or utilized topically to treat, forestall, or reduce the side effects of an infection. A particular disease is forestalled by inoculations.

As per EU regulation, a "restorative item" is any substance or mix of substances that is publicized as having properties for treating or forestalling illness in people "any substance or blend of substances that might be utilized in or directed to people fully intent on making a clinical conclusion or of reestablishing, changing, or remedying physiological capabilities through pharmacological, immunological, or metabolic activity.[2]

Process validation
When a lead compound has been found through the course of medication revelation, the course of medication improvement is utilized to acquaint a clever drug with the market. It involves pre-clinical examination involving microorganisms and creatures as well as clinical investigations on individuals. It might likewise include getting administrative endorsement to showcase the treatment.[3]

Process approval is the assessment of data got during the item's plan and creation to assess whether the cycle can reliably deliver products that satisfy a foreordained guideline. Rules for process approval have been laid out by administrative associations like the FDA and EMA.[4] The objective of cycle approval is to affirm that a scope of data sources bring about dependable, great results. As assembling input is gotten, process approval is a persistent cycle that should be frequently changed. Since completed item assessment isn't generally dependable, start to finish approval of creation processes is significant to assessing item quality. Process configuration, process capability, and progressing process confirmation are the three stages that make up process approval.

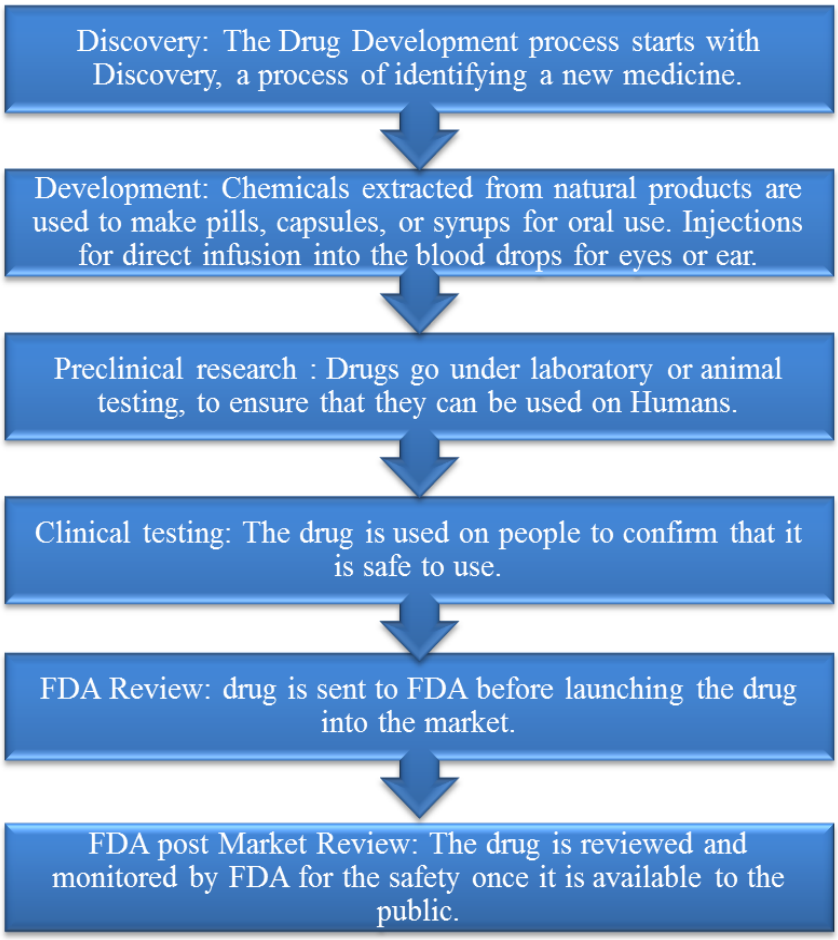


Figure 1: Drug development process.

Why is validation required?

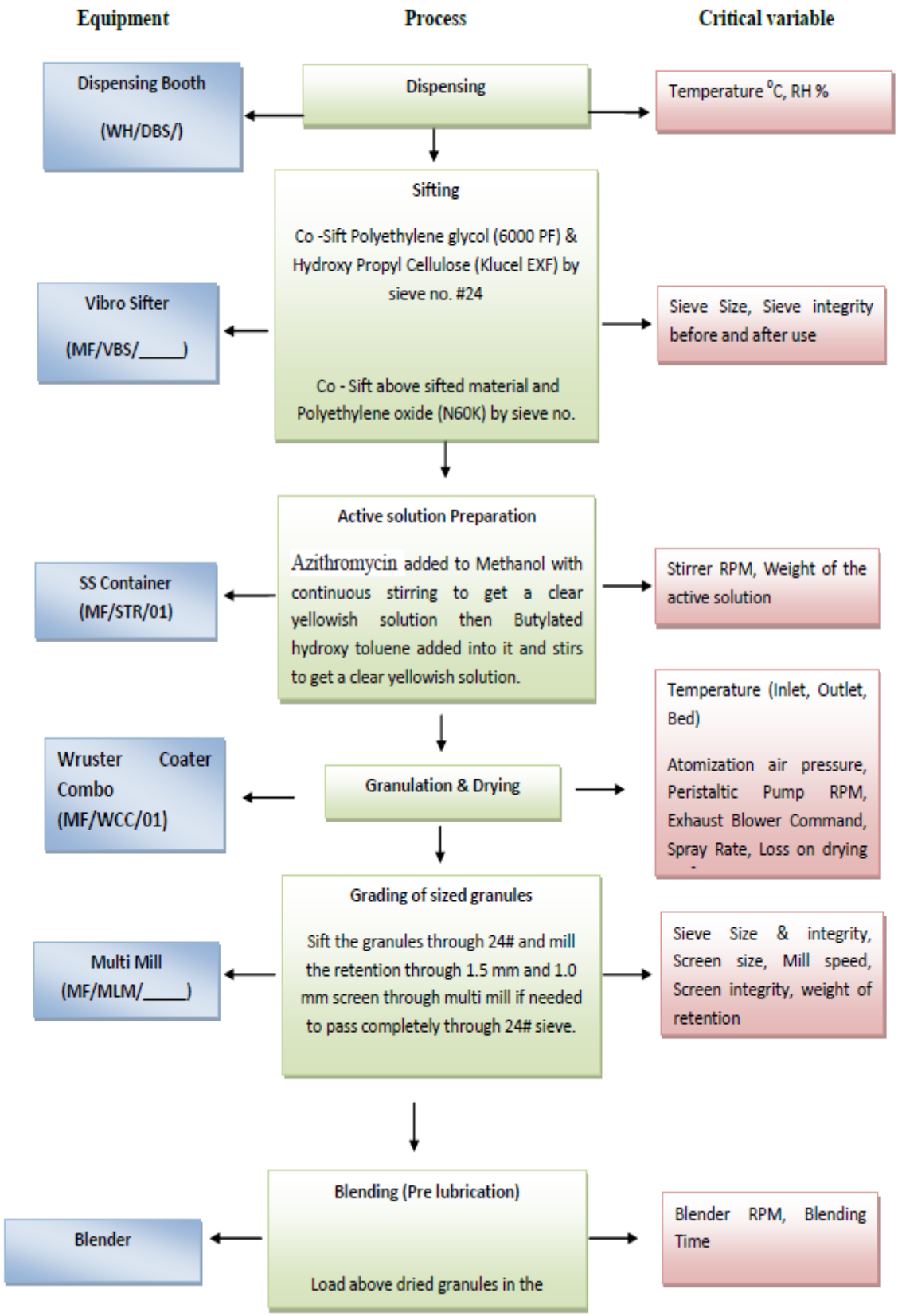
- It wouldn't be functional to use the apparatus without first comprehension whether it would bring about the ideal result.
- The drug area utilizes profoundly talented specialists, innovative structures and gear, and expensive materials.
- The business' future improvement relies upon the viable use of these assets. Costs related with item disappointments, dismissals, revamps, reviews, and grumblings represent a sizeable piece of the general assembling cost.
- A careful investigation and the executives of the assembling system — approval — is required on the off chance that disappointment is to be diminished and efficiency is to be expanded.
- The accompanying elements make approval an issue for the drug businesses:Confirmation of value.
- The accompanying meaning of interaction approval has been proposed by the US Food and Drug Administration (FDA):
- Laying out composed confirmation that a specific cycle, (for example, the making of drug measurement structures) will reliably bring about an item fulfilling its set boundaries and quality highlights is known as interaction approval.[5]

Preformulation study

In its broadest definition, preformulation refers to all the processes and investigations needed to transform an active pharmaceutical ingredient into an appropriate dosage form. It is an examination of the physical and chemical characteristics of a drug ingredient both by itself and in combination with excipients. Therefore, the present study evaluated granulations, developed an in vitro dissolution method, and identified if the medicine was compatible with the chosen polymer.

Preparation of powder (Granules)

One of the most basic unit processes in the creation of drug measurement structures, essentially tablets and containers, is granulation, a strategy for molecule development by agglomeration. Granules are basically delivered as a middle person with a size scope of 0.2-0.5 mm to be either pressed as a measurements structure or to be blended in with other excipients preceding tablet compaction or case filling, notwithstanding the way that they are utilized in the drug business and have molecule sizes in the scope of 0.2-4.0 mm. Roller compaction or slugging could be utilized to get dry granulation.


Equipment
Process
Critical variable
Dispensing Booth (WH/DBS/)
Dispensing
Temperature °C, RH %
Sifting
Co -Sift Polyethylene glycol (6000 PF) & Hydroxy Propyl Cellulose (Klucel EXF) by sieve no. #24
Co - Sift above sifted material and Polyethylene oxide (N60K) by sieve no.
Vibro Sifter (MF/VBS/____)
Sieve Size, Sieve integrity before and after use
Active solution Preparation
Azithromycin added to Methanol with continuous stirring to get a clear yellowish solution then Butylated hydroxy toluene added into it and stirs to get a clear yellowish solution.
SS Container (MF/STR/01)
Stirrer RPM, Weight of the active solution
Wruster Coater Combo (MF/WCC/01)
Granulation & Drying
Temperature (Inlet, Outlet, Bed)
Atomization air pressure, Peristaltic Pump RPM, Exhaust Blower Command, Spray Rate, Loss on drying
Grading of sized granules
Sift the granules through 24# and mill the retention through 1.5 mm and 1.0 mm screen through multi mill if needed to pass completely through 24# sieve.
Multi Mill (MF/MLM/____)
Sieve Size & integrity, Screen size, Mill speed, Screen integrity, weight of retention
Blending (Pre lubrication)
Load above dried granules in the
Blender
Blender RPM, Blending Time

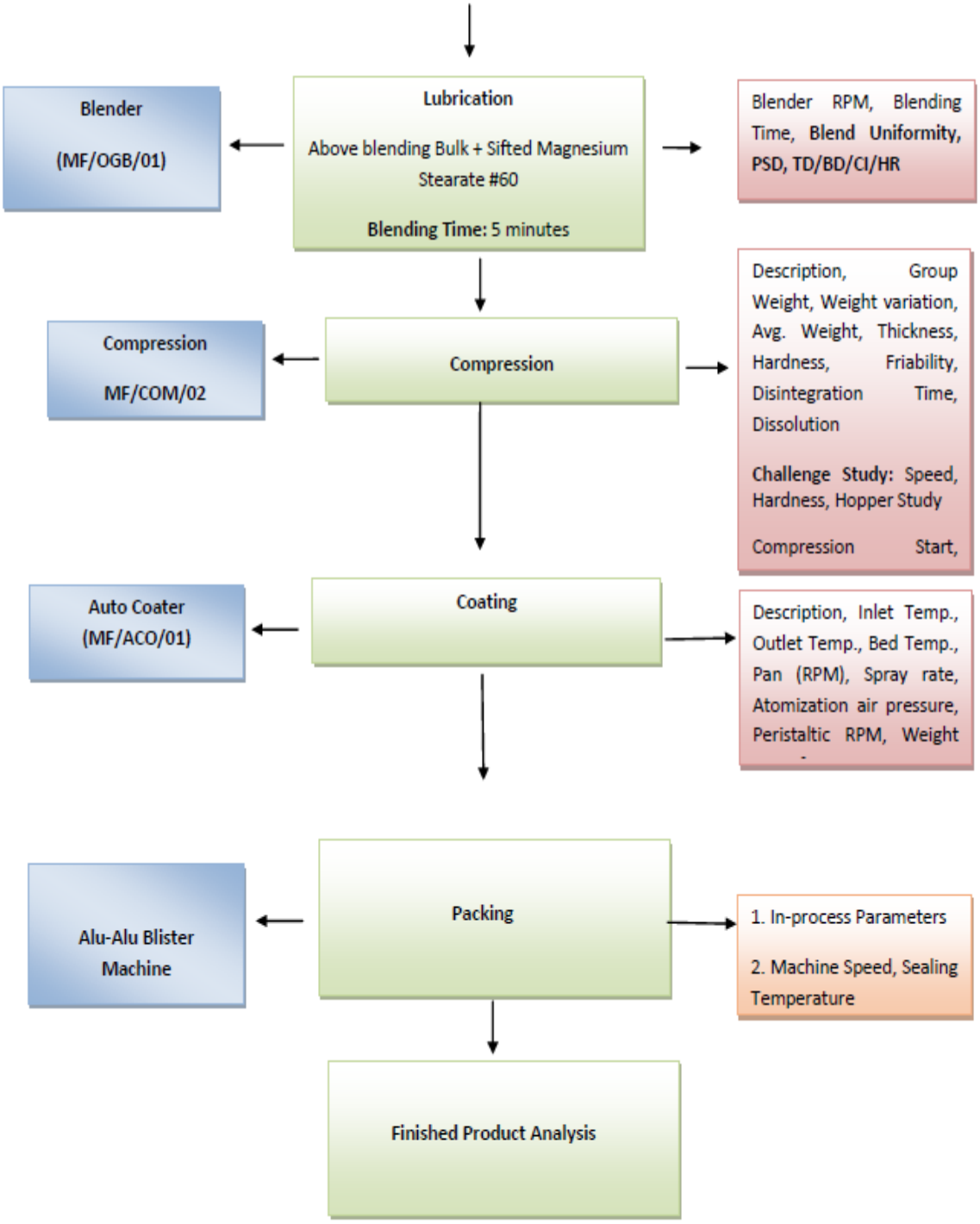


Figure 2: Process flow chart.

Evaluation of parameters

Drugs were classified according to their physical characteristics, including their compressibility index, angle of repose, density, and Hausner's ratio etc.[6]

Angle of repose

The funnel method was used to calculate the angle of repose. The carefully measured powder was put into a funnel. The funnel's height was adjusted such that the tip of the device just brushed the peak of the powder heap. The funnel was left open, letting the powder freely pour out onto the ground. The powder cone's diameter was measured.[7,8]

The angle of repose was calculated by using the following equation.

$$\tan(\theta) = h/r$$

Where 'h' and 'r' are the height and radius respectively of the powder cone.

Table 1: Standard values of angle of repose (θ).

Flowability	Angle of repose
Excellent	25-30
Good	31-35
Fair	36-45
Poor	45-55
Very poor	56-65
Very very poor	>66

Bulk density

Similar loose bulk densities (LBD). A graduated measuring cylinder was filled with a predetermined quantity of granules from each formula that had been previously lightly agitated to break any agglomerates that may have formed. After the initial volume was measured, the cylinder was allowed to drop under its own height at intervals of two seconds onto a hard surface. These formulas were used to determine LBD. After carefully levelling the powder and noting any disturbed apparent volume, the apparent bulk density in g/ml was computed using the formula below:[9,10]

LBD= Weight of the powder/volume of the packing

Determination of tapped bulk density[11,12]

An exact measurements of the medication was consumed; it had prior been placed into a 100 ml graduated chamber in the wake of going through a 20 # strainer. Then, at that point, utilizing a precisely tapped thickness analyzer that delivers a set drop at an ostensible pace of 300 drops each moment, the chamber containing the example was precisely tapped by raising and permitting it to fall under its own weight. The chamber was initially tapped multiple times, and the tapped volume (V1) was estimated to the closest graduated units. The tapping was then done 750 extra times, and the tapped volume (V2) was estimated to the closest reviewed units. The last volume (V2) 83 was picked assuming the distinction between the two volumes was under 2%.

TBD= Weight of the powder/tapped volume of the pressing

Compressibility index[13,14]

Carr's compressibility index, which was derived using the formula below, was used to determine the compressibility index of the granules:

Carr's index (%) = [(TBD-LBD)×100]/TBD

Hausner's ratio[15,16]

Hausner discovered that the DF/DO ratio was associated with interparticle friction and could therefore be utilised to forecast powder flow characteristics.[17] The formula below is used to calculate it:

Hausner's ratio = DF/DO

where DF is Tapped bulk density and DO is Loose bulk density.

Table 2: Standard values of Carr's Index and Hausner's ratio.

Type of flow	Carr's index	Hausner's Ratio
Excellent	<10	1.00-1.11
Good	11-15	1.12-1.18
Fair	16-20	1.19-1.25
Passable	21-25	1.26-1.34
Poor	26-31	1.35-1.45
Very poor	32-38	1.46-1.59
Very, Very poor	>38	>1.60

Development of tablets

By utilizing an interaction called wet granulation, tablets were made. Magnesium stearate was excluded from the piece that was totally joined for five minutes in a tumble blender prior to being plunged into a PVP isopropyl liquor crushing liquid. As per the recipe showed in the table beneath, an exact measure of the medicine and polymers were gauged.

The acquired wet mass was put through sifter #16 and permitted to dry for two hours at 60°C. The dry granules were put through channel #22 and afterward greased up with a magnesium stearate combination. A punching machine that ran on power was utilized to make the tablets. A solitary punch press with a 8 mm curved punch and a pressure power of 9 KN (fundamental work) or 12 KN (trial configuration) was utilized to pack the material following the granulation interaction. clusters of 10 pills were made for the primer work. There were 10 tablets in each clump of the preliminary (drug content in the tablet was 15 mg). For every detailing, five groups were made, and the different bunches of tablets' items are recorded in. The compacted tablets' typical weight, weight change, thickness, distance across, consistency of the substance, hardness, and friability were completely evaluated.

Utilizing stations' "First class" turning tablet pressure gear, the previously mentioned delivered mixes are compacted into tablets. The tablets are packed without embellishing or scoring utilizing 7mm round biconcave punches. Similar settings are utilized to set up each clump.

Table 3: Composition of tablets.

Ingredients	Formulation code (Quantity in mg)								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Nateglinide	25	25	25	25	25	25	25	25	25
Pvp	15	14	14	14.5	15	14	14.5	14.5	15
Magnesium Stearate	2	3	2	2.5	3	3	2	2.5	3

Evaluation of tablets
The following qualities were assessed in the prepared tablets:

Thickness and Diameter
For the requisite homogeneity in size and shape, the thickness and diameter of the tablets were precisely measured using a digital Vernier calliper.

Hardness
The strength of a tablet is determined by how hard it is. By measuring the amount of force needed to break the tablet across its circumference, it is put to the test. The hardness is expressed in kilogrammes (kg), and 4 kg is thought to be a sufficient hardness for uncoated tablets. For this, a Monsanto hardness tester is employed. Six pills were tested for hardness, and the average hardness was determined.

Friability test[18]
The loss of weight of tablets in a container due to the removal of small particles from their surfaces is known as friability. The friability test evaluates the tablet's resistance to abrasion during handling, packing, and transportation. The tablet's friability was evaluated using an Electrolab friability tester. Six (6) tablets were weighed precisely and put inside the device's chamber. The tablets were removed from the device after 100 spins, dusted again, and weighed. The weight loss reveals the pills' brittleness. Tablets may only have a friability of 1% at most, according to Indian Pharmacopoeia (IP). The algorithm below was used to calculate the percentage of friability:
% friability = (W1 - W2 / W1) × 100
Where,
W1 = weight of tablets before test
W2 = weight of tablets after test

Dissolution testing[19,20]
Utilizing an auto sampler, the produced tablets were assessed for in-vitro drug release tests. The following circumstances govern how core pills dissolve. The gathered findings are summarised and utilised to choose the optimal formulation. The results are shown in the tablet-specific Table below.

RESULTS
Solubility study of azithromycin[23]
Sparingly soluble in water, soluble in organic solvents like methanol and slightly soluble in ethanol.

Table 4: Solubility data of azithromycin in various buffers.

Medium	Solubility (mcg/ml)
1.2 pH buffer	105
6.8 pH buffer	22

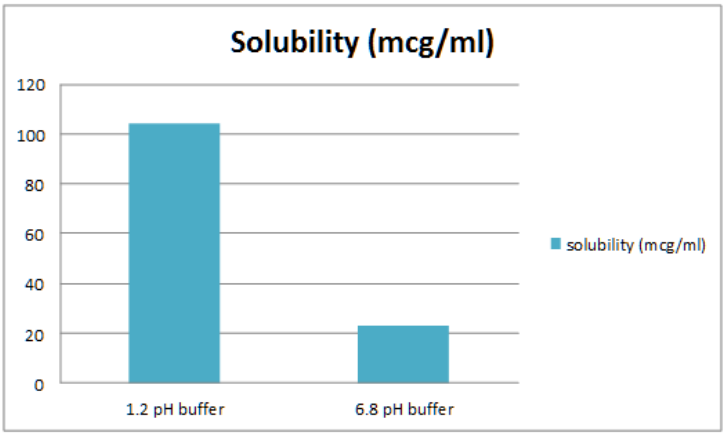


Figure 3: Solubility of azithromycin.

Evaluation of granulations[24]
Granulation, which includes the constant arrival of a prescription from covered or network type particles, is the significant cycle in the making of various measurements structures. A gathering of discrete particles connected together by bonds with a limited strength is alluded to as a granule. In spite of the fact that network tablets could have been delivered utilizing an immediate pressure method, wet granulation (non-fluid) is ideal in commonplace business assembling to accomplish sufficient substance homogeneity and dispose of stream related between tablet weight variety process. The current examination thusly utilized the wet granulation process. The actual characteristics of granules, like their size, shape, hardness, and surface qualities, can considerably affect how rapidly drugs contained in a heterogeneous plan break up. Point of rest, free mass thickness (LBD), tapped mass thickness (TBD), Carr's file (CI), and Hausner's proportion were estimated in the granules of restorative plans (HF). The tablets beneath show the outcomes that were acquired. The previously mentioned method didn't work with azithromycin granules to decide the point of rest. The granules of azithromycin went in point of rest from 21.99° to 23.70°, though the powder was too strong to even consider going through the channel.

Various grades of unrefined components were evaluated for mass and tapped thickness. It was found that the actions were enormously affected by the example size, and on the grounds that volumetric estimations are made outwardly, they are exceptionally conflicting from one examiner to another. In view of the formulae, the Carr's compressibility record (CI, percent) and Hausner proportion (HR) were additionally processed. The delivered azithromycin granules' Hausner's proportion values went from 1.154 to 1.348. The last option was accepted to be demonstrative of the made granules' positive stream qualities because of the granulation-prompted expansion in molecule size. Furthermore, because of a corresponding expansion in molecule size when contrasted with untreated powder, the granulation has diminished the tapped thickness. Carr's compressibility, an inference of mass densities for surveying the capacity of powder to stream,

Azithromycin's compressibility was found to be 54.05. The supposition that granulation expanded both stream capacity and compressibility was upheld by this finding, which was as per the aftereffects of point of rest and HF. It was found that there were next to no particles in the granules of azithromycin. The moment discharge powder combination showed great stream qualities (Angle of rest more than 27 and under 30). Results showed that a powder mix for guaranteed delivery might be straightforwardly squashed into tablets.

Other logical disciplines (counting geography) utilize the point of rest, a conventional methodology for portraying drug powder stream, to depict solids. Both the range of the base and the level of the granules that make up the cone, h, were estimated.

Table 5: Evaluation of granulations pre-compression studies.

Evaluation Parameters	Bulk density (g/cc)	Tapped density (g/cc)	Hausner`s ratio
F-1	0.46	0.56	1.21
F-2	0.46	0.48	1.04
F-3	0.45	0.52	1.20
F-4	0.52	0.58	1.11
F-5	0.44	0.50	1.13

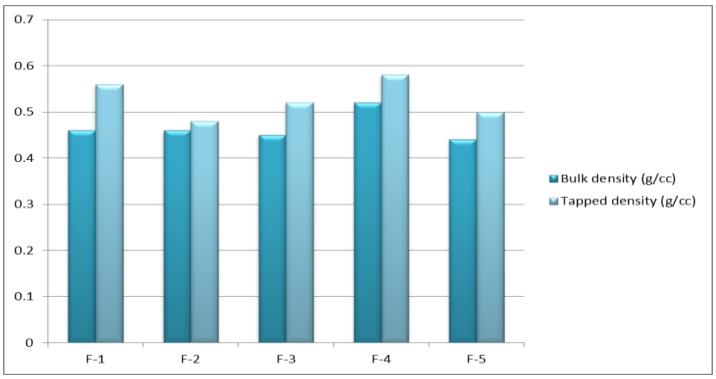


Figure 4: Bulk Density and Tapped density of azithromycin.

Table 6: Evaluation of granulations pre-compression studies.

Evaluation Parameters	Compressibility index (%)	Angle of repose (θ)
F-1	17.85	21.15
F-2	4.16	23.32
F-3	13.46	23.75
F-4	10.34	21.61
F-5	12	24.36

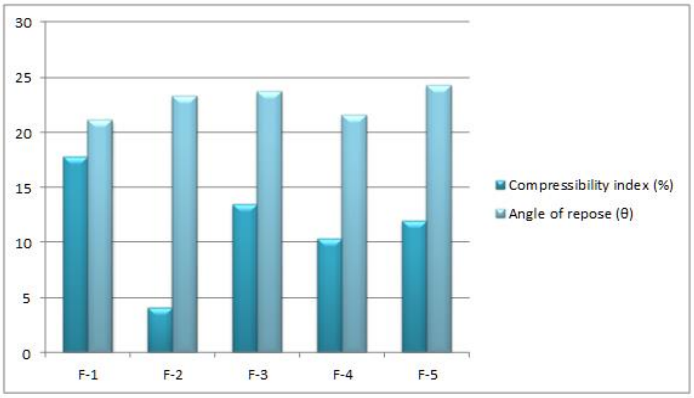


Figure 5: Compressibility Index and Angle of repose of azithromycin.

Determination of Parameters of drug (post-compression studies)

By turning the screw knob forward, the force being exerted to the tablet's edge is steadily increased until the tablet breaks. The scale's reading, which expresses the amount of pressure needed to break tablets in kilogrammes per square metre, is reported. A friabilator was loaded with a pre-weighed sample of tablets, and it was rotated 100 times.[25]

Table 7: Evaluation parameters of drugs.

Evaluation Parameters	Hardness (%)	Friability (%)	Thickness (mm)	Drug Content (%)
F-1	4.9	0.3	2.4	97.65
F-2	4.6	0.25	2.5	91.76
F-3	5.8	0.4	2.1	93.34
F-4	5.1	0.35	2.3	94.25
F-5	5.9	0.45	2.6	96.85

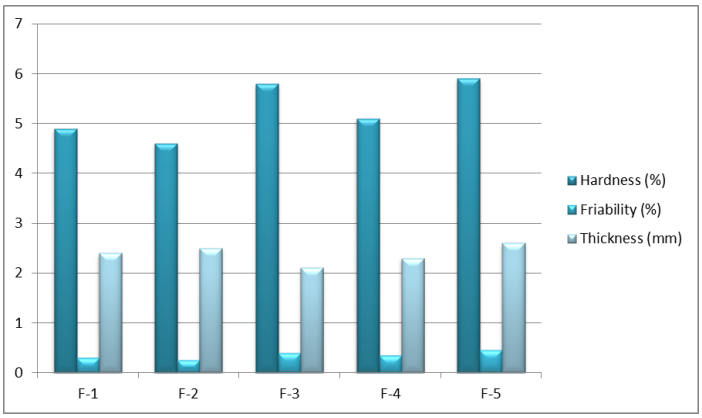


Figure 6: Hardness, Friability and Thickness of azithromycin.

Table 8: Dissolution data of optimized batches of tablets in 6.8 pH buffer.

Evaluation Parameters	Time (min) 0	Time (min) 10	Time (min) 20	Time (min)30
F-1	0	76.65	81.35	86.15
F-2	0	74.36	79.14	84.35
F-3	0	73.15	82.47	82.47
F-4	0	76.93	78.34	81.33
F-5	0	77.18	79.56	81.34

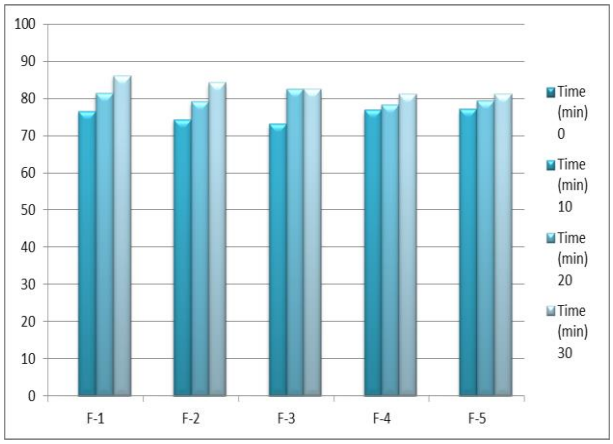


Table 7: Dissolution data of optimized batches.

Table 8: Evaluation parameters of batch which was kept for stability study.

Evaluation Parameters	Hardness (%)	Friability (%)
Before stability Storage	5.6	0.24
After 1 month Storage	6.3	0.45
After 2 month storage	6.0	0.25
After 3 month storage	6.1	0.41

The formulations were periodically removed from storage afterward and subjected to physical parameter analysis; the results are shown in the table above. There was no significant variation between the tested parameters before and after the formulations were aged in storage; all were confirmed to be within permissible limits.

Packaging is the grouping of several elements that surround a pharmaceutical product from the moment it is produced until it is used. Pharmaceutical product packaging is a vast, all-encompassing, and complex task.[26] Every conceivable dosage form for supplements, poultices, liquids, solids, powders, suspensions, and drops is made possible by packaging,[27] which also makes it possible to deliver life-saving medications, medical devices, treatments, and new products like medical nutritionals (nutraceuticals) to people all over the world.[28] When done effectively, it is transparent to the end user, but when done poorly, it is subject to widespread criticism.[29,30]

CONCLUSION

The complete group of work from the most recent five years on the creation and approval of techniques for antibacterial medications. Different methods have been produced for the creation and approval of medications. Various bacterial sicknesses, including those of the respiratory framework, skin, ear, and eye, as well as physically communicated illnesses, are treated with azithromycin. There are extra purposes for azithromycin not covered by this drug guideActual qualities of medications, for example, point of rest, thickness, compressibility file, Hausner's proportion, and so on, were utilized to classify them. The equation was used to get the angle of repose. ranged from 21 to 30. All constituents' compressibility indices were calculated using an equation. The range was 1 to 20. All components' Hausner's Ratios were calculated using an equation. It was between 1 and 1.50. Prepared tablets ware evaluated for post compression parameters like thickness and diameter, hardness, friability, disintegration time, drug content. For the requisite homogeneity in size and shape, the thickness and diameter of the tablets were precisely measured using a digital Vernier calliper. Tablets need a specific level of hardness, as determined by a Monsanto hardness tester. The tablets were put through a friability test. 20 pills were weighed and pulverised precisely. All the readings of parameters were acceptable.

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Conflict of interest

The authors declare no conflict of interest

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