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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 in:

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Specialty: Macromolecular Chemistry

Theme

Preparation, Optimization of polymeric formulations for oral administration of antibiotics

Presented by:

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Before the jury composed of:

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Appreciation

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A big thank you to all

DEDICATION

I dedicate this modest work

To the man of my life, my eternal example, my moral support and source of joy and happiness, the one who always sacrificed himself to see me succeed, to you

my father **MOHAMED**

To the most beautiful creature that God created on earth, the light of my days, the source of my efforts, Words will never be enough to express the immensity of my love and my gratitude towards you, the refuge where I find comfort and safety to you

my mother **Zahra**

to the people whose presence I enjoyed today, my brothers **Yasser, Iyad, Amir** and my sisters **Ikram, Mazouza, Fatima**, You are the pillars of my life, the stars that light my path, the most precious treasures that I possess

To my beloved **grandmother**, who is late and remains in our hearts. I always remember you in moments of joy and successes, small and large. Your little one has graduated, my love.

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To my friend and memory partner **Bochra** for her moral support, patience and understanding throughout this project

AMINA

DEDICATION

With all my feelings of respect, with the experience of my recognition, I dedicate my presentation of my diploma and my joy

To my father, despite his unexpected departure, his soul remains close to me, illuminating my path with his smile and his indelible image engraved in my memory. He has made me a strong and independent woman, pushing me to believe in my dreams and to achieve it whatever the circumstances. May God welcome his soul in his holy mercy.

To my paradise, to the apple of my eye, to the source of my joy and my happiness, my moon and the thread of hope that lights my path, my other half, **My mother**.

To my brothers **« SAID », « ALI » , « Abd El Rahmane »** and sisters**« Amel, Sihem ,Hanane ,Soria »**for the love they have for me, who have never stopped advising me, encouraging me and supporting me throughout my studies. Without forgetting my brother**« Ahmed »,** may God have mercy on him, who I still miss and who I hoped would see my success.

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To all who love me.

BOCHRA

Summary

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ABREVIATIONS LIST

PA	active principle
EC	Ethylcellulose
PEG	Ethylene glycol
CTA	Cellulose Triacetate
CF	cefalexin
FTIR	infrared spectroscopy
XRD	X-ray Diffraction Analysis
ABS	Absorbance
%PA	The percentage of the active ingredient released.
HCl	Hydrochloricacid
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 liquidabsorbed
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

Introduction

General Introduction

The term "Polymer Drugs" or "Polymeric Drugs" has been widely used for pharmaceutically active macromolecules, especially since the 173 rd National Meeting of the American Chemical Society in 1977 **[1].**

Since the drug was proposed for humans with a view to providing relief, several forms were developed. Each form has advantages and disadvantages. Thus, the researchers and manufacturers have always made efforts to improve the characteristics of these so-called conventional forms **[2-3].**

To reduce the number of drugs taken in the pharmaceutical field, several researchers have studied the usefulness of certain polymers in the different preparation techniques of the pharmaceutical form. Among the degradable/biodegradable, biocompatible polymers discovered over the last forty years, polysaccharides are a popular basis for targeted therapeutic delivery systems and are part of the polymers used in the composition of the active ingredient with controlled release **[4]**, the most polysaccharides interesting for Pharmaceutical applications Celluloses, chitins and chitosans, alginates and starches

In pharmaceutical forms where the active ingredient (drug) is dispersed in the matrix polymer, the release of this active principle is achieved by penetration of the liquid physiological inside the form to solubilize the active principle. Absorption of a drug is based on two factors: solubility and dissolution of the drug in the gastrointestinal environment. Certain drugs have low solubility in water, which weakens the achievement of a desired therapeutic effect, particularly Cefalexin.

Cefalexin is a first-generation cephalosporin antibiotic that is used to treat bacterial infections in various parts of the body, including: infections of your respiratory tract (chest and lungs), throat, sinuses, ears, skin and soft tissues.

The objective of this work is to find a dosage form which allows the increase in the solubility of Cefalexin. For this purpose we manufactured tablets based on derivatives such us Ethylcellulose either alone or in mixture with polyethlene glycol (PEG) and cellulose Cellulose such as the cellulose triacetate CTA which was obtained from cotton, to study the influence of polymers on the formulation. The synthesis was followed by the study of the release of active principle in two reconstituted media (pH 1.2 and 7.7). The prepared discs were characterized by FTIR, XRD followed by the biological study against the referenced bacterial strains.

In our work, we have chosen cephalexin as an active principle widely used in the pharmacological field and polymers (ethyl cellulose EC, polyethylene glycol PEG and cellulose triacetate CTA) because they are non-toxic polymers and used in marketed drugs.

The bibliographic part is includes two chapters:

- The first chapter will be devoted to the description about antibiotics in general.
- The second chapter describes the different Galenic forms and the release of active ingredients

The experimental part contains three sub-parts:

- First part concerned the synthesis of cellulose triacetate by an Esterification reaction using the anhydride acetic as an acetylating agent followed by the preparation of tablets (disks) based on EC polymer alone and in a mixture with other polymers such as polyethylene glycol PEG and cellulose triacetate CTA characterized by different analysis techniques: IR, XRD.
- Second part includes the kinetic study of release of the active ingredient “cefalexin”.
- Third part followed by the biological study of prepared tablets with respect to the referenced bacterial strains.

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Bibliography Part

Chapter 01: Generality of antibiotics

Chapter 01: Generality of antibiotics

I.1Historical and Definition:

Since the discovery of penicillin in 1928, a gradual decline in antibiotic discovery and development and the evolution of drug resistance in many human pathogens has led to the current antimicrobial resistance crisis **[1].**

In 1947, S. A. Waksman defined the term "antibiotic" as follows: "An antibiotic is a chemical substance, produced by micro-organisms, which has the capacity to inhibit the growth of and even to destroy bacteria and other micro-organisms" (Waksman 1947).

The history of antibiotics is linked to the discovery of bacterial microorganisms in 1887 with Pasteur and Joubert **[2].** In 1929, the microbiologist Alexander Fleming the action of penicillium notatum a green mold caused the lysis of staphylococcus colonies. After ten years, Florey and Chain purified penicillin quantities for the treatment of staphylococcal septicemia **[2-3].**

In 1963, Gentamicin was extracted from a mold From then on, researchers around the world continued to find new antibiotics and to create semi-synthetic varieties (such as Chloramphenicol) from existing strains, or to chemical synthesis (such as Sulfonamides, Quinolones) with the aim of greater efficiency **[3].**

Today, "antibiotic" has multiple meanings: an organic chemical of natural or synthetic origin that inhibits or kills pathogenic bacteria; any antimicrobial substance, or, in the Waksman tradition, limited to antimicrobial substances of microbial origin .**[4],** Antibiotics can produced by chemical synthesis which have antibacterial activity, this activity is manifested in a specific manner by the inhibition or modification of certain vital processes of synthetic or semi-synthetic microorganisms capable of opposing the multiplication or destroying bacteria, without affecting the host. Antibiotics aim to reduce or stabilize the quantity of bacteria present at the infectious site and to help the cells of the immune system begin the healing process **[3-5].**

I.2 Classification of Antibiotic

According to data in the literature, antibacterial agents can be classified into several major groups **[6]**.

I.2.1 Natural origin:

A natural antibiotic is a chemical substance that occurs in nature or a natural product, such as a plant, that has certain properties which kill or harm microbes like bacteria.

Among the 10,000 antibiotics of natural origin identified in the world, 20% come from fungi: Penicillium, Cephalosporium, Aspergillus, 70% come microfilament actinomycetes including the genus Streptomyces which is a major producer of antibiotics: tetracyclines, aminoglycosides and 10% come from bacteria (not actinomycetes), in particular of the genera Bacillus and Pseudomonas, for example bacitracin used for certain local treatments. **[7][2]**

I.2.2 Synthetic origin:

Synthetic antibiotics are obtained either from artificial derivatives or by recreating substances originally extracted from microorganisms. We distinguish antibiotics of synthetic origin for example: Sulfonamides, metronidazole, isoniazid, nalidixic acid and fluoroquinolones, and we also distinguish antibiotics of semi-synthetic origin; they are obtained by modifying in the laboratory a substance produced by a micro- body**. [8][1]**

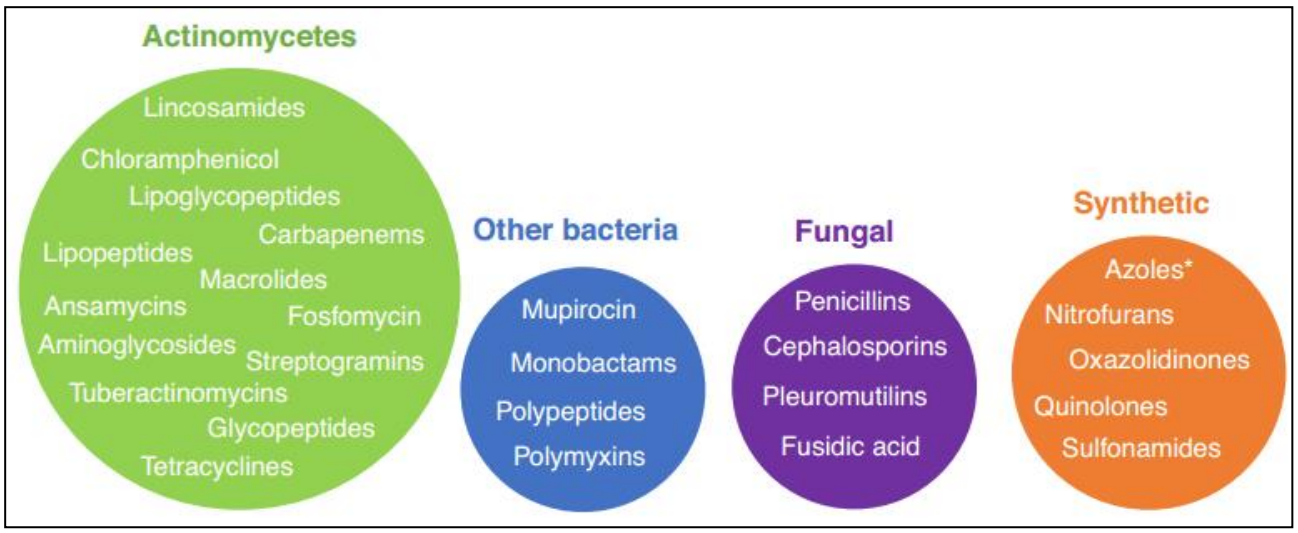

Figure 1. Most clinically relevant classes of antibiotic **[1]**

I.3 Mode of action of antibiotic

The structural diversity of the antibiotics is directly correlated to different mechanisms of action. Previous studies defined as main targets of antibiotics within the bacteria, the following: cell wall synthesis, protein synthesis, cell membrane function and nucleic acid synthesis, processes that play key roles in bacterial growth **[9]**. On this basis, the antibiotics can be classified by the mechanism of action as inhibitors of cell wall synthesis; protein synthesis, cell membrane function and nucleic acid synthesis (see Table 1). Another described antibiotic mechanism of action consists of blockage of key metabolic pathways **[10,11].**

Table 1. Antibiotics' classification by the mechanism of action.

Antibiotic Class		Target Site	Representatives
β-lactams	Penicillins	Cell wall synthesis	Penicillin G and Penicillin V, Methicillin, Oxacillin, Cloxacillin, Dicloxacillin, Nafcillin, Ampicillin, Amoxicillin, Carbenicillin, Ticarcillin, Mezlocillin, Piperacillin, Azlocillin, Temocillin
	Cephalosporins	Cell wall synthesis	**1st generation:** Cephalothin, Cephapirin, Cephradine, Cephaloridine, Cefazolin **2nd generation:** Cefamandole, Cefuroxime, Cephalexin, Cefprozil, Cefaclor, Loracarbef, Cefoxitin, Cefmetazole **3rd generation:** Cefotaxime, Ceftizoxime, Ceftriaxone, Cefoperazone, Ceftazidime, Cefixime, Cefpodoxime, Ceftibuten, Cefdinir **4th generation:** Cefpirome, Cefepime 5th generation: Ceftaroline, Ceftobiprole
	Carbapenems	Cell wall synthesis	Imipenem, Meropenem, Doripenem
	Monobactams	Cell wall synthesis	Aztreonam
Macrolides		Protein synthesis inhibitors—Inhibit 50 s subunit	Erythromycin, Azithromycin, Clarithromycin
Sulfonamides		Folic acid synthesis inhibitors	Prontosil, Sulfonamide, Sulfanilamid, Para-Aminobenzoic Acid, Sulfadiazine, Sulfisoxazole, Sulfamethoxazole, Sulfathalidine
Quinolones		DNA synthesis inhibitors	Nalidixic Acid, Ciprofloxacin, Norfloxacin, Pefloxacin, Enoxacin, Ofloxacin, Levofloxacin, Sparfloxacin, Lomefloxacin, Fleroxacin
Ansamycin		RNA synthesis inhibitors	Rifampin

There are two types of antibiotic modes of action:

- **Bacteriostatic action:** is a substance that inhibits the growth and growth of bacteria without killing them**.[1]**
- **Bactericidal action:** killing and accelerated death of bacteria depending on concentrations and duration acting on the DNA wall**.[1]**

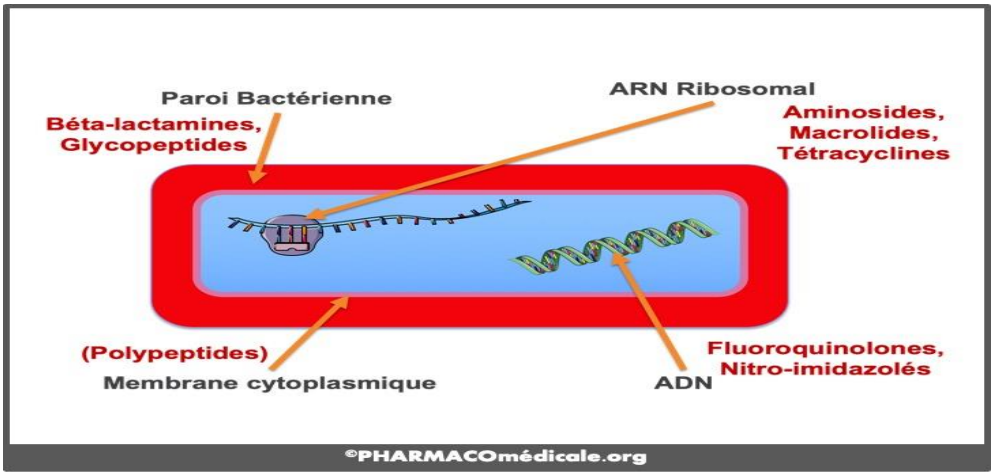

Figure 02: Mode of action of antibiotics on bacteria **[4]**

They can act on 4 different parts, in particular by **[1,2, 12]:**

- Action on the bacterial wall
- Action on the cytoplasmic membrane
- Action on ribosome RNA
- Action on bacterial DNA

I.4 Antibiotic activity conditions

In order to be able to exert its antibacterial activity an antibiotic, reach the target **[1]:**

- Penetrate the outer membrane.
- Wall.
- The cytoplasm membrane.
- Persist at sufficient concentrations

Recognize the target, and then the bacteria develop mechanisms to prevent one or other of these steps, and thus allow the emergence of resistance to antibiotics **[1].**

I.5 Antibiotic effectiveness criteria

To be effective, an antibiotic must meet its target or point of impact. If this target does not exist, the germ is insensitive to the antibiotic **[4]** you must**: [1]**

- It has a mode of action that allows it to act on these bacteria.
- It reaches where the bacteria is and at sufficiently high concentrations.
- That there remains sufficient time to allow it either to destroy it, which is what we call bactericide, or to stop its multiplication, which is called bacteristasis.

I.6 The criteria for choosing an antibiotic

There are 4 major criteria that must be taken into account when choosing antibiotic therapy:

I.6.1 Bacteriological criteria

Identification of the germ after microbiological sampling plus study of its sensitivity in vitro to antibiotics are of the greatest interest in the treatment of severe infections (sepsis, meningitis, etc.),or in the case of infections likely to be due to a Multi resistant germ (nosocomial infection). In the absence of the germ in question, the choice of antibiotic is based on the clinical diagnosis according to the germs, usually responsible for the prejudiced pathology and their usual sensitivity to antibiotics **[1][13][14].**

I.6.2 Pharmacokinetic criteria

The selected antibiotic must be disseminated and present in active form at the infected site at a concentration higher than its MIC for the germ under consideration.It should be chosen according to its diffusion characteristics (meninges, lungs or elimination in active form (bile, urine**).[1,13,15]**

I.6.3 Individual Criteria

The choice of an ATB must take into account the field: pregnant woman, child, infant, newborn, elderly, allergic, immunocompromised … these situations may lead to dosage adjustments or contraindications **[1][13][16].**

I.6.4 Risk criteria

Adverse effects: for equal effectiveness, the least toxic ATB should be preferred.Ecological risk: the use of adapted narrow-spectrum antibiotics will be preferred to that of broad-spectrum antibiotics which are more strongly resistant. Medico-economic benefits: to efficiency and equal tolerance, preference will be given to the cheapest antibiotic**.[1,13][17]**

I.7 Main family of antibiotics

We distinguish between the main classes of antibiotics:

I.7.1 Aminosides

Aminosides are valuable antibiotics due to their spectrum of action and their efficacy. However, their therapeutic coefficient is not excellent and their indications must be strictly respected and the patient closely monitored, which explains why prescribing physicians prefer antibiotics which are easier to manage. Moreover, their use is limited by the fact that they are not administered orally **[18][19].**

I.7.2 Macrolide

Macrolides are bacteriostatic antibiotics. They are inhibitors of RNA-dependent protein synthesis. They bind to the 50S subunit of ribosomes, blocking protein synthesis. From the structural point of view, these antibiotics are characterized by an oxygenated lactonic macrocyclic ring, to which two sugars are linked by glycosidic bonds (at least one ose is amino) **[20][21].**

I.7.3 Tetracyclines

Tetracycline antibiotics have in common a bacteriostatic activity as wellgood tissue and intracellular diffusion.They constitute a homogeneous group despite pharmacokinetic

differences. Cyclinsall have a four-cycle core of the type“naphthacene- carboxamide”, on which various radicalscome to substitute on the carbons of the system cyclic, including many hydroxy groups **[22][23].**

I.7.4 Quinolones

Quinolones occupy a growing place in human medicine. The most recent derivatives present a broad antibacterial spectrum, increased antibacterial activities and improved pharmacokinetic properties, with a very good tissue diffusion enabling systemic infections to be treated **[22].**

I.7.5 Polypeptides

Polypeptides distinguish 7 groups **[1][24]:**

- Cyclic peptides represented by Capreomycin, Viomycin
- Glycopeptides represented by Vancomycin.
- Glycolipopeptides represented by telcoplanin, laramoplanin
- Lipopeptides represented by Daptomycin, Polymyxin

Polypeptides can be divided into: Vancomycin, teicoplanin, polymyxin.

I.7.6 Beta-lactams

Beta-lactam antibiotics are one of the most commonly prescribed drug classes with numerous clinical indications. Their advent starting from the 30s of the twentieth century drastically changed the fight against bacterial infectious diseases**. [25]**

ß-lactams are bactericidal molecules with the particularity of all having a beta-lactam nucleus in their chemical structure, this is a large family of antibiotics most used in antibiotic prophylaxis and in antibiotic therapy, it is made up of several subclasses including derivatives of penicillin and cephalosporins. **[3] [26][27]**

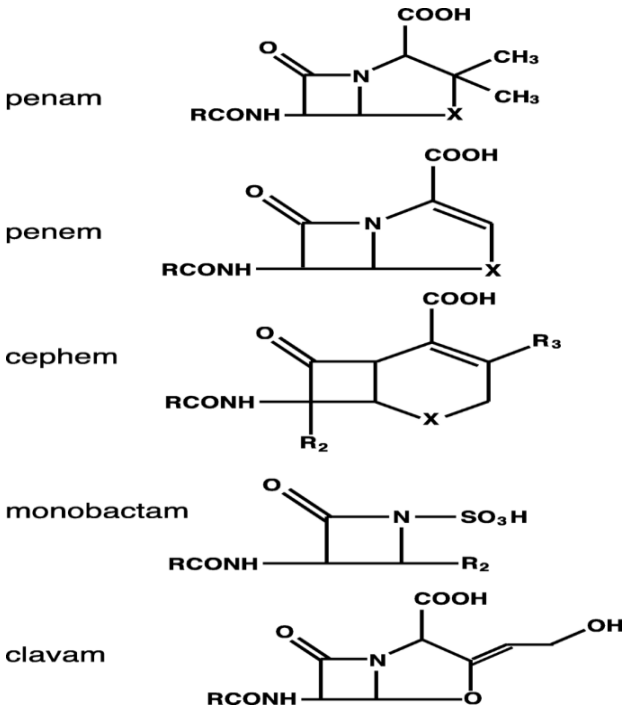

Figure 03. Structure of different classes of beta-lactam **[28][29]**

I.7.6.1 Penicillins

The penicillin family of antibiotics have bactericidal activity, excellent distribution throughout the body, low toxicity, and efficacy against infections caused by susceptible bacteria**.[30]** Penicillins belong to the large chemical family of beta-lactams, and are divided into six groups**: [31]**

- ***penicillin G*** or benzylpenicillin (parenteral route) and penicillin V or phenoxy-methyl-penicillin (oral route), sensitive topenicillinases
- ***M penicillins***, of which the leader, methicillin, acid-sensitive but resistant to penicillinases, is no longer marketed, as well asiso-oxazolyl-penicillins (oxacillin, cloxacillin), which are acid-fast.
- ***penicillins A*** (ampicillin, amoxicillin), acid-resistant, which have a broad spectrum; amoxicillin has a very good oral bioavailability.
- ***carboxy-penicillins*** (ticarcillin) and ureido-penicillins (piperacillin), which, beyond the spectrum of ampicillin, act onhospital enterobacteria and ticarcillin-susceptible Pseudomonas.
- ***amidino-penicillin*** (pivmecillinam)

I.7.6.2 Cephalosporins

The cephalosporins are a large group of related β-lactam antimicrobial agents. Favorable attributes of the cephalosporins include low rates of toxicity, relatively broad spectrum of activity, and ease of administration. Various cephalosporins are effective for treatment of many conditions,including pneumonia, skin and soft tissue infections, bacteremia, and meningitis**.[32]**

Their classification is based more on their spectrum of action, increasingly wider, than on a common chemical structure. They are thus classified, in first generation cephalosporins (ceflaxin, cefalotin, cefazolin, etc.) second generation (cefuroximes, cefoxitin, etc.), third generation (cefixime, cefepime..) and fourth (C4G) generation is also often called third generation expanded spectrum**.[33]**

I.7.6.2.1 Cefalexin

Cefalexin is a semi-synthetic derivative of Cephalosporin (which constitutes, with pencillins, the large family of beta-lactams). Its chemical formula is that of an acid: 7-beta acid (D-a arninophenyl-acetamido] -3-methyl-ceph-3-em-4-carboxylic)**.[34]**

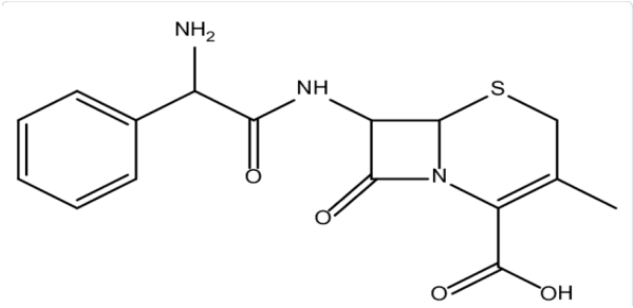

Figure04. Structure of cefalaxin **[35]**

I.7.6.2.2 Synthesis Mechanism of cefalexin

Cefalexin is synthesized from cephalophenylglycine, which is synthesized by reacting 7-aminocephalosporanic acid with a mixed anhydride synthesized by reacting *N*-carbobenzoxyphenylglycine and isobutyl chloroformate in the presence of triethylamine. Removing the *N*-carbobenzoxy protective group from the resulting product using hydrogen and a palladium on carbon catalyst givescephalophenylglycine in the form of an internal salt. Reducing this product with hydrogen using a palladium on barium sulfate catalyst results in the deacetoxylation at the third position of 7-aminocephalosporanic acid, making the desired cephalexin **.[32]**

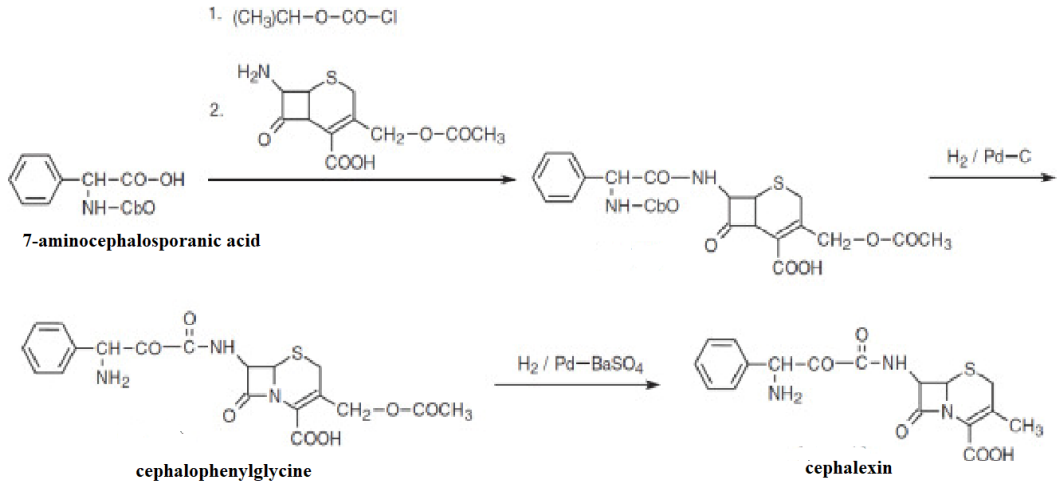

Figure 05. Synthesis routes for cefalexin**[32]**

I.7.6.2.3 Mechanisme of action

Cephalexin is a beta-lactam antibiotic that belongs to the first-generation cephalosporin class and is characterized by a beta-lactam ring in its structure. Within a bacterial cell, peptidoglycan provides mechanical stability to the cell wall. Cephalexin, along with other beta-lactam antibiotics, utilizes its beta-lactam ring to inhibit the synthesis of peptidoglycan, a crucial process in forming the bacterial cell wall.

More specifically, the beta-lactam ring of cephalexin binds to penicillin-binding proteins (PBPs), which effectively hinder the final stage of peptidoglycan synthesis, known as the transpeptidation reaction. This reaction is crucial for the cross-linking of bacterial peptidoglycan. By inhibiting this process, cephalexin disrupts cell viability, ultimately resulting in bacterial cell autolysis.**[37]**

Although this mechanism of cephalexin inhibits a crucial step in preserving the bacterial cell wall, bacteria can develop resistance to this antibiotic through various mechanisms:**[37]**

- The primary resistance mechanism involves bacterial expression of enzymes "beta-lactamases" that degrade beta-lactam antibiotics such as cephalexin.
- Moreover, bacteria can acquire resistance to cephalexin by modifying the PBPs, thereby altering the binding affinity of cephalexin to its target site.
- In addition, bacteria can synthesize efflux pumps that can expel cephalexin from within the bacterial cell.**[37]**

I.7.6.2.4 Cefalaxin used

Cefalexin is used to treat bacterial infections in various parts of the body, this includes: **[38]**

- Infections of your airways (chest and lungs).
- Throat, sinuses, ears.
- skin and soft tissue, kidneys and bladder
- Genitourinary tract infections, including acute prostatitis: E.coli, P.mirabilis, and Klebsiellasp**[39]**
- Cephalexin is also sometimes used for certain penicillin allergic patients who have a heart condition and are having a dental or upper respiratory tract (nose, mouth, throat, voice box) procedure, in order to prevent them from developing a heart valve infection.**[40]**

Its most common uses:

✓ **Urinary Tract Infection (UTI)**

Urinary tract infections (UTIs) are among the most common infections; 40% of women experience at least one during their lifetime, and about 10% get a UTI yearly. **[41]** Bacteria are the primary cause of UTIs. UTIs can occur anywhere in the urinary system—the urethra, the bladder, and even the kidneys, for example. **[41]** Despite this, UTIs in any area of the body share a few potential symptoms:

- Painful or difficult urination (sometimes called dysuria)
- Frequent urination
- lood in the urine (in severe infections)
- Stomach pain or cramping

Many UTIs are caused by E. coli bacteria, which cephalexin targets with relative ease. But cephalexin isn't a first-line prescription drug for UTIs—instead, providers primarily prescribe medication like nitrofurantoin, sulfamethoxazole/trimethoprim, and fosfomycin. **[42]**

✓ **Skin Infections**

Providers also use cephalexin to treat a variety of skin infections, including (but not limited to) **[43]:**

- Acne
- Impetigo
- Cellulitis

Treating bacterial skin infections like impetigo (caused by Streptococcus and Staphylococcus aureus bacteria) and cellulitis (typically caused by Streptococcus pyogenes bacteria, commonly associated with strep throat) makes sense**. [42,44]** And, while we often don't think of acne as bacterial, providers sometimes prescribe antibiotics in small doses to supplement oral and topical medications**. [45]**

✓ **Bone Infections**

Bone infections (called osteomyelitis) occur when bacteria penetrate the bone. This is an uncommon but very serious condition that can cause inflammation or even necrosis**. [46]** Risks for osteomyelitis include:

- Past bacterial infections
- Slowly healing, deep wounds
- Recent bone breaks
- Dental infections
- Recent surgeries

Providers use cephalexin to target two specific bacteria that can cause bone infections: S aureus (gram-positive) and P mirabilis (gram-negative). **[43]** They may

also prescribe it for use before and after a surgical procedure to prevent potential infections.

- ✓ **Lower Respiratory Tract Infection**

Providers also use cephalexin to treat bacterial lower respiratory tract infections, including **[43, 47]:**

- Bacterial pneumoni
- Bronchitis
- Bronchiolitis

A viral infection, bacteria, and fungi can all cause pneumonia, and it can take time for providers to determine which kind of pneumonia patients have. So, providers sometimes administer drugs like cephalexin in suspected cases of bacterial pneumonia while they await test results—this is especially common in patients with heart disease or diabetes**. [48, 49]**

Chapter 02:

Pharmaceutical forms and release of active substance

I. Introduction

Pharmaceutical chemistry is located at the crossroads of chemistry and pharmacology; its role is the study of any relationship between the structure of chemical bodies and their therapeutic properties. It concerns several activities: organic chemistry, physical chemistry, pharmacology, etc. It helps with the development, research, analysis and synthesis of therapeutic chemicals **[50].**

Among all the routes of administration, various expressions have been proposed to designate the dosage galenic forms making it possible to increase the duration of action of medicinal entities **[51, 52]**: sustained, controlled, delayed, slowed, extended, programmed release or action form. The oral route has always attracted great interest **[53]**. Forms taken orally present great ease of administration for the patient, while for researchers, the physiology of the gastrointestinal system can be easily modelled **[54, 55].**

The pharmaceutical forms intended for the oral route are numerous and have characteristics varied**. [56]** Galenic pharmacy, named after the famous 2nd century Greek physician, Galen, is the science and art of preparing an active ingredient to make it administrable to the patient in a form qualified as galenic **[57].**

II. Drug Composition (Galenic form):

Galenic formula is a medicine defined by its galenic formula which is in quality and quantity the different elements which enter into its composition we distinguish: [**58]**

II.1. The active principle (PA):

Any substance that has a therapeutic effect can be extracted from a natural source or synthesized chemically.

For PA to effectively exert its therapeutic activity, its blood concentration must reach a level sufficient for a therapeutic effect but not higher than the toxicity threshold. This blood concentration range is called the therapeutic zone **[59].**

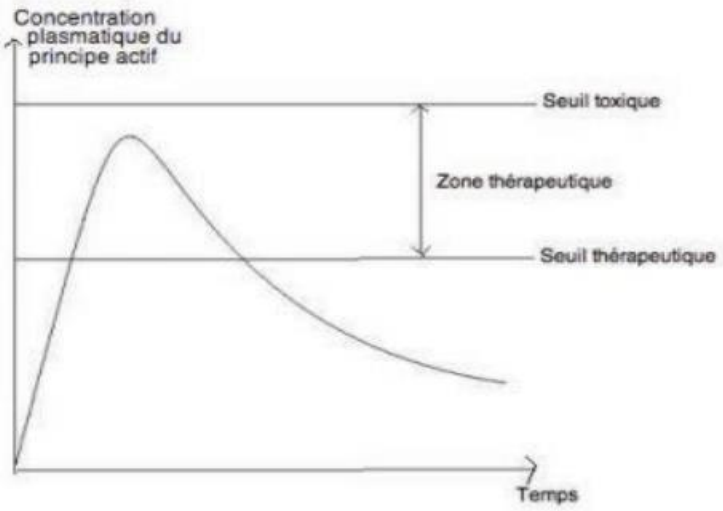

Figure 06: Concept of therapeutic zone

II.2 Excipients:

Any component other than the active principle intended to enter into the pharmaceutical composition of medicine, the function of which is to facilitate the administration, conservation and transport of this active principle to its absorption site.

- **Role of excipients:** Excipients can perform different functions:
  - ✓ Facilitate the administration of PA: (water for injectable preparations, the role of which will be to stabilize, solubilize or emulsify an SA), use of diluents (lactose, calcium dihydrogen phosphate, microcrystalline cellulose), use of coloring, flavoring , sweeteners (facilitates patient complacency, reducing possible bitterness).
  - ✓ Improvement of the stability: of the PA within the pharmaceutical form: as an antioxidant agent which will prevent premature oxidation of the PA, or of the excipient or of an antimicrobial agent (avoiding the development of micro-organisms: bacteria, fungi, yeasts in a solution, emulsion, suspension intended for multi-dose use after opening the preparation) **[60].**

III. Classification of dosage forms (Galenic forms):

Several types of dosage forms exist in pharmacology, the choice of medication is made according to the patient's data (sex, age, allergy, chronic illness, etc.). Below, we give the available medicinal forms:

III.1 Liquid forms

The liquid forms are homogeneous and of determined concentration. They are often packaged in single or multi-dose form; they are divisible into doses measured by volume (spoons, drops, etc.). They are absorbed easily, act quickly and are well tolerated. The main forms liquid galenics obtained by dissolution followed by various pharmaceutical operations are: syrups, suspensions and emulsions. **[61]**

Figure07: liquids dosage forms **[62]**

III.2 Solids forms

The solid forms of drugs play a central role in controlling their physicochemical properties and consequently the bioavailability. Multiple types of drug solid forms have been developed to achieve the desirable pharmaceutical profiles **[63];** Solid dosage forms include tablets, capsules, powders, and granules. Tablets and capsules are the most common solid dosage form**. [64]**

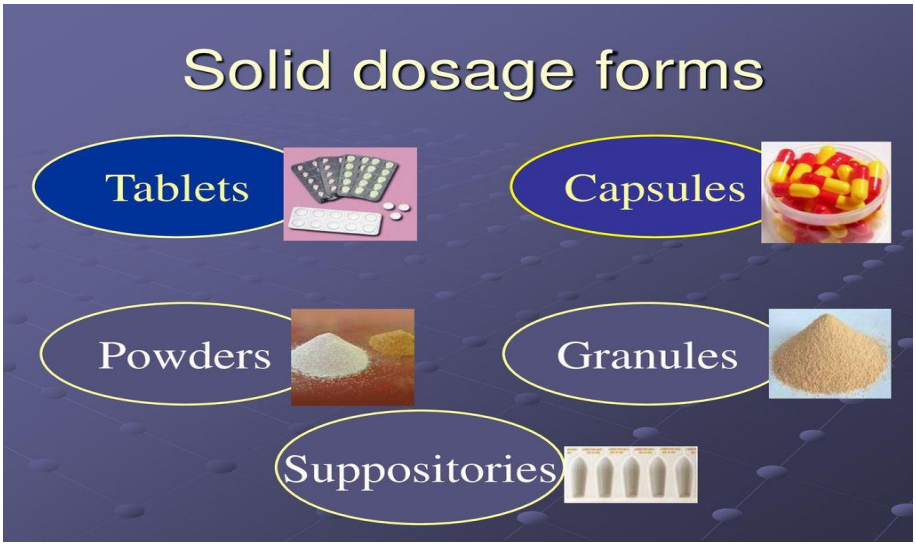

Figure08: solid dosage forms **[65]**

III.2.1 Tablet:

Most drugs are administered in the form of tablets or capsules that are taken orally ("swallowed"). The amount of drug is in the range of micrograms to several hundred milligrams. The aim is to get the drug in the right place in the body, with a concentration that is neither too high nor low, so within a "therapeutic window". Sometimes a more or less constant drug level is required; in other cases a short burst of drug is better. What happens largely depends on what the body does with the drug (a subject known as "pharmacokinetics"). **[66]**

Tablet is defined as a compressed solid dosage form containing medicaments with or without Excipients **[67]** According to the European and Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form prepared by compressing a drugs or a mixture of drugs, with or without diluents**[68]**. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. **[69]**

Tablets are generally used for systemic excretion of active ingredients. But there are also tablets with local release of the drug, for example, into the oral cavity, into the gastrointestinal tract, into the vagina, etc. **[70]**

Orally taken drugs can enter the body in several places **[66]**:

- Via the membranes of the mouth ("buccal" or "sublingual" administration)
- Via the membranes of the stomach.
- Via the membranes of the intestines.

III.2.1.a Types of pharmaceutical tablet:

There are several types of pharmaceutical tablets, including: **[71]**

- ✓ **Compressed Tablet:** provide rapid disintegration in gastric fluid after ingestion, allowing for quick absorption of the dosage form. They come coated or uncoated and are formed by compressing powdered, granular, or crystalline materials into the required shape.
- ✓ **Coated Tablets:** are compressed tablets that are coated in an additional layer, such as sugar or wax, to increase durability and ease of consumption. Examples include Advil and Diclofenac Potassium tablets.
- ✓ **Dispersible Tablets:** can be formulated as uncoated or coated tablets and offer uniform dispersion when suspended in water.
- ✓ **Effervescent Tablet**: are uncoated tablets that produce gaseous carbon dioxide when placed in water, causing it to quickly dissolve and produce a suspension of powdered material that is readily absorbed by the body once consumed.
- ✓ **Chewable tablets:** to be chewed in mouth before ingestion, mainly made for children and people that have difficulty in swallowing the intact tablet. Example chewable aspirin for children and antacid tablets. **[72]**

Prolonged Release Tablets: Prolonged-released tablets are also called sustained-release tablets and extended-release tablets. These are designed to release their medication in a predetermining manner over a prolonged period. Examples of Prolonged released tablets are Divalproex sodium extended-release tablets**. [73]**

III.2.1.b Advantages and Disadvantages of Tablets

- ➢ **Advantages [74]**

Tablet dosage form has number of potential advantages over the other solid dosage forms as well as liquid dosage forms such as:

1- Unit dosage form (dosage accuracy).
2- Compactness of dosage.
3- Easy to swallow
4- Highly soluble
5- Flexibility of dosage form

- ➢ **Disadvantages [74]**

1- highly amorphous substances are very difficult to compress
2- Poor wetting and slow dissolution drugs cannot be placed in the form of tablets.
3- Objectionable odor, bitter tasting and umectants substances need special treatment for compression.

IV. Classification of dosage forms according to the method of release:

The majority of oral dosage forms come in the form of tablets or capsules and can be divided into two main categories: Immediate release forms, and technologies of (non-immediate) forms modified, to which extended-release formulations belong. **[75]**

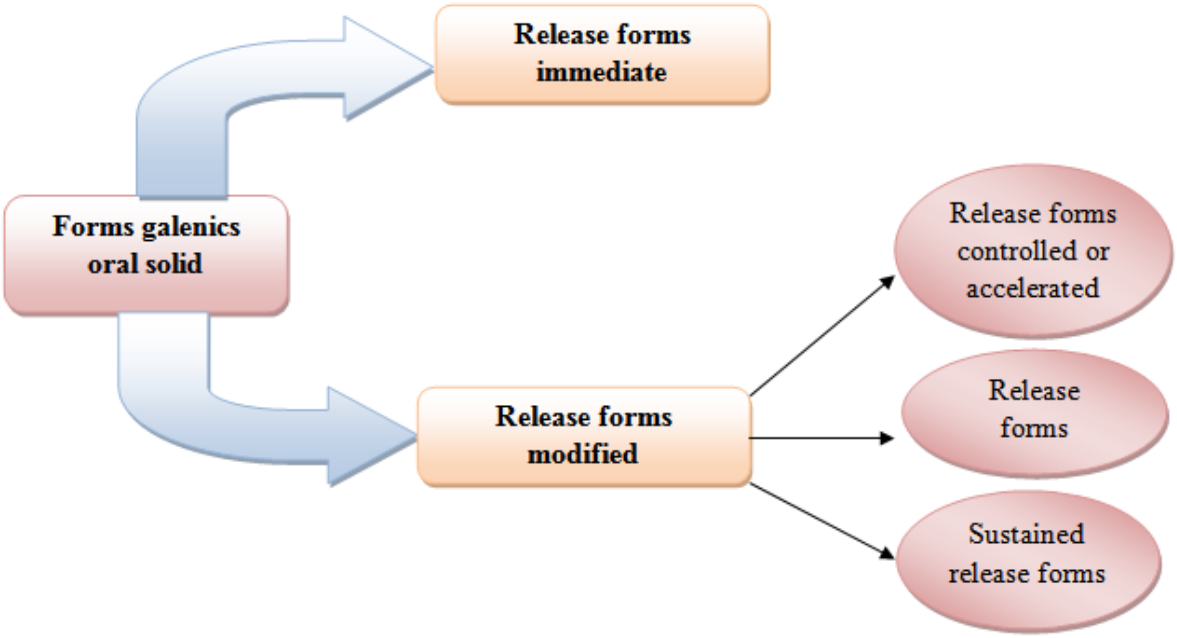

Figure 09: classification of dosage forms according to the method of release **[75]**

IV.1 Release forms immediate:

Immediate release forms must be capable of releasing the active ingredient(s). In the digestive tract, without delay or prolongation of its dissolution or absorption. Furthermore, it is specified that an immediate release form must be able to release at least 85% of the active ingredient incorporated during the hour.**[76]** .Sometimes this type of form requires repeated doses of medication at regular intervals throughout the throughout the day. Plasma concentrations of active ingredient will not reach then the therapeutic window only for a relatively narrow period of time, leading to poor sustained effectiveness and greater risks of toxicity in the event of non-compliance with the dosage. The only way to eliminate the peaks and valleys of plasma concentrations of a conventional therapy was an infusion permanent intravenous, cumbersome and expensive method. **[77]**

IV.2 Modified release dosage form:

The European Pharmacopoeia defines modified release tablets as “tablets, coated or not, which are prepared with special excipients, or by particular processes, or both, aimed at changing the speed, location or timing of the release of the active substances, The modified release form is a preparation where the release of the substance(s) active(s) has been the subject, as to its speed and/or location, of a deliberate modification resulting from an particular formulation and/or a special manufacturing process, and is therefore different from the form to be conventional release administered by the same channel. **[78]**

IV.2 Delayed or deferred release form

The release of the AP may be delayed in time or space compared to the immediate release. These formulations are called "delay forms". The plasma profile conventional is moved to the right. **[79]** La dissolution et l'absorption du principe actif s'effectuent au niveau intestinal. Ces formes empêchent l'irritation gastrique ou la dégradation des principes actifs fragiles à pH acide. Il s'agit majoritairement de formes gastro-résistantes. Les comprimés ou granulés sont recouverts d'un film polymérique, insoluble en milieu acide mais perméable à l'eau en milieu alcalin ou de type lipidique dégradé par les lipases intestinale.

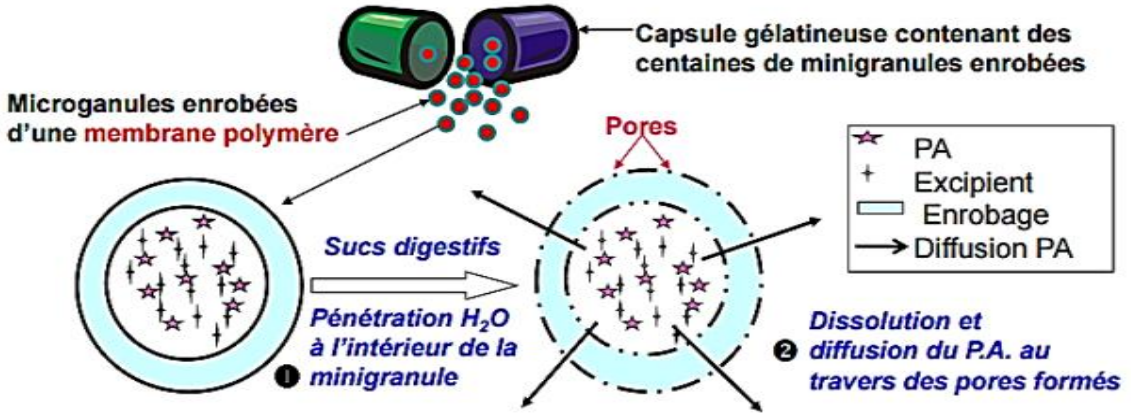

Figure10: Example of the delayed release of an active ingredient (AP)

IV.2.2 Prolonged or gradual release form:

Several pharmaceutical technologies make it possible to prolong the release of a principle active and thus reduce the frequency of administration compared to medications conventional. **[80]** Sustained release means that the active ingredient is released from its dosage form over a period of time. More or less extended period of time, in some cases at constant speed. The purpose being to obtain constant plasma levels or to reduce the frequency of administration for short-acting active ingredients for which prolonged action is desired **[81].** Sustained release is based on two principles: **[81]**

- The speed of release of the active ingredient from the galenic form is slower than in the case of conventional release. This step is prior to the dissolution steps and absorption. It therefore corresponds to the limiting factor which controls the dissolution and absorption.
- The duration of this release is spread over time.

IV.2.3 Controlled or accelerated release form:

A controlled release pharmaceutical form can be defined as a system capable of delivering an active substance to a fixed target, at a speed and for a expected duration to achieve the desired therapeutic effect **[82]** Accelerated release tablets are formulated to achieve a short disintegration time. They include **[83]:**

- Effervescent tablets

- Orodispersible tablets

The advantages of controlled release are numerous: **[84]**

- Reduction of daily catches.
- Increased comfort for the patient.
- Improvement in treatment compliance.
- Reduction of undesirable side effects by suppression of plasma peaks.

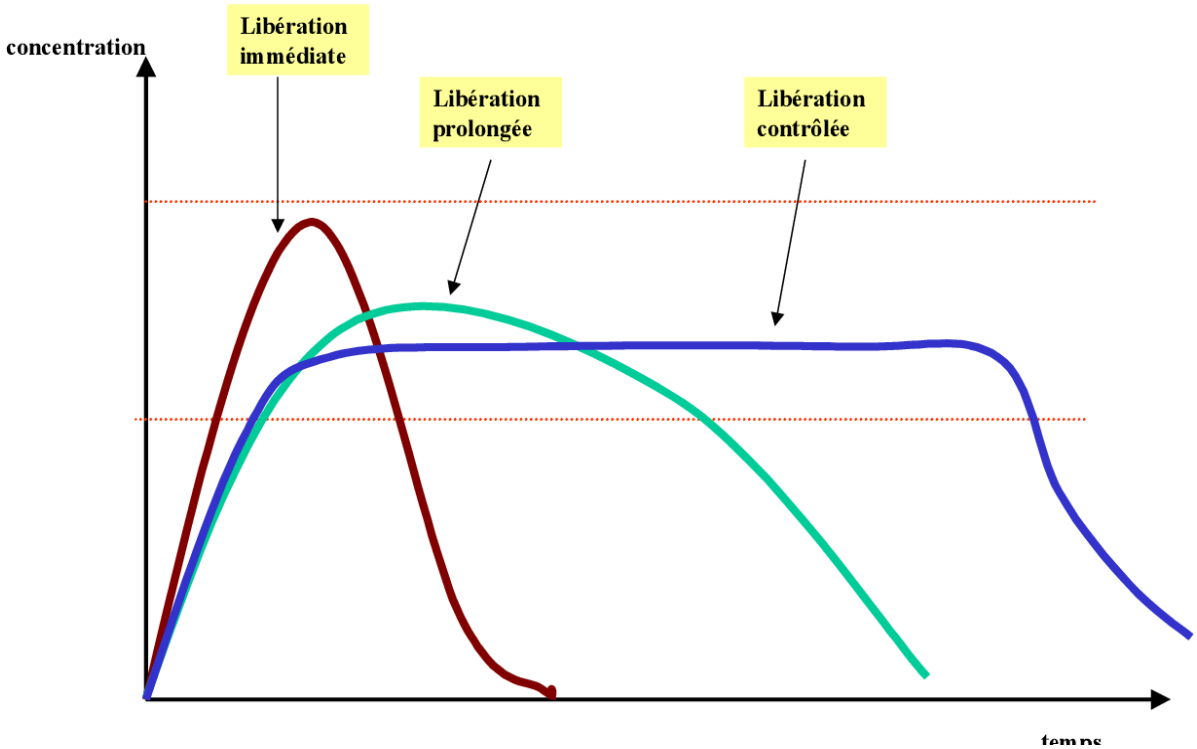

Figure11: Representation of the different release profiles: immediate, prolonged and controlled of an active ingredient **[84]**

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Experimental Part

The present work focuses on the development of new formulations based on Cefalaxin (Cf) in order to control its release simultaneously. For this purpose, two polymers were added as a matrix in the formulation of Tablets with EC using the same process of preparation for a regular drug release

In the first part , we will cite the products and materials used, the description of the synthesis of the CTA cellulose triacetate polymer and the active ingredient(Drug) “cefalexin Cf” and the characterization of the products obtained, then we will move on to the preparation of the forms galenic "tablets" based on EC alone or in a mixture of PEG and EC, CTA and EC then the study of the release of the active principle from these tablet in two physiological environments Stomach pH=1.2 and intestinal pH=7.7

I. Syntheses and characterizations

I .1 Products and Materials used

I .1.1 Materials used

- Agitateur magnétique
- Spectrophotomètre UV-Visible
- pH meter paper

I .1.2 Chemical products

- Ethyl cellulose Obtained from Fluka Analytical (USA product)
- Cefalaxin
- Sodium tetra Borate 10 hydrate (Borax) comes from Panreac(Barcelona-Spain)
- Ethanol
- PEG
- Cellulose Triacetate CTA (Synthesis)
- Sulfuric acid (96-98%) comes from Organics
- Acetic acid (99-100%) comes from Biochem Chemopharma)
- Acetic Anhydride comes from Merck
- NaCl, origin : Acros Organics
- HCl (36%) is a product of Stinnes Chemicals

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

Is a linear polysaccharide derived from the naturally occurring polymer, cellulose and therefore possesses its polymeric backbone which is based on the repeating structure of ß-anhydroglucose ring having three reactive hydroxyl functional groups **[1].**

EC is a hydrophobic cellulose derivative that is very strong, but also very brittle. Its hydrophobic properties can be used to prolong drug release when used in combination with other polymers **[2]**. It is insoluble in water but soluble in a variety of solvents **[3].**

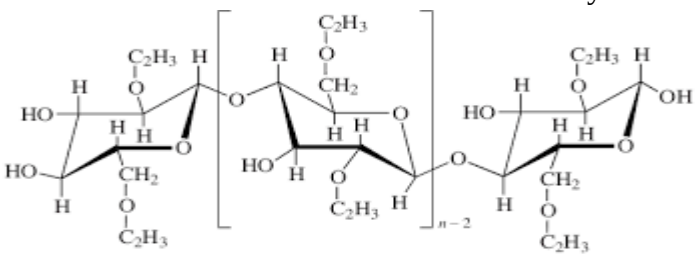


Figure01: Structural formula of ethyl cellulose. **[4]**

Ethylcellulose has been widely used in the pharmaceutical industry due to its many versatile properties such as **[5] [6]:**

- ✓ Insoluble in water but soluble in several organic solvents such as alcohols, ethers, ketones and esters.
- ✓ Stable against light, heat, oxygen, humidity and chemicals.
- ✓ It has the capacity to absorb pressure and therefore protect the tablet from fracture during compression.
- ✓ Non-swellable and insoluble in water, therefore its compactness and porosity play a key role in the release of the hydrophobic drug **[7].**
- ✓ Although it is insoluble in water, it can absorb water. This is due to its potential to establish hydrogen bonds with water, attributable to the difference in polarity between the oxygen atom and the ethyl group of the EC **[7, 8].**
- ✓ It can also be used in combination with water-soluble polymers to prepare sustained release film coatings which are frequently used for coating microparticles, pellets and tablets **[9].**

I .1.2 .b. Ethylene glycol (PEG)

Poly (ethylene glycol) (PEG) is a low toxic, hydrophobic, semi-crystalline polyether that is composed of (CH2 single bond CH2O) repeating units. PEG is also known as Polyoxyethylene or polyethylene oxide (PEO) **[10]** With properties that limit antigenicity, immunogenicity, cell adhesion, and protein binding , PEG homopolymer is a polyether which can be polymerized from ethylene oxide by condensation **[11].**

Polyethylene glycols (PEGs) are ethoxylated polymer-solubilizers that are readily soluble in water, ethanol, acetone, glycols and chloroform. Applicable for oral and topical formulations, these excipients can also be used as chemical intermediates in drug formulations. Our high and low molecular weight PEGs are available as liquids, semi-solids, and solids to suit your individual formulation needs **[12].**

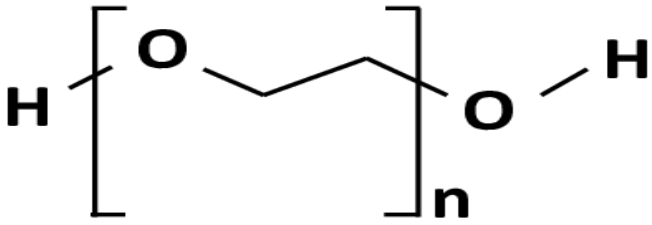


Figure02: Structural formula of PEG **[13]**

I. 2. Chemical synthesis of Cellulose Triacetate (CTA)

In a 250 ml flask equipped with a thermometer, 1.5 g of cotton (cellulose) are introduced, 12 ml of pure acetic acid and two drops of 95% sulfuric acid are added. The mixture is brought to reflux between 60-70 ° C for 30 min, the married bath is released and cooled with water, 12 ml of acetic anhydride are then added from the top of the refrigerant in small quantities, the mixture is heated again at 70°C until the cotton has completely disappeared (approximately 15 min).The medium is cooled and 5 ml of an aqueous solution of acetic acid at 20% by volume are added. The mixture is heated again between 60 and 70° C. (for 10 min).After complete cooling, the contents of the flask were poured into a 400 ml beaker, 100 ml of hot distilled water were added slowly while stirring, the cellulose triacetate precipitated, filtered through a Büchner then the product was washed with the water. The washing operation is repeated several times until neutralization, the final product is dried in the oven at 60°C **[14].**

Figure 03: **a)** Reflux heating assembly. **b)** Cellulose triacetate after drying

I .3 Tablet formulation

I .3 .1 Products used for tablet preparation

Cefalexin (Cefa), cellulose triacetate, Ethylcellulose (EC), Polyethylene Glycol, Ethanol (PEG), Amidon (Starch).

I .3 .2 Preparing the tablets

Four tablets of different compositions containing cefalexin were formulated (Table 01). The Tablets were prepared manually, using a few milligrams of cefalexin dispersed in Ethylcellulose alone or in mixture with other polymers as CTA and PEG. Absolute Ethanol is then sprayed into sufficient quantity of the four mixtures thoroughly crushed to obtain a final mass.

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

Tablets (quality)	**Before drying m(g)**	**After drying(g)**	**Yield %**
T1: 0,2g (EC)+0,1g(Cefa)	0,36	0,24	80%
T2:0,15 (EC)+0,15 (Cefa)	0,37	0,27	90%
T3:0,1(PEG)+0,1(Cefa)+0,1(EC)	0,33	0,23	76,66%
T4:0,1(CTA)+0,1(Cefa)+0,1(EC)	0,48	0,27	90%

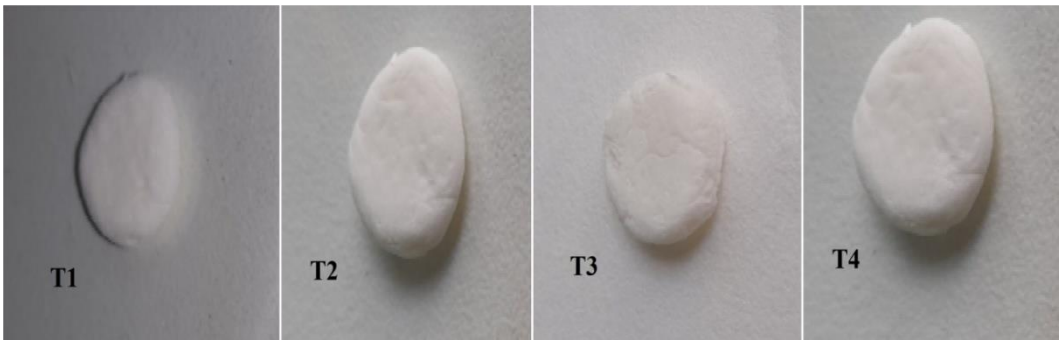


Figure 04: photo of tablets

I .4 Characterizations

I .4.1 Characterization of Cellulose Triacetate CTA:

The prepared polymer was analyzed by infrared spectroscopy; we were able to identify some characteristic bands of the CTA.

I .4 .1 .1 Fourier transforms infrared spectroscopy (FTIR):

The functional groups of samples were detected by infrared spectrometry at Fourier transform FTIR-600 (Agilent Technologies Cary Spectrophotometer), in the range of 4000-500 cm-1 wavelengths.

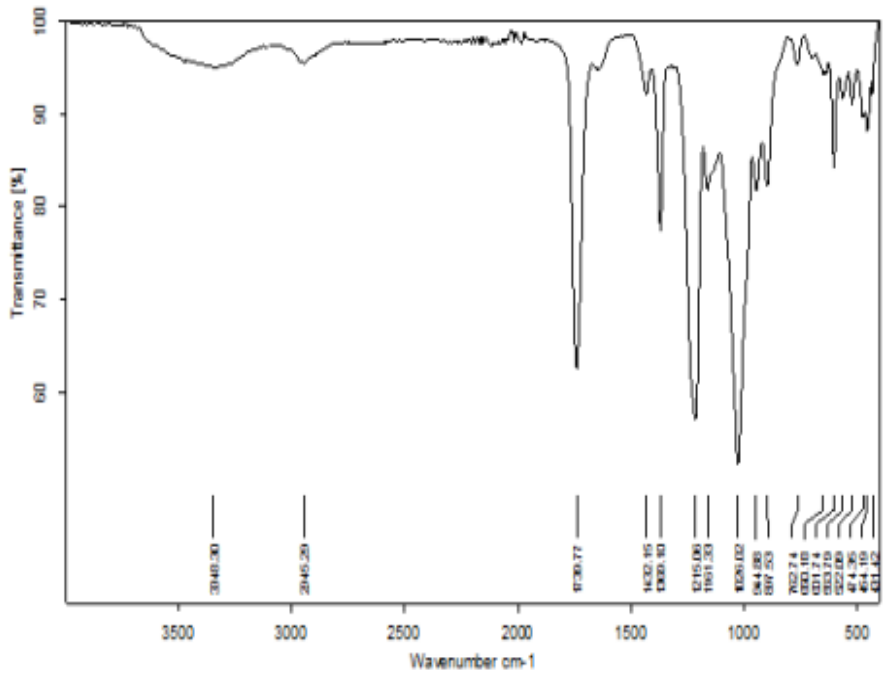


Figure 05: Infra Red Spectrum of Cellulose Triacetate

The characteristic bands of IR spectrum of CTA polymer have been collected in the following table02:

Table 02: The CTA IR Spectrum Characteristics bands

Wave number υ (cm-1)	**Functional groups**	**Nature**
1365	acetyl groups –C-CH3	Deformation
3348.30	O-H libre	Elongation
1739.77	C=O vibration of ester carbonyl	Elongation
2945.29	C-H aliphatic	Elongation
1432.15	aromatic C=C vibration	Deformation

I .4 .1.2 X-ray Diffraction Analysis XRD

The Bruker D2 Phaser SSD 160 diffractometer was used to report the Cellulose Triacetate CTA diffractogram. The instrument equipped with the detector scintillation. Samples were placed in a sample holder and scanned over a range from 0 to 80° and rotated at 30 rpm to obtain an average diffractogram of the samples. The XRD of CTA was done at the IBN KHALDOUNE University of TIARET.

The CTA diffractogram shows a broad band, confirming the structure amorphous of the polymer obtained.

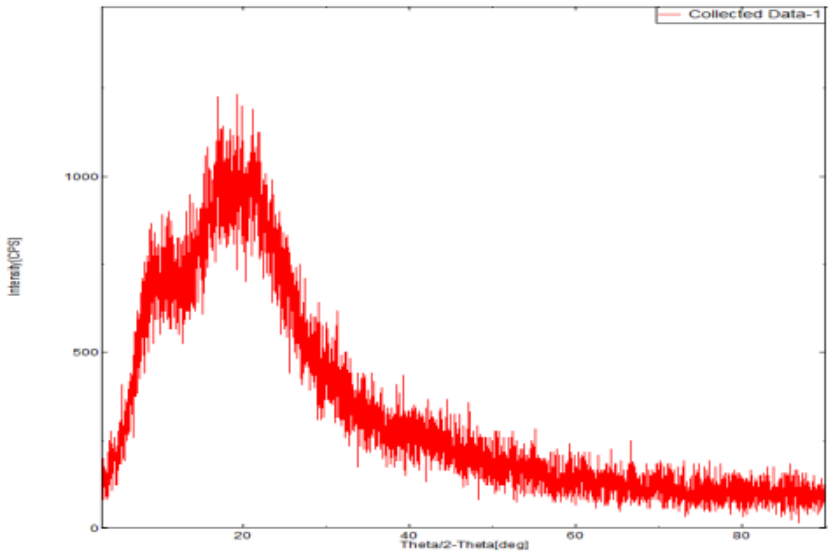


Figure 06: Difractogram XRD of cellulose triacetate polymer

I .4 .2 Characterization of cefalexin by FTIR:

The active substance "Cefalaxin" was characterized by FTIR. the IR spectrum presented in the (Figure 07) indicates the presence of major characteristic absorption bands at 3315.05 cm-1 (N-H), bands 1857.12 cm-1 may be due to the presence of C=O acid. A band at 1735.63 characterizing the C=O ketone bond, and another band at 1690.25 cm-1 indicating the presence of the carbonyl group C=O of the amide function, 3072.06 cm-1 C-H (aromatic) and around 1645.79 cm-1 -C=C- (aromatic).

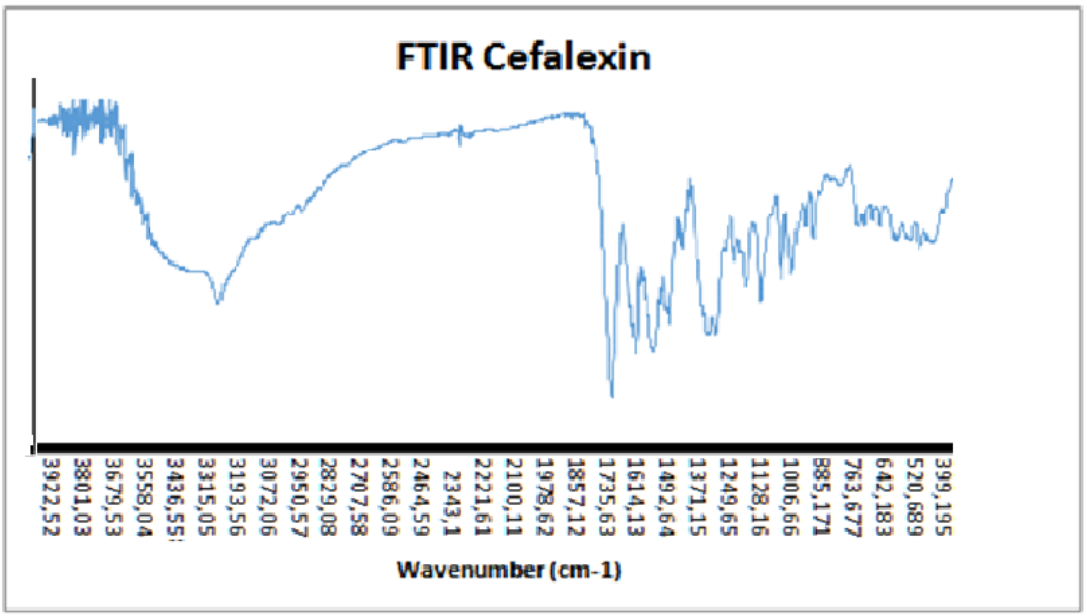


Figure 07: Infrared spectroscopy of Cefalaxin

I .4 .2.1 Infrared Spectroscopy of Ethylcellulose

FTIR spectra (Figure 08) Ethyl cellulose represents the C-H (aliphatic) stretching at 2858 cm-1, C-O-C (ether linkage) at 1122.37 cm-1, O-H (phenolic) stretching at 3436.55 cm-1, C-C (aromatic) at 1556.28 cm-1

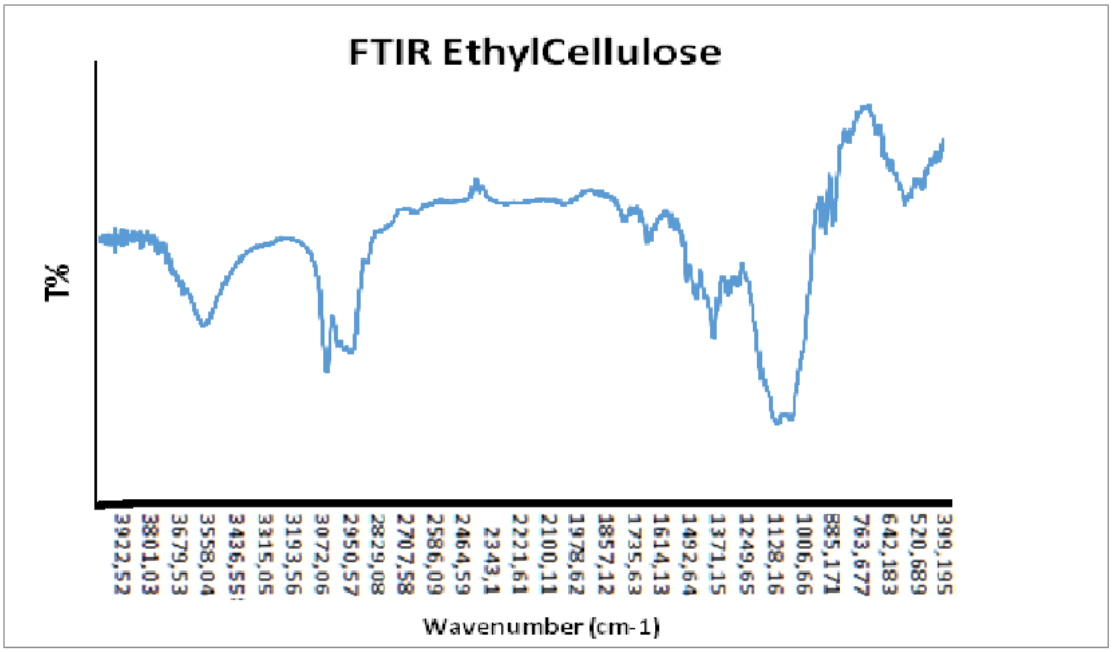


Figure 08: infrared spectroscopy of EC

Table03: The EC IR Spectrum Characteristics bands

Wave number υ (cm-1)	Functional groupings
2858 cm-1	C-H (aliphatic)
1122.37 cm-1	C-O-C (ether)
3436.55cm-1	O-H (phenolic)
1556.28 cm-1	C-C (aromatic)

I .4 .2.2 Infrared spectroscopy of Polyethylene glycol: (PEG)

The FT-IR spectra of PEG (Figure 09) The peaks at 3400 cm−1 are ascribed to O–H stretching. The band observed at approximately 2900 cm–1 was attributed to the C–H stretching vibrations of the –CH2 group. The band at 1060-1100 cm–1 was attributed to the C–O stretching vibration. The absorption at 1452 cm–1 was designated to the C–H bending vibrations of the –CH2 group

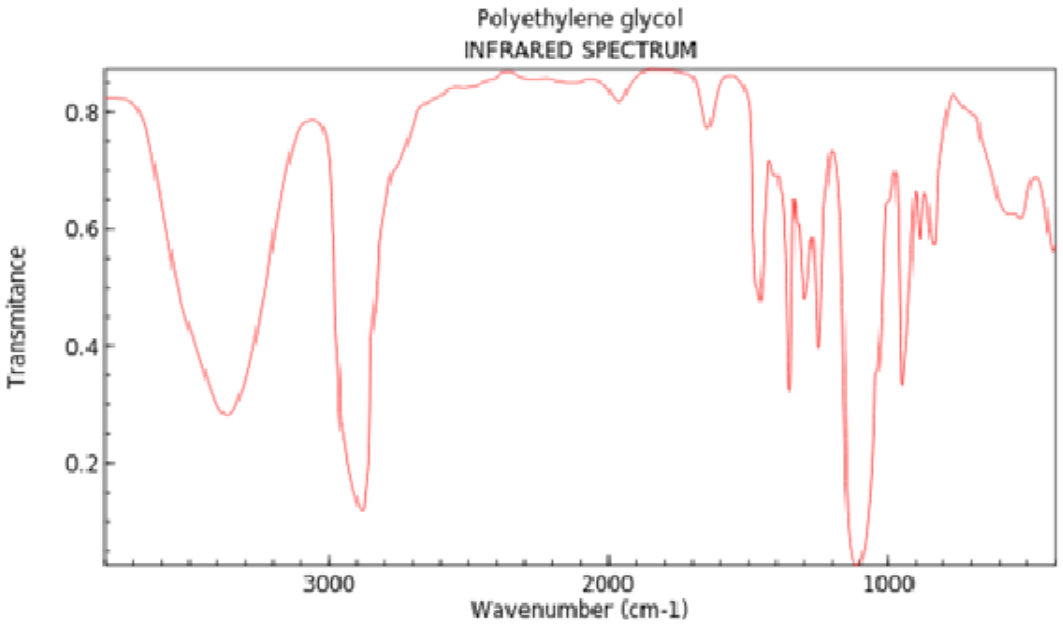


Figure 09: Infrared spectroscopy of PEG **[54]**

I .4.2.3 Infrared spectroscopy of Tablet 4:

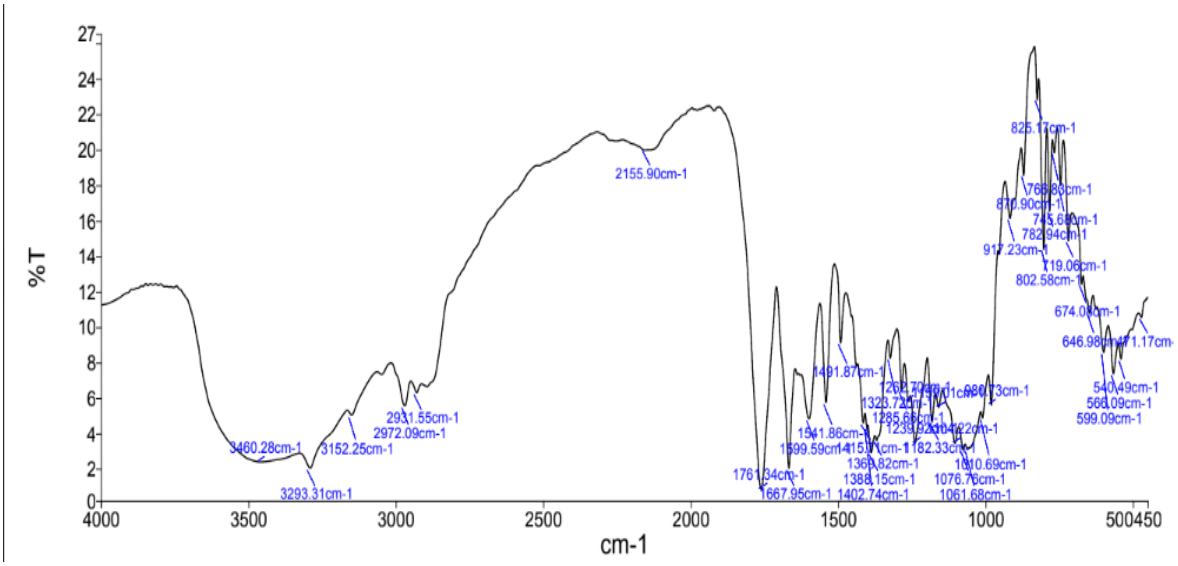


Figure10: Infrared spectroscopy of Tablet 4

The IR spectrum of Tablet 4 based on the polymer (CTA+EC) and CF allowed us to observe the main characteristic bands relating to the different groups present. We note the presence of the characteristic bands of the O-H alcohol group located at 3460.32 cm^{-1}, as well as that the characteristic bands around 3293.31 cm^{-1} N-H 2972.09cm^{-1}, 2931.55 cm^{-1} corresponding to aliphatic C-H, 2155.90 cm^{-1} C≡C, and around 1761.34 cm-1 C=O, 1667.94cm^{-1}, 1599.59 cm $^{-1}$, 1491.87 C=C aromatic vibrations and 1369.82cm^{-1} present the acetyl C-CH3 group

The results show that the spectrum of the Tablet 4 is only the sum of the FTIR spectra of Cefalexin, EC and CTA. The main absorption bands of CF which appear clearly in the disk spectrum

I .4.3 X-ray Diffraction Analysis

I .4.3.1 X-ray Diffraction Analysis of Cefalexin:

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°.

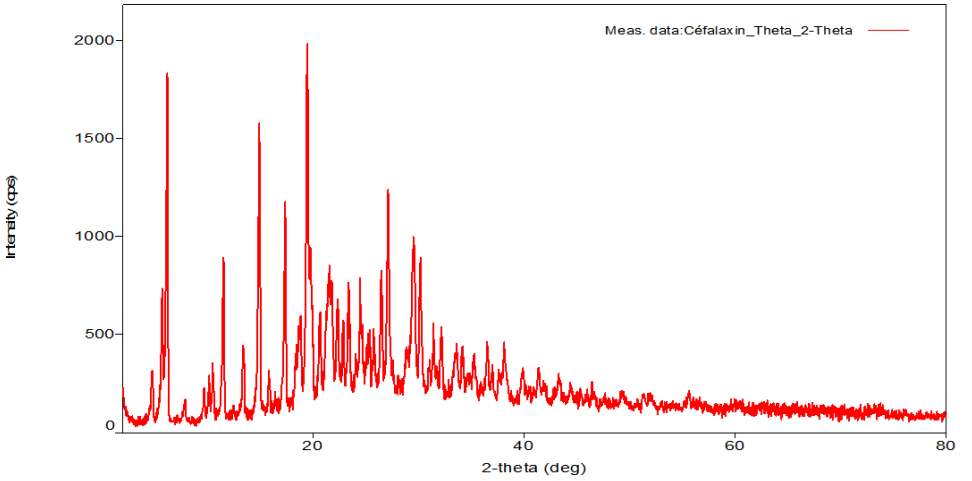


Figure 11: X-ray Deffraction analysis of cefalexin

The diffractogram of Cefalexin (Figure 11) clearly shows the presence of characteristic crystallinity peaks which appear in the form of a more intense peak as 2Θ=6.2°, 11.54°, 14.94°, 19.48° and 27.09°.

I.4 .3.2 X-ray Diffraction Analysis of EC

The following (Figure 12) 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

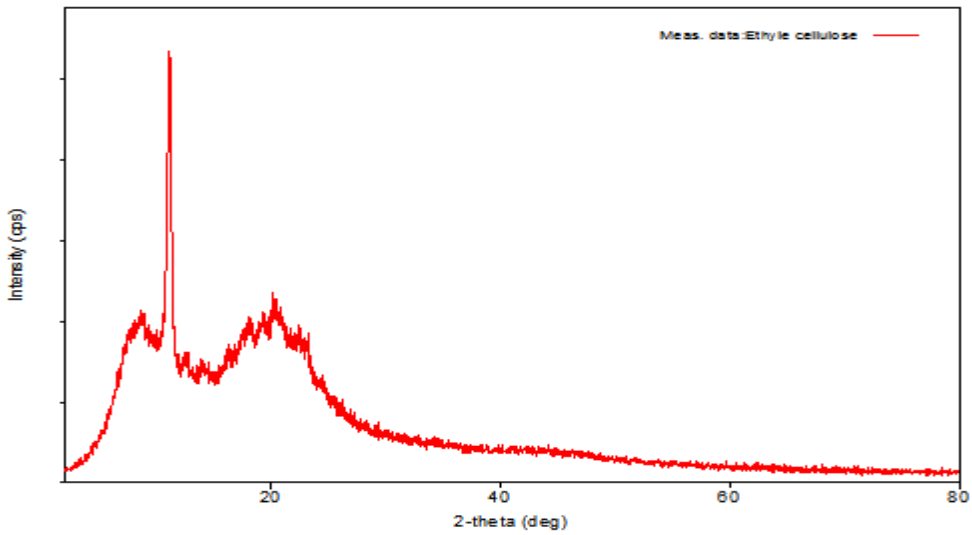


Figure 12: XRD Difractogram of EC

I .4 .3.3 X-ray Diffraction Analysis of Tablet

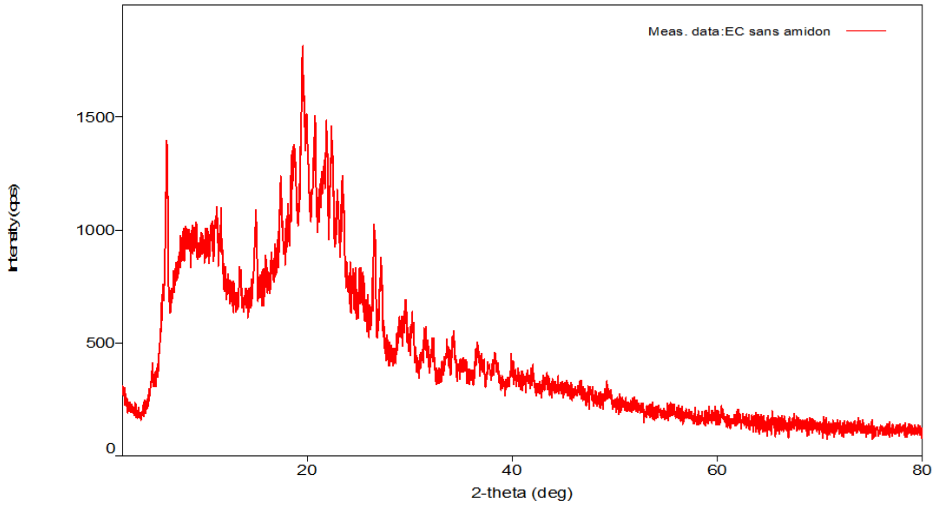


Figure 13: X-ray Deffraction of tablet T1

This (figure 13) presents the XRD patent of Tablet T1, the tablet is the mixture between Ethylcellulose and Cefalexin, the deffractogram clearly shows the presence of some peaks with different intensity. Those peaks are confirmed the presence of Cefalexine in the tablet in the broadband of EC which is a semi-crystalline polymer. This allows us to say that the cefalexins are dispersed in the polymer matrix; the presence of EC reduces the crystallinity of the cefalexin

II. Study of the kinetics of the release of active principle in pH=1.2 and pH=7.7

The release of the active ingredient was monitored using a UV-Vis spectrometer, previously calibrated at the wavelength λ_{max} of the active ingredient used (cefalexin) in the medium considered.

In the case where the drug is dispersed alone in the coating matrix, its release by diffusion through this matrix depends on three essential factors:

- The speed of "penetration" of the liquid into the dosage form through the polymer-matrix structure.
- The speed of "dissolution" of the active ingredient in the trapped liquid.
- The "diffusion" of the active ingredient through the polymer matrix.

The objective of this kinetic study is to compare the "prolonged and controlled" effect on the release of this active principle through different polymeric matrices.

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 experiments

II.2 Composition of the study environment

For our various kinetic studies, we chose to reconstitute two environments physiological pH = 1.2 and pH = 7.7, these environments correspond to the longest stay times most important during the digestive tract, they are prepared in accordance with standards described by the American Pharmacopoeia U.S Patent XX:

- **Gastric medium pH = 1.2:**

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

- **Intestinal environment of pH = 7.7:**

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

Artificially reconstituted physiological environments of pH = 1.2 and pH =7.7 at 37°C, will allow us to evaluate the effect of the matrix and its composition as well that the influence of the environment on the kinetics of release of the active principle from different formulations made.

II.3 Active ingredient calibration

For the active substance "cefalexin", we used the method which consists of first preparing a stock solution of a given concentration from which we prepare, by successive dilutions, a series of solutions of well-determined concentrations and analyzed by UV spectrophotometer -visible. 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 ingredient spectra were carried out on a JENWAY 7305 Liquid Spectrophotometer in two pH media (**1.2** and **7.7**) in the chemistry laboratory at the University of Ain Temouchent and confirmed in the laboratory at the university Ibn Khaldoun of Tiaret. The wavelengths are expressed in "nm" and are respectively 297nm.

Figure 14: JENWAY 7305 Liquid Spectrophotometer of UV

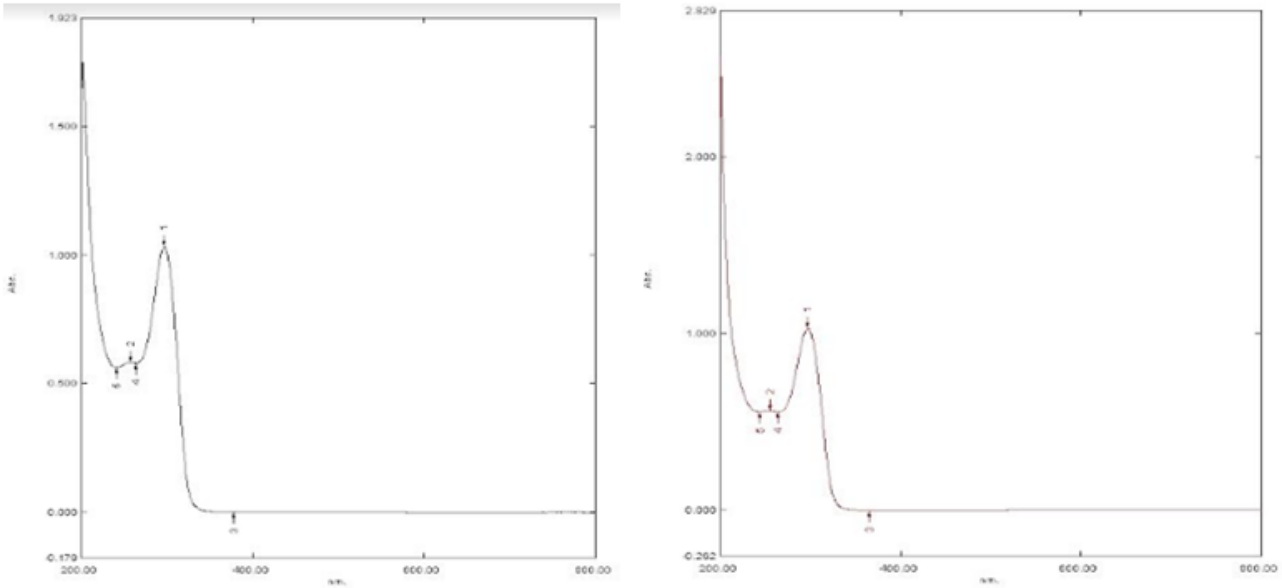


Figure15: a) Maximum wavelength **pH 1.2**; **b)** Maximum wavelength **pH 7.7**

II.3.2. Cefalexin calibration curve at pH=1.2

Table04: The dilutions different concentrations ceflexin in 25 ml of pH=1.2 (297nm)

C (mg/ml)	0,01	0,008	0,005	0,003	0,002
Abs (nm)	0,842	0,693	0,495	0,39	0,307

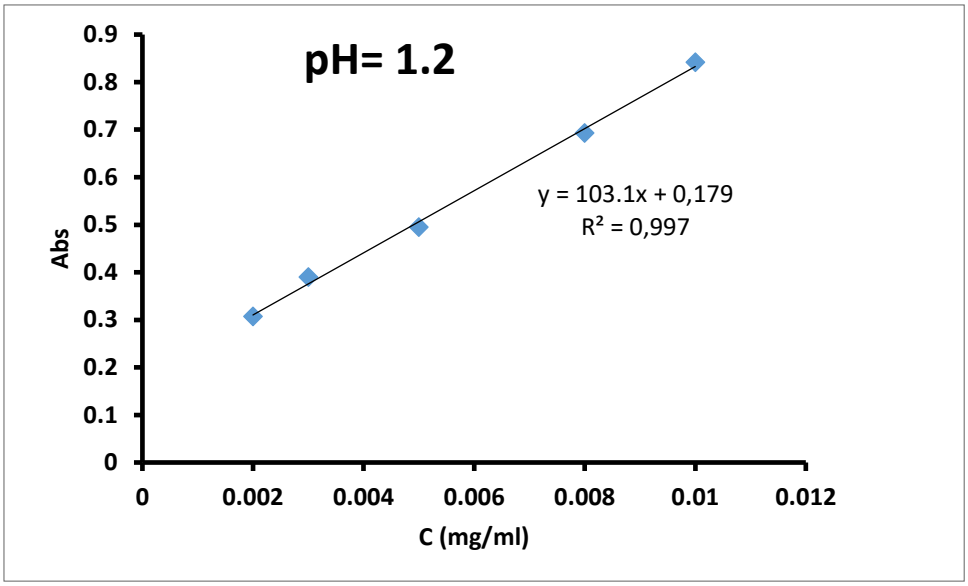


Figure16: Calibration curve of cefalexin at pH=1.2 (297nm)

II.3.3. Cefalexin calibration curve at pH=7.7

Table05: The dilutions different concentrations ceflexin in 25 ml of pH=7.7(297nm)

C (mg/ml)	0,01	0,008	0,005	0,003	0,002
Abs (nm)	0,543	0,448	0,335	0,235	0,206

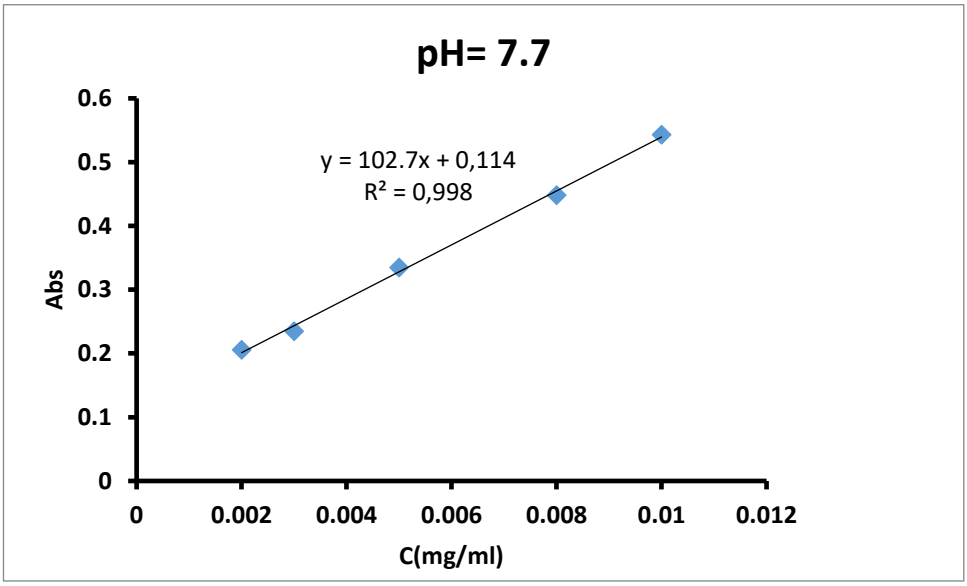


Figure17: Calibration curve of cefalexin at pH=7.7(297nm)

La droite A= f(C) étant linéaire, sa pente à l'origine correspond à Ɛmax

Table 06: Represents the values of λ max and Ɛmax of ascorbic acid in the different media

Active substance	medium pH	λ max (nm)	Ɛmax (L.mol-1 .cm-1)
Cefalexin	1.2	297	103.1
	7.7	297	102.7

II .4 Measurement conditions

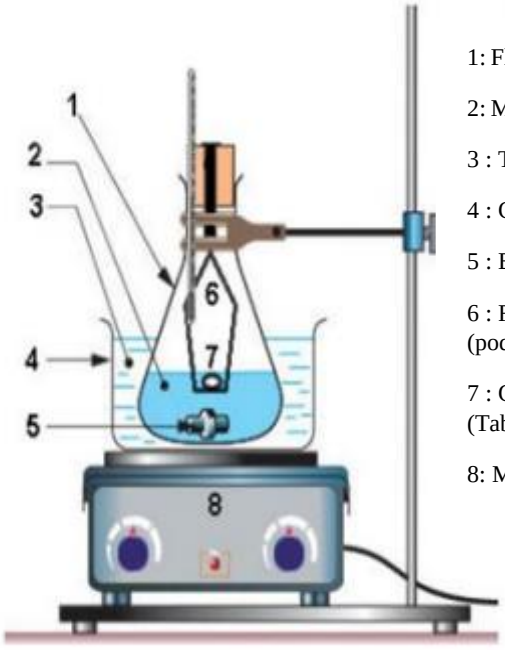
The kinetics corresponding to the different forms were carried out under the same operating conditions:

- Disk preparation: is done in the same way as explained.
- The support of the discs: it is made of fiber glass, a little high compared to the magnetic bar in order to avoid the shocks which may occur there and also allows good agitation and circulation of the liquid around the galenic form.
- Temperature (37°C), Stirring (500 r.p.m)
- Initial volume in the bottle (100 mL) and volume of the test portions (1 mL), in order to ensure better reproducibility of the results and to be able to compare them.
- Maximum wavelength: measurements are made using a UV device.

II .5 Kinetics of Cf release from discs

II .5 .1 Operating Mode and Experimental Device

In a 500mL capacity bottle, the dosage form was placed in 100mL of the study environment (pH=1.2; pH=7.7). The medium was maintained at 37°C and stirred at a rotation speed of 500 r.p.m using a magnetic stirrer. At each time "t" the disk is removed from the bottle, rolled on Joseph paper to remove the film of liquid which had formed, 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.



1: Flask

2: Medium

3 : Thermometer,

4 : Crystallizer,

5 : Bar magnet,

6 : Fiber support (pod)

7 : Galenic form (Tablet),

8: Magnetic stirrer.

Figure 18: Experimental device for releasing tablet

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:

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

$$mt = D.O .Vd . MM / \varepsilon.Vf$$

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

MM: 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 "disc" 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 cefalexin release

The PA release kinetic curves illustrate the quantity of PA released as a function of time in the environment ph1.2 and ph7.7.

The graph presents the release kinetic curves of four different systems:

starch-free EC tablet

CTA + EC

EC + PEG

II.5.2.1. Release of Cefalexin from EC Discs Alone:

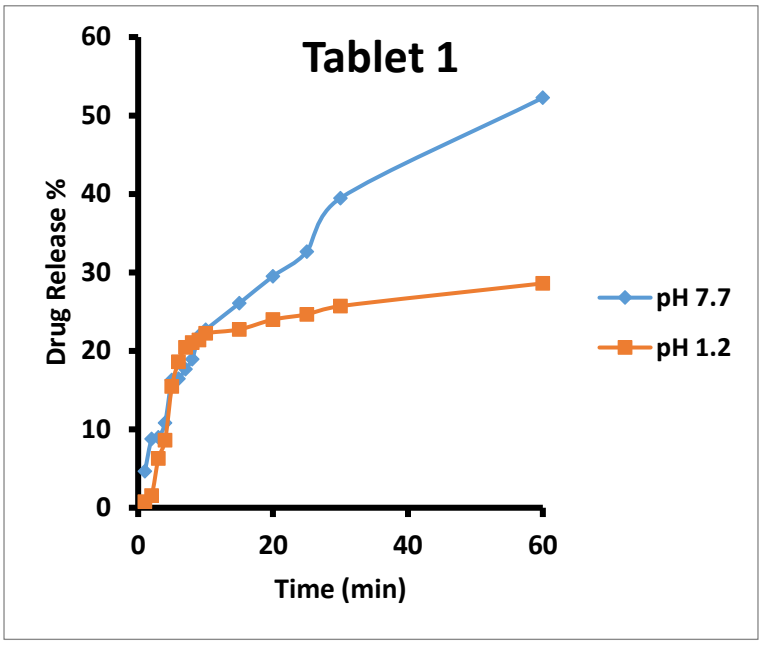


Figure19: % active ingredient cefalexin released as a function of time at pH=1.2 and pH=7.7 of T1 (T =37°C, 500 r.p.m)

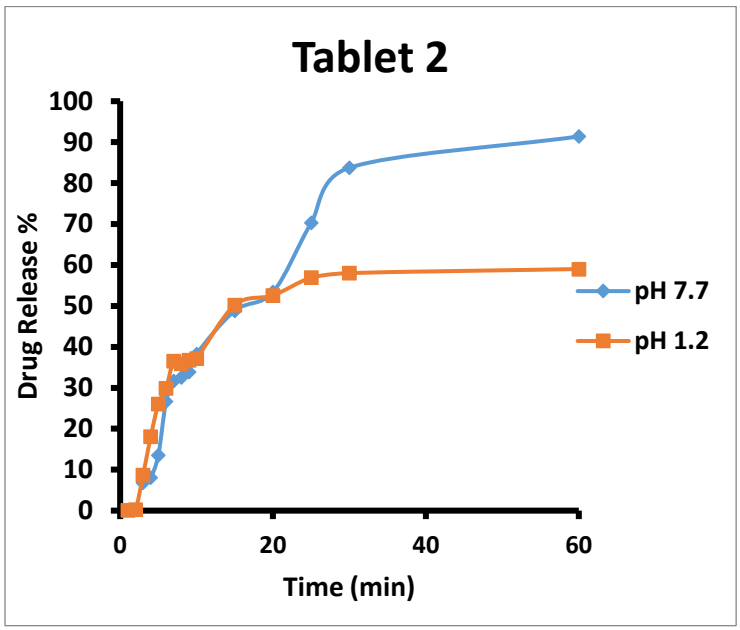


Figure20: % active ingredient cefalexin released as a function of time at pH=1.2 and pH=7.7 of T2 (T =37°C 500 r.p.m)

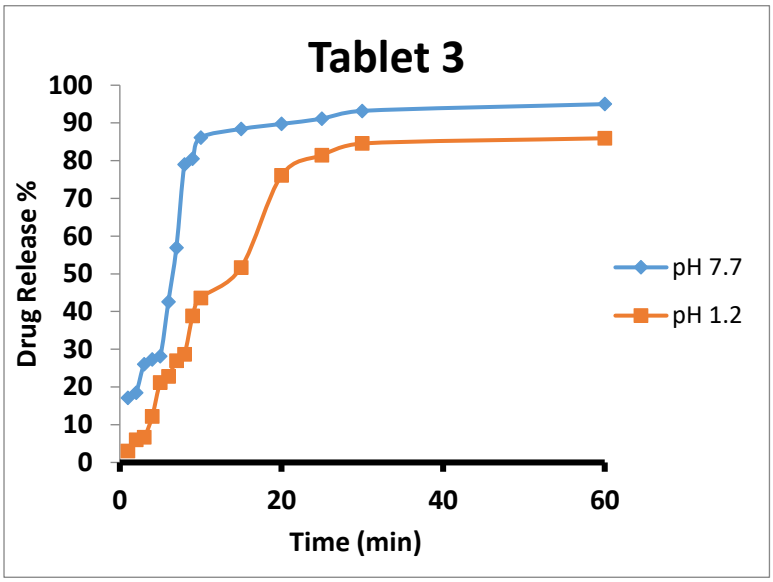


Figure21: % active ingredient cefalexin released as a function of time at pH=1.2 and pH=7.7 of T3 (T =37°C, 500 r.p.m)

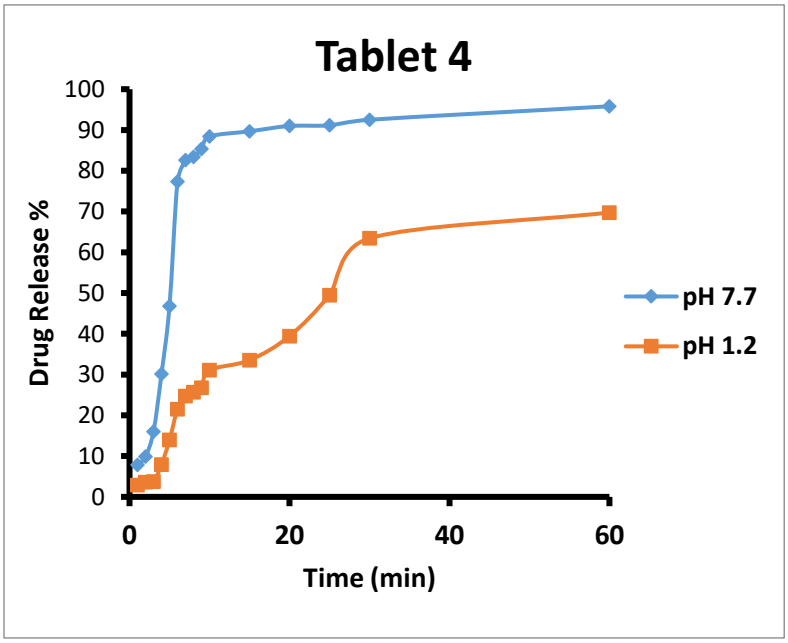


Figure22: % active ingredient cefalexin released as a function of time at pH=1.2 and pH=7.7 of T4 (T =37°C, 500 r.p.m)

For all the formulation loaded with CF, the percentage of active ingredient released is greater in the medium at pH=7.7 compared to the acidic medium pH=1.2

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 (the slope of the curve decreased steadily with time).

This type of release profile is consistent with the hypothesis that the diffusion of the active ingredient through the polymer plays a major role in the release kinetics. Upon contact of the formulation with the medium, the medium enters the system and dissolves the CF. Since CF is Moderately soluble in water and the initial charge of CF is relatively low, we could expect CF to dissolve quickly. Once dissolved, the CF diffuses through the coating polymer towards the dissolution medium.

The release of active ingredient cephalexin (Figure 19) from Tablet 1 EC alone(0.2EC/0.1CF) low than 29% in the pH 1.2 medium compared to 52.25 % in the pH 7.7 medium, the basique medium more influenced the morphology of a crystalline polymer by transferring it into an amorphous structure therefore quick release. The low release in both mediums compared with the other tablets maybe due to the presence of CF in the crystalline phase of EC, we can say that the CF released in both mediums is the quantity incorporated in the amorphous part of EC.

(Figure 20) shows the release of CF from Tablet 2 (0.15EC/0.15CF)we observed the release in medium pH 7.7 (90%) compared in medium pH 1.2 (59 %) therefore EC alone by a different mass the rapid release in basic medium compared to acidic medium, The solubility of cefalexin is higher in a basic medium (pH 7.7) than in an acidic medium, Therefore, a greater amount of cefalexin will be dissolved in the surrounding medium at pH (7.7), which could result in a faster release of the active ingredient.

In order to increase the release of CF in both mediums to optimize a good formulation in terms of type of polymer used, we prepared two diffrents Tablets using PEG and CTA on formulation with EC .

(Figure 21) presents the release of CF from Tablet 3, the figure shows that the release is a good release in the medium pH 7.7 (95%) because the polymer mixture is composed of polyethylene glycol (PEG) and ethyl cellulose (EC), in an acidic environment PH 1.2 the release was around 85.93%

The release from Tablet 4 of total active principle in the two environments following the amorphous morphology of CTA which allows the absorption of liquid in the formulation. The reslease in the acidic medium was 70% and in pH7.7 was around 96%. It can be explained that the increase comes from the absorption of the liquid from the medium and as a result cephalexin finds it easy to dissolve and diffuses through the polymer wall specially in basic medium.

According to all the CF release results we conclure that the good release of CF was observed from the Tablet 3 based on PEG and EC. PEG is a hydrophilic polymer which increases the solubility of cephalexin in the mixture, EC is a hydrophobic polymer that forms a porous matrix that retains cefalexin and controls its release. The combination of PEG and EC creates a favorable environment for the dissolution and diffusion of CF, allowing full release of the drug. In an acidic environment, EC can protonate, which reinforces its hydrophobic character and reduces the permeability of the matrix. The reduced permeability of the EC matrix at pH 1.2 hinders the diffusion of cephalexin out of the mixture, helping to slow its release.

II .5.3 Liquid absorption

At the same time as the 1mL samples are taken to determine the quantity of CF released, the discs 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 following table:

	T (min)	3	4	6	10	30	60
Liquid %	T1	6,45	9,67	12,9	16,12	29,03	35,48
	T2	7,69	11,53	15,38	19,23	26,92	34,61
	T3	7,4	11,11	18,51	26,62	33,33	45,48
	T4	3,22	6,45	9,67	12,9	29,03	59,25

Table 07: %liquid absorbed in all Tablets (T1, T2, T3 and T4) as a function of time at pH=7.7 at T°=37°C.

The table gives the percentage of the calculated liquid which represents the mass of the liquid absorbed in the dosage forms, it varies from 6 and 7% to approximately 36 and 45% for T1, T2 and T3 and from 3% to 59% for T4, Which shows that the polymeric matrix absorbs liquid which leads to the dissolution of the coated active ingredient.

III. 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.
- Klebsiellapneumoniae ATCC 70603
- Gram-positive bacteria: Staphylococcus aureus ATCC25923.
- "Yeast" fungal strains: Candida albicans ATCC10231

- **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 Mueller Hinton 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 **[16] [17]**

III.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 cefalexin 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**[17]**.

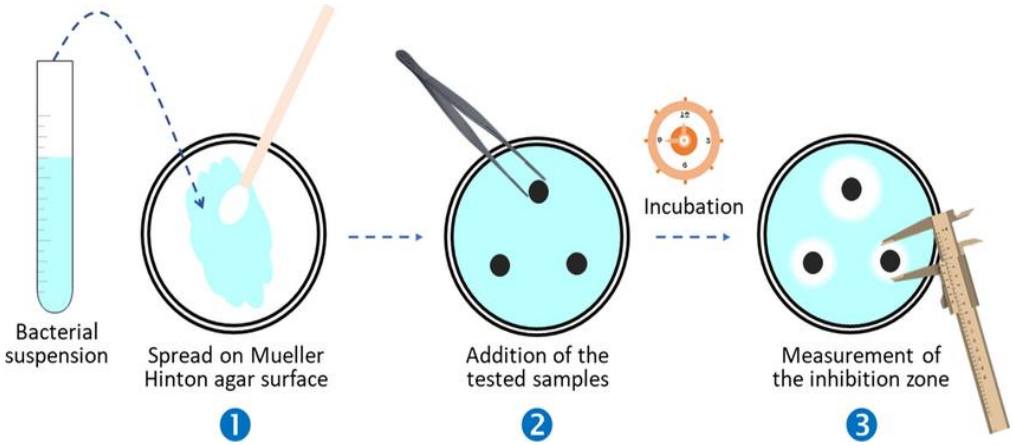


Figure 23: Schematic representation of the disk diffusion method

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.

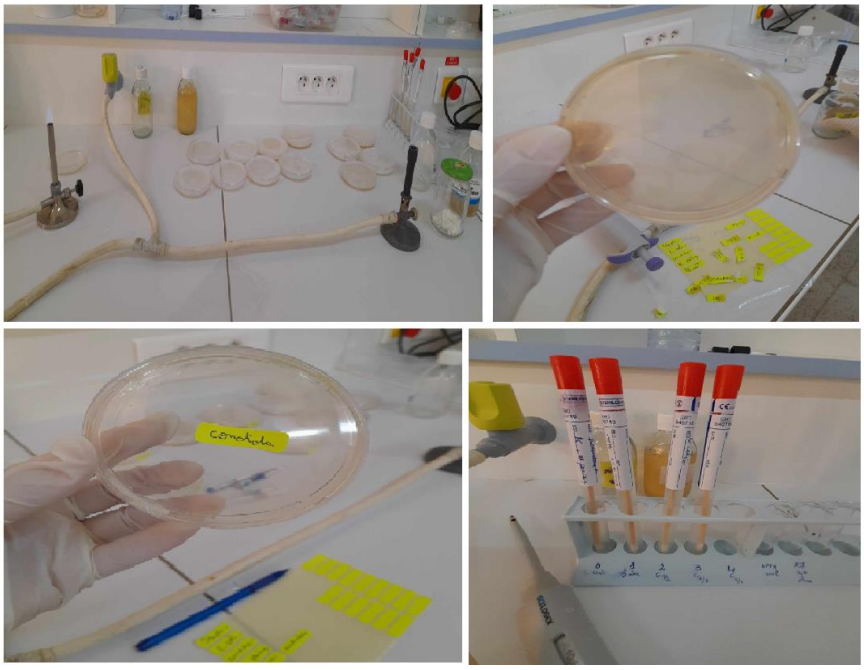


Figure 24: Seeding of culture medium

III.1.a Evaluation of the antibiotic activity of cefalexin in kinetic samples (pH7.7)

We took the kinetic sample of release of Cephalexin from ph7.7 then flowed into Petri dishes, After inoculation, four sterile disks are placed on M.H agar and deposit the samples for 5 min, 20min, 30min and 60min is remains for 24 at temperature 37°C.

III.1.b Results of biological tests:

After 24 hours of incubation, the petri dishes containing the disks soaked with the kinetic samples are timed after 5, 20, 30 and 60 min. The diameters of the inhibitory zones were noted as different from one strain to another, each zone was measured, in mm, we find the following diameters:

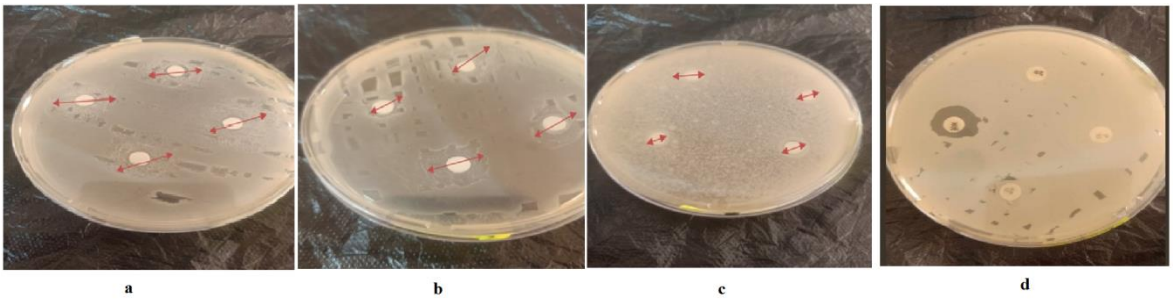


Figure 25: results of the microbial strains tested in E-coli (a: Tablet PEG/EC, b: Tablet EC, c: Tablet CTA/EC, d: Antibiograms)

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

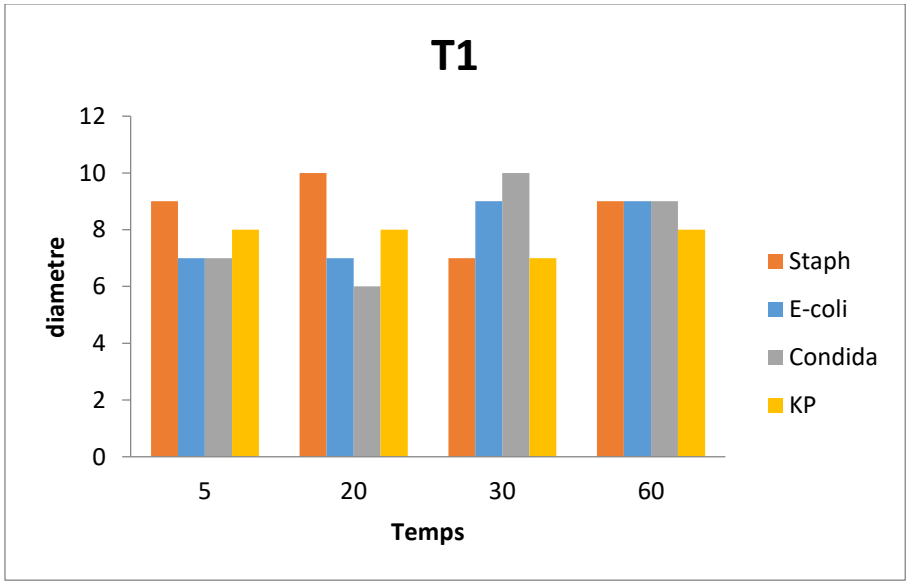


Figure26: antibacterial activity result of T1 (EC)

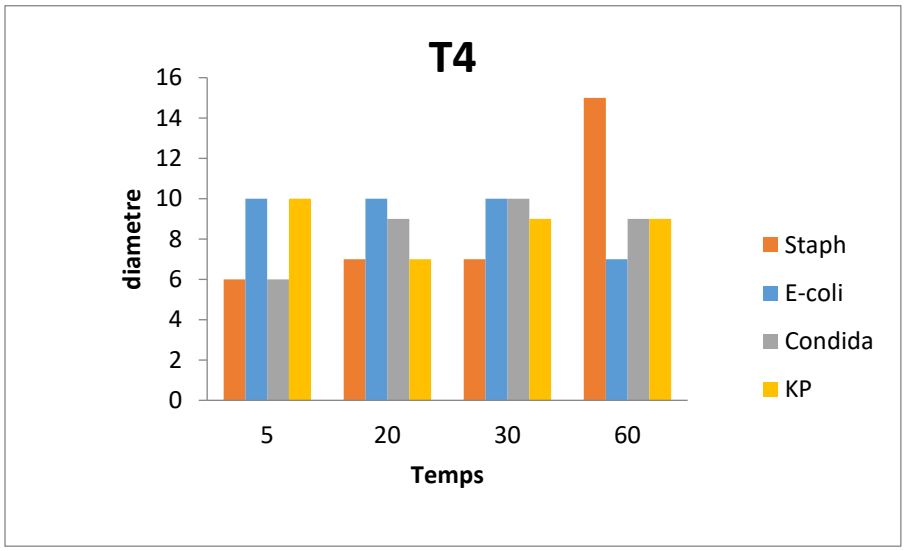


Figure27: antibacterial activity result of T4 (CTA/EC)

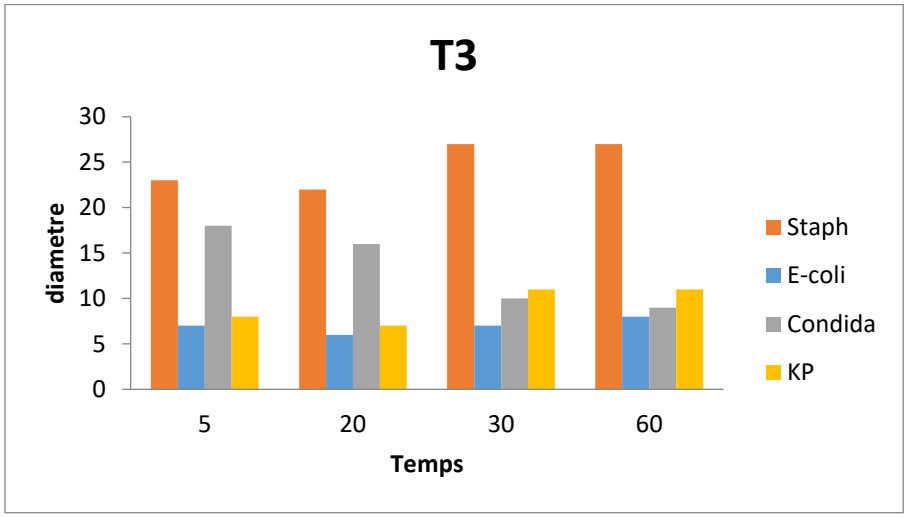


Figure28: antibacterial activity result of T3 (PEG/EC)

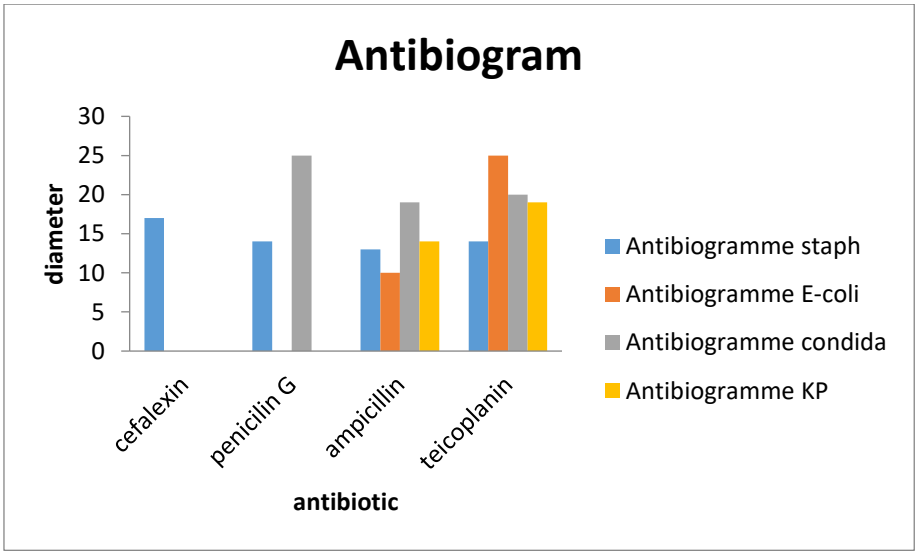


Figure29: antibiogram result

From the diagrams, we notice that the diameters are different for each kinetic sample for the four strains. results of antibacterial activity of T1 With regard to the staph strain the diameter increases to reach a maximum at 20 minutes and the same remark is noted for the staph strain which suggests that the maximum is released at 60 minutes of kinetics of release from T4 based on CTA/EC polymers and the release of kinetics from T3 based on PEG/EC polymers the diameter of the staph strain very high in 60 minutes because of the total release of CF from T3 and T4 which matches the results obtained in the first part, and for the antibiogram results our product degrade the staph bacteria more compared to our bacteria. The results obtained show better inhibition and the sensitivity of the strains towards the antibiotic used. The kinetic study of samples containing the highest concentration of the active ingredient reduces the bacterial population.

According to the Clinical Laboratory Standards Institute (CLSI), the results of the Kirby-Bauer disk diffusion susceptibility test are reported only as susceptible, intermediate, or resistant **[18]**.

TABLE 08: Zone diameter interpretative standards for Staphylococcus species **[18]**

***Staphylococcus* species**
(Zone Diameter, nearest whole mm)

	Resistant	Intermediate	Susceptible
Cefazolin (30 µg)	≤14	15-17	≥18
Clindamycin (2 µg)	≤14	15-20	≥21
Erythromycin (15 µg)	≤13	14-22	≥23
Gentamicin (10 µg)	≤12	13-14	≥15
Oxacillin (1 µg)	≤10	11-12	≥13
Penicillin G (10 µg)	≤28	--	≥29
Tobramycin (10 µg)	≤12	13-14	≥15
Vancomycin (30 µg)	--	--	≥15

The following table represents zone diameters for the tablets based on EC, CTA/EC and PEG/EC from the Staphylococcus species bacteria

Table09: Zone diameter for Staphylococcus species

Staph	**Diameter (mm)**		
Temps	**EC**	**CTA/EC**	**PEG/EC**
5	9	6	23
20	10	7	22
30	7	7	25
60	9	15	27

We notice that the diameters are different for each kinetic sample for the three disks. we note that the inhibition diameter for the three formulations is indeed greater than

18, especially for the tablet prepared on the basis of PEG/EC, compared with the CLSI results indicates that our formulation is susceptible compared to the other formulations. We can conclude that we have selected a good matrix from the kinetic and biological point of view.

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Conclusion

General conclusion

In this work was devoted to the preparation of forms pharmaceuticals: disks supporting the active ingredient “cefalexin”. In the preparation of these forms, three matrix polymers were used etylcellulose "EC", polyethylene glycol "PEG" and cellulose triacetate "CTA" which was obtained from cotton via an esterification reaction using acetic anhydride as an acetylating agent.

The discs developed in our study were prepared by mechanical compression with alcohol sprays. The first two tablets were obtained using EC polymer alone with different masses, T1 with 0.2g EC and T2 with 0.15g EC. The two other tablets prepared with mixture with PEG and CTA, after complete evaporation of the sprayed alcohol, we have determine the mass and calculate the yield.

The polymers used, Cefalexin and the prepared Tablets were characterized by FTIR, XRD, the synthesis was followed by another study of the release of active ingredients in reconstituted media (pH 1.2 and 7.7). The results of FTIR showed that the spectrum of the Tablet 4 is only the sum of the FTIR spectra of Cefalexin, EC and CTA. The main absorption bands of CF appeared clearly in the disk spectrum comfirmed the presence of CF into the Tablet 4.

This XRD technique makes it possible to characterize the nature of the polymer from a crystalline. Tablet T1 is the mixture between Ethylcellulose and Cefalexin, the pattent clearly showed the presence of some peaks with different intensity. Those peaks are confirmed the presence of Cefalexine in the tablet in the broadband of EC which is a semi-crystalline polymer. This allows us to say that the cefalexin are dispersed in the polymer matrix; the presence of EC reduces the crystalline of the cefalexin.

The release of the active ingredient was monitored using a UV-Vis spectrometer, previously calibrated at the wavelength λ_{max}=297nm of the active ingredient used (cefalexin) in the two medium considered

The solubilization and passage of the active principle towards the physiological fluid showed a release by diffusion.

The release kinetics of cefalexin are different from the prepared discs. shows that the study environment has a significant influence on the time, the percentage of PA release and the nature of the formulation prepared, whether a single polymer or Blend polymer. Release is increased when adding PEG and CTA to Polymer Blend with EC.

For all the formulation loaded with CF, the percentage of active ingredient released is greater in the medium at pH=7.7 compared to the acidic medium pH=1.2

The release of active ingredient cefalexin from Tablet 1 EC alone(0.2EC/0.1CF) low than 29% in the pH (1.2) medium compared to 52.25 % in the pH (7.7) medium, the basique medium more influenced the morphology of a crystalline polymer by transferring it into an amorphous structure therefore quick release.

The release of CF from Tablet 2 (0.15EC/0.15CF)we observed the release in medium pH (7.7) 90% compared in medium pH (1.2) 59 %, therefore EC alone by a different mass the rapid release in basic medium compared to acidic medium, The solubility of cefalexin is higher in a basic medium (pH 7.7) than in an acidic medium.

The release was good in the medium pH 7.7 (95%) because the polymer mixture is composed of polyethylene glycol (PEG) and ethyl cellulose (EC), in an acidic environment PH 1.2 the release was around 85.93%. The release from CTA of total active principle in the two environments following the amorphous morphology of CTA which allows the absorption of liquid in the formulation. The release in the acidic medium was 70% and in pH7.7 was around 96%.

According to all the CF release results we conclude that the good release of CF was observed from the Tablet 3 based on PEG and EC. PEG is a hydrophilic polymer which increases the solubility of cefalexin in the mixture, EC is a hydrophobic polymer that forms a porous matrix that retains cefalexin and controls its release. The combination of PEG and EC creates a favourable environment for the dissolution and diffusion of CF, allowing full release of the drug. The percentage of the calculated liquid which represents the mass of the liquid absorbed in the dosage forms, it varies from 6 and 7% to approximately 36 and 45% for T1, T2 and T3 and from 3% to 59% for T4, Which shows that the polymeric matrix absorbs liquid which leads to the dissolution of the coated active ingredient.

To demonstrate microbial activity, four bacterial strains and one fungal strain 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.

We noticed that the diameters are different for each kinetic sample for the three disks. we note that the inhibition diameter for the three formulations is indeed greater than 18, especially for the tablet prepared on the basis of PEG/EC, compared with the CLSI results indicates that our formulation is susceptible compared to the other formulations. We can conclude that we have selected a good matrix from the kinetic and biological point of view.

In vivo biological tests on such syntheses will be necessary in the future on living cells and animals such as rats to verify that the quantities released from the best formulations are compatible with the desired therapeutic concentrations.

Abstract: The objective in our study is the preparation of forms pharmaceuticals: disks supporting the active ingredient “cefalexin”. In the preparation of these forms, three matrix polymers were used Etylcellulose "EC", polyethylene glycol "PEG" and cellulose triacetate "CTA" which was obtained from cotton via an esterification reaction using acetic anhydride as an acetylating agent. The discs were prepared by mechanical compression with alcohol sprays. The polymers used, Cefalexin and the prepared Tablets were characterized by FTIR, XRD, the synthesis was followed by another study of the release of active ingredients in reconstituted media (pH 1.2 and 7.7) , the tablets followed by the biological study of prepared tablets with respect to the referenced bacterial strains. The results of FTIR showed that the spectrum of the Tablet 4 is only the sum of the FTIR spectra of Cefalexin, EC and CTA. The main absorption bands of CF appeared clearly in the disk spectrum comfirmed the presence of CF into the Tablet 4. This XRD technique makes it possible to characterize the nature of the polymer from a crystalline. This allows us to say that the cefalexin are dispersed in the polymer matrix; the presence of EC reduces the crystalline of the cefalexin. For all the formulation loaded with CF, the percentage of active ingredient released is greater in the medium at pH=7.7 compared to the acidic medium pH=1.2; The release was good in the medium pH 7.7 (95%) because the polymer mixture is composed of polyethylene glycol (PEG) and ethyl cellulose (EC), in an acidic environment PH 1.2 the release was around 85.93%. According to microbial activity, the inhibition diameter for the three formulations is indeed greater than 18, especially for the tablet prepared on the basis of PEG/EC. We can conclude that we have selected a good matrix from the kinetic and biological point of view.

Key words: Galenic form“Tablet”, cefalexin , EC , CTA, PEG, Kinetics of release, microbial activity

Résumé : L'objectif de notre étude est la préparation de formes pharmaceutiques : disques supportant le principe actif « céfalexine ». Dans la préparation de ces formes, trois polymères matriciels ont été utilisés : éthylcellulose « EC », polyéthylène glycol « PEG » et triacétate de cellulose « CTA » obtenu à partir de coton via une réaction d'estérification utilisant l'anhydride acétique comme agent acétylant. Les disques ont été préparés par compression mécanique avec des sprays d'alcool. Les polymères utilisés, Céfalexine et les Comprimés préparés ont été caractérisés par FTIR, DRX, la synthèse a été suivie d'une autre étude de la libération des principes actifs en milieu reconstitué (pH 1,2 et 7,7), les comprimés suivis de l'étude biologique des comprimés préparés avec par rapport aux souches bactériennes référencées. Les résultats du FTIR ont montré que le spectre du comprimé 4 n'est que la somme des spectres FTIR de la céfalexine, de l'EC et du CTA. Les principales bandes d'absorption de CF sont apparues clairement dans le spectre du disque, confirmant la présence de CF dans le disque 4. Cette technique XRD permet de caractériser la nature du polymère à partir d'un cristallin. Ceci permet de dire que les céfalexines sont dispersées dans la matrice polymère ; la présence de CE réduit le cristallin de la céfalexine. Pour toute la formulation chargée en CF, le pourcentage de principe actif libéré est plus important dans le milieu à pH = 7,7 par rapport au milieu acide pH = 1,2 ; La libération a été bonne dans le milieu pH 7,7 (95%) car le mélange de polymères est composé de polyéthylène glycol (PEG) et d'éthylcellulose (EC), dans un milieu acide PH 1,2 la libération était d'environ 85,93%. Selon l'activité microbienne, le diamètre d'inhibition pour les trois formulations est en effet supérieur à 18, notamment pour le comprimé préparé à base de PEG/EC. Nous pouvons conclure que nous avons sélectionné une bonne matrice du point de vue cinétique et biologique.

Mots clés : Forme galénique « Comprimé », céfalexine, EC, CTA, PEG, Cinétique de libération, activité microbienne

ملخص: الهدف في دراستنا هو تحضير الأشكال الصيدلانية: الأقراص الداعمة للمادة الفعالة “سيفالكسين”. في تحضير هذه الأشكال، تم استخدام ثلاثة بوليمرات أساس: Etylcellulose "EC"، بولي إيثيلين جلايكول "PEG" وثلاثي أسيتات السليلوز "CTA" الذي تم الحصول عليه من القطن عبر تفاعل الأسترة باستخدام أنهيدريد الأسيتيك كعامل أستيل. تم تحضير الأقراص بالضغط الميكانيكي باستخدام بخاخات الكحول. تم توصيف البوليمرات المستخدمة، سيفالكسين والأقراص المحضرة بـ FTIR، XRD، وأعقب التصنيع دراسة أخرى لتحرر المكونات النشطة في الوسط المعاد تكوينه (pH 1.2 و 7.7)، وأعقبت الأقراص دراسة بيولوجية للأقراص المحضرة مع فيما يتعلق بالسلالات البكتيرية المشار إليها. أظهرت نتائج FTIR أن طيف الجهاز اللوحي 4 هو فقط مجموع أطياف FTIR لـ Cefalexin وEC وCTA. ظهرت شرائط الامتصاص الرئيسية للسيفالكسين بشكل واضح في طيف القرص مما يؤكد وجود سيفالكسين في القرص 4. تتيح تقنية XRD هذه تحديد طبيعة البوليمر من خلال مادة بلورية. وهذا يسمح لنا أن نقول أن سيفالكسين منتشر في مصفوفة البوليمر؛ وجود EC يقلل من بلورة السيفالكسين. بالنسبة لجميع التركيبات المحملة بـ CF، تكون نسبة العنصر النشط المنطلق أكبر في الوسط عند درجة الحموضة = 7.7 مقارنة بالوسط الحمضي درجة الحموضة = 1.2؛ كان الإطلاق جيدًا في وسط درجة الحموضة 7.7 (95%) لأن خليط البوليمر يتكون من البولي إيثيلين جلايكول (PEG) وإيثيل السليلوز (EC)، وفي بيئة حمضية PH 1.2 كان الإطلاق حوالي 85.93%. وفقًا للنشاط الميكروبي، فإن قطر التثبيط للتركيبات الثلاثة أكبر بالفعل من 18، خاصة بالنسبة للأقراص المحضرة على أساس PEG/EC. يمكننا أن نستنتج أننا اخترنا مصفوفة جيدة من وجهة النظر الحركية والبيولوجية.

الكلمات المفتاحية: الشكل الجالينوسي "أقراص"، سيفالكسين، EC، CTA، PEG، حركية التحرر، النشاط الميكروبي