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Theme

Manufacturing process and quality control of a neuroleptic drug, Sulpuren® capsules (50mg).

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Dedication

I dedicate this dissertation to my mother ***"Radia"*** *and my father* ***"Mohammed"****, my role models, my guides, and the pillars of my success. Your love, advice, and unwavering support have allowed me to achieve this long-awaited goal*

To these exceptional girls, my sisters ***"Houria"****,* ***"Ikram"****, the twins* ***"Lilia & Widad",*** *and the little* ***"Nadjoua".*** *Your comforting arms, your joy of life, your listening ear, and your blind faith in me have allowed me to pursue my dreams to the end.*

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NADIA

Dedication

Dedications With the intensity of my emotions

I dedicate the fruit of this modest work to all that is in my heart:

My dear parents

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FAIROUZ

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List of abbreviations

ACP	Algerian Central Pharmacy
AP	Antipsychotic
API	Active Pharmaceutical Ingredient
CNS	Central Nervous System
EPE	Public Economic Enterprises
GMP	Good Manufacturing Process
HCl	Hydrochloric Acid
HPLC	High Performance Liquid Chromatography
IM	Intramuscular
INN	International NON-proprietary Name
IV	Intravenous
LCQ	Quality Control Laboratory
MAA	Marketing Autorisation Application
PVC	Polyvinyl Chloride
QA	Quality Insurance
RM	Raw Material
SC	Subcutanous
SNIC	National Society of Chemical Industries
UV	Ultraviolet
VA	Acceptance Value
WHO	World Health Organization

Glossary

- **Schizophrenia** is a common, severe mental illness that most clinicians will encounter regularly during their practice **(McCutcheon et al., 2020).**
- **Bipolar disorder** is a recurrent chronic disorder characterized by fluctuations in mood state and energy **(Grande et al., 2016).**
- **Levomepromazine; chlorpromazine; thioridazine; propericiazine haloperidol; pipotiazine; flufenazine; prochlorperazine:** are antipsychotics used in the treatment of psychiatric disorders, such as bipolar disorders and sleep disorders...ect **(Morimoto et al., 2022).**

Abstract

Objective: Initially, this study aims to expose the manufacture and physico-chemical and microbiological control of a generic drug called SULPUREN® 50 mg, a neuroleptic produced by the pharmaceutical group SAIDAL in Algeria, within the production site of El Harrache. This research focuses on understanding the different stages of production of this drug, resulting in a pharmaceutical product that complies with international standards, as well as the resulting physical-chemical and microbiological quality control.

Material and methods:

The physico-chemical inspection of grains of SULPUREN® 50mg product, semi-finished and finished products according to the 2017 European Pharmacopoeia by the application of pharmacotechnical tests including control of appearance, average mass and net average mass, and mass uniformity tests; plus analytical tests including dosage of the active pharmaceutical ingredient, dissolution test, and identification of active pharmaceutical ingredient in the finished product.

Microbiological control of the finished product focused on the detection and enumeration of total viable aerobic germs, total yeasts and molds, and the detection of specified micro-organisms such as *Escherichia coli* according to the 2017 European Pharmacopoeia.

Results and discussion: The results of the grains, semi-finished, and finished products obtained show that: the visual test is compliant, the average net mass is within the range of [108 mg and 132 mg], the active ingredient dosage has an absorption range of the sample that corresponds to that of the control solution (maximum at 291 nm and minimum at 266 nm), the dissolution results Q >= 80% in 60 minutes, and the percentage of related substances is less than 0.3%; the results of the microbiological analysis of the finished product indicate that the total viable count of germs, yeasts, and molds is below the limits set by the European Pharmacopoeia 2017, and that there is an absence of *Escherichia coli*. All the conclusions of this study strictly comply with an international standard as described in the European Pharmacopoeia 2017.As a result, the drug SULPUREN® 50 mg is certified of good pharmaceutical quality and therefore marketable.

Key words: SULPUREN® 50mg, neuroleptic, physico-chemical control, microbiological control.

Résumé

Objectif : Dans un premier temps, cette étude vise à exposer la fabrication et le contrôle physico-chimique et microbiologique d'un médicament générique appelé SULPUREN® 50 mg, un neuroleptique produit par le groupe pharmaceutique SAIDAL en Algérie, au sein du site de production d'El Harrache. Cette recherche se concentre sur la compréhension des différentes étapes de production de ce médicament, qui aboutissent à l'obtention d'un produit pharmaceutique conforme aux normes internationales, ainsi que sur le contrôle de la qualité physico-chimique et microbiologique qui en découle.

Materiel et méthodes

Le contrôle physico-chimique des grains de produit SULPUREN® 50mg, et des produits semi-finis et finis selon la Pharmacopée européenne 2017 par l'application des tests pharmacotechniques incluant le contrôle de l'aspect, de la masse moyenne et la masse moyenne nette, et des tests d'uniformité de masse; plus des tests analytiques incluant le dosage de principe actif, le test de dissolution, et l'identification de principe actif dans le produit fini.

Le contrôle microbiologique du produit fini a été axé sur la détection et le recensement des germes aérobie viables totaux, des levures et moisissures totales et la recherche des micro-organismes spécifiés comme *Escherichia coli* selon la Pharmacopée européenne 2017.

Résultats et discussion : Les résultats des grains, produits semi fini et fini obtenus montrent que : le test visuel est conforme, la masse moyenne nette se trouve dans l'intervalle [108 mg et 132 mg], le dosage de principe actif dont le domaine d'absorption de l'échantillon correspond à selui de la solution témoin (max à 291 nm et min à 266 nm), les résultats de dissolution Q>= 80% dans 60 min, et le pourcentage des substance apparentées est inférieure à 0,3% ; les résultats d'analyse microbiologique de produit fini indiquent que le nombre des germes viables totaux, des levures et des moisissures est inférieur aux limites fixées par la Pharmacopée européenne 2017, et l'absence d'*Eschirichia coli*. Toutes les conclusions de cette étude respectent rigoureusement une norme internationale telle que décrite dans la pharmacopée européenne 2017. De ce fait, le médicament SULPUREN® 50 mg est certifié de bonne qualité pharmaceutique et par conséquent, commercialisable.

Mots clés : SULPUREN® 50mg, neuroleptique, physico-chimique, contrôle microbiologique.

ملخص

الهدف: تهدف هذه الدراسة في البداية إلى شرح مراحل التصنيع والمراقبة الفيزيائية والكيميائية والميكروبيولوجية لدواء جنيس يسمى سولبيرين 50 ملغ، وهو دواء مضاد للذهان تنتجه مجموعة صيدال الصيدلانية في الجزائر، في موقع إنتاج الحراش، ويركز هذا البحث على فهم المراحل المختلفة في إنتاج هذا الدواء، والتي ينتج عنها منتج صيدلاني يتوافق مع المعايير الدولية، وكذلك مراقبة الجودة الفيزيائية والكيميائية والميكروبيولوجية التي تتبع ذلك.

المواد والأساليب:

الرقابة الفيزيائية الكيميائية الفيزيائية لمسحوق سولبيرين® 50مغ, و للمنتج الوسيط و النهائي ، وفقًا لدستور الأدوية الأوروبي لعام 2017 من خلال تطبيق الاختبارات الدوائية بما في ذلك مراقبة المظهر، ومتوسط الكتلة ومتوسط الكتلة الصافية، واختبارات توحيد الكتلة؛ بالإضافة إلى الاختبارات التحليلية بما في ذلك جرعة المادة الصيدلانية الفعالة، واختبار الذوبان، وتحديد المادة الصيدلانية الفعالة في المنتج النهائي.

تركز الرقابة الميكروبيولوجية للمنتج النهائي على اكتشاف وتحديد إجمالي الجراثيم الهوائية القابلة للحياة وإجمالي الخمائر والفطريات والكشف عن كائنات دقيقة محددة ، وفقًا لدستور الأدوية الأوروبي لعام 2017.

النتائج و المناقشة: تظهر نتائج المسحوق والمنتجات شبه النهائية والنهائية ما يلي: الاختبار البصري مطابق، والكتلة المتوسطة الصافية تتراوح بين [108 ملغ و132 ملغ]، ومجال امتصاص جرعة المادة الفعالة للعينة يتوافق مع مجال مجال امتصاص محلول الشاهد (الحد الأقصى عند 291 نم والحد الأدنى عند 266 نم)، ونتائج الذوبان Q>= 80% خلال 60 دقيقة، ونسبة المواد الدخيلة أقل من 0.3% ; تشير نتائج التحليل الميكروبيولوجي للمنتج النهائي إلى أن عدد الجراثيم القابلة للحياة الكلي، الخمائر والعفن أقل من الحدود المحددة من قبل الصيدلة الأوروبية 2017، وغياب الإشريكية القولونية . تتوافق جميع استنتاجات هذه الدراسة بشكل صارم مع المعايير الدولية كما هو موضح في دستور الأدوية الأوروبي 2017. ونتيجة لذلك، فإن عقار سولبيران 50 ملغ معتمد على أنه ذو جودة صيدلانية جيدة وبالتالي قابل للتسويق.

الكلمات المفتاحية: سولبيران 50 مغ , مضاد الذهان,مراقبة فيزيوكيميائي, مراقبة ميكروبيولوجي.

Content

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INTRODUCTION

INTRODUCTION

All over the world, the pharmaceutical industry plays an important role in healthcare systems. It comprises a wide range of public and private companies and services that develop, refine, perfect, manufacture and market medicines for the benefit of human and animal health. The pharmaceutical industry is mainly focused on the research and development of drugs to treat or prevent various diseases .on the research and development of drugs to treat or prevent various diseases **(Tait, 2002).**

To achieve this goal, the pharmaceutical industry needs an effective quality insurance (QA) system to guarantee the efficacy and safety of the products it brings to market. The American Association of Pharmaceutical Manufacturers has given the definition of the quality of a medicinal product or similar product as: « the combination of all the elements that contribute directly or indirectly to the safety, effectiveness and acceptability of the product » **(Diop *et al.*, 2009).**

According to WHO (World Health Organization) estimates, around 25% of medicines used in developing countries are falsified or of poor quality. In extreme situations, it will be possible to observe an exacerbation of the diseases treated. It is therefore essential to guarantee the quality of these medicines. Quality standards (pharmacopeia) and Good Manufacturing Practices (GMP) provide detailed descriptions of the medicinal product's characteristics as well as analytical methods to be used to verify it **(Diop *et al.*, 2009).** Compliance with the procedures mentioned in the marketing authorization application (MAA) before marketing the finished product guarantees this quality.

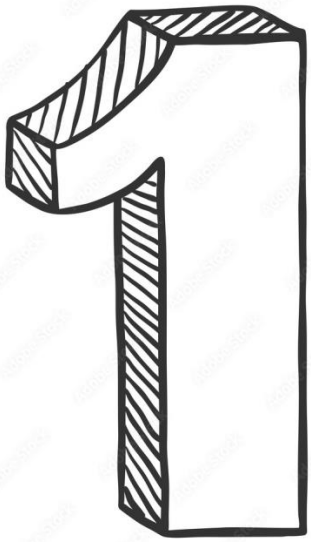
The main objective of the present study is to follow the physico-chemical and microbiological quality control stages of a neuroleptic drug sulpiride, trade name SULPUREN®, marketed in capsule form by the SAIDAL group, the leading pharmaceutical laboratory producing generic drugs in Algeria. This quality control was performed for the semi-finished and finished products of the studied drug throughout its manufacturing process in accordance with international pharmaceutical standards, in order to guarantee its therapeutic effectiveness and safety for patients.

This work is presented in three chapters:

In the first chapter, generalities and literature review on drugs, neuroleptic and sulpiride and drug quality control are developed.

The second describes the material used and the methods followed in the industrial quality control of sulpiride capsules.

The third chapter presents the different results obtained during the quality control process. Finally, a general conclusion closes the present study.



Chapter 1 Literature review

1. General information about drugs

Medicines or drugs play a vital role in the health system: they can be used to treat patients and prevent certain diseases. They can also be administered for diagnostic purposes, when they are only part of the examination, such as the administration of iodized contrast agents for radiological examination **(Prouchandy, 2018)**.

1.1 Definition of a drug

The French Public Health Code defines medicinal products as follows (article L5111-1[1]: "medicinal product" means any substance or composition presented as having

Curative or preventive properties with regard to human or animal diseases, as well as any

Animal diseases, as well as any substance or composition that may be used in humans or animals

Animals, with a view to making a medical diagnosis or to restoring, correcting or modifying their

Restore, correct or modify their physiological functions by exerting a pharmacological

Pharmacological, immunological or metabolic action". **(Mariko *et* al.)**

1.2 Composition of a drug

Generally, a medicine consists of two elements: the Active Pharmaceutical Ingredient (API) and excipients.

1.2.1 Active Pharmaceutical Ingredient

It is designed to treat or prevent a specific disease. It is dosed according to the strength of its action, its evolution in the body, and the patient´s profile **(Vandamme *et al.*, 2010)**.

1.2.2 Excipient

A substance that has no pharmacological effect, which, in combination with the API, will improve its form and its mode of administration. However, it can have adverse consequences **(Chippaux, 2004)**.

1.2.2.1 Classes of Excipient

- **Diluents:** constitute the majority of the solid forms, used in case the drug is insufficient to produce the necessary mass.

- **Lubricants:** minimize inter-particular friction, stop tablet material from sticking to die and punch surfaces, make it easier to remove tablets from die cavities, and increase the rate at which tablets granulate.
- **Binders and Adhesives:** enhances the properties of free flow by forming granules to the appropriate size and hardness.
- **Disintegrants:** encourage fragmentation or dissolution following ingestion.
- **Flavors:** cover up bad flavors **(Chaudhari, 2012).**

1.3 Types of medicines

There are two types of drugs, princeps (reference molecule) and generics.

1.3.1 Princeps or reference medicine

It is an original drug that has been protected by a patent in opposition to the generic drug **(Nouguez, 2006)**.

1.3.2 Generic

The generic version of a drug is the exact copy of an original drug whose exclusive patent for marketing by a pharmaceutical laboratory (20 years) has expired and is available to the public. The qualitative and quantitative composition of the generic drug of a reference speciality is identical, as is the pharmaceutical form **(Biraben *et al.*, 2007).**

1.4 Name of a drug

In pharmacy, three types of names are used to designate the active ingredients and specialties (which contain one or more active substances): the scientific name, the common name, and the brand name or fancy name **(Vandamme *et al.*, 2010)**.

1.4.1 Chemical name

As a rule, this name is long, difficult to remember and almost inaccessible to non-chemists. In addition, it does not provide any information regarding the action but it indicates the chemical composition (**Table 01**). It has been demonstrated that different scientific names can be independently assigned to the same substance in different countries **(Vandamme et al., 2010)**.

1.4.2 Common name

- **International NON-proprietary Name (INN)**

The INN is used to identify the active substance in medicines. It is a scientific term used to refer to a molecule (**Table 01**). It is important not to confuse INN with other names. No anatomical, physiological, pathological or therapeutic components are present in these structures **(Vandamme *et al.*, 2010)**.

1.4.3 Brand (trade) name

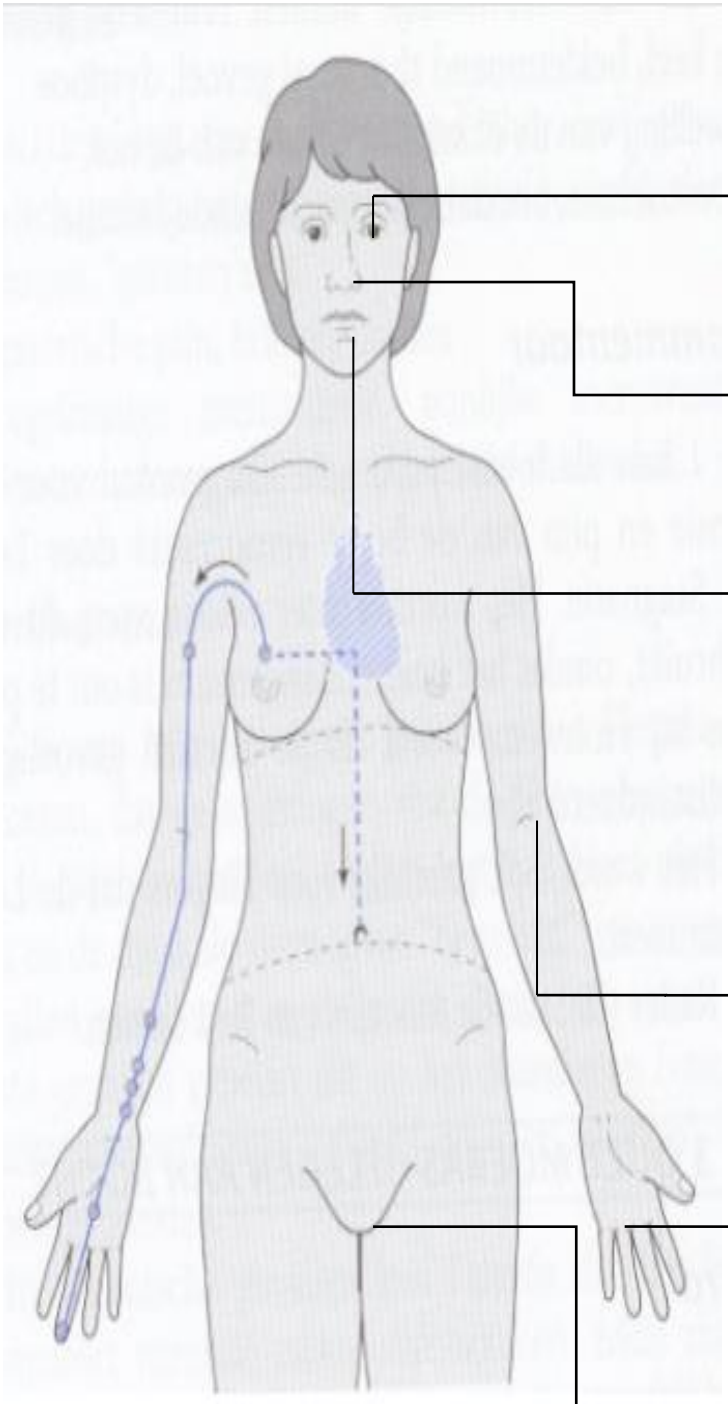
This is the lab brand (**Table 01**). These names have been filed and are protected from imitation. This fancy name is selected in order to avoid confusion with other drugs and not to mislead about the quality or characteristics of the specialty **(Vandamme et al., 2010)**.

Table 1: Sulpiride names**.**

Chemical name	INN	Trade names
N- (1- Ethylpyrrolidin- 2- ylmethyl)- 2- methoxy- 5- sulphamoylbenzamide **(Rama Rao and al., 1981)**	Sulpiride **(Rama Rao and al., 1981)**	SULPUREN®50mg **(Soufiane)**

1.5 Administration routes and dosage forms of a drug

When administering a drug, the desired effect may be local or systemic; depending on this criterion, different modes of administration will be used of various dug dosage forms (**Figure 1**).



Ophthalmic route:

- Eye drops 
- Ointments 

Respiratory (by inhalation):

- Inhalers 

Orale route :

- Solid : Tablet, capsule 
- Liquid : syrup, emulsion 

Parenteral route: IV IM SC

- Suspension, infusion 

Transcutaneous route (through the skin):

- Ointments 

Rectal rout:

Suppository, enemas, local cream

IM: Intramuscular.

IV: Intravenous.

SC: Subcutaneous.

Figure 1 : Some dosage forms of some drug administrative routes **(Prouchandy, 2018).**

2. Neuroleptics

2.4 Definition of neuroleptics

Antipsychotic (AP) or neuroleptic drugs are a class of psychotropic drugs. The drug management of psychotic disorders, such as schizophrenia and bipolar disorder, is their area of intervention **(Schmidlin, 2010)**.

Neuroleptics are mainly substances that act on the dopaminergic system. The role of the latter is to regulate emotional life and to control motivation, to modulate perception and to organize adaptive behaviors **(Franck *et* Thibaut, 2005)**.

2.5 Classification of neuroleptics

Neuroleptics, unlike homogenous molecules, are classified based on clinical effects and chemical structure. The second criterion is more significant as clinical effects are determined by the drugs chemical structure and action profile on different receptors, even though chemical structure cannot accurately predict therapeutic effects **(Franck *et* Thibaut, 2005)**.

2.5.1 Classification by clinical effect

- **Sedatives** (such as levomepromazine or chlorpromazine),which have significant vegetative effects;
- **Means** (such as thioridazine and propericiazine), with medical and moderate unwanted consequences;
- **Versatile drugs** (haloperidol, pipotiazine, flufenazine) which have a double action. Sedative, a hallucination and delirium-reducing effect, or a disinhibitory effect "encouraging" in deficit syndromes;
- **Disinhibitors** such as **sulpiride**, prochlorperazine or Tementil®, which can have very significant neurological effects in addition to their therapeutic effects **(Franck *et* Thibaut, 2005)**.

2.5.2 Classification by chemical structure

The chemical composition of molecules distinguishes different neuroleptic categories, each having a complex structure involving multiple cycles with different natures chains **(Franck *et* Thibaut, 2005).**

2.5.2.1 First generation neuroleptics

Four main categories of first-generation neuroleptics are identified:

- **Phenothiazins** were manufactured by modifying the lateral chain to obtain different tricyclic structures;
- **Butyrophenones,** (the main representative of which is the introduction of haloperidol in 1958 is remarkable. By its ability to counter hallucinations);
- Other **tricyclic substance** such as thioxanthene is caused by changes in the nucleus of Phenothiazins;
- And finally, the **benzamides** (leading: the sulpiride introducedin 1965, sometimes considered the first atypical, although thioridazine also has an atypic pharmacological profile) **(Franck *et* Thibaut, 2005)**.

2.5.2.2 Second generation neuroleptics

Second- generation neuroleptics are among the following main categories:

- That of **dibenzodiazepines** and derivatives that have a tricyclic structure similar to that of Phenothiazins substances (clozapine,olanzapine and quetiapine);
- The bicyclic structure of **benzisoxazoles** (risperridone);
- The presence of **imidazolidinones** (sertindole) **(Franck *et* Thibaut, 2005)**.

2.6 Sulpiride

2.6.1 Chemical structure

Sulpiride belongs to the class of benzamides obtained by formal condensation between the carboxy group of 2-methoxy-5-sulfamoylbenzoic acid and the primary amino group of (1-ethylpyrrolidin-2-yl) methylamine. It acts as an antidepressant, antiemetic, antipsychotic and dopaminergic antagonist. It is an N-alkylpyrrolidine, a sulfonamide and a member of the benzamide family. Its structure is shown in the **figure 2 (National Center for Biotechnology Information, 2024).**

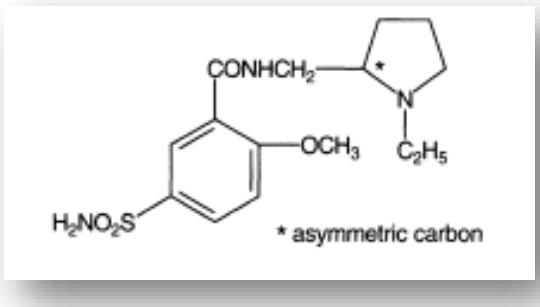


Figure 2 : Chemical structure of sulpiride **(Wagstaff *et al.*, 1994).**

2.6.2 Mode of action of sulpiride

The dopamine receptor has five subtypes, D1 through D5, and dopamine is the main agonist of these subtypes. Dopamine signaling controls mouvement and is crucial for reward-driven learning. Disorders and diseases such as schizophrenia, Parkinson's disease, Alzheimer's disease, and others are linked to abnormal dopaminergic activity **(Asad *et al.*, 2020).**

As for sulpiride, it is a substitute benzamide that has a selective dopaminergic blocking activity **(Caley *et* Weber, 1995).** Early pharmacological studies suggested that high-dose sulpiride primarily acts on post-synaptic dopamine receptors (D2) **(M'bitsi-Ibouily *et al.*, 2021).** However, sulpiride also blocks the D3 and D4 receptors **(Caley *et* Weber, 1995).**

D1 receptors and, Adrenergic, cholinergic, gamma-aminobutyric, histaminergic or serotoninergic receptors are not significantly blocked by sulpiride. And it has a low affinity for the D5 receptors **(Caley *et* Weber, 1995).**

The high activity of adenylate cyclase appears to be linked only to the stimulation of the D1 family receptors. Sulpiride does not inhibit increases in dopamine-stimulated adenylate cyclase activity, although it increases dopamine concentration in the brain **(Caley *et* Weber, 1995).** And it is the pharmacodynamic characteristic that distinguishes sulpiride as atypical AP **(Wagstaff *et al.*, 1994).**

As we gradually face up to the new challenges of the 21st century, the need for effective and sustainable antipsychotic delivery systems remains imminent **(M'bitsi-Ibouily *et al.*, 2021).**

Clinically, Sulpiride is a safe and effective pharmacotherapeutic drug for the treatment of acute schizophrenia **(Caley *et* Weber, 1995).**

2.6.3 Pharmacokinetic of sulpiride

Pharmacokinetics is the analysis of how a drug develops in the body. It is subdivided into four stages: absorption, distribution, metabolism and elimination **(Prouchandy, 2018).**

- **Absorption:**

This involves the movement of the drug from the external environment into the body and Physiological barriers by the active substance **(Prouchandy, 2018).**

Sulpiride is a chemical that is relatively hydrophilic. Following oral treatment, its gastrointestinal absorption is sluggish and poor **(Mauri *et al*., 1996).**

The oral bioavailability of sulpiride is low, with estimates of around 35% **(Caley *et* Weber, 1995).**

- **Distribution:**

The distribution of the drug in the different compartments of the body (plasma, organs and tissues) and its transport to its site of action **(Prouchandy, 2018).**

However, few benzamides are associated with this phenomenon (for example, sulpiride 40%) **(Naud, 2004).**

The mean peak plasma sulpiride concentration (Cmax) following an oral dosage ranges from 0.2 to 1.1 mg/L; the related mean time to Cmax (tmax) ranges from 1 to 6 hours. These differing outcomes are most likely a result of the various oral formulations that were used **(Mauri *et al*., 1996).**

It appears that sulpiride does not bind to plasma proteins and is distributed homogeneously between plasma and red blood cells **(Caley *et* Weber, 1995).**

In addition, Due to its limited lipid solubility **(Mauri *et al*., 1996).** Sulpiride does not pass easily through cerebrospinal fluid, necessitating a sufficient dosage to demonstrate its therapeutic effects on the central nervous system (CNS) **(Mauri *et al*., 1996).**

- **Metabolism:**

Sulpiride does not appear to have a significant first-pass metabolism, nor is it tightly bound to proteins, and no active metabolite has been identified **(Caley *et* Weber, 1995).**

- **Elimination:**

This stage is carried out by the haematopoietic organs: the liver, kidneys, skin, lungs and intestines. The untransformed active ingredient may be eliminated directly by the kidneys or bile or indirectly by elimination of a previously metabolised product **(Prouchandy, 2018).**

Benzamides are only metabolised to a limited extent. Degradation periods are around 7 hours. Very short, in the case of sulpiride (benzamides) **(Naud, 2004).**

Sulpiride is eliminated mainly via the renal system **(Caley *et* Weber, 1995)**, in unchanged form **(Mauri *et al*., 1996),** at a concentration of 90% (for benzamides in general) **(Naud, 2004).**

2.6.4 Indications

Sulpiride as a dishibiting antipsychotic, it is recommended for the treatment of both acute and chronic schizophrenia, with substantial effective and autistic symptoms **(Wagstaff *et al*., 1994).**

At lower dosages, it results in a higher recovery rate from negative symptoms than from positive ones, but at higher dosages, it is equally effective on both types of symptoms **(Mauri *et al*., 1996).**

Other indications:

Sulpiride is mainly used in the treatment of dysthymia, depressive disorders and vertigo **(Laux, 2022).**

2.6.5 Contraindication

- The use of sulpiride is completely prohibited in patients with phaeochromocytoma due to the risk of hypertensive crisis **(Mauri *et al.*, 1996).**
- It is also contraindicated for people with a prolactine tumor **(Faure *et* BELON, 2022).**

2.6.6 Adverse effects

The frequency of adverse effects of sulpiride seems to be globally lower than typical antipsychotics:

- Extra pyramidal reactions seem to be modest.
- Autonomic effects
- Impotence in men, and it reduced women's gonadal function.
- Neuroleptic malignant syndrome **(Mauri *et al.*, 1996).**

3 Pharmaceutical quality control

3.1 Pharmaceutical quality concepts

3.1.1 Quality

The concept of quality is much more complex than it seems. Such us for the company or organization: Quality implies the application of a policy aimed at constantly mobilizing all its personnel to improve:

- The quality of its products and services,
- The efficiency of its operations,
- The relevance and consistency of its objectives **(Deeb, 2008).**

3.1.2 Quality Insurance

According to ISO (International Organization Standardization) 9000:2005, Quality insurance (QA) is the "Quality management section aimed at ensuring the satisfaction of quality requirements" **(Buisine, 2016)**.

3.1.3 Good Manufacturing Practices

Quality insurance is based on GMP; they ensure the rigorous manufacture and control of the products, complying with the quality standards suitable for their use and required by the marketing authorization.GMP are used in both production and quality control **(Nehari, 2021)**.

3.1.4 Good Laboratory Practice

The principles of good laboratory practice are often defined as an organizational system that encompasses all organizational and operational aspects related to the implementation of non-clinical chemical safety assessments. The objective is to ensure the quality, reproducibility, and integrity of the data produced for regulatory purposes so that it can be internationally recognized without the need to reproduce the studies **(Feinberg, 2009).**

3.1.5 Pharmacopoeia

Pharmacopeias are books that describe, and explain the methods of preparing and controlling medicines, dating back to 1560 **(Jaussaud, 2012).**

3.1.6 Marketing Authorization

MAA ensures that the medicinal product has an appropriate quality, safety, and efficacy profile and that it can be supplied under specific conditions of use. There is no economic consideration in the MAA procedure **(Feroyard, 2014).**

3.2 Quality control

3.2.1 Definition

Quality control is a component of GMP, which is to verify whether a product meets its definition or specifications. It covers sampling, specifications, and control, as well as organizational, documentation, and dissemination procedures. These ensure that control has been achieved, and that raw materials, packaging, and products may not be put into circulation for use, sale, or supply unless their quality has been deemed to be satisfactory**. (Nehari, 2021).**

3.2.2 Physico-chemical control

Physico-chemical tests are carried out on samples from the bath to be controlled to verify the pharmaceutical quality of medicines available on the market. The objective of physical and chemical controls is to define the characteristics of the various forms of therapeutic molecules and to identify and measure the medication. The APIs are used to detect the presence of their potential. The impurities must be also assessed and determined. Pharmacological characteristics related to the pharmaceutical method are shown by the disaggregation. Indeed, in addition to the identification and dosage of active substances and impurities **(Penoukou *et al.)*.**

3.2.3 Microbiological control

The experiments described to monitor the presence of mesophilic bacteria, molds, and aerobic yeasts allow for the identification of mesophilic bacteria, molds, and yeasts that can develop into aerobics.

The main objective of these tests is to verify whether a product meets the microbiological requirements set out in its monograph as well as in the pharmacopoeia. However, in the context of the European pharmacopoeia, these methods can also be used to verify the effectiveness of antimicrobial preservation and to monitor the quality of pharmaceutical materials or preparations **(Roche, 2006).**

CHAPTER

Material and methods

1. Intership duration and location

Our study was carried out at the SAIDAL Company in El Harrach (Zemirli), between February and April2024.

The aim of our work is to deepen the study of the different stages of quality control of a solid form based on a neuroleptic drug: sulpiride capsules (SULPUREN®, 50 mg), in compliance with the regulatory requirements (GMP, etc…).

1.1 Presentation and organization of SAIDAL company

SAIDAL is the first pharmaceutical laboratory producing generic medicines in Algeria.

Founded in 1982 to respond to the need to establish a local pharmaceutical industry capable of guaranteeing the availability of medicines and improving citizens ´access to treatments, SAIDAL is now organized into an industrial group specializing in the development, production, and marketing of medicinal products for human use.

1.2 History

1969: Establishment of the Algerian central pharmacy (ACP) by presidential decree with the mission of ensuring the monopoly of the state on the import, manufacture, and marketing of pharmaceutical products for human use.

1971-1975: The realization of the production unit of EL Harrach and the purchase unit in two stages (1971 and 1975) of the biotics and pharma units by ACP.

1982: SAIDAL was created following the restructuring of the Algerian central pharmacy (PCA) and benefited, in this context, from the transfer of the factories of EL Harrach, Dar El Beida, and Gue De Constantine.

1988: Official integration of the antibiotic complex of Medea, which then belonged to the SNIC (National Society of Chemical Industries).

1989: SAIDAL became EPEs (public economic enterprises) with management autonomy following the implementation of economic reforms.

1997: Restructuring of SAIDAL.

1998: Transformation into an industrial group with three branches (pharmaceutical, biotic, and antibiotical).

2014: SAIDAL adopts a new organization by merging, absorption, the antibiotical, pharmaceutical, and biotic branches owned by 100%. **Source: SAIDAL Group official website https://saidalgroup.dz/.**

1.3 EL HARRACH plant (internship location)

The new EL HARRACH (ZEMIRLI) **(Figure 3)** plant is show in the following **(diagram 1)** is the first to be completed under the 2010/2014 development plan. Covering an area of over 39,000m^2, the plant specializes in the production of dry forms (tablets and capsules).Il inaugurated on October 28, 2019. **Source: SAIDAL Group official website https://saidalgroup.dz/.**

Figure 3 : Group SAIDAL-Unit of El Harrcah (Zemirli)**.**

In this industry, there is a department for the production of medications and a laboratory to carry out the necessary analyses to ensure their effectiveness and safety **(diagram 1)**.

Diagram of the SAIDAL El Harrach unit

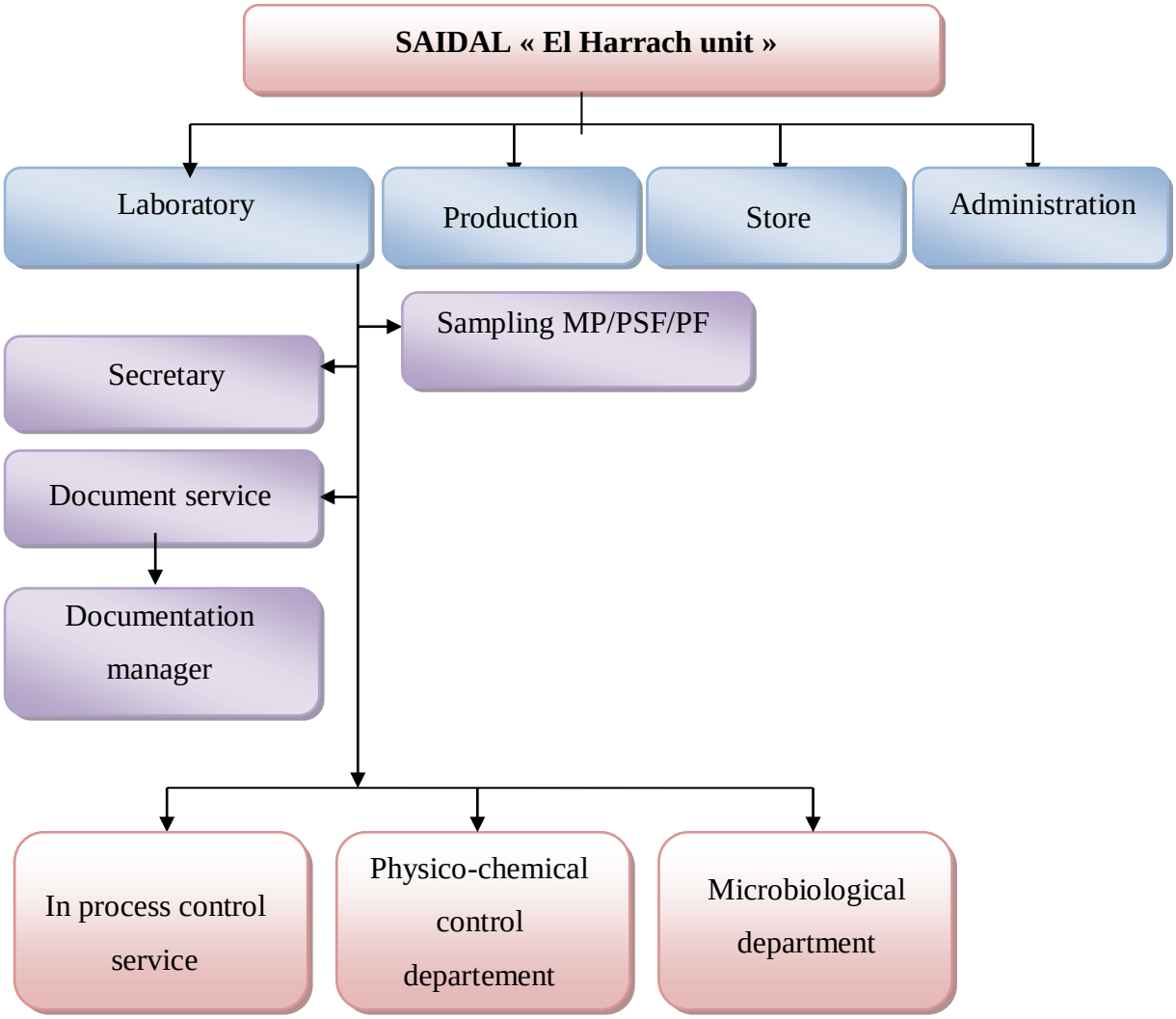


Diagram 1: Organization diagram of the SAIDAL enterprise « El Harrach unit ».

2. Material and methods

2.1 Material

2.1.1 Product presentation

SULPUREN® 50mg (trade name) **(Figure 4)** presented as capsules administered orally. This medicine belongs to the group of neuroleptics (It is prescribed in case of psychosis). It belongs to the benzamide family (sulpiride thread head introduced in 1965, sometimes considered the first atypical). The dose is 50mg. This medication is indicated in the treatment of certain forms of anxiety in adults and in the therapy of certain serious behavioral disorders of adults and children over 6 years of age. The **table (2)** below shows the pharmacokinetic properties of SULPUREN® 50 mg.

Figure 4 : Capsule Box SULPUREN® 50 mg**.**

Table 2 : Properties of SULPUREN® 50mg.

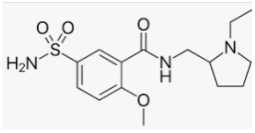
Pharmacokinetic data	
Bioavailability	35% (orally) **(Caley *et* Weber, 1995).**
Protein binding	40% **(Naud, 2004).**
Metabolism	Sulpiride is poorly metabolized in humans **(Caley *et* Weber, 1995).**
Elimination half-life	Oral : 7 hours **(Naud, 2004).**
Excretion	Is essentially renal **(Caley *et* Weber, 1995).**

2.1.2 Raw materials

2.1.2.1 Active ingredient

API characteristics are present in the following **table (3).**

Table 3: Physicochemical properties of SULPUREN® 50mg **(Saidal, European pharmacopoeia 11th edition, 2023).**

INN	**Chemical structure**	**Molar mass**	**UICPA name**	**Molecular formulation**
SULPUREN ® 50mg		341,4 g/mol	N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxy-5-sulfamoylbenzamide	$C_{15}H_{23}N_3O_4S$

2.1.2.2 Excipients

The role of the excipients present in the drug SULPUREN® 50mg are presented in the following **table (4)**

Table 4 : The excipients used in the formulation of SULPUREN® 50mg and their roles**.**

Name	Role
Lactose monohydrate	Diluent
Methylcellulose	Binding agent
Magnesium stearate	Lubricant
Talc	Lubricant

2.1.3 Equipment

2.1.3.1 Equipment used in production process

This process require the use of several pieces of equipment such as: mixer granulator, dry calibrator, capsule filler, and many other equipment **(Appendix)**

2.1.3.2 Equipment used in the control

Our study required the use of laboratory reactives (purified water, 96% ethanol, methanol, etc.), raw materials (sulfide and extracts), and some control equipment (balance, IR spectral photometer, UV-Vis spectrophotometer, HPLC chromatograph, test tubes, vials, etc.) (**Appendix).**

2.2 Methods

2.2.1 Production

2.2.1.1 Before weighing

A. Receipt of raw materials

Once suppliers have received raw materials (RM) (active ingredients, excipients) as well as capsules and packaging items (labels, leaflets, cartons, plastic, etc.) in accordance with SAIDAL's requirements, as set out in an annual program forwarded by General Management, these items will first be stored in specific areas known as analysis instances. The aim of this stage is to complete a project. Physico-chemical and microbiological analyses to verify compliance, in accordance with the appropriate procedures and requirements in force.

B. Scheduling

Once compliance has been verified, the laboratory creates and signs an analysis bulletin including batch number and supplier information, which serves as a guide throughout the manufacturing process.

2.2.1.2 Weighing

It is essential to follow a few precise steps before weighing. First of all, the weighing area and the scales (which have different capacities: 6 kg, 30 kg, 300 kg) must be thoroughly cleaned. A proof of ownership must then be prepared.

Weighing is carried out in a specific area that complies with current weighing standards, such as humidity, temperature, calibration and qualification. A professional carries out this process wearing all the necessary protective equipment, such as a gown, bib, cap and overshoes, to avoid contamination of the raw materials.

Once the quantities of raw materials have been accurately measured, a certificate is completed, indicating the following: weighing order, weighing room, equipment used quantity of product, batch number, name and signature of the person in charge, and weighing date.

2.2.1.3 After weighing

Once the raw materials have been weighed, the bags containing the RM are placed separately in empty drums. After being weighed, they were stored in the specific room for raw materials.

2.2.1.4 Manufacturing process

The manufacturing process of a drug may vary depending on its shape and composition, it **i**ncludes several stages such as formulation, mixing and grinding. Each step is subject to strict standards to guarantee the safety, effectiveness and quality of the drug.

- **Priciple**

It includes several key stages such as weighing, mixing of the excipients, encapsulation, packaging and labeling. Each step is carried out according to the standards of the European pharmacopoeia 2017, 9th edition to guarantee the effectiveness of the finished product.

A. Granulation

- **The binding solution:**

Pour purified water through a stainless steel decalitre into the INOXPA solution tank, and then add methyl cellulose and dissolve cold, then shake the solution.

Add a further volume of purified water and continue stirring until dissolved. Let stand until foam disappears.

- **Powder mixing:**

The raw materials are loaded into the P800 granulator mixer under agitation using the suction lance. Load in the following order:

1. Lactose monohydrate
2. Sulpiride
3. Methyl cellulose.

- **Dry powder mixing:**

The powders are placed in separate, suitable stainless steel containers or polyethylene bags. The powders are then dry-mixed in the Granulator mixer.

- **Fountain solution and granulation:**

Inject the fount solution continuously until exhausted, while keeping the powders the powders with the peristaltic pump.

Once wetting is complete, increase mixer speed to and homogenizes the preparation.

- **Wet calibration and grain drying:**

Start by preheating the Kiln Feed Room (LAF) to 60°C, and then lower the temperature 30°C.

Next, perform wet sizing and transfer the wet grain from the pelletizer mixer to the LAF CAP600 DIOSNA using the wet calibrator and pneumatic conveyor.

Finally, dry the grain until its moisture content reaches ≤ 1%.

- **Dry grading:**

Transfer the dry grain from the LAF to the BIN via the FERWITT dry grader and pneumatic conveyor.

B. External Mixing and Lubrication:

Start by mixing the grain, selecting the SULPUREN® 50mg recipe on the BIN mixer control panel.

For lubrication, add magnesium stearate and talc to the grain, then mix.

C. Capsule filling:

To ensure that the capsule filling process complies with pharmaceutical quality standards, a series of methodical steps must be scrupulously followed:

First of all, the work area must be meticulously prepared.

Cleanliness and adequate lighting to optimize operating conditions. The next step is to fit the specific accessories adapted to the capsule format Size 3 on the BOSCH GKF1400 capsule filler. Then activate the required format, such as "SULPUREN 50 "mg format.

While the reservoir is being filled with empty capsules, at the same time, prepare the tank by mixing the necessary powders and pouring them into the BIN container connected to the machine's hopper.

Careful monitoring of machine operation is crucial. It is also essential to set the agglomeration pressure to specification to ensure consistency of capsule mass.

- During the manufacturing process, regularly take samples of filled capsules for pharmaco-technical analysis. This may include physico-chemical tests. The results of these analyses must be recorded on a control card to guarantee traceability and regulatory compliance.

D. Packaging

❖ **Primary packaging:**

Primary packaging, which involves the direct packaging of the drug, can be achieved using blister packs with a transparent PVC (polyvinyl chloride) thermoforming film **(Figure 5)**. A printed aluminum lidding film is used to seal the lid onto the blister pack **(Figure 6)**.

Figure 5 : SULPUREN® 50mg packaging, transparent PVC thermoforming film.

Figure 6 : SULPUREN® 50mg packaging, printed aluminum lidding film.

❖ **Secondary packaging :**

Secondary packaging, also known as outer packaging, is responsible for presenting and protecting the primary packaging units; grouping together several individual of the pharmaceutical product.

2.2.2 Quality control methods

Quality control methods include physico-chemical and microbiological tests to assess purity and for the identification and dosing of APIs, as well as the detection of contaminants. GMP, guide these processes to ensure compliance with international standards of RM, semi-finished products and finished products.

Purpose: Ensure efficiency, safety and compliance with regulatory standards.

2.2.2.1 Physicochemical control

A. Physico-chemical control of raw material

Already done in 2023.

B. Physico-chemical control in process

The physico-chemical tests carried out on Sulpuren® 50mg drug grains are shown in the following **table (5)**.

Table 5 : Physico-chemical control of grains**.**

Tests	Standards
Aspect: The visual analysis of the aspect is based on the shape and color of the grain.	White grain with no foreign particles
Humidity: It is controlled by the desiccators.	≥ 1
Dosage: Operate by Ultraviolet (UV) absorption spectrophotometry	41,66% ± 5% (39,577% to 43,743%)

- **Dosage of API:**

Operate by Ultraviolet (UV) absorption spectrophotometry

Analysis techniques for molecular spectroscopy include UV/visible **(Figure 7)** absorption spectroscopy. It offers the possibility of carrying out structural analysis as well as many quantitative determinations **(Burgot, G. *et* Burgot, J. L., 2011).**

Principle of UV-Visible absorption spectrophotometer

The principle of this technique is that a specific wavelength beam of light, whether in the near or visible UV range, passes through the solution to be analyzed **(Figure 8)**. The measurement of the amount of absorbed light makes it possible to calculate the concentration of the absorbent substance present in the solution **(Degallaix, 1998).**

Figure 7 : UV-visible domain **(Ley, 2020).**

Increasingly concentrated, the sample absorbs more light, within the limits of Beer Lambert's proportionality **(Isabelle, 2014):**

$$A = log\left(\frac{I}{I_0}\right) = \varepsilon cl$$

Where:

$\boldsymbol{A}$: Absorbance Measurement.

$\boldsymbol{I_0}$: Incident intensity.

$\boldsymbol{I}$: Intensity of radiation that has passed through the sample.

$\boldsymbol{L}$: The width of the tank where the sample is inserted.

$\boldsymbol{C}$: Concentration of the absorbing species.

$\boldsymbol{\varepsilon}$: The extinction coefficient of the studied species and wavelength **(Calvet, 2005).**

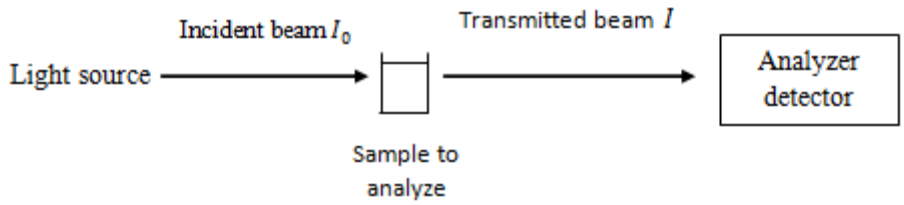


Figure 8 : Spectrophotometer operating procedure **(Ley, 2020).**

✓ **Operating mode :**

- **Preparation of control solution:**

Dissolve 125 mg of sulpiride working standard in a flask of 100 ml, and then add aqueous acetic acid 10% solution until the total volume is reached.

Then transfer 5 ml of this mixture to a 50 ml flask and make up to the required volume with the same solution.

- **Preparation of the test solution:**

Grind the grain, and then transfer a quantity corresponding to 125 mg of Sulpiride into a 100 ml volumetric flask. Adjust volume with 10% aqueous acetic acid, shake for 15 minutes and filter.

Take 5ml of the filter in a 50 ml flask and add to the volume with the same solvent.

Reading with UV-Visible absorption spectrophotometer at λ=291nm.

✓ **Calculation formula:**

$$\boldsymbol{Dosage}\ \% = \frac{\boldsymbol{OD_t}}{\boldsymbol{OD_w}} \times \frac{\boldsymbol{PeT}}{\boldsymbol{Pe}} \times \boldsymbol{purity}$$

Where:

$\boldsymbol{OD_t}$: Optical density of the solution to be examined.

$\boldsymbol{OD_w}$**:** Optical density of control solution.

$\boldsymbol{PeT}$: Test dose of Sulpiride in control solution (mg).

$\boldsymbol{Pe}$: Sample test taking (mg).

$\boldsymbol{Purity}$: Content of active ingredient working standard expressed in %.

C. Physico-chemical control of semi finished product

- **Tests carried out by production**

The physico-chemical tests carried out on SULPUREN® 50mg capsules at the production department are shown in the following **table (6)**.

Table 6 : Physic-chemical control of semi finished product carried out by production and standard of each test.

Tests	Standards
• **Aspect**	Hard gelatin capsules, size 3, have an opaque white color with the SULPUREN logo in black and the SAIDAL logo on the head in green. Filled with lightly granulated powder.
• **Average mass**	170mg ± 3,25 % 164,47 mg to 175,52 mg
• **Closure length test**	15,9 mm ± 0,3 mm 15,6 mm to 16,2 mm
• **Disaggregation time**	Disaggregation of all the capsules must be ≤ 30 minutes.

- **Aspect**

Perform this test at start-up and every 30 minutes thereafter.

- **Average masse**

Perform this test on 20 capsules, at start-up to set up the machine, then every 30 minutes.

- **Closure length test**

Perform this check on 10 capsules using a caliper, at start-up for machine adjustment, then every 1h.

- **Disaggregation time**

Place one capsule in each of the 6 grinding tubes. If the capsules float on the surface of the liquid, a disc can be added. Place the assembly in the cylindrical vase containing water purified at 37° C ± 2° C. Let the device operate for 30 min.

➢ **Tests carried out by quality control laboratory (LQC)**

The physico-chemical tests carried out on SULPUREN® 50mg capsules by quality control laboratory are shown in the following **table (7).**

Table 7 : The controls applied to the semi finished product carried out by LQC and the standard of each test**.**

Tests	Standards
❖ **Pharmacotechnical tests** • **Aspect**	Hard gelatin capsules, size 3, have an opaque white color with the SULPUREN logo in black and the SAIDAL logo on the head in green. Filled with lightly granulated powder.
• **Average mass**	170 mg ±7, 5% S1= 157, 25 mg ≤ Am ≤ S2= 182, 75 mg
• **Average net mass**	120 mg ± 10% S1= 108, 0 mg ≤ Am net ≤ S2= 132, 0 mg
• **Mass uniformity**	- Not more than 02 capsule outside the net average mass range ± 10%. - No capsule outside the net average mass range ± 20%
❖ **Analytical tests** • **Dosage of API**	50, 0 mg/capsule ± 5%

Operate by Ultraviolet (UV) absorption spectrophotometry	(47.5 to 52.5) mg/ capsule.
• **Dissolution** Operate by Ultraviolet (UV) absorption spectrophotometry	Dissolution rate ≥ 80% (Q) in 60 minutes.

❖ **Pharmacotechnical tests**

- **Average mass**

✓ **Operating mode :**

Weigh 20 filled capsules individually, calculate the average mass:

- **Average net mass**

Weigh 20 capsules individually in an accurate manner, ensuring that the identity of each capsule is preserved, empty every capsule from its contents by an appropriate manner, weigh the empty capsules individually accurately and calculate the net mass of each capsule's content by subtracting the mass of the blank capsule from the gross weight of the capsule.

- **Mass uniformity**

Weigh one full capsule without losing any fragments from the envelope, open the capsule, and empty it as completely as possible. Weigh the envelope and calculate the content mass by difference. Repeat the operation on 19 other capsules to determine the average net mass.

❖ **Analytical tests**

- **Dosage**

✓ **Procedure:**

Preparation of control solution

Dissolve 125 mg of sulpiride working standard in a 100-milliliter (mL) flask and fill up to volume with a 10% aqueous acetic acid solution; shake for 5 minutes. Transfer 5 mL of the above solution into a 50-mL flask, and fill up to volume with the same solvent.

Sample preparation:

After having the average net mass of 20 capsules, weigh and dissolve 300 mg of a powder mixture of 20 capsules (equivalent to 125 mg of sulpiride) in a flask of 100 mL with a 10% aqueous acetic acid solution. Fill up to the volume with the same solvent and shake for 15 min. Filter. Remove 5 mL of filtrate into a 50-mL flask and fill up to volume with the same solvent **(Figure 9)**.

Figure 9 : Sample preparation.

Reading:

Measure the optical density of each prepared solution using a spectrophotometer set to 291 nm, using a hydrochloric acid solution 10% as a reading blank. Calculate the percentage of sulpiride using the formula below:

$$\textbf{Dosage } {}^{\textbf{mg}}/_{\textbf{capsule}} = \frac{\textbf{OD}_\textbf{t}}{\textbf{OD}_\textbf{w}} \times \frac{\textbf{Pet}}{\textbf{Pe}} \times \textbf{NET Aw} \times \frac{\textbf{Purity}}{\textbf{100}}$$

Where:

NET Aw: Of 20 capsules (mg.)

Pet: Sulpiride in control solution taking (mg.)

Pe: Sample test taking.

$\mathbf{OD_t}$: Optical density of the solution to be examined.

$\mathbf{OD_w}$**:** Optical density of control solution.

Purity: Content of active ingredient working standard expressed in %.

- **Dissolution**

✓ **Procedure:**

Adjust equipment operating conditions (temperature, dissolution medium, stirring speed, medium volume, dissolution time and wavelength).

Preparation of the hydrochloric acid (HCL) 0.1N solution:

Dissolve 8.3 ml hydrochloric acid in purified water, then fill up to 1000 ml with the same solvent.

Preparation of the control stock solution:

Weigh and dissolve 55.6 mg sulpiride working standard in a 100 ml flask with HCL 0.1N

Preparation of the control solution:

Take 1ml of the control stock solution, then fill up to 10 ml with the same solvent.

Preparation of the test solution:

Introduce one capsule into each vase in dissolutest **(Figure 10)** filled with 900 mL of HCL 0.1N. After completion of the dissolution time, pass some of the test solution through a syringe filter 0.45 µm, discarding the first filtrate. Measure the absorbance of the test and control solutions at 292 nm, using the dissolution medium as a blank (HCL 0.1N). Calculate the dissolution percentage using the formula below:

$$\boldsymbol{Q}\ (\%) = \frac{\boldsymbol{OD_t}}{\boldsymbol{OD_w}} \times \frac{\boldsymbol{Pew \times 9}}{\boldsymbol{500}} \times \boldsymbol{Purity}$$

Where:

ODt: Optical density of the test solution.

ODw: Optical density of control solution.

Pew: Test sample of control solution.

Purity: Content of active ingredient working standard expressed in %.

Standards: dissolution rate ≥ 80% (Q) in 60 minutes.

Figure 10 : Dissolutest**.**

D. Physico-chemical control of finished product

Physico-chemical tests on finished products are listed in the **table (8)** below.

Table 8 : Controls applied to the finished product carried out by LCQ and the standards of each test**.**

Tests	Standards
❖ **Pharmacotechnical tests** • **Aspect**	Hard gelatin capsules, size 3, have an opaque white color with the SULPUREN logo in black and the SAIDAL logo on the head in green. Filled with lightly granulated powder.
• **Average mass**	170 mg ±7, 5% S1= 157, 25 mg ≤ Am ≤ S2= 182, 75 mg
• **Average net mass**	120 mg ± 10% S1= 108, 0 mg ≤ Am net ≤ S2= 132, 0 mg
• **Uniformity of unidosis preparations**	- **Level 1 :** VA ≤ 15% If VA is higher than the standard, perform the test on the next 20 units, and calculate the VA on 30 units

	- **<u>Level 2</u> :** VA ≤ 15% with 0, 75M ≤ each estimated content ≤ 1, 25M
❖ **Analytical tests** • **Dosage of API** Operate by Ultraviolet (UV) absorption spectrophotometry	50, 0 mg/capsule ± 5% (47.5 to 52.5) mg/ capsule.
• **Dissolution** Operate by Ultraviolet (UV) absorption spectrophotometry	Dissolution rate ≥ 80% (Q) in 60 minutes.
• **API identification (Sulpiride) by:** - Absorption spectrophotometry in UV	The dosing solution must have a maximum absorption at 291nm±2 and a minimum absorption at 266nm±3.
- Chemical reaction with copper sulfate	There must be a characteristic green precipitation.
• **Related substances** Operate by High Performance Liquid Chromatography (HPLC)	In the chromatogram obtained by solution (1) the sum of the surfaces of all the secondary peaks is not greater than the surface of the main peak in the chromatogram of the solution (2) (0, 3%)

❖ **Pharmacotechnical tests:**

• **Uniformity of unidosis preparations**

Mass variation :

Take 30 capsules.

Weigh 10 capsules individually, exactly ensuring that the identity of each capsule is preserved. Empty each of its contents by an appropriate means.

Weigh the empty capsules individually in an accurate manner and calculate the net mass of the contents of each capsule by subtracting the weight of the blank capsule from the gross mass of that capsule.

Calculate the active substance content of each capsule from the individual mass of the capsule content and the dosage result.

Calculate the acceptance value (VA) using the formula:

$$VA = |M - \bar{X}| + KS$$

$\bar{X}$**:** Average estimated individual content.

$$\bar{X} = \sum \frac{xi}{n}$$

$$\text{Xi} = \frac{A}{\bar{W}} \times Wi$$

Xi: Estimated individual content.

A: Content of the active substance, obtained by the method of dosing the active ingredient.

$\overline{W}$**:** Average individual mass WI.

K: Acceptability constant: **If** n = 10, k = 2, 4

If n = 30, k = 2

S: Sample default deviation.

$$S = \left[\frac{[\sum_i^n (Xi - \bar{X})^2]}{n-1}\right]^{1/2}$$

M: Reference value.

If: 98, 5**%** ≤ $\bar{X}$ ≤ 101, 5; M=$\bar{X}$**.** **And** VA = KS

If : $\bar{X}$ < 98, 5; M= 98, 5%. **And** VA= $|98,5 - \bar{X}| + KS$

If : $\bar{X}$ > 101, 5; M= 101, 5%. **And** VA = $|101,5 - \bar{X}| + KS$

- **API identification (sulpiride) by:**

- **Absorption spectrophotometry in UV**
- **Chemical reaction with copper sulfate:**

Treat in a mortar the powder content of 5 capsules with 10mL of methanol and then filter.

To the filter add 2mL of a 1% copper sulfate solution in the methanol.

- **Related substances:**

Operate by High Performance Liquid Chromatography (HPLC)

Chromatography in its various forms is commonly used as a separation technique and analytical technique **(Hamilton, 2012).**

- **Principle of HPLC**

This method of identification and measurement is based on the phenomenon of the retention of a chemical species caused by an eluant (moving phase) in a column. (stationary phase). A mixture is injected into the column, and the species are eliminated one after the other. At the exit of the column, a chromatogram with pictures associated with each substance can be obtained through a detector (a UV-visible spectrophotometer).

The surface below each picture is linked to the concentration of a specific chemical substance.

The retention time (time at which a species is selected and detected) is represented in abscise, which gives a qualitative characteristic to the substance **(Lejeune, 2020).**

✓ **Procedure:**

Solution (1) (solution to be examined):

Add 20 ml of methanol to a quantity of capsule powder equivalent to 0.2 g of Sulpiride, shake for 5 minutes, filter, evaporate the filtrate to dryness, and dissolve the residue in the mobile phase in 200 ml **(Figure 11).**

Figure 11 : Preparation of the test solution**.**

Solution (2):

Dilute 3 volumes of solution (1) to 100 volumes of mobile phase, and dilute 1 volume from this solution to 10 volumes of mobile phase.

Solution (3) (system conformity):

Solution with 0.01% (m/v) Sulpiride working standard and 0.01% (m/v) Sulpiride impurity B working standard in the mobile phase.

Mobile phase:

To 10 volumes of HPLC-grade acetonitrile, 10 volumes of HPLC-grade methanol and 80 volumes of a solution containing 6.8% (m/v) potassium dihydrogen orthophosphate and 0.1% (m/v) sodium octanesulfonate, adjust to pH 3.3 using orthophosphoric acid **(Figure 12).**

Degas the mobile phase in ultrasound.

Figure 12 : Mobile phase preparation**.**

The column:

- Made of stainless steel.
- **Dimensions:** l = 25 centimeters (Cm), Ø = 4.6 mm.
- **Stationary phase:** octylsilyl silica gel.
- **Temperature:** ambient.
- **Flow raet:** 1 to 1.5 mL/min.
- **Detection:** spctrophotometer at 240 nm.
- **Injection volume:** 20 µl (microliter).

$$\boldsymbol{imp}\ \% = \frac{\boldsymbol{SE}}{\boldsymbol{ST}} \times \frac{\boldsymbol{CT}}{\boldsymbol{CE}} \times \mathbf{100}$$

Where:

SE: Test peak area obtained by HPLC.

ST: Sample peak area obtained by HPLC.

CT: Control concentration.

Ce: Concentration of the solution to be tested.

Figure 13 : Ready-made solutions**.**

2.2.2.2 Microbiological control of finished product

The analysis shall carry out the microbial purity control of the finished product by applying the following techniques:

Count of total viable germs:

- Total viable aerobic germs.
- Total Mold/yeast.

Research of specified micro-organisms:

- *Escherichia coli.*

- **Count of total viable germs :**

- Turn on the benzen burner.
- Cleaning of the straw and blisters with alcohol.

  Sample preparation:

Take 60 capsules (equivalent to 10 grams) and dilute them in 90 ml of a pH 7.0 sodium chloride peptoned tompon solution containing 2% tween in a marie bath at 40° C for 30 minutes. Then homogenize to obtain a ‹‹ homogenization A ››.

Perform one dilution at 1/10, starting with the first dilution in the same tompon solution **(Figure 14).**

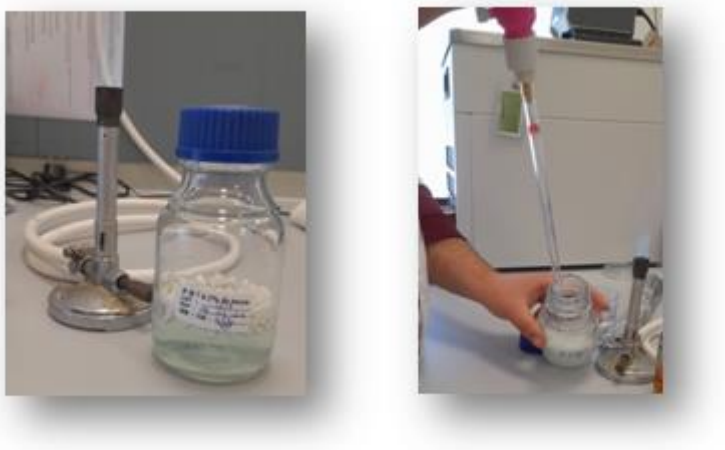


Figure 14 : Sample preparation**.**

Plate counting

Note: Incubate a negative test for each control at each temperature.

Deep seeding :

- Use Petri dishes with a diameter of 90 millimeters (mm).
- Prepare at least two petri dishes per dilution and per medium.
- Insert 1 ml of the prepared dilution of the test sample into each.
- Add 15 to 20 ml (at a temperature not exceeding 45°C) of a casein pepton agar medium and soya liquefied for bacteria and incubates at 30-35°C for 3-5 days.
- Add 15 to 20 ml (at a temperature not exceeding 45°C) of Sabauraud liquefied dextrose agar medium for yeasts and molds and incubate at 20-25°C for 5-7 days.

Reading and interpretation of results

Standards are listed in the **table (9)**.

- **Research of specified micro-organisms:**

- From "homogenization A," take 10 ml, corresponding to 1g of product, and sow 100 ml of liquid medium with casein and soy peptons.
- Homogenize and incubate at 30-35°C for 18–24 hours.
- Shake the container and then take 1 ml and sow 100 ml of Mac Conkey liquid medium and incubate at 42–45 °C for 24-48 hours.

- Make subcultures of Mac Conkey agar medium and incubate at 30-35°C for 18–72 hours.

Reading and interpretation of results

The growth of non-mucoid red colonies of bacteria in gram-negative sticks indicates the presence of *E. coli*, which is confirmed by appropriate biochemical tests.

The product satisfies the test if no colonies of the type described are observed or if the biochemical tests are negative **(table 9)**.

Table 9 : Criteria for acceptance of microbiological quality of capsules**.**

Tests	Standards
- Total viable aerobic germs. - Total Mold/yeast. - *E. coli* research.	**≤ 1000 UFC/g** **≤ 100 UFC/g** **Absence**

In summary, the medication SULPUREN 50mg underwent various controls at three levels: on the grain mixture, on the capsules, and on the finished product **(diagram 2)**. The main types of control include, first of all, physicochemical analyses such as appearance and average weight control, or analytical methods like dissolution testing and active ingredient dosage.

The second type is the microbiological control of finished products to detect the number of total viable germs, molds, yeasts, and the presence of pathogenic microorganisms.

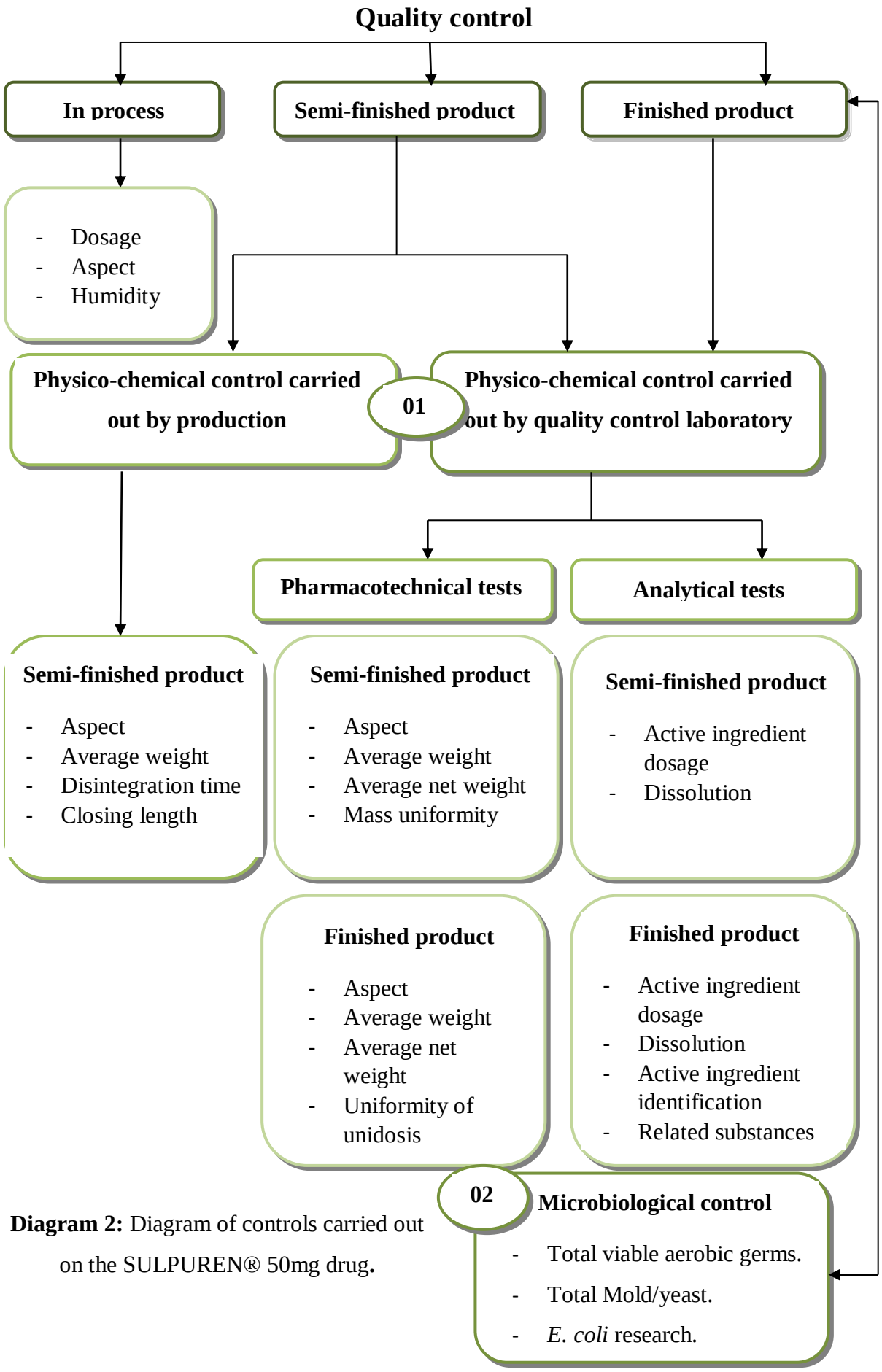
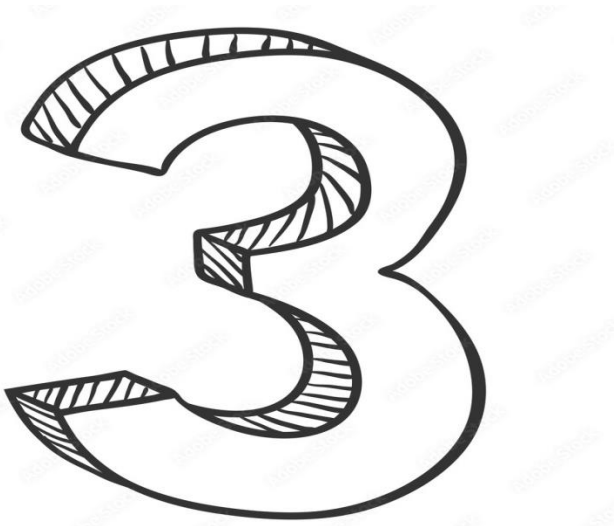


Diagram 2: Diagram of controls carried out on the SULPUREN® 50mg drug.

CHAPTER



Results and discussion

1. Results

1.1 Result of physico-chemical control

1.1.1 Physico-chemical results of in-process control

- **Aspect:**

The result of the visual analysis is based on the shape and color of batch (005) grain, and it is shown in the **table (10).**

Table 10 : Visual grain test results**.**

N° batch	Results	Standards
005	White grain with no foreign particles.	Conform

- **Humidity:**

Humidity result is determined by desicateur at 100° (therms-balance) for batch (005), and it is shown in the **table (11).**

Table 11 : Humidity results**.**

N° batch	Results	Standards
005	0,18	Less than 1 **Conform**

- **Dosage of API**

The results of UV spectrophotometry are shown in the following **table (12)**.

Table 12 : Spectrophotometric grain assay results**.**

N° batch	OD_t	OD_w	*PeT*	*Pe*	Results	Average of results	Standards
005 High	0,9045	0,926	125,1	300,2	40,76%	41,18%	**Conform**
005 Medium	0,921	0,926	125,1	300,6	41,45%		
005 Low	0,919	0,926	125,1	300,8	41,33%		

Application :

$$Dosage\%\ High = \frac{0,9045}{0,926} \times \frac{125,1}{300,2} 100,14 = 40,76\%$$

$$\boldsymbol{Dosage\%\ Medium = \frac{0,921}{0,926} \times \frac{125,1}{300,6} 100,14 = 41,45\%}$$

$$\boldsymbol{Dosage\%\ Low = \frac{0,919}{0,926} \times \frac{125,1}{300,8} 100,14 = 41,33\%}$$

1.1.2 Result of physic-chemical control of Semi-finished Product

- **Tests carried out by production**
  - **Aspect, average mass and length:**

The results of the aspect, average mass and closure length of batch (005) capsules are shown in the **table (13).**

Table 13 : Results for aspect and average weight for 20 capsules, closure length for 10 capsules during filling**.**

		Aspect and average weight			**Closure length**		
Control frequency		Each 30 minutes			Each 1h		
Hour	Aspect	Average mass	Length	Hour	Aspect	Average mass	Length
8h30min	**Conform**	171 mg		14h30min	**Conform**	174 mg	
9h00	**Conform**	174 mg	16,00 mm	15h00	**Conform**	172 mg	15,85 mm
9h30min	**Conform**	172 mg		15h30min	**Conform**	171 mg	
10h00	**Conform**	171 mg	15,99 mm	16h00	**Conform**	172 mg	15,98 mm
10h30min	**Conform**	173 mg		16h30min	**Conform**	174 mg	
11h00	**Conform**	175 mg	15,87 mm	17h00	**Conform**	174 mg	15,83 mm
11h30min	**Conform**	172 mg		17h30min	**Conform**	173 mg	
13h00	**Conform**	173 mg	15,89 mm	18h00	**Conform**	174 mg	15,87 mm
13h30	**Conform**	173 mg		18h30min	**Conform**	175 mg	
14h00	**Conform**	172 mg	16,00 mm	19h00	**Conform**	172 mg	15,88 mm

  - **Disintegration time:**

The results of the disintegration time for batch (005) are shown in the following **table (14).**

Table 14 : Disintegration time test results **(Original, 2024).**

N° bath	Results	Standards
005	**Min:**6min	Conform
	Max:9min	

- **Tests carried out by quality control laboratory**
- **Pharmacotechnical tests**
  - **Aspect**

The result of the visual analysis is based on the shape and color of batch (005) grain, and is shown in the **table (15).**

Table 15 : Capsule visual test results**.**

N° batch	Results	Standards
005	Hard gelatin capsules, size 3, opaque white, with black SULPUREN and green SAIDAL logos on top filled with lightly granulated powder.	Conform

- **Average weight:**

The average mass results for the 20 capsules filled for bath (005) are shown in the following **table (16).**

Table 16 : Average capsule mass results**.**

N° bath 005	Results	Standards
Start	171,46 mg	Conform
Medium	172,39mg	Conform
End	172,28mg	Conform

- **Net average weight:**

The results of the average net mass of the 20 capsules for batch (005) are shown in the **table (17).**

Table 17 : Net average weight results**.**

N° bath 005	Results	Standards
Start	121,79mg	Conform
Medium	126,09mg	Conform
End	122,46mg	Conform

- **Mass uniformity :**

The results of the Mass uniformity of the 20 capsules for batch (005) are shown in the **table (18).**

Table 18 : Mass uniformity test results**.**

N° bath 005	Results	Standards
Start	**10%** [109,60-133,96]mg	Conform
	20% [97,42-146,14]mg	
Medium	**10**% [109,467-133,793]mg	Conform
	20% [97,30-145,956]mg	
End	**10%** [110,84-135,48]mg	Conform
	20% [98,53-147, 8]mg	

❖ **Analytical tests:**

- **Dosage:**

Operate by UV absorption spectrophotometry. Results For batch (005) are shown in the following **table (19).**

Table 19 : UV spectrophotometry results**.**

Start		Medium		End	
Essay	**Reading**	**Essay**	**Reading**	**Essay**	**Reading**
OD Control 1	0,9034	OD Control 1	0,9086	OD Control 1	0,8963
OD Control 2	0,9024	OD Control 2	0,9134	OD Control 2	0,8937
OD Control 3	0,9022	OD Control 3	0,9146	OD Control 3	0,8897
Average OD	**0,903**	**Average OD**	**0,912**	**Average OD**	**0,8932**
OD Test 1	0,8831	OD Test 1	0,8864	OD Test 1	0,8859
OD Test 2	0,8839	OD Test 2	0,8852	OD Test 2	0,8806
OD Test 3	0,8879	OD Tets 3	0,8837	OD Tets 3	0,8816
Average OD	**0,885**	**Average OD**	**0,885**	**Average OD**	**0,8827**

Table 20 : Spectrophotometric capsule dosage results**.**

N° bath 005	OD_t	OD_w	PeT (mg)	Pe (mg)	Purity	Results	Standards
Start	0,885	0,903	125	300,40	100,14	49,75	Conform
Medium	0,885	0,912	125	300,2	100,14	51,01	Conform
End	0,8827	0,8932	125	300,6	100,14	50,39	Conform

Application:

$$\boldsymbol{Dosage\left(\frac{mg}{capsule}\right) = \frac{ODt}{ODw} \times \frac{pet}{pe} \times NETAW \times \frac{purity}{100}}$$

Start:

$$\boldsymbol{Dosage\left(\frac{mg}{capsule}\right)} = \frac{0{,}885}{0{,}903} \times \frac{125}{300{,}40} \times 121{,}79 \times \frac{100{,}14}{100} = \mathbf{49{,}75}\%$$

Medium:

$$\boldsymbol{Dosage\left(\frac{mg}{capsule}\right)} = \frac{0{,}885}{0{,}912} \times \frac{125}{300{,}2} \times 126{,}09 \times \frac{100{,}14}{100} = \mathbf{51{,}01}\%$$

End:

$$\boldsymbol{Dosage\left(\frac{mg}{capsule}\right)} = \frac{0{,}8827}{0{,}8932} \times \frac{125}{300{,}6} \times 122{,}46 \times \frac{100{,}14}{100} = \mathbf{50{,}39}\%$$

- **Dissolution test:**

Reading 6 tubes at 292 nm for batch (005) are shown in the following **table (21).**

Table 21 : Dissolution test results**.**

OD		OD witness	Pe_w	Purity	Q%
Do(01)	0,3968	0,3883	55,6	100,14	102,41%
Do(02)	0,3962				102,26%
Do(03)	0,3969				102,18%
Do(04)	0,3865				99,78%
Do(05)	0,3870				99,88%
Do(06)	0,3922				101,23%

Average Q%	101,29
Minimum	99,78
Maximum	102,41

Application:

$$\boldsymbol{Q\%} = \frac{\boldsymbol{ODt}}{\boldsymbol{ODw}} \times \frac{\boldsymbol{PEw \times 9}}{\boldsymbol{500}} \times \textbf{purity}$$

$$Q\% = \frac{0{,}3968}{0{,}3883} \times \frac{55{,}6 \times 9}{500} \times 100{,}14 = 102{,}41\%$$

$$Q\% = \frac{0{,}3962}{0{,}3883} \times \frac{55{,}6 \times 9}{500} \times 100{,}14 = 102{,}26\%$$

$$Q\% = \frac{0{,}3959}{0{,}3883} \times \frac{55{,}6 \times 9}{500} \times 100{,}14 = 102{,}18\%$$

$$Q\% = \frac{0{,}3865}{0{,}3883} \times \frac{55{,}6 \times 9}{500} \times 100{,}14 = 99{,}78\%$$

$$Q\% = \frac{0{,}3870}{0{,}3883} \times \frac{55{,}6 \times 9}{500} \times 100{,}14 = 99{,}88\%$$

1.1.3 Result of physic-chemical control of finished Product

❖ **Pharmacotechnical testing:**

- **Aspect:**

The results for the aspect of the finished product for batch (005) are shown in **table (22).**

Table 22 : Visual test results for finished product**.**

N° batch	Result	Standard
005	Opaque white capsule, size 03, with black SULPUREN on the body and two green SAIDAL logos on the head, filled with a lightly granulated white powder.	Conform

- **Average weight:**

The result of the average weight of the 20 capsules in batch (005) of finished product is shown in the **table (23).**

Table 23 : Average weight results for finished product**.**

N° batch	Result	Standard
005	171,51 mg	Conform

- **Net average weight:**

Net average weight results for finished product, is shown in the **table (24).**

Table 24 : Net average weight results for finished product**.**

N° batch:	Result	Standard
005	121,245 mg	Conform

- **Uniformity of unidosis preparations, (European pharmacopeia 9th edition 2017).**

➢ **Variation in mass:**

Variation mass results are shown in the **table (25).**

Table 25 : Variation mass results**.**

	START			
	Average Of Individual Weights	**average weight OF empty capsule**	**Net average weight**	**CONTENT**
CAP 1	169,4	51,2	118,2	100,26
CAP 2	172,1	52,2	119,9	101,70
CAP 3	173,3	51	122,3	103,74
CAP 4	173,4	51,2	122,2	103,65
CAP 5	169,7	49,9	119,8	101,62
CAP 6	169	50,4	118,6	100,60
CAP 7	168,3	49,2	119,1	101,02
CAP 8	167,3	50,2	117,1	99,33
CAP 9	169,6	49,7	119,9	101,70
CAP 10	170,5	51,7	118,8	100,77
	AVERAGE		119,59	101,44

Dosage	101,44
Standard Déviation	1,40
K	2,4
KS	3,35

M=X	3,35
M≥101,5	3,41
M≤98,5	6,29

VA1	3,35

- **Analytical tests:**

- **Identification of PA (SULPIRIDE).**

  a) **Identification of PA (SULPIRIDE) by ultraviolet (UV) absorption spectrophotometry.**

Identification result of PA (Sulpiride) by ultraviolet (UV) absorption spectrophotometry is shown in the following **table (26)** and **(Figure 15).**

Table 26 : Identification results (a)**.**

N° batch	Result	Standard
005	Maximum absorption: **292,32 nm** Minimum absorption: **266,32nm**	Conform

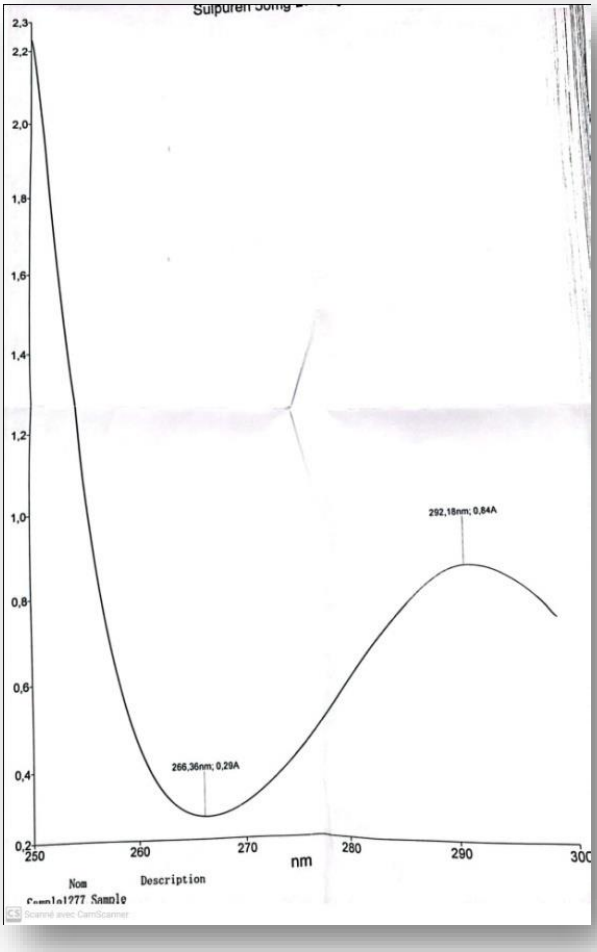


Figure 15 : Identification of API (Sulpiride) by ultraviolet absorption spectrophotometry (a) result**.**

b) Identification of API (Sulpiride) by chemical reaction with copper sulfate

Identification of API (Sulpiride) by chemical reaction with copper sulfate.is shown in the following **table (27).**

Table 27 : Identification results (b).

N° batch	Result	Standard
005	Characteristic green precipitate.	Conform

- **API dosage**

Operation by UV absorption spectrophotometry. Result is shown in the following **table (28).**

Table 28 : Dosage test results for finished product**.**

Net average weight			121,25	
Pe witness	125			
Pe test	300,00			
absorbance	0,8827	0,8758	0,8724	0,877
Test	0,9083	0,9064	0,9066	0,907
Purity	**Title**		**Water%**	100,14
	100,14		0	
Dosage	52,33			

Application:

$$\boldsymbol{Dosage}\left(\frac{\boldsymbol{mg}}{\boldsymbol{capsule}}\right) = \frac{0{,}907}{0{,}877} \times \frac{125}{300} \times 121{,}25 \times \frac{100{,}14}{100} = \mathbf{52{,}33}\%$$

- **Dissolution test:**

Operation by ultraviolet (UV) absorption spectrophotometry, results are shown in the following **table (29).**

Table 29 : Dissolution test results**.**

OD		OD witness	Pe_w	Purity	Q%
OD(01)	0,3954	0.4199	55,6	100,14	94,37
OD(02)	0,408				97,38
OD(03)	0,4151				99,07
OD(04)	0,4222				100,77
OD(05)	0,4096				97,76
OD(06)	0,4177				99,70

Average Q%	98,18
Minimum	94,37
Maximum	100,77

Application:

$$Q\% = \frac{0,3954}{0,4199} \times \frac{55,6}{500} \times 9 \times 100,14 = \mathbf{94,37}\%$$

$$Q\% = \frac{0,408}{0,4199} \times \frac{55,6}{500} \times 9 \times 100,14 = \mathbf{97,38}\%$$

$$Q\% = \frac{0,4151}{0,4199} \times \frac{55,6}{500} \times 9 \times 100,14 = \mathbf{99,07}\%$$

$$Q\% = \frac{0,4222}{0,4199} \times \frac{55,6}{500} \times 9 \times 100,14 = \mathbf{100,77}\%$$

$$Q\% = \frac{0,4096}{0,4199} \times \frac{55,6}{500} \times 9 \times 100,14 = \mathbf{97,76}\%$$

$$Q\% = \frac{0,4177}{0,4199} \times \frac{55,6}{500} \times 9 \times 100,14 = \mathbf{99,70}\%$$

- **Apparent substances:**

By liquid chromatography

All the results for related substances are shown in the following tables and figures. **Standard ≤ 0.3%.**

Table 30 : Calculation results for impurities **(Original, 2024).**

N° batch	Result	Standard
005	0.013%	Conform

Application :

$$\boldsymbol{imp}\ \% = \frac{\boldsymbol{SE}}{\boldsymbol{ST}} \times \frac{\boldsymbol{CT}}{\boldsymbol{CE}} \times \mathbf{100}$$

$$imp\ \% = \frac{SE}{ST} \times \frac{\frac{pe}{100} \times \frac{3}{100} \times \frac{1}{10}}{\frac{pe}{100}} \times 100$$

$$imp\ \% = \frac{SE}{ST} \times \frac{3}{10}$$

$$imp\ \% = \frac{2567}{55541} \times \frac{3}{10} = \mathbf{0,013}\%$$

Table 31 : HPLC results for related substances**.**

		Retention time	**Peak air**	**Tailing factor**
S1	Sulpiride	5,923	15030004	/
	Imp.01	11,915	2567	/
S2	Sulpiride	6,008	55541	1,233
S3	Sulpiride	5,961	1901501	1,286
	Sulpiride imp. B	7,219	2490927	1,228

S1: Solution (1); **S2:** Solution (02); **S3:** Solution (3); **Imp.01:** Impure 01, and Imp.B**:** Impure B

The results of the peaks observed in the chromatogram indicate that:

- The two peaks present in solution (3) (Sulpiride and impurity B) **(Figure16)** have good resolution as they have been correctly separated (the system is compliant).
- The surface area of the secondary peak (impurity peak) **(Figure 18)** visible in solution (1) is smaller than that of the main peak in the chromatogram obtained with solution (2) **(Figure 17).**
- The impurity level obtained (0.013%) is below the required standard of 0.3%. These results in compliance with standards.

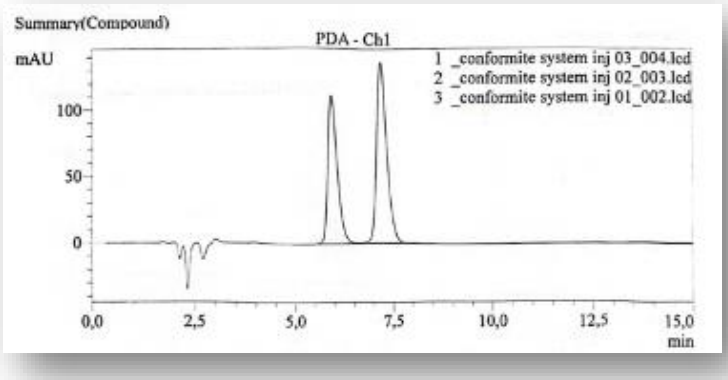


Figure 16 : HPLC chromatogram of S3 (system comformity)**.**

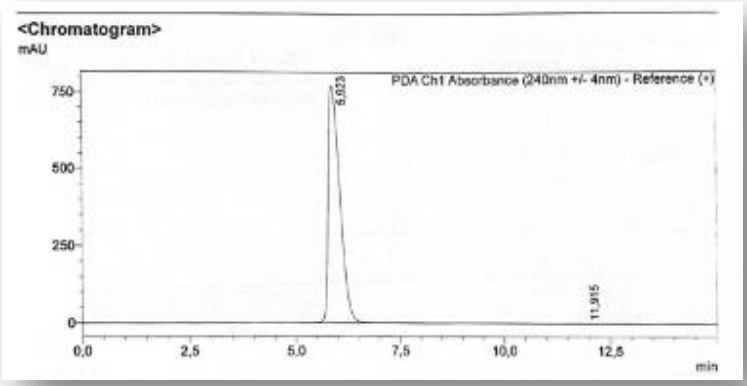


Figure 17 : HPLC chromatogram of control solution (S2)**.**

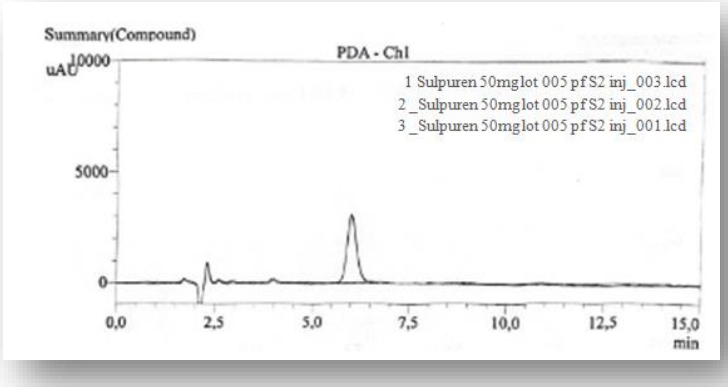


Figure 18: HPLC chromatogram of the solution to be tested (S1)**.**

1.2 Results of microbiological testing of finished products

Microbiological test results for capsule (SULPUREN®50mg), are shown in the following **table (32).**

Table 32 : Microbiological test results for capsule (Sulpuren® 50mg)**.**

Test	Results	Standards
Total viable aerobic count	00	$\leq 10^3$
Fungal counts	00	$\leq 10^2$
Testing for *Escherichia coli*	Absence	Absence

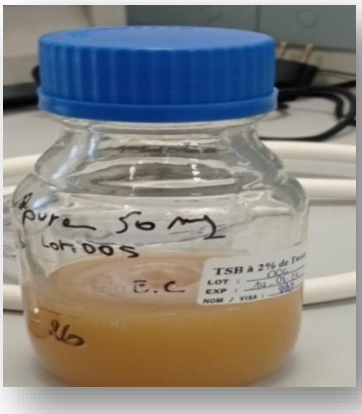


Figure 19 : *Escherichia coli* result**.**

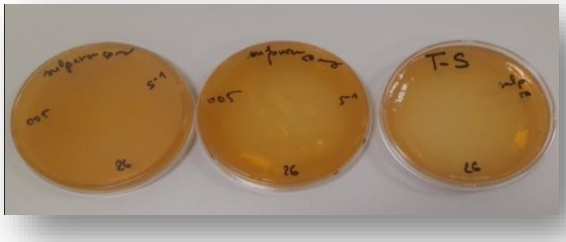


Figure 20 : Fungal counts result**.**

Figure 21 : Total viable aerobic count result**.**

2. General Discussion:

The quality of SULPUREN ®50mg capsule is quite clear from these results. Based on the European Pharmacopoeia 2017 9th edition. The quality tests carried out on the semi-finished and finished product SULPUREN® 50mg capsule, which are mainly limited to physicochemical (pharmacotechnical and analytical) and microbiological tests, made it possible to determine their conformity with the established standards. Finally, it has been established that the various studies carried out on the semi-finished and finished product of SULPUREN® 50mg conform to the standards of the European Pharmacopoeia 2017 9th edition.

CONCLUSION

CONCLUSION

Quality risk management is one of the main objectives of companies, regardless of their field of activity. As far as a pharmaceutical company is concerned, this is of increasing importance because the product marketed is a medicine, which remains an essential element in the field of public health.

Through our graduation internship at the Saidal El Harrach unit (Zemirli), we have been able to explore and acquire solid knowledge in the field of the pharmaceutical industry

In order to evaluate the quality of SULPUREN® 50 mg, all the methods recommended by the European Pharmacopoeia are used. The manufacturing process, including weighing raw materials, granulation, filling, and packaging, was carried out following international standards and GMP. This includes different physical and chemical methods to identify and measure the purity of the preparations analyzed in order to guarantee their quality.

According to the physical, chemical, and microbiological control criteria, it has been demonstrated that the semi-finished product and the finished product meet the standards of the European Pharmacopoeia, which confirms our hypothesis. Based on all the analyses and various controls carried out, it is demonstrated that SULPUREN® 50 mg is a generic drug in the form of capsules that meets all the criteria of quality, effectiveness, and safety.

In general, all the results obtained after the various controls and analyses of the generic drug SULPUREN® produced within the pharmaceutical company Saidal meet the standards required by the European Pharmacopoeia.

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APPENDIX

Manufacturing equipment :

- Scales (with different capacities: 6 kg, 30 kg, and 300 kg)
- Solution preparation tank.
- Mixer granulator P800.
- LAF CAP600.
- Calibreur sec.
- Wet calibrator and pneumatic conveyor.
- Suction lance and peristaltic pump.
- Stainless steel containers or polyethylene bags.
- BIN.
- Capsule filler.

Table 01: Roles of equipment used in manufacturing **(Original work).**

Name	Brand	Role
Solution preparation tank	INOXPA	Designed for preparation of sterile pharmaceutical products
Mixer granulator P800	Diosna	Used to assemble fine solid particles into larger ones, known as granules.
LAF CAP600		Designed for the production of dry mixtures
Calibreur sec	FREWITT	Designed for size calibration
BIN	/	For the storage and transport of pharmaceutical powders or mixtures

Capsule filler	BOSCH	Designed to fill the powder in capsules.

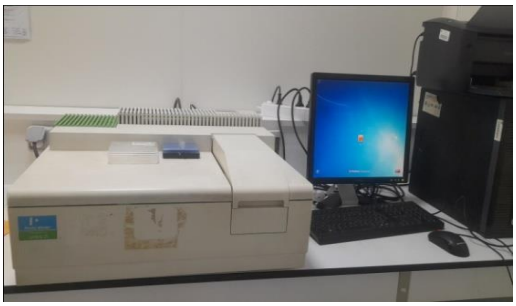
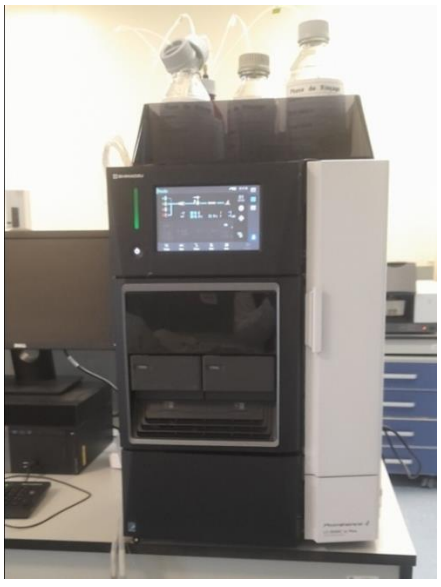
Equipment used for physic-chemical control

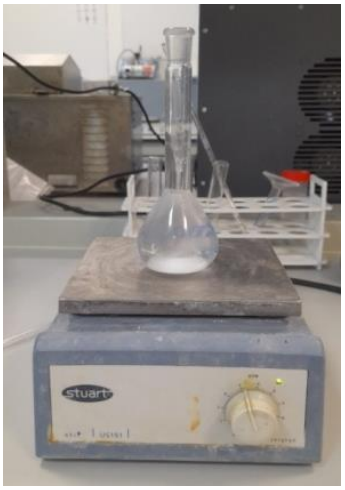
- Precision balance.
- Magnetic agitator.
- Disintegration tester.
- UV-visible absorption spectrophotometry, and tank.
- Dissolutest.
- Hight performance liquid chromathography HPLC.
- Desiccator.
- Caliper.
- Laboratory glassware (flasks, graduated pipettes, weighing shoe, funnel, syringe filter 0,45 µm, test tubes, beakers, spatula…).

Equipment used for microbiological control:

- Drying oven set at 30- 35° C.
- Drying oven set at 20- 25° C.
- Drying oven set at 42- 44° C.
- Vortex agitator.
- Water bath set at 100° C.
- Water bath set at 45° C.
- Colony counter.
- Bunsen burner.
- Glassware (petri dish 90mm diameter, bottle, graduated pipette)

Table 2: Quality control equipment **(Original work).**

Name	Brand	Role	Figure
UV-visible absorption spectrophotometry	PerkinElmer precisely.	Measure the intensity of light in a solution to be studied.	
Drying oven set at 30-35° C	BINDER Best conditions for your success	Heats elements to a regulated temperature.	
Hight performance liquid chromatography	SHIMADZU Excellence in Science	Dosing, identification and separation of chemical constituents in a complex mixture.	

Colony counter		Designed to digitize the number of bacterial or fungal colonies that have developed after an incubation period on a petri dish.	
Magnetic agitator		Automatically assure the agitation of a solution.	
Precision balance	METTLER TOLEDO	Measure the mass of solids and liquids with a high degree of accuracy	

PH meter	METTLER TOLEDO	Perform pH measurements	

Growth medium

- Sodium chloride peptoned tompon solution.
- Casein pepton agar medium and soya liquefied
- Sabauraud liquefied dextrose agar medium
- Liquid medium with casein and soy peptons.
- Mac Conkey liquid medium
- Mac Conkey agar medium

Reagents:

- Aqueous acetic acid solution 10%.
- Hydrochloric acid (HCL) 0.1N solution.
- Methanol.
- Purified water.