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Comparative Study of the Dissolution Profiles of IRBEZART® 150 mg (Generic) and APROVEL® 150 mg (Reference Drug).

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List of Abbreviations

API: Active Pharmaceutical Ingredient

ARB: Angiotensin II Receptor Blocker

AT1: Angiotensin II Type 1 Receptor

BP: British Pharmacopeia

BSC: Biopharmaceutics Classification System

CIOMS: Council for International Organizations of Medical Sciences

CTD: Common Technical Documents

CV: Variation Coefficient

DRTL: Dissolution Research and Testing Laboratory

EMA: European Medicines Agency

ESC: European Society of Cardiology

FDA: Food and Drug Administration

GI: Gastrointestinal

GIT: Gastrointestinal Tract

GLP: Good Laboratory Practices

GMP: Good Manufacturing Practices

HCL: Hydrochloric Acid

HPLC: High-Performance Liquid Chromatography

ICH: International Council for Harmonization

IP: Indian Pharmacopeia

IPC: In-Process Control

IR: Immediate Release

IUPAC: International Union of Pure and Applied Chemistry

IVIVC: In Vitro-In Vivo Correlation

KP: Kilopond

LDM: Laboratoires de Diagnostic Maghrébins

MR: Modified Release

NDA: New Drug Application

OSD: Oral Solid Dosage

PEG: Polyethylene Glycol

PQC: Physicochemical Quality Control

PVDC: Polyvinylidene Chloride

PVA: Polyvinyl Alcohol

PVC: Polyvinyl Chloride

pH: Potential of Hydrogen

Ph.Eur: European Pharmacopeia

Ph.Int: International Pharmacopeia

QA: Quality Assurance

QC: Quality Control

RH: Relative Humidity

R&D: Research and Development

RSD: Relative Standard Deviation

USAN: United States Adopted Names

USP: United States Pharmacopeia

UV: Ultraviolet

WHO: World Health Organization

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General introduction

1- General introduction

The absorption of a drug after oral administration depends on three main steps: first, the active pharmaceutical ingredient (API) must be released from its dosage form; second, it must dissolve in the physiological fluids of the gastrointestinal tract (GIT); and third, it must permeate the intestinal epithelium to reach systemic circulation. That being said, drug release and dissolution play a key role, making *in vitro* dissolution testing a valuable predictor of *in vivo* drug performance (ICH M9, 2019; WHO, 2023).

In recent years, dissolution testing has become increasingly important to both pharmaceutical manufacturers and regulatory agencies to predict the *in vivo* performance of oral solid dosage forms and to support bioequivalence claims. It is now a mandatory requirement for marketing authorisation. These tests have evolved considerably and serve as essential tools for quality control, guaranteeing consistency between production batches, guiding formulation development, and providing insight into the drug′s bioavailability profile (EMA, 2023; WHO, 2023).

Hypertension and cardiovascular diseases remain leading causes of morbidity and mortality worldwide, necessitating effective antihypertensive therapies. Irbesartan, an angiotensin II receptor antagonist, is widely prescribed for managing hypertension and diabetic nephropathy. The availability of generic formulations such as IRBEZART® provides cost-effective alternatives to brand-name drugs like APROVEL®, thereby improving patient accessibility. However, ensuring therapeutic equivalence between generic and reference products is essential for maintaining clinical efficacy and safety.

This study aims to:

- Investigate the dissolution kinetics of the API irbesartan from an immediate-release generic tablet, **Irbezart® 150 mg**, produced by the LDM group in Algeria ;
- Compare the dissolution profiles of IRBEZART® 150 mg (generic) and APROVEL® 150 mg (reference drug) ; produced by Sanofi in France, under standardized conditions.
- Determine the therapeutic equivalence of the generic tablet relative to the reference drug, to support its substitution in today’s clinical practice.

This dissertation is structured in two main parts. The first is the theoretical one that covers three main subjects; general principles of pharmacology, antihypertensive drugs, and dissolution kinetics with biopharmaceutical classifications. The second is the practical section which was conducted at the *Laboratoires de Diagnostic Maghrébins* (LDM) in Elkhroub, Algeria. This part details the materials and methods used to study the dissolution kinetics of **Irbezart® 150 mg** tablets, presents the results, and interprets the findings.

Bibliographic review

2. Bibliographic Review

2.1. Pharmacology and Drug Generalities

2.1.1. Pharmacology

Pharmacology is the scientific study of how drugs interact with living organisms, encompassing the entire journey of a drug from its origin to its effects on the body. This includes understanding:

- History and sources of drugs
- Physicochemical properties
- Dosage forms
- Routes of administration
- Pharmacokinetics
- Pharmacodynamics
- Clinical uses
- Potential adverse effects (Ritter et al., 2023).

There are several branches of pharmacology, among which a key branch is:

2.1.1.1. Clinical Pharmacology

This branch focuses on evaluating the pharmacological actions of drugs in humans, determining the optimal routes of administration, and establishing safe and effective dosage ranges through clinical trials. It bridges basic pharmacological science with clinical practice. Its aim is to optimise therapeutic outcomes and reduce adverse effects (Lertora & Vanevski, 2012; CIOMS, 2017).

2.1.1.2. Pharmacy

Pharmacy complements pharmacology by dealing with the identification, selection, standardisation, compounding, preservation, and dispensing of medicinal substances to ensure their quality and safety.

Within pharmacology, two fundamental concepts guide drug action and disposition:

2.1.1.3. Pharmacodynamics

Pharmacodynamics studies what the drug does to the body, including the biological and therapeutic effects mediated through interactions with cellular targets. Drugs can act upon the body as:

- Enzyme inhibitors
- Hormones
- Neurotransmitter substances
- Inhibitors of transport processes
- Blockers of neurotransmitter inactivation (Rang et al., 2023)

2.1.1.4. Pharmacokinetics

Pharmacokinetics examines what the body does to the drug. It covers:

- Absorption
- Distribution
- Metabolism
- Excretion (ADME)

These processes influence drug concentration and duration of action (Rang et al., 2023). In in vivo bioequivalence studies, the pivotal pharmacokinetic parameters AUC (area under the concentration-time curve) and Cmax (maximum concentration) are generally used to assess the rate and extent of drug absorption (ICH M9, 2019).

2.1.1.5. Pharmacotherapeutics

"Pharmacotherapeutics focuses on the rational selection and use of drugs to prevent and treat diseases effectively" (Brunton et al., 2020).

2.1.1.6. Pharmacovigilance

Pharmacovigilance (PV) encompasses the coordinated activities, measures, and systems implemented within the pharmaceutical industry to ensure the ongoing safety of medicines throughout their lifecycle. According to the World Health Organization (WHO), pharmacovigilance is defined as:

"The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problems."

The development of pharmacovigilance was driven by historical drug safety tragedies, such as chloroform-related deaths in the 19th century and the 1937 sulphanilamide disaster, which highlighted the critical need for systematic drug safety monitoring (Kumar et al., 2023).

Modern pharmacovigilance systems have advanced considerably, incorporating spontaneous adverse event reporting, signal detection methodologies, and risk management strategies. Despite these improvements, challenges persist, including underreporting of adverse drug reactions (ADRs), variability in data quality, and regulatory disparities across regions. Ongoing efforts aim to enhance education and awareness, improve surveillance infrastructure, harmonise regulations, and integrate emerging technologies such as artificial intelligence and automation to improve the timeliness and accuracy of safety monitoring (Kumar et al., 2023).

2.1.1.7. Pharmacopoeia

Pharmacopoeia is a legally binding collection of standards and quality specifications for medicines used in pharmaceutical manufacturing and quality control. It includes tests for identity, purity, potency, and performance characteristics such as dissolution testing and stability. Examples include:

- British Pharmacopoeia (BP)
- United States Pharmacopoeia (USP)
- European Pharmacopoeia (Ph. Eur.)
- Indian Pharmacopoeia (IP)
- International Pharmacopoeia (Ph. Int.) (Julius & Naffisa, 2024; WHO, 2020)

2.1.2. Generalities on Drugs

2.1.2.1. Definition of a Drug

A drug is generally defined as any substance or mixture of substances intended to be used in the diagnosis, treatment, mitigation, or prevention of disease, or to affect the structure or any function of the body (WHO, 2023).

A drug is generally composed of two main components:

- **Active Pharmaceutical Ingredient (API):** The pharmacologically active substance that produces the intended therapeutic effects. Its dosage depends on the patient's physiological condition (e.g., child or adult). Most often, the API constitutes a small proportion of the drug compared to the excipients (Makkad, 2017).
- **Excipient:** An inert substance from a therapeutic standpoint, used to facilitate drug preparation, enhance appearance or taste, ensure preservation, and aid in administration and absorption of the API.

2.1.2.2. Excipients Used in Tablets

"Excipients are used in multiple areas and formats, depending on the type of medication, the route of administration, and the specific needs of the patient" (DC Fine Chemicals, 2024). Examples include:

- **Diluents:** Fillers added to tablets to increase volume and influence drug release.
- **Binders:** Help ingredients stick together during tablet formation.
- **Disintegrants:** Facilitate the breakdown of tablets into smaller fragments in the body.
- **Lubricants:** Reduce friction during tablet manufacturing, preventing sticking to equipment.
- **Glidants:** Improve the flow properties of powders or granules.
- **Preservatives:** Extend shelf life and prevent microbial contamination (Makkad et al., 2025).

2.1.2.3. Drug Discovery and Background

The pharmaceutical industry experienced substantial growth during and after World War II. This was driven by the need for reliable domestic drug production due to disrupted supply chains and the demand for lifesaving medications. A landmark achievement from this period was the commercial availability of penicillin in 1944, 15 years after its discovery by Sir Alexander Fleming in the UK.

Since then, scientific innovation has led to numerous new drugs and therapies, significantly improving global health. Modern research focuses on understanding disease mechanisms at a molecular level, enabling targeted drug design and novel therapeutic strategies.

One of the most significant recent advancements is the growth of **biologic medicines**, including monoclonal antibodies, therapeutic proteins, immunotherapies, and vaccines. These are transforming treatment across many disease areas. Biologics are the fastest-growing segment in the prescription drug market and are expected to maintain this trajectory.

Additionally, new dosage forms, strengths of previously approved drugs, generics, and biologics are regularly approved. Many pharmaceutical companies operate internationally, with drugs often reaching foreign markets before domestic ones. Regulatory approval varies by country, but global collaboration—especially through the **International Council for**

Harmonisation (ICH)—is promoting the alignment of standards and more streamlined approval processes (Lloyd V. et al., 2014).

2.1.2.4. Sources of Drugs

New drugs can be derived from natural sources, synthesised in laboratories, or developed through biotechnology. Historically, many drugs were discovered accidentally, but today, research is primarily targeted toward specific disease mechanisms. The main sources of drugs include:

a) Natural Sources

- **Plants:**

  Plants have historically been a rich source of medicinal compounds. Notable examples include **reserpine** from *Rauwolfia serpentina*, and **vincristine** and **vinblastine** from *Vinca rosea*. Only a small fraction of known plant species has been studied for therapeutic potential. Plant-based compounds may be used directly or chemically modified into semi-synthetic drugs, such as **cortisone** and **oestrogens** derived from *Dioscorea* species.

- **Animals:**

  Biologically active substances are also derived from animals. Examples include **insulin**, **thyroid extract**, and **pituitary hormones**, typically extracted from the glands of cattle, sheep, and pigs. **Oestrogens** can be obtained from the urine of pregnant mares. Animal tissues are also essential in vaccine production.

b) Laboratory Synthesis

- **Synthetic Drugs:**

  These are entirely developed in the laboratory by organic chemists. While early synthetic drugs were often discovered through trial and error, modern synthesis involves rational drug design targeting specific biological mechanisms.

- **Semi-Synthetic Drugs:**

  These are chemically modified natural products. The modifications improve pharmacological properties such as efficacy, safety, and bioavailability, making the drugs more effective for therapeutic use (Lloyd et al., 2014).

- **Biotechnology-Derived Products:**
  Biotechnological advancements have greatly expanded drug development. Techniques such as fermentation and recombinant DNA are used to produce active ingredients like **hormones**, **monoclonal antibodies**, and **antibiotics** (Almeida et al., 2011).
    - **Recombinant DNA Technology:**
      This involves inserting human genes into microorganisms to produce therapeutic proteins like **insulin**, **growth hormone**, **interferons**, and the **hepatitis B vaccine**.
    - **Monoclonal Antibodies (mAbs):**
      Produced by stimulating immune cells to generate targeted antibodies, mAbs are widely used in diagnostics (e.g., pregnancy tests) and in the treatment of various diseases (Lloyd et al., 2014).
    - **Gene Therapy:**
      Gene therapy involves modifying a patient's genetic material to treat or prevent disease. It may work by:
      a) Replacing a disease-causing gene with a healthy copy,
      b) Inactivating a malfunctioning gene, or
      c) Introducing a new or modified gene into the body.
      Common gene therapy tools include **viral vectors**, **plasmid DNA**, and **gene-editing technologies** (FDA, 2018).

2.1.2.5. Drug Nomenclature

Drug nomenclature is a standardised system used to name pharmaceutical substances, ensuring clarity and safety in medical communication. Since drugs can be identified by multiple names (chemical, generic, brand), standardisation helps prevent confusion among healthcare professionals and regulators.

The nomenclature process includes:

- **Empirical formula:** Denotes the elemental composition.
- **Chemical name:** Assigned based on IUPAC rules, reflecting the molecular structure.
- **Code number:** Used during research and development (e.g., SQ 14,225 for captopril).

- **Nonproprietary (generic) name:** A simplified, commonly used name (e.g., **amoxicillin**), assigned by the U.S. Adopted Names (USAN) Council in collaboration with the FDA.
- **Brand name:** Assigned by the manufacturer for commercial purposes.

Generic names must meet specific criteria:

- Unique and unambiguous,
- Easy to pronounce (preferably one word, no more than four syllables),
- Often include a class-indicating suffix (e.g., "-olol" for beta-blockers).

Note: USAN designations are only granted to single chemical entities, not combination products (Lloyd et al., 2014).

2.1.2.6. Drug Development and Approval Process

The drug development and approval process is a multi-phase journey designed to ensure safety, efficacy, and quality. This process applies to both innovative (brand-name) and generic drugs.

a. Preclinical Research

- Synthesis and characterisation of compounds.
- Short-term and long-term **animal testing**.
- Submission of safety data for a 30-day review before human trials.

b. Clinical Research

- **Phase 1:** First-in-human trials to assess safety.
- **Phase 2:** Evaluation of effectiveness and side effects.
- **Phase 3:** Large-scale trials confirming efficacy and monitoring adverse events.

c. New Drug Application (NDA) Review

- Submission of the NDA to regulatory authorities (e.g., FDA).
- Review and approval decision.

d. Post-Marketing Surveillance

- Ongoing monitoring of adverse reactions.
- Surveys and sampling tests.

- Inspections of manufacturing and distribution facilities.

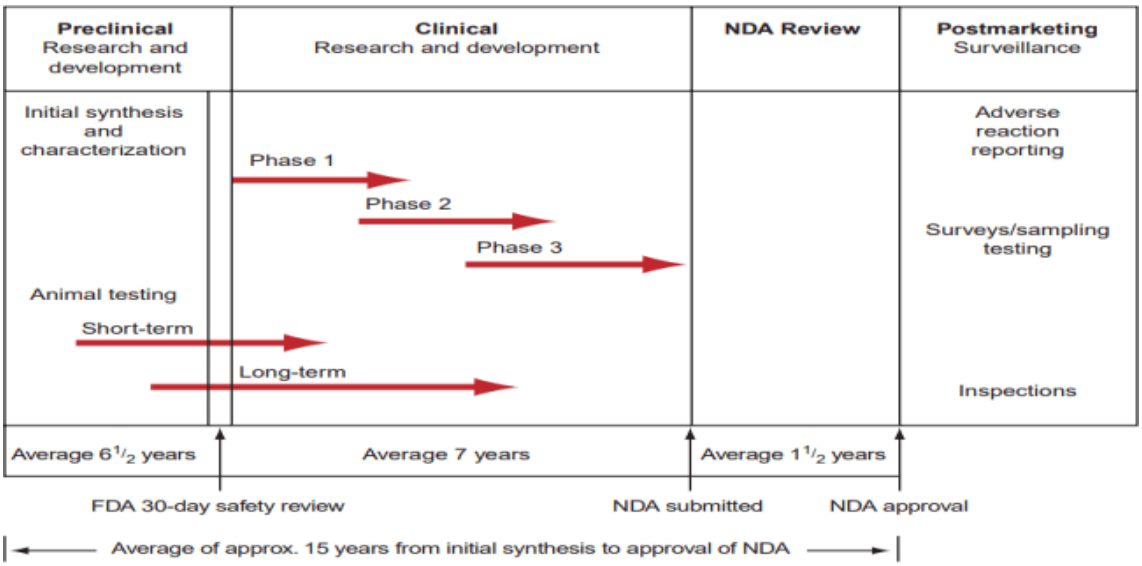

Figure 1: Overview of the drug development process (PhRMA, 2012).

2.1.3. Dosage Forms

"Drugs are typically administered as formulated preparations rather than as pure substances" *(*Aulton e*t al., 2014).*

Dosage forms are pharmaceutical preparations designed to deliver a drug safely, efficiently, and in a patient-acceptable manner. They contain **excipients** to help solubilise, stabilise, preserve, and enhance drug performance.

Key considerations in dosage form design include:

- Drug stability
- Dose uniformity
- Patient acceptability
- Bioavailability

Dosage forms are selected based on the type of disease, route of administration, and specific patient needs. Common examples include:

- **Oral**: tablets, capsules, syrups
- **Parenteral**: injections
- **Topical**: creams, ointments
- **Inhalation**: aerosols, powders

Even for complex biotechnological and polymer-based drugs, formulation principles remain the same. These are often delivered via parenteral or respiratory routes. Effective dosage form design requires the integration of **biopharmaceutical**, **physicochemical**, and **therapeutic** factors (Aulton et al., 2014).

2.1.3.1. Classification of Dosage Forms

Dosage forms can be classified according to four main criteria:

- Route of administration
- Physical form
- Uses and applications
- Site of application

  (Choudhary, 2025)

a) Classification According to Route of Administration

Each administration route requires specific formulations to overcome biological barriers, enhance drug absorption, and improve patient compliance. The choice of route depends on the drug's properties, the desired onset and duration of action, and the condition being treated.

Table 1: Dosage forms for different administration routes (Aulton & Taylor, 2018).

Administration Route	Dosage Forms
Oral	Solutions, syrups, suspensions, emulsions, gels, powders, granules, capsules, tablets
Rectal	Suppositories, ointments, creams, powders, solutions
Topical	Ointments, creams, pastes, lotions, gels, solutions, topical aerosols, foams, transdermal patches
Parenteral	Injections (solution, suspension, emulsion), implants, irrigation and dialysis solutions
Respiratory	Aerosols (solution, suspension, emulsion, powder), inhalations, sprays, gases
Nasal	Solutions, inhalations
Eye	Solutions, ointments, creams
Ear	Solutions, suspensions, ointments, creams

b) Classification According to Physical Form

Drugs can also be classified by their physical form. Each form is selected based on physicochemical properties, route of administration, and intended use.

Table 2: Dosage forms based on physical form (Aulton & Taylor, 2018).

Physical Form	Use	Dosage Forms
Solid	Internal Use	Tablets, Capsules, Pills, Granules, Effervescent Granules, Fine Powder
	External Use	Dusting Powder, Insufflations, Dentifrices, Snuff
Semi-solid	—	Ointments, Creams, Gels, Pastes
Liquid	Internal Use	Syrups, Linctus, Drops, Elixirs
	External Use	Liniments, Lotions, Gargles, Throat Paints, Mouthwashes, Sprays, Eye Lotions, Eye Drops, Nasal Drops
	—	Emulsions, Suspensions
Gaseous	—	Inhalers, Aerosols

In our study, we focused more on **tablets**, which fall under **oral solid dosage (OSD) forms**.

2.1.3.2. Oral Solid Dosage (OSD) Forms

This term refers to a final drug product ingested through the mouth, dissolved in the digestive tract, and absorbed into the bloodstream. OSDs dominate the pharmaceutical market for three main reasons:

- Convenient oral administration
- Clear physical differentiation
- Optimised manufacturing processes

(DiPospero, 2024)

a) Types of OSD Forms

- **Tablets:** Compressed mixtures of active pharmaceutical ingredients (APIs) and excipients.
- **Capsules:** APIs enclosed in hard or soft soluble shells.
- **Granules:** Agglomerated particles of APIs and excipients.
- **Sachets:** Granules or powders packed in pouches for single-dose use.
- **Lozenges:** Flavoured solid doses that dissolve slowly in the mouth (Dhudhat, 2022).

Tablets and capsules are the most common OSDs. Tablets may be coated or uncoated. Capsules often involve layering the drug substance and dry ingredients around a seed material. Each form may differ in bioavailability and release profile, depending on therapeutic use. Therefore, manufacturing platforms, equipment, and technologies must be adapted accordingly.

The main goal of OSD production is to ensure uniform ingredient distribution and consistency in dissolution and bioavailability (DiPospero, 2024).

2.1.4. Manufacture of Tablets

"Although the unit operations may involve various equipment and technologies, there is a well-defined progression from raw materials into the final product." *(DiPospero,* 2024).

Tablet production follows a systematic process:

1. **Raw Material Preparation:** All APIs and excipients are tested for quality and compliance with pharmacopoeial standards. Approved materials are accurately weighed and dispensed.
2. **Granulation:** Improves flow and compression characteristics. Two methods exist:
    - **Wet Granulation:** A granulating liquid is added to form a wet mass, which is then dried and sieved into uniform granules. This method is most common due to enhanced compressibility.
    - **Dry Granulation:** Used for moisture-sensitive materials. Powders are compressed into larger masses and then milled into granules (Philanto Wellness, 2024).

3. **Blending:** Ensures uniform mixing of APIs and excipients. This may occur before and after granulation, depending on the formulation (DiPospero, 2024).
4. **Tablet Compression:** Granules are compressed into tablets of desired shape and size.
5. **Coating (Optional):** Film or sugar coatings may be applied to protect the drug, mask taste, or improve appearance (Salawi, 2022).

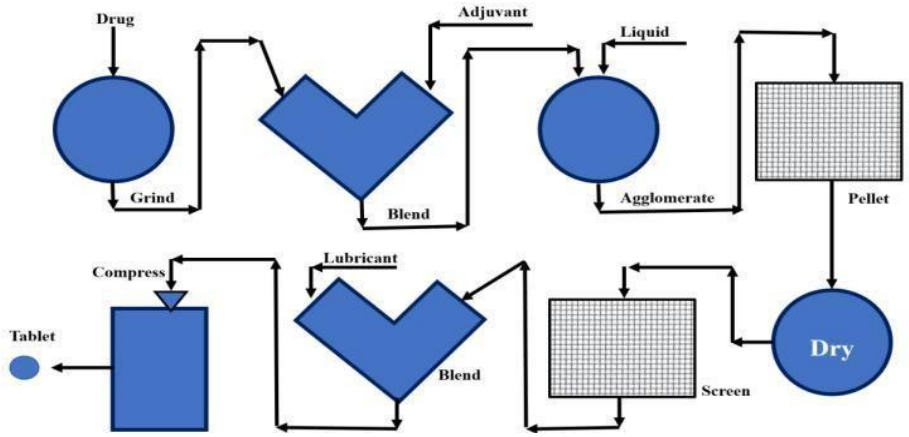

Figure 2: Manufacturing Process Flow (Dhudhat, 2024)

Post-Production Steps:

- **Quality Control:** Tablets are tested for weight, content uniformity, disintegration, dissolution, etc., to ensure they meet required specifications.
- **Packaging:** Tablets are packed in suitable containers (e.g., blister packs, bottles, strip packs) to protect them from moisture, light, and contamination.
- **Storage and Distribution:** Tablets are stored in climate-controlled warehouses to maintain stability throughout their shelf life (Baystate Health, 2023).

2.1.5. Drug Release

Tablets can be categorised based on their drug release profiles:

a) Immediate-Release (IR) Systems

Designed to release the drug quickly after administration, offering fast onset of action. Common forms include:

- Disintegrating tablets
- Chewable tablets
- Effervescent tablets

- Sublingual and buccal tablets
  (Aulton et al., 2014)

b) Modified-Release (MR) Systems

Used when a rapid release is not desired. These systems:

- Deliver the drug at a controlled rate
- Release at predefined time intervals
- Target specific areas within the GI tract
  They typically use special excipients and must be swallowed whole (Aulton et al., 2014).

c) Prolonged-Release Tablets

These release the drug slowly over time, often following **zero-order kinetics**:

M = kt

Where:

- *M* = cumulative drug released
- *t* = time
  (Aulton et al., 2014)

Goals:

- Maintain steady plasma levels
- Reduce dosing frequency
- Minimise side effects and concentration fluctuations
- Improve patient adherence (Bramankar & Jaiswal, 2009)

d) Pulsatile-Release Tablets

Release drugs in one or more distinct bursts after a time delay. Used in conditions requiring chronotherapy (e.g., night-time disorders, hormone therapy). Types include:

- **Time-controlled systems**
- **Stimuli-responsive systems** (e.g., pH, enzymes, temperature)
- **Externally regulated systems** (Basu et al., 2012)

e) Delayed-Release Tablets

Designed to release the drug after a specific lag time. A common example is **enteric-coated tablets**, which resist dissolution in stomach acid and release the drug in the intestine (Aulton

et al., 2014). These may also be combined with prolonged-release technologies for targeted delivery.

2.1.6 – Quality Assurance

Quality assurance (QA) can be defined as "part of quality management focused on providing confidence that quality requirements will be fulfilled" (ASQ, 2024). QA provides assurance to management, customers, and regulatory authorities that all pharmaceutical products meet established quality standards.

To ensure quality, QA encompasses several good practices, including:

- Good Manufacturing Practices (GMPs)
- Good Laboratory Practices (GLPs)
- Stability studies
- Analytical validation
- Pharmaceutical development
- Risk management
- The Common Technical Document (CTD)
- Good Distribution Practices (GDPs)

  (Meriem & Aya, 2021)

2.1.7 – Quality Control

Quality control (QC) is defined as "the operational techniques and activities used to fulfil requirements for quality" (ASQ, 2024). While QA focuses on how a product is made, QC emphasizes **product testing** and **inspection** to ensure all materials and finished products conform to established standards. This includes:

- Specification setting
- Sampling
- Testing
- Analytical validation

  (WHO, 2024)

2.1.7.1 – Quality Control of Tablets

At the core of QC are **in-process controls (IPC)**, which monitor critical stages during manufacturing to ensure the final product meets predefined specifications (Shargel, Wu-Pong

& Yu, 2016). Additionally, **stability studies** are essential to confirm that the drug retains its identity, strength, quality, and purity throughout its shelf life by simulating storage conditions (Aulton & Taylor, 2018).

a) **In-Process Controls**

The initial evaluation involves assessing the **general appearance**—size, shape, colour, odour, and taste. Thickness should remain within ±5% of the standard value. Uniform colour is critical, and any variation (known as mottling) suggests potential quality issues.

Additional key tests include:

- **Hardness Test:** Measures tablet resistance to breakage during handling and storage. Instruments include Strong-Cobb, Schleuniger, and Erweka testers.
- **Friability Test:** Evaluates a tablet's tendency to break under mechanical stress. Using the Roche Friabilator, tablets are rotated at 25 rpm for 100 revolutions.
    - Initial weight (W1) and final weight (W2) are recorded.
    - % Friability is calculated as:

      Friability (%)=W1−W2W1×100\text{Friability (\%)} = \frac{W1 - W2}{W1} \times 100Friability (%)=W1W1−W2×100

    - A loss of less than 0.1% to 0.5% is acceptable.
- **Weight Variation Test:** Twenty tablets are individually weighed and compared to the average. According to USP:
    - ≤ 80 mg: ±10%
    - 80 mg to <250 mg: ±7.5%
    - ≥ 250 mg: ±5%
- **Disintegration Test:** Assesses how quickly a tablet breaks down. Six tablets are tested in glass tubes with mesh screens in fluid maintained at 37 ± 2°C.
    - Uncoated tablets: should disintegrate within 15 minutes
    - Plain coated tablets: within 60 minutes
- **Dissolution Test:** Twelve tablets are placed in separate vessels containing pH-specific buffer solutions simulating GI conditions. Samples are collected at defined intervals to determine release rate (Dasari et al., 2017).

b) Stability Tests of Tablets

A drug is considered stable when its essential properties remain unchanged or change within acceptable limits until its expiration date (Julius & Naffisah, 2024).

The goal of **stability testing** is to determine how a drug's quality varies over time under environmental influences such as temperature, humidity, and light. It helps define the shelf life and storage recommendations (ICH, 2003).

2.1.8 – Regulatory Authorities

Regulatory authorities oversee the entire process of drug development and approval to ensure public health safety.

- **U.S. Food and Drug Administration (FDA):** Regulates all pharmaceutical activities in the U.S., including Investigational New Drug (IND) and New Drug Applications (NDA).
- **European Medicines Agency (EMA):** Manages the scientific evaluation of medicines in the EU.
- **World Health Organization (WHO):** Issues international guidelines for drug safety, quality, and bioequivalence, especially for low- and middle-income countries.

All these agencies require extensive safety, efficacy, and quality data before granting marketing approval (FDA, 2020; WHO, 2018).

2.2 – Antihypertensive Drugs

2.2.1 – Definition

Antihypertensive drugs are a class of pharmacological agents used to manage hypertension by lowering elevated arterial blood pressure and reducing the risk of cardiovascular complications (Laurent, 2017).

2.2.2 – Hypertension

Hypertension, or high blood pressure, is a chronic medical condition characterized by a persistent elevation of systolic blood pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg (McEvoy et al., 2024).

While the **ESC 2024 Guidelines** classify hypertension primarily based on blood pressure values, it is generally divided into two major types:

2.2.2.1 – Primary Hypertension

- Accounts for most cases
- Idiopathic with no identifiable cause
- Likely due to genetic and environmental factors
- Managed with lifestyle modifications and pharmacotherapy (Bludorn & Railey, 2024)

2.2.2.2 – Secondary Hypertension

- Represents approximately 10% of cases
- Caused by identifiable, often treatable conditions such as:
    - Renovascular disease
    - Primary aldosteronism
    - Obstructive sleep apnea
- Other contributors include renal parenchymal disease, thyroid disorders, congenital adrenal hyperplasia, and certain drugs or herbal supplements (Bludorn & Railey, 2024)

2.2.3 – Hypertension Prevalence in Algeria

The estimated prevalence of hypertension among Algerian adults is approximately **one-third**, with only **58.9%** of affected individuals aware of their condition. Elderly women are the most impacted group (Kichou et al., 2025).

2.2.4 – Common Symptoms of Hypertension

Often called the "silent killer," hypertension may present no symptoms. However, prolonged high blood pressure can lead to:

- Chest pain (angina)
- Heart attacks
- Irregular heartbeat
- Sudden cardiac death

(Sharma et al., 2024)

2.2.5 – Consequences of Sustained Blood Pressure

Long-term hypertension can lead to serious complications across multiple organ systems.

Table 3: Consequences of Sustained High Blood Pressure

(Faraci & Scheer, 2024)

Organ System	Complication	Clinical Impact
Renal	Chronic kidney disease, End-stage renal disease	Progressive renal failure, Increased drug toxicity
Cardiovascular	Coronary heart disease, Heart failure, Aneurysms	Myocardial ischemia, Reduced cardiac output, Cerebral aneurysms
Neurological	Stroke, Small vessel disease, Cerebrovascular disease	Long-term disability, Cognitive decline, Chronic cerebral hypoperfusion

2.2.6 – Irbesartan

Irbesartan is a **selective angiotensin II receptor blocker (ARB)** commonly used as an antihypertensive agent. It is also indicated for **delaying the progression of diabetic nephropathy** in patients with type 2 diabetes and hypertension. Its dual mechanism—blood pressure reduction and renal protection—makes it a preferred choice in high-risk patients (Krishna et al., 2024).

2.2.6.1 – History of Irbesartan

First investigated in 1992 by Cazaubon et al. and Bernhart et al., Irbesartan was initially marketed as **Aprovel** by **Sanofi** in 1997. Since its introduction, efforts have focused on improving production yield and avoiding costly purification methods and hazardous solvents (Ochsenbein et al., 2024).

2.2.6.2 – Structure of Irbesartan

Irbesartan is a biphenyl tetrazole derivative and an imidazole-containing compound in which a 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one moiety is substituted at position 1 by a biphenyl group bearing a tetrazole ring at the para position (Ochsenbein et al., 2024).

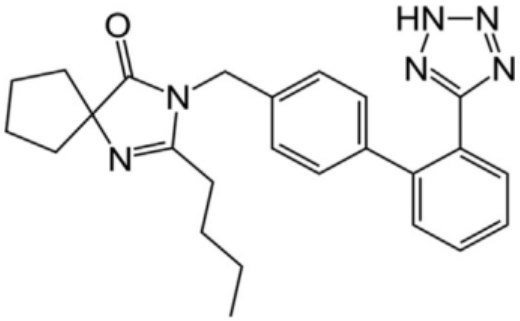

Figure 4: Structure of Irbesartan (Krishna, P.S. et al., 2024)

2.2.6.3 – Chemical and Physical Properties

Irbesartan's key identifiers, chemical characteristics, and physical properties relevant to its pharmaceutical behavior are listed in the table below (Krishna et al., 2024; Darwish et al., 2021; Karatza & Karalis, 2020).

Table 4: Key identifiers, chemical and physical properties of Irbesartan.

Property	Value
IUPAC Name	2-butyl-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one
DrugBank ID	DB01029
PubChem CID	3749
Molecular Formula	$C_{25}H_{28}N_6O$
Molecular Weight	428.5 g/mol
PKa	4.12 (tetrazole)
BCS Classification	Class II

Property	Value
Formulation	Film-coated tablet
Physical State	White crystalline powder
Melting Point	180–181 °C
LogP	4.5
Solubility	• 5.9×10^{-2} mg/L at 25 °C • Practically insoluble in water • Soluble in organic solvents like methanol, methylene chloride

2.2.7 – Pharmacology of Irbesartan

2.2.7.1 – Mechanism of Action

Irbesartan, an angiotensin II receptor blocker (ARB), is known for its long-lasting antihypertensive effect due to an extended half-life ranging from 11 to 15 hours. Owing to its sustained therapeutic action, irbesartan is typically administered once daily (Krishna et al., 2024).

Its mechanism of action involves selective and high-affinity binding to the angiotensin II type 1 (AT_1) receptor, which is predominantly located in tissues such as vascular smooth muscle, heart, kidneys, aorta, and adrenal glands. By blocking the AT_1 receptor, irbesartan inhibits the vasoconstrictive effects of angiotensin II and prevents stimulation of aldosterone secretion. This dual blockade results in relaxation of vascular smooth muscle and suppression of aldosterone production, ultimately leading to a significant reduction in blood pressure.

In the absence of irbesartan, angiotensin II readily binds to AT_1 receptors, promoting vasoconstriction and aldosterone release, thereby raising blood pressure (Darwish et al., 2021).

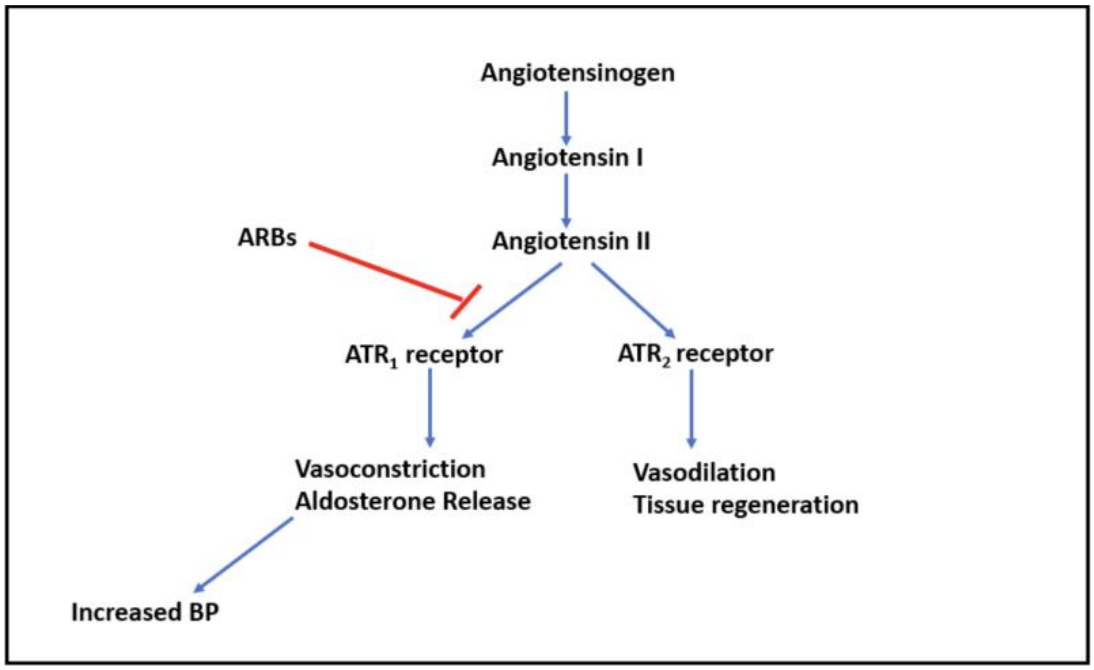

Figure 4: Mechanism of action of ARBs (BioPharma, 2020)

2.2.7.2 – Pharmacokinetics of Irbesartan

a) Absorption and Distribution

Irbesartan demonstrates high oral bioavailability (60–80%), and its absorption is not significantly affected by food. After oral administration, the time to reach maximum plasma concentration (T_{max}) ranges from 1.5 to 2 hours.
The drug has an apparent volume of distribution ranging from 53 to 93 litres. Approximately 90% of plasma irbesartan is bound to proteins, primarily albumin and α_1-acid glycoprotein, facilitating widespread systemic distribution (Darwish et al., 2021).

b) Metabolism:

Irbesartan is primarily metabolised in the liver through glucuronidation and oxidation. The major enzyme involved is **CYP2C9**, with **CYP3A4** contributing minimally.

- Glucuronidation by **UGT1A3** leads to the formation of the **M8 metabolite**.
- Oxidation produces the **M3 metabolite**.
- Hydroxylation by **CYP2C9** results in metabolites M4, M5, and M7, which are then further metabolised into **M1** and ultimately oxidised to **M2**.
- M4 can also be oxidised to **M6** before further conversion to M2.
- A minor metabolite, **SR 49498**, is formed via an unidentified pathway (Krishna et al., 2024).

c) Elimination:

Irbesartan is eliminated via both renal and biliary routes. Approximately 20% of a radiolabeled oral dose is recovered in the urine, and the remainder is excreted in the faeces. Less than 2% of the dose is excreted unchanged in the urine. The terminal elimination half-life is between 11 and 15 hours. Total plasma clearance ranges from 157 to 176 mL/min, while renal clearance is considerably lower at 3.0 to 3.5 mL/min (Darwish et al., 2021).

2.2.7.3 – Indications and Usage of Irbesartan

Irbesartan is indicated for the treatment of:

- Primary (essential) hypertension in adults
- Renal protection in hypertensive patients with type 2 diabetes mellitus
- Cases with laboratory evidence of impaired renal function (Krishna et al., 2024)

2.2.7.4 – Dosage and Administration

The usual adult dosage for hypertension starts at **150 mg once daily**, which may be increased to a maximum of **300 mg once daily** based on the patient's blood pressure response. For hypertensive patients with diabetic nephropathy, the recommended maintenance dose is **300 mg once daily** (Husain et al., 2011).

2.2.7.5 – Adverse Effects

Adverse effects reported more frequently in patients treated with irbesartan compared to those receiving placebo in clinical trials include:

- Diarrhoea
- Dyspepsia/Heartburn
- Musculoskeletal trauma
- Fatigue
- Upper respiratory tract infection
- Headache (Husain et al., 2011)

2.2.7.6 – Contraindications and Precautions

Pregnancy:

Irbesartan is contraindicated during the **second and third trimesters** of pregnancy, as it can significantly impair fetal renal function. Potential complications include:

- Oligohydramnios
- Fetal lung hypoplasia
- Skeletal deformities
- Neonatal complications such as skull hypoplasia, anuria, hypotension, renal failure, and even death

  Irbesartan should be discontinued immediately upon detection of pregnancy (Husain et al., 2011; Darwish et al., 2021).

Hypersensitivity:

Patients with known hypersensitivity to irbesartan or any of its excipients should avoid the drug due to the risk of severe allergic reactions (Kamal et al., 2019).

Use with Other Antihypertensives:

When used in combination with other antihypertensive agents, irbesartan may enhance blood pressure-lowering effects. Dose adjustments may be necessary to avoid excessive hypotension (Hill & Vaidya, 2023).

Combination with Aliskiren:

Irbesartan is **strictly contraindicated** in patients with diabetes and renal impairment who are also being treated with **aliskiren**, due to a significantly increased risk of **acute kidney injury** and **hyperkalemia** (Fu et al., 2017).

Potassium-Sparing Agents:

Use with **potassium-sparing diuretics** or **potassium supplements** is not recommended, as this can elevate the risk of **hyperkalemia**, potentially leading to life-threatening **cardiac arrhythmias** (Laurent, 2017).

2.3 – Dissolution Kinetics

2.3.1 – Definition of Dissolution

Dissolution is the process by which a drug is released from its dosage form and dissolves in a surrounding solution over time, influencing its **bioavailability**, **absorption**, and **therapeutic efficacy**. This time-based drug release is key to assessing a drug's *in vitro* performance (Ghayas et al., 2013).

2.3.1.1 – Background

Comparative dissolution profiling plays a pivotal role in the regulatory approval of generic drugs by evaluating their **bioequivalence** to established reference products. Regulatory agencies such as the **FDA** and **EMA** require manufacturers to present dissolution data demonstrating that the release rate of the API from the generic drug is comparable to that of the standard product. This ensures that the generic version achieves a similar therapeutic effect in patients.

A robust dissolution profile may also qualify a generic drug for a **biowaiver**, eliminating the need for extensive *in vivo* bioequivalence studies. This not only accelerates the approval process but also significantly reduces development costs, contributing to more affordable medications. Therefore, dissolution testing is both a regulatory requirement and a crucial factor in pharmaceutical quality assurance and public health (Wagh et al., 2024).

2.3.2 – Mechanism of Dissolution

The dissolution of the active pharmaceutical ingredient (API) from an immediate-release tablet involves two key steps:

- **Disintegration**: The tablet breaks into smaller granules, increasing the surface area for interaction with the dissolution medium.
- **Solubilisation**: The exposed drug particles dissolve in the surrounding medium to form a homogeneous drug solution (Ghayas et al., 2013).

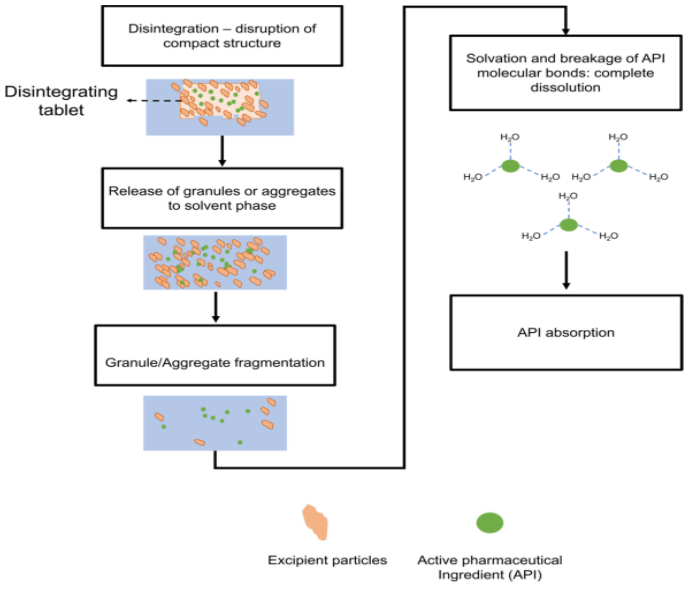

Figure 5: API release in immediate-release tablets (Jange et al., 2023)

Disintegration followed by dissolution is the **rate-limiting step** in drug absorption. Without rapid disintegration, the surface area available for dissolution remains limited, slowing down absorption.

Irbezart® 150 mg contains a superdisintegrant, **croscarmellose sodium**, which improves dissolution, leading to a **2.26-fold higher release rate** compared to pure irbesartan. The inclusion of superdisintegrants in solid oral formulations accelerates disintegration and enhances dissolution, bioavailability, and the pharmacological effect (Merwe et al., 2020).

2.3.3 – Dissolution Parameters

2.3.3.1 – Dissolution Apparatus

As per the USP monograph, **Apparatus 1, 2, 3, and 4** (Table 7) are the most widely used for oral dosage forms. Among these, **USP Apparatus 1 (basket)** and **USP Apparatus 2 (paddle)** are the most frequently employed for immediate- and extended-release formulations (Gray & Rosanske, 2020).

For irbesartan, a BCS Class II drug, **USP Apparatus 2 (paddle)** is preferred due to its ability to address dissolution-limited absorption. The paddle's agitation ensures proper mixing and effective wetting (Vlachou & Karalis, 2021).

Table 5: Dissolution Apparatus Used for Oral Dosage Forms (Wagh et al., 2024)

USP Apparatus	Description	Dosage Forms
I	Basket	Tablets, capsules, floating forms
II	Paddle	Tablets, capsules, enteric-coated
III	Reciprocating Cylinder	Extended-release drug products
IV	Flow-Through Cell	Implants, powders, suspensions

2.3.3.2 – Dissolution Medium

The choice of dissolution medium depends on where the drug is most soluble and aims to simulate various regions of the gastrointestinal tract:

- **pH 1.2 Hydrochloric Acid Buffer**: Simulates the stomach's acidic environment. Irbesartan, being weakly acidic, remains largely in non-ionised form, which is less soluble in water (Karatza & Karalis, 2020).
- **pH 4.5 Acetate Buffer**: Reflects fed stomach conditions or transitional pH during GI transit. Partial ionisation occurs here, improving solubility (Vlachou & Karalis, 2021).
- **pH 6.8 Phosphate Buffer**: Mimics the small intestine, where solubility increases due to ionisation, enhancing drug absorption (Karatza & Karalis, 2020).

2.3.3.3 – Sampling Time Points

Multiple short intervals (10, 15, 30, 45, and 60 minutes) are used for statistical comparison. If ≥85% of the API is dissolved within 15 minutes, only a single sampling point is required for immediate-release tablets (Cascone, 2017).

- **Extended-release** systems require sampling over 12 hours.
- **Delayed-release** tablets undergo an initial acid phase test to confirm gastro-resistance, followed by buffer transfer and interval sampling (Eltanany et al., 2020).

Sampling may be **manual or automatic**, depending on the apparatus. Samples are filtered, diluted, and analysed using **UV-spectrophotometry** or **HPLC** (Gray & Rosanske, 2020).

2.3.3.4 – Other Parameters

- **Volume**: Standard volume is **900 mL**, ensuring *sink conditions* (Teleki et al., 2020; Gray & Rosanske, 2020).
- **Temperature**: Maintained at **37 ± 0.5°C** to reflect in vivo conditions (Kadam et al., 2019).
- **Rotation Speed**:
    - **USP 2 Paddle**: 50 rpm (increased to 75 rpm to resolve coning).
    - **USP 1 Basket**: 100 rpm for uniform exposure (Yoshida et al., 2023).

2.3.4 – Factors Affecting Dissolution

2.3.4.1 – Drug Physicochemical Properties

- **Solubility**: Influenced by salt form, hydration state, and polymorphism. Amorphous and anhydrous forms dissolve faster (Lu et al., 2025).
- **Particle Size & Surface Area**: Micronisation enhances dissolution, especially for hydrophilic drugs (Sun et al., 2012; Ghayas et al., 2013).

- **Salt Formation**: Sodium salts of weak acids dissolve faster due to improved ionisation (Gupta et al., 2018).

2.3.4.2 – Formulation Factors

- **Excipients**: Hydrophilic excipients enhance wettability and dissolution; hydrophobic ones may hinder it (Patel et al., 2021).
- **Binders & Disintegrants**: Their type, quantity, and incorporation method affect dissolution. Starch increases dissolution rates by improving disintegration (Patel et al., 2021).
- **Lubricants**: Hydrophobic lubricants like magnesium stearate may retard dissolution; surfactants like **SLS** can enhance it by improving wettability and microenvironment pH (Moreton, 2024).
- **Surfactants & Polymers**: Aid solubilisation of hydrophobic drugs and control release in specific GI regions (Kamaly et al., 2016).

2.3.4.3 – Apparatus-Related Factors

Dissolution accuracy may be affected by:

- Irregular agitator motion
- Rotational speed variations
- Temperature instability
- External vibrations (FDA, Guidance for Industry, 2010)

2.3.4.4 – Test Parameters

These include:

- Granulation method
- Compression force
- Dissolution medium pH, surface tension, and viscosity (Mudie et al., 2020; Raju et al., 2024)

2.3.4.5 – Miscellaneous Factors

Include:

- Adsorption
- Sorption
- Humidity

- Physiological/in vivo considerations (Dash et al., 2010; Awa et al., 2015)

2.3.5 – BCS Classification System and Dissolution

The **Biopharmaceutics Classification System (BCS)** categorises drugs into four classes based on solubility and intestinal permeability (ICH M9, 2019; Sharma et al., 2021). It helps predict in vivo drug performance and supports **biowaivers** for BCS Class I and III drugs.

- **Bioequivalence**: Similarity in bioavailability between two drug products after administration of the same molar dose.
- **Bioavailability**: The rate and extent to which an API is absorbed and becomes available in systemic circulation (WHO, 2024).

2.3.5.1 – Key Parameters in BCS

- **Solubility**
- **Permeability**
- **Dissolution** (ICH M9, 2019; Samineni et al., 2022)

2.3.5.2 – BCS Classes

Drugsareclassifiedintofourmainclassesunderthissystem,as follows in table 8:

Table 6: Bio-Pharmaceutical Classification

BCS Class	Solubility	Permeability	Key Notes
I	High	High	Rapid absorption
II	Low	High	Dissolution limits absorption
III	High	Low	Permeability limits absorption
IV	Low	Low	Poor bioavailability

2.3.6 – Comparison of Dissolution Profiles

Dissolution profiles may be evaluated via **model-independent**, **model-dependent**, or **statistical** methods (Diaz et al., 2016).

For immediate-release formulations, **comparison at 15 minutes** is critical. If >85% is dissolved, profiles may be accepted as similar without further mathematical evaluation (FDA, 1997).

2.3.6.1 – Model-Independent Methods

a) Similarity Factor (f_2)

$$f_2 = 50 \times log\left\{\left[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

$f2$:is thesimilarity factor,
n:is thenumber of timepoints,

Rt:isthemeanpercentreferencedrugdissolvedattimetafterinitiationofthestudy;

Tt: is the mean percent test drug dissolved at time t after initiation of the study (EMA, 2010).

b) Difference Factor (f_1)

The difference factor (f1) calculates the percentage difference between two curves at each time point and assesses the relative in accuracy between them, following FDA criteria.

$$f_1 = \left\{\left[\sum_{t=1}^{n}|R_t - T_t|\right] \Big/ \left[\sum_{t=1}^{n} R_t\right]\right\} \times 100$$

Table 7: Limits for similarity and difference factors (Waghetal.,2024).

Difference Factor (f_1)	**Similarity Factor (f_2)**	**Inference**
0	100	Identical profiles
<15	>50	Profiles are considered similar

Materials and methods

3-Materials and methods

This section provides a detailed overview of the institutional context, experimental setting, regulatory framework, and analytical procedures used in our study.

The primary objective of our study is to evaluate whether the dissolution profile of Irbezart® 150mg, a marketed drug developed and tested by LDM, is comparable to that of Aprovel® 150mg, a branded reference product developed by Sanofi. This comparison is fundamental in demonstrating pharmaceutical equivalence, particularly in the context of generic drug evaluation.

3.1- Laboratoires de Diagnostic Maghrébins (LDM)

All experimental part was conducted at the LDM Quality Control Laboratory (Fig. 8), a facility with several specialised departments designed to oversee the quality and consistency of pharmaceutical products.

Fig. 6: Picture showing LDM Group company logo.

3.1.1- LDM group history

LDM's history dates back to 1997 when the Elammouchi brothers founded a pharmaceutical import company in Constantine, in the El Khroub region. Over the years, with growing experience and an expanding customer base, the company established its first production unit. Today, more than 700 employees work daily to fulfil the mission set 25 years ago.

As a family-owned business, LDM has a long-term vision. The company is highly aware of the significant health challenges, especially highlighted by the global Covid-19 pandemic, and strives every day to provide real added value to its partners and meet the needs of patients.

3.1.2- LDM group profile

LDM is a rapidly expanding Algerian company with employees from diverse professional backgrounds, forming a skilled multidisciplinary team. It is recognised as a leading player in Algeria's pharmaceutical and para-pharmaceutical industry.

The company's manufacturing facility is located in the Oued Hamimime industrial zone in El Khroub, Constantine province. This major investment complies with international standards and strictly adheres to global quality norms.

Specialising in the manufacturing and distribution of health products, LDM produces premium quality pharmaceuticals both for major industry brands under license and for its own generic portfolio.

With ambitious goals to become a key regional player and a leader in pharmaceutical exports, LDM continues to recruit qualified human resources and invests in efficient production tools.

Key figures of LDM

- 25 years of expertise in local production ;
- Over 700 employees
- More than 20 pharmaceutical products produced under license
- Over 100 pharmaceutical products manufactured in total

3.1.3- LDM products

LDM laboratories offer patients a wide range of brand-name and generic medications in various forms such as tablets, capsules, sachets, gels, creams, syrups, and ointments. Their products cover about twelve therapeutic areas, including: cardiovascular medicines, statins, antihypertensives e.g. irbezart®, beta-blockers, metabolism & nutrition, gastroenterology & hepatology, analgesics e.g. panadol®, standard paracetamol, pulmonology, infectiology-parasitology, dermatology, neurology and psychiatry.

LDM thus provides a comprehensive portfolio of essential medicines across multiple key therapeutic fields, focusing on accessibility and variety in dosage forms to meet patient needs effectively (LDM, 2025).

3.1.4- Key Departments at LDM

The LDM site is made up of the:

1. Reception and Administrative offices,
2. Production unit,
3. Materials and reagents storage area,
4. Raw and finished products storage area,

5. Quality control laboratories,

6. Water/ waste water treatment plan (Julius and Nafisah, 2024).

- **Quality Control department**

  1. Microbiological Quality Control Department – responsible for microbial testing and contamination control.

  2. Physicochemical Quality (PQC) Control Department –our work was carried out there.

  3. In Process Control (IPC) Department.

- **The role of the PQC department**

This department ensures product quality during various stages of manufacturing. It conducts routine checks to validate production parameters and confirm that the product meets regulatory and internal specifications for identity, potency, and dissolution.

The department is subdivided into three operational branches:

- Research and Development (R&D): Focuses on formulation and method development.
- Routine Tasks Team: Conducts routine quality checks on ongoing production batches. Our work was done with this team.
- Raw Materials Team: Handles the verification and testing of starting and intermediary substances (Julius and Nafisah, 2024).

3.2- Experimental setting

3.2.1- Uses of API and reference standards

A pure sample of Irbesartan was used as a standard reference in our dissolution studies. This API was obtained from CTX Life sciences Pvt. Ltd., a globally recognised supplier. The API plays two primary roles in our study ; It is used to create a standard calibration curve to quantify Irbesartan in test solutions and it serves as a control reference to validate the accuracy and sensitivity of the analytical method (CTX Life sciences, 2024).

This ensures that the detected concentration of dissolved drug reflects the true content released from the tablet, enhancing the analytical precision of our dissolution profile comparison (ICH, 2005).

3.2.2- Regulatory guidelines and protocols

All experimental procedures adhered to:

- LDM's Internal Technical File for Dissolution Testing (LDM, 2025)
- Specifications and procedures defined in the European Pharmacopoeia (European Pharmacopoeia Commission, 2023)

These documents define key analytical parameters, apparatus configurations, sampling time points, media composition, and acceptable result ranges, providing the regulatory and procedural blueprint for the work conducted.

3.2.3- Test product description

The test drug, Irbezart® 150 mg, is a commercially available formulation containing Irbesartan as its API. Irbesartan is an angiotensin II receptor antagonist widely used in the management of hypertension. This section presents a comparative analysis of the dissolution profile of Irbezart® against that of the reference product, Aprovel® 150 mg, in order to evaluate their in vitro performance and potential therapeutic equivalence.

Table 8: Generic drug description (LDM, 2025).

Attribute	**Details**
Product Designation/code	Irbezart®150mg/PFLDM288
Manufacturer	LDM
Active ingredient	Irbersartan
Source API	CtxLifesciences Pvt.Ltd
Primary packaging/code	PVC/PVDCWhite250µm/40g/m, L2 124mm /ACPR0045. ALUIrbezart150 MG(25µm LZ122mm)/ACPR0406-001
Secondary packaging/code	Irbezartcase150mg(101x 65x33mm)/ACSE0528-001 WhiteLDMCarton/ACSE0045
Lot number	24007
Manufacturing date	Feb-24
Expiry date	Jan-26
Pharmaceutical form	Film-coatedtablets
Class	AngiotensinIIReceptorBlocker(ARB)
Type of study	The study is Carried out in the Context of manufacturing batchesonanindustrialscale(3lots).
Controlprocedure reference	PCPFLDM288/PH/01andPCPF LDM288/MC/01
ReferenceSpecificationsheet	SCPFLDN288/01
Packaging	Eachboxincludes03Blisters,eachblistercontains10 tablets
Administration	Oral
Storage	Below30,KeepawayfromMoistureandDirectsunlight
ShelfLife	2 years

3.2.4- Reference product

Aprovel® 150mg, developed by Sanofi, is the brand name product containing Irbesartan as its API. In this study, Aprovel® 150 mg is used as the reference product for comparing the dissolution profile of the generic formulation, Irbezart® 150 mg, described above. This comparison aims to assess the in vitro performance and potential bioequivalence between the two products.

Table 9: Reference drug description

Attribute	**Details**
CommercialName	Aprovel®
Manufacturer	Sanofi
Active Ingredient	Irbersartan
Strength	150mg
Lot Number	24007
ManufacturingDate	Feb-24
ExpiryDate	Jan-26
PharmaceuticalForm	Film-coatedtablets
Class	AngiotensinIIReceptorBlocker(ARB)
Dosage	OnceDaily(AsperDoctor's Prescription)
Packaging	BlisterPackets
Administration	Oral
Storage	Below30,KeepawayfromMoistureandDirect sunlight
ShelfLife	Typically2-3years

3.2.4- Apparatus and reactives

The different apparatus and reactives used in this study were detailed in appendices.

3.2.5- Methodology

Dissolution studies were conducted in multiple pH media to simulate different physiological conditions encountered in the GIT. The media used included pH 1.2 (simulated gastric fluid), pH 4.5 (mildly acidic environment), and pH 6.8 (simulated intestinal fluid).

The reason for using these three specific pH conditions was based on the biopharmaceutical properties of Irbesartan and its solubility profile:

- pH 1.2: This medium mimics the highly acidic environment of the stomach, where drug dissolution begins. It helps determine how well the drug dissolves under gastric conditions, which is especially important for drugs with pH-dependent solubility.

- pH 4.5: This medium represents a transitional pH found in the upper small intestine and is used to assess whether the drug maintains consistent dissolution under slightly acidic conditions. It is particularly useful for identifying solubility variations that might occur in this region.
- pH 6.8: Since the primary site of drug absorption for Irbesartan is the small intestine, testing dissolution at this pH provides insight into the drug release in the intestinal environment, where most oral drugs are absorbed.

3.2.5.1- Preparation of dissolution media

Three buffer solutions were prepared as following ;

- **Buffer solution pH 1.2**

  250ml of the Sodium Chloride solution 0.2M were mixed with 425ml of the Hydrochloric Acid solution 0.2M and filled it up to 1000ml with purified water.
- **Buffer solution pH 4.5**

  2.99g of Sodium Acetate Trihydrate were mixed with 14 ml of Acetic Acid Solution 2N, then filled it up to 1000ml with purified water.
- **Buffer solution pH 6.8**

  250ml of Potassium Monophosphate solution 0.2M were mixed with 112 ml of Sodium Hydroxide Solution 0.2M, then filled it up to 100ml with purified water.

3.2.5.2- Preparation of dissolution samples

The comparative dissolution profiles was conducted between Irbezart®(generic) and Aprovel® (standard drug) to verify the rate of drug release from a solid dosage form in accordance with the monograph requirements of the LDM technical file. A total of 12 tablets from each drug were randomly selected across multiple blister packs to ensure total representation of the entire lot.
The dissolution study was performed using the USP 2 apparatus on the Dissolutest PTW 1220.

The following dissolution parameters were applied ; 1000 ml of dissolution medium filled each vessel, an equilibrium temperature of 37°C ± 0.5°C, before each new medium addition, the rotation speed was set to 50 rpm ± 2 rpm, sampling time points were 10, 15 and 30 minutes, with a single sampling time added ifrelease of 85% is achieved within 15 minutes. In which three dissolution media were utilised, comprising hydrochloric acid buffer (pH 1.2), acetate buffer (pH 4.5), and phosphate buffer (pH 6.8).

For each 20 ml sample collected from each vessel, 5 ml was diluted with 50 ml of the dissolution medium. After dilution, the sample was filtered through a syringe filter with a pore size of

0.45µm to ensure accurate spectrophotometry results. The analysis of the samples was conducted using UV/visible spectrophotometry.

3.2.5.3- Preparation of the assay (Standard solution)

A standard solution was prepared following a precise protocol to verify the label claim of 150 mg pure irbesartan in both drugs. This solution serves asa calibration reference to compare against the test samples for UV/visiblespectrophotometric analysis, enabling the determination of the API concentration thereby eliminating bias.

The standard solution was prepared according to the following procedure:
150 mg of pure irbesartan standard was weighed using an analytical balance and transferredinto a 100ml volumetric flask. To dissolve the standard, 20 ml of methanol was added to the flask. The mixture was then subjected to ultrasonic agitation for 5 minutes to facilitate complete dissolution of the irbesartan powder. After ultrasonic treatment, the solution was allowed to rest briefly before being adjusted to the final volume of 100 ml using the appropriate dissolution medium (pH 1.2, pH 4.5, or pH 6.8). This adjustment ensured that the standard solution matched the conditions used in the dissolution testing. 5 ml of the prepared standard solution was diluted with 50 ml of dissolution medium. A second dilution was carried out by taking 5 ml of this intermediate solution and diluting it again with 50 ml of dissolution medium. The final solution was filtered through a syringe filter with a pore size of 0.45µm to remove any suspended matter that could interfere with spectrophotometricmeasurements.The resulting solution had a final irbesartan concentration of 0.015 mg/ml.

Following the same procedure, another standard solution was prepared to ensure no medium interference therefore validating the accuracy of the UV/visible spectrophotometric analysis.

3.2.5.4- UV/Visible spectrophotometric analysis

The UV/visible spectrophotometric analysis was conducted on samples obtained from the dissolution testing of Irbezart® (generic) and Aprovel® (standard drug). The primary objective of this analysis was to quantify the concentration of the API in each sample using a validated analytical method.

The analysis involved the use of a UV/visible spectrophotometer, with measurements taken at a wavelength of 244 nm, which is standard for the API irbesartan.
Before taking any measurements, a blank was used for baseline correction for each dissolution medium to account for any background absorbance. This blank is the same dissolution medium in which the drugs are to be dissolved.

Following calibration, each sample was placed in the spectrophotometer, and the absorbance was measured. The concentration of the API in each sample was calculated using the Beer-Lambert law. The concentrations obtained were then used to calculate the percentage of API released at each sampling time point, providing a comprehensive dissolution profile for both Irbezart® and Aprovel®.

For each sampling time point, six replicate measurements were taken as mandated by the LDM technical file for statistical accuracy. For pure irbesartan (Assay), an additional three measurements are taken to ensure reproducibility of the results.

- **Calculation of the optical density/ absorbance**

The optical densities were directly provided by the UV/visible spectrophotometer using the Beer-Lambert law:

$$A = \log (I_0 / I) = \varepsilon LC.$$

Where:

A: is the absorbance or optical density,

I_0: is the intensity of radiation before passing through the sample,

I: is the intensity of radiation after passing through the sample,

ε: is the absorption coefficient at a given wavelength,

L: is the path length of the sample,

C: is the concentration of the solution.

NB: This law is applicable only to diluted solutions.

- **Calculation of the Dissolution percentage (P%)**

From the optical density measured with the UV/visible spectrophotometer, the dissolution percentage of Irbezart® was calculated using the following formula:

"Irbesartan (%)"=A_e/A_s × P_s/V_e ×5/50×5/50×1000×50/5×(100-"LODs")/100×T_s/100×100/150

Where:

Ae: Absorbance of the test sample (essai).

At: Absorbance of the standard solution.

Ps: Weight of the standard used to prepare the standard solution (in mg).

Ts: content of irbesartan on its dried basis

LODs: loss on drying.

Ve: Volume of the test sample (in mL).

- **Calculation of the corrected Dissolution percentage (Q)**

To correct for sample removal in dissolution testing, it is necessary to account for both the volume of the sample removed and the amount of drug lost with each sample. Therefore, the value of Q was calculated using the correction formula at each cumulative sampling point for all 12 samples. Practically, the values of Q were automatically calculated using an Excel spreadsheet, and the formula for this calculation is presented below:

$$Q\%=(A\_"cumulative" /LC)\times 100.$$

Where:

LC: label claim of the drug

A cumulative: total amount of drug that has been released into the dissolution medium over time

$$A\_"cumulative" = [\![\sum_{T}(i=1)]\!] \perp n\ (C\_i\times V\_s)+C\_n\times(V\_m-n\times V\_s).$$

Where:

Ci: Concentration of drug at each sampling interval (mg/mL),

Vs: Volume of sample withdrawn (mL),

Cn: Concentration of drug at the current sampling interval,

Vm: Total volume of dissolution medium (mL),

n: Number of samples taken before the current one.

- **Calculation of Statistical Parameters**

After calculating the dissolution percentage, we determined the average of each percentage for the different time intervals, then we calculated the standard deviation of the 12 tablets for the different time intervals, and finally, we proceeded to calculate the coefficient of variation.

The average of the sample X is given by:

$$\bar{x}=1/n \quad [\![\sum_{T}(i=1)]\!] \perp n\ x\_i.$$

The Standard deviation (SD) of the sample is given by:

$$S=\sqrt{(1/(n-1) \quad [\![\sum_{T}(i=1)]\!] \perp n\ (x\_i-\bar{x}\ )\hat{}2\ ).}$$

The Variation coefficient CV%/ RSD is given by:

$$CV="Standard\ Deviation" /"Mean" \times 100.$$

Note, according to the LDM technical file, the coefficient of variation should not vary by more than 20% for the initial points of the dissolution kinetics and 10% for the other points.

- **Calculation of the difference and similarity factors**

According to ICH M9 guidelines (2019), for comparative dissolution profile procedure, If 85% of the active ingredient is released within at least 15 minutes for both products, the profiles are considered similar. Otherwise, the similarity factor (f2) must be calculated.

$$F_2=50\times\log((1+1/n \quad [\sum_{T}(t=1)] \perp n\ (R_t-T_t)^2)^{(-0.5)})\times 100.$$

Where:

Rt: is the average percentage released of the reference product.

Tt: is the average percentage released of the test product

Another factor (difference factor f1) can also be calculated although it is not mandatory.

$$f_1=(1/n \quad [\sum_{T}(i=1)] \perp n\ |R_i-T_i|)\times 100.$$

Where:

Ri: is the percentage of drug released from the reference product at time point i,

Ti: is the percentage of drug released from the test product at time point i,

n: is the number of time points.

The difference factor f1 must be less than or equal to 15 and the similarity factor f2 must be greater than or equal to 50, which is between 50 and 100(Wagh et al., 2024).

Results and interpretation

4- Results and interpretation

This section presents the results from the comparative dissolution testing of Irbezart® and Aprovel® across different pH media. The analysis focuses on the percentage of drug released over time. The findings are interpreted according to pharmacopeial standards and regulatory guidelines to determine whether Irbezart® demonstrates pharmaceutical equivalence to the standard drug, Aprovel®.

4.1- Acceptance Criteria

- The coefficient of variation (CV %) of the 12 results at the first sampling point must not exceed 20%.
- The CV% of the12 results at other sampling points must not exceed 10%.
- If the data for both the test product and the reference product show more than 85% dissolution within 15 minutes, the profiles are considered similar without requiring further mathematical calculations; only one time point above 85% is needed.
- The difference factor (f1) must be less than or equal to15 (optional).
- The similarity factor (f2) must be greater than or equal to50 (between 50 and 100).

Results for pH1.2 medium

The table below reveals results of dissolution profile between the Irbezart® and Aprovel® respectively. This data is represented in percentage dissolution, min, and max RSD values.

Table 10: Percentage dissolution profiles of Irbezart®150mg and Aprovel®150mg at pH=1.2.

pH 1.2	**Irbezart® 150mg**			**Aprovel® 150mg**		
Sample Nº	**Sampling time**			**Sampling time**		
	10 min	**15 min**	**30 min**	**10 min**	**15 min**	**30 min**
Vessel 1/12	84	100	101	97	103	103
Vessel 2/12	96	104	101	102	101	104
Vessel 3/12	104	99	102	100	101	103
Vessel 4/12	102	103	97	100	100	104
Vessel 5/12	103	102	100	97	98	102
Vessel 6/12	104	103	100	101	100	102
Vessel 7/12	100	104	101	98	100	101
Vessel 8/12	103	98	101	99	99	101
Vessel 9/12	103	103	101	99	98	104
Vessel 10/12	88	103	102	100	101	101
Vessel 11/12	89	104	102	99	101	100
Vessel 12/12	99	104	102	101	102	101
Min	**84**	**98**	**97**	**97**	**98**	**100**
Max	**104**	**104**	**102**	**102**	**103**	**104**
Average	**98**	**102**	**101**	**99**	**100**	**102**
Standard deviation	**7.2**	**2.2**	**1.5**	**2**	**1**	**1**
RSD	**7.4**	**2.1**	**1.5**	**2**	**1**	**1**
Norme	**20%**	**10%**	**10%**	**20%**	**10%**	**10%**

The dissolution profiles of Aprovel® and Irbezart® were compared using a pH 1.2 buffer medium. The results show that at 10 minutes, Irbezart®released an average of 98% compared to the 99% for Aprovel® which shows a slightly higher rate of dissolution for Aprovel® at the same time point **(Table 10).**

Irbezart® also shows a higher relative standard deviation (RSD) of 7.4%, compared to 2% of Aprovel® at the same time point, which is over all acceptable as it remains within the limit of 20% set by the LDM technical file.

After 15 minutes, both products exceeded 85% drug release, 102% for Irbezart®and 100% for Aprovel®, with RSD values of 2.1% and 1% respectively. This demonstrates that both formulations meet the standard requirements, which states that if more than85%of the drug is released within15 minutes, the dissolution profiles can be considered similar without the need to calculate the similarity factor (f2). After 30 minutes, both products show a complete dissolution, with values showing an average of 101% for Irbezart®and 102% forAprovel®, the RSD values remains below the 10% threshold.

Results for pH 4.5 medium

The table 11 shows findings of dissolution profile of both Irbezart® and Aprovel® respectively at pH=6.8. These data are represented in percentage dissolution, min, max, and RSD values.

Table 11: Percentage dissolution profiles of Irbezart®150mg and Aprovel®150mg at pH=4.5.

pH 4.5	Irbezart® 150mg			Aprovel® 150mg		
Sample Nº	Sampling time			Sampling time		
	10 min	15 min	30 min	10 min	15 min	30 min
Vessel 1/12	92	88	91	90	103	96
Vessel 2/12	82	86	89	79	89	99
Vessel 3/12	88	84	78	82	85	82
Vessel 4/12	91	86	84	82	83	97
Vessel 5/12	91	88	87	94	84	95
Vessel 6/12	80	85	84	86	89	91
Vessel 7/12	84	89	91	85	88	89
Vessel 8/12	86	80	90	83	83	97
Vessel 9/12	88	84	87	80	85	93
Vessel 10/12	82	87	81	78	82	97
Vessel 11/12	91	86	85	85	84	96
Vessel 12/12	86	82	90	84	90	97
Min	**80**	**80**	**78**	**78**	**82**	**82**
Max	**92**	**89**	**91**	**94**	**103**	**99**
Average	**87**	**85**	**86**	**84**	**87**	**94**
Standard deviation	**4.2**	**2.5**	**4.2**	**4.5**	**5.7**	**4.7**
RSD	**4.9**	**2.9**	**4.9**	**5.4**	**6.5**	**5.0**
Norme	**20%**	**10%**	**10%**	**20%**	**10%**	**10%**

The dissolution profile between Irbezart® and Aprovel® were compared using an acetate pH 4.5 buffer dissolution medium. At the 10 minutes sampling time. Both drugs showed high dissolution rates with an average of 87% for Irbezart® and 84% for Aprovel®. Aprovel® also exhibited a higher relative standard deviation (RSD) of 5.4% compared to 4.9% for Irbezart® at the same time point which is overall acceptable as it remains within the limit of 20% set by the LDM technical file.

After 15 minutes, both products exceeded 85% drug release. 85% for Irbezart® and 87% for Aprovel® with RSD values of 2.9% and 6.5%, respectively. This demonstrates that both formulations meet the standard requirements which states that if more than 85% of the drug is released within 15 minutes. The dissolution profiles can be considered similar without the need to calculate the similarity factor (f2) (ICH M9, 2019).

After 30 minutes, both products demonstrated a complete dissolution with values showing an average of 86% for Irbezart® and 94% for Aprovel®. The RSD values remain below the 10% threshold.

Results for pH6.8 medium

The following table (Table 12) presents the dissolution profile outcomes of both the Irbezart® and the Aprovel® at pH=6.8. These data are represented in percentage dissolution; min, max and RSD values.

Table 12: Percentage dissolution profiles of Irbezart®150mg and Aprovel®150mg at pH=6.8.

pH 6.8	Irbezart® 150mg			Aprovel® 150mg		
Sample Nº	Sampling time			Sampling time		
	10 min	15 min	30 min	10 min	15 min	30 min
Vessel 1/12	89	99	98	72	87	96
Vessel 2/12	88	99	98	75	89	95
Vessel 3/12	89	98	110	68	88	93
Vessel 4/12	89	98	97	71	89	92
Vessel 5/12	89	98	99	74	89	97
Vessel 6/12	89	98	99	78	86	95
Vessel 7/12	88	99	97	85	90	94
Vessel 8/12	90	98	96	78	91	93
Vessel 9/12	89	96	97	73	91	94
Vessel 10/12	88	100	96	82	89	92
Vessel 11/12	87	98	98	77	90	92
Vessel 12/12	87	97	97	75	90	91
Min	**87**	**96**	**95**	**68**	**86**	**91**
Max	**90**	**100**	**110**	**85**	**91**	**97**
Average	**88**	**98**	**98**	**75**	**89**	**93**
Standard deviation	**0.7**	**1.0**	**3.9**	**4.7**	**1.4**	**1.9**
RSD	**0.8**	**1.0**	**3.9**	**6.2**	**1.5**	**2.0**
Norme	**20%**	**10%**	**10%**	**20%**	**10%**	**10%**

The dissolution profiles of Aprovel® and Irbezart® were compared using a pH 6.8 phosphate buffer medium.

The results display that at 10 minutes Irbezart® released an average of 88% of the API with a low RSD of 0.8% indicating the rapid and the consistent drug release. In contrast, Aprovel released 75% of the drug at the same time point with a higher RSD of 6.2% which remains within the acceptable limit of 20% set by the LDM technical file.

After 15 minutes, both products exceeded 85%; drug release of 98% for Irbezart® and 89% for Aprovel® with RSD values of 1.0% and 1.5%; respectively. These findings demonstrate that both formulations meet regulatory requirements which state that if more than 85% of the drug is released within 15 minutes, the dissolution profiles can be considered similar without the need to calculate the similarity factor (f2) (ICH M9, 2019).

After 30 minutes, both products revealed nearly a complete dissolution with average values of 93% for Aprovel® and 98% for Irbezart®. The RSD values remain below the 10% threshold.

Conclusion

The results obtained from the three dissolution mediums, with a coefficient of variation for all the first points not exceeding 20%, are summarized in the following table (Table 13):

Table 13: Comparative dissolution profiles of Irbezart®150mg and Aprovel®150mg at three different pH (pH =1.2 ; 4.5 ; and 6,8).

	Irbezart® 150mg			**Aprovel® 150mg**		
	10 min	**15 min**	**30 min**	**10 min**	**15 min**	**30 min**
pH 1.2	98	102	101	99	100	102
pH 4.5	87	85	86	84	87	94
pH 6.8	88	98	98	75	89	93

As a conclusion; the three pH media showed dissolution more than 85% in 15 min:

At pH1.2: The data for the test product and the reference product show dissolution of 102% and 100%, consecutively.

At pH4.5: The data for the test product and the reference product show dissolution of 85% and 87%, in that order.

At pH6.8: The data for the test product and the reference product show dissolution of 98% and 89%, respectively.

Therefore, the dissolution profile of the Irbezart® 150 mg product is considered similar to the reference product which is Aprovel® 150 mg.

Conclusion and perspectives

5- Conclusion and perspectives

One of the most important aspects concerning generic drugs is their therapeutic equivalence to the standard drug. In this study, a comparative dissolution profiles of a generic drug Irbezart®150 mg by LDM and a standard drug Aprovel® 150 mg by Sanofi was carried out. The results of this study demonstrated that the generic formulation Irbezart® 150 mg is pharmaceutically equivalent to the reference drug Aprovel® 150 mg, based on the similarity of their *in vitro* dissolution profiles. These findings reinforce confidence in the therapeutic interchangeability of generic products when proper quality standards are met. From a public health perspective, this contributes to greater accessibility to essential hypertension treatments without compromising therapeutic outcomes.

Looking forward, several perspectives may be explored to build upon this research:

- ✓ *In vivo* bioequivalence studies would further confirm the therapeutic equivalence of Irbezart® ;
- ✓ Stability studies of Irbezart® under various storage conditions to ensure that its dissolution profile remains consistent throughout its shelf life ;
- ✓ Investigating how manufacturing parameters such as compression force, excipient quality, or granulation method affect the dissolution performance of the generic product ;
- ✓ Expansion of similar comparative dissolution studies to other dosage forms of irbesartan (e.g. 75 mg or 300 mg) ;
- ✓ Comparative evaluations of other generic drugs, especially for critical-dose medications.

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Résumé

Résumé

Cette étude présente une analyse comparative in vitro de la dissolution de l'Irbezart® 150 mg, une formulation générique, et de l'Aprovel® 150 mg, le médicament de référence. Les deux formulations contiennent de l'irbésartan, un antagoniste des récepteurs de l'angiotensine II largement utilisé dans le traitement de l'hypertension artérielle. L'objectif principal de ce travail était d'évaluer la performance de dissolution in vitro de la formulation générique Irbezart® et de vérifier son équivalence pharmaceutique avec le médicament de référence Aprovel®, afin d'assurer une cohérence thérapeutique et la conformité aux normes réglementaires. Le test de dissolution a été réalisé à l'aide de la machine PTW 1220 Dissolutest, dans des conditions standardisées (50 rpm, 37 ± 0.5°C), dans trois milieux de dissolution de pH différents (1,2 ; 4,5 ; 6,8), simulant les différentes conditions gastro-intestinales. Un total de douze comprimés de chaque formulation, choisis aléatoirement à partir de différents lots de production, a été analysé pour garantir un échantillonnage représentatif. Six échantillons ont été prélevés dans chaque cuve à des intervalles de temps définis, et analysés par spectrophotométrie UV-visible. Une courbe d'étalonnage validée a été utilisée pour quantifier le pourcentage d'irbésartan libéré à chaque point de mesure, avec une solution standard préparée et analysée dans les mêmes conditions. Les valeurs d'absorbance obtenues ont servi au calcul du pourcentage de médicament dissous. Une analyse statistique incluant la moyenne, l'écart-type et le coefficient de variation a été réalisée pour garantir la reproductibilité et la fiabilité des données. Les résultats obtenus ont montré que les deux formulations atteignaient un pourcentage de dissolution ≥ 85 % en moins de 15 minutes dans tous les milieux, indiquant une dissolution rapide et complète, ce qui élimine le besoin de comparaison mathématique supplémentaire. Conformément aux lignes directrices réglementaires, la similitude des profils de dissolution entre Irbezart® et Aprovel® soutient la conclusion que les deux produits sont équivalents sur le plan pharmaceutique in vitro. Ces résultats renforcent la qualité et l'efficacité de la formulation générique et soutiennent son interchangeabilité avec le produit de marque. Ils contribuent également à l'évaluation continue des médicaments génériques et soulignent l'importance du test de dissolution comme outil fiable d'assurance qualité pharmaceutique.

Mots clés : Irbésartan, profile de dissolution, médicament générique, Aprovel®, Irbezart®, contrôle qualité.

Abstract

Abstract

This investigation presents a comparative *in vitro* dissolution analysis of Irbezart® 150 mg, a generic formulation, and Aprovel® 150 mg, the reference drug. Both formulations contain irbesartan, an angiotensin II receptor blocker widely used in hypertension treatment. The main objective of the present study was to evaluate the *in vitro* dissolution performance of the generic formulation Irbezart® and assess its pharmaceutical equivalence to the reference drug Aprovel®, thereby ensuring therapeutic consistency and compliance with regulatory standards. The dissolution test was carried out using the PTW 1220 Dissolutest machine under standardized conditions (50 rpm, 37 ± 0.5°C) in three dissolution media of varying pH (1.2, 4.5, and 6.8), intended to simulate different gastrointestinal environments. A total of twelve tablets from each formulation, randomly selected from different production batches, were analyzed to ensure representative sampling. Six samples were collected from each vessel at specified time intervals and analyzed using UV-Visible spectrophotometry. A validated calibration curve was employed to quantify the percentage of irbesartan released at each time point, in which a standard solution was also prepared and analysed under the same conditions. The obtained absorbance values were used to calculate the percentage of drug dissolved. Statistical analysis, including calculation of the mean, standard deviation, and coefficient of variation, was performed to ensure data reproducibility and reliability. The obtained results showed that both formulations achieved a drug release dissolution percentage of ≥ 85% within 15 minutes across all pH media, indicating rapid and complete dissolution; so eliminating the need for further mathematical comparison. Based on regulatory guidance, the similarity in dissolution profiles between Irbezart® and Aprovel® that were closely matched, supports the conclusion that the two products are pharmaceutically equivalent *in vitro*. These findings reinforce the quality and the efficacy of the generic formulation and support its interchangeability with the branded product. They also contribute to ongoing efforts in generic drug evaluation and underscore the importance of dissolution testing as a reliable tool in pharmaceutical quality assurance.

Key words: Irbesartan, dissolution profile, generic drug, Aprovel®, Irbezart®, quality control.

ملخص

ملخــص

تُقدم هذه الدراسة تحليلًا مقارنًا **في المختبر** لسرعة انحلال دواء ®Irbezart 150 ملغ، وهو مستحضر جنيس، و ®Aprovel 150ملغ، وهو الدواء المرجعي. يحتوي كلا المستحضرين على مادة الإربيسارتان، وهي من مثبطات مستقبلات الأنجيوتنسين II، وتُستخدم على نطاق واسع في علاج ارتفاع ضغط الدم. الهدف الرئيسي من هذا العمل هو تقييم أداء الانحلال في المختبر للمستحضر الجنيس ®Irbezart والتحقق من تكافؤه الصيدلاني مع الدواء المرجعي®Aprovel ، وذلك لضمان الاتساق العلاجي والامتثال للمعايير التنظيمية. حيث تم إجراء اختبار الانحلال باستخدام جهاز **PTW 1220 Dissolutest**ضمن ظروف معيارية (50 دورة في الدقيقة، 37 ± 0.5 درجة مئوية)، وفي ثلاث بيئات انحلال مختلفة من حيث الرقم الهيدروجيني (1.2، 4.5، 6.8)، لمحاكاة ظروف الجهاز الهضمي. تم اختيار اثني عشر قرصًا من كل مستحضر بشكل عشوائي من دفعات إنتاج مختلفة لضمان تمثيل عيني موثوق. جُمعت ست عينات من كل وعاء في أوقات زمنية محددة، وتم تحليلها باستخدام جهاز المطيافية فوق البنفسجية-المرئية. كما تم استخدام منحنى معايرة مثبت لقياس النسبة المئوية للإربيسارتان المُتحرر في كل نقطة زمنية، مع تحضير محلول قياسي وتحليله بنفس الشروط. استخدمت قراءات الامتصاصية لحساب النسبة المئوية للدواء المُذاب. كما أُجريت تحليلات إحصائية شملت المتوسط، والانحراف المعياري، ومعامل التباين لضمان موثوقية البيانات وتكرارها. أظهرت النتائج المتحصل عليها أن كلا المستحضرين حققا نسبة انحلال ≤ 85٪ خلال أول 15 دقيقة في جميع البيئات، مما يشير إلى انحلال سريع وكامل، وبالتالي لا حاجة لمزيد من المقارنة الرياضية. ووفقًا للإرشادات التنظيمية، فإن تشابه منحنيات الانحلال بين ®Irbezart و ®Aprovelيدعم الاستنتاج بأن المنتجين متكافئان صيدلانيًا في المختبر. تعزز هذه النتائج من جودة وفعالية المستحضر الجنيس، وتدعم قابليته للاستبدال بالدواء الأصلي، كما تساهم هذه الجهود في تقييم الأدوية الجنيسة وتؤكد أهمية اختبار الانحلال كأداة موثوقة لضمان جودة المنتجات الصيدلانية.

الكلمات المفتاحية:

إربيسارتان، المنحنى الانحلالي، دواء جنيس، ®Aprovel، ®Irbezart، مراقبة الجودة.

Appendices

Appendix I: Absorbance Data and Sample Analysis

The raw absorbance data collected during the experimental analysis of the samples collected after drug dissolution. The tables include measurements for Irbesartan standard solution (std), Aprovel® (princeps) and Irbezart®(Ldm) at varying time intervals(10, 15,and 30minutes). Absorbance values (WL244,0) are reported without modification to ensure traceability.

Sample tables_pH1.2

	Sample ID	Type	Ex	Conc	WL244,0	Comments
1	blanc	Unknown		*****	-0.000	
2	std_1_L1	Unknown		*****	0.651	
3	std_1_L2	Unknown		*****	0.651	
4	std_1_L3	Unknown		*****	0.650	
5	std_1_L4	Unknown		*****	0.651	
6	std_1_L5	Unknown		*****	0.651	
7	std_1_L6	Unknown		*****	0.650	
8	std_2_L1	Unknown		*****	0.651	
9	std_2_L2	Unknown		*****	0.650	
10	std_2_L3	Unknown		*****	0.651	
11	Priceps_pH1,2_10mn_cp01	Unknown		*****	0.556	
12	Priceps_pH1,2_10mn_cp02	Unknown		*****	0.553	
13	Priceps_pH1,2_10mn_cp03	Unknown		*****	0.552	
14	Priceps_pH1,2_10mn_cp04	Unknown		*****	0.554	
15	Priceps_pH1,2_10mn_cp05	Unknown		*****	0.553	
16	Priceps_pH1,2_10mn_cp06	Unknown		*****	0.594	
17	Priceps_pH1,2_10mn_cp07	Unknown		*****	0.591	
18	Priceps_pH1,2_10mn_cp08	Unknown		*****	0.589	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
19	Priceps_pH1,2_10mn_cp09	Unknown		*****	0.589	
20	Priceps_pH1,2_10mn_cp10	Unknown		*****	0.585	
21	Priceps_pH1,2_10mn_cp11	Unknown		*****	0.581	
22	Priceps_pH1,2_10mn_cp12	Unknown		*****	0.581	
23	Priceps_pH1,2_15mn_cp01	Unknown		*****	0.699	
24	Priceps_pH1,2_15mn_cp02	Unknown		*****	0.720	
25	Priceps_pH1,2_15mn_cp03	Unknown		*****	0.608	
26	Priceps_pH1,2_15mn_cp04	Unknown		*****	0.618	
27	Priceps_pH1,2_15mn_cp05	Unknown		*****	0.612	
28	Priceps_pH1,2_15mn_cp06	Unknown		*****	0.679	
29	Priceps_pH1,2_15mn_cp07	Unknown		*****	0.632	
30	Priceps_pH1,2_15mn_cp08	Unknown		*****	0.596	
31	Priceps_pH1,2_15mn_cp09	Unknown		*****	0.710	
32	Priceps_pH1,2_15mn_cp10	Unknown		*****	0.734	
33	Priceps_pH1,2_15mn_cp11	Unknown		*****	0.712	
34	Priceps_pH1,2_15mn_cp12	Unknown		*****	0.704	
35	Priceps_pH1,2_30mn_cp01	Unknown		*****	0.682	
36	Priceps_pH1,2_30mn_cp02	Unknown		*****	0.706	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
37	Priceps_pH1,2_30mn_cp03	Unknown		*****	0.699	
38	Priceps_pH1,2_30mn_cp04	Unknown		*****	0.630	
39	Priceps_pH1,2_30mn_cp05	Unknown		*****	0.693	
40	Priceps_pH1,2_30mn_cp06	Unknown		*****	0.692	
41	Priceps_pH1,2_30mn_cp07	Unknown		*****	0.704	
42	Priceps_pH1,2_30mn_cp08	Unknown		*****	0.703	
43	Priceps_pH1,2_30mn_cp09	Unknown		*****	0.703	
44	Priceps_pH1,2_30mn_cp10	Unknown		*****	0.693	
45	Priceps_pH1,2_30mn_cp11	Unknown		*****	0.689	
46	Priceps_pH1,2_30mn_cp12	Unknown		*****	0.692	
47						

	Sample ID	Type	Ex	Conc	WL244,0	Comments
1	Blanc	Unknown		*****	0.000	
2	std1l1	Unknown		*****	0.767	
3	std1l2	Unknown		*****	0.767	
4	std1l3	Unknown		*****	0.768	
5	std1l4	Unknown		*****	0.766	
6	std1l5	Unknown		*****	0.768	
7	std1l6	Unknown		*****	0.768	
8	std2l1	Unknown		*****	0.767	
9	std2l2	Unknown		*****	0.766	
10	std2l3	Unknown		*****	0.767	
11	Ldm_10mn_1	Unknown		*****	0.794	
12	Ldm_10mn_2	Unknown		*****	0.731	
13	Ldm_10mn_3	Unknown		*****	0.799	
14	Ldm_10mn_4	Unknown		*****	0.783	
15	Ldm_10mn_5	Unknown		*****	0.788	
16	Ldm_10mn_6	Unknown		*****	0.792	
17	Ldm_10mn_7	Unknown		*****	0.765	
18	Ldm_10mn_8	Unknown		*****	0.786	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
19	Ldm_10mn_9	Unknown		*****	0.791	
20	Ldm_10mn_10	Unknown		*****	0.670	
21	Ldm_10mn_11	Unknown		*****	0.681	
22	Ldm_10mn_12	Unknown		*****	0.755	
23	Ldm_15mn_1	Unknown		*****	0.766	
24	Ldm_15mn_2	Unknown		*****	0.793	
25	Ldm_15mn_3	Unknown		*****	0.755	
26	Ldm_15mn_4	Unknown		*****	0.791	
27	Ldm_15mn_5	Unknown		*****	0.783	
28	Ldm_15mn_6	Unknown		*****	0.784	
29	Ldm_15mn_7	Unknown		*****	0.799	
30	Ldm_15mn_8	Unknown		*****	0.749	
31	Ldm_15mn_9	Unknown		*****	0.786	
32	Ldm_15mn_10	Unknown		*****	0.789	
33	Ldm_15mn_11	Unknown		*****	0.799	
34	Ldm_15mn_12	Unknown		*****	0.798	
35	Ldm_30mn_1	Unknown		*****	0.791	
36	Ldm_30mn_2	Unknown		*****	0.792	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
37	Ldm_30mn_3	Unknown		*****	0.799	
38	Ldm_30mn_4	Unknown		*****	0.755	
39	Ldm_30mn_5	Unknown		*****	0.783	
40	Ldm_30mn_6	Unknown		*****	0.782	
41	Ldm_30mn_7	Unknown		*****	0.785	
42	Ldm_30mn_8	Unknown		*****	0.790	
43	Ldm_30mn_9	Unknown		*****	0.788	
44	Ldm_30mn_10	Unknown		*****	0.796	
45	Ldm_30mn_11	Unknown		*****	0.795	
46	Ldm_30mn_12	Unknown		*****	0.796	
47						

Sample tables –pH4.5

	Sample ID	Type	Ex	Conc	WL244,0	Comments
1	Blc	Unknown		*****	0.000	
2	Priceps_pH1,2_10mn_cp01	Unknown		*****	0.108	
3	Priceps_pH1,2_10mn_cp02	Unknown		*****	0.095	
4	Priceps_pH1,2_10mn_cp03	Unknown		*****	0.099	
5	Priceps_pH1,2_10mn_cp04	Unknown		*****	0.099	
6	Priceps_pH1,2_10mn_cp05	Unknown		*****	0.113	
7	Priceps_pH1,2_10mn_cp06	Unknown		*****	0.104	
8	Priceps_pH1,2_10mn_cp07	Unknown		*****	0.103	
9	Priceps_pH1,2_10mn_cp08	Unknown		*****	0.100	
10	Priceps_pH1,2_10mn_cp09	Unknown		*****	0.096	
11	Priceps_pH1,2_10mn_cp10	Unknown		*****	0.094	
12	Priceps_pH1,2_10mn_cp11	Unknown		*****	0.102	
13	Priceps_pH1,2_10mn_cp12	Unknown		*****	0.101	
14	Priceps_pH1,2_15mn_cp01	Unknown		*****	0.124	
15	Priceps_pH1,2_15mn_cp02	Unknown		*****	0.108	
16	Priceps_pH1,2_15mn_cp03	Unknown		*****	0.103	
17	Priceps_pH1,2_15mn_cp04	Unknown		*****	0.100	
18	Priceps_pH1,2_15mn_cp05	Unknown		*****	0.101	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
19	Priceps_pH1,2_15mn_cp06	Unknown		*****	0.108	
20	Priceps_pH1,2_15mn_cp07	Unknown		*****	0.106	
21	Priceps_pH1,2_15mn_cp08	Unknown		*****	0.100	
22	Priceps_pH1,2_15mn_cp09	Unknown		*****	0.103	
23	Priceps_pH1,2_15mn_cp10	Unknown		*****	0.099	
24	Priceps_pH1,2_15mn_cp11	Unknown		*****	0.101	
25	Priceps_pH1,2_15mn_cp12	Unknown		*****	0.109	
26	Priceps_pH1,2_30mn_cp01	Unknown		*****	0.118	
27	Priceps_pH1,2_30mn_cp02	Unknown		*****	0.122	
28	Priceps_pH1,2_30mn_cp03	Unknown		*****	0.101	
29	Priceps_pH1,2_30mn_cp04	Unknown		*****	0.120	
30	Priceps_pH1,2_30mn_cp05	Unknown		*****	0.117	
31	Priceps_pH1,2_30mn_cp06	Unknown		*****	0.112	
32	Priceps_pH1,2_30mn_cp07	Unknown		*****	0.110	
33	Priceps_pH1,2_30mn_cp08	Unknown		*****	0.119	
34	Priceps_pH1,2_30mn_cp09	Unknown		*****	0.115	
35	Priceps_pH1,2_30mn_cp10	Unknown		*****	0.120	
36	Priceps_pH1,2_30mn_cp11	Unknown		*****	0.118	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
37	Priceps_pH1,2_30mn_cp12	Unknown		*****	0.119	
38	Priceps_pH1,2_45mn_cp01	Unknown		*****	0.116	
39	Priceps_pH1,2_45mn_cp02	Unknown		*****	0.110	
40	Priceps_pH1,2_45mn_cp03	Unknown		*****	0.108	
41	Priceps_pH1,2_45mn_cp04	Unknown		*****	0.117	
42	Priceps_pH1,2_45mn_cp05	Unknown		*****	0.118	
43	Priceps_pH1,2_45mn_cp06	Unknown		*****	0.112	
44	Priceps_pH1,2_45mn_cp07	Unknown		*****	0.116	
45	Priceps_pH1,2_45mn_cp08	Unknown		*****	0.120	
46	Priceps_pH1,2_45mn_cp09	Unknown		*****	0.111	
47	Priceps_pH1,2_45mn_cp10	Unknown		*****	0.122	
48	Priceps_pH1,2_45mn_cp11	Unknown		*****	0.109	
49	Priceps_pH1,2_45mn_cp12	Unknown		*****	0.116	
50	Priceps_pH1,2_60mn_cp01	Unknown		*****	0.111	
51	Priceps_pH1,2_60mn_cp02	Unknown		*****	0.108	
52	Priceps_pH1,2_60mn_cp03	Unknown		*****	0.109	
53	Priceps_pH1,2_60mn_cp04	Unknown		*****	0.114	
54	Priceps_pH1,2_60mn_cp05	Unknown		*****	0.107	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
55	Priceps_pH1,2_60mn_cp06	Unknown		*****	0.117	
56	Priceps_pH1,2_60mn_cp07	Unknown		*****	0.118	
57	Priceps_pH1,2_60mn_cp08	Unknown		*****	0.121	
58	Priceps_pH1,2_60mn_cp09	Unknown		*****	0.103	
59	Priceps_pH1,2_60mn_cp10	Unknown		*****	0.111	
60	Priceps_pH1,2_60mn_cp11	Unknown		*****	0.113	
61	Priceps_pH1,2_60mn_cp12	Unknown		*****	0.101	
62	LDM_pH1,2_10mn_cp01	Unknown		*****	0.139	
63	LDM_pH1,2_10mn_cp02	Unknown		*****	0.124	
64	LDM_pH1,2_10mn_cp03	Unknown		*****	0.132	
65	LDM_pH1,2_10mn_cp04	Unknown		*****	0.137	
66	LDM_pH1,2_10mn_cp05	Unknown		*****	0.138	
67	LDM_pH1,2_10mn_cp06	Unknown		*****	0.121	
68	LDM_pH1,2_10mn_cp07	Unknown		*****	0.126	
69	LDM_pH1,2_10mn_cp08	Unknown		*****	0.129	
70	LDM_pH1,2_10mn_cp09	Unknown		*****	0.132	
71	LDM_pH1,2_10mn_cp10	Unknown		*****	0.123	
72	LDM_pH1,2_10mn_cp11	Unknown		*****	0.138	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
73	LDM_pH1,2_10mn_cp12	Unknown		*****	0.129	
74	LDM_pH1,2_15mn_cp01	Unknown		*****	0.132	
75	LDM_pH1,2_15mn_cp02	Unknown		*****	0.129	
76	LDM_pH1,2_15mn_cp03	Unknown		*****	0.127	
77	LDM_pH1,2_15mn_cp04	Unknown		*****	0.130	
78	LDM_pH1,2_15mn_cp05	Unknown		*****	0.133	
79	LDM_pH1,2_15mn_cp06	Unknown		*****	0.128	
80	LDM_pH1,2_15mn_cp07	Unknown		*****	0.134	
81	LDM_pH1,2_15mn_cp08	Unknown		*****	0.121	
82	LDM_pH1,2_15mn_cp09	Unknown		*****	0.127	
83	LDM_pH1,2_15mn_cp10	Unknown		*****	0.132	
84	LDM_pH1,2_15mn_cp11	Unknown		*****	0.129	
85	LDM_pH1,2_15mn_cp12	Unknown		*****	0.124	
86	LDM_pH1,2_30mn_cp01	Unknown		*****	0.140	
87	LDM_pH1,2_30mn_cp02	Unknown		*****	0.137	
88	LDM_pH1,2_30mn_cp03	Unknown		*****	0.120	
89	LDM_pH1,2_30mn_cp04	Unknown		*****	0.129	
90	LDM_pH1,2_30mn_cp05	Unknown		*****	0.134	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
91	LDM_pH1,2_30mn_cp06	Unknown		*****	0.130	
92	LDM_pH1,2_30mn_cp07	Unknown		*****	0.140	
93	LDM_pH1,2_30mn_cp08	Unknown		*****	0.139	
94	LDM_pH1,2_30mn_cp09	Unknown		*****	0.134	
95	LDM_pH1,2_30mn_cp10	Unknown		*****	0.124	
96	LDM_pH1,2_30mn_cp11	Unknown		*****	0.131	
97	LDM_pH1,2_30mn_cp12	Unknown		*****	0.139	
98	LDM_pH1,2_45mn_cp01	Unknown		*****	0.148	
99	LDM_pH1,2_45mn_cp02	Unknown		*****	0.142	
100	LDM_pH1,2_45mn_cp03	Unknown		*****	0.135	
101	LDM_pH1,2_45mn_cp04	Unknown		*****	0.147	
102	LDM_pH1,2_45mn_cp05	Unknown		*****	0.144	
103	LDM_pH1,2_45mn_cp06	Unknown		*****	0.138	
104	LDM_pH1,2_45mn_cp07	Unknown		*****	0.148	
105	LDM_pH1,2_45mn_cp08	Unknown		*****	0.145	
106	LDM_pH1,2_45mn_cp09	Unknown		*****	0.142	
107	LDM_pH1,2_45mn_cp10	Unknown		*****	0.138	
108	LDM_pH1,2_45mn_cp11	Unknown		*****	0.147	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
109	LDM_pH1,2_45mn_cp12	Unknown		*****	0.149	
110	LDM_pH1,2_60mn_cp01	Unknown		*****	0.139	
111	LDM_pH1,2_60mn_cp02	Unknown		*****	0.147	
112	LDM_pH1,2_60mn_cp03	Unknown		*****	0.155	
113	LDM_pH1,2_60mn_cp04	Unknown		*****	0.152	
114	LDM_pH1,2_60mn_cp05	Unknown		*****	0.147	
115	LDM_pH1,2_60mn_cp06	Unknown		*****	0.154	
116	LDM_pH1,2_60mn_cp07	Unknown		*****	0.151	
117	LDM_pH1,2_60mn_cp08	Unknown		*****	0.146	
118	LDM_pH1,2_60mn_cp09	Unknown		*****	0.153	
119	LDM_pH1,2_60mn_cp10	Unknown		*****	0.154	
120	LDM_pH1,2_60mn_cp11	Unknown		*****	0.148	
121	LDM_pH1,2_60mn_cp12	Unknown		*****	0.142	
122	LDMPH4.510MINCPP1	Unknown		*****	0.107	
123						

Sample tables_ pH6.8

	Sample ID	Type	Ex	Conc	WL244,0	Comments
1	BLANC	Unknown		*****	0.000	
2	std_1_L1	Unknown		*****	0.595	
3	std_1_L2	Unknown		*****	0.593	
4	std_1_L3	Unknown		*****	0.594	
5	std_1_L4	Unknown		*****	0.594	
6	std_1_L5	Unknown		*****	0.593	
7	std_1_L6	Unknown		*****	0.595	
8	std_2_L1	Unknown		*****	0.594	
9	std_2_L2	Unknown		*****	0.594	
10	std_2_L3	Unknown		*****	0.595	
11	PRINC_Ph6,8_10mn_cp_01	Unknown		*****	0.421	
12	PRINC_Ph6,8_10mn_cp_02	Unknown		*****	0.442	
13	PRINC_Ph6,8_10mn_cp_03	Unknown		*****	0.396	
14	PRINC_Ph6,8_10mn_cp_04	Unknown		*****	0.418	
15	PRINC_Ph6,8_10mn_cp_05	Unknown		*****	0.433	
16	PRINC_Ph6,8_10mn_cp_06	Unknown		*****	0.455	
17	PRINC_Ph6,8_10mn_cp_07	Unknown		*****	0.498	
18	PRINC_Ph6,8_10mn_cp_08	Unknown		*****	0.454	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
19	PRINC_Ph6,8_10mn_cp_09	Unknown		*****	0.425	
20	PRINC_Ph6,8_10mn_cp_10	Unknown		*****	0.478	
21	PRINC_Ph6,8_10mn_cp_11	Unknown		*****	0.451	
22	PRINC_Ph6,8_10mn_cp_12	Unknown		*****	0.437	
23	PRINC_Ph6,8_15mn_cp_01	Unknown		*****	0.513	
24	PRINC_Ph6,8_15mn_cp_02	Unknown		*****	0.523	
25	PRINC_Ph6,8_15mn_cp_03	Unknown		*****	0.518	
26	PRINC_Ph6,8_15mn_cp_04	Unknown		*****	0.522	
27	PRINC_Ph6,8_15mn_cp_05	Unknown		*****	0.525	
28	PRINC_Ph6,8_15mn_cp_06	Unknown		*****	0.507	
29	PRINC_Ph6,8_15mn_cp_07	Unknown		*****	0.527	
30	PRINC_Ph6,8_15mn_cp_08	Unknown		*****	0.533	
31	PRINC_Ph6,8_15mn_cp_09	Unknown		*****	0.533	
32	PRINC_Ph6,8_15mn_cp_10	Unknown		*****	0.524	
33	PRINC_Ph6,8_15mn_cp_11	Unknown		*****	0.531	
34	PRINC_Ph6,8_15mn_cp_12	Unknown		*****	0.530	
35	PRINC_Ph6,8_30mn_cp_01	Unknown		*****	0.574	
36	PRINC_Ph6,8_30mn_cp_02	Unknown		*****	0.567	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
37	PRINC_Ph6,8_30mn_cp_03	Unknown		*****	0.553	
38	PRINC_Ph6,8_30mn_cp_04	Unknown		*****	0.548	
39	PRINC_Ph6,8_30mn_cp_05	Unknown		*****	0.580	
40	PRINC_Ph6,8_30mn_cp_06	Unknown		*****	0.565	
41	PRINC_Ph6,8_30mn_cp_07	Unknown		*****	0.563	
42	PRINC_Ph6,8_30mn_cp_08	Unknown		*****	0.556	
43	PRINC_Ph6,8_30mn_cp_09	Unknown		*****	0.560	
44	PRINC_Ph6,8_30mn_cp_10	Unknown		*****	0.550	
45	PRINC_Ph6,8_30mn_cp_11	Unknown		*****	0.549	
46	PRINC_Ph6,8_30mn_cp_12	Unknown		*****	0.543	
47	LDM_Ph6,8_10mn_cp_01	Unknown		*****	0.519	
48	LDM_Ph6,8_10mn_cp_02	Unknown		*****	0.515	
49	LDM_Ph6,8_10mn_cp_03	Unknown		*****	0.520	
50	LDM_Ph6,8_10mn_cp_04	Unknown		*****	0.519	
51	LDM_Ph6,8_10mn_cp_05	Unknown		*****	0.522	
52	LDM_Ph6,8_10mn_cp_06	Unknown		*****	0.519	
53	LDM_Ph6,8_10mn_cp_07	Unknown		*****	0.518	
54	LDM_Ph6,8_10mn_cp_08	Unknown		*****	0.525	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
55	LDM_Ph6,8_10mn_cp_09	Unknown		*****	0.520	
56	LDM_Ph6,8_10mn_cp_10	Unknown		*****	0.513	
57	LDM_Ph6,8_10mn_cp_11	Unknown		*****	0.511	
58	LDM_Ph6,8_10mn_cp_12	Unknown		*****	0.512	
59	LDM_Ph6,8_15mn_cp_01	Unknown		*****	0.581	
60	LDM_Ph6,8_15mn_cp_02	Unknown		*****	0.578	
61	LDM_Ph6,8_15mn_cp_03	Unknown		*****	0.577	
62	LDM_Ph6,8_15mn_cp_04	Unknown		*****	0.576	
63	LDM_Ph6,8_15mn_cp_05	Unknown		*****	0.577	
64	LDM_Ph6,8_15mn_cp_06	Unknown		*****	0.574	
65	LDM_Ph6,8_15mn_cp_07	Unknown		*****	0.580	
66	LDM_Ph6,8_15mn_cp_08	Unknown		*****	0.574	
67	LDM_Ph6,8_15mn_cp_09	Unknown		*****	0.565	
68	LDM_Ph6,8_15mn_cp_10	Unknown		*****	0.586	
69	LDM_Ph6,8_15mn_cp_11	Unknown		*****	0.573	
70	LDM_Ph6,8_15mn_cp_12	Unknown		*****	0.565	
71	LDM_Ph6,8_30mn_cp_01	Unknown		*****	0.586	
72	LDM_Ph6,8_30mn_cp_02	Unknown		*****	0.583	

	Sample ID	Type	Ex	Conc	WL244,0	Comments
73	LDM_Ph6,8_30mn_cp_03	Unknown		*****	0.659	
74	LDM_Ph6,8_30mn_cp_04	Unknown		*****	0.581	
75	LDM_Ph6,8_30mn_cp_05	Unknown		*****	0.592	
76	LDM_Ph6,8_30mn_cp_06	Unknown		*****	0.589	
77	LDM_Ph6,8_30mn_cp_07	Unknown		*****	0.579	
78	LDM_Ph6,8_30mn_cp_08	Unknown		*****	0.571	
79	LDM_Ph6,8_30mn_cp_09	Unknown		*****	0.577	
80	LDM_Ph6,8_30mn_cp_10	Unknown		*****	0.573	
81	LDM_Ph6,8_30mn_cp_11	Unknown		*****	0.583	
82	LDM_Ph6,8_30mn_cp_12	Unknown		*****	0.581	
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Appendix II: Raw numerical data for the dissolution profiles

Detailed quantitative data from the dissolution profile study conducted on Irbezart® and Aprovel® atthedifferenttimeintervals.Thevaluesincludeabsorbancereadings,calculatedpercentagesofdrug release (P% and Q %), as well as statistical indicators such as mean release (MOY %), range (Min– Max), standard deviation (ECART-TYPE), and relative standard deviation (RSD). These measurementswereobtainedusingUV-spectrophotometryincompliancewiththedissolutiontesting protocol under controlled laboratory conditions.

Irbezart®profile_pH1.2

Smp_T=10min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,767	37,6	0,731	1000	101,1	0,2	150	95,6	95,6					
CP 2	0,767	37,6	0,731	1000	101,1	0,2	150	95,5	95,5					
CP 3	0,767	37,6	0,799	1000	101,1	0,2	150	104,4	104,4					
CP 4	0,767	37,6	0,783	1000	101,1	0,2	150	102,3	102,3					
CP 5	0,767	37,6	0,788	1000	101,1	0,2	150	103,0	103,0					
CP 6	0,767	37,6	0,792	1000	101,1	0,2	150	103,5	103,5	99	88	104	5,7	5,8
CP 7	0,767	37,6	0,765	1000	101,1	0,2	150	100,0	100,0					
CP 8	0,767	37,6	0,786	1000	101,1	0,2	150	102,7	102,7					
CP 9	0,767	37,6	0,791	1000	101,1	0,2	150	103,4	103,4					
CP 10	0,767	37,6	0,670	1000	101,1	0,2	150	87,5	87,5					
CP 11	0,767	37,6	0,682	1000	101,1	0,2	150	89,1	89,1					
CP 12	0,767	37,6	0,755	1000	101,1	0,2	150	98,7	98,7					
Smp_T=15min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,767	37,6	0,766	1000	101,1	0,2	150	100,1	100,0					
CP 2	0,767	37,6	0,793	1000	101,1	0,2	150	103,6	103,5					
CP 3	0,767	37,6	0,755	1000	101,1	0,2	150	98,7	98,7					
CP 4	0,767	37,6	0,791	1000	101,1	0,2	150	103,4	103,3					
CP 5	0,767	37,6	0,783	1000	101,1	0,2	150	102,3	102,3					
CP 6	0,767	37,6	0,784	1000	101,1	0,2	150	102,4	102,5	102	98	104	2,2	2,1
CP 7	0,767	37,6	0,799	1000	101,1	0,2	150	104,4	104,4					
CP 8	0,767	37,6	0,749	1000	101,1	0,2	150	97,9	97,9					
CP 9	0,767	37,6	0,786	1000	101,1	0,2	150	102,7	102,7					
CP 10	0,767	37,6	0,789	1000	101,1	0,2	150	103,1	102,9					
CP 11	0,767	37,6	0,799	1000	101,1	0,2	150	104,4	104,3					
CP 12	0,767	37,6	0,798	1000	101,1	0,2	150	104,3	104,2					
Smp_T=30min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,767	37,6	0,791	1000	101,1	0,2	150	103,4	101,3					
CP 2	0,767	37,6	0,792	1000	101,1	0,2	150	103,5	101,4					
CP 3	0,767	37,6	0,799	1000	101,1	0,2	150	104,4	102,3					
CP 4	0,767	37,6	0,755	1000	101,1	0,2	150	98,7	96,7					
CP 5	0,767	37,6	0,783	1000	101,1	0,2	150	102,3	100,3					
CP 6	0,767	37,6	0,782	1000	101,1	0,2	150	102,2	100,2					
CP 7	0,767	37,6	0,785	1000	101,1	0,2	150	102,6	100,5	101	97	102	1,5	1,5
CP 8	0,767	37,6	0,790	1000	101,1	0,2	150	103,2	101,2					
CP 9	0,767	37,6	0,788	1000	101,1	0,2	150	103,0	100,9					
CP 10	0,767	37,6	0,796	1000	101,1	0,2	150	104,0	102,0					
CP 11	0,767	37,6	0,795	1000	101,1	0,2	150	103,9	101,8					
CP 12	0,767	37,6	0,796	1000	101,1	0,2	150	104,0	102,0					

Aprovel®profile_pH1.2

Smp_T=10min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,651	30,5	0,556	1000	101,1	0,2	150	86,8	86,8					
CP 2	0,651	30,5	0,553	1000	101,1	0,2	150	86,4	86,4					
CP 3	0,651	30,5	0,552	1000	101,1	0,2	150	86,2	86,2					
CP 4	0,651	30,5	0,554	1000	101,1	0,2	150	86,5	86,5					
CP 5	0,651	30,5	0,553	1000	101,1	0,2	150	86,4	86,4					
CP 6	0,651	30,5	0,594	1000	101,1	0,2	150	92,8	92,8	90	86	93	2,8	3,1
CP 7	0,651	30,5	0,591	1000	101,1	0,2	150	92,3	92,3					
CP 8	0,651	30,5	0,589	1000	101,1	0,2	150	92,0	92,0					
CP 9	0,651	30,5	0,589	1000	101,1	0,2	150	92,0	92,0					
CP 10	0,651	30,5	0,585	1000	101,1	0,2	150	91,4	91,4					
CP 11	0,651	30,5	0,581	1000	101,1	0,2	150	90,7	90,7					
CP 12	0,651	30,5	0,581	1000	101,1	0,2	150	90,7	90,7					
Smp_T=15min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,651	30,5	0,699	1000	101,1	0,2	150	109,2	108,9					
CP 2	0,651	30,5	0,720	1000	101,1	0,2	150	112,4	112,2					
CP 3	0,651	30,5	0,608	1000	101,1	0,2	150	95,0	94,9					
CP 4	0,651	30,5	0,618	1000	101,1	0,2	150	96,5	96,4					
CP 5	0,651	30,5	0,612	1000	101,1	0,2	150	95,6	95,5					
CP 6	0,651	30,5	0,679	1000	101,1	0,2	150	106,0	105,9	104	93	114	7,9	7,6
CP 7	0,651	30,5	0,632	1000	101,1	0,2	150	98,7	98,6					
CP 8	0,651	30,5	0,596	1000	101,1	0,2	150	93,1	93,1					
CP 9	0,651	30,5	0,71	1000	101,1	0,2	150	110,9	110,7					
CP 10	0,651	30,5	0,734	1000	101,1	0,2	150	114,6	114,4					
CP 11	0,651	30,5	0,712	1000	101,1	0,2	150	111,2	111,0					
CP 12	0,651	30,5	0,704	1000	101,1	0,2	150	109,9	109,8					
Smp_T=30min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,651	30,5	0,682	1000	101,1	0,2	150	106,5	104,4					
CP 2	0,651	30,5	0,706	1000	101,1	0,2	150	110,3	108,1					
CP 3	0,651	30,5	0,699	1000	101,1	0,2	150	109,2	107,0					
CP 4	0,651	30,5	0,630	1000	101,1	0,2	150	98,4	96,4					
CP 5	0,651	30,5	0,693	1000	101,1	0,2	150	108,2	106,1					
CP 6	0,651	30,5	0,692	1000	101,1	0,2	150	108,1	105,9	106	96	108	3,1	2,9
CP 7	0,651	30,5	0,704	1000	101,1	0,2	150	109,9	107,8					
CP 8	0,651	30,5	0,703	1000	101,1	0,2	150	109,8	107,6					
CP 9	0,651	30,5	0,703	1000	101,1	0,2	150	109,8	107,6					
CP 10	0,651	30,5	0,693	1000	101,1	0,2	150	108,2	106,1					
CP 11	0,651	30,5	0,689	1000	101,1	0,2	150	107,6	105,5					
CP 12	0,651	30,5	0,692	1000	101,1	0,2	150	108,1	105,9					

Irbezart®profile_pH4.5

Smp_T=10min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,122	30,5	0,139	1000	99,7	0,3	150	92,1	92,1					
CP 2	0,122	30,5	0,124	1000	99,7	0,3	150	82,2	82,2					
CP 3	0,122	30,5	0,132	1000	99,7	0,3	150	87,5	87,5					
CP 4	0,122	30,5	0,137	1000	99,7	0,3	150	90,8	90,8					
CP 5	0,122	30,5	0,138	1000	99,7	0,3	150	91,4	91,4					
CP 6	0,122	30,5	0,121	1000	99,7	0,3	150	80,2	80,2	87	80	92	4,2	4,9
CP 7	0,122	30,5	0,126	1000	99,7	0,3	150	83,5	83,5					
CP 8	0,122	30,5	0,129	1000	99,7	0,3	150	85,5	85,5					
CP 9	0,122	30,5	0,132	1000	99,7	0,3	150	87,5	87,5					
CP 10	0,122	30,5	0,123	1000	99,7	0,3	150	81,5	81,5					
CP 11	0,122	30,5	0,138	1000	99,7	0,3	150	91,4	91,4					
CP 12	0,122	30,5	0,129	1000	99,7	0,3	150	85,5	85,5					
Smp_T=15min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,122	30,5	0,132	1000	99,7	0,3	150	87,5	87,5					
CP 2	0,122	30,5	0,129	1000	99,7	0,3	150	85,5	85,5					
CP 3	0,122	30,5	0,127	1000	99,7	0,3	150	84,2	84,2					
CP 4	0,122	30,5	0,130	1000	99,7	0,3	150	86,1	86,2					
CP 5	0,122	30,5	0,133	1000	99,7	0,3	150	88,1	88,2					
CP 6	0,122	30,5	0,128	1000	99,7	0,3	150	84,8	84,8	85	80	89	2,5	2,9
CP 7	0,122	30,5	0,134	1000	99,7	0,3	150	88,8	88,7					
CP 8	0,122	30,5	0,121	1000	99,7	0,3	150	80,2	80,2					
CP 9	0,122	30,5	0,127	1000	99,7	0,3	150	84,2	84,2					
CP 10	0,122	30,5	0,132	1000	99,7	0,3	150	87,5	87,4					
CP 11	0,122	30,5	0,129	1000	99,7	0,3	150	85,5	85,5					
CP 12	0,122	30,5	0,124	1000	99,7	0,3	150	82,2	82,2					
Smp_T=30min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,122	30,5	0,140	1000	99,7	0,3	150	92,8	90,9					
CP 2	0,122	30,5	0,137	1000	99,7	0,3	150	90,8	89,0					
CP 3	0,122	30,5	0,120	1000	99,7	0,3	150	79,5	77,9					
CP 4	0,122	30,5	0,129	1000	99,7	0,3	150	85,5	83,8					
CP 5	0,122	30,5	0,134	1000	99,7	0,3	150	88,8	87,0					
CP 6	0,122	30,5	0,130	1000	99,7	0,3	150	86,1	84,4					
CP 7	0,122	30,5	0,140	1000	99,7	0,3	150	92,8	90,9	86	78	91	4,2	4,9
CP 8	0,122	30,5	0,139	1000	99,7	0,3	150	92,1	90,3					
CP 9	0,122	30,5	0,134	1000	99,7	0,3	150	88,8	87,0					
CP 10	0,122	30,5	0,124	1000	99,7	0,3	150	82,2	80,5					
CP 11	0,122	30,5	0,131	1000	99,7	0,3	150	86,8	85,1					
CP 12	0,122	30,5	0,139	1000	99,7	0,3	150	92,1	90,3					

Aprovel®profile_pH 4.5

Smp_T=10min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,122	30,5	0,108	1000	99,7	0,3	150	89,5	89,5					
CP 2	0,122	30,5	0,095	1000	99,7	0,3	150	78,7	78,7					
CP 3	0,122	30,5	0,099	1000	99,7	0,3	150	82,0	82,0					
CP 4	0,122	30,5	0,099	1000	99,7	0,3	150	82,0	82,0					
CP 5	0,122	30,5	0,113	1000	99,7	0,3	150	93,6	93,6					
CP 6	0,122	30,5	0,104	1000	99,7	0,3	150	86,1	86,1	84	78	94	4,5	5,4
CP 7	0,122	30,5	0,103	1000	99,7	0,3	150	85,3	85,3					
CP 8	0,122	30,5	0,100	1000	99,7	0,3	150	82,8	82,8					
CP 9	0,122	30,5	0,096	1000	99,7	0,3	150	79,5	79,5					
CP 10	0,122	30,5	0,094	1000	99,7	0,3	150	77,9	77,9					
CP 11	0,122	30,5	0,102	1000	99,7	0,3	150	84,5	84,5					
CP 12	0,122	30,5	0,101	1000	99,7	0,3	150	83,7	83,7					
Smp_T=15min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,122	30,5	0,124	1000	99,7	0,3	150	102,7	102,6					
CP 2	0,122	30,5	0,108	1000	99,7	0,3	150	89,5	89,3					
CP 3	0,122	30,5	0,103	1000	99,7	0,3	150	85,3	85,3					
CP 4	0,122	30,5	0,100	1000	99,7	0,3	150	82,8	82,8					
CP 5	0,122	30,5	0,101	1000	99,7	0,3	150	83,7	83,8					
CP 6	0,122	30,5	0,108	1000	99,7	0,3	150	89,5	89,4	87	82	103	5,7	6,5
CP 7	0,122	30,5	0,106	1000	99,7	0,3	150	87,8	87,8					
CP 8	0,122	30,5	0,100	1000	99,7	0,3	150	82,8	82,8					
CP 9	0,122	30,5	0,103	1000	99,7	0,3	150	85,3	85,3					
CP 10	0,122	30,5	0,099	1000	99,7	0,3	150	82,0	82,0					
CP 11	0,122	30,5	0,101	1000	99,7	0,3	150	83,7	83,7					
CP 12	0,122	30,5	0,109	1000	99,7	0,3	150	90,3	90,2					
Smp_T=30min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,122	30,5	0,118	1000	99,7	0,3	150	97,7	95,8					
CP 2	0,122	30,5	0,122	1000	99,7	0,3	150	101,1	99,1					
CP 3	0,122	30,5	0,101	1000	99,7	0,3	150	83,7	82,0					
CP 4	0,122	30,5	0,120	1000	99,7	0,3	150	99,4	97,4					
CP 5	0,122	30,5	0,117	1000	99,7	0,3	150	96,9	95,0					
CP 6	0,122	30,5	0,112	1000	99,7	0,3	150	92,8	90,9	94	82	99	4,7	5,0
CP 7	0,122	30,5	0,110	1000	99,7	0,3	150	91,1	89,3					
CP 8	0,122	30,5	0,119	1000	99,7	0,3	150	98,6	96,6					
CP 9	0,122	30,5	0,115	1000	99,7	0,3	150	95,3	93,4					
CP 10	0,122	30,5	0,120	1000	99,7	0,3	150	99,4	97,4					
CP 11	0,122	30,5	0,118	1000	99,7	0,3	150	97,7	95,8					
CP 12	0,122	30,5	0,119	1000	99,7	0,3	150	98,6	96,6					

Irbezart®profile_pH6.8

Smp_T=10min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,594	30,4	0,519	1000	99,7	0,3	150	88,5	88,5					
CP 2	0,594	30,4	0,515	1000	99,7	0,3	150	87,9	87,9					
CP 3	0,594	30,4	0,520	1000	99,7	0,3	150	88,7	88,7					
CP 4	0,594	30,4	0,519	1000	99,7	0,3	150	88,5	88,5					
CP 5	0,594	30,4	0,522	1000	99,7	0,3	150	89,1	89,1					
CP 6	0,594	30,4	0,519	1000	99,7	0,3	150	88,5	88,5	88	87	90	0,7	0,8
CP 7	0,594	30,4	0,518	1000	99,7	0,3	150	88,4	88,4					
CP 8	0,594	30,4	0,525	1000	99,7	0,3	150	89,6	89,6					
CP 9	0,594	30,4	0,520	1000	99,7	0,3	150	88,7	88,7					
CP 10	0,594	30,4	0,513	1000	99,7	0,3	150	87,5	87,5					
CP 11	0,594	30,4	0,511	1000	99,7	0,3	150	87,2	87,2					
CP 12	0,594	30,4	0,512	1000	99,7	0,3	150	87,3	87,3					
Smp_T=15min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,594	30,4	0,581	1000	99,7	0,3	150	99,1	99,0					
CP 2	0,594	30,4	0,578	1000	99,7	0,3	150	98,6	98,5					
CP 3	0,594	30,4	0,577	1000	99,7	0,3	150	98,4	98,3					
CP 4	0,594	30,4	0,576	1000	99,7	0,3	150	98,3	98,2					
CP 5	0,594	30,4	0,577	1000	99,7	0,3	150	98,4	98,3					
CP 6	0,594	30,4	0,574	1000	99,7	0,3	150	97,9	97,8	98	96	100	1,0	1,0
CP 7	0,594	30,4	0,580	1000	99,7	0,3	150	98,9	98,8					
CP 8	0,594	30,4	0,574	1000	99,7	0,3	150	97,9	97,8					
CP 9	0,594	30,4	0,565	1000	99,7	0,3	150	96,4	96,3					
CP 10	0,594	30,4	0,586	1000	99,7	0,3	150	100,0	99,8					
CP 11	0,594	30,4	0,573	1000	99,7	0,3	150	97,8	97,6					
CP 12	0,594	30,4	0,565	1000	99,7	0,3	150	96,4	96,3					
Smp_T=30min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,594	30,4	0,586	1000	99,7	0,3	150	100,0	98,0					
CP 2	0,594	30,4	0,583	1000	99,7	0,3	150	99,5	97,5					
CP 3	0,594	30,4	0,659	1000	99,7	0,3	150	112,4	110,2					
CP 4	0,594	30,4	0,581	1000	99,7	0,3	150	99,1	97,2					
CP 5	0,594	30,4	0,592	1000	99,7	0,3	150	101,0	99,0					
CP 6	0,594	30,4	0,589	1000	99,7	0,3	150	100,5	98,5	98	95	110	3,9	3,9
CP 7	0,594	30,4	0,579	1000	99,7	0,3	150	98,8	96,8					
CP 8	0,594	30,4	0,571	1000	99,7	0,3	150	97,4	95,5					
CP 9	0,594	30,4	0,577	1000	99,7	0,3	150	98,4	96,5					
CP 10	0,594	30,4	0,573	1000	99,7	0,3	150	97,8	95,8					
CP 11	0,594	30,4	0,583	1000	99,7	0,3	150	99,5	97,5					
CP 12	0,594	30,4	0,581	1000	99,7	0,3	150	99,1	97,2					

Aprovel®profile_pH 6.8

Smp_T=10min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,594	30,4	0,421	1000	99,7	0,3	150	71,8	71,8					
CP 2	0,594	30,4	0,442	1000	99,7	0,3	150	75,4	75,4					
CP 3	0,594	30,4	0,396	1000	99,7	0,3	150	67,6	67,6					
CP 4	0,594	30,4	0,418	1000	99,7	0,3	150	71,3	71,3					
CP 5	0,594	30,4	0,433	1000	99,7	0,3	150	73,9	73,9					
CP 6	0,594	30,4	0,455	1000	99,7	0,3	150	77,6	77,6	75	68	85	4,7	6,2
CP 7	0,594	30,4	0,498	1000	99,7	0,3	150	85,0	85,0					
CP 8	0,594	30,4	0,454	1000	99,7	0,3	150	77,5	77,5					
CP 9	0,594	30,4	0,425	1000	99,7	0,3	150	72,5	72,5					
CP 10	0,594	30,4	0,478	1000	99,7	0,3	150	81,5	81,5					
CP 11	0,594	30,4	0,451	1000	99,7	0,3	150	76,9	76,9					
CP 12	0,594	30,4	0,437	1000	99,7	0,3	150	74,5	74,5					
Smp_T=15min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,594 *	30,4	0,513	1000	99,7	0,3	150	87,5	87,4					
CP 2	0,594	30,4	0,523	1000	99,7	0,3	150	89,2	89,1					
CP 3	0,594	30,4	0,518	1000	99,7	0,3	150	88,4	88,2					
CP 4	0,594	30,4	0,522	1000	99,7	0,3	150	89,1	88,9					
CP 5	0,594	30,4	0,525	1000	99,7	0,3	150	89,6	89,4					
CP 6	0,594	30,4	0,507	1000	99,7	0,3	150	86,5	86,4	89	86	91	1,4	1,5
CP 7	0,594	30,4	0,527	1000	99,7	0,3	150	89,9	89,9					
CP 8	0,594	30,4	0,533	1000	99,7	0,3	150	90,9	90,8					
CP 9	0,594	30,4	0,533	1000	99,7	0,3	150	90,9	90,7					
CP 10	0,594	30,4	0,524	1000	99,7	0,3	150	89,4	89,3					
CP 11	0,594	30,4	0,531	1000	99,7	0,3	150	90,6	90,4					
CP 12	0,594	30,4	0,530	1000	99,7	0,3	150	90,4	90,3					
Smp_T=30min	Abs Std 244	P STD	Abs Ess 244	Vess (ml)	T	LOD	LC	P%	Q%	MOY(%)	Min(%)	Max(%)	ECARTYPE	RSD
CP 1	0,594	30,4	0,574	1000	99,7	0,3	150	97,9	96,0					
CP 2	0,594	30,4	0,567	1000	99,7	0,3	150	96,7	94,8					
CP 3	0,594	30,4	0,553	1000	99,7	0,3	150	94,3	92,5					
CP 4	0,594	30,4	0,548	1000	99,7	0,3	150	93,5	91,6					
CP 5	0,594	30,4	0,580	1000	99,7	0,3	150	98,9	97,0					
CP 6	0,594	30,4	0,565	1000	99,7	0,3	150	96,4	94,5	93	91	97	1,9	2,0
CP 7	0,594	30,4	0,563	1000	99,7	0,3	150	96,0	94,1					
CP 8	0,594	30,4	0,556	1000	99,7	0,3	150	94,9	93,0					
CP 9	0,594	30,4	0,560	1000	99,7	0,3	150	95,5	93,6					
CP 10	0,594	30,4	0,550	1000	99,7	0,3	150	93,8	92,0					
CP 11	0,594	30,4	0,549	1000	99,7	0,3	150	93,7	91,8					
CP 12	0,594	30,4	0,543	1000	99,7	0,3	150	92,6	90,8					

Appendix III :Dissolutest PTWS 1220

Principle:

TheDissolutestPTW1220isintendedfordeterminingthecomplianceofsolidoralpharmaceutical

formswithdissolutionrequirements.

Device Description:

ThePTW1220offersahigh-capacitysetupfortesting12samplesinasingle run.

This bath design provides identical physical conditions for all 12 samples inside the dissolution vessels: the same tool speed, the same temperature, and immunity to potential internal and external vibration sources. Thetestpositionsare arrangedintworows(6+6)andallowforstaggeredstart times.

Each vessel is individually covered. Each lid is equipped with openings for sample withdrawal, as well as for temperature or pH measurements.

Figure9:PTWS1220–USP/EP Tablet Dissolution Testing Instrument

User Interface:

Alargecolourtouchscreenallowscontroloftheinstrument'svariousmechanicalfeatures,such as

the stirring speed of thetool,liftmechanism,andheating.Instrumentcontrolis menu-driven.

Status messages and color changes on the screen inform the user about the condition of the instrument'scriticalparameters—forexample,ifthetargetbathtemperaturehasnotbeenreached.A status bar provides a quick overview and uses the familiar green-yellow-red signal light system.

Access to the instrument can be password-protected if necessary. If certain operational parameters are routinely used, they can be saved within a test method for quicker setup. These parameters may include tool speed, target bath temperature, sampling time, etc.
Thememorycapacityforstoringtest methodsisvirtually unlimited.

At the beginning of the test, a screensavercan be activated displaying key information in large text, ensuring visibility even when the operator is not standing directly in front of the instrument.

StirringTools

The PTWS 1220 uses the PharmaTest MonoShaftdesign. Tools consist of the main shaft plus interchangeable tool heads (adapters). The main shaft remains in place in the instrument regardless of the tool head being used. The clearance of each tool from the vessel base will always be correct once the main tool shaft has been installed and fixed in its position.
A wide variety of different stirring tools is available while the standard configuration includes USP/EP App. 2 Paddle stirrers.

Figure10:USP 2Adapter

Vessel Centering System

ThePTWS1220featuresathree-pointindividualcenteringsystemforeachdissolutionvessel(picture shows view from below). The vessels are held in position by three adjustable noses and are inserted into the instrument support framework. Each vessel is correctly centered against the stirring tool, while this position is secured even when the vessels are removed for cleaning and placed back afterwards. The access points for sampling as well as the openings for the tools are contained in an auxiliary, low evaporation, vessel cover.

Lift Mechanism

Theupperdriveismotorizedandelectronicallycontrolleditofferseightprogrammablepositions :an upper cleaning position and lower working positions are programmable depending on the type of stirring tool used.
The upper position offers ideal access to the stirring tools and vessels for a change of tools and cleaning steps between the dissolution tests. The rigid design of the electronically driven lift mechanism ensures that the whole lift drive mechanism is positioned in a way sothat the tool shafts are always kept parallel and at a 90° angle to the vessel walls when in the working position.

Figure11:Lifting mechanism

Heating System

The ultra-fast heating system is installed on an easy to remove platform within the stainless steel housing. The heat up time of the water bath has been reduced by approx. 40% compared to previous models. Access to pump, heater and all safety sensor system is possible without to move the bath from its qualified position. The connections between the heater and the bath are made by “quick connect fittings” for easy connection and disconnection. Water is pumped through the system using a powerful, yet quiet, circulation pump.
The pump itself is spring mounted (to limit vibration transmission) and the flow-through heater is protected from overloading (overheating in case of control electronics failure) via a thermal fuse as well as a thermo switch for added security. With service and maintenance in mind, access to the compact pump and heater section is easily achieved without having to move the main body of the instrument.

Water Bath

The U-shaped water bath rests on vibration absorbers to avoid any vibration transfer from either inside the instrument or even from external equipment placed on the same bench surface, to satisfy the requirements from USP <711>. The bath cover can also be easily unscrewed for cleaning. The water bath contains a water diffuser for faster heating and to ensure that heated water is evenly distributed throughout the whole bath. A tap allows emptying the bath if this is required.

Installation and Start-Up

- Before powering the device and placing the vessels, ensure that the connecting pipes are filled by manually purging the air (using the pump) and that there are no leaks.
- Place and secure the test vessels.
- Fill the bath with water up to the recommended level.
- Power on the device using the red ON/OFF button located on the pump.

- The main screen will appear:
    a. Press “Reference” until it turns green to access the instrument.
    b. Press “Quick Start.”
    c. Enter the batch number (e.g., 1.2.3.4), then press OK.
    d. Enter the rotation speed according to the analysis protocol, then press OK.
    e. Set the temperature to 37 ±0.5°C, then press OK.
    f. Wait for the target temperature to be reached (colour changes from yellow to green).
    g. Press “Lift Position” to raise or lower the stirring tools (paddles or baskets).
    h. Press “Table Dropped” after placing the product to be analysed.
    i. A countdown timer will appear on the screen.

Advantages

- Test 12 samples in one instrument with identical conditions for comparative studies (Biowaiver)
- 6 front line and 6 back line vessels for easy access in manual operation
- Rigid aluminium water bath cover
- Individual 3-point vessel centerings
- Excellent access to all vessel
- Staggered start feature for convenient manual sampling
- Screen saver functionality offers most important information at a glance (stirrer speed, bath temperature, time to next sampling interval, elapsed time, media temperature etc.)
- Wake up functionality to start heating at a pre-programmed time
- Programmable infinity test
- MonoShaft™ system to avoid re-adjustment of immersion depth
- Ultra-fast heating system with excellent temperature stability due to newly designed heat exchanger
- Water diffuser for even temperature distribution
- Vibration absorber to avoid vibration transfer into the USP/EP vessels
- Spring loaded pump assembly to eliminate vibration transfer to the frame work
- Extraordinary safety features for pump and heating system, flow control, digital temperature control, water level sensor, thermo switch, thermo fuse
- DQ/QC, IQ and OQ documents included free of charge

Key Features

- Automated temperature check and log at all sampling times
- Fully USP <711/724> and EP <2.9.3/4> compliant
- 12 stirred positions in a 6 + 6 arrangement, 2 extra vessels for refilling or standard media
- Rigid motorised lift drive to raise and lower the head
- Individually coded Borosilicate vessels
- File up a nearly unlimited number of different test descriptions (methods)
- Instrument suitability check prior to start of a test run
- Staggered start capability
- Vessel low evaporation sealing covers
- Drainage tap to empty the bath
- CFR compliant method management and user administration with access control
- Built-in thermo printer to print a test-log at the end of a run
- Optical and acoustic signals to inform about sampling intervals, timer count down function
- Status bar with traffic light information on display shows the instrument status by different colours (green = ready to use, yellow = preparing to use, red = error encountered)

- OQ, PQ interval warning with programmable interval
- Interfaces: USB port for remote control of the PTWS 1220, RS-232 port to connect serial devices, I/O port for remote control of external instruments in automated applications, like DSR-M, pumps and PTFC-16
- Calibration menu for stirrer speed, bath temperature

Technical Specifications

Parameter	Specification
Display	6″ - 320×240 pixel color LCD, illuminated
Data Entry	Resistive touch screen, alpha-numerical and functional keys
Acoustic Signal	Acoustic signal for operator information at programmable intervals
Timer	Programmable sampling times, wake-up and sleep mode, operation time, countdown
Stirrer Position	8 freely programmable stirrer immersion positions (paddle over disk, transdermal)
Testing Method Descriptions	Unlimited number of test descriptions stored on SD card
User Access Control	Multiple level access control
OQ, PQ Control	Programmable reminder intervals for OQ/PQ testing
Printer	Built-in thermo printer
Number of Stirred Vessels	12 (6 + 6 arrangement)
Standard Vessels	1 L USP/EP borosilicate glass vessel, each individually coded
Speed Control	25 – 250 RPM
Speed Accuracy	±2% of set speed, typically < 1%
Stirrer Shaft Wobble	Better than 0.2 mm total run out
System Tools	MonoShaft™ stirrer design; tools & vessels coded; supports USP/EP app. 1, 2, 5, 6
Heating System	Pump + 1500W heater for fast heating
Heater Range	25 – 45°C
Heater Accuracy	± 0.2°C inside the water bath
Heat Up Process	Energy-saving, programmable “wake-up” and “sleep” functions
Water Circulation	External system with internal diffuser
Vibration Elimination	Water bath on vibration absorbers; spring-loaded pump assembly
Calibration	Built-in for speed, temperature; programmable OQ/PQ intervals with alarms
Bench Space Requirements	Approx. 1120 x 700 mm
Packaging	Approx. 1370 x 780 x 870 mm (W x D x H)
Weight	75 kg net, 100 kg gross
Certification	All components certified to USP / EP requirements
CE / EMC Certification	Provided
Validation	All IQ & OQ documents included

Appendix IV: Calibration of the Mettlertoledo® pH meter

To calibrate a MettlerToledo pH meter, use standardised buffer solutions and follow the instrument's specific calibration instructions. Mettlertoledo® meters offer automatic or manual calibration options, and you'll need to select your calibration points (e.g., pH 4, 7, 9, or 10) and run the calibration procedure by immersing the sensor in the buffer solutions.

Calibration Process:

Prepare:
Choose the appropriate buffer solutions for your calibration points. Mettlertoledo meters typically use standard pH buffers (e.g., pH 4.01, 7.00, 9.21).
Select Calibration:
On the Mettlertoledo meter, navigate to the calibration menu or settings and select the desired calibration mode (automatic or manual).
Immerse Sensor:
Carefully immerse the sensor into the first buffer solution, ensuring the electrode and temperature probe are fully submerged.
Start Calibration:
Follow the prompts on the meter display to start the calibration process. The meter will typically measure the pH of the buffer solution and adjust accordingly.
Repeat for Multiple Points:
If you are performing a multi-point calibration (e.g., 2 or 3 points), repeat the immersion and calibration steps for each buffer solution.
View Results:
Once the calibration is complete, the meter will display the results, such as the slope and offset of the calibration.
Important Considerations:

- Accuracy: Ensure the buffer solutions are fresh and at the correct temperature.
- Cleaning: Rinse the sensor with deionised water after each calibration point to remove any residual buffer.
- Troubleshooting: If the calibration fails, consult the Mettler Toledo instruction manual or contact Mettlertoledo for assistance.

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Comparative Study of the Dissolution Profiles of IRBEZART® 150 mg (Generic) and APROVEL® 150 mg (Reference Drug).

Dissertation for obtaining a professional Master's degree in Biotehnology and Qality Conrol

Abstract

This investigation presents a comparative *in vitro* dissolution analysis of Irbezart® 150 mg, a generic formulation, and Aprovel® 150 mg, the reference drug. Both formulations contain irbesartan, an angiotensin II receptor blocker widely used in hypertension treatment. The main objective of the present study was to evaluate the *in vitro* dissolution performance of the generic formulation Irbezart® and assess its pharmaceutical equivalence to the reference drug Aprovel®, thereby ensuring therapeutic consistency and compliance with regulatory standards. The dissolution test was carried out using the PTW 1220 Dissolutest machine under standardized conditions (50 rpm, 37 ± 0.5°C) in three dissolution media of varying pH (1.2, 4.5, and 6.8), intended to simulate different gastrointestinal environments. A total of twelve tablets from each formulation, randomly selected from different production batches, were analyzed to ensure representative sampling. Six samples were collected from each vessel at specified time intervals and analyzed using UV-Visible spectrophotometry. A validated calibration curve was employed to quantify the percentage of irbesartan released at each time point, in which a standard solution was also prepared and analysed under the same conditions. The obtained absorbance values were used to calculate the percentage of drug dissolved. Statistical analysis, including calculation of the mean, standard deviation, and coefficient of variation, was performed to ensure data reproducibility and reliability. The obtained results showed that both formulations achieved a drug release dissolution percentage of ≥ 85% within 15 minutes across all pH media, indicating rapid and complete dissolution; so eliminating the need for further mathematical comparison. Based on regulatory guidance, the similarity in dissolution profiles between Irbezart® and Aprovel® that were closely matched, supports the conclusion that the two products are pharmaceutically equivalent *in vitro*. These findings reinforce the quality and the efficacy of the generic formulation and support its interchangeability with the branded product. They also contribute to ongoing efforts in generic drug evaluation and underscore the importance of dissolution testing as a reliable tool in pharmaceutical quality assurance.

Key words: Irbesartan, dissolution profile, generic drug, Aprovel®, Irbezart®, quality control.

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