

**KEY ROLE OF ANTIBIOTICS IN HEALTH CARE SYSTEM****\*<sup>1</sup>Prachi Nagpal, <sup>2</sup>Kunal Kaushik and <sup>3</sup>Mayank Bansal**<sup>1,3</sup>Jaipur College of Pharmacy, Jaipur.<sup>2</sup>Delhi College of Pharmacy, Delhi.Article Received on  
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**\*Corresponding Author****Prachi Nagpal**Jaipur College of Pharmacy,  
Jaipur.**ABSTRACT**

The development of a drug product is a complex endeavour, encompassing phases such as drug discovery, laboratory testing, animal studies, clinical trials, and regulatory approval. Process controls, including inspection of raw materials, in-process monitoring, and setting targets for the final product. Process validation, as mandated by the cGMP regulations, is essential at both general and specific levels as outlined in parts 210 and 211. Analytical estimation and process validation of Ciprofloxacin HCl tablet dosage form would be carried out. Three consecutive batches of Ciprofloxacin HCl are F1, F2 & F3 will be taken for process validation studies. All the critical parameters would be evaluated for fixing the optimum process parameter. Analytical evaluation of Pre-formulations parameters, Post formulations parameters, preparing validation protocol, Execution of validation protocol.

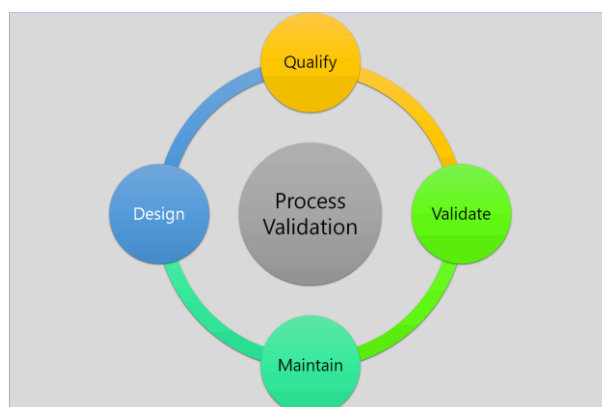
**KEYWORDS:** Validation, Antibiotics, Ciprofloxacin, Tablets, Analysis.**INTRODUCTION****VALIDATION**

A program called pharmaceutical validation verifies that apparatus, systems, procedures, or methods work as anticipated. It covers all the important parameters during the manufacturing process of any pharmaceutical dosage form. In the end, validation is a program that shows how procedures, tools, systems, and equipment are supposed to be used during the entire manufacturing (Gheen, 2022).

In essence, validation entails assessing the validity or proving the effectiveness of processes. It is a collaborative effort involving professionals from diverse disciplines within a plant.

This approach rests on the premise that quality, safety, and efficacy are integral to the product's design or construction. Quality assurance extends beyond mere inspection or testing of in-process and finished products; it involves controlling every step of the manufacturing process to ensure that the final product meets all quality specifications.

The development of a drug product is a complex endeavour, encompassing phases such as drug discovery, laboratory testing, animal studies, clinical trials, and regulatory approval. Process controls, including inspection of raw materials, in-process monitoring, and setting targets for the final product, are vital elements. The aim is to continuously monitor and validate the manufacturing process, even after validation is achieved. Moreover, adherence to current Good Manufacturing Practice necessitates the establishment of well-documented procedures for process controls to ensure ongoing performance monitoring.



**Fig 1: Basic concept of Process Validation.**

## STAGES OF PROCESS VALIDATION

### Stage-1 Process Design

In the initial phase, the focus is on delineating the manufacturing process in a manner that ensures consistent production of a medicinal product meeting predetermined quality standards. Achieving this goal requires the validation team to thoroughly understand the intricacies of the process. Various sources and techniques are employed to gather pertinent process information.

- Product development endeavours provide valuable insights.
- Understanding the functionalities and limitations of production equipment is crucial.
- Predictions regarding factors contributing to variability are considered.
- Design of experiment (DOE) studies are conducted to explore different variables.

### Stage-2 Process Qualification

In the second stage, known as Process Qualification, the focus shifts to evaluating the effectiveness of the process design for ensuring quality production. This involves a comprehensive assessment conducted through several steps.

- a. Facility Design
- b. Utilities and Equipment Qualification
- c. Process Performance Qualification

### Stage-3 Continued Process Verification

Following process design and qualification, the third stage of process validation focuses on establishing mechanisms to consistently uphold the validated process during routine production. Continued process verification involves several key practices.

- a) Utilizing statistical process control (SPC) to monitor and sample process parameters and quality attributes continuously.
- b) Conducting scheduled maintenance of the facility, utilities, equipment, and associated assets.
- c) Implementing good documentation practices throughout the validation process.

### SCOPE OF VALIDATION

d) Defining the scope of pharmaceutical validation presents a considerable challenge due to its extensive coverage across various aspects of pharmaceutical manufacturing. Nonetheless, upon close inspection of pharmaceutical operations, several key areas emerge for validation consideration (Pant, Hussain and Ashok, 2023).

### IMPORTANCE OF VALIDATION

Validation holds significant importance across various facets of pharmaceutical manufacturing.

- a) Ensuring quality assurance
- b) Meeting time constraints effectively
- c) Optimizing processes for efficiency
- d) Ensuring the quality of raw materials
- e) Validating the reliability of packaging materials
- f) Verifying the performance of equipment
- g) Validating the suitability of facilities

## TYPES OF PROCESS VALIDATION

- a. **Prospective Validation-** Prospective validation, conducted during the developmental phase (also known as premarket validation), aids in identifying potential risk factors within the production process. This method involves breaking down the process into distinct steps to scrutinize critical aspects like mixing time, relative humidity (RH), and temperature.
- b. **Concurrent Validation-** Concurrent validation occurs during routine production stages and builds upon the thorough examination of the process conducted during prospective validation. Close monitoring of the initial three production-scale batches is essential. Concurrent validation is conducted under the following circumstances.
- c. **Retrospective Validation-** Retrospective Validation relies on historical and testing data from batches manufactured in the past. It involves analysing trends and verifying whether the process adheres to the permissible range of parameters. This analysis can be conducted through computer-based systems or manual methods.
- d. **Process Re-Validation-** Revalidation is necessary to ensure that any alterations made to the process environment, whether deliberate or inadvertent, do not negatively impact process attributes and product quality.

## MASTER FORMULA RECORD

The Master Formula Record (MFR) serves as a comprehensive document for pharmaceutical products, encompassing details of their manufacturing processes. It is crafted by the research and development team within the company. Subsequently, manufacturing units utilize the MFR as a basis to create other documents such as Batch Manufacturing Records (BMR) and Batch Packaging Records (BPR).

## PROCESS VALIDATION PROTOCOL

A documented strategy outlining the approach for conducting process validation; it will detail the individuals responsible for different tasks and establish parameters for testing, including sampling plans, testing methodologies, and specifications. This plan will delineate product attributes and equipment requirements. It will also define the minimum number of batches required for validation studies and establish acceptance criteria.

**Table 1: Process Validation Protocol.**

S.No.	Process Validation Protocol
i.	Objective
ii.	Label claim
iii.	Validation team and responsibility
iv.	Scope of protocol
v.	Manufacturing formula
vi.	Process flow chart
vii.	Critical steps, variables to be studied & acceptance criteria
viii.	Pre requisites for process validation
ix.	General tests for raw material
x.	List and qualification of equipment's/instruments
xi.	Manufacturing and sampling procedures
xii.	Process validation report
xiii.	Discussion
xiv.	Future scope

## ANTIBIOTICS

Antibiotics are tailored to specific bacterial infections and cannot be indiscriminately swapped between different types of infections. When used correctly, antibiotics are generally safe with minimal side effects, as healthcare providers can customize treatment based on individual patient needs, including the type of antibiotic, dosage, and duration.

### Mechanism of Action

**Inhibition of cell wall synthesis:** The structure of the bacterial cell wall includes numerous tiers of peptidoglycan, which are made up of peptide chains and sugars known as glycans. These glycans, consisting of N-acetyl muramic acid (NAM) and N-acetyl glucosamine (NAG), are linked together with the assistance of trans glycosidases. Additionally, the connection between the D-alanyl-D-alanine segment of the peptide chain and glycine residues occurs in the presence of penicillin-binding proteins (PBPs), contributing to the strengthening of the cell wall (Khanal, 2022).

**Inhibition of membrane function:** The cytoplasmic membrane regulates the passage of molecules and ions in and out of the cell through integral transporter proteins, maintaining selective permeability. Antibiotics targeting fatty acid synthesis and membrane phospholipids disrupt the function of this membrane. These antibiotics exert a detergent-like effect, creating random pores that result in the leakage of cellular molecules, inhibition of respiration, increased water uptake, and eventual cell death. Gram-positive bacteria, with their thicker cell walls providing protection, demonstrate a natural resistance to such antibiotics.

## TABLETS

Tablets are solid medications comprising active pharmaceutical ingredients and additional substances known as excipients. They typically possess a solid, circular shape with a flat and convex surface. These dosage forms provide a specific quantity of medication in a single unit and are categorized as solid unit dosage forms.

## METHODOLOGY

**Determination of melting point:** Small quantity of drug was placed into a sealed capillary tube. The tube was placed in the melting point apparatus. The temperature in the apparatus was gradually increased and the temperature at which entire drug gets melted was noted.

**Solubility studies:** The Solubility of ciprofloxacin hydrochloride was determined in distilled Water, methanol, dimethyl formamide and dilute alkali and in dilute acids.

**Preparation of standard curve in distilled water:** Accurately weighed 100 mg of ciprofloxacin and was dissolved in 100 ml of distilled water, from this stock solution 10 ml was withdrawn and transferred into 100 ml volumetric flask. Volume was made with distilled water in order to get standard stock solution containing 100 ug/ml. From this standard stock solution, a series of dilution (10, 20, 30, 40, 50 ug/ml) were prepared using distilled water. The absorbance of these solutions was measured spectrophotometrically against blank of ciprofloxacin at 278 nm for ciprofloxacin HCL. Absorbance of drug at different concentrations were calculated and graph was plotted (Adama Diaman, K. 2023).

**Infrared spectroscopic analysis:** The FTIR spectrums of moisture free samples of Drug, all excipients and physical mixture recorded on IR spectrophotometer. The scanning range varies from 4000 - 400 cm<sup>-1</sup> and resolution was 1 cm<sup>-1</sup>.

**Preparation of tablets:** Different formulations of Ciprofloxacin (F1-F3) were prepared by Wet Granulation method by using different excipients like Microcrystalline cellulose, Starch, Magnesium Stearate, Sodium Benzoate, Talc and Water.

**Table 2: Formulation Containing.**

Ingredients	F1	F2	F3
Ciprofloxacin	1.460Kg	1.460Kg	1.460Kg
MCC	75gm	75gm	75gm
Starch	210gm	210gm	210gm
Sodium starch glycolate	34.5gm	34.5gm	34.5gm

<b>Titanium dioxide</b>	4.5gm	4.5gm	4.5gm
<b>Benzoate</b>	2.25gm	2.25gm	2.25gm

**Angle of repose:** Angle of repose is an indication of fractional forces existing between granules particles. The maximum angle possible between the surface of the pile of granules and the horizontal plane gives the angle of repose.

**Bulk density:** Bulk density of powder is the ratio of the mass of an untapped powder sample and its volume indicating the contribution of the intra-particulate void volume. The bulk density is expressed in g/ml. Bulk density is determined by weighing powder into a dry graduated 250 ml cylinder.

**Bulk density= Mass of the Blend powder/ Volume occupied by the powder blend**

**Tapped density:** Tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing a powder sample. After observing the initial powder volume to weight, the measuring cylinder or vessel is mechanically tapped and volume readings are taken until little less than 1% further volume change is observed. The mechanical tapping is achieved by raising the cylinder or vessel and allowing it to drop under its own weight at specified distance. Secure the cylinder in the holder of the apparatus with weighed powder sample. Measure 100-200 taps and observe the corresponding volumes to the nearest graduated unit.

**Tapped density = Mass of the powder Blend taken/ Tapped Volume of the powder blend**

**Carr's index:** The Carr's Index and Hausner's ratio are measures of the porosity of a powder to be compressed. They measure the relative importance of interparticle interactions. For poor flow materials there are frequently greater interparticle interactions and a greater difference between the bulk and tapped densities. These differences are reflected in the compressibility Index and Hausner's Ratio. Carr's Index was calculated using the following formula.

**Carr's Index-100\* (TD-BD)/ TD**

**Hausner's Ratio:** The Hausner's Ratio is a number that is correlated to the flow ability of a powder or granular material Hausner's ratio is calculated using following formula.

**Hausner's ratio= TD/BD**

## EVALUATION OF TABLETS

The formulation tablets were evaluated for the following physical parameters.

**Thickness:** Thickness depends on the die filling, physical properties of material to be compared. There is possible of small variation in the thickness of individual tablet in a batch. But it should not be appear to the unaided eye. The thickness and diameter can be measure by vernier caliper.

**Weight variation test:** Twenty tablets were selected randomly and weighed individually. Calculate average weight compare the individual tablet weight to the average. Not more than two of individual weight derivate from the average weight by more than percentage shown in tablet and none derivate by more than twice the percentage.

**Hardness:** Tablets must possess sufficient strength or hardness and can be measured by Monsanto hardness tester. Ten tablets were randomly picked from each formulation and were evaluated for hardness and can be expressed in kg/cm<sup>2</sup>.

**Friability:** Friability can be performed in Roche friabilator, Pre weighed ten tablets were introduced in the friabilator. Then the machine was operated for 100 revolutions. Tablets were dropped from a distance of six inches each revolution. Tablets were then dusted and reweighed. LOSs of less than 1% in weight is considered to be within the specification and acceptable.

**Disintegration Time:** This test determines whether tablet disintegrates with in prescribed time when placed in liquid medium.

**Drug content: Assay: (BY HPLC)**

**Mobile Phase preparation:** A mixture of 87 volume of 0.025 M phosphoric acid, previously adjusted with triethylamine to a pH of 3.0 + 0.1.

**Chromatic condition**

Apparatus: HPLC

Column: C18

Wave length: 278nm

Injection volume: 10 ul Flow

Rate: 1,5ml/min

Column Temperature: 30°C

Type of detector: UV



**Standard Preparation:** Weigh accurately 50 (mg of Ciprofloxacin into 100 ml volumetric flask and makeup volume with 0.01 M HCl.

**Sample Preparation:** Weight and powder 20 tablets. Weight accurately a quantity of the powder containing about 50 mg of ciprofloxacin and make up the volume with 0.01 M HCl (Abdu Hussein 2022).

### **In vitro Dissolution studies**

**Procedure of Dissolution of tablets:** Six tablets of Ciprofloxacin (Film Coated tablets) were introduced in the dissolution apparatus. The medium used was 900 ml of water and the dissolution medium were maintained at the temperature of 37.5, the RPM was set at 50. The Dissolution was carried out for 30 minutes and sample withdrawn at predetermined intervals. The estimation was carried out by UV method.

**Standard Preparation:** Weigh accurately 50 mg of Ciprofloxacin and transfer into a 100 ml volumetric flask. Dissolve and dilute up to volume with dissolution media. Take 1ml from above solution and transfer into 100ml volumetric flask, dissolve and dilute up to volume with dissolution media.

**Sample Preparation:** The dissolution parameters were set and one tablet is placed in each basket and care was taken to exclude air bubbles from the surface of the tablets and immediately the apparatus was started, 10ml of the sample was withdrawn and filter through whatmann filter paper, 10ml of solution was replaced in to dissolution medium, the same procedure was repeated at other time intervals. Take 1ml from above solution and transfer into 100 ml volumetric flask and volume make up (Gao, Z. 2022).

**Drug release kinetics:** The release kinetics was studied by various kinetic models such as zero- order plot, first-order plot, Higuchi plot, and Korsmeyer-Peppas plot. To study the release kinetics of the nanoparticle gel data obtained from in vitro drug release studies was plotted in various kinetic models: Zero-order as cumulative amount of drug releases versus time, first order as long cumulative % of drug remaining versus time, Higuchi model as cumulative % of drug released versus square root of time, and Korsmeyer-Peppas model as log cumulative % drug release versus long time. The best fit model was confirmed by the value of correlation coefficient near to one (Shripathy 2023).

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