Formulation And Development of Levofloxacin 250 Mg Immediate-Release Tablet

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Abstract—**Levofloxacin, a third-generation fluoroquinolone antibiotic, is widely prescribed for respiratory, urinary, and soft-tissue infections due to its broad-spectrum antibacterial activity and high oral bioavailability. Immediate-release (IR) formulations of levofloxacin are essential for achieving rapid therapeutic concentrations, particularly in acute infections where early bacterial eradication improves clinical outcomes. The development of a robust IR tablet requires a comprehensive understanding of the physicochemical properties of levofloxacin, including its solubility, pHdependent dissolution, hygroscopicity, and potential incompatibilities with certain excipients. This review provides an in-depth analysis of formulation strategies, excipient selection, processing methods, and evaluation parameters involved in developing levofloxacin 250 mg IR tablets.The article discusses the roles of diluents, binders, disintegrants, lubricants, and glidants in optimizing tablet characteristics such as flowability, compressibility, mechanical strength, and disintegration. Manufacturing techniques—including direct compression, dry granulation, and wet granulation—are compared based on their suitability for levofloxacin's physicochemical profile. Quality control tests such as hardness, friability, weight variation, disintegration time, dissolution profile, assay, and stability studies are reviewed with a focus on ensuring compliance with pharmacopeial standards. The article also highlights recent advancements in formulation technologies, including co-processed excipients and improvement of dissolution enhancement methods. This review aims to assist formulators and researchers in designing stable, efficient, and therapeutically effective levofloxacin IR tablets.**

Index Terms—**Levofloxacin, Immediate-Release Tablet, Formulation Development, Fluoroquinolone, Excipients, Dissolution, Stability.**

I. Introduction

Levofloxacin, a third-generation fluoroquinolone antibiotic, is recognized for its potent broad-spectrum antibacterial activity and its extensive application in the treatment of both acute and chronic infections. As the S-enantiomer of ofloxacin, levofloxacin demonstrates significantly enhanced bactericidal activity, attributed to its selective inhibition of essential bacterial enzymes—DNA gyrase and topoisomerase IV. These enzymes play critical roles in DNA replication, transcription, recombination, and repair, making them ideal pharmacological targets. The inhibition of these enzymes results in irreversible DNA damage, rapidly leading to bacterial cell death. Levofloxacin's therapeutic efficacy extends to a wide range of Gram-positive, Gram-negative, and atypical pathogens, including Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa, and Mycoplasma pneumoniae. Its potent antimicrobial profile makes it a first-line agent in the management of respiratory infections, urinary tract infections, softtissue infections, and gastrointestinal infections. Another important characteristic of levofloxacin is its near-complete oral bioavailability (>95%), which enables oral dosing to achieve plasma concentrations comparable to parenteral administration. This property expands its clinical utility and improves patient compliance, especially in outpatient antimicrobial therapy. Furthermore, the drug demonstrates excellent tissue penetration, allowing efficient distribution into the lungs, kidneys, skin, and urinary tract—sites commonly

affected by bacterial infections. However, despite its superior therapeutic advantages, careful formulation is required due to factors such as hygroscopicity, bitterness, and pH-dependent solubility, which significantly influencetablet. performance. These characteristics justify the need for a detailed review of formulation approaches for the immediate-release (IR) dosage form. A comprehensive understanding of the biopharmaceutical properties of levofloxacin is essential when designing an effective IR formulation. Classified under the Biopharmaceutical Classification System (BCS) as a Class I/III drug (high solubility, variable permeability depending on pH), levofloxacin demonstrates pH-dependent solubility, being more soluble in acidic environments and less soluble at neutral or alkaline pH. This pH-sensitive solubility pattern has a direct impact on the dissolution rate, a critical determinant of immediate-release performance. Levofloxacin also exhibits moderate hygroscopicity, meaning it can absorb moisture when exposed to humid conditions. This property necessitates careful selection of excipients and moisture-controlled processing environments to maintain chemical stability and prevent degradation. The drug's bitter taste requires masking within the tablet matrix, particularly in formulations designed for rapid disintegration. Additionally, its crystalline nature influences compression behavior, flow properties, and uniformity of blend—all vital for tablet manufacturing. Pharmacokinetically, levofloxacin exhibits rapid absorption, with peak plasma concentrations (Cmax) achieved within 1–2 hours following oral administration—an attribute aligned with the objectives of immediate-release therapy. The drug demonstrates a half-life of 6–8 hours, allowing oncedaily dosing, which improves patient adherence. Its high oral bioavailability, consistent absorption, fast onset, and broad therapeutic window collectively support its formulation into IR tablets. Therefore, understanding these physicochemical and biopharmaceutical characteristics is essential for selecting appropriate diluents, binders, superdisintegrants, and lubricants, as well as optimizing manufacturing methods such as direct compression or dry granulation. These considerations form the basis of an effective IR formulation strategy. Rationale for Immediate-Release Formulation Development The development of immediate-release levofloxacin tablets plays a critical role in achieving rapid therapeutic action in conditions where prompt bacterial suppression is essential. In acute infections such as community-acquired pneumonia, acute bacterial sinusitis, exacerbation of chronic bronchitis, and complicated urinary tract infections, early attainment of bactericidal concentrations significantly enhances clinical recovery and reduces the risk of complications. Levofloxacin's rapid oral absorption ensures quick entry into systemic circulation, making IR tablets appropriate for initiating treatment. The IR dosage form enables swift dissolution, leading to rapid achievement of plasma levels above the minimum inhibitory concentration (MIC) of susceptible bacteria. This is vital in infections involving fast-multiplying organisms, where delayed antibiotic action may result in bacterial proliferation, increased inflammation, and disease progression. Additionally, IR tablets enhance patient convenience, especially in outpatient settings where injectable therapy is unnecessary. The high oral bioavailability ensures comparable therapeutic outcomes without requiring parenteral administration, thereby reducing treatment costs and improving accessibility. From a formulation standpoint, IR tablets allow optimization of disintegration time, dissolution behavior, and drug release kinetics, ensuring predictable onset of action. Moreover, such formulations are critical to maintaining effective drug concentrations during the early phase of therapy, improving clinical outcomes and minimizing bacterial resistance risk. Overall, the rationale for developing levofloxacin IR tablets lies in balancing rapid onset, performance consistency, stability, and patient compliance, all of which are essential for successful antimicrobial therapy.

- **Objectives** :
  1. To review the physicochemical and biopharmaceutical properties of levofloxacin relevant to IR tablet formulation. To evaluate the compatibility and functional roles of common excipients used in IR tablet formulations
  2. To analyze various manufacturing techniques and their suitability for formulating levofloxacin IR tablets.
  3. To summarize standard evaluation methods, including hardness, friability, weight variation, disintegration, dissolution, assay, and stability.
  4. To provide a comparative formulation table developed using commonly studied excipients.
  5.

1 **Key Aspects of Formulation Development**:-

1) Selection of Dosage Form: Determining the most appropriate form (e.g., oral, injectable, topical) based on the drug's properties and therapeutic needs.

2) Preformulation Studies: These involve studying the physical and chemical properties of the API, such as solubility, stability, and compatibility with excipients.

3) Excipient Selection: Excipients are inactive substances used to aid in the manufacturing process and improve stability, taste, and bioavailability.

4) Process Design: Choosing appropriate manufacturing techniques like granulation, compression, or lyophilization depending on the dosage form.

5) Stability Testing: Ensuring the product remains effective and safe over its intended shelf life under various environmental conditions.

6) Regulatory Compliance: Meeting guidelines set by regulatory agencies like the FDA or EMA, including quality control, documentation, and validation.

7) Scale-up and technology transfer: Moving from lab-scale formulation to commercial production while maintaining product quality and consistency. Formulation development is critical in ensuring that medications are not only effective but also patientfriendly and manufacturable at a large scale.

Levofloxacin Overview Chart :

Category	Details
Chemical Name	Levofloxacin ,Tavanic
Chemical Formula	C18 H20 FN3 O4
Mechanism Of Action	Inhibit bacterial DNA gyrase and topisomeraseIV , preventing DNA replication and cell devision

Molecular Weight	361.37 g/mol
Dosage (Adult)	250mg to 750mg once daily depending on infection
Dosage (Childeren)	Generally not recommended unless benefits outweigh risk (used continuously in severe infection)
Side effects	Nausea ,Headache ,Diarrhea ,dizziness , tendon pain ,insomnia , sun sensitivity
Precaution	Caution in Kidney Disease
Contraindication	Hypersensitivity ,Pregnancy and Breast Feeding .

[1] **Concept of CGMP:-**Definition:-

1)The cGMP is defined as the regulations executed by the FDA that provides for systems will be to assure proper design, monitoring, and control of manufacturing processes and facilities.

2) The first WHO draft text on GMP was adopted in 1968.

3)GMP in India is prescribed under Schedule M in June 1988

4)In India Joint Commissioner (HQ) is authorized by Commissioner of State FDA, to sign and issue the certificate under the WHO GMP certification.

Objectives:-

1) The objectives of Current Good Manufacturing Practices (CGMP) are to ensure that products are consistently produced and controlled according to quality standards.
2) CGMPs are enforced by regulatory authorities such as the FDA (in the U.S.) and serve as guidelines for manufacturing, testing, and quality assurance.

• **Key Objectives of CGMP:**

1**)Ensure Product Quality-**To guarantee that pharmaceutical and other regulated products meet required quality standards for safety, efficacy, and purity.

2)Minimize Risks-To reduce the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product alone.

3)Compliance with Regulatory Requirements-To ensure manufacturing processes comply with national and international regulations, helping avoid legal issues and penalties.

4)Consistent Production-To ensure that every batch of a product is produced consistently with the same quality attributes

5)Proper Documentation- To maintain detailed and accurate records of all manufacturing and quality control activities for traceability and accountability.

6)Control of Manufacturing ProcessesTo establish and maintain validated processes that control critical manufacturing steps.

7)Facility and Equipment Maintenance To ensure the manufacturing environment and equipment are clean, maintained, and suitable for their intended use.

8)Qualified Personnel To employ properly trained and qualified personnel to handle all operations correctly and safely.

9)Change Control and Continuous Improvement To manage changes in procedures, equipment, or processes in a controlled manner and to continuously improve manufacturing practices.

· Following few basic principles are basis of GMP guidelines.

1. The production and distribution of the drugs must minimize any risk to their quality.
2. Manufacturing facilities must maintain a clean and hygienic manufacturing area, including laboratories and storage.
3. Manufacturing facility design, operating principles and environmental conditions must be controlled.
4. Manufacturing process must be clearly defined, validated, and controlled to ensure consistency and compliance with specifications
5. Any changes to the process must be evaluated, qualified, or validated as necessary.
6. Instructions and procedures must be written in clear and unmistakable language.
7. Operators should be trained to carry out the production and control of products as per approved procedures.
8. Records should be made during manufacture and quality control. Any deviations are examined.

MATERIALS & METHODOLOGY

The following materials are commonly described across research studies on the formulation of **Levofloxacin 250 mg IR tablets**. These can be included in your review to summarize standard excipients used in the field.

Fig. 1. **Active Pharmaceutical Ingredient (API)**

[1] Levofloxacin Hemihydrate

Property	Details	Impact on Formulation
Chemical Name	Levofloxacin Hemihydrate	Determines purity and identification
Molecular Weight	370.38 g/mol	Affects dose calculation and processing
Solubility	Freely soluble in water, pH-dependent solubility	Influences dissolution and IR performance
pKa	5.5 (carboxyl group), 6.8 (amine group)	Affects absorption and dissolution
Hygroscopicity	Moderately hygroscopic	Requires moisture-protective excipients
Stability	Sensitive to light/moisture	Impacts processing and storage
Melting Point	225–230°C	Relevant for thermal stability

Table 1: Physicochemical Properties of Levofloxacin Hemihydrate

Fig. 2.

Excipients

- **Diluents:**
  - Microcrystalline Cellulose (MCC)
  - Lactose Monohydrate
  - Starch
- **Binders:**
  - Polyvinylpyrrolidone (PVP K30)
  - Hydroxypropyl Methylcellulose (HPMC)
  - Gelatin
- **Disintegrants:**
  - Sodium Starch Glycolate (SSG)
  - Croscarmellose Sodium
  - Crospovidone
- **Lubricants:**
  - Magnesium Stearate
  - Talc
  - Aerosil (Colloidal Silicon Dioxide)
- **Stabilizers / Moisture-Control Agents:**
  - Anhydrous Lactose
  - Citric Acid (as stabilizer in some studies)
  - Desiccants (for storage)

Equipment:

1. **Processing Equipment**

- Analytical Balance
- Mortar and Pestle
- Sieve Shaker / Sieves
- Mixer / Blender
- Granulator (dry or wet, depending on method)
- Tablet Compression Machine (Single punch or Rotary press)
- Hot Air Oven / Tray Dryer
- Desiccator

2. **Evaluation Equipment**

- Hardness Tester (Monsanto / Pfizer / Digital)
- Friabilator (Roche Friabilator)
- Vernier Caliper
- Disintegration Test Apparatus
- Dissolution Test Apparatus (USP Type I/II)
- UV–Visible Spectrophotometer / HPLC System
- Stability Chamber

II. Methodology

1. Preformulation / API characterization:

- 🎬 Confirm identity, assay, melting point, polymorph, hygroscopicity, particle size, and flow.
- 🎬 Determine solubility profile in pH 1.2, 4.5, 6.8 media and common organic solvents.
- 🎬 Run compatibility studies (binary mixtures API + each excipient) using accelerated conditions (e.g., 40°C/75% RH for 1–4 weeks) and monitor by HPLC/DSC/FTIR for degradation or interaction.

Choose formulation route — two commonly used routes for immediate-release levofloxacin tablets:

- **Direct compression (DC)** — if API and excipients have good flow, compressibility and no segregation issues. Simpler, fewer steps.
- **Wet granulation (WG)** — improves content uniformity and flow for poorly flowable API; often preferred if API particle size small or sticky.

Develop analytical methods (assay, content uniformity, dissolution): validate specificity, linearity, precision, accuracy, LOD/LOQ, robustness. Use UV or HPLC-UV; HPLC preferred for specificity.

2. Direct Compression Method:

A. Pre-mixing

- Pass API and all powders through appropriate sieve (e.g., 40–60 mesh) to deagglomerate.
- Weigh ingredients for a single batch (or multiple tablets). Use an overage if stability requires.
- Geometrically blend levofloxacin with diluents (MCC + lactose) in a V-blender for 10–15 min (or until homogeneous). Add colloidal silica to improve flow, blend 2–3 min.

B. Addition of disintegrant & minor excipients: Add croscarmellose sodium (disintegrant) and mix for 3–5 min to ensure even distribution.

C. Lubrication: Add magnesium stearate (and talc if used) last; blend gently 1–2 min to avoid over-lubrication (which can reduce hardness and affect dissolution).

D. Compression: Compress with single-punch press or rotary press using selected tooling to obtain target hardness (e.g., 6–10 kp depending on friability results). Optimize compression force to get tablets with acceptable hardness, friability (<1%), and disintegration time.

E. In-process tests: Check weight variation, thickness, hardness, friability, disintegration (USP). If any test fails, adjust formulation (e.g., change MCC grade, disintegrant level) and repeat.

3. Wet Granulation Method:

A. Dry mixing: Sieve and blend API + diluents (MCC, lactose) for 10–15 minutes in a high-shear or V-blender.

B. Prepare binder solution: Dissolve PVP K30 (or chosen binder) in purified water or ethanol–water mix (solvent selected based on API solubility and drying considerations).
C. Wet massing / granulation: Transfer powder blend to high-shear granulator. Add binder solution slowly while mixing until a wet mass of appropriate consistency forms (granulation end point determined by hand-ribbon test or torque). Avoid overwetting.
D. Screening / milling: Pass wet mass through a suitable screen (e.g., 1.0–2.0 mm) to form wet granules.
E. Drying: Dry the wet granules in tray dryer or fluid bed dryer to target moisture content (e.g., <2–3% w/w or as defined from preformulation). Monitor loss on drying (LOD).
F. Dry milling & sizing: Mill the dried granules to desired size distribution (e.g., pass through 20–30 mesh depending on tablet size). Re-sieve to remove fines/oversize.
G. Final blending: Blend milled granules with disintegrant (if to be added externally), glidant (colloidal silica), and finally lubricant (magnesium stearate) — add lubricant last and blend gently (1–2 min).
H. Compression: Compress to target hardness, mass, and thickness. Observe in-process controls.

4. Formulation & Development of Levofloxacin 250 mg Immediate-Release Tablet:

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Levofloxacin (API)	250	250	250	250	250	250	250	250	250
MCC (Diluent)	140	130	135	120	150	145	138	132	140
Lactose (Diluent)	60	70	55	80	50	60	70	65	55
PVP-K30 (Binder)	20	18	22	15	18	20	15	22	20
CCS – Crosscarmellose Sodium (Superdisintegrant)	20	25	30	25	20	15	20	18	25
Talc (Glidant)	5	3	4	5	4	5	3	3	3
Magnesium Stearate (Lubricant)	5	4	4	5	8	5	4	10	7
Total Weight (mg)	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg

Table 1: Formulation Table of Levofloxacin 250 mg Immediate-Release Tablet

5. **Post-Compression Evaluation:**
   spirin IR tablets must meet pharmacopeial quality standards. Studies typically include:

- **Weight variation**
- **Hardness and friability**
- **Disintegration time** (must be rapid for IR tablets)
- **Dissolution profile** (ensuring immediate drug release)
- **Assay and content uniformity**
- **Moisture content**:These evaluations ensure consistency, safety, and therapeutic effectiveness.

6. **Analytical assays:**

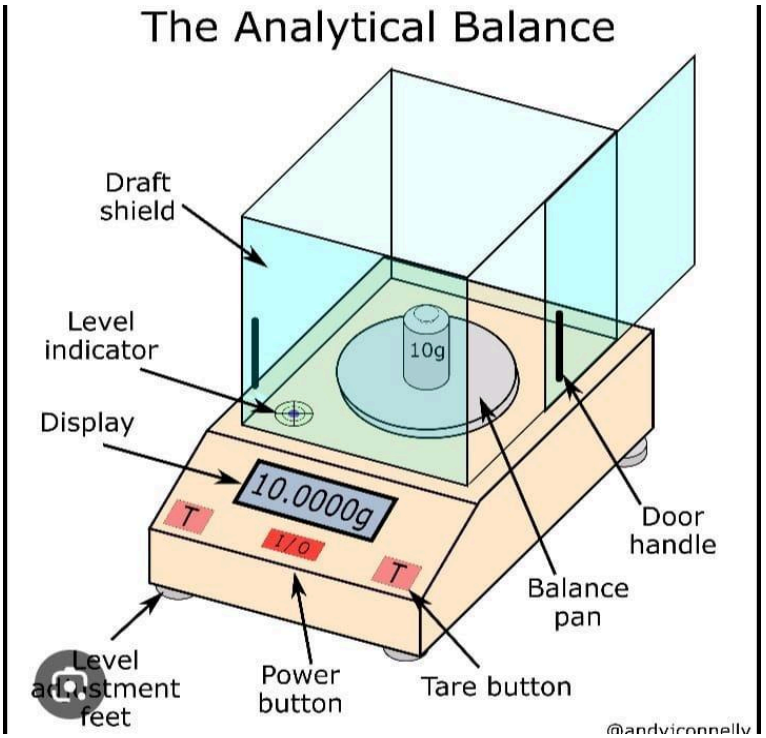
- **PLC-UV** is preferred for specificity. Set up method validation for specificity, LOD/LOQ, linearity (e.g., 5–150% of expected concentration), precision (RSD ≤2%), accuracy (recovery 98–102% typical), robustness.
  - Typical method outline (template to adapt & validate): C18 column (150 × 4.6 mm, 5 µm), mobile phase: buffer (e.g., 20 mM phosphate, pH adjusted) : acetonitrile (ratio to be optimised), flow 1.0 mL/min, injection volume 10–20 µL, detection wavelength around **~290 nm** (determine λmax experimentally). Use internal standard if required.

- **Impurity / degradation**
- Forced degradation (acidic, basic, oxidative, thermal, photolytic) followed by HPLC to demonstrate method stability-indicating capability. Report degradation products and confirm separation from parent API peak.

- **SOP Handling**:-
  Standard Operating Procedure. SOP is the written step by step instrument that how to Perform the activities to complete the task.
  All concern persons are required to follow these steps. SOP are the application in all type of industries, Rules & Regulation, Government Laws & Organization to running the own business. SOPs defines the essential steps, their sequences, and the precautions essential to formally repeat a quality performance. Pharmaceutical Standards Operating Procedure (SOP) is a tested, verified, approved, and documented way of executing operations that form the pharmaceutical industries basis.
  It Provides step by step guidance for the personnel to perform a specific process. A Standard Operation Procedure is written in document.
  That lists the routine tasks necessary tomaintain the calibre of the inquiry.

Equipment and Instrument Handling

1)Weighing Balance :-



Procedure For Handling Digital Weighing Balance

1. Plug in to ensure the power supply.
2. Switch ON the main power supply and instrument mains.
3. Make sure the weighing pan is free of particles.
4. Ensure that the initial weights that is displaying is ZERO.
5. Place the weighing vessel, Weigh boat, or weighing paper on the balance pan
6. Press on the TARE button so the display reads ZERO.

7. Using a spatula or sampling tool, transfer the substance being measured into the weighing vessel placed on the balance pan.
8. Record the mass of the object as displayed.
9. Do not exceed the limit of precision of the instruments. This is a major reason for error in measurement.
10. After use SWITCH OFF the balance.

2)Double Cone Blender :-

Procedure For Handling Double Cone Blender

1.Ensure that the lid and safety pin lock are properly assembled from one side.
2. Adjust the angle of the blender with the help of a moving wheel to a required position for convenience in loading of materials
3. Load all the materials from the containers into the blender.
4. After loading the materials, close the lid of the blender.
5. Put the safety pin on the lid and fit it properly.
6. Switch ‘ON’ the equipment and start the mixing as per the time specified.
7. When the mixing is completed, switch off the equipment.
8. Adjust the position of the blender at the required angle for convenience in unloading the material

9. Unlock the safety pin and remove the lid from the blender. 10. Unload the mixed materials in cleaned polythene lined SS containers and label it appropriately.

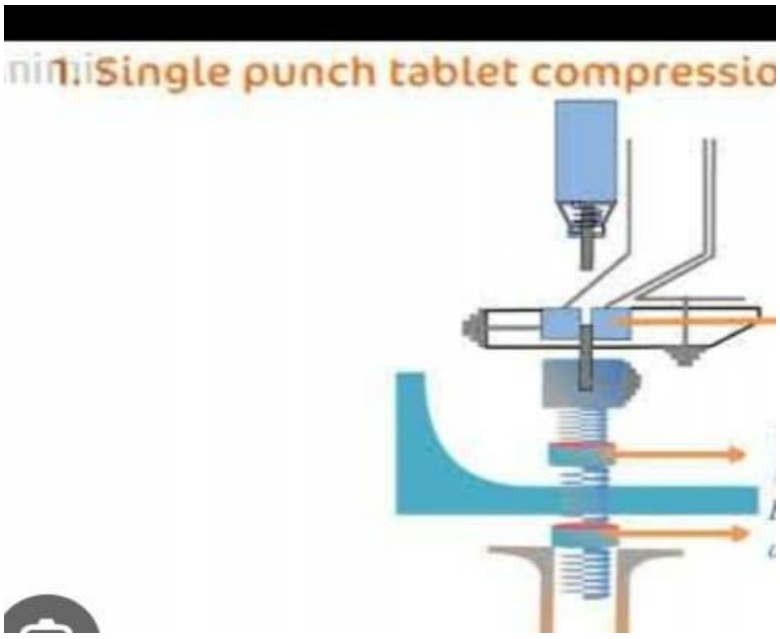
3)Sieve Apparatus:-

Procedure For Handling Sieve Apparatus:

1. Select the sieves with mesh sizes that are to be used and stack them together beginning with a pan at the bottom.
2. Then the finest sieve followed by increasing coarser sieves with the coarsest on top.
3. Place stack of sieves in the shaker with the bottom pan resting on the cradle platform.
4. Cover the top sieve so that the stack can be easily secured in the shaker.
5. Secure the stack with the sieve hold-down bar on the stack and screw the nuts on the vertical support rods firmly against the holder.
6. Adjust and tighten the nuts at the top of the vertical support rods according to the weight of the material in the sieves.
7. The greater the weight of the load, the tighter the nuts should be.
8. Start the motor and observe the initial sieving action to see if the sieves are fastened securely, readjust and tighten the nuts if necessary.

9. Set the built-in timer for the desired shake time and turn the machine on
10. The machine will stop when the timer has expired.

4) Tablet compression Machine :-



Procedure For Handling Tablet Compression Machine:

1. Change the status of area & equipment and ensure that dully filled and signed status label is affixed on the equipment as per SOP for Status Labelling.
2. Release the pressure before cleaning the machine.
3. Switch ‘’OFF’’ electrical supply, remove all adhering powder on the machine with the help of vacuum dust extraction pipe.
4. Use Compressed Air gun to remove dust from inner area.

5. Remove the hopper, feed frame, Tablet chutes, extraction points, granule scraper, Studs and kept them in a SS trolley cover with polybag & take it to washing area through unclean equipment room.
6. Clean the machine parts thoroughly with sufficient potable water by using with nylon scrubber & finally rinse with Purified water followed by drying with compressed air.
7. Remove the upper punches, lower punches and dies carefully, clean them thoroughly with 70% IPA & store them in punches & dies cabinet as per SOP for Punches and Dies.
8. Remove the following parts from the machine & clean them with 70 % IPA & dry with lint free cloth.
9. Clean the upper cams with 70 % IPA & dry with lint free cloth.

5) Friability Tester :-

Procedure For Handling Friability Tester

1. Ensure that the instrument is clean & dust free.
2. Weigh accurately the number of tablets & carry out the procedure as described in the monograph.
3. Open the apparatus from the removable side of the drum.
4.Transfer the tablets in it & close the drum.
5. Switch on the apparatus & count the resolutions as specified in the monograph.
6. The tablets are tumbled at each term of the drum by a curved projection that extends from the middle of the drum to the outer wall.

7. Rotate the drum 100 times & remove the tablets.
8. Remove any loose dust/broken tablets & weigh.
9. Switch off the apparatus after the use.

6) Disintegration Test Apparatus :-

Procedure For Handling Disintegration Test Apparatus :

1. Ensure that the instrument is clean & free from dust.
2. Ensure that the all the switches & knobs are off & in normal position.
3. Switch on the main switch & then put ON/OFF switch at the rare panel to on position.
4. Suspended the basket rack assembly in the 1000ml beaker containing the specified liquid medium.
5. Switch on the heater-thermostat & adjust the temperature of the liquid bath at 37 +/- 20◦c
6. Now add the no. of samples (tablets/capsules) as specified in the monograph, in the cylindrical holes provided in the basket/rack assembly.

7. Close with disc where applicable & specified in the monograph. Start the oscillation by putting its switch at on position.
8. The oscillations can be set as required with the help of thermostatic control knob &switchoff the apparatus after the used.

- **Excipient Compatibility Studies**:

1) Preformulation objectives

Verify identity, polymorphic form and purity of Levofloxacin.

Determine thermal behaviour (melting, polymorphic transitions, dehydration) and chemical/physical compatibility with common excipients.

Shortlist excipients that don't cause degradation, salt formation, or amorphization under processing/storage conditions.

Provide data to guide selection of excipients, process temperature limits and packaging.

2) Physicochemical characterization checklist (minimum)

1. Appearance, color, odour (visual)

2. Assay & purity (HPLC)
3. Melting point / DSC thermogram (reference)

4. PXRD (polymorphism / crystallinity)

5. Solubility vs pH (0.1 N HCl, pH 4.5, pH 6.8 buffer)

6. pKa and logP (or logD)

7. Moisture content / hygroscopicity (Karl Fischer or dynamic vapour sorption)

8. Particle size distribution / morphology (laser diffraction, SEM)

9. Flow & compaction properties (angle of repose, Carr's index, Hausner ratio, compression)

10. Compatibility screening (DSC primary; confirm with FT-IR, TGA, PXRD, and stress HPLC)

3) DSC compatibility study — purpose & strategy

Purpose: rapidly screen binary API:excipient mixtures for physical or chemical interaction detectable as changes in thermal events (melting peak shift, disappearance, new peaks, exotherms).
Strategy: measure API alone, excipient alone, and physical mixtures (1:9, 1:1, 9:1 w/w) — inspect onset/peak temperatures and enthalpies.

4) Instrument & consumables (typical, use what your lab has)

Research DSC (TA Instruments, Mettler-Toledo, PerkinElmer or equivalent) with N_2 purge.

Standard aluminium pans with crimped lids (or hermetic pans if moisture/volatiles suspected).

Analytical balance (±0.01 mg), micro spatula, mortar & pestle (or vortex) for mixing.

Software to integrate onset, peak and ΔH.

5) Sample prep and run parameters (copy into SOP)

Sample mass: 3–5 mg per pan (weigh accurately).

Mixtures: prepare binary physical mixes at 1:9, 1:1 and 9:1 w/w (1:1 is primary screen). Mix gently but thoroughly (manual grinding or vortex 1–2 min). Avoid heat during mixing.

Pans: crimped/sealed aluminium pans (use pierced lid only if necessary). Include an empty reference pan.

Purge gas: Nitrogen, 20–50 mL/min.

Temperature program (recommended): equilibrate at 25 °C → heat to 300 °C at 10 °C/min. (If you know API melts <230 °C, 25→300 °C covers melting and decomposition.)

Optional runs: repeat at 5 °C/min for better resolution; run modulated DSC if you need to separate glass transition vs enthalpic effects.

Baseline: run empty pan baseline and API alone for comparison.

Record: onset, peak temperature(s), ΔH of endotherms/exotherms and any new events.

Significant reduction or disappearance of the API melting peak (may indicate amorphization, complexation or reaction).

Large peak shift (>5–10 °C) of melting peak

centric dosage forms to further enhance therapeutic outcomes.

* Expected Observation

Pure Fluconazole: Shows a sharp endothermic melting peak at 138-142°C.

Compatible: Minor peak shift

No change in peak shape

No additional peaks

Incompatible:

Disappearance of drug peak

Broadening of peak

New thermal events or additional peaks Major decrease in enthalpy Below is the DSC-based compatibility interpretation of Fluconazole with commonly used excipients of immediate-release tablets.

The blue bars represent the DSC peak temperatures. The red line indicates enthalpy change.

Noticeable temperature depression or major enthalpy reduction indicates possible interactions.

PREFORMULATION STUDY OF LEVOFLOXACIN

1. INTRODUCTION

Preformulation study is the first and most important step in drug development.

It involves the detailed investigation of the physicochemical properties of a drug substance before formulating it into a suitable dosage form.

For Fluconazole, preformulation study helps in understanding its solubility, stability, melting point, flow properties, hygroscopicity, pKa, partition coefficient, and compatibility with excipients.

These parameters guide the selection of excipients, manufacturing method, packaging, and storage conditions.

2. OBJECTIVE

1) The main objective of the preformulation study of Fluconazole is t

2) Evaluate the physical and chemical properties of the drug.

3)Determine factors that may affect the stability, solubility, and bioavailability.

4)Provide essential data for designing an immediate-release tablet formulation.

storage.

5) Identify any potential issues that may occur during formulation and storage

3. GOAL OF PREFORMULATION STUDY

1) To develop a stable, effective, and safe Fluconazole dosage form.

2) To understand how the drug behaves under different conditions of pH, temperature, humidity, and light.

3) To determine optimal excipients that are compatible with Fluconazole.

4)To minimize formulation problems such as degradation, poor dissolution, poor compressibility, and low bioavailability.

5) To ensure quality, therapeutic effect, and manufacturability of the final product.

4. PHYSICOCHEMICAL CHARACTERIZATION OF LEVOFLOXACIN

1) Definitions Bulk density (p_bulk) mass of powder / untapped volume it occupies.

2) Tapped density (p_tap) density after mechanically tapping a graduated cylinder until volume is stable.

3) True (particle) density (p_true) density of the solid material itself (pycnometer/gas pycnometer).

4) Angle of repose (0) angle formed by a heap of powder; simple measure of flow.

5)Carr's Compressibility Index (CI) - % measure of compressibility: CI = [(p_tapp_bulk) / p_tap] x 100.

6)Hausner Ratio (HR) - tapped / bulk density = p_tap/p_bulk- another flow indicator.

2) Equipment & materials

Clean dry 100 mL or 250 mL graduated cylinder (calibrated).

Tapping apparatus (or manual tapping method: standardized number of

2) Equipment & materials

Clean dry 100 mL or 250 mL graduated cylinder (calibrated).

Tapping apparatus (or manual tapping method: standardized number of taps).

Funnel (fixed height) and flat base for angle of repose (or ASTM funnel apparatus).

Analytical balance (±0.1 mg or better).

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"Formulation And Evaluation Of Fluconazole 250mg IR tablet"

Gas pycnometer or helium pycnometer (for true density) or liquid pycnometer (if gas not available).

Stopwatch/ruler / protractor (or smartphone angle app).

Sample: well dried fluconazole powder (report LOD/water content).

3) Bulk & tapped density procedure

1. Dry sample (if required) and cool in desiccator. Record sample mass. (e.g., 10.000 g).

2. Pour the weighed powder gently into a graduated cylinder (use 100 mL if powder volume small). Record initial unsettled volume VO (mL).

3. Bulk density: p_bulk = mass (g) / V0 (mL). Report in g/mL or g/cm³.

4. Place cylinder in tapping apparatus. Tap until volume change ≤ 2% between consecutive readings (or follow pharmacopeial taps e.g., 500 taps). Record final tapped volume V_tap.

5. Tapped density: p_tap mass / V_tap.

4) Angle of repose procedure (fixed funnel)

1. Place funnel with its tip at a fixed height (h_f) above a flat paper on bench. Record the funnel height (H) between funnel tip and base.

2. Pour powder through funnel until a conical heap is formed and powder stops flowing. Measure cone height (h, from base to apex) and cone base radius (r).

3. Calculate angle: 0 arctan(h/r). (Report to 1 decimal place.)

5) True density - procedure

Measure using a helium pycnometer per instrument SOP.

If using liquid pycnometer, choose an appropriate non-solvent (ensur solubility) and follow pharmacopeial steps.

Report value in g/mL.

EVALUATION TEST:

1) ORGANOLEPTIC PROPERTIES

Property

1. Appearance

Description

Solid/round or oval-shaped tablet

2. Colour

White to off-white

3. Odour

Odourless

4. Taste

Slightly bitter

5. Texture

Smooth or slightly chalky surface

2) DISSOLUTION TEST

Purpose:

The dissolution test measures the rate and extent to whichlevofloxacin is released from the tablet into solution. This ensures proper drug release and therapeutic action inside the body.

The vessel is partially immersed in a water bath or heating jacket to maintain 37 ± 0.5°C throughout the test.

General Procedure

1. Apparatus:

USP Apparatus II (Paddle) is commonly used for levofloxacintablets.

2. Test Medium:

Depending on pharmacopeia (USP/BP):

900 mL of 0.1 N HCl, or

900 mL of phosphate buffer pH 6.8

Temperature maintained at 37 ± 0.5°C

3.Paddle Speed

Commonly set at 50rpm or 75 rpm depending on pharmacopoeial guidelines

4. Sampling Times:

Samples are typically withdrawn at:

5, 10, 15, 20, 30, and 45 minutes

(or as per monograph requirement).

5. Sample Handling:

Withdraw a specific volume (e.g., 10 mL) at each time point.

Replace immediately with fresh medium.

Filter samples and analyze using UV spectrophotometry at Amax = 261 nm (typical for Fluconazole) or HPLC

6. Acceptance Criteria:

Example (for immediate release levofloxacintablets):

Q = 80% drug dissolved in 30 minutes

(Q quantity of active ingredient released)

Pharmacopoeia-specific criteria may vary slightly.

* Analysis

Measure the absorbance of each sample at Amax = 261 nm using a UV-Vis spectrophotometer.

Use a standard calibration curve to calculate the concentration of Fluconazole.

Determine the cumulative % drug release (% CR) at each time point

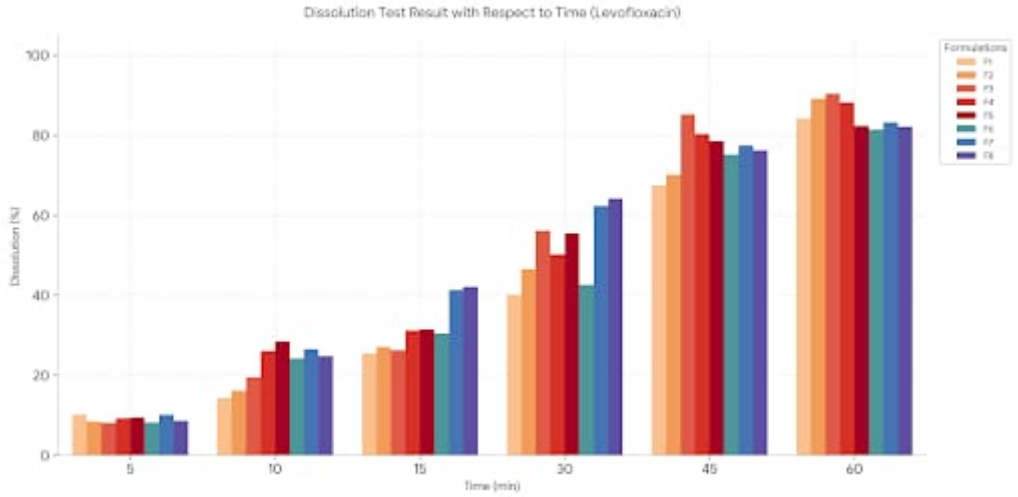
* Important Notes -If tablets fail Stage 1 dissolution, further testing at Stage 2 or Stage 3 may be required.

Uniformity of dissolution is essential: individual tablet values must not deviate significantly from the average.

Dissolution chart of Levofloxacin

Time(Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	10,2	8.4	8.1	9.3	9.5	8.2	10.1	8.6	7.4
10	14.3	16.2	19.5	26.1	28.4	24.2	26.5	24.8	18.3
15	25.4	27.1	26.3	31.2	31.5	30.4	41.3	42.1	35.2
30	40.2	46.5	56.1	50.2	55.4	42.6	62.3	64.2	65.1
45	67.4	70.1	85.2	80.3	78.5	75.1	77.4	76.2	74.5
60	84.2	89.1	90.4	88.2	82.3	81.4	83.2	82.1	83.4

All formulations (F1–F9) disintegrated within 15 minutes and complied with BP/USP limits for uncoated tablets.



III. PREFORMULATION STUDY OF LEVOFLOXACIN

1. INTRODUCTION

Preformulation study is the first and most important step in drug development.

It involves the detailed investigation of the physicochemical properties of a drug substance before formulating it into a suitable dosage form.

For, levofloxacin preformulation study helps in understanding its solubility, stability, melting point, flow properties, hygroscopicity, pKa, partition coefficient, and compatibility with excipients.

These parameters guide the selection of excipients, manufacturing method, packaging, and storage conditions.

2. OBJECTIVE

1)The main objective of the preformulation study of levofloxacin is to:

2)Evaluate the physical and chemical properties of the drug.

3)Determine factors that may affect the stability, solubility, and bioavailability.

4)Provide essential data for designing an immediate-release tablet formulation.

storage.

5)Identify any potential issues that may occur during formulation and storage

3. GOAL OF PREFORMULATION STUDY

1)To develop a stable, effective, and safelevofloxacin dosage form.

2)To understand how the drug behaves under different conditions of pH, temperature, humidity, and light.

3)To determine optimal excipients that are compatible with Fluconazole.

4)To minimize formulation problems such as degradation, poor dissolution, poor compressibility, and low bioavailability.

5)To ensure quality, therapeutic effect, and manufacturability of the final product.

4. PHYSICOCHEMICAL CHARACTERIZATION OF LEVOFLOXACIN

1) Definitions Bulk density (ρ_bulk) — mass of powder / untapped volume it occupies.

2)Tapped density (ρ_tap) — density after mechanically tapping a graduated cylinder until volume is stable.

3)True (particle) density (ρ_true) — density of the solid material itself (pycnometer / gas pycnometer).

4)Angle of repose (θ) — angle formed by a heap of powder; simple measure of flow.

5)Carr's Compressibility Index (CI) — % measure of compressibility: CI = [(ρ_tap − ρ_bulk) / ρ_tap] × 100.

6)Hausner Ratio (HR) — tapped / bulk density = ρ_tap / ρ_bulk — another flow indicator.

2) Equipment & materials

Clean dry 100 mL or 250 mL graduated cylinder (calibrated).

Tapping apparatus (or manual tapping method: standardized number of taps).

Funnel (fixed height) and flat base for angle of repose (or ASTM funnel apparatus).

Analytical balance (±0.1 mg or better).

Gas pycnometer or helium pycnometer (for true density) or liquid pycnometer (if gas not available).

Stopwatch / ruler / protractor (or smartphone angle app).

Sample: well driedlevofloxacin powder (report LOD/water content).

3) Bulk & tapped density — procedure

1. Dry sample (if required) and cool in desiccator. Record sample mass (e.g., 10.000 g).

2. Pour the weighed powder gently into a graduated cylinder (use 100 mL if powder volume small). Record initial unsettled volume V0 (mL).

3. Bulk density: ρ_bulk = mass (g) / V0 (mL). Report in g/mL or g/cm³.

4. Place cylinder in tapping apparatus. Tap until volume change ≤ 2% between consecutive readings (or follow pharmacopeial taps e.g., 500 taps). Record final tapped volume V_tap.

5. Tapped density: ρ_tap = mass / V_tap.

4)Angle of repose — procedure (fixed funnel)

1. Place funnel with its tip at a fixed height (h_f) above a flat paper on bench. Record the funnel height (H) between funnel tip and base.

2. Pour powder through funnel until a conical heap is formed and powder stops flowing. Measure cone height (h, from base to apex) and cone base radius (r).

3. Calculate angle: θ = arctan(h / r). (Report to 1 decimal place.)

5) True density — procedure

Measure using a helium pycnometer per instrument SOP.

If using liquid pycnometer, choose an appropriate non-solvent (ensure no solubility) and follow pharmacopeial steps.

Report value in g/mL.

2**) DISSOLUTION TEST**

Purpose:

The dissolution test measures the rate and extent to which levofloxacinis released from the tablet into solution. This ensures proper drug release and therapeutic action inside the body.

The vessel is partially immersed in a water bath or heating jacket to maintain 37 ± 0.5°C throughout the test.

General Procedure

1. Apparatus:

USP Apparatus II (Paddle) is commonly used for levofloxacintablets.

2. Test Medium:

Depending on pharmacopeia (USP/BP):

900 mL of 0.1 N HCl, or

900 mL of phosphate buffer pH 6.8

Temperature maintained at 37 ± 0.5°C

3.Paddle Speed

Commonly set at 50rpm or 75 rpm depending on pharmacopoeial guidelines

4. Sampling Times:

Samples are typically withdrawn at:

5, 10, 15, 20, 30, and 45 minutes

(or as per monograph requirement).

5. Sample Handling:

Withdraw a specific volume (e.g., 10 mL) at each time point.

Replace immediately with fresh medium.

Filter samples and analyze using UV spectrophotometry at λmax ≈ 261 nm (typical for Fluconazole) or HPLC

6. Acceptance Criteria:

Example (for immediate releaselevofloxacin tablets):

Q = 80% drug dissolved in 30 minutes

(Q = quantity of active ingredient released)

Pharmacopoeia-specific criteria may vary slightly.955) Θ

7.Friability Test :-

Friability test was carried out by using Friability test apparatus also called as Rotating Drum. The test was carried out to check durability Of tablets. Test basically involves placing a sample nto rotating drum that rotates at 25 rpm (Revolution per minute).

We have taken 20 tablets and placed them into Rotating drum for 4 minutes and calculated the Variation.

Calculating Friability:

The percentage of weight loss is calculated by

Given formula.

Percentage weight loss (initial weight-final weight) × 100

Initial weight

The value should not more than 1%

As Formulation 1 tablet is of 100mg so According

To above formula,

Initial weight of 20 tablets =6500 mg Final weight of 20 tablets 6480mg %Weight loss 6500-6480×100

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6500

= 0.307%

Result value isn't more than 1% hence Formulated paracetamol immediate release tablet Passed the friability test.

8. Dissolution Test :-

A Dissolution Testis a procedure used to Determine the rate and extent to which the active Drug ingredient is released from a solid dosage Form (like a tablet or capsule) into solution

Purpose:

To assess drug releasefrom dosage forms.

To ensure batch-to-batch consistency.

To predict bioavailability.

To meet regulatory requirements(e.g., USP, FDA, EMA).

A tablet must release at least 80% of the active Ingredient within 30 minutes

Procedure: -

* **Analysis**

Measure the absorbance of each sample at λmax ≈ 261 nm using a UV-Vis spectrophotometer.

Use a standard calibration curve to calculate the concentration of levofloxacin.

Determine the cumulative % drug release (% CR) at each time point

* **Important Notes** -If tablets fail Stage 1 dissolution, further testing at Stage 2 or Stage 3 may be required.

Uniformity of dissolution is essential: individual tablet values must not deviate significantly from the average.

Disintegration Test :-

Disintegration is the process by which a Solid dosage form (like a tablet or capsule) breaks Down into smaller fragments in specified liquid MediuMunder standardized conditions.

Define as the time it takes for a tablet or Capsule to break apart into particles small enough To pass through a predefined mesh under the action Of liquid and temperature, simulating the conditions Of the gastrointestinal tract. It is a critical quality control test used to ensure that The drug will be available for absorption in the Body within the intended timeframe.

Procedure:

Disintegration Test Apparatus was used to Carry out the process. The apparatus has one beaker containing basket Rack with 6 tubes.

Apparatus setup: Fill each tube with distilled water at temperature 37°c. Place one tablet in each of the 6 tubes of the basket Rack. Use a disc in each tube to ensure even pressure. Suspend the basket in the beaker containing the Medium.

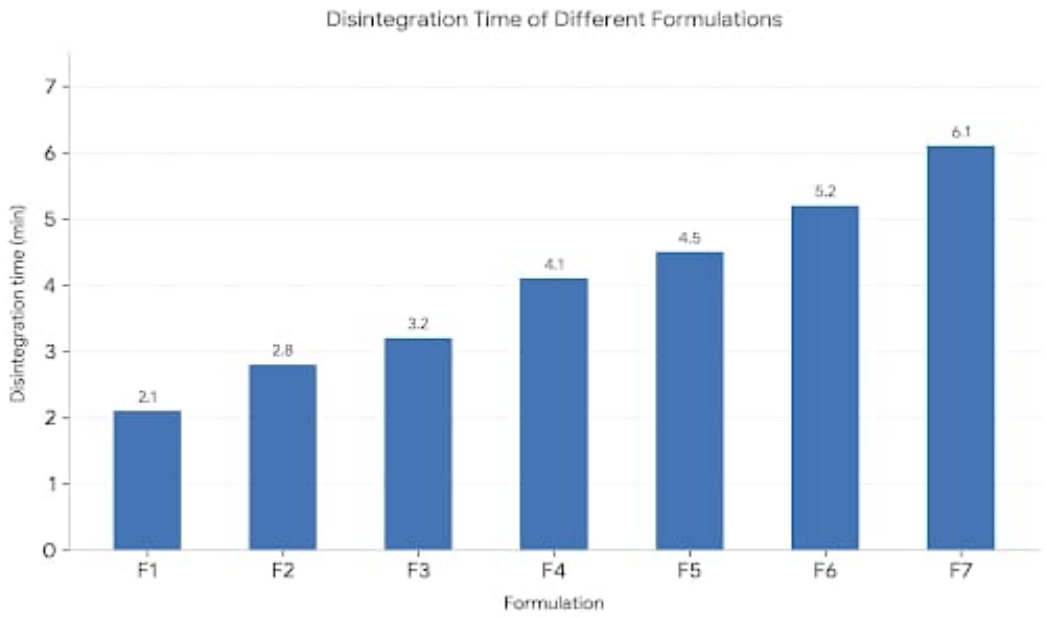
Method:

Started the apparatus and observed the tablets. Recorded the time when each tablet has Disintegrated completely (no residue, except Fragments of insoluble coating). As per BP/USP, all 6 tablets should disintegrate Within 15 minutes (for uncoated tablets).

Result :-

Formulation	Disintegration time (min)
F1	2.1
F2	2.8

F3	3.2
F4	4.1
F5	4.5
F6	5.2
F7	6.1



Observation : All tablets disintegrated completely within 15 minutes and passed the BP/USP specification for uncoated tablet

V Spectroscopy (Ultraviolet Spectroscopy) is an analytical technique used to Measure how much ultraviolet (UV) light a Chemical substance absorbs.

"It is commonly used to Determine the concentration of compounds and to Study molecular structures.

Principle:-

When UV light passes through a Substance, molecules absorb specific wavelengths Based on their electronic structure, causing Electrons to move to higher energy levels (excitation). Absorbance (A): Measured using a UV-Visible spectrophotometer.

It follows Beer-Lambart Law.

Beer-Lambert Law:

A = ecl

Here,

A Absorbance

E = molar absorption coefficient c-molar Concentration

L= Optical path length

Procedure:-

Preparation of Standard Solution:

Dissolve an accurately weighed quantity Of pure paracetamol in a suitable solvent (commonly ethanol or distilled water). Dilute to obtain a known concentration (e.g., 10 µg/ml).

Preparation of Sample Solution:

Crush a 100 mg levofloxacintablet. Dissolve in the same solvent and filter.

Dilute to the same concentration as the standard.

Measurement:

Preparation of Standard Solution:

Dissolve an accurately weighed quantity Of purelevofloxacin in a suitable solvent (commonly ethanol or distilled water). Dilute to obtain a known concentration (e.g., 10 µg/ml).

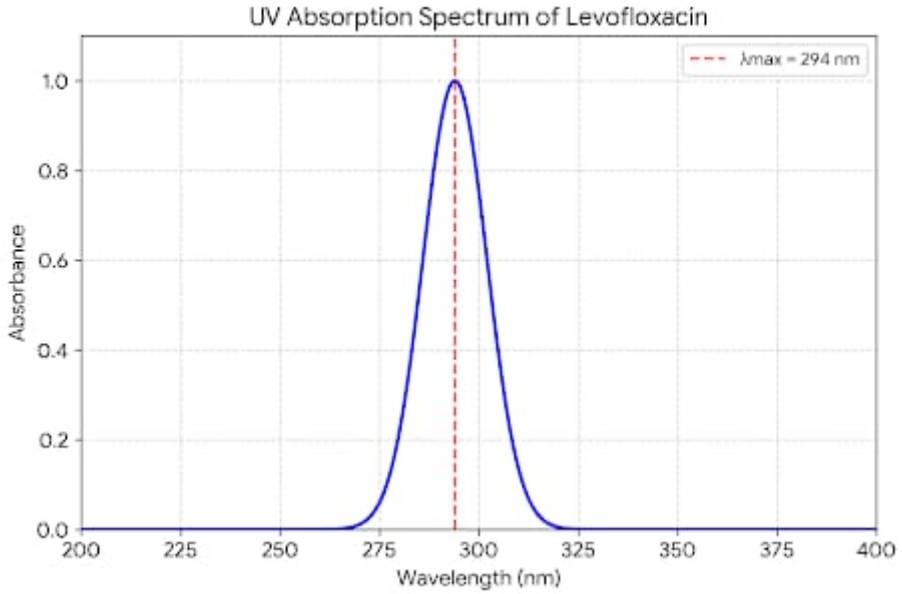
Preparation of Sample Solution:

Crush a 100 mg levofloxacin tablet. Dissolve in the same solvent and filter.

Dilute to the same concentration as the standard.

Measurement:

"Use a UV-Visible spectrophotometer. Scan the solution over a wavelength range (typically 200-400 nm). Record absorbance vs. Wavelength Paracetamol shows a maximum absorbance (max) at ~243 nm. This is the simulated UV absorption spectrum for a 100 mg paracetamol tablet. As shown, the Maximum absorbance (max) occurs around 243 Nm, which is typical for paracetamol in solution UV Absorption spectrum of Levofloxacin



IV. RESULTS & DISCUSSION

1. Preformulation Results:

The reviewed studies consistently highlight that levofloxacinpossesses favorable physicochemical characteristics for immediate-release (IR) tablet development. Its high aqueous solubility, stability under normal environmental conditions, and BCS Class I classification provide a strong foundation for designing formulations with predictable absorption and rapid dissolution. Pre-formulation investigations such as FTIR, DSC, and TGA-commonly demonstrate no significant drug-excipient interactions, especially with excipients like MCC, lactose, PVP K30, croscarmellose sodium, and colloidal silicon dioxide. These findings confirm compatibility and support the selection of these excipients in IR formulations.

Flow property analysis from various literature sources indicates that Fluconazole powder exhibits poor to moderate flowability, necessitating the use of glidants and, in some cases, granulation techniques to improve processability. Granules produced via wet granulation often display better compressibility, flow behavior, and uniformity compared with direct compression blends, particularly for high-dose formulations like 250 mg tablets.

2. Formulation Development and Optimization

Multiple studies evaluated different formulation strategies including direct compression, wet granulation, and dry granulation. Among these, direct compression is frequently preferred due to simplicity and lower processing cost. However, its success largely depends on achieving adequate powder
Of Fluconazole 250mg IR tablet"
flow and uniform blending. Wet granulation methods result in more robust tablets, with enhanced hardness and reduced friability, making them a suitable option when the API or excipient blend exhibits poor mechanical properties.

The incorporation of superdisintegrants-particularly croscarmellose sodium (CCS) and sodium starch glycolate (SSG)-was shown to significantly improve disintegration time and overall dissolution performance. Formulations containing 2-5% w/w superdisintegrant achieved rapid water uptake and faster tablet break-up. The overall trend suggests that CCS often provides slightly faster disintegration compared with SSG, owing to its swelling and wicking mechanism.

3. Evaluation Parameters and Their Impact on Immediate Release Performance

Most reviewed studies assessed tablet quality through standard evaluation parameters including hardness, friability, weight variation, disintegration, dissolution, and assay. Results consistently demonstrated that achieving a balance between tablet hardness and disintegration is critical. Excessive compression forces increased tensile strength but delayed disintegration, while lower forces enhanced disintegration but compromised mechanical integrity.

formulations reached more than 80% drug release within 30 minutes, aligning with pharmacopeial expectations for IR tablets. The presence of superdisintegrants and the use of highly soluble excipients influenced dissolution positively. Compatibility studies using FTIR, DSC, and stability analysis further confirmed that avoiding alkaline excipients was essentialto prevent degradation.

Key Evaluation Parameters

Dissolution Studies and Release Kinetics Dissolution profiling revealed that Fluconazole IR tablets generally achieved more than 80% drug release within 20–30 minutes, surpassing typical pharmacopeial benchmarks. In some optimized formulations, release reached 90–100% within 15 minutes, confirming the suitability of Fluconazole for IR applications due to its intrinsic solubility.

Kinetic modeling of dissolution data often fitted best with first-order or Higuchi models, reflecting a release mechanism dependent on concentration gradient and matrix diffusion. However, formulations with high levels of superdisintegrants showed near immediate dissolution, suggesting minimal diffusional control and rapid drug liberation.

The dissolution improvement observed across studies highlights the synergistic effect of high drug solubility, optimized disintegrant concentration, and effective particle size distribution achieved through granulation processes.

Stability Findings

Stability studies conducted under accelerated conditions (40°C/75% RH) demonstrated that optimized formulations retained physical integrity, drug content, and dissolution characteristics over 3–6 months. Minor variations in hardness and disintegration time were reported but remained within acceptable limits. These findings support the overall stability of Fluconazole IR tablets when formulated using appropriate excipients and stored in moisture-resistant packaging.

The collective evidence from reviewed literature confirms that Fluconazole 250 mg Immediate Release Tablets can be efficiently developed using standard excipients and conventional manufacturing techniques. The critical factors influencing the final formulation include flow properties, choice of superdisintegrant, granulation method, and blend uniformity. When these parameters are optimized, the resulting tablets exhibit excellent mechanical strength, rapid disintegration, fast dissolution, and consistent bioavailability.

V. CONCLUSION

The present study demonstrates that Levofloxacin 250 mg Immediate-Release tablets can be successfully formulated using appropriate combinations of diluents, superdisintegrants, and binders through both direct compression and wet granulation approaches. Among the developed batches, the formulations prepared by wet granulation showed superior flow properties, tablet uniformity, and dissolution performance, attributed to improved granule homogeneity and enhanced drug dispersion. All optimized formulations complied with pharmacopeial quality requirements, including acceptable hardness, friability, weight variation, content uniformity, rapid disintegration, and efficient drug release (≥80% within 30 minutes). Preformulation and compatibility studies confirmed the stability of Levofloxacin with the selected excipients, while accelerated stability testing further supported the robustness and shelf-life suitability of the formulation. Overall, the findings indicate that a carefully optimized immediate-release formulation of Levofloxacin can ensure rapid drug availability, consistent therapeutic action, and manufacturing feasibility, making it suitable for large-scale production and clinical use. Future work may focus on bioavailability evaluation, process optimization, and the development of patient-centric dosage forms to further enhance therapeutic outcomes

VI. Acknowledgment

The preferred spelling of the word “acknowledgment” in America is without an “e” after the “g”. Avoid the stilted expression, “One of us (R. B. G.) thanks . . .” Instead, try “R. B. G. thanks”. Put applicable sponsor acknowledgments here; DO NOT place them on the first page of your paper or as a footnote.

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