الجمهورية الجزائرية الديمقراطية الشعبية
People's Democratic Republic of Algeria
وزارة التعليم العالي والبحث العلمي
Ministry of Higher Education and Scientific Research
جامعة عين تموشنت بلحاج بوشعيب
University –Ain Temouchent- Belhadj Bouchaib
Faculty of Science and Technology
Departement Of Chemistry

End of studies project
For the attainment of a Master's degree
Field: Material Science
Sector: chemistry
Specialty: Macromolecular Chemistry

Theme

Development of new pharmaceutical forms for oral administration followed by microbial study

Presented by:

Miss. RAHOU Khouloud

Before the jury composed of:

Dr BENNABI Lamia	MCA	UAT.B.B (Ain Temouchent)	President
Pr BELARBI Lahcene	Pr	UAT.B.B (Ain Temouchent)	Examiner
Dr SEDIRI Khaldia	MCB	UAT.B.B (Ain Temouchent)	Supervisor

Academic year **2024/2025**

Appreciation

Firstly, I would like to express my gratitude to Allah, my God, who granted me the patience and courage to complete this work.

I want to begin by acknowledging my deep appreciation for my supervisors, **Mrs K. SEDIRI,** Conference maitre B at the University "Belhadj BouchaibAin Temouchent for her dedicated time, effort, and understanding in assisting me to succeed in my studies. Her extensive wisdom and wealth of experience have been a constant source of inspiration throughout my work.

My sincere thanks go to **Mrs BENNABI Lamia**, Conference maitre A at the University "Belhadj BouchaibAin Temouchent", for having done us the honor of chairing this jury and for carrying out the experiments necessary for writing this project.

To **Mr BELARBI Lahcene,** Professor at the University "Belhadj Bouchaib Ain Temouchent". Thank you for agreeing to participate in order to evaluate and judge this modest work, please find here the expression of my sincere thanks.

We are also very grateful to the Head of the Department, **Mrs Z. BAILICHE**, Professor at University of Ain Temouchent, for her great help in the smooth running of our research.

We would also like to thank **Mrs H. Azzi** and **Mrs N. Fekih** for their invaluable help with characterization; we were able to successfully write this project.

We would particularly like to thank the laboratory staff: **Mrs. Bahria** , **Mrs. Wahiba** and **Mrs Karima** at the Chemistry Laboratory and **Mr. Ahmed** , **Mrs Choukria** at the Biology Laboratory at the "Belhadj Bouchaib- Ain Témouchent" University for their their Availability and their help and thank you again for your support and encouragement throughout our work Experimentation.

Last and not least, a warm thanks to all the professors in the Department of Matter Sciences at the University -Ain Temouchent- Belhadj Bouchaib, for the quality of their teaching and the information they gave me during these years of study. Their passion for research inspired me and motivated me to give my maximum effort to my research project.

Finally, I'd like to thank the doctoral student **Belkadi Amel** for helping me with many aspects of my research, as well as the laboratory and my family, who have encouraged and motivated me throughout my studies.

A big thank you to all

DEDICATION

I dedicate this modest work:

To **my dear parents** who have sacrificed their lives for the success of my studies.

To my sister **Wafaa** and my brother **Farouk**

For **my grandfather** who was an idol for me an example of the most cultural man in my family in all fields who is no longer part of this world

For my maternal and paternal family **Rahou and Haddou**

For my best friend from the primary school: **Zitouni Assala**

For my friends: **Chaima**,**Asma**,**Ikram** and **Mounira**

And to all my teachers.

Summary

List of Figures

Bibliography part:

Chapter I :

Chapter II:

Experimental part

List of tables

Bibliography part

Chapter I :

Chapter II :

Experimental part

ABREVIATIONS LIST

PA	active principle
EC	Ethylcellulose
HPMC	Hydroxypropyl-methylcellulose
AMX	Amoxicillin
FTIR	infrared spectroscopy
XRD	X-ray Diffraction Analysis
ABS	Absorbance
%PA	The percentage of the active ingredient released.
HCl	Hydrochloric acid
Borax	Sodium tetra borate 10 hydrate
Min	Minute.
g	Gram
ML	Milli liter
Mg	Milligram
A	Absorption
ε	Specific absorption coefficient (L. mol-1.cm-1).
C	The concentration in mol/L of the solution.
L	The length of the quartz cell (1cm)
liquid abs%	The percentage of liquid absorbed
OD	Optical density
mt	The mass of active ingredient at time “t”
Mi	Initial mass of the active ingredient.
Vd	The volume of the dilution flask in ml
Vf	The volume of the release liquid contained in the bottle in ml

Mm	The molar mass of the principle of the active ingredient (g/mol)
mt ‘	mass of the galenic form at time “t” of weighing
m0	initial mass of the “dry” dosage form.
Yield%	Yield.
M.H	Mueller-Hinton
mm	Milli-meter
Re	Rference
Ge	Generic
PO	Per-os
FDA	Food and drug administration
GI	Gastro-intestinal
IV	Intravenous
IM	Intramuscular
SC	Subcutaneous
IR	Immediate-release

Introduction :

General Introduction :

Introduction:

Polymers have evolved progressively in many fields, especially in the pharmaceutical field, “polymeric drugs”, due to the need for performance, safety and efficacy in medical treatments. The most widely used polymers for Pharmaceutical applications are polysaccharides: Celluloses, chitins and chitosans, alginates and starches, due to their nature, biodegradability/degradability and biocompatibility **[1].**

As early as the 1950s, polymers were used as excipients in solid formulations **[2]**, and between 1970 and 1980 the emergence of controlled-release polymers such as polymethacrylates or lactide-glycolide copolymers (PLGA), as well as cellulose-derived polymers, led to the development of sustained-release pharmaceutical forms **[3]** .After the 1990s, their role expanded with the advent of nanotechnology, which enabled new techniques to target the location of drugs in the body (specialized).

In this new pharmaceuticals forms the drug is dispersed in the matrix polymer and the release of this active principle (PA) into the body is done by its diffusion through the polymer, the factors influence this process are: the speed of penetration of the liquid into the galenic form and the dissolution of the active principle.

Amoxicillin is a widely an antibacterial antibiotic from beta lactams family especially from penicillin’s, this type of antibiotic is active against many type of bacteria especially the gram-negative bacteria which is a type of strong bacteria **[4].**it is used to treat bacterial infections of ear , nose ,lungs ,sinusitis **…[4-8].**

The objective of this work is to find a new pharmaceutical form for oral administration followed by microbial study to reduce the number of drugs taken in the pharmaceutical field .for the purpose we made tablets with the active principle (AMX) and polymers which are derivative from cellulose: Ethylcellulose (EC) and Hydroxypropyl-methylcelulose (HPMC).

This work was followed by the study of the release of the active principle (AMX) in two pH media (1.2 stomach and 7.4 intestinal) ;the prepared tablets were characterized by FTIR and XRD followed by biological study against the referenced bacterial strains .

In our work, we have chosen amoxicillin as an active ingredient widely used in pharmacological field and polymers: Ethylcellulose (EC) and hydroxypropyl-methycellulose (HPMC) because they are non-toxic and used in marketed drugs.

The bibliographic part is includes two chapters:

- The first chapter will be about generality of pharmacology and types of drugs either the different galenic forms or the drug delivery systems.
- The second chapter describes the types of antibiotics and generality about them also information about the active principle (AMX) and it’s mode of action.

General Introduction :

- The experimental part contains three sub-parts:
  - First part concerned the synthesis of tablets based on active principle AMX and two types of polymers: the first two formulations were made by Ethylcellulose (EC) by different weight and the third formulation was made by Hydroxypropyl-methylcellulose (HPMC).
  - Second part includes the kinetic study of release of the active ingredient "Amoxicillin".
  - Third part is characterizing of tablets by different analysis techniques: IR, XRD.
  - The fourth part followed by the biological study of prepared tablets with respect to the referenced bacterial strains.

References:

[1] Caliceti, P., Salmaso, S., & Bersani, S. (2009). Polysaccharide-based anticancer prodrugs. In R. L. H. Reddy & P. Couvreur (Eds.), *Macromolecular anticancer therapies: Cancer drug discovery and development* (Vol. 2, pp. 163–219). Springer New York.

[2] Rowe, R. C., Sheskey, P. J., & Quinn, M. E. (2009). *Handbook of Pharmaceutical Excipients*. Pharmaceutical Press.

[3] Langer, R., & Folkman, J. (1976). Polymers for the sustained release of proteins and other macromolecules. *Nature*, 263(5580), 797–800.

[4] Akhavan, B. J., Khanna, N. R., & Vijhani, P. (2023). Amoxicillin. In *StatPearls* [Internet]. StatPearls Publishing.

[5] Shulman, S. T., Bisno, A. L., Clegg, H. W., et al. (2012). Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update. *Clinical Infectious Diseases*, 55(10), e86–e102.

[6] Matsumoto, H., Shiotani, A., & Graham, D. Y. (2019). Current and future treatment of *Helicobacter pylori* infections. *Advances in Experimental Medicine and Biology*, 1149, 211–225.

[7] Chow, A. W., Benninger, M. S., Brook, I., et al. (2012). IDSA clinical practice guideline for acute bacterial rhinosinusitis. *Clinical Infectious Diseases*, 54(8), e72–e112.

[8] Rosenfeld, R. M., Piccirillo, J. F., Chandrasekhar, S. S., et al. (2015). Clinical practice guideline (update): adult sinusitis. *Otolaryngology–Head and Neck Surgery*, 152(2 Suppl), S1–S39.

Chapter I :

Generality of pharmacology

I- Pharmacology :

I.1. Definition and history:

The word "pharmacology" is derived from the Greek word "pharmakon," which means both poison and remedy **[1-3].**Pharmacology is the study of how chemicals can alter the functions of living things. Because its primary original aim was to give treatments a scientific basis, the subject really evolved in a more specialized sector. Pharmacology originated later than the other medical sciences because its study requires a sufficient understanding of the normal functioning of the organism (physiology) and the perturbations of these caused by illnesses (pathology) **[4].**

The goal of general pharmacology is to study the nature of the chemical reactions that occur when drugs act on cells. The obvious way to do this is to use physicochemical methods. However, any such attempt immediately raises the following fundamental difficulties. First, the structure of the simplest cell is much more complex than any system studied by a physical chemist. This complexity greatly reduces the ability for simple quantitative estimates. Even if we know that the binding of a certain number of molecules to a cell will cause a certain dysfunction, we still do not know that the observed effect is determined by the proportion of bound drug. Moreover, in most cases, the entry of drugs into cells is a complex process involving the adsorption and binding of molecules **[4].**

With the creation of Rudolf Buchheim as a professor at the University of Dorpat in 1847, pharmacology emerged as a separate scientific discipline. In 1869, he was succeeded by his student, Oswald Schmiedeberg, who made important advances in the field, such as creating experimental techniques for medical research **[5].**

In 1872, Schmiedeberg was appointed professor at the University of Strassbourg, where he educated a number of aspiring pharmacologists. Teofilo Hernando, one of his students, introduced pharmacology as a separate science in Spanish universities at the beginning of the 20th century, demonstrating his influence outside of Germany **[5].**

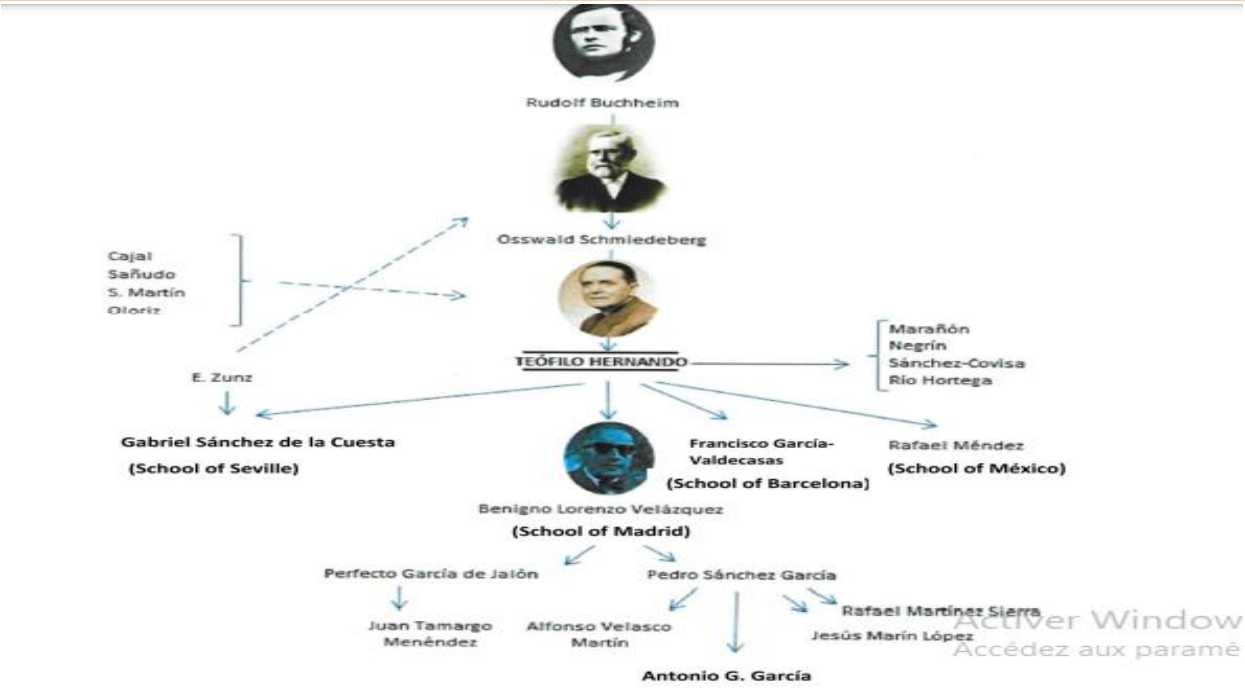


Figure 1: Scheme showing some of the schools of pharmacologists that directly or indirectly, descended from Teofilo Hernando **[5].**

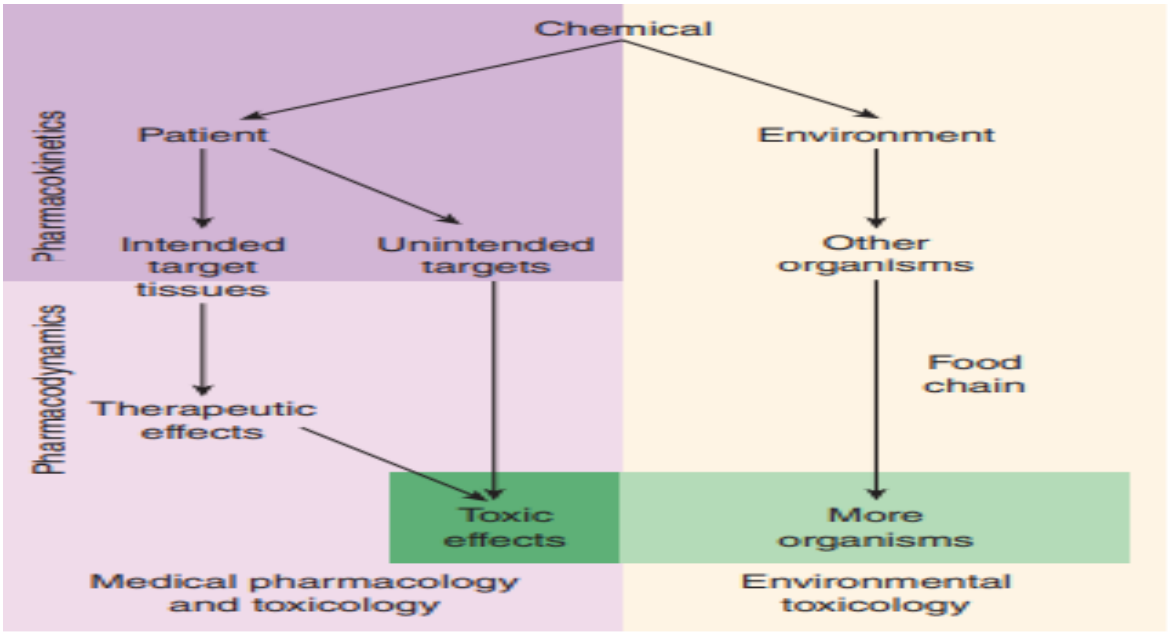


Figure 2: principal fields of pharmacology research.

There are two major categories into which chemical actions can be separated. Understanding how drugs act as chemicals on specific organisms, particularly humans and domestic animals, is the goal of medical pharmacology and toxicology, which is the first (left) field. Both positive and negative effects are present the subject of pharmacokinetics talk about medicament absorption, elimination and distribution .on the other part there is pharmacodynamic which concern the actions of chemicals on organism. Environmental toxicology, the second domain (right) is focused on how chemicals affect all living things and how long they can survive as a species and in groups **[6].**

I.2. General Principles of pharmacology:

I.2.1. Nature of drugs:

Drugs are substances that alter biological processes by means of chemical interactions. Usually, they function as either antagonists (inhibitors) or agonists (activators) of particular receptors. Additionally, some medications may interact with water molecules or other medications. Drugs can be synthetic (xenobiotics) or natural (hormones), and poisons are substances that have negative effects. Toxins are biologically derived poisons **[6, 10].**

I.2-2.Drug's physical characteristics:

For any medicines that interacts with his receptor, it must have the right composition, form, electric charge, and size. Other than this, this drug needs to move from his administration site to the action site and be eliminated or inactivated in the special place. The form of medicament, solid, liquid, or gaseous, influences the way it is administered **[6, 10].**

I.2.3. Drug Reactivity and Receptor Bonds:

Covalent electrostatic, or hydrophobic, bonds allow drugs to interact with receptors. Strong and regularly reversible covalent bonds result in long-lasting effects even after the drug is eliminated from the body, as is the case with aspirin's interaction with cyclooxygenase **[6, 10].**

II. Drugs:

The word "medicine" is Latin. Medicinal: Drug **[1].**Any material or combination of materials advertised as having the ability to treat or prevent disease in humans or animals, as well as any material or combination of materials that may be used in or administered to humans or animals in order to make a medical diagnosis or to restore, correct, or modify their physiological functions through the action of pharmacological, immunological, or metabolic mechanisms **[11].**

II.1-origin of drugs: There are several sources of drugs **[1].**

II.1.1.Natural:

a) Vegetable: This technique focuses on the use of plants (phytotherapy), whole plants (tea), or essential oils. They extract from alkaloids (quinine and morphine) and heterosides (digitalis) the active principles **[1, 9].**

b) Animal: They use blood and plasma of humans and animals, the active principles are extracted from hormones and enzymes. (insulin from the pancreas and heparin from the lungs) **[1, 9].**

c) Mineral: water, clay, bicarbonate of Ca+, iodine, and sodium chloride are used like active principles **[1, 9].**

II.1.2.Synthetic or artificial:

There are diverse medicines made by synthesis; they have the same effect as natural medicines when they are fixed on special receptors (ex: sulfamides, chloramphenical)**[1, 9].**

II.1.3.Semi-artificial or semi-synthetic:

An inactive natural substance can be modified by chemicals in a laboratory into medicines. This is how a series of hemi-synthetic penicillins were obtained from the amino acid amino_6_penicillium **[1, 9].**

II.2-Composition of medicines (drugs) : (Galenic forms) :

II.2.1.Active principle (PA):

The active principle: medicines react with one or diverse active principles destined for the pharmacological action. It is the part of the medicine that gives curative properties or preventive properties and the principal component for medicine (obligatory) **[1, 9, 12].**

II.2.2.Adjuvant:

A molecule or substance added to the active principle to enhance its pharmacological effect in parallel with the PA; ex. (local anesthetic combined with vasoconstrictor) **[1].**

II.2.3.Excipient :

An inert material called an excipient is used in drug formulation to give the active pharmaceutical ingredient (API) a suitable medicinal form and guarantee its uniform distribution. Its main functions include making the drug preparation process easier, guaranteeing chemical stability, and making sure the drugs compatible with the body, other excipients, and the active ingredient **[1, 12].**

To prevent negative effects like allergic reactions or intolerance (such as lactose intolerance), the excipient needs to be non-reactive, chemically stable, and inert. Depending on the therapeutic needs, it may affect the drug's release rate, encouraging either a slow or rapid release. The amount of the excipient is denoted as "QSP" (quantity sufficient to form one unit of the active ingredient) in the drug's composition. The excipient is still a secondary, optional component of the drug's composition, despite its significance **[1, 12].**

Macromolecules are used as excipients because of their diverse functions like binding, lubrication, disintegration, and stabilization. These excipients include natural, semi synthetic, and synthetic polymers, such as sodium alginate, chitosan, cellulose derivatives, polyethylene glycols, and xanthangum. Multifunctional polymers,which also offer properties like mucoadhesion, enzyme inhibition, and improved drug absorption, are increasing utilized across various drug delivery routes**[13].**

Designation	Trade name	Supplier
Polyvinyl alcohol	PVA SRP80®	Merck

Sodium alginate	Protanal PH6160®	FMC Biopolymer
	Protanal CR8223®	
	Manucol LKX®	
Propylene glycol alginate	Kelcoloid K3B426®	
Pregelatinized corn starch + mannitol	LAB 4435®	Asahi kasei chemicals
Ethyl cellulose	Ethocel 10 CP®	Colorcon
HPMC (hypromellose)	Benecel K4MDC®	Ashland

Table 1: synthesis of the tested functional excipients **[12].**

II.2.3.1-excipient origins :

-Among the five **animal sources** of excipients are lactose, gelatin, stearic acid, bee wax, honey, musk, lanolin, and others **[14].**

-**Sources of vegetables** include starch, guargum, peppermint, turmeric, arginates, acacia, and more **[14].**

-Calcium phosphate, silica, talc, calamine, asbestos, kaolin, paraffin, and soforth are examples of **mineral sources [14].**

-Synthetic: polyethylene glycols, polysorbates, lacticacid, boricacid, saccharin and povidone **[14].**

III.Drugs classification :

Therapeutic and pharmacological properties are the base of drugs classification. this system of classification reflect on both therapeutic classes (based on pathology treated) and pharmacological classes (based on drugs pharmacological actions) **[1].**

III.1.Therapeutic classes:

We sad that this class based on the diseases they treat **[1].**

III. 2.Pharmacological classes:

Into each therapeutic class drugs are divided by theirs pharmacological actions (how they affect on the body) **[1].** For example: the "Anti-infectives" are included in

therapeutic class,we have pharmacological classes like antibiotics ;antiseptics ;antiparasitics ;antifungals and antivirals. **[1].**

III.3.Pharmacological categories :

These are subcategories into each pharmacological class. Example: in antibiotics we have categories like: beta-lactams ,macrolides and tetracyclines. **[1].**

III.4.Pharmacological groups :

Subdivision into each pharmacological category. Ex: into Beta-lactams, there are groups like penicillins and cephalosporins**.** due to this complexity some drugs are related to one specific family,while others may belong to several like aspirin. **[1].**

-Examples of Therapeutic Families:

Antibiotic family	Examples
Anesthetics (painkiller)	Ketamine
Analgesics: a painkiller also	Codeine
Sedatives : soothing effect on organs	Diazipam
Antiperitics: these drugs are used against fever	Aspirin
Anti-inflammatories : against inflammation	loratadine
Anti-biotics : assault bacteria	penicillin
Antivirals: react against viruses	Aciclovir
Antiparasitics : they react against parasites	Chloroquine
Antifungals : used against allergies	Ketoconazole
Anti-emetics, which act against vomiting	Domperidone

Laxatives, which stimulated efecation	Lactulose
Cough-suppressants, which combat coughing	Ephedrine
Bronchodilators, which dilate the bronchial tubes	Theophylline
Mucolytics, which thin bronchial secretions	Chymopsine
expectorants, which increase bronchial secretions	Eucalyptol
Anti-hypertensives, which combat hypertension	Clonidine
Diuretics, to increase urine secretion (diuresis)	Lasilix
Psychotropic drugs for the treatment of psychiatric illnesses (neuroleptics, anxiolytics, antidepressants, hypnotics...)	-Antidepressants, which treat depression ,e.g : fluoxetine. -anxiolytics, which reduce anxietye,e.g : dbromazine. -Neuroleptics, which reduce psychotic symptoms,e.g: chlorpromazine. -Hypnotics, which induce sleep (sleeping pills) ex: thiopental

Table 2: families of antibiotics **[1].**

IV. Classification of dosage forms:

IV.1.Solid dosage forms:

(E.g.: tablets, capsules, suppositories) must disintegrate to release the drug. Disintegration of a dosage form may be impaired under certain conditions (e.g., dry mouth due to aging, disease, or concomitant medications slows the dissolution of a nitro glycerin tablet). On the other hand, a drug may be specially formulated to disintegrate only in certain parts of the gastro-intestinal (GI) tract (e.g., enteric-coated tablets disintegrate in the small intestine), to protect the drug from stomach acid (e.g., erythromycin), or to protect the stomach from irritating drugs (e.g., enteric-coated aspirin). Tablets and capsules can also be

formulated to release the drug slowly (controlled-release, extended-release, or sustained-release formulations) and extend its duration of action. Extended-release formulations are particularly useful for drugs that have a very short duration of action **[15].**

IV.1.1.Polymer formulations:

Are special classes of solid dosage forms that incorporate the drug into a matrix and then gradually release the drug over an extended period of time or at a specific site.Examples include transdermal patches and drug-eluting stents. New polymer formulations for intravenous (IV) drug delivery are also being developed **[15].**

IV.2.Semi-solid formulations:

Include creams, ointments, and pastes. These formulations are often applied topically to the skin and require the drug to be released and diffused through the skin **[15].**

IV.3. Liquid formulations:

Can be suspensions or solutions that do not require the formulation to dissolve and therefore are often more easily absorbed than solid formulations. Suspensions or solutions are also beneficial for patients who are unable to swallow tablets or capsules. The drug in a suspension is not dissolved in the liquid carrier. Therefore, the drug must first dissolve before it can be absorbed. The drug in a solution is already dissolved. Therefore, solutions are often absorbed faster than suspensions. Drug solutions can also be injected directly into the bloodstream **[15].**

V.Different pharmaceutical forms:

-The dosage form of a drug (also called galenic form) must enable the active ingredient to reach the target organ as quickly and effectively as possible. This is an important aspect of medicine, as the right method of administration means greater effectiveness and lower risks.The dosage form is chosen by the doctor based on the site of action, duration of action (immediate, delayed) and patient (adult, child) **[16-18].** There are many different pharmaceuticle forms. The most known are:

- Oral, administered by mouth

- Injectable, administered by injection

- Dermal, applied to the skin

- Inhalation, administered by aerosol

- Rectal, inserted through the rectum **[16-18].**

V.1.Oral dosage forms:

-Oral dosage forms are the most commonly used. They account for 80% of dosage forms **[16-18].**

V.1.1.Tablets:

-Tablets are preparations of different shapes and appearances, which consist of a mixture of active ingredients and excipients **[19].**Compressed from a powder. To ensure durability and mask the taste, tablets are often surrounded by a film or coating (film) **[16-18].**

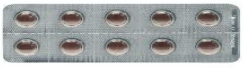
Tablet type	Coating	Decomposition time	Examples
Film-coated	Very thin polymer film	⩽30 min	Bactrim® 
Film-coated	Thicker coating, Often colored	⩽60 min	Brufen® 
Dragee	Sugar-based	⩽60 min	Becozym® 

Table 3 : types of tablets **[19].**

-there are several types of tablets:

V.1.1.a.Enteric-coated tablets: are designed to dissolve in the intestines and not be broken down by gastric juices. They must be swallowed whole. Extended-release tablets release their active ingredient gradually, reducing the daily dose. Tablets should be swallowed with water, except for certain types of tablets, such as effervescent or dispersible tablets, which should be dissolved in water, or sublingual tablets, which dissolve under the tongue for a quick onset of action. Lozenges are used to treat mouth and throat problems **[16-18].**

V.1.1.b.Capsules: consist of two gelatin shells containing a powder and are also swallowed with water, but can be opened to release their contents if necessary. Some capsules release their active ingredient gradually. They are not suitable for children under 6 years of age **[16-18].**

V.1.1.c. Liquid forms such as syrups and drinking solutions are more suitable for children and allow for adjusted doses. Oral suspensions should be shaken well before use **[16-18].**

V.2.Dermal forms: medecines are applied tipically or systimically to the skin in dermal forms; including ointments,creams,gels,solutions and powders**[16-18].**

V.3.Transdermal devices:

Dermal forms Patches and other transdermal devices enable the active ingredient to gradually enter the bloodstream through the skin. You can wear patches for a few days. dermal forms The Medicines Agency advises against cutting the patch unless instructed, seeking advice from a physician or pharmacist regarding patch application location, and switching the patch application site every day to avoid irritation in order to prevent medication errors. Since poisoning has been documented, especially with nicotine patches, it is crucial to keep patches out of children's reach. It's important to disclose wearing the patch during medical exams because it may result in burns during defibrillation or MRI. Additionally, since the sun and hot sports can accelerate the release of the active ingredient into the bloodstream, you should stay away from sources of extreme heat **[16, 17, 18, 20].**

V.4.Injectable :

-Injections are used when certain active ingredients such as insulin, heparin or vaccines cannot be absorbed by the intestine. They are also chosen for their rapid and intense effect. Depending on the product, injections can be intramuscular, subcutaneous or intravenous. They are available in different forms: solution in ampoules, prefilled syringes, prefilled pens or dissolving powders **[38].**

V.5.Administration forms for the nose, ears and eyes:

Are also common. Nasal drops are administered in the form of drops or sprays, ear drops should be used in the supine position and can be warmed, while eye drops are instilled into the lower eyelid and must be stored properly **[16-18].**

V.6.Inhalation forms :

-For the treatment of respiratory diseases such as asthma deliver drug particles directly into the bronchi. Aerosols with metered valves or powder devices facilitate administration, and a demonstration of use is recommended to ensure correct use **[16-18, 21].**

V.7.Rectal forms : Suppositories are used to treat people who have trouble swallowing medication or to treat certain rectal or anal conditions topically. They should be stored away from heat. Enemas should be injected into the rectum using a cannula attached to a slightly elevated container **[16-18].**

V.8.Vaginal forms : Ovules, vaginal capsules, and vaginal tablets are preparations for topical treatment of certain vaginal conditions. The ovule is inserted into the vagina in a lying position. If it melts, you may experience an uncomfortable discharge **[16-18].**

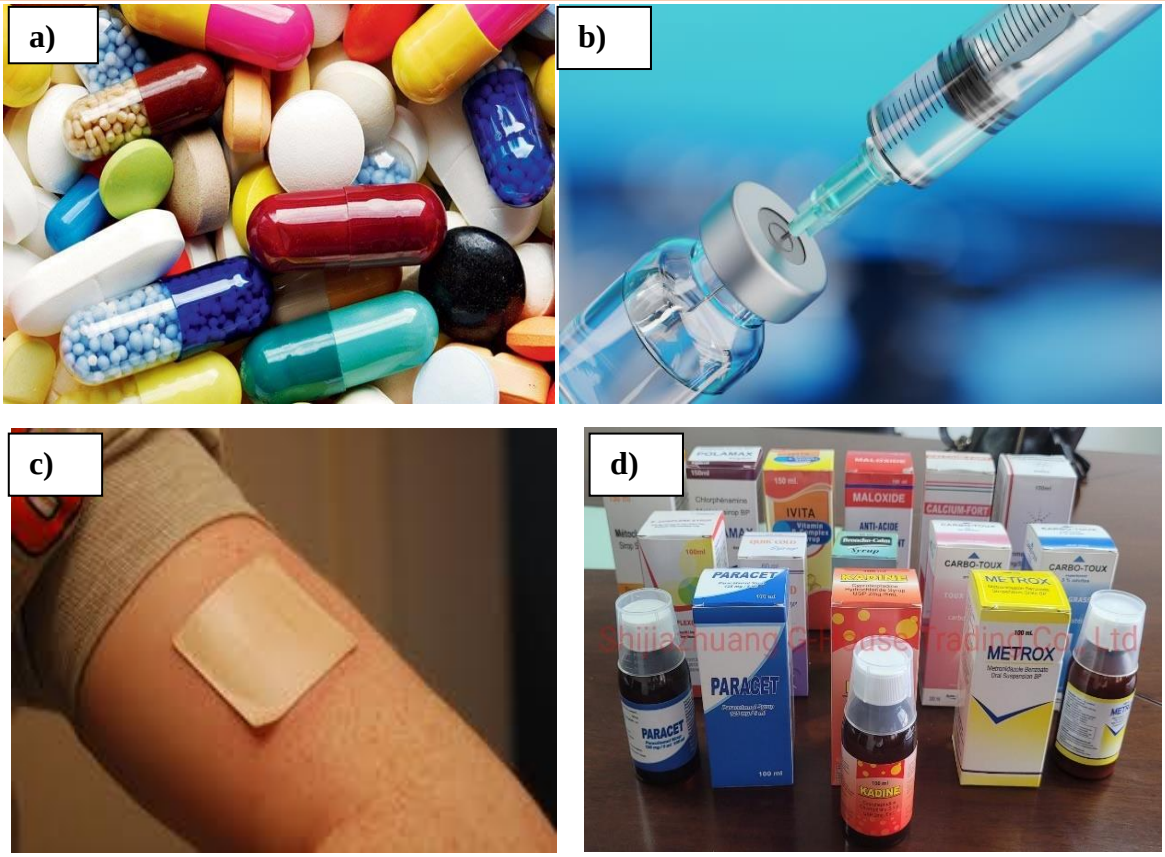


Figure 3: Different pharmaceutical forms

a).Tablets b).Injectable c).Transdermal patch

d).syrup

VI. Routes of drugs administration:

-The process of introducing a medication, liquid, or other substance into the body is known as a route of administration. Usually categorized according to the site of application, these routes can be local (topical, ocular) or systemic (oral, intravenous). While local routes focus on particular regions for localized effects, systemic routes transport medications into the bloodstream for distribution throughout the body **[26-28].**

VI.1.Oral:

The stomach or intestines absorb drugs after they are swallowed. Often used for convenience, but bioavailability is decreased by the first-pass effect. such as Tablets, capsules, syrups .they are easy to administer but they have a variable absorption **[29-31].**

VI.2.Sublingual:

Located beneath the tongue to avoid the GI tract and absorb directly into the blood stream **[30].**

VI.3. Buccal:

Stored within the cheek for oral mucosal absorption **[30].**

VI.4. Rectal:

Given by enemas or suppositories. It helps to partially avoid first-pass metabolism when oral administration is not feasible **[30].**

VI.5. Intravenous Routes (IV)

These include injections and avoid the GI tract: Intravenous **(IV):** Administered straight into a vein for accurate dosage and prompt action Directly into a vein

They have a rapid effect and a precise dosing; But they Requires medical supervision and the risk of infection **[30-31].**

VI.6. Intramuscular (IM):

Injectable into the muscles, such as the buttocks or thighs. Blood flow to the muscle is necessary for absorption. They are known by theirs slower absorption and they are Suitable for large volumes, but they are painful **[30-31].**

IV.7.Subcutaneous (SC):

Injected under the skin for gradual absorption, they are easy to administer, suitable for self-injection,But they have Slower absorption compared to IV **[30-31].**

IV. 8. Intrathecal:

Injected into the spinal canal for central nervous system effects, they have a local effect on the spinal cord but they requires precise methods **[30-31].**

IV.9. Inhalation route:

The drug is inhaled into the lungs and rapidly absorbed through the alveoli, they have a rapid absorption and they are suitable for respiratory conditions but they require specialized equipments **[30-31].**

IV.10. Nasal route:

The drug is administered through the nasal cavity and absorbed through the nasal mucosa, they are rapidly absorbed but they are limited to certain drugs **[30-31].**

IV.11.Topical route:

The drug is applied directly to the skin or mucous membranes for local effects **[30].**they are easy to administer and they have a minimal systemic absorption but they are limited to skin conditions **[31].**

IV.12. Transdermal route :

The drug is administered through a patch on the skin for prolonged systemic absorption **[30].** They offer controlled and consistent administration, improved therapeutic bioavailability, are non-invasive and easy to apply, reduce the risk of under- and overdosing, and are patient-friendly; however, they are limited to specific drugs, may cause skin irritation, have variable absorption rates, limited dose flexibility, higher costs, and face technological limitations **[32].**

IV.13. Vaginal route:

The drug is administered as a cream or suppository and absorbed through the vaginal wall **[30].**they are suitable for treating vaginal conditions but they have limited systemic absorption **[33].**

IV.14.Ocular Route:

Drugs are applied directly to the eye. they have a local effect and a minimal systemic absorption but they are limited to eye conditions **[34].**

VII. Drug delivery systems:

Drug delivery systems, popularly known as controlled-release systems, manipulate the rate, time and duration of drug release in the body. This consequently improves therapeutic efficacy, safety and patient compliance. The description of the most important forms of release is detailed here with scientific references to support it **[42-45].**

VII.1. Immediate-release drugs (IR)

Immediate-release drugs release the active ingredient immediately upon administration. These are typically used for fast-acting drugs. However, that may usually lead to increased peak plasma levels hence increasing the risk of side effects **[42-45].**

VII.2.Sustained-release drugs release:

The active ingredient gradually and continuously over a longer period of time which is usually several hours. They are designed to maintain therapeutic plasma concentrations for a longer period of time so that the frequency of dosing can be reduced. These systems can be classified into two basic categories **[42-45].**

VII.2.1. Repeated or fractionated release

These systems release the active ingredient at multiple time points, thereby maintaining effective plasma concentrations over a longer period of time. Examples include multilayer or dual-core tablets**[42-45].**

VII.2.2. Sustained or time-contoured delivery

In these systems, the drug is made available at several times, thus keeping effective plasma levels continuous for a prolonged period. For example, multilayer or dual-core tablets **[42-45].**

VII.3. Altered release

Sustained-release dosage forms release the active ingredient at specified times or over a specified period of time. These comprise delayed or targeted release systems which release the active ingredient in particular areas of the gastrointestinal tract **[42-45].**

VII.4. Advanced controlled-release systems

These systems utilize several novel technologies for the control of drug release. Some important ones are:

VII.4.1.Osmotic systems: An osmotic gradient powers these systems and allows for constant release rate of the active ingredient. For instance, OROS (Osmotic Controlled Release Oral Drug Delivery System) is designed to release the active ingredient in a controlled manner for a prolonged period of time **[42-45].**

VII.4.2.Bioadhesive systems: These systems utilize active ingredients developed in carriers that adhere to the mucosa, therefore allowing prolonger release at the site of action **[42-45].**

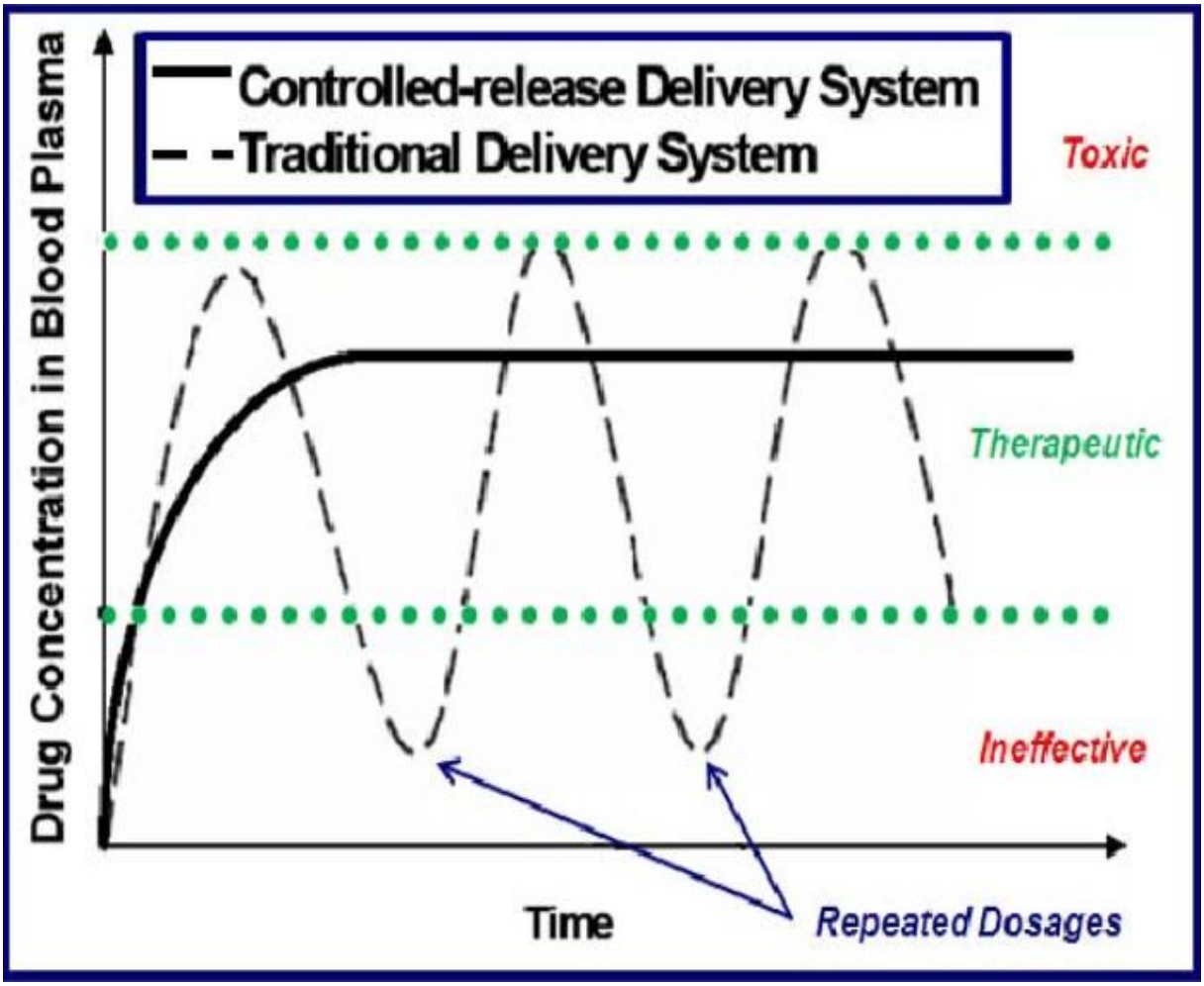


Figure 4: Typical release profiles for controlled-release and traditional drug delivery systems.

References:

[1] Torche, S., & Beroual, K. *Pharmacologie générale*. Institut des Sciences Vétérinaires El Khroub.

[2] Bensegueni Tounsi, L. (2013-2014). *Cours de pharmacologie générale* (3e année Docteur vétérinaire). ISVK Constantine.

[3] Bousquet-Mélo, A. (2007). *Cours de pharmacologie générale*. École Nationale Vétérinaire de Toulouse.

[4] Clark, A. J. (2012). *General pharmacology* (Vol. 4). Springer Science & Business Media.

[5] Aldea-Perona, A. M., Beledo, J. F., Iniesta, J. F., García, A. G., and all. (2024). An account on the history of pharmacology in Spain. *Pharmacological Research*, 107104.

[6] Katzung, B. G., Masters, S. B., & Trevor, A. J. (Eds.). (2004). *Basic & Clinical Pharmacology*. McGraw-Hill.

[7] Wehrlé, P. (2012). *Formes pharmaceutiques et voies d'administration pharmacologie et thérapeutique*. IFSI S1, Faculté de Pharmacie, Université de Strasbourg.

[8] Vercauteren, J. (2011). *Plan formule et illustrations du cours de pharmacognosie*. Université Montpellier I. Laboratoire de Pharmacognosie.

[9] Benyoussef, S., Belguith, J., & Hadiji, R. (2015-2016). *Introduction à l'enseignement de pharmacie* (Cours de Pharmacie & Toxicologie, 2e année DV). École Nationale de Médecine Vétérinaire de Sidi Thabet, Tunisie.

[10] Katzung, B. G. *Basic principles (Introduction)*.

[11] *Article L.5111-1 du Code de la santé publique*, France. Publié le 13/06/2016, mis à jour le 16/03/2022.

[12] Google, J. (2008). *Développement et évaluation de mini comprimés flottants à libération prolongée* (Thèse de doctorat en sciences pharmaceutiques). Université de Bruxelles.

[13] Karolewicz, B. (2016). A review of polymers as multifunctional excipients in drug dosage form technology. *Saudi Pharmaceutical Journal*, 24(5), 525–536.

[14] Chaudhari, S. P., & Patil, P. S. (2012). Pharmaceutical excipients: A review. *International Journal of Advances in Pharmacy, Biology and Chemistry (IJAPBC)*, 1(1).

[15] Bardal, S. K., Waechter, J. E., & Martin, D. S. (2011). *Applied Pharmacology*. Elsevier Health Sciences.

[16] Ordre des pharmaciens du Québec. (2019). *Les différentes formes pharmaceutiques*.

[17] Liguori, Dr. (2016). *Les formes pharmaceutiques*.

[18] *Vidal de la famille* (2012).

[19] *Formes pharmaceutiques et voies d'administration*. IFSI [Mode de compatibilité].

[20] *Dispositifs transdermiques : renforcement de l'information pour améliorer le bon usage* (11/2014).

[21] *Aérosols-doseurs et inhalateur de poudre sèche : 10 idées reçues au banc d'essai*. Vidal.fr (05/2016).

[22] Rang, H. P., Dale, M. M., Ritter, J. M., Flower, R. J., & Henderson, G. (2015). *Rang and Dale's Pharmacology* (8th ed.). Elsevier.

[23] Brunton, L. L., Hilal-Dandan, R., & Knollmann, B. C. (Eds.). (2017). *Goodman & Gilman's: The Pharmacological Basis of Therapeutics* (13th ed.). McGraw-Hill Education.

[24] Golan, D. E., Tashjian, A. H., Armstrong, E. J., & Armstrong, A. W. (2016). *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy* (4th ed.). Wolters Kluwer.

[25] Katzung, B. G., & Trevor, A. J. (2020). *Basic and Clinical Pharmacology* (15th ed.). McGraw-Hill Education.

[26] Academically Global. *Routes of Drug Administration*.

[27] IJPSR. *Routes of Drug Administration*.

[28] StatPearls – NCBI Bookshelf. *Medication Routes of Administration*.

[29] Kwan, K. C. (1997). Oral bioavailability and first-pass effects. *Drug Metabolism and Disposition*, 25(12), 1329–1336. Erratum in: *Drug Metab Dispos* 1998 Mar;26(3):288–9.

[30] IJPSR. (2020). https://romanpub.com/resources/ijpsr%20v11-2020-7.pdf

[31] Gennaro, A. R. (Ed.). (2000). *Remington: The Science and Practice of Pharmacy* (20th ed.). Lippincott Williams & Wilkins.

[32] *Textbook of Pharmaceutical Sciences and Drug Delivery Systems*.

[33] Andrew, S. M., et al. (2009). Vaginal drug delivery systems. *Pharmaceutical Development and Technology*.

[34] Agarwal, S., et al. (2007). Ocular drug delivery systems. *Current Drug Delivery*.

[35] Philippu, A., & Seifert, R. (2023). History of pharmacology: The Institute of Pharmacology of the University of Strasbourg. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 396(1), 19–33.

[36] Ahuja, S., & Scypinski, S. (Eds.). (2001). *Handbook of Modern Pharmaceutical Analysis* (Vol. 3). Elsevier.

[37] Qiu, Y., He, X., Zhu, L., & Chen, B. (2017). Product and process development of solid oral dosage forms. In *Developing Solid Oral Dosage Forms* (pp. 555–591). Academic Press.

[38] Jones, D. H. (2011). *Injectable Fillers: Principles and Practice*. John Wiley & Sons.

[39] Buchheim, R. (1853–1856). *Lehrbuch der Arzneimittellehre* [Textbook of Pharmacology].

[40] Philippu, A., & Seifert, R. (2022). History of pharmacology: 1—the Department of Pharmacology of the University of Tartu (Dorpat): genealogy and biographies. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 396(1), 5–17.

[41] Pokrovskii, M. V., Avtina, T. V., Belousova, Y. V., & Elena, V. V. (2021). Oswald Schmiedeberg – the "father" of experimental pharmacology. *Research Results in Pharmacology*, 7(1), 1–10.

[42] Li, X. – Design of Controlled Release Drug Delivery Systems

[43] Kumar, V. – *Controlled Drug Delivery Systems: Current Status and Future Directions*

[44] Chaturvedi, K. – *The Controlled Drug Delivery Systems: Past Forward and Future Back*

[45] Kesharwani, P. – *Controlled release drug delivery systems: Principles and design*

[46] BOUDENDOUNA Abdel Hakim ,Novembre 2010 ; Méthodologie de la formulation d'une forme orale solide à libération prolongée.,

Chapter II : generality of antibiotics and amoxicillin :

I.Antibiotics :

I.1.Definition :

The word antibiotic is derived from the word antibiosis (i.e. against life). Antibiotics are chemical substances obtained from various microorganisms (bacteria, fungi, actinomycetes) that inhibit the growth of other microorganisms and eventually kill them. The differences between antibiotics may lie in their physical, chemical and pharmacological properties, antimicrobial spectrum and mechanism of action. They are able to cure diseases caused by bacteria such as pneumonia, tuberculosis and meningitis and save millions of lives around the world **[1-2].**

I.2.Types of antibiotics:

There are different families of antibiotics. The most important are beta-lactams (penicillins and cephalosporins), macrolides, aminoglycosides, cyclins, and quinolones **[1-2].**

I.2.1.Beta-lactam antibiotics

I.2.1.a. Penicillin:

Which have long been widely used antibiotics in general medicine. They are divided into different classes according to their range of effects. Type G penicillins are not as effective against bacteria as type A penicillins (such as amoxicillin or ampicillin). Amoxicillin is sometimes combined with clavulanic acid to prevent it from being destroyed by certain bacteria. These antibiotics are effective against a wide range of infections, including respiratory, digestive, urinary, genital, and dental infections, and can be used by pregnant or breastfeeding women. Side effects are rare but can include severe allergic reactions. Drugs from the same family are contrain dicated in case of allergy to penicillin **[1-2].**

Table 01: examples of penicillins with their status

.Re : Reference drug

. Ge : Generic drug

	Medicines	status
Simple Penicillins	AMOXICILLIN ALMUS	**Ge**
	AMOXICILLIN ARROW	**Ge**

AMOXICILLIN ARROW LAB	**Ge**
AMOXICILLIN BGR	**Ge**
AMOXICILLIN BIOGARAN	**Ge**
CLAMOXYL	**Re**
CLOXACILLIN ARROW	**Ge**
CLOXACILLIN BIOGARAN	**Ge**
CLOXACILLIN EG	**Ge**
EXTENCILLINE	**Ge**
ISTOPEN	**Ge**
ORACILLINE	**Ge**
ORBENIN	**Re**

Penicillins with Beta-lactamase Inhibitor	AMOXICILLIN/CLAVULANIC ACID ALMUS	**Ge**
	AMOXICILLIN/CLAVULANIC ACID ARROW	**Ge**
	AUGMENTIN	**Re**
	LEVMENTIN	**Re**

I.2.1.b.Cephalosporins :

Are antibiotics closely related to penicillin (they have a similar mechanism of action). They are divided into three groups: first, second, and third generation. They are taken orally to treat a variety of infections, especially those of the lungs, bronchi, sinuses, throat, ears, and urinary tract. Injectable cephalosporins are mainly for hospital use. They can usually be used during pregnancy and breastfeeding. Cephalosporins can cause allergies, especially in people who are allergic to penicillin **[1-2].**

Table 02:examples of cephalosporins and theirs status:

Medecines	**Status**
ALFATIL	Ge
CÉFADROXIL BIOGARAN	Ge
ALMUS CERPHIXIME	Ge
CERPHIXIME EG	Ge

Orelox	Re

I.2.1.c.Carbapenems :

.These antibiotics are prescription drugs and are only used in hospitals in certain situations. They work against certain bacteria that have become resistant to other penicillins. They are given by injection into a vein **[1-2].**

I.2.2.Cyclatin :

Is an antibiotic that inhibits the synthesis of bacterial proteins. It is active against Chlamydia and Mycoplasma as well as other bacteria that multiply within cells. Infections in these multiples sites are useful to treat respiratory infections, infections of the genital tract, and acne. Doxycycline will also be used to treat malaria a infection. Minocycline may cause severe hypersensitivity reactions and should be utilized only when there are infections malleable to other cyclins. **[1-2].**

Owing to dental hazards, these antibiotics should not be ingested post the fourth month of pregnancy, in kids below 8 years old, or alongside retinoids for acne. They may also induce photosensitization so sun exposure should be avoided. These should be taken with a full glass of water and not while lying down to avert damage to the esophagus. **[1-2].**

Antibiotics : cyclines

Doxy **Ge**

Doxycycline arrow **Ge**

Mynocine **Re**

I.2.3.Aminoglycosides :

These antibiotics are effective against Gram-positive bacteria, especially Staphylococci. They do not actually cross the intestinal wall and are therefore administered by injection. They can be used to treat various infectious diseases,

especially urinary tract and kidney diseases, because they are excreted through the kidneys in active form. This group of antibiotics may have toxic effects on the inner ear or kidneys. These effects are mainly observed in cases of excessively high doses or pre-existing renal insufficiency. **[1-2].**

-Antibiotiques aminosides (Nebcine ;Tobi). **[1-2].**

I.2.4. Macrolides :

These antibiotics work against certain gram-positive bacteria. They are used for infections of the nose, throat, and ears (especially when penicillin cannot be used), as well as infections of the bronchi, lungs, skin, genitals, and mouth. Some macrolides, especially erythromycin, carry a risk of interactions with many common medications. Some macrolides can be used during pregnancy. Their side effects are mainly related to digestion. **[1-2].**

Antibiotiques macrolides : Azdose , Azithromycine arrow lab Ge ,Azithromycine Bgr Ge , Rovamycine , Rulid Re ,Zeclar Re ,Zithromax Re **[1-2].**

Antibiotics macrolides combined with an imidazole:

Birodogyl **Re**

Rodogyl **Re**

Spiramycine metronidazole almus **Ge**

I.2.5.Fluoroquinolones :

Fluoroquinolones have been widely used as effective antibiotics for more than 30 years. Due to the risk of very rare but serious side effects, health authorities restricted their use (oral or injection) to absolutely necessary cases in 2019. This restriction does not apply to creams, ointments or eye drops. Some non-fluorinated quinolones (nalidixic acid, flumequine, pipecolic acid) have been gradually withdrawn from the market because they are considered non-essential **[3].**

Fluoroquinolones are potent antibiotics with grave adverse effects such as pain and rupture of tendons, disorders of muscles and joints, cardiac affections, neuropathy, and disturbances of sleep, mood, memory, and senses. The manifestation can take a period between 2 days up to several months after the end of treatment. However, some patients are more predisposed to these effects; notably elderly patients or those with kidney failure as well as patients receiving corticosteroids. In case of worrying symptoms (pain, palpitations, respiratory difficulties,sensory disorders), a consultation should be done as soon as possible. These antibiotics should not be used in pregnancy or lactation; use in case of risk factors (e.g., aneurysm) should be very careful **[3].**

Ciflox **Re**

tavanic **Re**

I.2.6.Clindamycine :

Antibacterial: prevents bacterial proliferation by binding to bacterial ribosomes and inhibiting protein synthesis **[4-8].**

-Side effects: Allergy**,** Diarrhea (increases risk of C. difficile colitis)

Type : Dalacin 600mg .

I.2.7.Tetracycline : the same mechanism of action of clindamycine **[4-8].**

-Tetracycline PO.

-Doxycycline (Vibramycin) PO.

- Minocycline (Minocin) PO.

-Side effects: Various side effects

- Light sensitivity

- Tooth discoloration and bone damage (do not use in pregnant women and children under 8 years old)

- Digestive system and liver damage

- Damage to the central nervous system (dizziness = minocycline,dizziness = tigecycline)

- Allergies

- Children under 18 years old should not take tigecycline **[4-8].**

I.2.8.Vancomycin :

Oral formulations are not absorbed from the gastrointestinal tract and therefore cannot be used sequentially with intravenous formulations. The only indication for oral medication is Clostridium difficile colitis.

-Bactericidal: destroys bacterial wall primarily by inhibiting bacterial synthesis. Inhibits synthesis of bacterial cytoplasmic membrane. Inhibits synthesis of bacterial RNA. **Type :**Vancomycin (Glycopeptide family) **[4-8].**

-Side effects: Red man syndrome (not allergy, but histamine release)→ Depends on how fast vancomycin is given. Nephrotoxicity , Ototoxicity **[4-8].**

I.2.9.Metronidazole :

Is used to treat C. difficile colitis and as an antiparasitic (flagyl). Because of its low molecular weight, the bactericide diffuses into the germ through the wall and kills it by generating free radicals. The most common side effects include digestive issues and dark urine**[4-8].**

I.2.10.Sulfonamides and Trimethoprim : Sulfonamides are often used in combination with trimethoprim **[4-8].**

-Mode of action : Bacteriostatic: prevents bacterial proliferation by continuously disrupting folate synthesis **[4-8].**

-Most common combinations:

- Trimethoprim/sulfamethoxazole or

-TMP/SMX (Septra, Bactrim) IV/oral

-Side effects: Allergies (most common)**,**Neonatal jaundice**,**Do not use in the last trimester of pregnancy,Digestive disorders **[4-8].**

I.2.11.Linezolid :

Antibacterial: prevents bacterial proliferation by binding to bacterial ribosomes and inhibiting protein synthesis **[4-8].**

Linezolid (Zyvoxam) IV/oral

Oxazolidinones

Side effects: Pancytopenia (most common)**,**Optic nerve damage **[4-8].**

I.2.12.Daptomycin:

Surfactant-inactivated: Do not use to treat lung infections. **[4-8].**According to the Transparency Committee's 2008 opinion, daptomycin is indicated for the treatment of the following infections in adults:

– Complicated skin and soft tissue infections

– Right-sided infective endocarditis caused by Staphylococcus aureus **[9].**

I.2.13.Nitrofurantoin : Diuretic only; concentrated only in the urinary tract, causing diarrhea... **[4-8].**

I.2.14.Fosfomycin: For the treatment of uncomplicated cystitis in women and adolescents **[4-8].**

II/-Amoxicillin :

II.1. Generality:

Amoxicillin is a widely used beta-lactam antibacterial drug that is approved by the U.S. Food and Drug Administration (FDA) for use in primary care. Amoxicillin is an aminopenicillin that counteracts antibiotic resistance by adding an extra amino group to penicillin. This amino group is added to:

– Better penetrate certain bacteria, especially so-called Gram-negative bacteria, which are generally harder to reach.

– Better resist certain bacterial defense mechanisms (such as enzymes called beta-lactamases, which break down classic penicillin**s) [10].**

-Amoxicillin is active against a wide range of Gram-positive bacteria and has additional protection against some Gram-negative bacteria compared to penicillin. The spectrum of activity of amoxicillin includes activity against Streptococcus spp. and enhanced efficacy against Listeria monocytogenes and Enterococcus spp. In addition, amoxicillin is active against Haemophilus influenzae, some strains of Escherichia coli, Actinomycetes spp., Clostridium spp., Salmonella spp., Shigella spp. and Corynebacterium spp. This course provides a detailed overview of amoxicillin's indications, mechanisms of action, usage,

contraindications, and side effects. It provides clinicians with a comprehensive understanding of amoxicillin to enhance their ability to optimally treat their patients' infectious diseases **[10].**

-Approved uses of amoxicillin (according to the FDA):

Amoxicillin is an antibiotic that is officially approved to treat many common bacterial infections, especially when the bacteria do not produce beta-lactamase (an enzyme that makes some bacteria resistant to antibiotics) **[10].**

It is widely used to treat many common bacterial infections :

-Ear, nose and throat infections – such as sore throats, tonsillitis and middle ear infections **[10,11].**

-Stomach and intestinal infections – especially against Helicobacter pylori (a bacteria that can cause ulcers), usually in combination with other medicines **[10,12].**

-Lung infections – including bronchitis and pneumonia **[10,13].**

-Sinusitis – when bacteria invade the sinuses (acute sinusitis) **[10,14].**

-Skin infections – caused by certain bacteria, such as Streptococcus, Staphylococcus or E. coli **[10,15].**

-Urinary tract infections (UTIs) – including cystitis caused by bacteria such as E. coli or Enterococcus **[10,16].**

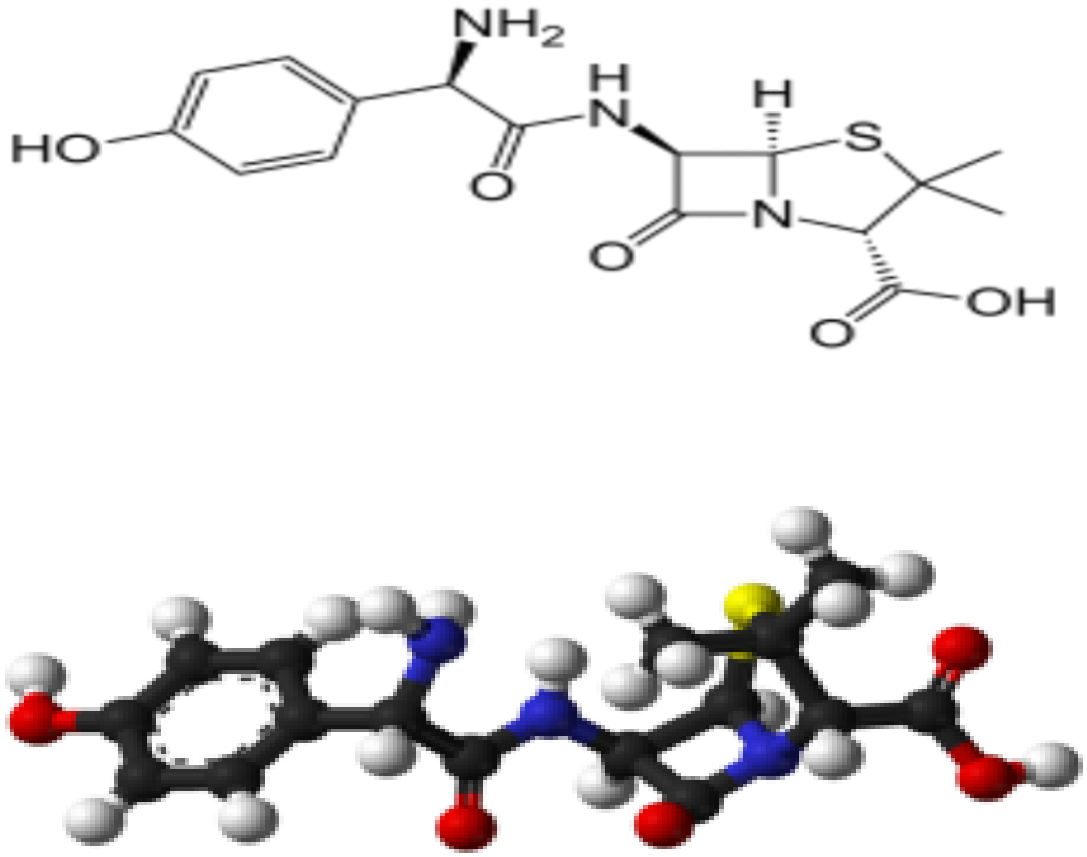


Figure 01: structure of amoxicillin

II.2. Mode of action :

Amoxicillin is a beta-lactam antibiotic. These antibiotics hinder processes necessary for the building of the bacterial wall.

-Details:

-Bacteria have a tough wall to protect them. To build this wall, they use proteins called penicillin-binding proteins (PBPs) **[10,17].**

-Amoxicillin binds to these PBPs, thereby preventing transpeptidation, which allows the cell wall building blocks to cross-link **[10,17].**

-Without these links, the wall becomes weak and unstable. This activates enzymes within the bacteria (autolytic enzymes), which break down the cell wall. The bacteria die **[10,17].**

-This mode of action is called bactericidal (directly kills the bacteria) **[10,17].**

II.3.Resistance and beta-lactamase inhibitors:

Some bacteria have learned to defend themselves against amoxicillin by producing beta-lactamases. This enzyme breaks down the beta-lactam ring of amoxicillin, rendering it ineffective **[10,18].**

Amoxicillin is used in combination with a beta-lactamase inhibitor, such as clavulanic acid or sulbactam.These inhibitors bind irreversibly to beta-lactamases and prevent their action. They themselves are not bactericidal, but they protect amoxicillin so that it remains effective against bacteria that produce this enzyme **[10,18].**

II.4. Pharmacokinetics :

II.4.1. Absorption (how the drug enters the blood): Amoxicillin is resistant to gastric acid, so it is not destroyed when taken orally (as a tablet or syrup).It is quickly absorbed into the blood. Peak blood concentrations are reached about 1 to 2 hours after ingestion **[10].**

II.4.2. Distribution (where the drug enters the body): Amoxicillin diffuses into many body tissues and fluids. Exception: it does not penetrate the brain and spinal cord very well unless the membranes are inflamed (e.g. meningitis). About 20% of amoxicillin is bound to blood proteins (this is moderate binding) **[10].**

II.4.3. Metabolism (transformation of the drug in the body) : Amoxicillin is partially transformed (metabolized) by the following reactions: Oxidation **;**Hydroxylation;Deamination It enters cells via specific transporters, the so-called OAT 1 and 3 (organic anion transporters) **[19-20].**

II.4.4. Elimination (excretion of the active ingredient) : The half-life (the time it takes for half of the active ingredient to be excreted) is about 61 minutes (quite short).About 60% of the dose is excreted unchanged in the urine within 6 to 8 hours. Taking probenecid at the same time will slow down the elimination of amoxicillin. This means that the active ingredient stays in the body longer **[10].**

II.5.Gastro-intestinal release studies of amoxicillin:

Studies have shown that amoxicillin is well absorbed in the duodenum and jejunum, but absorption is reduced in the ileum and almost absent in the colon **[21].** Since the release of amoxicillin is very low or non-existent, studies have been conducted and new formulations have been developed to improve its release in the stomach to treat specific diseases and improve efficacy **[22-23].**

II.6.Reactions of amoxicillin in the body :

II.6.1. Oxidation :

. The liver enzymes (cytochrome P450 among others) modify the molecule of amoxicillin by adding oxygen or removing hydrogen.the Purpose of this reaction is to : Slight modification of the molecule to make it more water-soluble so that it can be excreted through urine **[24-25].**

II.6.2. Hydroxylation :

.This is a type of oxidation; the enzyme introduces an -OH group (hydroxyl group) at a particular position of the molecule, generally on a side chain. This makes the molecule soluble in water and so easy to excrete **[24-25]**.

II.6.3. Deamination :

. An enzyme removes the amine group ($-NH_2$) from the molecule of amoxicillin.This can alter or inactivate the molecule. This reaction of amoxicillin, however, is very rare **[24-25]**.

References:

[1] Alagarsamy, V. (n.d.). *Textbook of Medicinal Chemistry*.

[2] Ilango, K., & Valentina, P. (n.d.). *Medicinal Chemistry Pharm.D*.

[3] Fluoroquinolones et quinolones : restrictions d'utilisation et retrait du marché d'APURONE (fluméquine).

[4] Gilbert, D., et al. (2013). *The Sanford Guide to Antimicrobial Therapy* (43rd ed.).

[5] Association des pharmaciens du Canada. (2007). *Compendium des produits et spécialités pharmaceutiques* (9e éd.).

[6] Mandell, G. L., Douglas, R. G., & Bennett, J. E. (2010). *Principles and Practice of Infectious Diseases* (7e éd.).

[7] Régie de l'assurance maladie du Québec. (2009). *Liste des médicaments*, 23 février.

[8] Versalovic, J., et al. (2011). *Manual of Clinical Microbiology* (10e éd.).

[9] Goehringer, F., & Hénard, S. (2017). Recommandations pour la prescription de Daptomycine (CUBICINâ) au CHRU de Nancy. *Commission du Médicament, CHRU Nancy*.

[10] Akhavan, B. J., Khanna, N. R., & Vijhani, P. (2023). Amoxicillin. In *StatPearls* [Internet]. StatPearls Publishing.

[11] Shulman, S. T., Bisno, A. L., Clegg, H. W., et al. (2012). Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update. *Clinical Infectious Diseases*, 55(10), e86–e102.

[12] Matsumoto, H., Shiotani, A., & Graham, D. Y. (2019). Current and future treatment of *Helicobacter pylori* infections. *Advances in Experimental Medicine and Biology*, 1149, 211–225.

[13] Chow, A. W., Benninger, M. S., Brook, I., et al. (2012). IDSA clinical practice guideline for acute bacterial rhinosinusitis. *Clinical Infectious Diseases*, 54(8), e72–e112.

[14] Rosenfeld, R. M., Piccirillo, J. F., Chandrasekhar, S. S., et al. (2015). Clinical practice guideline (update): adult sinusitis. *Otolaryngology–Head and Neck Surgery*, 152(2 Suppl), S1–S39.

[15] Sartelli, M., Guirao, X., Hardcastle, T. C., et al. (2018). 2018 WSES/SIS-E consensus on skin and soft-tissue infections. *World Journal of Emergency Surgery*, 13, 58.

[16] Tan, C. W., & Chlebicki, M. P. (2016). Urinary tract infections in adults. *Singapore Medical Journal*, 57(9), 485–490.

[17] Bernatová, S., Samek, O., Pilát, Z., et al. (2013). Mechanisms of bacteriostatic versus bactericidal action using Raman spectroscopy. *Molecules*, 18(11), 13188–13199.

[18] Weber, D. J., Tolkoff-Rubin, N. E., & Rubin, R. H. (1984). Amoxicillin and potassium clavulanate. *Pharmacotherapy*, 4(3), 122–136.

[19] Szultka, M., Krzeminski, R., Jackowski, M., & Buszewski, B. (2014). Identification of in vitro metabolites of amoxicillin by LC-ESI/MS. *Chromatographia*, 77(15), 1027–1035.

[20] Peng, J., Ladumor, M. K., & Unadkat, J. D. (2021). Pregnancy-induced changes in renal clearance of drugs. *Drug Metabolism and Disposition*, 49(10), 929–937.

[21] Barr, W. H., Zola, E. M., Candler, E. L., et al. (1994). Differential absorption of amoxicillin. *Clinical Pharmacology & Therapeutics*, 56(3), 279–285.

[22] Grosso, R., & de-Paz, M. V. (2022). Amoxicillin gastroretentive formulations. *Pharmaceutics*, 14(7), 1340.

[23] Lopes-de-Campos, D., Pinto, R. M., Lima, S. A. C., et al. (2019). Targeted delivery of amoxicillin. *International Journal of Nanomedicine*, 14, 2781–2795.",

[24] Szultka, M., Krzeminski, R., Jackowski, M., & Buszewski, B. (2014). Amoxicillin metabolites in human liver microsomes. *Chromatographia*, 77(15), 1027–1035.

[25] Niwa, T., Morimoto, M., Hirai, T., et al. (2016). Penicillin antibiotics and CYP450. *Journal of Toxicological Sciences*, 41(1), 143–146.

[26] Kay, A., Burran, S., & Howell, L. (2018). *General Microbiology*. Dalton State.

[27] Roy, J. (2011). *An Introduction to Pharmaceutical Sciences: Production, Chemistry, Techniques and Technology*. Elsevier.

[28] Kushwaha, A., & Gupta, P. (2023). Amoxicillin: pharmacokinetics and implications. *PEXACY International Journal of Pharmaceutical Science*, 2(6), 42–64.

[29] Walsh, R., Ahmed, S., & Zhang, M. (2020). An overview on amoxicillin: Its indication and side effects. *Journal of Antimicrobial Agents*, 6(2), 1–4.

[30] Malfertheiner, P., Megraud, F., O'Morain, C. A., et al. (2017). Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report. *Gut*, 66(1), 6–30.

[31] Drugwatch. (n.d.). *Amoxicillin – Uses, Dosage, Side Effects and Interactions*. Retrieved from https://www.drugwatch.com/drugs/amoxicillin/

Chapter III :

Experimental part

The present work focused on developing a new formulation or pharmaceutical form of amoxicillin (AMX) for oral administration. This involved combining powdered amoxicillin with two polymers: Ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC), followed by kinetic and microbial studies.

First, we will present the products and materials used, the preparation of tablets using EC and HPMC, and theirs characterizations. Then, we will study the release of the active ingredient from these tablets in two physiological environments: the stomach (pH = 1.2) and the intestine (pH = 7.4). biological test is needed to confirm the kinetics study of AMX%

I. Synthesis:

I .1 Products and Materials used:

I .1.1 Materials used

- Magnetic stirrer.
- Balance
- Spectrophotometre UV-Visible
- pH meter paper
- Beakers
- Volumetric flasks
- Thermometer
- Spatula

I .1.2 Chemical products

- Ethyl cellulose (EC)
- Amoxicillin (AMX)
- Sodium tetra Borate 10 hydrate (Borax)
- Ethanol
- hydroxypropyl-methylcellulose (HPMC)
- Sodium chloride (NaCl)
- chlorhydric acid HCl (36%)
- distilled water

I. 1. 2. a. Ethylcellulose (EC):

Ethylcellulose is a polymer derived from cellulose, which is the main component of plant cell walls (e.g. cotton or wood). It is modified cellulose: some of the hydroxyl groups (-OH) naturally present in the cellulose chain are replaced by ethyl groups (-C_2H_5), which changes its physicochemical properties (semi_crystalline). It (unlike crude cellulose) is insoluble in water.Soluble in organic solvents such as alcohol, chloroform or

Acetone. Non-toxic, biodegradable, biocompatible. Excellent ability to form moisture-proof films. Thermoplastics: moldable or hot-melt **[1].**

Scope:

1. Pharmaceuticals: tablet coatings, sustained-release preparations **[1]**
2. Food: (Additive E462) | Thickener, stabilizer, texturizer **[2]**
3. Cosmetics: thickener in creams, gels, sprays **[3]**
4. Industry: inks, paints, varnishes, plastics

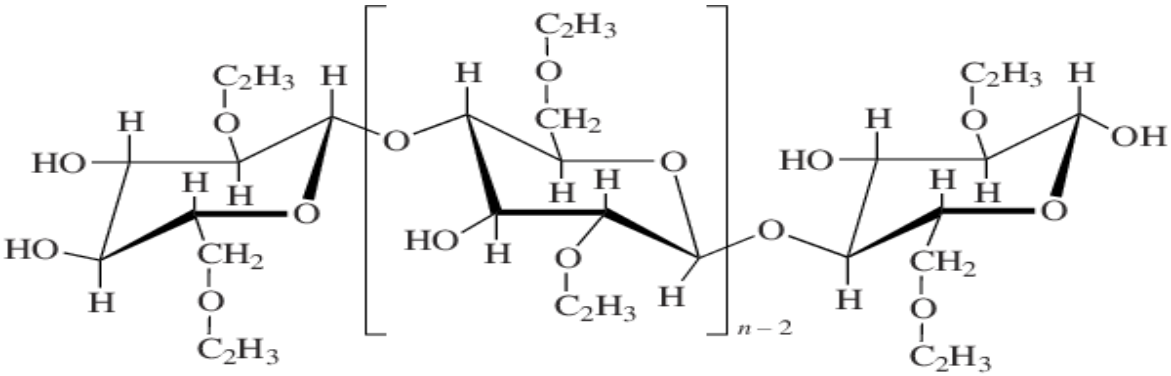


Figure 01: structural formula of ethylcellulose **[4].**

I .1.2 .b. Hydroxypropyl-methyl-cellulose:

Hydroxypropyl methylcellulose (HPMC) or hypromellose is a chemically modified, water-soluble derivative of cellulose (amorphous). It is used in a wide range of industries due to its non-toxicity, biodegradability and versatility. In the pharmaceutical field, it is used as a binder for tablets and eye drops, film coating polymer and controlled release matrix. In food, it is used as a thickener and stabilizer (E464), while in cosmetics and construction, it serves to improve texture, adhesion and water retention. HPMC's molecular weight and substitution degree dictate the characteristics of HPMC, and so it finds versatile application in a number of areas **[5-7].**

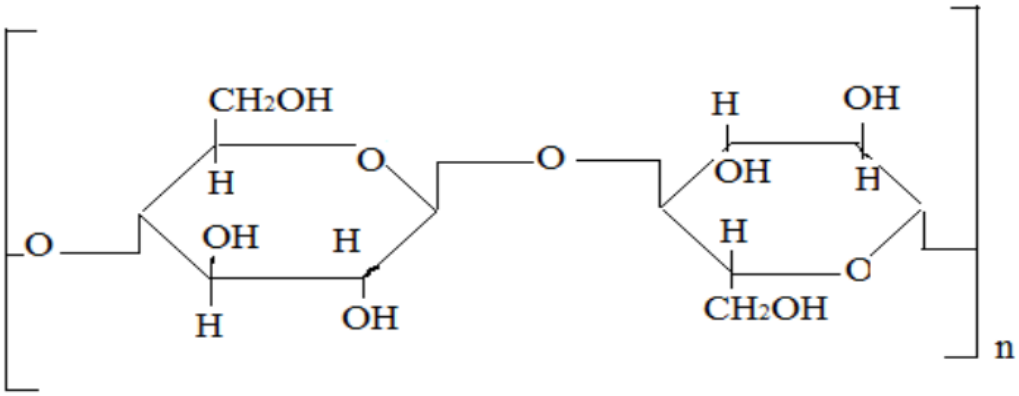


Figure 02: structural formula of HPMC

I.2.Tablets formulation:

I.2.1.Preparing tablets:

We made three different formulations charged amoxicillin (AMX) with two types of polymer; the two first formulations are made by ethyl cellulose (EC) and amoxicillin (with different masses and the 3rd formulation is made by the combination of the two polymers EC and hydroxypropyl-methylcellulose (HPMC) with AMX , a drops of Ethanol was added to the powders to produce a homogenous mixture and molded with some starch to produce the final tablets .

Table 01: The different formulations were presented in the next table

Tablet	Weight (before drying)	Weight (after drying)	Yield (%)
T1:0.2g(EC)+0.1g(AMX)	0.40g	0.29g	96.67%
T2:0.15g(EC)+0.15g(AMX)	0.44g	0.31g	98%
T3:0.15g(EC)+0.05g(HPMC)+0.1g(AMX)	0.46g	0.31g	98%

Figure 03: Tablets formulated T1, T2 and T3

II. Study of the kinetics of the release of the active principle in ph=1.2 and ph=7.4:

The release of the active ingredient is carried out in two ph environment (1.2 stomach and 7.4 intestines) ,monitored by UV-vis spectrophotometer at a specific wavelength corresponding to the active principle's maximum absorption **λmax** (AMX), in order to determine the percentage of the liquid absorbed in each ph environment and deduce where is the best liberation environment of ph and the influence of polymers about this liberation **.**

The aim of this kinetic study is to compare the effects of sustained and controlled release of the active ingredient through different polymer matrices. In other words, the aim is to

analyze how different polymer formulations can affect the speed and duration of drug release over time, to optimize its therapeutic efficacy.

When the drug is dispersed alone in the polymer matrix, it is released into the body by diffusion through the polymer matrix. 3 factors influence this release process:

1. **The speed of penetration of the liquid into the dosage form**: this refers to the speed with which the liquid (body fluid) penetrates the polymer matrix surrounding the drug (rapid penetration = accelerated release).
2. **The speed of dissolution of the active ingredient in the trapped liquid:** once the liquid has penetrated the polymer matrix, the PA (AMX) must dissolve in the liquid to diffuse.
3. **The diffusion of the active ingredient through the polymer matrix:** once the drug has been dissolved in the liquid, it must diffuse through the polymer matrix to leave the system and be released into the body, and this depends on the structure and nature of the polymer, as well as the solubility of PA.

II.1 Factors influencing material transfers:

➢ **Medium stirring speed**

The concentration of the solution should be uniform at all points in the solution. This uniformity is maintained thanks to the action of a magnetic stirrer (rotation speed fixed at 750 r.p.m for all experiments).

➢ **The temperature of the medium**

The influence of temperature is very important in diffusion phenomena (the solubility of the active ingredient and diffusion). All our experiments were carried out at constant temperature 37°C (human body temperature), using a heating stirrer.

➢ **The nature of the medium, pH and volume**

- The nature of the environment influences the solubility of the active ingredient, which will influence the diffusion.
- The pH of the medium influences the rate of hydrolysis and the solubility of the active ingredient.
- The volume of the medium influences on the one hand the solubility of the active agent, and on the other hand its mass released at infinite time (equilibrium time).

➢ **"Non-sink" method:**

Where the chosen volume (100 ml) is used for the entire experiment. The concentration of the active ingredient increases during the experiment.

➢ **“Sink” method:**

.The volume is constantly renewed by virgin liquid, the volume used is therefore greater.

The first method (non-sink) is much easier to perform, and it is this method that we used in all our experiment

II.2.Composition of the pH study environment:

For our study of kinetics we have prepared two ph environment pH=1.2 which is the stomach environment and pH=7.4 which is determined by the intestine part of the organism at a temperature of 37°c (the temperature of the human organism) and this study is controlled at a long time with collecting samples and take the mass at each time of the disc, then controlled by uv-vis spectrophotometer to read absorbance at each time.

- **Gastric medium pH = 1.2:**

HCl: 1N 80ml, NaCl: 2g, Distilled water: 1l

- **Intestinal environment of pH = 7.4:**

HCl: 0.1N (20ml), Borax (sodium tetra borate 10 hydrate): 0.025N (500ml), Distilled water: (1 liter)

.This parameter (pH and T) will allow us to the effect or the influence of the matrix and the ph environment on kinetic of the release of the active principle (AMX) from the different formulations made.

II.3. Calibration curve of AMX:

The aim of this step is to determine ε of the beer-lambert rule after drawing the calibration curve of the active ingredient in each ph (1.2 and 7.4) using the method of preparing a stock solution with PA and making a series of dilutions after reading the absorbance in the UV visible spectrophotometer (with known concentrations).

From the Beer Lambert relation we thus establish the calibration line representing the optical density, at maximum of the absorption band, depending on the concentration.

$$A = \varepsilon . C . l$$

A: Absorption
ε: Specific absorption coefficient (L. mol-1.cm-1).
C: The concentration in mol/L of the solution.
L: The length of the quartz cell (1cm).

II.3.1.Determination of the maximum wavelength for both pH by UV Vis:

The active principle spectra were carried out on the Perkin Elmer LAMBDA 25, 35, & 45 UV/Vis Spectrophotometers spectrophotometer in two ph environment (pH=1.2and 7.4) in the chemistry laboratory at the University of Belhadj Bouchaib Ain Temouchent ,the wavelength are expressed in (nm) and respectively are :230 nm and 280 nm.

Figure 04: Perkin Elmer LAMBDA 25, 35, & 45 UV/Vis Spectrophotometers

a) **b)**

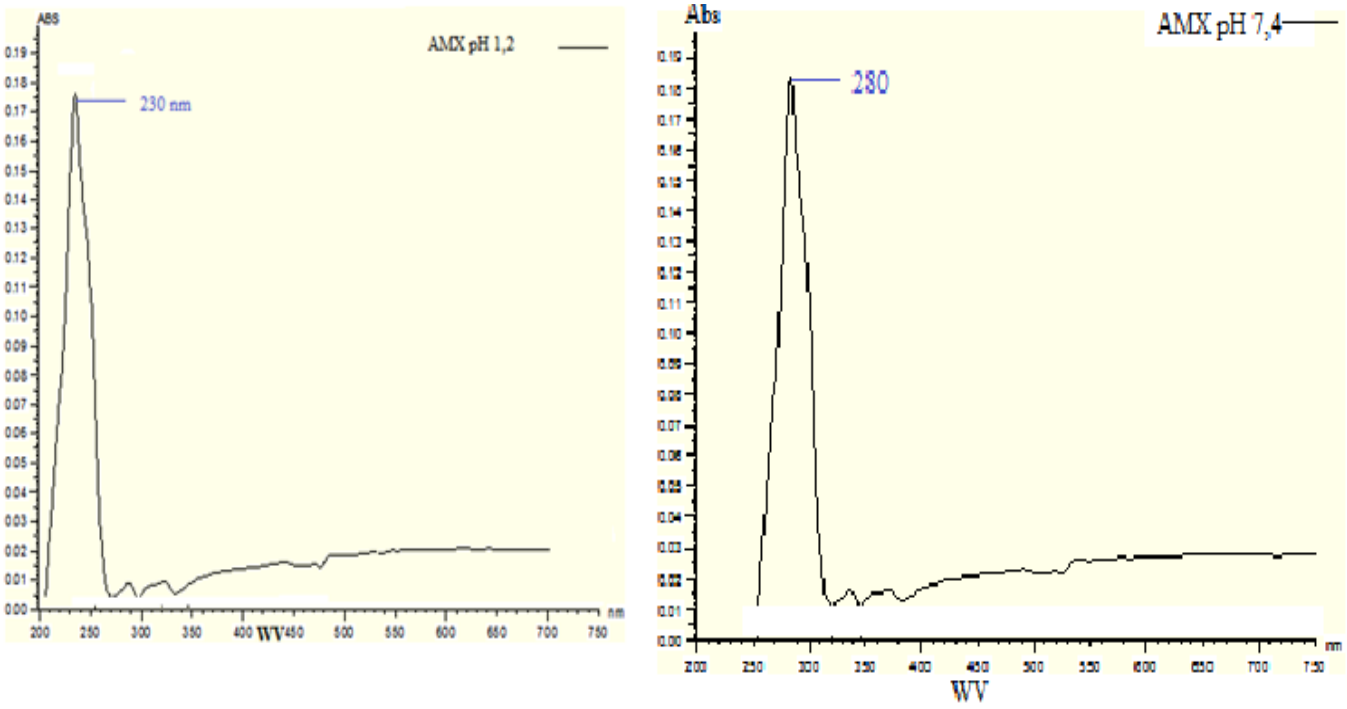


Figure 5: a) Maximum wavelength **pH 1.2**; **b)** Maximum wavelength **pH 7.7**

II.3.2.Amoxicillin calibration curve at pH=1.2 :(λmax=230nm)

Table 02: The dilutions different concentrations amoxicillin in 50 ml of pH=1.2 (230nm)

C (Mg/L)	0	0.001	0.0008	0.0006	0.0004	0.0002
Abs (nm)	0	0.182	0.14	0.11	0.0754	0.0328

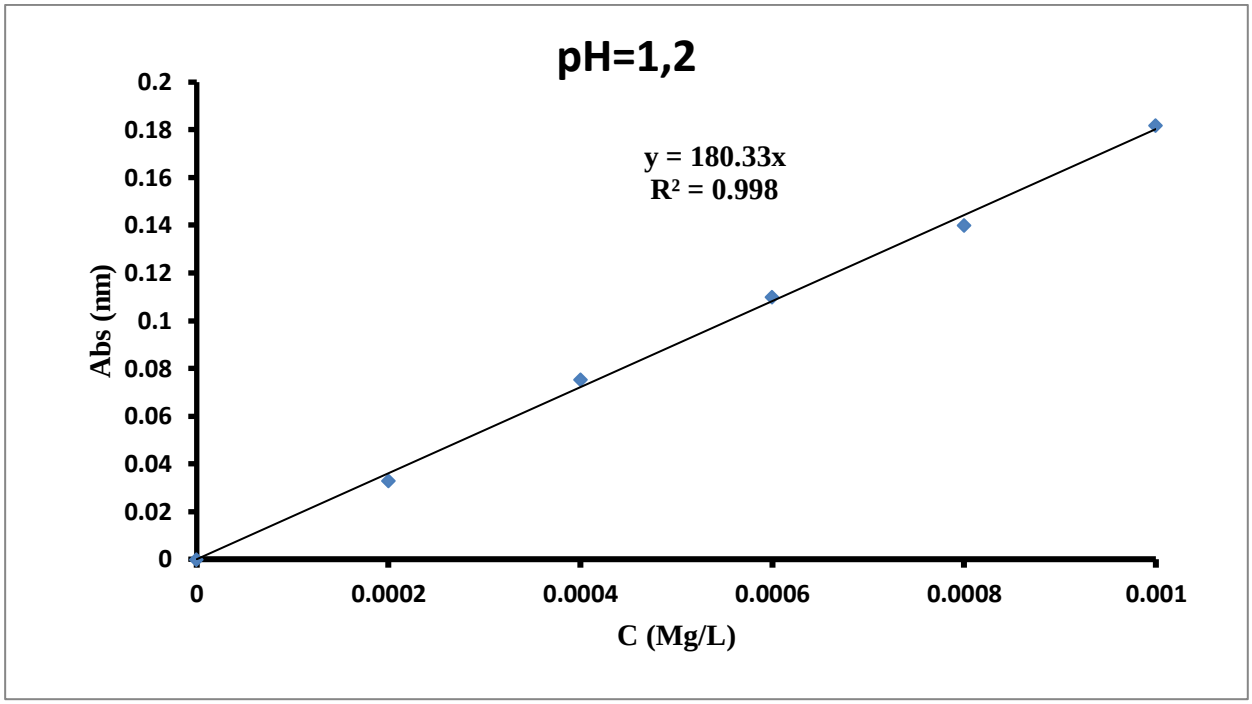


Figure 06: Calibration curve of amoxicillin at pH=1.2 (230 nm)

II.3.3.Amoxicillin calibration curve at pH=7.7: (λmax=280nm)

Table03: The dilutions different concentrations amoxicillin in 50 ml of pH=7.7(280nm)

C(Mg/l)	0.001	0.0008	0.0006	0.0004	0.0002
Abs(nm)	0.256	0.2	0.158	0.1	0.05

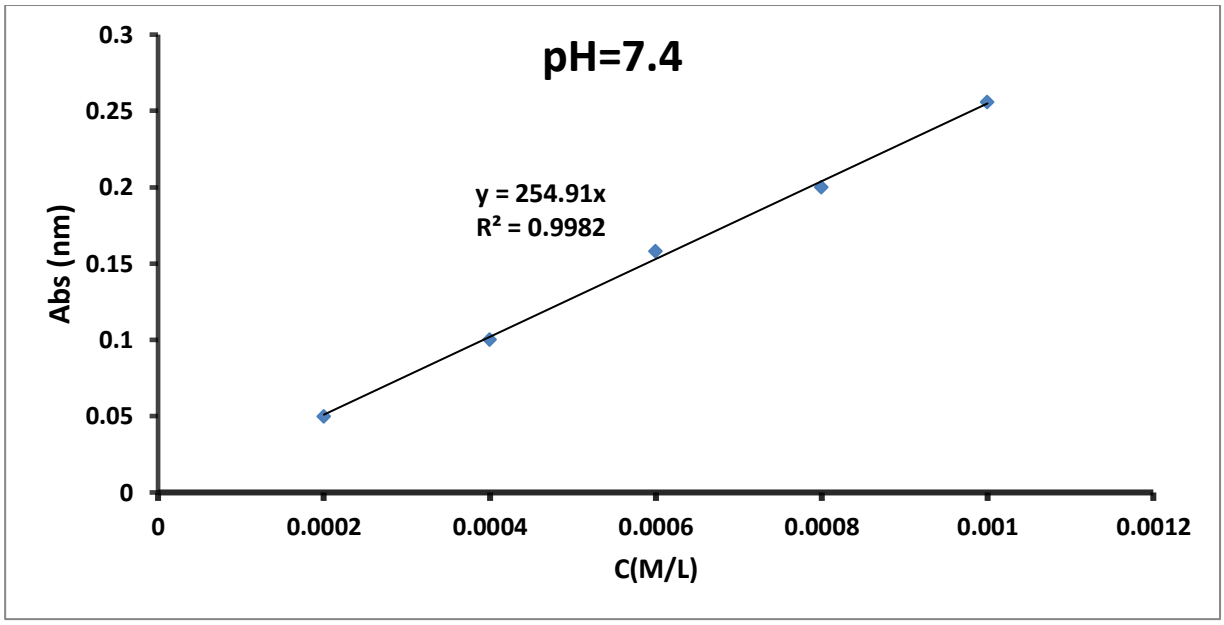


Figure 07: Calibration curve of amoxicillin at pH=7.7(280nm)

.The line being Linear A= f (c); its slope at the origin corresponds to Ɛ max

Table 04: Represents the values of λ max and Ɛ max of amoxicillin in the different media

Active substance	Ph medium	λ max (nm)	Ɛmax (L.mol-1 .cm-1)
Amoxicillin	1.2	230	180,3
	7.4	280	254,9

Under UV irradiation, amoxicillin undergoes photochemical degradation, which is influenced significantly by the pH of the medium. UV light, can excite electrons in chemical bonds, especially π-bonds (double bonds) and lone pair electrons on heteroatoms. In the case of amoxicillin, the β-lactam ring, phenol ring, amide, and amine groups are particularly sensitive to UV-induced excitation and breakdown.

In an acidic medium (pH 1.2), amoxicillin is chemically unstable even without light, due to the susceptibility of its β-lactam ring to acid-catalyzed hydrolysis. When exposed to UV light, this instability is amplified. The β-lactam ring contains a strained four-membered cyclic amide, whose C–N bond is weakened under acidic conditions and even more reactive when excited by UV. The light provides the energy needed to break this bond, leading to ring opening and loss of antibiotic activity. Additionally, the aromatic ring in the amoxicillin structure can undergo photo-oxidation, especially through excitation of the π→π* transitions in the benzene ring. As a result, in pH 1.2 under UV light, amoxicillin rapidly degrades, forming products like penicilloic acids and other photolytic fragments that no longer exhibit antibacterial properties.

In contrast, in a neutral or physiological medium (pH 7.4), amoxicillin is more chemically stable, and the degradation caused by UV light is less aggressive. However, UV light can still initiate photochemical reactions. At this pH, the phenolic hydroxyl group, primary amine, and carboxylic acid groups are mostly ionized, affecting the molecule's overall reactivity and electronic configuration. The aromatic ring remains the most UV-sensitive site, and photolysis can still occur via $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, especially involving the C=C and C=O bonds. Although the β-lactam ring is less prone to hydrolysis at pH 7.4, it can still be affected by prolonged UV exposure, leading to partial loss of activity. However, the overall degradation is slower and less severe than in acidic conditions.

Generally, amoxicillin degrades much more rapidly under UV light in acidic media, mainly due to acid-facilitated cleavage of the β-lactam C–N bond and UV-induced excitation of the aromatic π-bonds. In a neutral medium, UV degradation still occurs, primarily affecting aromatic and carbonyl groups, but at a slower rate. These reactions result in structural modifications that reduce or eliminate the antibiotic function of amoxicillin, highlighting the need to protect such drugs from UV exposure, particularly in acidic environments.

II.4. Measurement conditions:

The kinetics method is performed under the following conditions:

- Preparation of disks of different formulations (as we have already done).
- The disc support is a glass fiber with a magnetic stirrer to homogenize the mixture around a galenic form.
- Temperature (37°c) and agitation (500 r.p.m).
- The initial volume of the bottle is 100ml and the sampling tubes 1ml in each time taken.
- Absorbance measurement with a visible uv spectrophotometer at maximum wavelength.

II.5. Kinetics of AMX release from tablets:

II .5 .1 Experimental methods:

.We placed the 500ml bottle in a water bath and fill it with 100ml of pH solution (either 1.2 or 7.4) using a magnetic stirrer and set the temperature 37°C and stir at 500 r.p.m. At each time "t" the disk is removed from the bottle, then weighed, and at the same time a volume Vp = 1mL of the liquid medium is taken. The volume taken diluted by a dilution volume Vd =10ml of the same physiological medium. The density optical (OD) is then determined by UV for each sample.

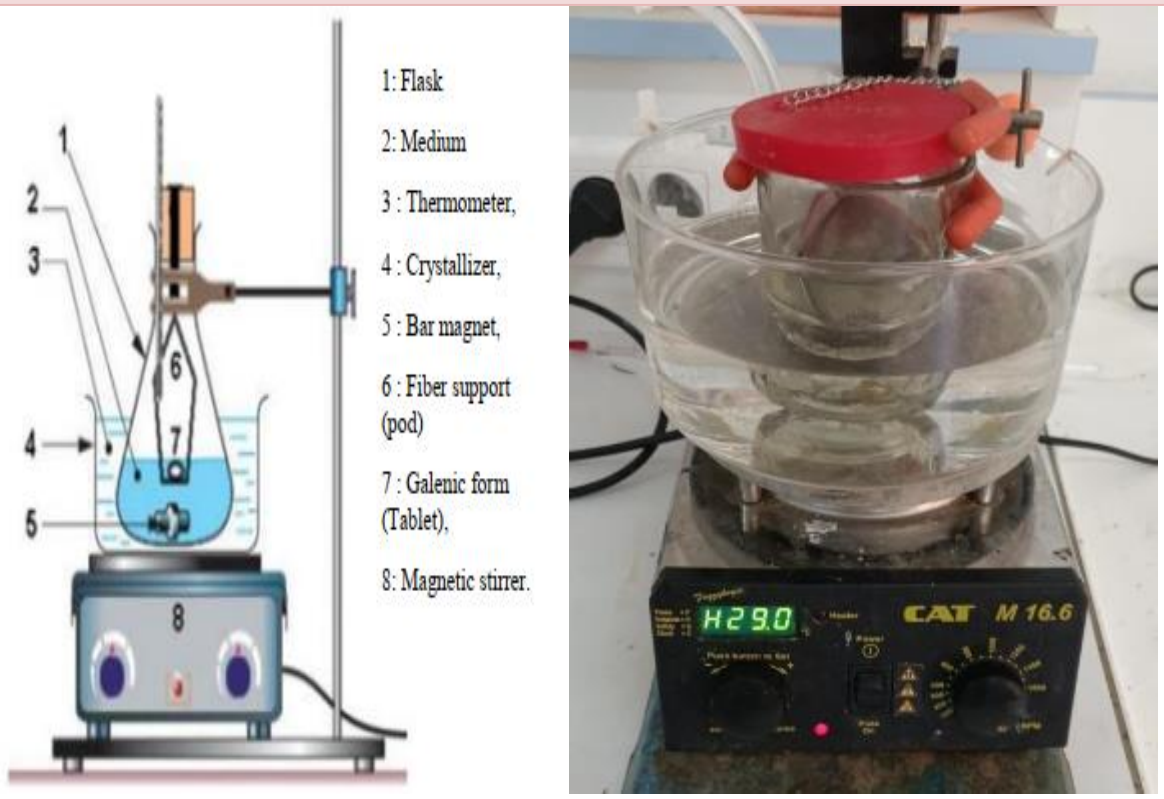


Figure 08: Experimental device for drug release from tablets

II .5 .1.a. The rate of PA released

.The rate of PA released is therefore calculated in relation to the real mass of active agent according to the following relationship:

$$\%PA = (mt/mi).100$$

$$mt = D.O \cdot Vd \cdot M / \varepsilon.Vf$$

mt: The mass of active ingredient at time "t"
mi: Initial mass of the active ingredient**.**
Vd: The volume of the dilution flask in ml
Vf: The volume of the release liquid contained in the bottle in ml
M: The molar mass of the principle of the active ingredient (g/mol)

II .5 .1.b Calculation of the quantity of liquid absorbed by the dosage form:

The quantity of liquid absorbed by the "Tablet" dosage form is calculated by the classic "weight monitoring" method. To calculate the mass of the absorbed liquid (mt'), we apply the following equation:

$$mt = mt' - m0$$

mt : mass of liquid absorbed by the galenic form at time "t"
mt ' : mass of the galenic form at time "t" of weighing
m0: initial mass of the "dry" dosage form.

The percentage of liquid absorbed by the dosage form is calculated relative to the initial mass of the dosage form.

% liquid abs = (mt/m0).100

II .5.2 Study of amoxicillin release:

The PA release kinetic curves illustrate the quantity of PA released as a function of time in the environment pH 1.2 and pH 7.7
The graph presents the release kinetic curves of 3 different systems:

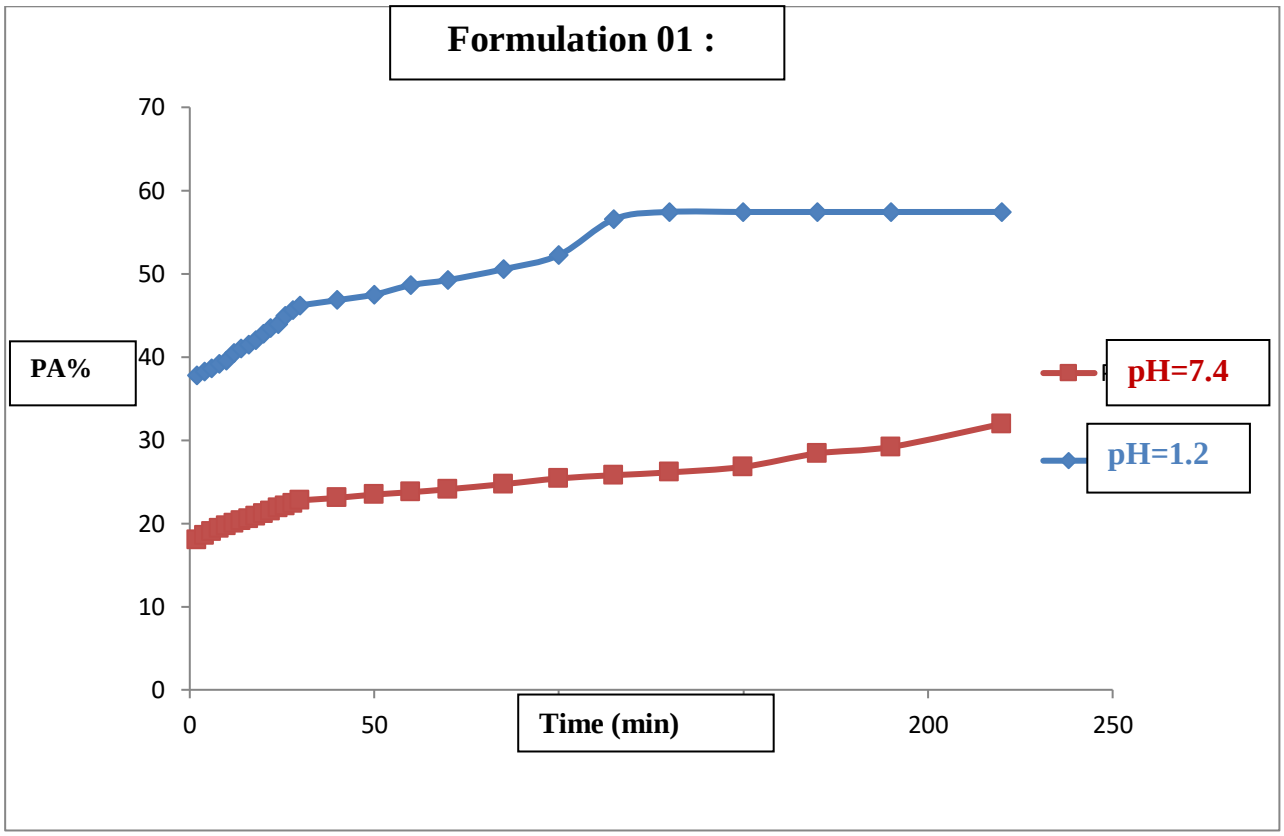


Figure 09: T1% active ingredient amoxicillin released as a function of time at pH=1.2 and pH=7.4 (T=37°c and 500 r.p.m)

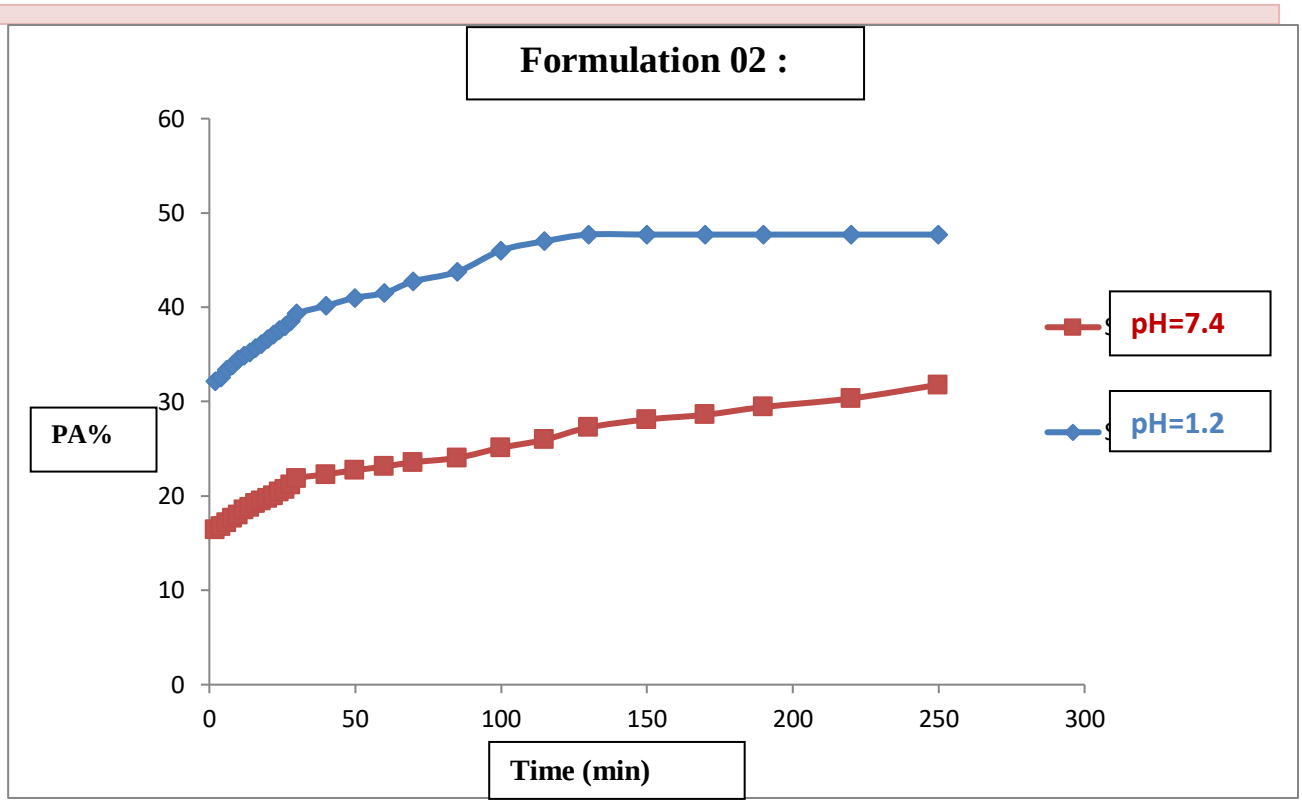


Figure 10: T2 % active ingredient amoxicillin released as a function of time at PH=1.2 and PH=7.4 (T=37°c and 500 r.p.m)

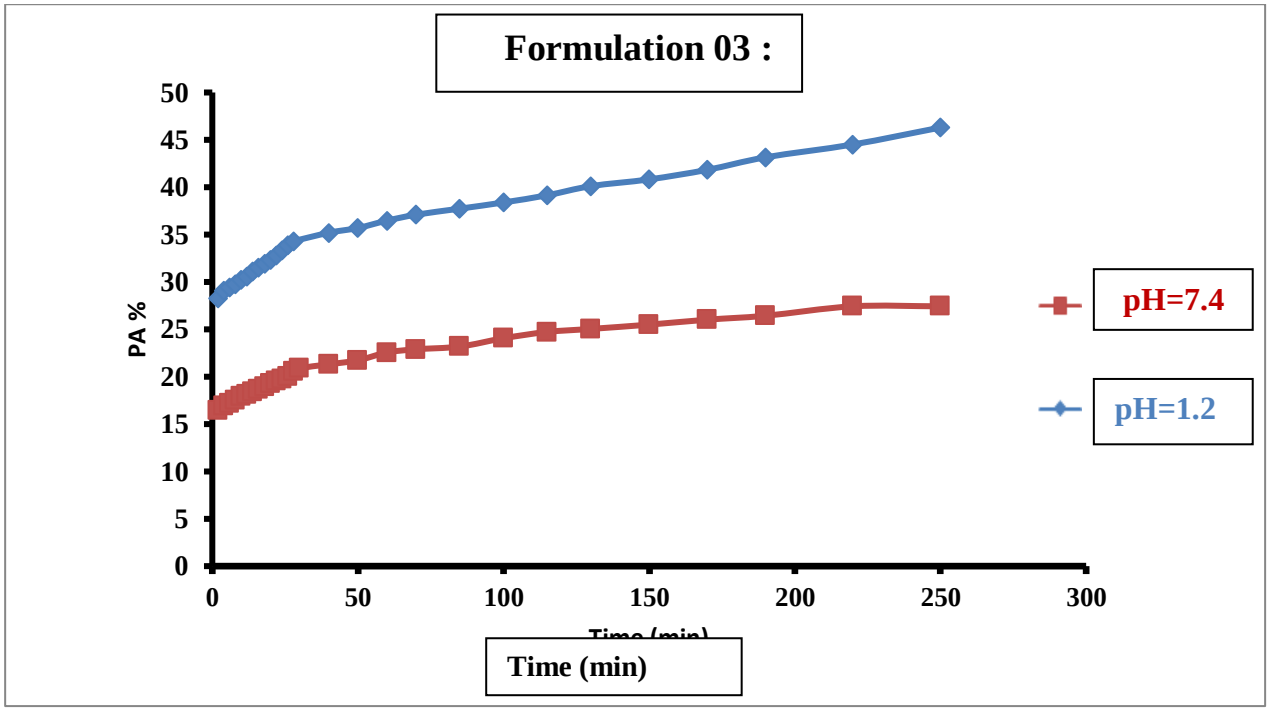


Figure 11: T3 % active ingredient amoxicillin released as a function of time pH=1.2 and pH=7.4 (T=37°c and 500 r.p.m)

II.5.3.Interpretation of the results of the AMX kinetic study in the two PH (1.2 and 7.4) media:

In our study, we observed that all three formulations showed **a** higher release of amoxicillin (AMX) in acidic medium (pH 1.2) compared to the neutral/basic medium (pH 7.4). This pH-dependent release makes sense because AMX is more soluble in acidic conditions, and the polymers we used especially ethylcellulose (EC) respond differently depending on the pH**.** In all formulations, the release followed a classic pattern: a fast release at the beginning, followed by a gradual decrease, which indicates that diffusion through the polymer matrix is the main factor controlling release**.**

When the tablet comes into contact with the surrounding medium, the liquid penetrates the polymer matrix and dissolves the AMX. Because AMX has moderate water solubility and isn't present in a high concentration in our system, it dissolves fairly quickly. Once dissolved, the drug diffuses through the polymeric structure into the medium. But the efficiency of this process depends heavily on the amount of polymer and drug used in each formulation.

Take Formulation 1 (0.2g EC + 0.1g AMX)**,** for example. Here we used a higher amount of EC, which created a thicker matrix, but the release was still good in acidic pH up to 57.42%, suggesting that even with more polymers, the drug was still able to diffuse effectively because of the swelling behavior of EC in acidic conditions and the balance we maintained with drug content. Then in Formulation 2 (0.15g EC + 0.15g AMX)**,** we increased the drug load and reduced the polymer. This led to slightly lower cumulative release (47.71%), which could be because the higher drug content may have saturated the matrix early, slowing down further diffusion as time passed.

Then we have Formulation 3 (0.15g EC + 0.05g HPMC + 0.1g AMX), where we added HPMC (Hydroxypropyl Methylcellulose)**.** That clearly affected the release pattern. HPMC is a hydrophilic and pH-sensitive polymer, and in acidic conditions, it forms a gel layer that swells slowly and creates a barrier to drug diffusion. This is likely why the release in this case was the lowest in pH 1.2 (46.29%) compared to the other two. And at pH 7.4, the release was even more limited (27.42%), probably because of AMX's lower solubility in neutral/basic conditions, combined with the thicker gel formed by HPMC, which further slowed down drug movement.

HPMC behaves quite differently based on the pH: in acidic media, it swells more slowly, forming a compact gel that delays the release. In a more basic environment like pH 7.4, it hydrates faster, but the higher viscosity of the gel and lower solubility of AMX still prevent fast release. So, when we added HPMC, we achieved a more controlled and sustained release, which could be useful for specific cases where we want extended drug action or delayed release**.**

But beyond just release, we also have to consider how AMX behaves under UV , since our formulations were tested for photostability. AMX contains a β-lactam ring, an aromatic ring, and amide groups, all of which are sensitive to UV . Under acidic conditions (pH 1.2), AMX becomes highly unstable under UV exposure**.** The β-lactam ring can break down quickly, especially under both acid hydrolysis and photodegradation, resulting in loss of activity. The

UV light excites π bonds and lone pairs, especially in the C–N bond of the β-lactam ring and C=C bonds of the aromatic ring, which makes it easier for the drug to degrade.

At pH 7.4, AMX is relatively more stable, but UV still causes partial degradation, mainly through oxidation of the aromatic and amide groups. So even though the drug doesn't break down as fast as it does in acidic conditions, prolonged UV exposure still reduces its activity. That's why the choice of polymer—and its ability to protect the drug from light—is very important. A higher polymer content or the use of polymers like HPMC, which form a thicker gel or barrier, could help reduce the exposure of AMX to light, adding some degree of photo protection.

In general, we saw that the amount of polymer and drug really determines how the tablets behave. More polymer usually means slower diffusion, but if the ratio is balanced, we can still get high release in the right conditions. More drug might increase early release but doesn't always mean higher total release in the end. And adding HPMC helps create a controlled-release system, ideal for longer-acting drug formulations.

All three formulations were clearly better for gastric (stomach) delivery, especially Formulations 1 and 2, which released AMX more quickly in acidic pH. Formulation 3, with HPMC, gave us a slower and more controlled release, which could be really beneficial when we need extended drug action. At the same time, we have to consider UV stability, especially in acidic environments where AMX degrades more quickly—meaning our formulation strategy can also help protect the drug and improve its shelf life.

II .5.4.Liquid absorption

During the dissolution process, we observed that the tablet undergoes a swelling phenomenon (gonflement) when it comes into contact with the dissolution medium—whether it's acidic (pH 1.2) or basic/neutral (pH 7.4). This swelling is a critical part of the release mechanism, as it affects how water enters the tablet, how the drug dissolves, and how it diffuses outward.

The extent and behavior of swelling depend heavily on the type of polymer used in the formulation. In our case, we used ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC), each of which reacts differently in acidic and basic environments.

In acidic medium (pH 1.2), the swelling of EC is relatively limited but sufficient to allow water penetration and initiate drug diffusion. EC is a hydrophobic polymer, so it doesn't dissolve in water but it does absorb water and expand, forming a porous matrix**.** This allows the medium to slowly penetrate, dissolve the amoxicillin (AMX), and then permit its diffusion. The swelling here is slower and less intense, but still effective enough to support a steady release, especially because AMX is more soluble in acidic conditions.

When HPMC is present like in Formulation 3 the behavior is different. In acidic conditions, HPMC swells slowly due to lower ionization of its functional groups, forming a dense gel layer on the tablet surface. This gel controls the movement of water into the core and slows down the outward diffusion of AMX. The result is a more controlled, sustained release. The

swelling of HPMC in acid is more compact and forms a stronger barrier, which explains why this formulation released less AMX than the others.

In basic or neutral medium (pH 7.4), we see a more pronounced swelling, especially for HPMC. At this pH, the ionization of hydroxyl and methoxyl groups in HPMC is higher, leading to faster water uptake and the formation of a thicker, more expanded gel layer. This increased swelling could allow more water to reach the drug, but in our case, the overall drug release was still lower. That's likely because AMX is less soluble at pH 7.4, so even though swelling is higher, the amount of drug dissolving and diffusing remains limited.

For EC in basic medium, swelling still occurs but is **not** significantly different from acidic conditions, since EC does not rely on pH for its swelling behavior it simply hydrates slowly regardless of pH. However, the combination of slower drug solubility at pH 7.4 and the hydrophobic nature of EC mean fewer drugs are released overall.

Swelling starts with water penetrating the outer layer of the tablet, causing the polymers especially HPMC to hydrate and expand**,** forming a gel. In acidic medium, swelling is slower and tighter, supporting a more controlled release. In basic medium, swelling is faster and more extensive, but that doesn't always lead to higher drug release, especially if the drug (like AMX) isn't very soluble at that pH. The nature and amount of the polymer, combined with the medium's pH, directly influence how much the disc swells, how fast it releases the drug, and how effectively the drug diffuses out**.**

At the same time as the 1mL samples are taken to determine the quantity of AMX released, the tablets removed from the liquid have been weighed beforehand, and the mass of the tablet immersed in the liquid is obtained. Some values are classified in the table5.

Table 05: %liquid absorbed in all Tablets (T1, T2, T3) as a function of time at pH=1.2 at T°=37°C.

	Time (min)	2	14	30	60	250
Liquid %	**T1**	4,54545	13,63636	18,18181	18,18181	22,72727
	T2	3,7037	3,7037	7,4074	11,11111	14,8148
	T3	17,24137	27,58620	27,58620	31,03448	34,48275

According to the table 5 , we observed that the Tablet T3 absorbs more liquid than T1 and T2 at all time points.

- At just 2 minutes, T3 has already absorbed **~17%**, while T1 and T2 remain below 5%.
- By 250 minutes, T3 reaches **~34.5%** absorption, which is notably higher than T1 (~22.7%) and T2 (~14.8%).

T1 contains only EC and AMX, and EC (ethyl cellulose) is hydrophobic and water-insoluble. However, it can swell moderately in an acidic environment, allowing for some liquid absorption and diffusion of AMX.

Though T2 has the same components as T1, the higher proportion of EC (relative to AMX) may contribute to lower porosity or slower liquid penetration, thus limiting absorption. EC forms a denser matrix, reducing fluid intake.

The highest absorption on T3 due to the presence of HPMC. HPMC is hydrophilic and has strong water-absorbing and gel-forming capabilities, which increase water uptake and swelling. This behavior can form a gel barrier, controlling the drug release rate.

III.Characterization part:

III.1.FTIR spectrums:

III.1.1.FTIR characterization of AMX: the following figure represents the IR spectrum of AMX:

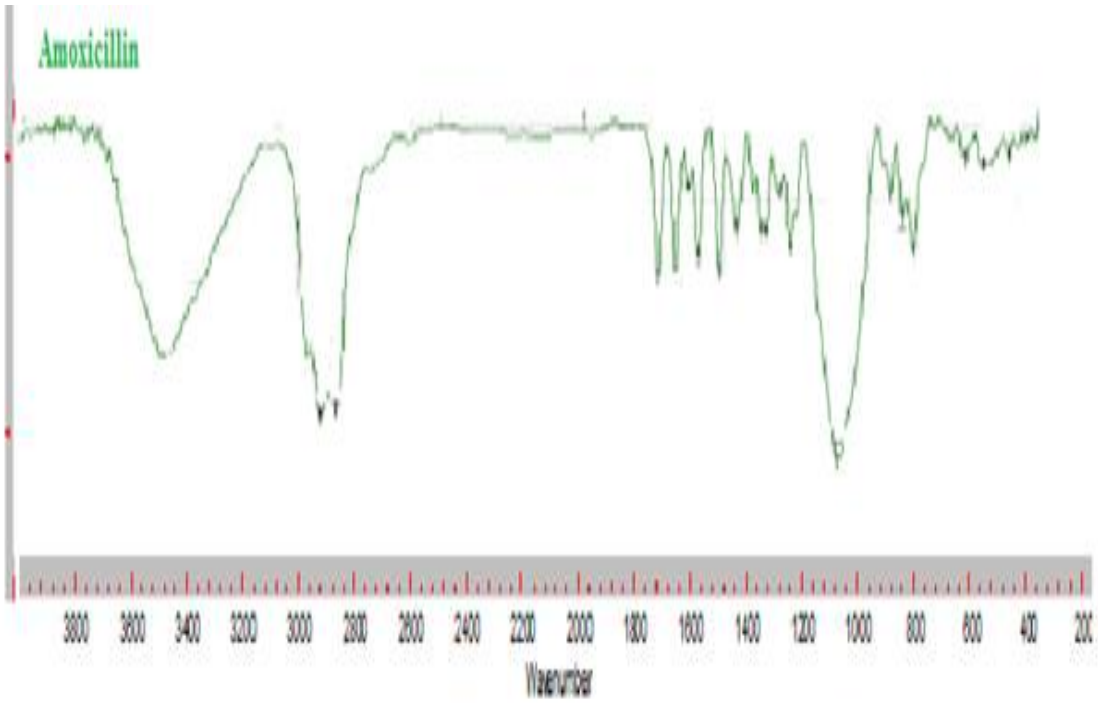
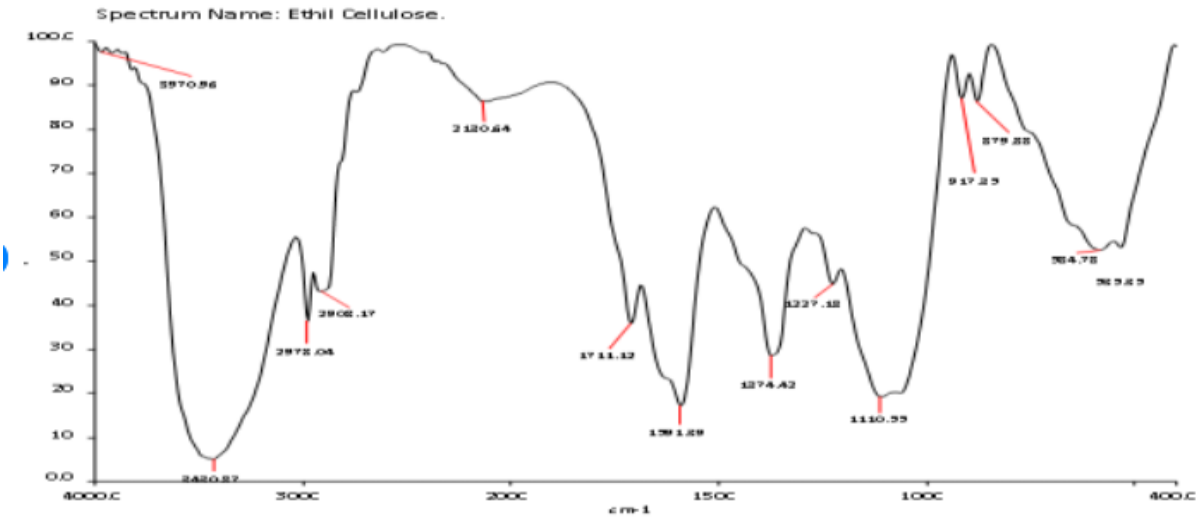


Figure 12: FTIR spectrum of AMX **[10]**

This spectrum shows the presence of peaks:

- Alcohol function (OH) at 3400 cm-1
- Amine function (NH2) at 3500 cm-1
- S-C at 2000 cm-1
- Aromatic N-C at 1370 cm-1
- Vibration C=O (carboxylic acid) at 1730 cm-1
- Vibration –OH (carboxylic acid also) at 2950 cm-1

III.1.2.FTIR spectrum of EC:



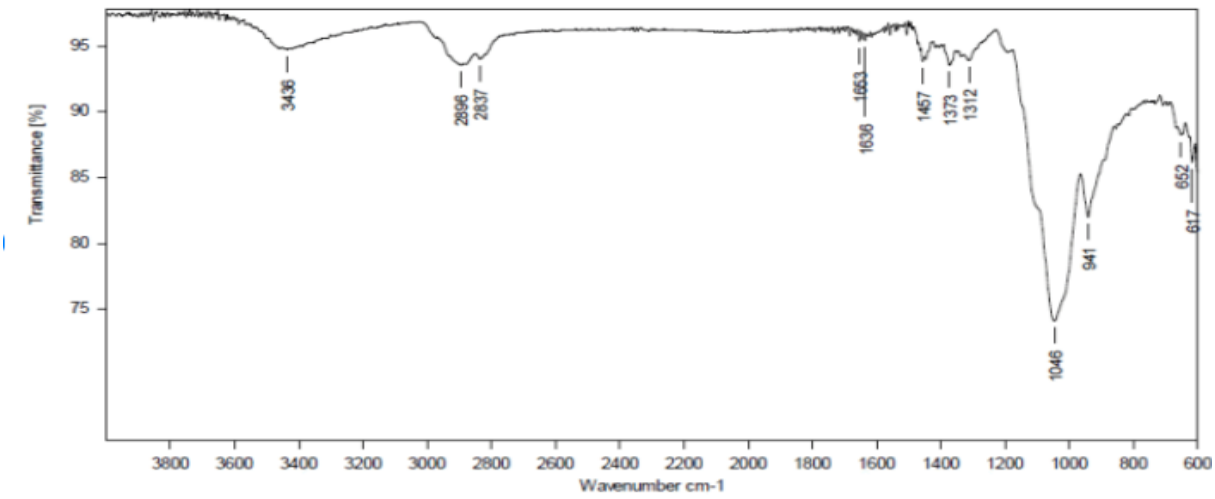
FT-IR spectra for Ethyl cellulose polymer

Figure 13: FTIR spectrum of EC **[11]**

The characteristic bands of EC:

- Aliphatic C-H at 2858 cm-1
- Ether C-O-C at 1122.37 cm-1
- Phenol O-H at 3436.55 cm-1
- Aromatic C-C at 1556.28 cm-1

III.1.3.FTIR spectrum of HPMC:



IR spectra of HPMC K 15

Figure 14: FTIR spectrum of HPMC **[12]**

The characteristic bonds of HPMC:

- O-H a broad bond between 3200 and 3600 cm-1
- Aliphatic C-H 2800-3000 cm-1
- C=O (ester) at 1700-1730 cm-1
- C-O-C (ether or ester) at 1050-1150 cm-1
- Deformation C-H (CH3) 1370-1470 cm-1
- C-O and C-C at 900-1200 cm-1

III.1.4.Infrared spectroscopy of the tablets made:

III.1.4.1.FTIR of tablet 3 (EC+HPMC+AMX):

The next spectrum shows the FTIR of tablet 3 before and after the AMX release:

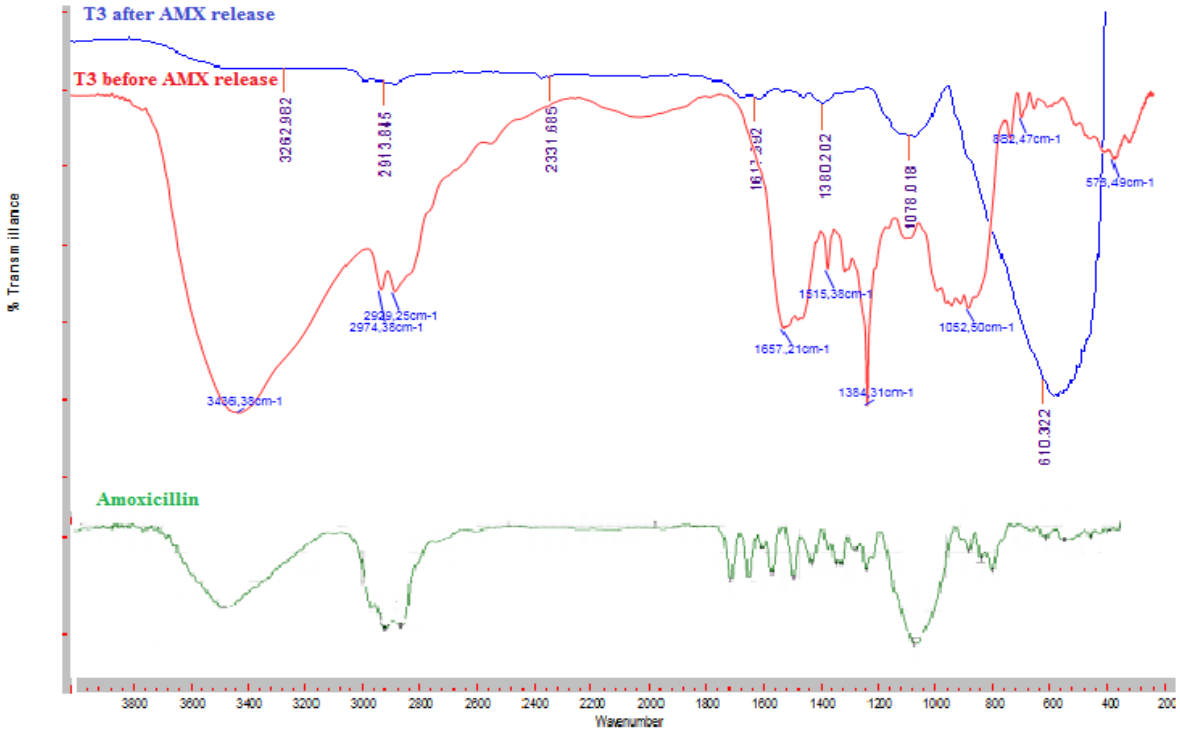


Figure 15: Spectrums IR of AMX pure, T3 before and after release.

In this spectrum we have the AMX spectrum to compare the characteristic bonds with our tablet of the third formulation before and after the release:

The spectrum of tablet which prepared by EC and HPMC indicates the presence of several characteristic bonds of AMX in the tablet 3: Aromatic bonds N-C at 1384.31 cm-1 and large bond OH at 3425 cm-1 (of EC and HPMC and AMX) and the bond of S-C at 2090-

2100 cm-1.Those bonds confirms the presence of the antibiotic agent AMX in the formulation before the release kinetics.

The tablet spectrum after release kinetics: indicated the disappearances of the characteristic bonds of AMX which confirms that the release study was well done in comparison with the percentage of AMX release

III.1.4.2.FTIR of tablet 2 (EC +AMX):

The next spectrum shows the FTIR of tablet 2 before and after the AMX release:

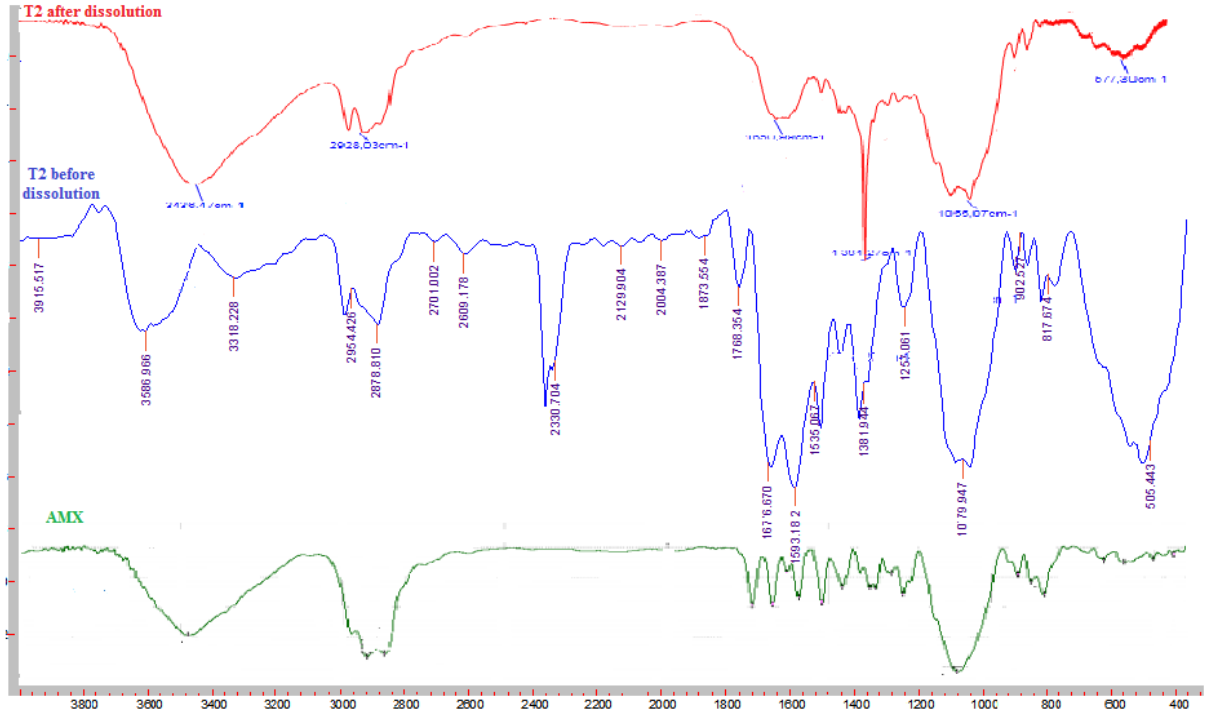


Figure 16: Spectrums IR of AMX pure, T2 before and after release.

In this spectrum we have the AMX spectrum to compare the characteristic bonds with our tablet of the second formulation before and after the release:

The spectrum of tablet which prepared by EC indicates the presence of several characteristic bonds of AMX in the tablet 2: Aromatic bonds N-C at 1384.31 cm^{-1} and large bond OH at 3425 cm^{-1} (of EC and AMX) and the bond of S-C at 2090-2100 cm^{-1}

Those bonds confirm the presence of the antibiotic agent AMX in the formulation before the release kinetics.

The tablet spectrum after release kinetics: there are peaks of AMX at 1380 cm^{-1} indicated the disappearances just of some characteristic bonds of AMX which indicates that

AMX release was not complete and was also confirmed by the kinetic study of tablet 2 in pH 7.4 at 31.79%.

IV.2.X-Ray-Diffraction (XRD):

This technique makes it possible to characterize the nature of the polymer from a crystallinity point of view. The device used is a powder diffractometer. The analyzes were carried out at ambient temperature. The sample to be analyzed is deposited in powder form on a flat support. The general acquisition conditions correspond to an angular range in 2Θ of up to 80°.

IV.2.1. XRD of EC:

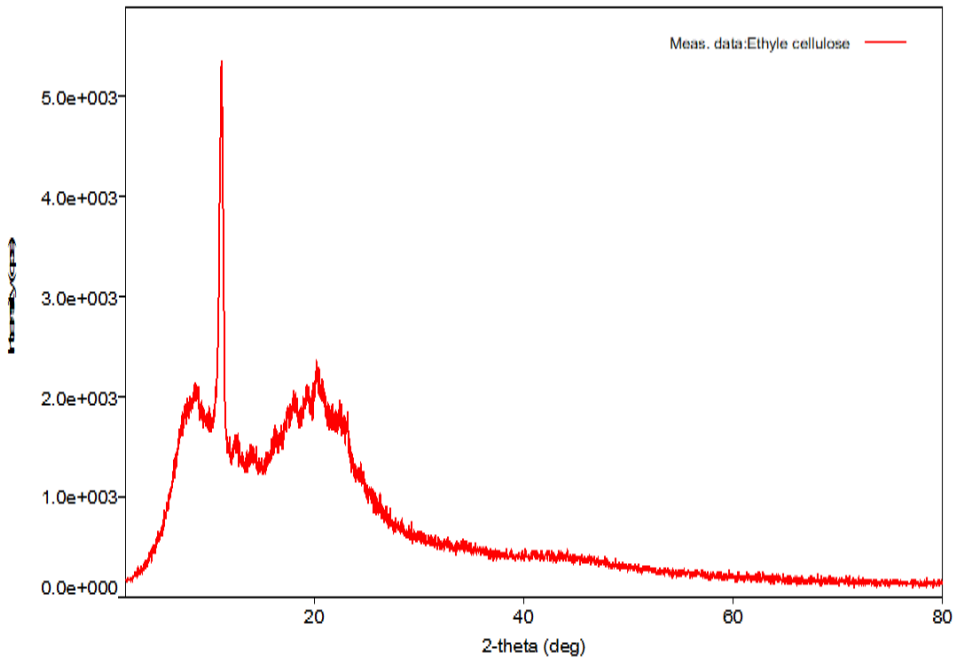


Figure 17: x-ray diffraction of EC **[13]**

The Figure 23 presents the XRD of Ethylcellulose , The diffractogram clearly shows the presence of an intense peak at 2Θ=11.16° of crystallinity and shows also a broadband presents amorphous properties therefore the EC polymers semi-crystalline polymer

IV.2.2.XRD of AMX:

The diffractogram of Amoxicillin (Figure 24) clearly shows the presence of characteristic crystallinity peaks which appear in the form of a more intense peak

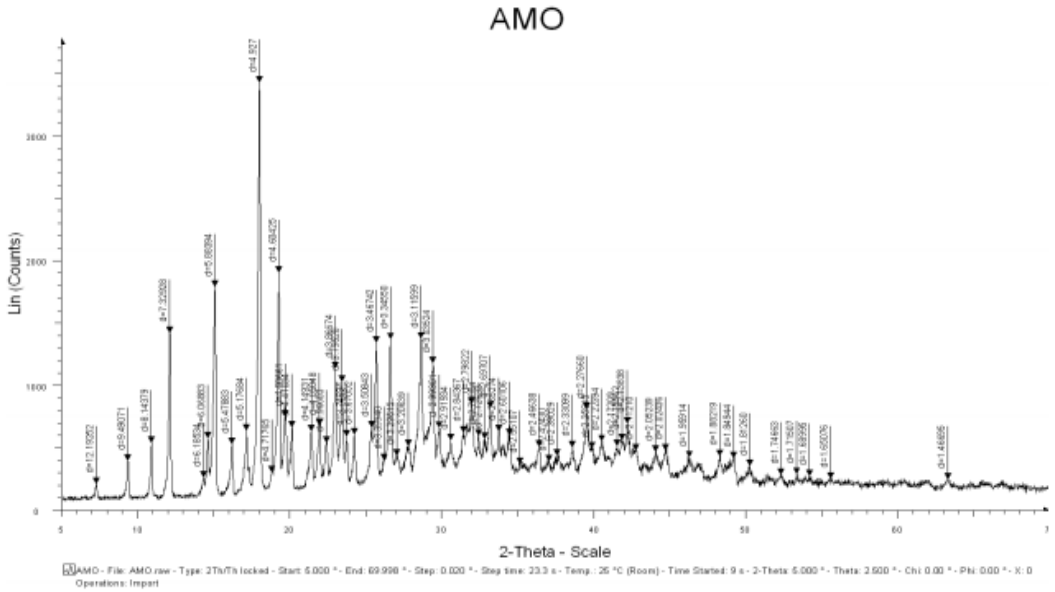


Figure 18:X-ray diffraction of AMX **[14]**

.

IV.2.3.XRD of HPMC:

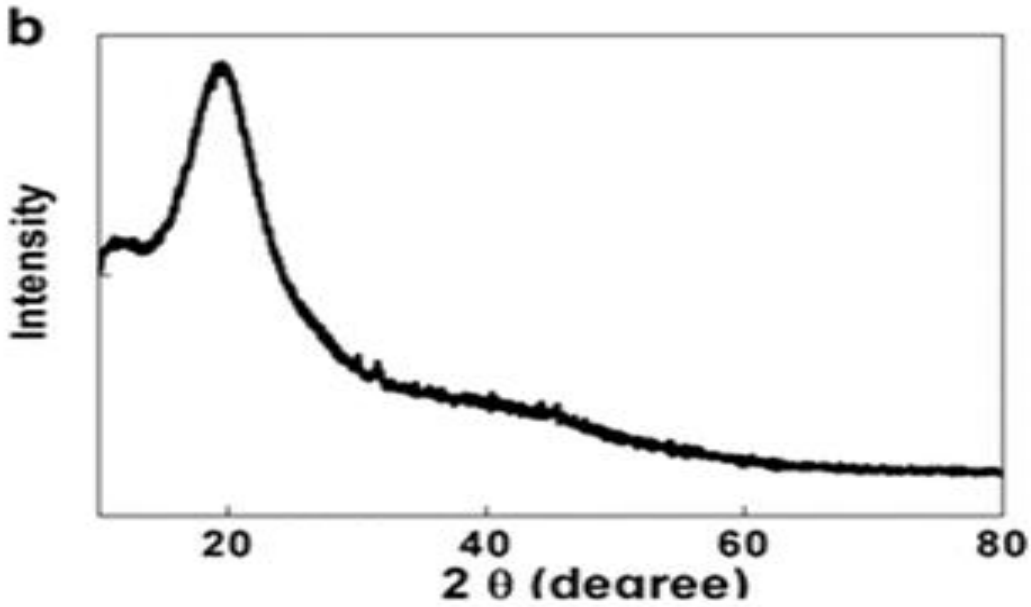


Figure 19: X-ray diffraction of HPMC **[15]**

The HPMC diffractogram shows broad peaks confirming that it has amorphous structure.

IV.2.4.XRD of tablet 2 (EC+AMX): with the comparaison of the diffractograms of AMX and EC:

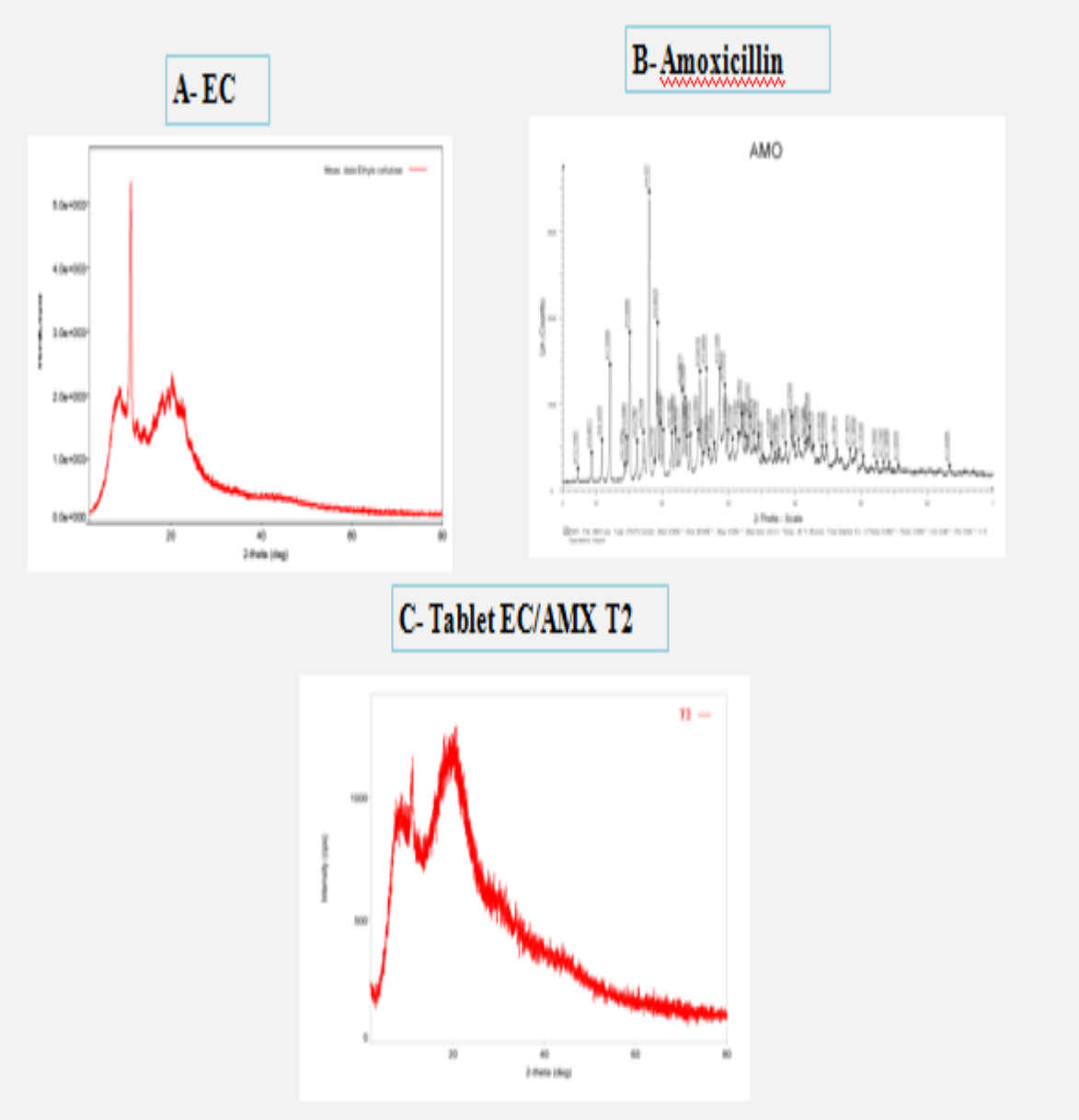


Figure 20: XRD patents of EC, AMX and T2

The peaks present in the tablet 2 diffractogram are less intense with the presence of a broad bond of amorphous part of the polymer which shows that AMX is present in the tablet and the presence of EC reduces the crystallinity of AMX.

IV.2.5.XRD of tablet 3 (EC+HPMC+AMX): with comparison also with XRD of EC, AMX and HPMC:

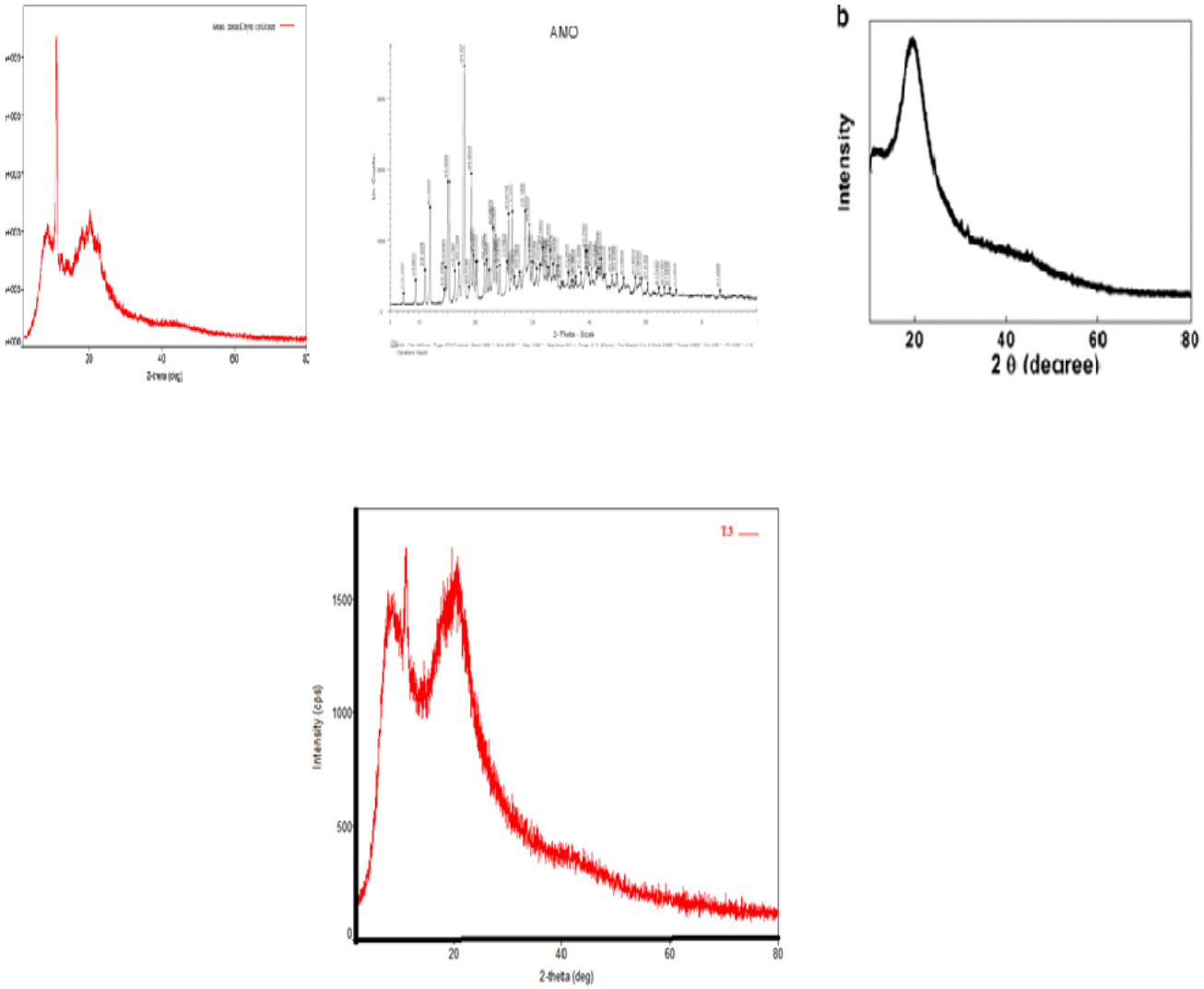


Figure 21: XRD patent of EC, AMX, HPMC and T3

The peaks present in the tablet 3 diffractogram are less intense with the presence of some broad bond of amorphous part of the polymer of EC and HPMC which shows that AMX is present in the tablet and the presence of HPMC and also the presence of EC which reduces the crystallinity of AMX.

IV. Biological study of EC-based formulations: Antibacterial and Antibiotic Activity

To demonstrate microbial activity, four bacterial strains and one fungal strain were tested against the prepared discs.

- **Bacterial strains**

The bacterial strains used are referenced and coded as follows:

- Gram-negative bacteria: Escherichia coli ATCC25922.
- Gram-negative bacteria : Pseudomonas aeruginosa ATCC27853.
- Gram-positive bacteria: Staphylococcus aurous ATCC25923.

- **Mueller-Hinton agar**

Mueller-Hinton agar is the only solid culture medium for the study of sensitivity that has been validated by the NCCLS. It is recommended to always use agar M-H for agar diffusion tests, depending on the guidelines international standards and the NCCLS. Since the way Mueller-Hinton agar is prepared may affect the results of the disk diffusion procedure, it is very important to refer to Section C below for instructions on preparation and quality control of this environment **[8-9].**

IV.1.The Kirby-Bauer disk diffusion method:

Mueller-Hinton agar was prepared, autoclaved for 20 minutes at 130C°, and then flowed into Petri dishes. After inoculation, four sterile 6 mm discs diameter are placed on M.H agar, the discs soaked with 15 µL of the sample from the kinetic. A disk control loaded with 15 µg of Amoxicillin is incubated with the loaded disks with the kinetics sample were incubated at 30°C for 24 hours, to then compare the diameters in order to test the inhibitory activity**[9]**.

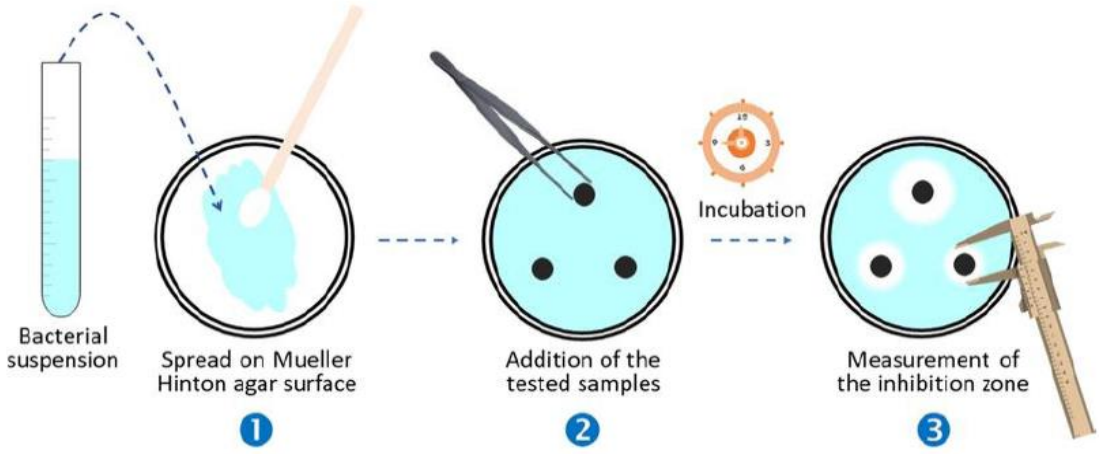


Figure 22: Schematic representation of the disk diffusion method

The technique consists of using paper discs impregnated with the different products to be tested. The discs are placed on the surface of an agar uniformly seeded with a suspension of the bacteria to be studied. Each antibiotic diffuses from the disk into the agar and determines a concentration gradient there.

a- Preparation of the suspension:

A bacterial suspension with a density equivalent to the standard of 0.5 Mac Farland (0.1-0.08) which corresponds to 10_8 colony forming units per milliliter (CFU/ml) this at a wavelength of 620 nm.

b- Seeding:

Seeding is carried out by sterile swabs on Petri dishes containing MH agar. A swab is dipped in the standardized bacterial suspension then rubbed over the entire agar surface, from top to bottom in tight streaks. The operation is repeated three times, rotating the box 60° each time. The boxes thus inoculated were left for 15 minutes.

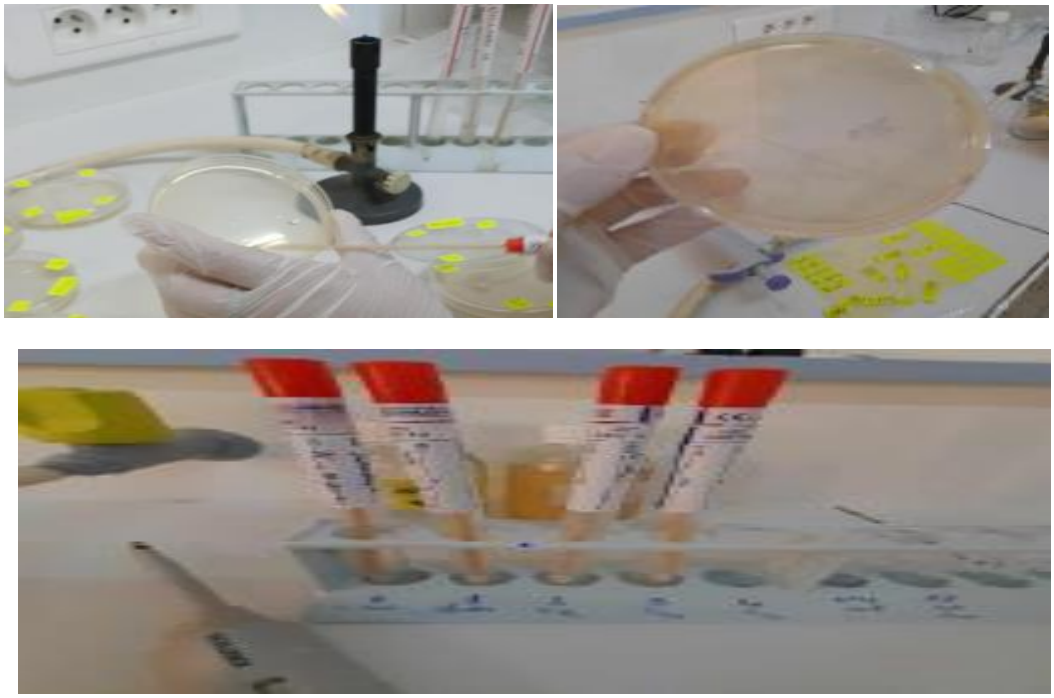


Figure 23: Seeding of culture medium

IV.1.a Evaluation of the antibiotic activity of amoxicillin in kinetic samples (pH7.7)

We took the kinetic sample of release of AMX from pH7.4 and Ph1.2 then flowed into Petri dishes, After inoculation, four sterile disks are placed on M.H agar and deposit the samples for **4** min,**85** min,**115**min and **220** min is remains for 24 at temperature 37°C.

IV.1.b Results of biological tests:

After 24 hours of incubation, the petri dishes containing the tablets soaked with the kinetic samples are timed after 4, 85,115 and 220 (min).the diameters of the inhibitory zones were noted as deferent from one strain to another ,zone were measured in mm

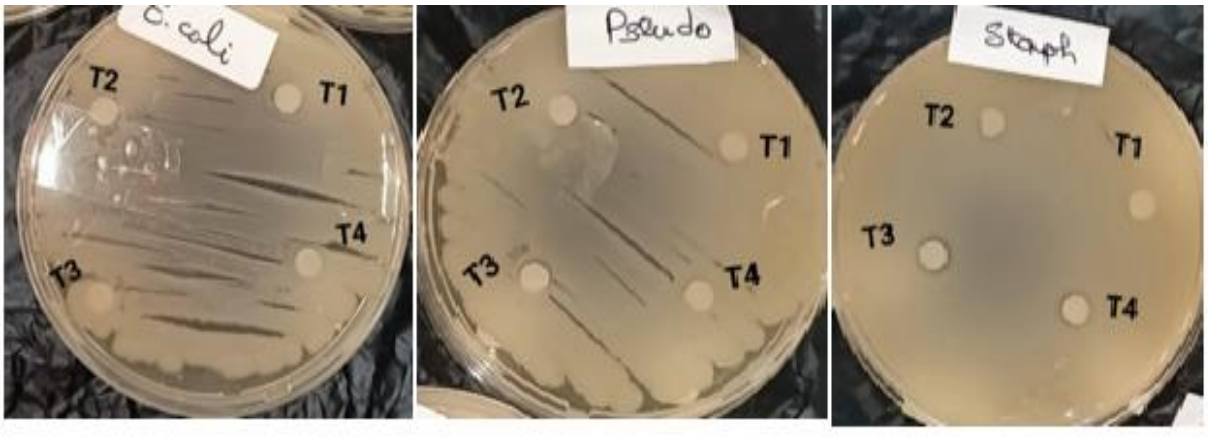


Figure 24: results of the microbial strains of the 1st formulation at pH7.4 tested in E-coli, pseudo and staph.

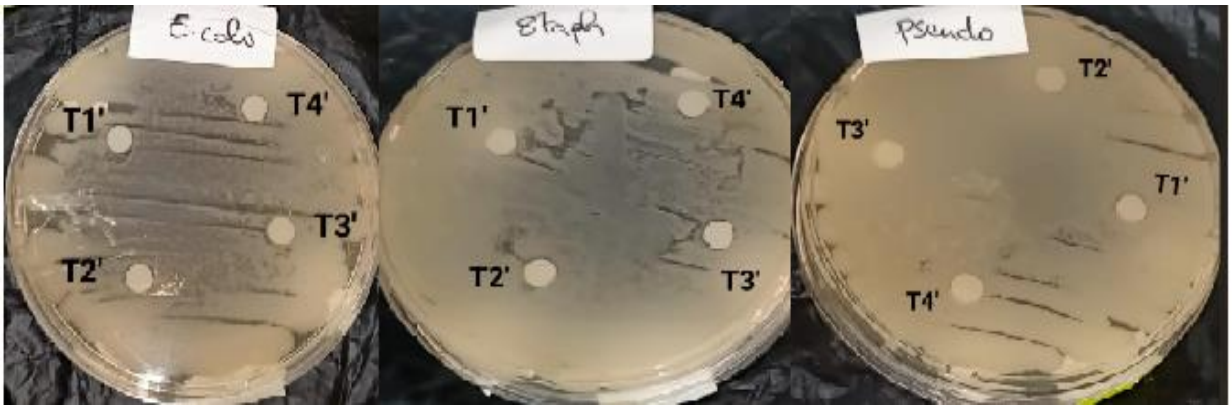


Figure 25: results of the microbial strains of the 2nd formulation at pH1.2 tested in E-coli ; pseudo and staph.

The diameters noted for tablet 2 (pH 7.4) and tablet 3 (pH 1.2):

Table 06: results of microbial study of tablet 1 (pH 7.4):

Diameters (mm)			
Time(min)	E-coli	Staph	Pseudo
4 min	6	0	0
85min	6	5	0
115min	0	6	5
220min	9	7	7

Table 07: results of microbial study of tablet 2 (pH 1.2):

Diameter (mm)			
Time (min)	E-coli	Staph	Pseudo
4 min	6	6	0
85 min	6	6	0
115 min	8	6	6
220 min	9	7	8

We observed from both tablets, the zone of inhibition (diameter in mm**)** increases with time. This aligns with the release kinetics of AMX, where more drugs are released as time progresses. We have at 220 min :

- Tablet 1 (pH 7.4): Zones up to **9 mm** (E. coli), **7 mm** (Staph, Pseudo)
- Tablet 2 (pH 1.2): Slightly better, up to **9 mm** (E. coli), **8 mm** (Pseudo)

The results of the antibacterial evaluation of AMX release kinetics from the discs are represented in the Histograms below:

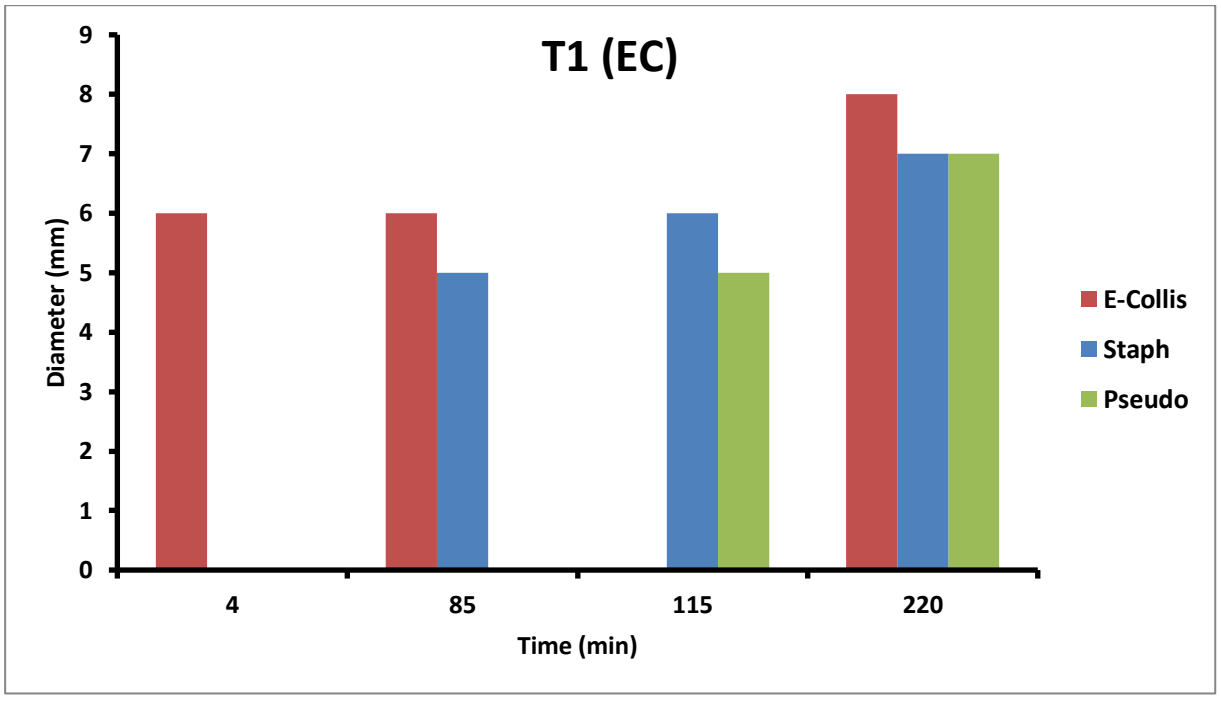


Figure 26: Results of microbial study of tablet 1 at different strain.

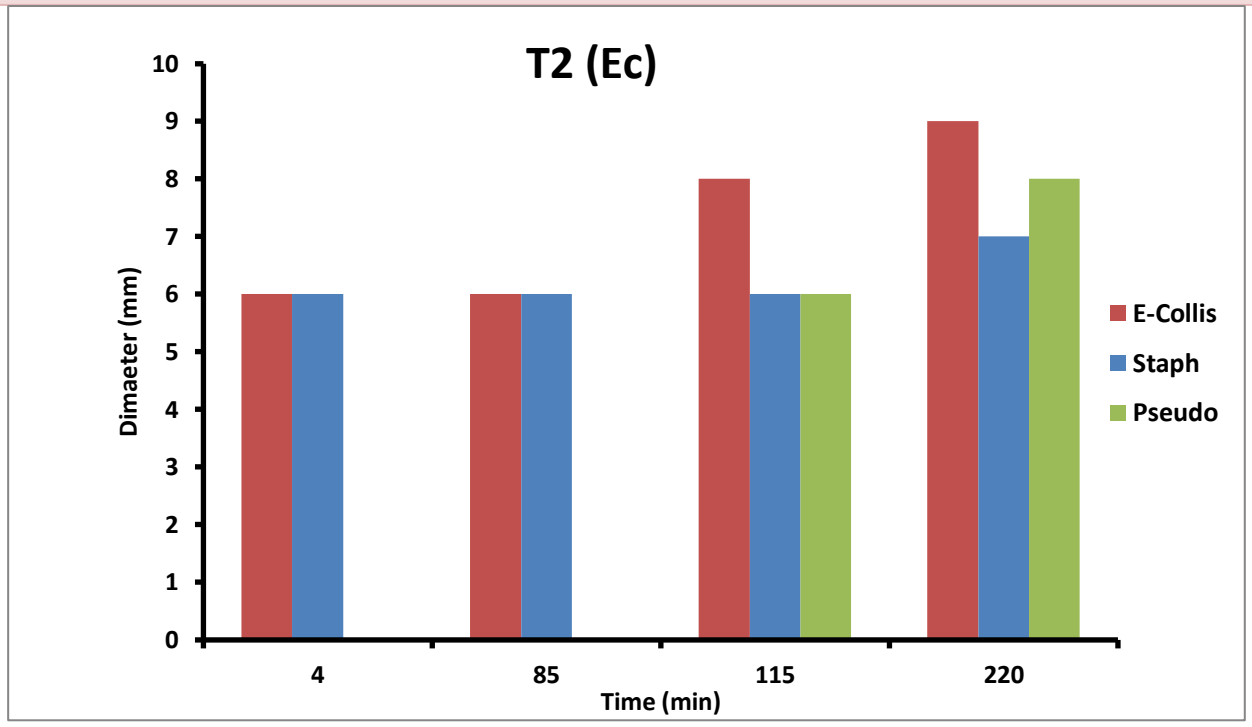


Figure 27: Results of microbial study of tablet 2 at different strain.

The results were collected in the last two histograms, we can explain that:

 E. coli is inhibited early in both formulations (even at 4 min), suggesting it is more sensitive to low concentrations of AMX.

 Staphylococcus shows inhibition after 85 min in T1 and immediately in T2, indicating slightly higher sensitivity or faster drug availability in the acidic environment.

 Pseudomonas aeruginosa is more resistant; inhibition is only seen at later stages (115–220 min), and only when AMX concentration becomes sufficiently high.

We observed also that the pH mediums have an influence on the antibacterial activity of formulation (T1, T2):

- Tablet 2 (T2) in acidic pH shows slightly faster and broader antibacterial action, especially at earlier time points. This matches the earlier kinetic data showing higher AMX release in acidic conditions**.**
- Tablet 1 (T1) in basic pH shows delayed onset, with activity against Pseudomonas only appearing at 115 min and beyond.

We can explain that the acidic medium (pH 1.2) enhances AMX release, leading to earlier and more effective antibacterial activity**.** This suggests that the formulations are better suited for stomach-targeted delivery, where AMX is released faster and can start acting earlier.

We can conclude that the antibacterial activity results are consistent with the AMX release kinetics observed in the formulations. In particular, faster AMX release under acidic conditions, as seen with Tablet 2 (T2, pH 1.2), leads to earlier and more pronounced antibacterial effects. This is evident from the larger inhibition zones recorded at earlier time points compared to those in neutral or basic conditions. Among the tested bacteria, *Pseudomonas aeruginosa* exhibited the highest resistance, with significant inhibition only appearing at later stages when AMX concentrations had increased sufficiently. These findings confirm the effectiveness of the pH-dependent release design, demonstrating that AMX is more efficiently released and active in stomach-like acidic environments. This supports the suitability of the formulation for targeted delivery to the stomach, where rapid therapeutic action is desired.

Refrences:

[1] Wasilewska K, Winnicka K. Ethylcellulose—A pharmaceutical excipient with multidirectional application in drug dosage forms development. *Materials (Basel)*. 2019;12(20):3386. doi:10.3390/ma12203386. PMID: 31627271; PMCID: PMC6829386.

[2] U.S. Food and Drug Administration (FDA). *Everything Added to Food in the United States (EAFUS)*. 2020.

[3] Seddiqi H, Oliaei E, Honarkar H, Jin J, Geonzon LC, Bacabac RG, Klein-Nulend J. Cellulose and its derivatives: Towards biomedical applications. *Cellulose*. 2021;28(4):1893–1931.

[4] *Effect of the content of ethyl cellulose-rubber blend on physicochemical properties of adhesive composition*. *Polymer Science Series D*. July 2008.

[5] Benson HAE, Roberts MS, Leite-Silva VR, Walters KA. Hydroxypropyl Methylcellulose. In: *Cosmetic Formulation*. Taylor & Francis; 2019.

[6] Omidian H, Park K. Hydroxypropyl Methylcellulose. In: *Comprehensive Biomaterials*. Elsevier; 2011.

[7] Almeling S, et al. Hydroxypropylmethylcellulose. In: *Review Papers on Pharmaceutical and Biomedical Analysis*. Elsevier; 2012.

[8] National Committee for Clinical Laboratory Standards (NCCLS). *Performance Standards for Antimicrobial Susceptibility Testing; Ninth Informational Supplement*. Document M100-S9, Vol. 19, No. 1, Table 21. Wayne, PA: NCCLS; 1999.

[9] National Committee for Clinical Laboratory Standards (NCCLS). *Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data; Approved Guideline*. Document M39-A. Wayne, PA: NCCLS; 2002.

[10] AL-KADUMI A. S. H., AL-TAMEEMI M., ABDULKAREEM H. M., SALMAN N. K., 2020 ; Méthodes de détermination de l'amoxicilline : analyse moléculaire, absorption atomique, spectrophotométrie FTIR et HPLC.

[11] MARIMUTHU S., NANTHEESWARAN S., SHANMUGARATHINAM A., PURACHIKODY A., 2012 ; Formulation et caractérisation de microsphères flottantes de céfuroxime axétil. Int. J. Pharm, 2, 526-533.

[12] IQBAL F. M., AHMAD M., TULAIN U. R., 2017 ; Synthèse par rayonnement micro-ondes d'un réseau polymérique à base d'HPMC greffée avec poly(vinylalcool-co-acide acrylique) et évaluation in vitro. Acta Pol. Pharm, 74(2), 527-541.

[13] TRIVEDI M. K., BRANTON A., TRIVEDI D., NAYAK G., MISHRA R., JANA S., 2015 ; Caractérisation physico-chimique et thermique de l'éthylcellulose et de la méthylcellulose traitées par champ bioénergétique. Int. J. Biomed. Mater. Res., 3(6), 83-91.

[14] BAJPAI S. K., SHAH F. F., BAJPAI M., JADAUN M., JYOTISH P., 2017 ; Libération dynamique de l'amoxicilline à partir d'un film oralement dissolvable (ODF) à base de caséine et d'alginate de sodium. J. Drug Res. Dev, 3(2), 1-7.

[15] GOWTHAM G. K., HEGDE V. N., MESHK S., SUKRUTHA S. K., SOMASHEKAR R., 2015 ; Synthèse et caractérisation de composites polymères à base d'HPMC dopés par des particules de suie de carbone. J. Res. Updates Polym. Sci., 4(2), 62.

Conclusion

General conclusion:

In this work was devoted to the preparation of forms pharmaceuticals: Tablets supporting the active ingredient “Amoxicillin”. In the preparation of these forms, tow matrix polymers were used Etylcellulose "EC", hydroxypropyl methylcellulose (HPMC).

The formulated tablets were prepared by mechanical compression with alcohol spray. The first two tablets were prepared by EC and AMX with different masses and the 3rd was made using HPMC and EC with AMX, after complete evaporation of the sprayed alcohol, we have determined the mass and calculate the yield%.

Polymers, amoxicillin and prepared tablets were characterized by FTIR and DRX, and the tablets were also followed by a kinetic study in two different environments of pH 1.2 (stomach) and 7.4 (intestine). FTIR results obtained from T2 and T3 tablets before release indicate the presence of several amoxicillin and EC peaks as well as HPMC in T3 (formulation) and after release in T2 we didn't observe a total disappearance of AMX peaks matches with the kinetic study of T2 in pH 7.4 of 31.79% , for T3 we noticed a disappearance of AMX peaks also matches with the kinetic after release pH 1.2 of 46.30%.

This XRD technique makes it possible to characterize the nature of the polymer from a crystalline. Tablet T2 is the mixture between Ethylcellulose and Amoxicillin, the pattern clearly showed the presence of some peaks with different intensity. Those peaks are confirmed the presence of Amoxicillin in the tablet in the broad-band of EC which is a semi-crystalline polymer. This allows us to say that the Amoxicillin is dispersed in the polymer matrix; the presence of EC reduces the crystalline of the Amoxicillin. The XRD pattern of the T3 also showed the presence of intense and broad peaks crystalline and amorphous peaks which confirm the formulation of T3 were based on EC, HPMC and AMX and also the presence of EC reduces the crystalline of the Amoxicillin.

The release of the active ingredient was monitored using a UV-Vis spectrometer, previously calibrated at the wavelengths **λmax=230nm** at pH 1.2 and **λmax=280nm** at pH 7.4 of the active ingredient used amoxicillin.

In the three formulations we made, there was an increase in release in the pH =1.2 medium (stomach). For all the formulation loaded with AMX, the percentage of active ingredient released is greater in the medium at pH=1.2 compared to the medium at pH=7.4. A

classic curve-shaped release profile was observed in all cases: At early times, the release rate was high and then gradually decreased during the observation period.

All three formulations show pH-dependent AMX release, with significantly higher release in acidic conditions, indicating their suitability for stomach-targeted drug delivery. Formulations 1 and 2 (EC + AMX) release the drug more rapidly than Formulation 3, which contains HPMC. This is likely due to HPMC's gel-forming, water-soluble nature, which slows drug diffusion, unlike EC, which swells and allows faster release. Therefore, Formulation 3 may be better for sustained release, while Formulations 1 and 2 are more effective for faster release in acidic environments.

As shown in the results of calculation the Liquid absorbed % from the tablets during the dissolution, Tablet T3 consistently absorbs more liquid than T1 and T2 at all time intervals. Notably, T3 absorbs approximately 17% of liquid within just 2 minutes, compared to less than 5% for T1 and T2. After 250 minutes, T3 reaches about 34.5% absorption, significantly higher than T1 (22.7%) and T2 (14.8%). T1 and T2 both contain EC and AMX, but T1 has a lower EC-to-AMX ratio, which may result in a more porous structure and better fluid uptake. In contrast, T2's higher EC content likely forms a denser matrix that limits liquid penetration. The enhanced absorption in T3 is attributed to the presence of HPMC, a hydrophilic polymer known for its strong water absorption and gel-forming properties. This contributes to increased swelling and the formation of a gel layer that not only retains more liquid but also modulates the drug release.

To demonstrate microbial activity, three bacterial strains which are the positive and negative bacteria; we have applied the classical method of diffusion of antibiotic disks on Muller Hinton (MH) agar which is a standardized medium for all bacteria were tested against the prepared discs. After incubation at 24h at 37°c, we observe an increase in the diameters of inhibition zones.

After 24 h of incubation, we observed that the antibacterial activity results are consistent with the AMX release kinetics observed in the formulations. In particular, faster AMX release under acidic conditions, as seen with Tablet 2 (T2, pH 1.2), leads to earlier and more pronounced antibacterial effects. This is evident from the larger inhibition zones recorded at earlier time points compared to those in neutral or basic conditions. Among the tested bacteria, *Pseudomonas aeruginosa* exhibited the highest resistance, with significant inhibition

only appearing at later stages when AMX concentrations had increased sufficiently. These findings confirm the effectiveness of the pH-dependent release design, demonstrating that AMX is more efficiently released and active in stomach-like acidic environments. This supports the suitability of the formulation for targeted delivery to the stomach, where rapid therapeutic action is desired.

Future in vivo biological studies on living cells and animal models, such as rats or rabbits, will be essential to confirm that the amount of drug released from the most effective formulations aligns with the required therapeutic concentrations.

ملخص: هدفت هذه الدراسة إلى تطوير وتقييم أقراص محملة بالأموكسيسيلين باستخدام إيثيل السليلوز (EC) وهيدروكسي بروبيل ميثيل السليلوز (HPMC) كبوليمرات مصفوفة. تم تحضير ثلاث تركيبات: T1 وT2 تحتوي على EC بنسب مختلفة من AMX، وT3 تجمع بين EC وHPMC وAMX. وقد أكد التوصيف باستخدام FTIR وDRX وجود وتشتت الأموكسيسيلين في المصفوفات البوليمرية. أظهرت دراسات إطلاق الدواء في البيئات الحمضية (درجة الحموضة 1.2) والقاعدية (درجة الحموضة 7.4) إطلاقًا أعلى في البيئات الحمضية لجميع التركيبات، وخاصة T1 وT2، مما يجعلها مناسبة للإطلاق المستهدف في المعدة. أظهرت تركيبة T3، التي تحتوي على HPMC، إطلاقًا أبطأ وأكثر تحكمًا بسبب خصائصها المكونة للهلام. أظهرت اختبارات امتصاص السوائل أن T3 امتص كمية أكبر بكثير من الماء بسبب الطبيعة المحبة للماء لـ HPMC، وبالتالي المساهمة في إطالة إطلاق الدواء. وقد أظهرت الاختبارات المضادة للبكتيريا أن سلوك الإطلاق أثر بشكل مباشر على النشاط المضاد للميكروبات. أدى الإطلاق السريع في البيئات الحمضية إلى تثبيط بكتيري مبكر وأكثر فعالية، وخاصة بالنسبة لـ T2. وتثبت هذه النتائج صحة مفهوم الإطلاق الحساس لدرجة الحموضة وتسلط الضوء على إمكانات هذه التركيبات لتوصيل الدواء بشكل مستهدف وفعال في البيئات المعدية.

الكلمات المفتاحية: الشكل الجالينوسي "أقراص"، أموكسيسيلين، EC، HPMC , حركية التحرر، النشاط الميكروبي

Abstract: This study aimed to develop and evaluate amoxicillin-loaded tablets using ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC) as matrix polymers. Three formulations were prepared: T1 and T2 using EC with different AMX ratios, and T3 combining EC, HPMC, and AMX. Characterization by FTIR and XRD confirmed the presence and dispersion of AMX in the polymer matrices. Drug release studies in acidic (pH 1.2) and basic (pH 7.4) media showed higher release in acidic conditions for all formulations, especially T1 and T2, making them suitable for stomach-targeted delivery. T3, containing HPMC, showed slower and more controlled release due to its gel-forming properties. Liquid absorption tests showed T3 absorbed significantly more water due to HPMC's hydrophilic nature, contributing to sustained drug release. Antibacterial tests demonstrated that the release behavior directly influenced antimicrobial activity. Faster release in acidic conditions led to earlier and stronger bacterial inhibition, particularly in T2. These results validate the pH-sensitive design and highlight the potential of these formulations for targeted, effective drug delivery in gastric environments.

Key words: Galenic form"Tablet", Amoxicillin , EC , HPMC , Kinetics of release, microbial activity

Résumé : Cette étude visait à développer et évaluer des comprimés chargés en amoxicilline en utilisant l'éthylcellulose (EC) et l'hydroxypropylméthylcellulose (HPMC) comme polymères matriciels. Trois formulations ont été préparées : T1 et T2 contenant de l'EC avec des proportions différentes d'AMX, et T3 combinant EC, HPMC et AMX. La caractérisation par FTIR et DRX a confirmé la présence et la dispersion de l'amoxicilline dans les matrices polymériques. Les études de libération du médicament dans des milieux acide (pH 1,2) et basique (pH 7,4) ont montré une libération plus importante en milieu acide pour toutes les formulations, en particulier T1 et T2, les rendant adaptées à une libération ciblée dans l'estomac. La formulation T3, contenant du HPMC, a présenté une libération plus lente et contrôlée en raison de ses propriétés de formation de gel. Les tests d'absorption de liquide ont montré que T3 absorbait significativement plus d'eau grâce à la nature hydrophile du HPMC, contribuant ainsi à une libération prolongée du médicament. Les tests antibactériens ont démontré que le comportement de libération influençait directement l'activité antimicrobienne. Une libération plus rapide en milieu acide a entraîné une inhibition bactérienne plus précoce et plus efficace, notamment pour T2. Ces résultats valident le concept de libération sensible au pH et soulignent le potentiel de ces formulations pour une administration ciblée et efficace du médicament dans des environnements gastriques.

Mots clés : Forme galénique « Comprimé », Amoxicilline , EC, HPMC, Cinétique de libération, activité microbienne