

**Ministry of Higher Education
And Scientific Research
University of Al-Qadisiyah**

College of Science

Department of Chemistry



Development and Application of Protein/ Polyethylene glycol/ ZnO Matrix for Cephalexin Delivery Systems

A Thesis Submitted By

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**To the council of College of Sciences, University of Al-Qadisiya as a
partial Fulfillment of the Requirements of degree of Master of
Science Chemistry**

Supervised By

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2025 A.D

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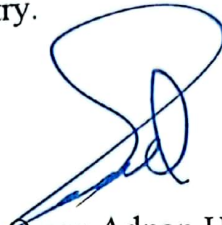
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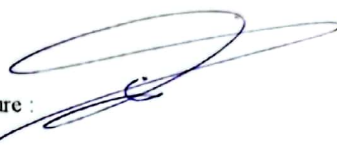
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Dedication

To the first teacher of humanity, the Noble Prophet
Muhammad (peace be upon him and his purified progeny),
And to the final guide among the Imams of
righteousness, the savior of humanity, the awaited Imam
Al-Mahdi (may Allah hasten his reappearance).

To the one whose satisfaction reflects the satisfaction of the
Almighty,

To the kindest soul, the warmest embrace, the ocean of
tenderness, the mountain of dignity, and the legend of
loyalty—my late father, may Allah have mercy on his soul.

To the one beneath whose feet Paradise lies, whose prayers
ease every hardship—my beloved mother.

To my wife's parents, whose virtues words cannot fully
express.

To the shining star in my sky, my steadfast support, my
strength in times of need, and the light guiding my path—
my beloved wife.

To the secret of life and the blessing of existence, who
captured my heart and soul—my children.

To my dear brothers and sisters



Ahmed Kadhim

Acknowledgments

All praise is due to Allah, whose blessings are countless and whose grace is immeasurable—the Lord of all worlds and the One who governs the affairs of all creation.

I would like to express my sincere gratitude and deep appreciation to my esteemed supervisor, Professor Dr. Oraas Adnan Hatem, for proposing this research topic and generously supervising my thesis. Her continuous efforts, valuable advice, and insightful guidance were instrumental in overcoming the challenges I faced throughout my work. She has been a true mentor and a steadfast support—may Allah grant her continued health and success .

My heartfelt thanks also go to the respected Head of the Chemistry Department, Professor Dr. Bassam Faron Abd, for his kind support and encouragement.

I am also grateful to the Dean of the College of Science, University of Al-Qadisiyah, and the Department of Chemistry for granting me the opportunity to complete my research.

Finally, I extend my deepest thanks to my beloved mother, my dear wife, my brothers and sisters for their unwavering support and encouragement. I am also thankful to everyone who contributed in any way to the completion of this work. I wish them all continued success and prosperity.

Ahmed

Abstract

This thesis focused on the synthesis and evaluation of biodegradable hydrogel polymeric matrices based on soy protein isolate (SPI) and gelatin (Gel) blended with polyethylene glycol (PEG) and zinc oxide nanoparticles (ZnO) for the controlled release of cephalexin and antibacterial activity. The formulations were optimized by varying polymer ratios and crosslinking agent volumes.

Hydrogel matrices were synthesized through chemical crosslinking using glutaraldehyde, with varying concentrations (0.5, 1.0, and 1.5 mL) to study their influence on the structural and functional properties of the hydrogels. The optimal formulation for hydrogel matrix was found at 0.7 g SPI (or Gel) and 0.3 g PEG with 0.5 mL glutaraldehyde, yielding a maximum swelling ratio.

The swelling behavior of the hydrogel systems was evaluated through kinetic analysis using both first-order and second-order swelling models in simulated gastric fluid and simulated intestinal fluid. The SPI/PEG hydrogel exhibited swelling percentages of 274% in SIF and 140% in SGF, while the Gel/PEG hydrogel demonstrated significantly higher swelling percentages, reaching 1205% in SIF and 678% in SGF.

pH had a significant impact on the swelling behavior. Swelling ratios were markedly higher in simulated intestinal fluid (pH 6.8) than in simulated gastric fluid (SGF, pH 1.2). This is attributed to the ionization of functional groups in the matrix structure at neutral to basic pH, enhancing hydrophilicity and water uptake. In contrast, the acidic environment of SGF suppresses ionization, reducing osmotic swelling pressure. This pH-dependent behavior confirms the hydrogels' suitability for targeted drug release in the intestinal tract.

At a concentration of 100 ppm, the maximum absorbance wavelength (λ_{max}) of cephalexin in distilled water was determined to be 261 nm using UV-Visible spectrophotometry. Drug release studies aligned with swelling behavior: in SIF, Gel/PEG released 99.89% of

cephalexin and SPI/PEG released 89.34% within 24 hours, whereas in SGF, drug release dropped to 44.24% and 38%, respectively. Kinetic analysis showed that drug release followed the Higuchi model, indicating diffusion-controlled mechanisms. The Gel/PEG matrix in SIF showed the best fit ($R^2 = 0.812$, $KH = 0.0466$).

FTIR spectroscopy confirmed successful drug incorporation and crosslinking, while SEM imaging revealed clear morphological differences before and after drug loading, including increased surface roughness and particle clustering. Antibacterial evaluation using the agar well diffusion method demonstrated that the formulation containing Gel/PEG/ZnO/cephalexin achieved the largest inhibition zone (20 mm) against *Staphylococcus aureus*. This strong antibacterial effect is due to the synergistic activity of ZnO nanoparticles (which damage bacterial membranes) and cephalexin (which inhibits cell wall synthesis).

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List of Symbols

Symbol	Physical meaning
CDDS	Controlled Drug Delivery System
CT	Total liberation in time ∞
Ct	releasing at time t
DDS	Drug Delivery Systems
FTIR	Fourier Transform infrared Spectroscopy
Gel	Gelatin
KH	Higuchi dissolution constant
PEG	Poly Ethylene glycol
pH	Potential of Hydrogen
SEM	Scanning Electron Microscopy
SGF	Simulated Gastric Fluid
SIF	Simulated Intestinal Fluid
SPI	Soy protein isolation
UV-Vis	Ultraviolet-visible spectroscopy
λ_{max}	Maximum Wavelength
ZnO Nps	Zinc Oxid Nanoparticles

Chapter One
Introduction and Literature
Review

1.1 Introduction

Medicines have been used to extend life and improve health since ancient times. Drug delivery has changed recently and will change more. Biomedical engineers have not only helped understand biological barriers to drug delivery, such as drug diffusion and circulation in the body and drug transport through tissues and cells, but they have also developed several novel clinically used methods[1].

Medical treatments have extended life and improved health since ancient times. Recently and soon, drug delivery will shift. Besides understanding biological barriers to drug delivery, such as drug dispersion and circulation in the body and drug transport across tissues and cells, biomedical engineers have invented various unique clinically used approaches[2,3]

The growth of controlled-release devices for medicine delivery has led to medical advances in recent decades. These systems manage pharmaceutical release to reduce administration frequency and ensure long-term efficacy. Controlled-release formulations can administer the medication slowly, zero-order, or first-order, or provide a quick initial dose followed by a controlled-release period [4].

Nanotechnology, which enables the building of nanostructures with improved properties suited for applications involving drug delivery, is among the most promising strategies for accomplishing this goal. The potential of nanotechnology to alter and regulate material properties at the molecular level has drawn a lot of attention because it makes it possible to create highly effective and precise medication carriers. In addition to drug delivery, these nanostructures are being investigated for use in electronics, magnetic materials, optoelectronics, catalysis, and biomedical engineering . Different techniques are used by targeted methods for delivering drugs to diseased regions or cells. These Systems can maximize drug accumulation at the targeted location while reducing systemic exposure by taking advantage of elements such as particular cell surface receptors, pH gradients, or magnetic fields. A interdisciplinary approach incorporating knowledge from pharmaceutical sciences, material science, bioengineering, and medical research is necessary in order to develop medication delivery systems. To ensure increase patient

comfort, decrease toxicity, and boost medication efficacy, scientists and researchers are always working to develop and improve these systems [5-11] .

Due to their strong drug binding, low cytotoxicity, biodegradability, and abundance, protein-based polymers may be employed as biopolymer drug delivery vehicles. Absorbs well into targeted cells. Polypeptide primary sequences contain functional groups, therefore their unique protein structure allows surface changes. The digestive system easily breaks down proteins [12].

Bioactive peptides from enzymes may have physiological effects in vivo. Soy protein is the most common plant protein and is being studied as a renewable, eco-friendly, biodegradable, noncytotoxic, biocompatible, and ecologically friendly medicine delivery mechanism. Functional meal soy protein derivatives support several biological functions that promote health and prevent sickness. They are anti-cholesterolemic, anti-carcinogenic, and protect against obesity and kidney disease . An upgraded kind of soy protein, soy protein isolate (SPI), offers great nutritional value and is utilized in many dishes .SPI interacts with numerous substances as an amphiphilic biopolymer with active, functional side chains. Glutamate, aspartate, and leucine in conglycinin and glycinin's main subunits generate the protein's globular shape. These subunits can cross-link and chemically change polymeric hydrogels for biological applications due to their reactive groups. As one of the cheapest naturally occurring proteins and easily processable, SPI, a large soybean oil byproduct, can be made into a mass-produced hydrogel. SPI, one of the most studied plant-based hydrogels, is used in culinary and nutraceutical applications due to its low cost, emulsifying capabilities, gelling capacity, and technical and nutritional benefits [13,14] .

Gelatin, a collagen-derived protein, is biocompatible and biodegradable. After biodegradation, metabolites from low-antigenicity animals help produce collagen. Gelatin is sensitive to pH, temperature, biological stimuli, and other environmental changes. Gelatin capsules have delivered medication since 1834. They can increase pharmaceutical ingestion, manage dosage, and improve use and storage. Hydrogels, gelatin nanospheres, nanogels, and nanofibers have replaced tiny capsules as nanomaterials have evolved. Drug

delivery carrier materials based on gelatin are popular in the pharmaceutical business [15, 16]

1.2 Benefits and implications for healthcare

Healthcare has been transformed in a number of ways by the creation of sophisticated drug delivery systems:

Increased therapeutic efficacy: Drugs are more likely to reach their intended locations of action when delivered via targeted delivery systems. These methods can increase medication concentrations at the target site and produce better results by reducing systemic exposure.

Decreased side effects: Compared to conventional medication administration techniques, drug delivery systems can greatly lower the incidence of systemic side effects. These devices improve patient safety and tolerability by focusing medication activity at the intended site and reducing exposure to healthy tissues [17]

1.3 Evolution of Drug Delivery Systems

A drug delivery system (DDS) is a formulation or device that enhances the safety and efficacy of a pharmaceutical agent by regulating the rate, timing, and site of drug release within the body. This technique involves managing the pharmaceutical product, liberating its active constituents, and transporting them through biological membranes to the target site of action. Modern drug delivery devices have only been around for 60 years. Prior to 1950, all of the medications were made into pills or capsules that released the drug immediately as they came into contact with water and had no control over the kinetics of it. Numerous medication delivery systems have been created over this time, as seen in the [18]:

Systems for controlled release: Systems with controlled release enable long-term and regulated drug release for a long time. This method minimizes adverse effects and lowers the frequency of drug delivery by maintaining a steady therapeutic level of the drug in the body. Microneedles, implanted devices, and transdermal patches are a few types of controlled release systems.

Systems for intended drug delivery : Targeted drug delivery systems are engineered to administer drugs directly to the site of action. decreasing systemic side effects and increasing efficacy. These systems employ a variety of targeting techniques, including stimuli-responsive materials, antibody-drug conjugates, and ligand-receptor interactions. Hydrogels, liposomes, and nanoparticles are a few of the promising delivery systems for targeted drugs.

Systems of inhaling drugs: Inhalation drug delivery devices are especially helpful in the treatment of respiratory disorders like cystic fibrosis, asthma, and chronic obstructive pulmonary disease (COPD). Drugs are effectively delivered to the lungs using inhalers, nebulizers, and dry powder inhalers, guaranteeing quick absorption and localized action.

Systems for delivering drugs through implants: Drugs can be delivered straight into particular tissues or organs via implantable drug delivery systems. They frequently comprise biocompatible components and have the ability to be programmed to dispense medications at preset intervals. These systems include microchips, stents, and implantable pumps. They are frequently employed for long-term medication administration, including pain relief and hormone therapy.

Systems for drug delivery based on nanotechnology: Drug delivery has seen new opportunities thanks to nanotechnology, which enables controlled release and precise targeting. Drugs can be encapsulated by nanoparticles, which prevents them from degrading and makes facilitating access to certain cells or tissues. Nanoparticles can aggregate in tumours and administer chemotherapeutic agents directly to cancer cells, minimising damage to healthy organs, this technique has demonstrated considerable promise in the treatment of cancer.

1.4 Comparing Controlled and Conventional Drug Delivery Systems

The dosage is inadequately sustained within the therapeutic range, and the body swiftly excretes conventional dosage forms (tablets, capsules, syrups, etc.). The medication metabolises fast following a single standard dose, resulting in a short increase in drug levels followed by an exponential decline. The duration may be insufficient to elicit a meaningful

therapeutic effect, leading to a sub-therapeutic response. Figure 1 illustrates the alterations in plasma drug concentrations inside traditional drug delivery systems (DDS). Consequently, many strategies have been employed to sustain the drug's plasma concentration beyond the minimal effective concentration (MEC) while remaining below the hazardous threshold. [19].

While it might appear more advantageous to administer a single dose instead of several doses distributed at consistent intervals, the former leads to fluctuations in the drug's plasma levels,. often falling below effective levels and rising over harmful ones. Individuals who take many doses in one day are less likely to follow instructions. Giving a single dose that is more than what is required is another tactic, which has adverse effects in addition to the ones the drug is supposed to cause. Figure (1.1). In order to sustain the desired therapeutic impact for an extended duration and keep the plasma drug levels constant during the therapeutic window, controlled-release DDSs are therefore required. The disadvantages of conventional DDS are illustrated in Figure (1.2)[20].

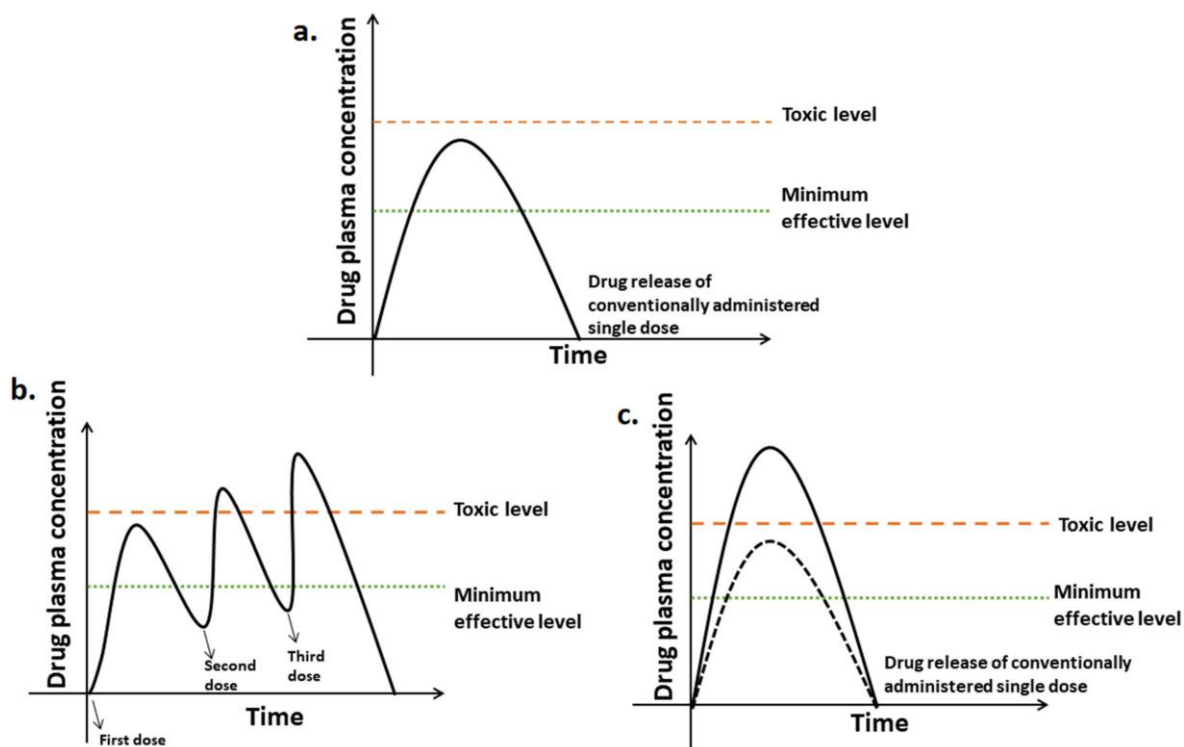


Figure (1.1) Plasma drug levels that fluctuate over time as a result of (a) a single standard dose, (b) multiple doses, and (c) an increased single dose[20].

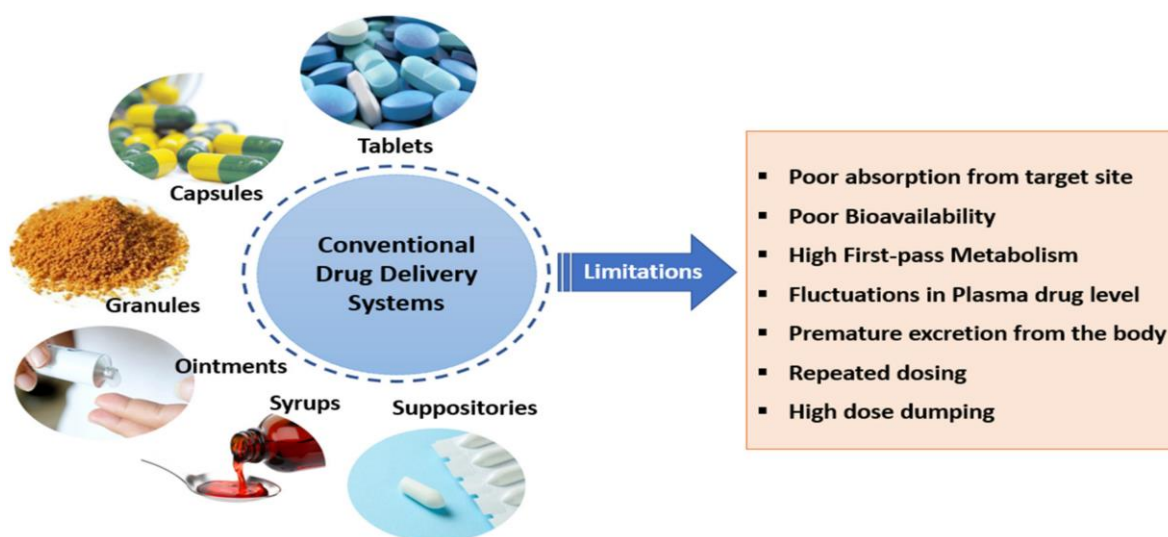


Figure (1.2) Constraints in conventional drug delivery systems [20].

1.5 Controlled drug delivery system (CDDS)

A broad variety of prolonged action formulations that offer continuous release of their active components at a predetermined rate and for a predetermined amount of time are referred to as controlled release dosage forms. Although these devices have lately been created for parenteral administration, ocular insertion, and transdermal application, the bulk of these formulations are intended for oral delivery. The principal objective of this system's development is to extend the duration of effect, which will increase patient compliance. A controlled drug delivery system has a number of benefits over traditional medication delivery [21, 22].

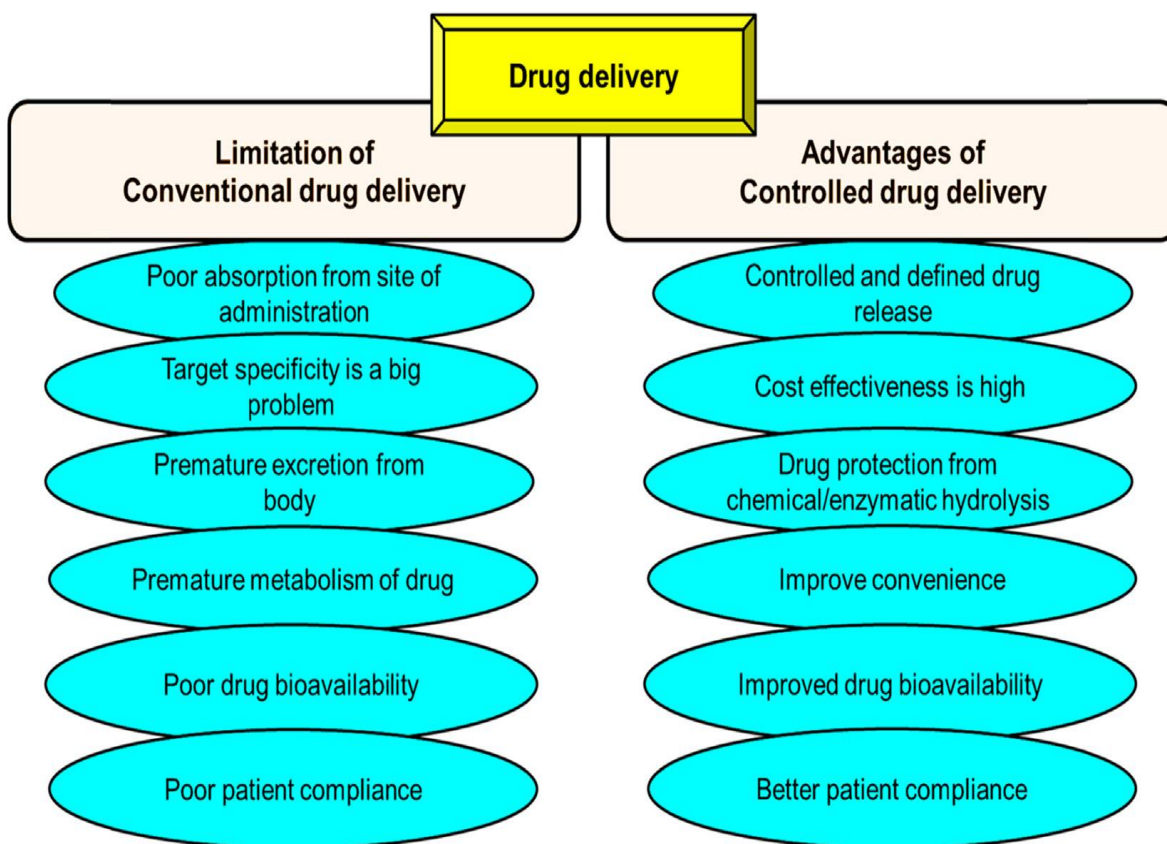


Figure (1.3) Benefits of CRDDS[23]

As a result, the medication is only effective where it is intended to be administered. Physicians find certain features of targeted DDSs more appealing than those of traditional DDSs. In addition to having a shorter half-life than medications taken by conventional ways, they are poorly soluble, unstable, and poorly absorbed. Furthermore, the specificity and therapeutic index of medications in conventional DDSs are lower than those in targeted DDSs. By maintaining a steady concentration of the medication in the blood plasma and removing the chance of both an inefficient dose (underdose) and an overdose, controlled drugs can provide more effective treatment see Figure (1.4) It displays the drug's concentration in the blood plasma. through the use of traditional, regulated medication release methods[23].

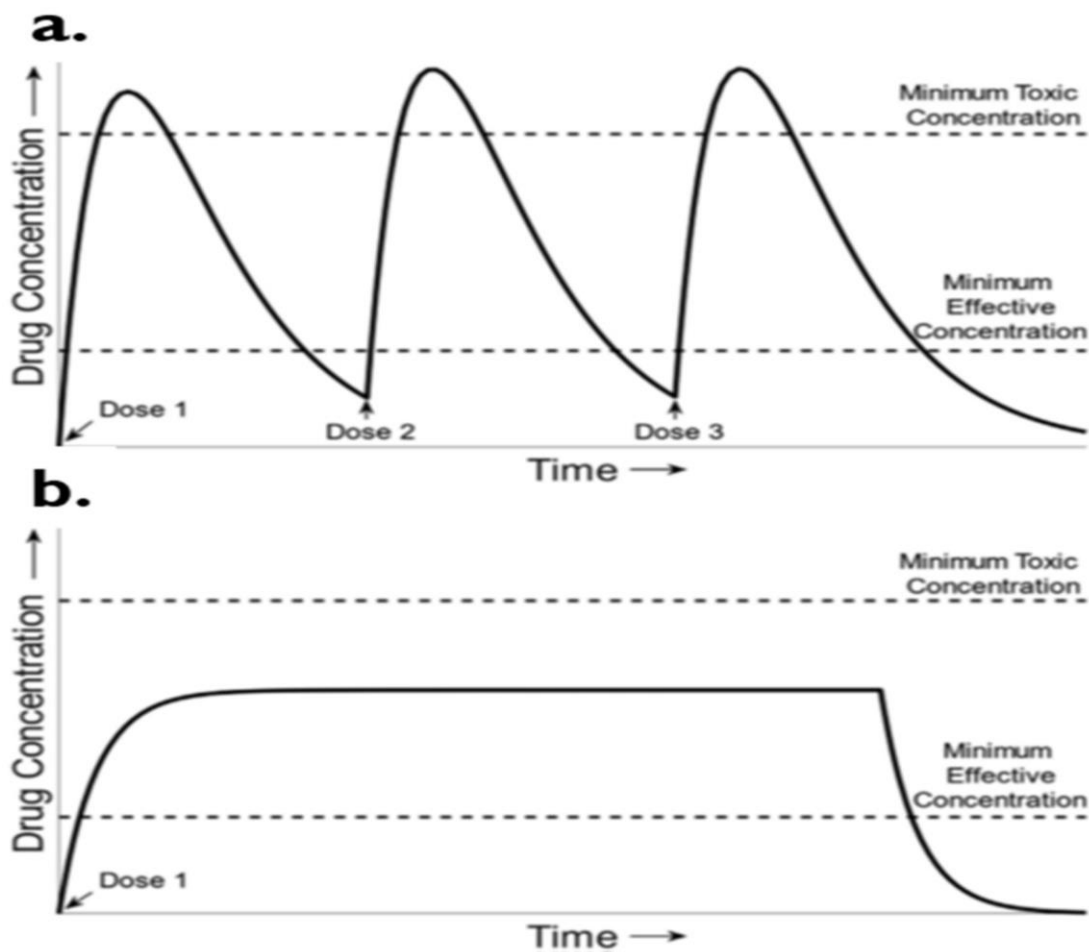


Figure (1. 4) A typical bolus of (a) Conventional DDS; (b) Controlled DDS[20]

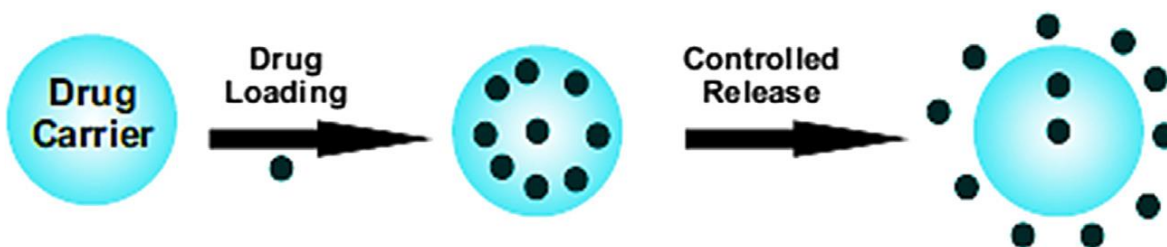


Figure (1.5) Mechanism of CRDDS [23]

1.6 Hydrogels in Regulated Pharmaceutical Delivery Systems

Hydrogels have garnered significant interest among polymeric systems because they can function as drug carriers or barriers that regulate release rates, thanks to their ability to emulate biological tissues. Hydrogels are three-dimensional, cross-linked, hydrophilic networks that expand without dissolving when exposed to water environments. They have been utilized in various applications, particularly in medicine delivery and controlled release systems. Hydrogels can safeguard pharmaceuticals from environmental factors, including certain enzymes and the acidic pH of the stomach. Their porosity facilitates the incorporation of medicines into the hydrogel matrix, permitting eventual controlled release. Furthermore, hydrogels can regulate drug release by modifying their structure in reaction to environmental cues, including pH, temperature, and ionic strength.

The diffusion-controlled mechanism is the primary approach utilized to characterize drug release from polymeric hydrogels. This process can be classified into two primary types: polymeric reservoirs and polymeric matrices. Polymeric reservoirs comprise a polymeric membrane encasing a drug-laden core. Conversely, in polymeric matrix systems, the medication is uniformly distributed throughout the three-dimensional hydrogel framework as shown in figure (1.6) [24].

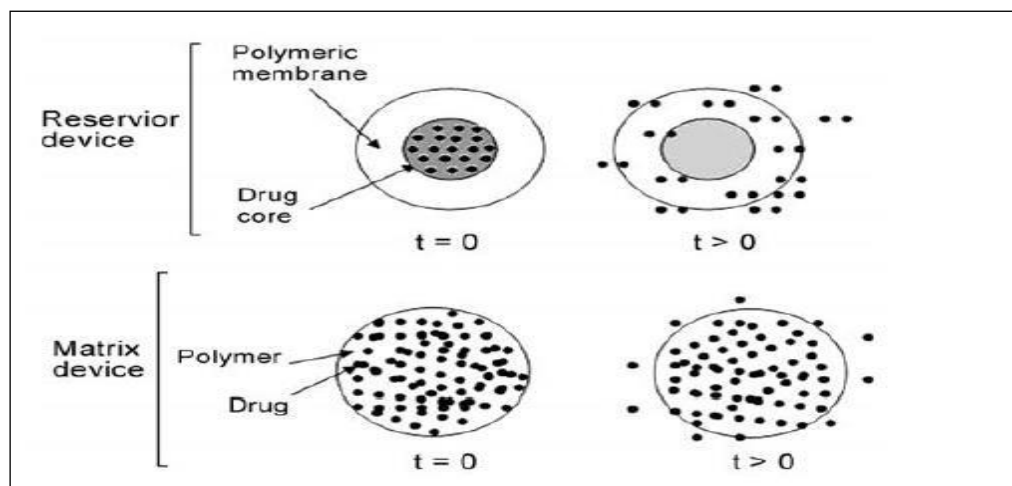


Figure (1.6) Schematic depiction of diffusively regulated reservoir and matrix devices

[24]

1.7 Polymeric pharmaceutical carriers

A drug delivery system targeting specific tissue must demonstrate outstanding efficacy in sustaining drug concentration by safeguarding the active pharmaceutical ingredient from acidic conditions and enzymatic breakdown until its release at the intended site.

Several fundamental factors are essential in assessing the efficacy of drug carriers, including:

- 1- The presence of functional groups that aid in degradation and solubilization is crucial.
- 2- The presence of a principal polymeric backbone is also crucial.

In the early 1970s, researcher Ringsdorf successfully linked a pharmacological molecule to a polymer carrier via covalent bonding. This technique was formulated based on the pharmacokinetic characteristics and distribution of the drug within target tissues, particularly as numerous therapeutic medicines are tiny molecular compounds prone to breakdown or destruction during transport. Consequently, there arose a necessity for an appropriate and efficient delivery method that could guarantee the medicine arrives at its target tissue without compromising its efficacy [25].

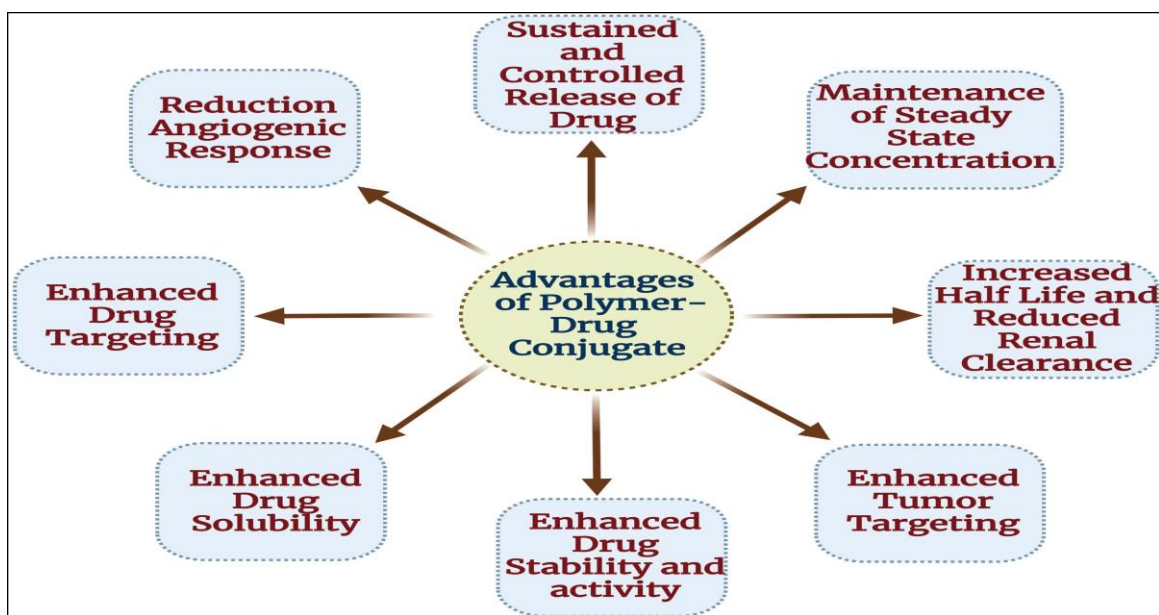


Figure (1.7) Benefits of polymer-drug conjugates[26]

1.8 Mechanism of drug-polymer interaction

The medication is connected to the polymer chains via two types of linkages[27, 28]:

1- Chemication link

In the polymer, the medication is covalently bonded to the gel, endowing the medicine with novel features and qualities. Consequently, the polymer must be chosen based on precise criteria to prevent interactions that may diminish the drug's efficacy and effectiveness, as well as to avoid certain repulsive forces. This method enhances the efficiency and efficacy of medications by conjugating hydrophobic pharmaceuticals with certain polymers, resulting in alterations in solubility and conductivity. Binding may occur via the polymer's terminal groups or through its side pendant groups. This form of binding is crucial in drug delivery systems. Covalent bonding mechanisms are recorded in medical applications and have been employed in tissue engineering, sensors, cell transplantation, and enzymatic processes. The notion of covalent bonding between a pharmaceutical agent and a polymer gel was initially introduced by scientist Helmut Ringsdorf in 1975, when he successfully synthesized a polymer including pendant groups capable of interacting with the drug and active compounds.

2- Physical link

Polymer gels can adhere to drug carriers by specific physical pressures, resulting in release mechanisms that are influenced by environmental variables, including physical or physicochemical changes. This form of physical bonding is evident in systems dependent on diffusion mechanisms, such as reservoir and network systems, as well as those utilizing swelling and osmosis mechanisms.

1.9 Swelling in polymeric Matrix

Swelling transpires inside the polymer matrix through the absorption of moisture from the surrounding environment of the polymer gel Figure (1.8). The drug release mechanism is associated with the polymer's swelling till it disperses to the target tissue. This process may be influenced by various parameters, including the density of crosslinking in the polymer structure, the release factor, and the polymer makeup. The proportion of swelling can be determined using the subsequent equation [29]:

$$\text{swelling ratio} = \frac{W_s - W_d}{W_d} \times 100\% \quad \dots\dots\dots(1.1)$$

W_s denotes the weight of the sample post-swelling, while W_d signifies the weight of the sample pre-swelling. The polymeric network infused with the medicine disintegrates within the human body due to several external forces, alongside those inherent to the polymer structure, resulting in the formation of smaller particles. This phenomenon is referred to as physical erosion of polymers, characterised by the slow passage of water from the external environment into the polymer matrix [30] .

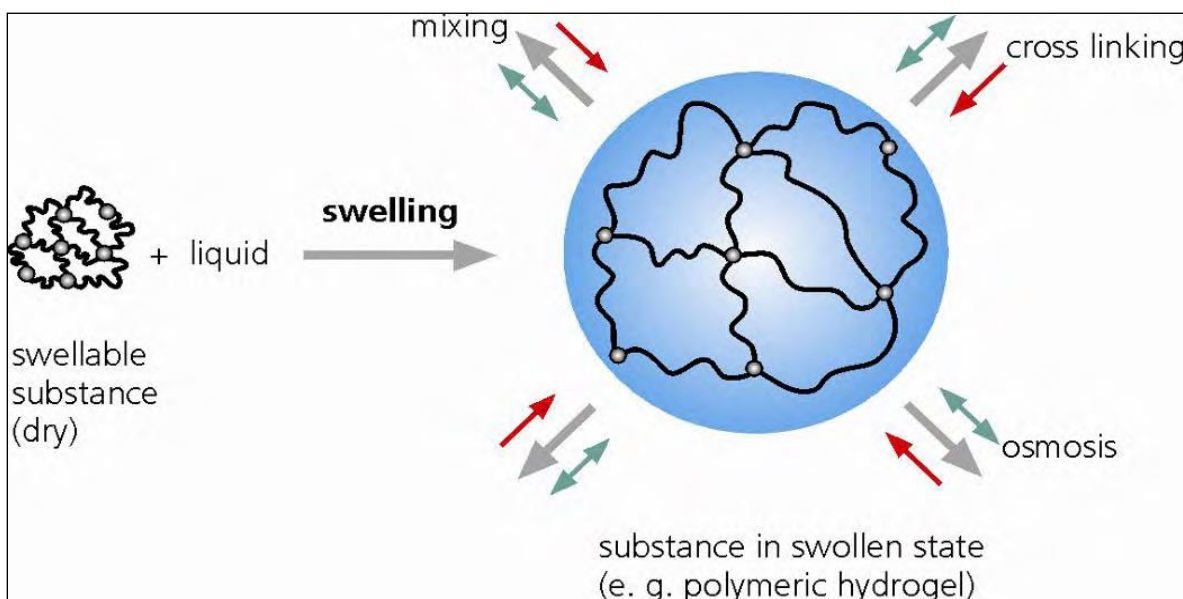


Figure (1.8) Swelling process in polymeric matrix [30]

1.10 Kinetic Modeling of Drug Release from Controlled Drug Delivery Systems

The behavior of controlled-release systems varies; some function as slow-release systems conforming to established kinetic models, while others first release a portion of the drug dose to rapidly achieve the desired therapeutic concentration in the body. They follow specific kinetic patterns to maintain a stable active drug concentration in the body for the longest possible duration. Multiple kinetic models have been proposed to elucidate the drug release mechanism. Given the rapid advancements in drug delivery techniques, *in vitro* drug release data are often utilized as a logical means to predict *in vivo* behavior [31]. The methodologies utilized to examine the kinetics of regulated drug release can be broadly classified into three main categories:

- Statistical approaches include techniques such as exploratory data analysis and multivariate processes, notably analysis of variance (ANOVA).

- **Model-Dependent Methods:** These methods include fitting data to specific mathematical models, including zero-order, first-order, Higuchi, Korsmeyer–Peppas, Hixson–Crowell, Baker–Lonsdale, and Weibull models .
- **Model-Independent Approaches:** These methodologies are not contingent upon known mathematical frameworks. Common examples include: Discrepancy factor (f1) and congruence factor (f2) [32] .

1.10.1 Zero-order model

The release of drugs from non-degradable or slowly degradable systems can be characterized by the zero-order model, represented by the following equation[33]:

$$Q_0 - Q_t = k_0 t \quad \dots\dots(1.2)$$

Where Q_t represents the amount of drug released at time t , Q_0 is the initial amount of drug, and K_0 is the zero-order rate constant in units of concentration/time.

This model is applicable for characterizing drug release in various systems, including certain transdermal systems, polymer-coated mesh tablets for poorly soluble medicines, and osmotic systems.

1.10.2 First Order Model

The drug release mechanism adhering to the first-order model can be articulated using the subsequent equation[34]:

$$\log C = \log C_0 - \frac{Kt}{2.303} \quad \dots\dots(1.3)$$

C denotes the quantity of drug released at time t , C_0 signifies the initial quantity of drug, and K represents the first-order rate constant measured in units of 1/time. Plotting the laboratory data as the logarithm of concentration against time yields a straight line with a slope of -2.303 .

1.10.3 Higuchimodel

The inaugural mathematical model for elucidating drug release from a retinal matrix system was proposed by Higuchi in 1961[35]. Originally intended for planar systems, it was subsequently broadened to encompass geometric shapes and diverse systems. This model is predicated on the subsequent assumptions[36]:

- The initial concentration of the drug in the retinal layer significantly exceeds its solubility.
- Drug diffusion transpires just in one dimension.
- Drug molecules are considerably smaller than the thickness of the retinal layer.
- Retinal edema and rehydration are overlooked.
- Pharmacological diffusion is consistent.

The release kinetics are characterized by the subsequent equation:

$$f_t = Q = A\sqrt{D(2C - C_s) C_s t} \dots\dots(1.4)$$

Where Q denotes the quantity of drug released per unit area A at time t, C signifies the initial quantity of drug, C indicates the solubility of the drug, and D represents the diffusion coefficient. The mathematical model for studying drug release from a planar heterogeneous lattice system, where the drug concentration within the lattice is below its solubility and release transpires through the lattice pores, is as follows[37]:

$$f_t = Q = \sqrt{\frac{D\delta}{\tau}} (2C - \delta C_s) C_s t \dots\dots\dots(1.5)$$

Where δ represents lattice porosity and τ denotes lattice tortuosity. The Higuchi model can generally be condensed into a formula referred to as the simplified Higuchi model.

$$f_t = Q = K_H K t^{1/2} \dots\dots\dots(1.6)$$

Where K_H represents the Higuchi dissolution constant.

1.11 Advantages of utilising nanoparticles for drug delivery

The following are some benefits of employing nanoparticles as a pharmaceutical delivery mechanism[38,39]:

1. The size and surface features of nanoparticles can be carefully controlled to help deliver medicine effectively, using different methods for both passive and active targeting.
2. Nanoparticles regulate and prolong drug release during the process to enhance therapeutic efficacy and reduce adverse effects, modifying the medication's organ distribution both during transit and at the target location, as well as its subsequent clearance.
3. The qualities of controlled release and particle disintegration can be readily adjusted by selecting appropriate matrix components. The relatively high drug loading and the capacity to absorb medications into systems without triggering any chemical responses are essential components in preserving pharmacological activity.
4. To achieve site-specific targeting, magnetic guiding or targeting ligands can be affixed to particle surfaces.
5. The system can be delivered intraocularly, parenterally, nasally, or orally, among other ways.

The many processes for creating metal nanoparticles are described in Figure (1.9). A suitable starting material (precursor) is reduced in size to create nanoparticles. This size reduction can be accomplished through various physical, chemical, and biological methods.

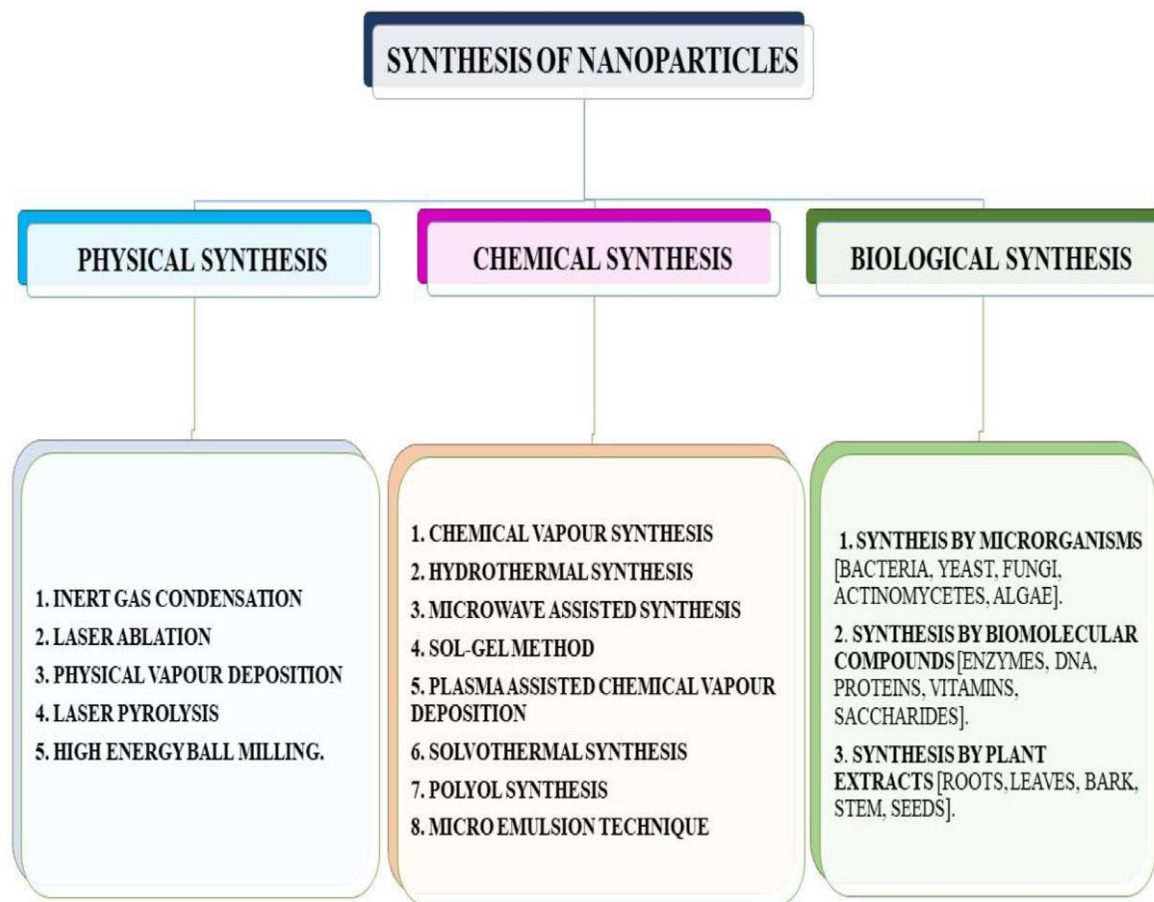


Figure (1. 9) Different approaches to nanoparticle production [40]

1.12 Nanocarriers

The possibility of nanotechnology to effectively diagnose and cure a wide range of malignancies has recently drawn more interest. The disadvantages of conventional methods for delivering anticancer drugs, including nonspecificity, severe side effects, blast release, and harm to healthy cells, have been circumvented by using nanocarriers. Nanocarriers offer preferential cumulation at the target location, increasing the bioavailability and therapeutic efficacy of antitumor medicines. Only a small number of nanocarriers have been clinically approved to carry anticancer medications to their intended areas, despite the fact that many have been produced. Figure (1.10) shows the overview of types of nanoparticles that have been studied in drug release systems [41,42].

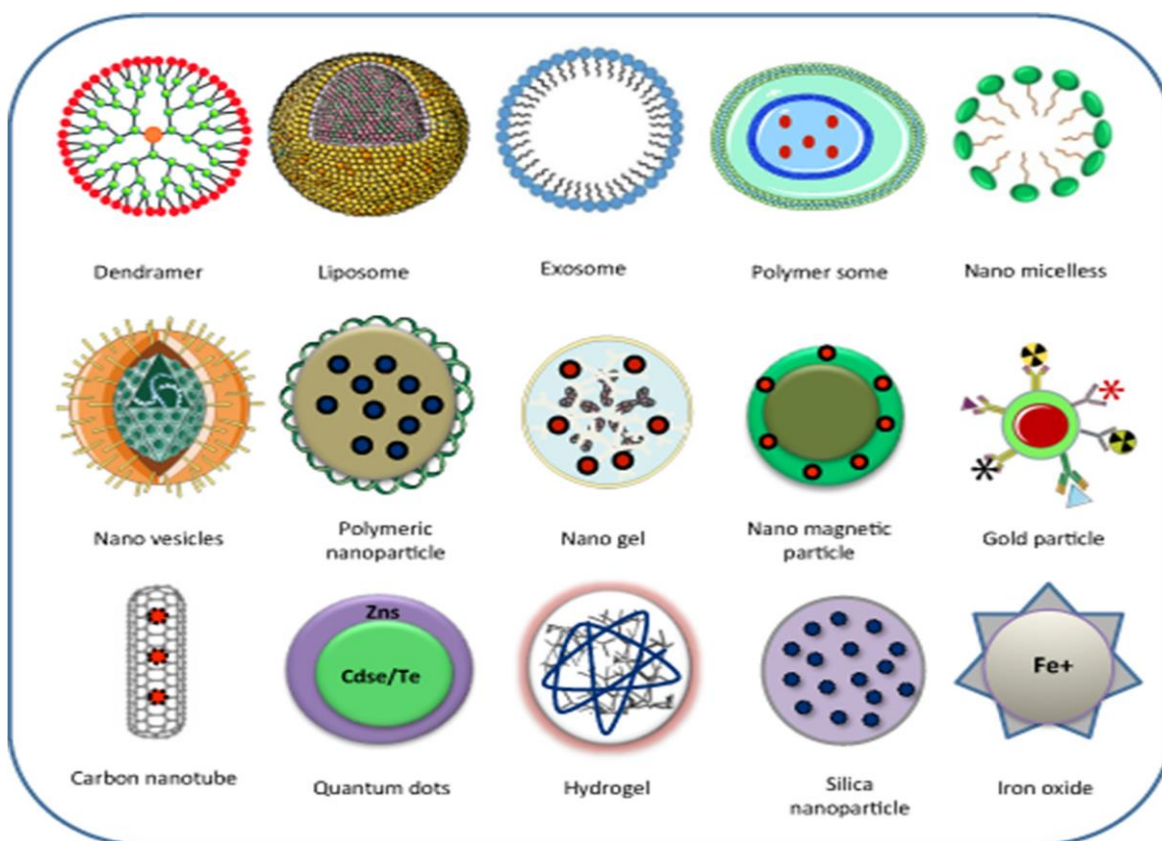


Figure (1.10) Types of Nano Drug molecules [42]

1.13 The Used Materials

1.13.1 ZnO Nanoparticles

ZnO is identified as a versatile, strategic, functional, and promising inorganic material with diverse applications. Zn and O are classified as II–VI semiconductors due to their positions in groups two and six of the periodic table, respectively. ZnO exhibits distinctive optical, chemical sensing, electrical conductivity, semiconducting, and piezoelectric properties. It is characterised by inherent n-type electrical conductivity, a substantial excitonic binding energy (60 meV) at room temperature, and a comparatively wide band gap (3.3 eV) in the near-UV spectrum. Due to these characteristics, ZnO can be utilised across various domains. The substantial band gap of ZnO considerably influences its optical absorbance and electrical conductivity, among other properties[43–45]. The emission of excitons may endure higher ambient temperatures, and doping ZnO with other

metals enhances its conductivity. The nanoscale amalgamation of ZnO has stimulated investigation into its potential as an innovative antibacterial agent. In addition to their unique antibacterial activities, ZnO-NPs exhibit significant catalytic and photochemical activity, as well as antifungal characteristics. Under both the UVA and UVB wavelength bands, from 315 to 400 nm and 280 to 315 nm, ZnO shows substantial optical absorption, contributing to its antibacterial efficacy and functioning as a UV barrier in cosmetic formulations[46-48].

ZnO nanoparticles (NPs) and nanorods (NRs) represent recent advancements in photodynamic therapy (PDT) with numerous potential clinical applications. They lead in these applications due to their elevated quantum yield and size-dependent tunable emission across a wide spectrum of light, rendering them suitable for both diagnostic and anticancer purposes in various microbial and nonmicrobial therapies. The current nanodependent PDT approach employing NPs and NRs is rapid, noninvasive, biocompatible under low-light circumstances, user-friendly, and exhibits minimal permeability under standard conditions. It also enhances endogenous fluorescence. ZnO nanorods, which have a large surface area compared to their volume and are safe for living tissues, can act as a carrier for photosensitisers and provide the natural white light needed to kill cancer cells [49-52].

One of ZnO nanoparticles' primary attributes is its low toxicity and biodegradability. Zinc dioxide (Zn^{2+}) is a necessary mineral for humans. Trace element with many metabolic functions (about 10 mg per day is recommended)[53- 56].

1.13.2 Cephalexin

Cephalexin, sometimes spelled cefalexin, is a first-generation, semisynthetic cephalosporin antibiotic that is meant to be used orally. In 1969, cephalexin became the first oral cephalosporin to be used in therapeutic settings. It is monohydrate of 7 – methyl – 3 – cephem – 4 – carboxylic acid (D-alpha-amino-alpha-phenylacetamido). The chemical formula of cephalexin is $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_4\text{S}\cdot\text{H}_2\text{O}$, with a molecular weight of 365.41 g/mol. Figure (1.11) illustrates the chemical structure of cephalexin[57].

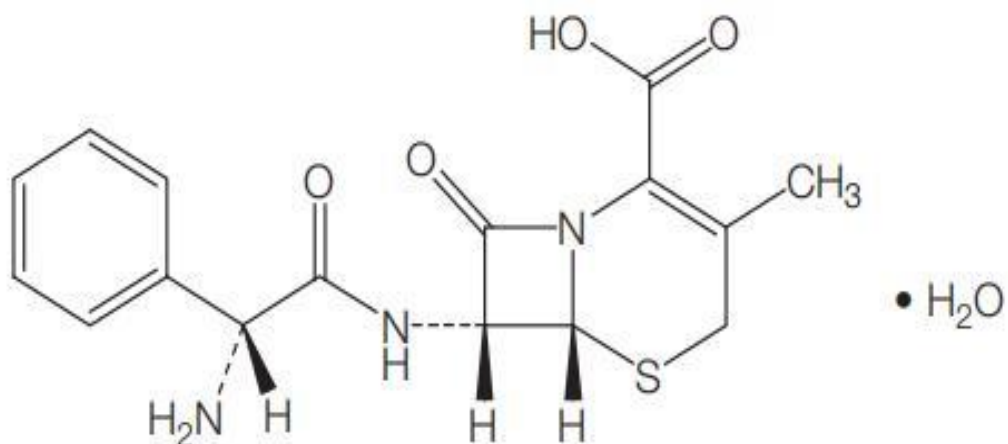


Figure (1. 11) The chemical structure of cephalexin [58]

Cephalexin possesses a core structure common to other cephalosporin antibiotics. Cephalexin possesses an unsubstituted methyl group at the third position and a D-phenylglycyl group as a substituent at the seventh position. The molecule possesses both an acidic and a basic group, rendering it a zwitterion. The isoelectric point of cephalexin in water ranges from 4.5 to 5. Cephalexin exists as a crystalline monohydrate. It possesses a harsh taste and is a crystalline white material. At ambient temperature, water solubility is minimal; concentrations of amounts of 1 or 2 mg/ml may dissolve easily, but achieving larger concentrations proves more difficult. Each capsule contains cephalexin monohydrate equivalent to either 250 mg (720 mmol) or 500 mg (1439 mmol) of cephalexin[59]. Cephalexin's molecular weight is roughly 347.39 g/mol, and its chemical formula is $C_{16}H_{17}N_3O_4S$. A carboxylic acid group and an amide group are part of its chemical structure, which enhances its stability and solubility. Cephalexin is usually used orally, and because of its capacity to withstand acidic conditions in the stomach, it can be absorbed efficiently in the gastrointestinal system[60].

The physicochemical characteristics of cephalexin, such as its lipophilicity and solubility, are essential for its distribution and absorption inside the body. Because of its moderate water solubility, the medication can be more easily formulated into oral dosage forms. Its ability to effectively permeate bacterial cell walls due to its lipophilic nature increases its antibacterial activity[61].

The action mechanism of cephalexin is a crucial element for bacterial survival and structural integrity; Cephalexin is aimed at the bacterial cell wall serves a vital function. Penicillin binding proteins (PBPs) are important for building and keeping the bacterial cell wall intact by linking peptidoglycan layers, which is where penicillin attaches [62].

1.13.3 Soy protein isolation (SPI)

The food industry makes extensive use of soy protein isolate (SPI), a type of premium plant protein with favorable physicochemical and nutritional qualities. A culinary component derived from soybean meal that is high in protein is SPI. As early as 1903, researchers began looking into the separation of soy protein. Based on their solubility at various pHs, soy proteins are separated. Wolf first explained the conventional SPI procedure in 1983[63]. The fundamental actions consist of Dehulling, flaking, hexane extraction of oil, and flash desolventising of the protein-rich defatted meal reduce protein denaturation, thereby enhancing the solubility of the protein in WF. Proteins are extracted by dissolving them in water at 60°C, with a solvent-to-solids ratio of 10:1 and a pH range of 8 to 11. The insoluble fiber is then removed by centrifugation. After bringing the pH down to 4.2–4.5, the protein precipitates, and centrifugation is used to separate the protein curd from the soluble carbohydrates (whey). After being water-washed, the protein curd is centrifuged once more. After being cleaned and neutralized to pH 6.8, the protein curd is spray-dried[64].

A plant protein made from soybeans, soy protein isolate (SPI) is growing in popularity due to its excellent nutritional content and inexpensive. Given that 7S (β -conglycinin) and 11S globulins (glycinin) are constitutive proteins, SPI has strong surface activity qualities. SPI exhibits significant promise as drug delivery nanocarriers due to its many functional and biologically useful qualities, including emulsification, gelling, and film formation. Members of the Apo A – E lipoprotein family share structural similarities with SPI, including reduced water solubility. Remarkably, the hydrophobic residues that are hidden within proteins can become visible on their surface following exposure to a thermally induced denaturation process. This leads to improved adsorption onto the hydrophobic surface and greater water solubility. Consequently, denatured SPI may be employed to stabilize nanosuspensions[65]. Furthermore, SPI has a balanced composition of charged,

polar and nonpolar amino acids, enabling a range of medications to be included. Glycinin (molecular weight = 360000 , roughly 60%) and β – conglycinin(molecular weight = 180000 ,about 40%)are the main constituents of SPI[66].

1.13.4 Gelatin

Collagen, the most prevalent and structurally stable protein in the animal kingdom, is thermally denatured to produce gelatin, a largely pure protein food ingredient. The production of gelatin, a water-soluble proteinaceous material, involves partly hydrolysing collagen derived from animal dermis, white connective tissue and osseous structures is used to alter the tertiary , secondary and to some extent , primary configurations of native collagen[67, 68].

Gelatin is a significant hydrocolloid and high molecular weight polypeptide that has gained popularity among the general due in great part to its gelling and thickening qualities, and is a component in many food items. In contrast to other hydrocolloids, which are primarily polysaccharides, Gelatin is a digestible protein that encompasses all essential amino acids, excluding tryptophan. Due to exposure to a variety of environmental factors, most notably temperature, the amino acid composition might differ between species, especially with regard to proline and hydroxyproline. Collagen can come from diverse sources to make gelatin. The primary commercial sources are hides, fish, and bovine osseous remains. Gelatin comes from no plant origins, and it has no chemical connection to other substances known as vegetable gelatin, including seaweed extracts [69-72].

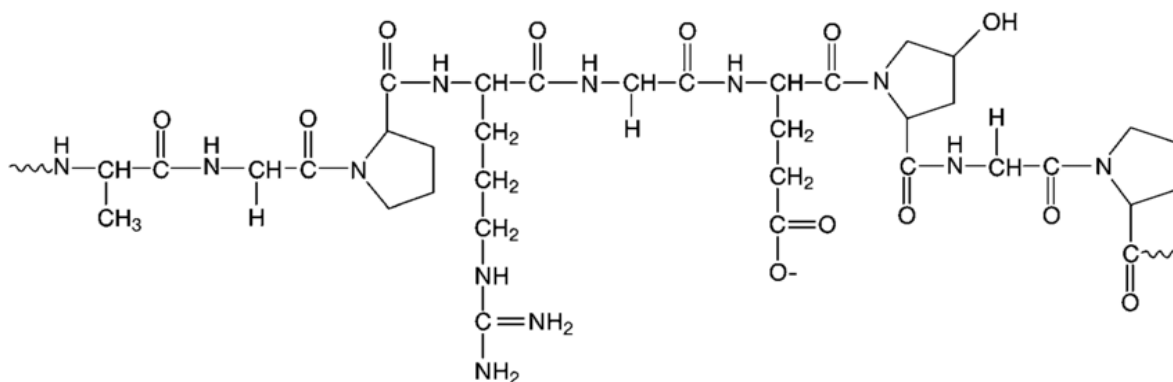


Figure (1.12) The chemical structure of cephalexin Gelatin[73]

1.13.5 Polyethylene glycol (PEG)

Synthetic, multipurpose, and extremely hydrophilic, polyethylene glycol (PEG) has a variety of chain lengths and a significant quantity of functional end groups. It has a variety of uses in biological, biophysical, and biochemical research. It is also used as a component in food goods, cosmetics, and medicinal therapy. When n denotes the number of ethylene oxide units, PEG's general formula is $\text{HO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{H}$ Figure (1.13). Ethylene oxide is used as a reaction initiator in a ring-opening polymerization process with either water or methanol to create diol PEG or methoxy-PEG (mPEG). The chain length and, thus, the molecular weight of the resulting PEG polymers vary [74, 75].

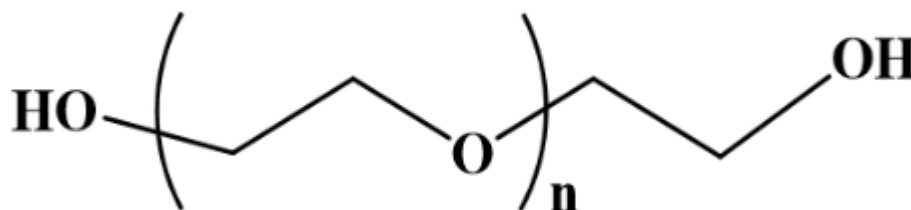


Figure (1.13) Structure of polyethylene glycol chemically [76]

Many different applications make considerable use of PEG and PEG compounds with different molecular weights. They are authorized for use in a variety of pharmaceutical applications, the food sector, and cosmetic preparations[77, 78]. PEG are frequently employed as an excipient in a variety of pharmaceutical formulations, including injectable formulations, aqueous solutions, ointment bases, oral pills, tablets, capsules, suppositories, laxatives, and emulsions. In order to improve therapeutic efficacy, they have recently been extensively employed in drug delivery applications by PEGylation, which is the conjugation of PEG molecules to drug molecules or nanocarriers [79].

PEGs are also frequently found in skin disinfectants, cosmetics, and other household goods. PEGs function as skin conditioners, humectants, emulsifying agents, and penetration enhancers when applied topically. As a result, they are widely utilized in the production of shampoos, soaps, face and hair care products, toothpaste, shaving creams, lipsticks, skin lotions, and many other everyday household items[80].

1.14 Literature Review

In 2014 Eun Mi Lee *et al.*[81] studied Novel alginate gelatin hybrid nanoparticles were synthesised by a method termed single oil in water (O/W) emulsification. AGNPs were employed to culture human keratinocytes for two weeks to assess the biocompatibility of the produced AGNPs. The outcomes of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay were juxtaposed with cells cultivated on AGNPs and in two-dimensional (2D) culture. Alginate and gelatin may form an electrostatic connection, as indicated by the drug release profile, facilitating controlled drug release from AGNPs. For the first time, alginate-gelatin hybrid nanosystems have been created, showing they could be useful in regenerative medicine and for delivering drugs and treatments to cells.

In 2017, Maria Antonieta Anaya Castro *et al.*[82] investigated and evaluated The spray-drying method demonstrated the effectiveness of soy protein isolate and acylated soy protein as encapsulation carriers for oral medicinal applications. The SPI acylation was conducted by the Schotten–Baumann method. acylated soy protein 's solubility declined in acidic environments but remained unaffected by basic ones, despite having an acylation rate of 41%.

In 2017 Xiao Huang *et al.*[83] studied the exciting new developments in ZnO-based drug delivery systems at the nanoscale: moving from passive to intelligent tactics. They demonstrated that zinc oxide is widely utilized in biomedical applications, is generally regarded as safe, it has successfully cleared clinical hurdles to obtain authorization from the drug administration and food.

In 2018 Marina Martínez-Carmona *et al.*[84] studied the most recent advancements in ZnO-based nanoplatform therapeutic applications and drug delivery for a variety of diseases, such as bacterial infections and cancer.

In 2019 Maria Antonieta Anaya Castro *et al.*[85] studied If spray-drying succinylated soy protein (SPS) may be utilized as a wall material to encapsulate ibuprofen (IBU), a prototypical hydrophobic drug. The soy protein isolate has a 1/1.5 molar ratio (NH₂/succinic anhydride) and a 93% succinylation rate. As indicated by the solubility results at 37°C show that this chemical change made the protein less soluble below its isoelectric point but more soluble in alkaline condition.

In 2020, Saloni Mehra *et al.* [11] studied The soy protein isolate underwent microwave-assisted grafting. Graft copolymerisation of 4-hydroxyphenylbutanoic acid and acrylic acid was conducted using potassium persulfate as the initiator and N,N-methylene-bis-acrylamide as the cross-linker to synthesise the [AA-co-HPBA]-SPI-g hydrogel. To combat bacterial infections in the oral cavity, the model antibiotic ciprofloxacin was released at a basic pH using the SPI-g (AA-co-HPBA) hydrogel, which was examined as a strategy for regulated and sustained drug administration. The drug release profile for SPI-g (AA-co-HPBA) hydrogels was analysed at pH 7.4 using LCMS at the parts per billion level. The hydrogel exhibited a network structure, high porosity, enhanced thermal stability, and pH-responsive properties, rendering it non-cytotoxic and polycrystalline. The hydrogel can serve as a regulated drug delivery device for the treatment of oral bacterial infections.

In 2023 Francesca Milano *et al.*[70] investigated the widely used methods for creating micro- or nanosized DDSs based on gelatin. We draw attention to gelatin's capacity to transport a variety of bioactive substances and its capacity to adjust and regulate the release kinetics of specific medications. Methodological and mechanistic descriptions of the desolvation, nanoprecipitation, coacervation, emulsion, electrospray, and spray drying processes are provided, together with a thorough examination of how the primary variable parameters affect the characteristics of the DDSs. Finally, a detailed discussion of the findings from preclinical and clinical research employing DDSs based on gelatin is provided.

In 2023 ,Osama A. Madkhali[69] studied using gelatin nanoparticles to treat viral illnesses. These nanoparticles are appealing choices for medication administration because of their intrinsic qualities. Because of their biocompatibility, they can communicate with biological systems without producing negative side effects, and their biodegradability guarantees that, after their purpose is fulfilled, they can decompose in the body without harm. Additionally, their ability to release drugs under controlled conditions guarantees that therapeutic substances can be administered over an extended length of time, improving the effectiveness of treatment.

In 2024 ,Ruiyan Xu and Sun Qian[72] studied The environmentally friendly synthesis of gelatin hydrogel nanoparticles with potential uses in the treatment of stomach cancer is shown in this work using a dual application method. Bisphenol breastfeeding and BPA

sensing. Gelatin hydrogel nanoparticles were created without the use of hazardous chemicals or solvents by employing a green and freeze-drying technique. The nanoparticles demonstrated outstanding biocompatibility and encouraging prospects for use in drug delivery systems (DDS) for the treatment of gastric cancer. The gelatin nanoparticles' potential for targeted therapy was demonstrated by the controlled release of anticancer medications from them. Furthermore, researchers investigated the use of gelatin hydrogel nanoparticles for BPA detection.

In 2024 Viswanathan Kaliyaperumal [86] studied Using a straightforward casting process, a new multipurpose biofilm was produced. The biofilm consisted of gelatin, chitosan, and zinc oxide nanoparticles conjugated with 5-fluorouracil (5-FU), as well as polyvinyl alcohol plasticised with glycerol. The single-step co-precipitation method used to synthesise the 5-FU-conjugated nanoparticles presented an innovative strategy. The characterisation validated effective drug conjugation, indicating the presence of bar-shaped nanoparticles measuring between 90 and 100 nm. The kinetics of drug release were assessed using the Korsmeyer–Peppas model indicating a regulated release mechanism. The versatility of the gelatin–chitosan film was highlighted by studies that showed pH-dependent characteristics in its maximum swelling ratio. Due to their potent anticancer action against skin cancer cells and lack of cytotoxicity towards human fibroblasts, these biofilms demonstrated potential for use in biomedical applications.

In 2024 Soha Gomaa *et al.* [87] studied Evaluate the anti-tumour and anti-inflammatory effects of ZnONP nanocomposites in conjunction with systemic chemotherapeutic agents doxorubicin (DOX) and folic acid (FA) using both cultured and living organism models Ehrlich ascites carcinoma (EAC) tumour cell lines. Furthermore, evaluate the capability of ZnONP nanocomposites as a drug delivery system for cancer chemotherapy.

In 2024 Josh E. Eixenberger *et al.* [88] studied a novel method that uses ZnO nanoparticles (nZnO) to photo-irradiate with UV light (365 nm) to cause the quick release of lipid-encapsulated medications. According to in vitro research, encapsulating nZnO effectively reduces its cytotoxicity; however, this can be restored when the lipid coating is removed. By using 5(6)-carboxyfluorescein as a hydrophilic drug-loading model, we demonstrate how medicines can be co-loaded into liposomes with nZnO. The majority of the dye can be released within 60 minutes after photoirradiation, according to kinetic

studies, which also shed light on the variables influencing release kinetics. These investigations showed that the triggered release groups were more hazardous, and the viability profiles of the T47D breast cancer cell model showed a significant difference. According to these findings, by regulating therapeutic release, this approach of co-encapsulating nZnO and chemotherapy medications may reduce systemic toxicity while enabling the localized, selective killing of cancer.

1.15 The Aim of the Research

The aims of this study are :

- 1- Develop hydrogel-based polymeric matrices using natural and synthetic components (gelatin, soy protein isolate, polyethylene glycol, and ZnO nanoparticles), and incorporate the antibiotic cephalexin for potential application in sustained oral drug delivery.
- 2- Investigate the physicochemical properties of the prepared matrices, including their structural integrity, surface morphology, and compatibility using FTIR and SEM analysis.
- 3- Evaluate the pH-responsive swelling behavior and drug release kinetics of the matrices under simulated gastric and intestinal conditions, determining the influence of crosslinking density and monitoring cephalexin release over time using UV-Vis spectrophotometry.
- 4- Assess the antibacterial activity of the drug-loaded hydrogels against common pathogens (*Staphylococcus aureus* and *Escherichia coli*), and identify the optimal formulation based on swelling behavior, release profile, and antimicrobial efficacy for improved performance in controlled drug delivery.

Chapter Two
Experimental Part

2.1 Introduction

This chapter presents the materials, equipment, and procedures used that were for preparing the polymeric matrices, drug loading, and conducting characterization, swelling, drug release, and antibacterial tests.

2.2 The Chemicals Used

The chemicals used in this experiment are listed in Table (2.1), and utilized without further purification.

Table (2.1) The Chemicals Used

No.	Chemicals	The Company provided	Orgin	Percentage or Purities
1	Soy Protein Isolation (SPI)	Shandong Wonderful Biotech Co. ltd	China	90%
2	Gelatin	Geltech Co., Ltd	South Korea	99%
3	Polyethylene glycol (PEG)	Jungwoo Co.,Ltd	South Korea	99%
4	ZnO Nanoparticles	NHTNM Co.,Ltd	China	98%
5	Cephalexin	General Company for Pharmaceuticals, Samarra	Iraq	99%
6	Glutaraldehyde	Central Drug House Co., ltd	India	25% W/V %
7	Hydrochloric Acid	J.K.. Baker. Netherlands	India	35-38% W/V %
8	Sodium Hydroxide	Meru Chem Pvt.Ltd	India	98%
9	Monopotassium phosphate	CDH	India	98%
10	Sodium Chloride	BDH	UAE	99%

2.3 Instrumentation

Table 2.2 lists the instruments used in this study along with their respective manufacturers.

Table (2.2) Instrumentation

No.	Instrumentation	Companies	Places
1	Sensitive balance	German state of Sartorius, BL 210 S	Al-Qadisiyah University, College of Science
2	Digital pH meter	Singapore, OAKTON-2100	Al-Qadisiyah University, College of Science
3	Magnetic Stirrer with Heating Plate	Germany, Heidolph Mr. Hei- Standard	Al-Qadisiyah University, College of Science
4	UV-Visible spectrophotometer with double beams	Japan's Shimadzu UV-1800	Al-Qadisiyah University, College of Science
5	Infrared spectroscopy using the Fourier-	Japan's Shimadzu FTIR-8400S	Al-Qadisiyah University, College of Science
6	Laboratory Incubator	Memmert, Germany's Laboratory Incubator, Model IN55	Al-Qadisiyah University, College of Science
7	Scanning Electron Microscopy (SEM)	450 gadget from FESEM FEI Nova Nano SEM	Tehran University

2.4 Preparation of standard solutions

2.4.1 Standard solution preparation and the Cephalexin Calibration Curve

A standard solution of cephalexin (molecular weight = 347.39 g/mol) was prepared at a concentration of 100 ppm. UV–Visible spectroscopy was utilized to determine the maximum absorbance wavelength (λ_{max}) of cephalexin within the spectral range of 200–400 nm. The analysis identified the λ_{max} at 261 nm, as illustrated in Figure (2.1).

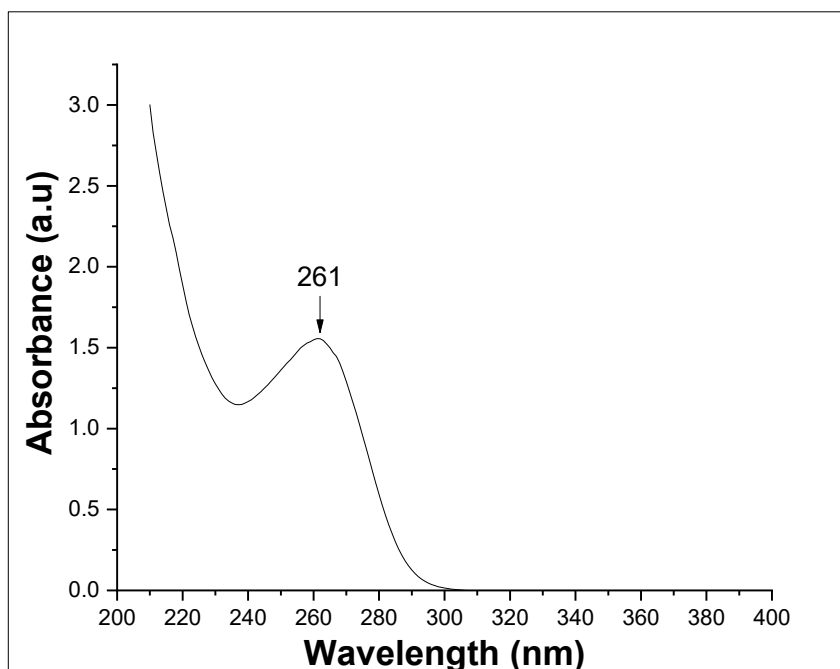


Figure (2.1) UV–Vis absorption spectrum of cephalexin

To construct the calibration curve for cephalexin, five standard solutions with concentrations ranging from 20 to 100 ppm were prepared. The absorbance of each solution was measured at the maximum wavelength ($\lambda_{\text{max}} = 261$ nm). As depicted in Figure (2.2), the calibration curve was generated by plotting absorbance against concentration and applying the least squares linear regression method.

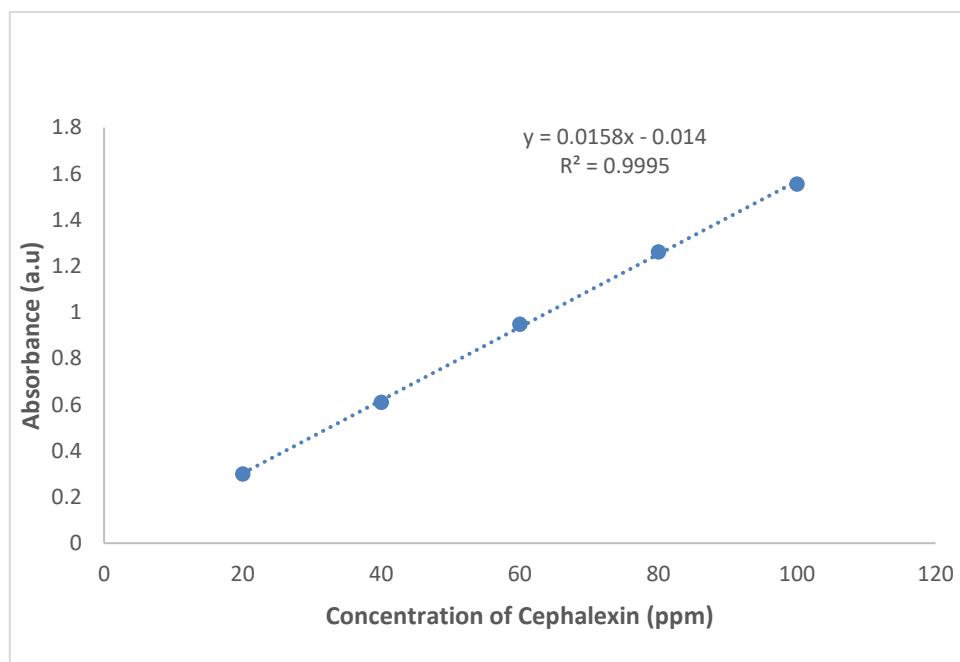


Figure (2.2) Calibration Curve for Cephalexin

2.4.2 Preparation of Simulated Gastric Fluid:

Based on data obtained from the Encyclopedia of Medicines, a non-enzymatic simulated gastric fluid (SGF) was prepared. Two grams of sodium chloride (NaCl) were dissolved in 500 mL of distilled water under continuous stirring. Subsequently, 10 mL of concentrated hydrochloric acid (HCl) was added, and the volume was adjusted to 1000 mL with distilled water. The final solution simulates the acidic conditions of gastric fluid, with a target pH of approximately 1.2 [79].

2.4.3 Preparation of Simulated Intestinal Fluid:

Following the guidelines of the American Academy of Dermatology, a non-enzymatic simulated intestinal fluid (SIF) was prepared. Initially, 8.6 grams of monopotassium phosphate (KH_2PO_4) were dissolved in 250 mL of purified water. Subsequently, 190 mL of a 0.2 M sodium hydroxide (NaOH) solution was added, and the total volume was adjusted to 1000 mL with purified water. This buffer solution mimics the pH and ionic environment of intestinal fluid, typically around pH 6.8 [79].

2.5 Preparation of the Hydrogel Polymeric matrix

2.5.1 Preparation of the Hydrogel Polymeric matrix for SPI

The preparation of the SPI-based hydrogel matrix began with the dissolution of 1 g of soy protein isolate (SPI) in 10 mL of deionized water. The pH of the solution was gradually adjusted to approximately 11 by the dropwise addition of 5 M NaOH to ensure complete solubilization of the protein, resulting in a viscous SPI solution. In a separate step, 1 g of polyethylene glycol (PEG) was dissolved in 10 mL of deionized water by heating the mixture to 50–60 °C under continuous stirring, followed by cooling to about 40 °C. The SPI and PEG solutions were then combined at room temperature under constant stirring. The pH of the resulting polymer blend was adjusted to neutral (7.0) using dilute hydrochloric acid or acetic acid to optimize the subsequent crosslinking reaction. Subsequently, 0.1 g of zinc oxide nanoparticles were incorporated into the mixture and meticulously dispersed to ensure uniform distribution, with the option of pre-dispersion in a minimal volume of water to improve homogeneity. Approximately half an hour after thorough mixing, the mixture was allowed to sit at room temperature. The final mixture was then spooned into a mould or Petri dish and let to sit undisturbed for a while [80].

2.5.2 Preparation of the Gelatin-Based Hydrogel Polymeric Matrix

One gramme of gelatin has been dissolved in ten millilitres of distilled water. A solution of polyethylene glycol (PEG) was prepared by dissolving 1 g of polyethylene glycol in 10 ml of water, which was then gradually added while continuously stirring the mixture for 20 minutes to ensure consistency at a temperature of 50°C. The pH of the solution was adjusted to approximately 11 by incorporating a 5 molar sodium hydroxide solution to enhance the dissolution of gelatin. Subsequently, 0.1 g of zinc oxide nanoparticles was introduced and uniformly dispersed through continuous stirring. Subsequently, 1 ml of glutaraldehyde was introduced dropwise, and stirring was maintained for an additional hour to guarantee adequate time for cross-linking between the gelatin and PEG. The final solution was cast into a Petri dish and left at ambient temperature until full gelation and

drying occurred. The same process was repeated using reduced gelatin quantities (0.7 g and 0.3 g) to generate hydrogel variants exhibiting differing swelling capacities. Among these, the mixture comprising 0.7 g gelatin, 0.3 g PEG, and 0.5 mL glutaraldehyde produced the most structurally consistent and stable hydrogel [80].

2.6 Effect of Crosslinking Agent on the Swelling Ratio of the Polymeric Matrix

The influence of varying concentrations of the crosslinking agent on the swelling behavior of the polymeric matrix was investigated. Swelling characteristics were assessed for both gelatin- and SPI-based hydrogel networks in the absence of glutaraldehyde and in the presence of 0.5, 1.0, and 1.5 mL of the crosslinker. This analysis aimed to determine how increased crosslinking density affects the water uptake capacity of the hydrogel matrices.

2.7 Analysis of the Swelling Ratio of the Prepared Polymeric Matrix

The swelling behaviour was assessed by submerging the laboratory-synthesized hydrogel samples in water solutions at ambient temperature (27 °C). After 24 hours, the samples were extracted and delicately wiped using filter paper to remove excess surface moisture. The swelling ratio of each hydrogel was then determined using the following formula [81]:

$$SR = \frac{ws - wd}{wd} \times 100\% \quad \dots\dots\dots (1)$$

Where (SR) represents the swelling ratio of the hydrogel sample, Wd represents the weight of the dry sample, while Ws denotes the swollen weight .

2.8 Preparation of the Drug-Loaded Hydrogel Polymeric Matrix

A quantity of 0.01 g of cephalexin was accurately weighed using a precision electronic balance and incorporated into the components of the hydrogel polymeric matrixes . The mixture was stirred thoroughly at room temperature for 30 minutes to ensure uniform drug distribution. Subsequently, the formulation was cast into Petri dishes and left to dry at

ambient conditions. The same steps were followed for the gelatin-based hydrogel polymeric matrix [82].

2.9 Examination of Cephalexin Release from Hydrogel-Based Polymeric Matrices

The release kinetics of the drug from the prepared samples were assessed by placing the sample in a simulated gastric fluid solution and simulated intestinal fluid on a shaker at a speed of 160 rpm. The concentration of cephalexin was monitored over time at a wavelength of 261nm.

2.10 Assessment of Drug Release Percentage from the Hydrogel Polymeric Matrix

The drug release percentage from the laboratory-prepared samples can be determined by immersing the matrix samples in SGF (stomach fluid) and SIF (intestinal fluid) solutions. Concentration was quantified over time at the drug's maximum wavelength. Ultraviolet spectroscopy was employed to monitor the drug release rates from the polymer matrix over time utilising the equation shown below: [83]:

$$\text{Release \%} = \frac{\text{concentration of drug released with Time}}{\text{concentration of drug loaded}} \times 100 \% \dots\dots (2)$$

2.11 Characterizations

2.11.1 FTIR Measurement

Functional group analysis of completely dried cephalexin-loaded and unloaded hydrogel matrix samples was conducted using Fourier transform infrared (FT-IR) spectroscopy, ranging from 4000 to 400 cm⁻¹.

2.11.2 SEM Measurement

Scanning Electron Microscopy (SEM) was employed to evaluate the morphological characteristics of the SPI/PEG/ZnO and Gel/PEG/ZnO polymeric matrices, both before and after the incorporation of the model antibiotic drug, cephalexin. Micrographs were obtained at a magnification scale of 200 nm to observe nanoscale surface features and morphological transitions resulting from drug loading.

A scanning electron microscope (SEM) was used to analyze the morphology of hydrogel matrix both before and after the addition of cefalexin samples. Well-dried hydrogel samples were gold-sputtered before morphological analysis.

2.11.3 Antibacterial Tests

The antibacterial efficacy of hydrogel formulations was assessed using agar well diffusion assays against two bacterial strains: *Staphylococcus aureus* (gram-positive) and *Escherichia coli* (gram-negative). Bacterial suspensions were formulated in sterile saline solution at a final concentration of 1.5×10^8 colony-forming units per millilitre. The turbidity was calibrated to McFarland standard 0.5 to guarantee uniformity. Each bacterial culture was evenly spread on Mueller-Hinton agar plates utilising sterile swabs. The wells were subsequently filled with hydrogel test formulations and incubated at 37°C for 24 hours. Following incubation, the widths of the transparent zones surrounding each well were measured in millimetres to evaluate the extent of bacterial growth inhibition, hence demonstrating the antimicrobial efficacy of each sample [83].

Chapter Three

Results and Discussion

3.1 Introduction

This chapter details the experimental observations and analytical interpretations related to the prepared polymeric matrices. Emphasis is placed on evaluating their physicochemical behavior, drug release kinetics, surface morphology, and antimicrobial performance.

3.2 FTIR Measurement for polymeric matrix

3.2.1 FTIR Spectral Analysis of SPI/PEG/ZnO Hydrogel Matrix Before and After Cephalexin Loading

The molecular interactions within the soy protein (SPI)/polyethylene glycol (PEG)/ZnO hydrogel system before and after cephalexin loading were investigated using Fourier-transform infrared (FTIR) spectroscopy, as illustrated in Figures 3.1 and 3.2. The hydrogel matrix was chemically crosslinked using glutaraldehyde to improve structural integrity. The FTIR spectrum of the unloaded hydrogel (SPI1) displayed several characteristic peaks corresponding to the primary components of the composite. A strong and broad absorption band at 3292.49 cm^{-1} was attributed to O–H and N–H stretching vibrations, indicating extensive hydrogen bonding between SPI and PEG. The methylene groups of PEG contributed to C–H stretching bands around 2883.58 cm^{-1} . The protein backbone of SPI was confirmed by the presence of prominent amide bands, with Amide I observed at approximately 1653 cm^{-1} corresponding to C=O stretching, and Amide II bands between 1533.41 and 1506.41 cm^{-1} related to N–H bending and C–N stretching [94–97]. Additionally, a group of peaks ranging from 1147.65 to 1029.99 cm^{-1} was associated with C–O–C ether linkages in PEG chains [98, 99]. A low-intensity peak at 842.89 cm^{-1} , attributed to Zn–O stretching vibrations, confirmed the presence of ZnO nanoparticles in the hydrogel matrix [100].

Upon loading cephalexin (spectrum SPI2), significant spectral changes were observed, confirming drug incorporation and interaction with the hydrogel network. A new peak at 1751.36 cm^{-1} emerged, corresponding to C=O stretching vibrations from the carboxylic group of cephalexin. Additionally, a weak peak around 1666.50 cm^{-1} was identified, potentially arising from the β -lactam carbonyl stretch or overlapping with the Amide I band, indicating possible hydrogen bonding between cephalexin and the SPI matrix. The

increased absorption intensity at 3302.13 cm^{-1} suggests additional N–H contributions from cephalexin forming hydrogen bonds with the hydrogel components. Furthermore, enhanced and broadened signals were detected between 1280.73 and 1031.92 cm^{-1} , which may be attributed to C–N and C–O bonds from cephalexin involved in hydrogen bonding or dipolar interactions with SPI or PEG. A novel peak at 696.30 cm^{-1} , absent in the unloaded sample, was also observed, suggesting structural involvement of cephalexin within the ZnO-containing matrix, possibly due to interactions with the aromatic or ring-related vibrations of the drug.

Overall, the FTIR spectral modifications confirm the successful encapsulation of cephalexin into the SPI/PEG/ZnO nanocomposite. The interactions, primarily through hydrogen bonding and physical entrapment, suggest that the matrix can enhance drug stability, entrapment efficiency, and enable controlled release behavior. These findings support the potential use of the developed hydrogel system as a promising platform for biomedical drug delivery applications.

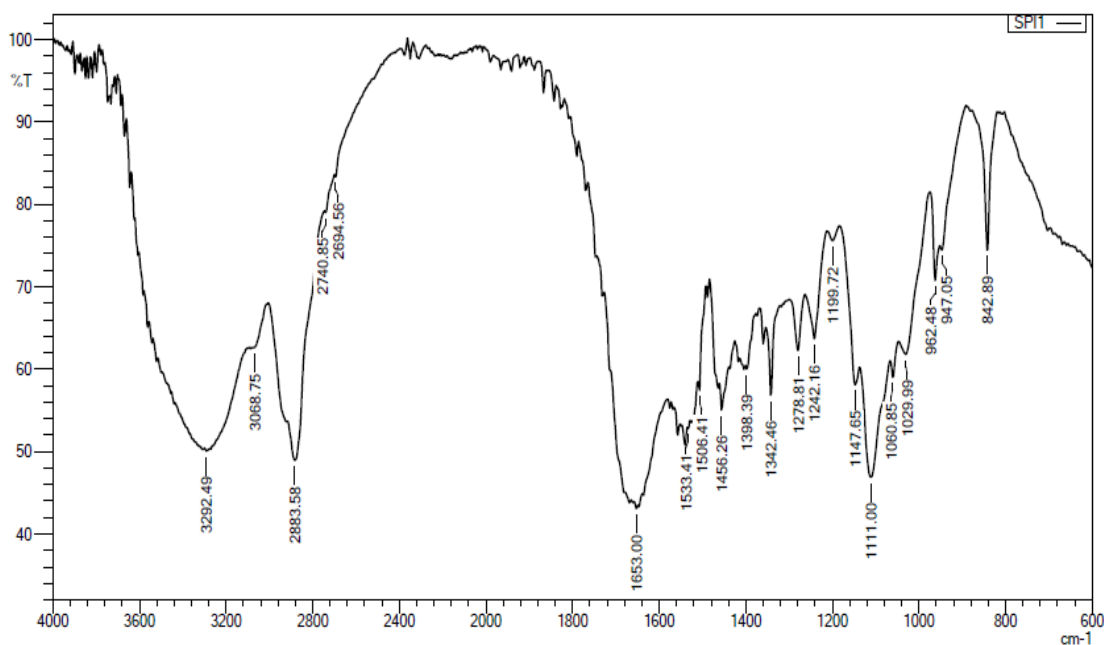


Figure (3.1) FTIR spectrum of the SPI/PEG/ZnO hydrogel matrix before cephalexin loading.

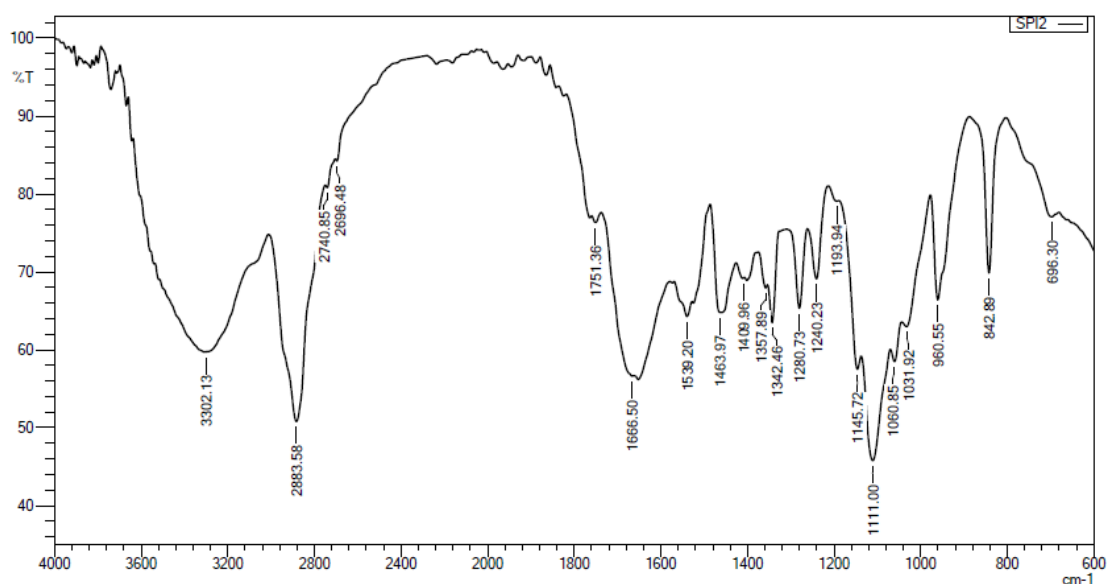


Figure (3.2) FTIR spectrum of the SPI/PEG/ZnO hydrogel matrix after cephalixin loading.

3.2.2 FTIR Analysis and Discussion of Gel/PEG/ZnO Polymeric Matrix Before and After Cephalixin Loading

The gelatin/PEG/ZnO nanoparticle-based hydrogel system, chemically crosslinked using glutaraldehyde, was analyzed using Fourier-transform infrared (FTIR) spectroscopy to investigate structural features and drug incorporation behavior before and after the loading of cephalixin, as shown in Figures 3.3 and 3.4. The FTIR spectrum of the unloaded formulation (G1) revealed a broad and intense absorption band around 3290.56 cm^{-1} , corresponding to O–H and N–H stretching vibrations, which are indicative of extensive intermolecular hydrogen bonding within the polymer network composed of gelatin and PEG [101, 102]. In the region $2937.59\text{--}2881.65\text{ cm}^{-1}$, characteristic C–H stretching vibrations of methylene groups were observed, attributable to the PEG chains [103].

Gelatin protein backbone was confirmed by the presence of amide I and amide II bands, with a prominent peak at 1651.07 cm^{-1} corresponding to C=O stretching (amide I) and another at 1539.20 cm^{-1} attributed to N–H bending (amide II), both typical of collagen-derived biopolymers [104]. These bands reflect the integrity of gelatin's secondary

structure within the hydrogel. Several additional peaks were present in the range 1200–600 cm^{-1} , which can be attributed to C–O stretching vibrations from PEG, Zn–O stretching, and other matrix-related interactions [106]. Specifically, bands around 1145–1026 cm^{-1} relate to C–O–C ether vibrations, while absorption near 842.95 cm^{-1} and 690.86 cm^{-1} confirm the presence of Zn–O bonds, indicating the successful incorporation of ZnO nanoparticles into the hybrid network [105].

Following cephalixin incorporation (G2), significant spectral alterations were observed that clearly demonstrate the interaction between the drug and the hydrogel components. A distinct new absorption peak at 1766.80 cm^{-1} was identified, corresponding to the C=O stretching vibration of the β -lactam ring in cephalixin. This confirms the successful integration of the drug into the polymer matrix. Additionally, a peak emerged at 1692.62 cm^{-1} , which likely represents additional carbonyl functionality from the carboxyl or β -lactam moieties of cephalixin. The amide I and II bands also showed slight increases in intensity, suggesting enhanced hydrogen bonding interactions between cephalixin and the matrix polymers, possibly involving gelatin amide groups and PEG hydroxyls.

In the fingerprint region (1200–600 cm^{-1}), minor shifts and increased absorbance were detected, particularly between 1283.52 and 1030.27 cm^{-1} , which may be associated with C–N and C–O stretching vibrations of cephalixin engaged in hydrogen bonding or dipolar interactions with the matrix. Additionally, the Zn–O band at ~ 842 cm^{-1} remained consistent in position but slightly increased in intensity, while a new signal near 690.37 cm^{-1} may indicate interaction between cephalixin and ZnO nanoparticles. These modifications in the spectral profile point to intermolecular interactions, including hydrogen bonding, dipole–dipole forces, and possibly weak electrostatic attractions between cephalixin and the gelatin/PEG/ZnO nanocomposite.

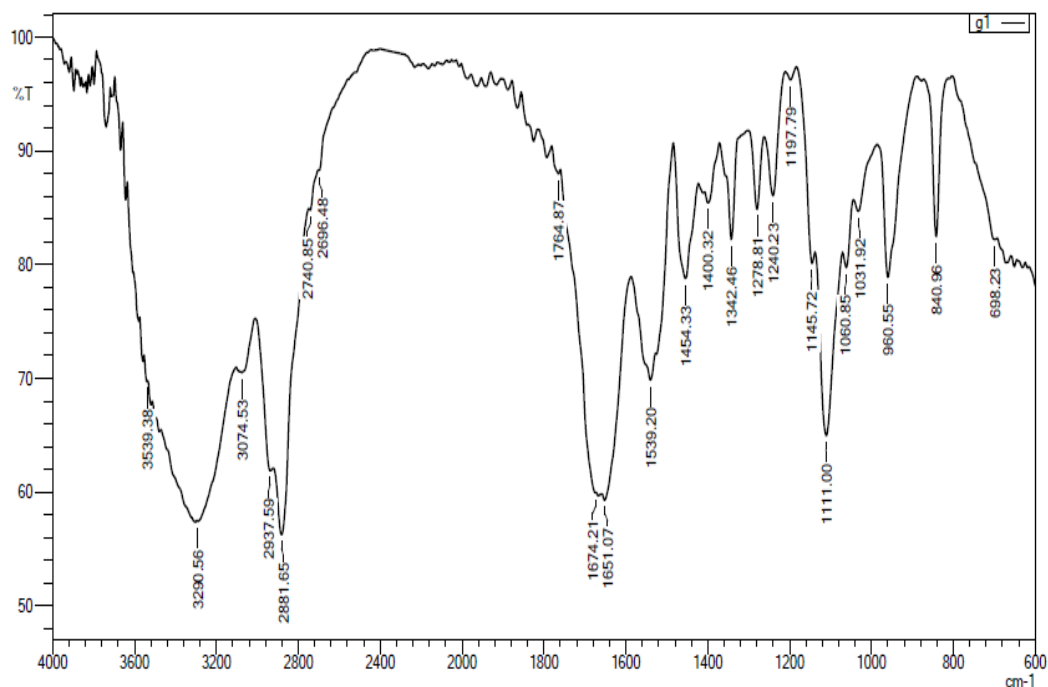


Figure (3.3) FTIR spectrum of the Gel/PEG/ZnO hydrogel matrix before cephalixin loading.

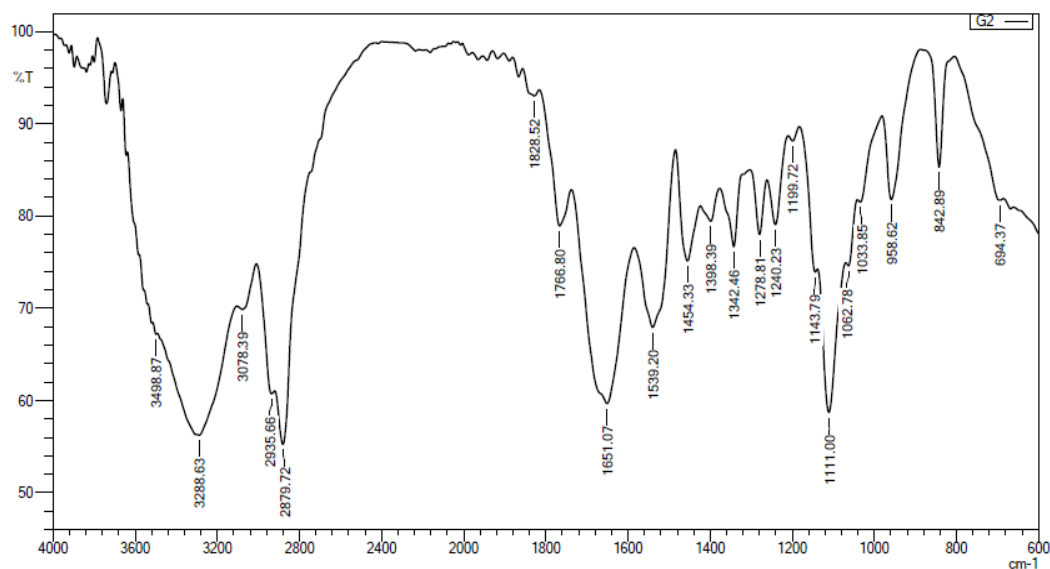


Figure (3.4) FTIR spectrum of the Gel/PEG/ZnO hydrogel matrix after cephalixin loading.

3.3 Study of swelling ratios of prepared polymeric compositions

The swelling properties of the prepared polymeric nanocomposite hydrogels were evaluated by immersing the samples in distilled water for 24 hours under ambient conditions. Swelling ratio serves as a crucial parameter in assessing the hydrogel ability to absorb water and is directly related to its potential as a controlled drug delivery system. The results are presented in Figures 3.5 and 3.6 for SPI/PEG/ZnO and Gel/PEG/ZnO systems, respectively.

Among the SPI-based compositions, the formulation containing 0.3 PEG and 0.7 SPI exhibited the highest swelling ratio, reaching 256%, indicating a more open polymeric network capable of greater water uptake. In contrast, the 1PEG:1SPI and 0.7PEG:0.3SPI formulations demonstrated significantly lower swelling ratios, 21.95% and 0%, respectively. This trend highlights the impact of polymer ratios on the hydrophilicity and network architecture of the SPI-based matrices. The limited swelling in PEG-rich formulations may be attributed to increased crosslinking density and reduced protein content, both of which restrict water penetration and network expansion.

In the gelatin-based series, a similar trend was observed; however, the swelling capacity was substantially higher across all compositions. The 0.3PEG:0.7Gelatin hydrogel reached a maximum swelling ratio of 1132%, while the 1PEG:1Gelatin and 0.7PEG:0.3Gelatin compositions recorded 738% and 233%, respectively. This enhanced swelling behavior of gelatin-based hydrogels, as shown in Figure 3.6, can be attributed to gelatin intrinsic hydrophilic nature and greater capacity for hydrogen bonding with water molecules. The presence of additional polar functional groups in gelatin, such as amide and carboxylic moieties, promotes greater water absorption compared to soy protein isolate.

The superior swelling performance of gelatin-based matrices indicates their potential advantage in drug delivery applications where rapid hydration and high fluid uptake are desirable. Moreover, the data underscore the tunability of hydrogel properties through compositional modifications, offering design flexibility for targeted biomedical applications.

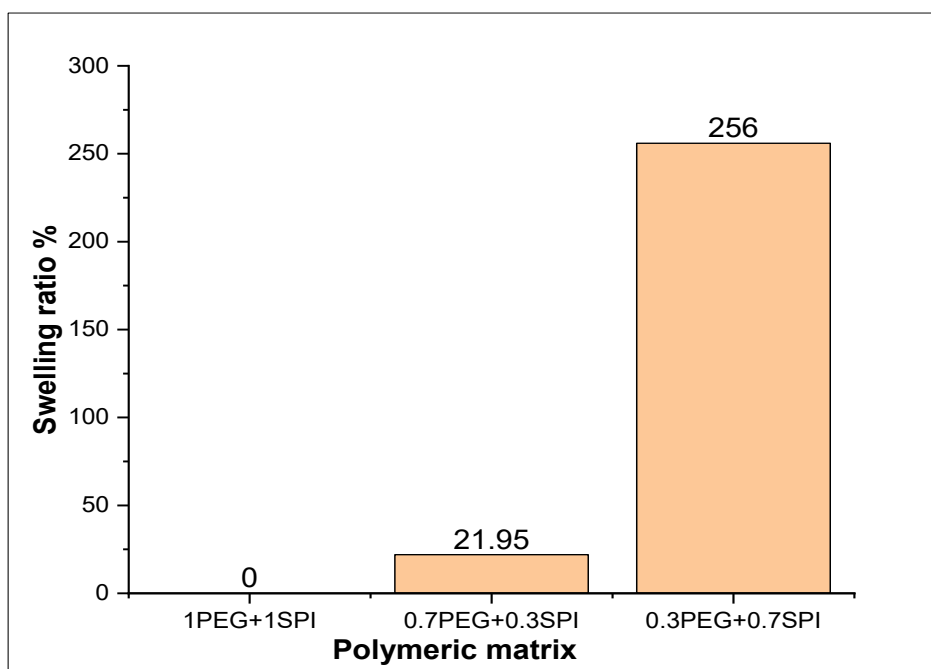
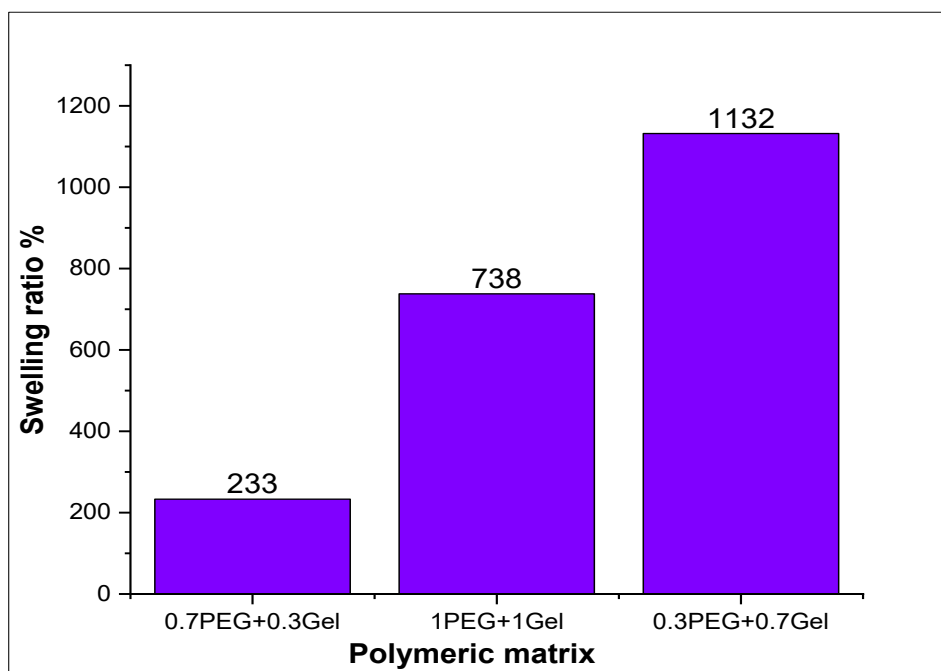


Figure (3.5) Swelling ratio of SPI /PEG/ZnO



Figures (3.6) Swelling ratio of Gel/PEG/ZnO

3.4 Study the effect of the crosslinking agent on the swelling ratio of the polymeric matrix

The swelling characteristics of SPI and gelatin samples were examined by incorporating varying quantities of glutaraldehyde. The samples lacking a crosslinking agent exhibited no swelling and instead disintegrated in the water solution. This results from the elevated solubility of SPI, gelatin, and PEG. Consequently, a crosslinking agent is essential in any polymeric network comprising SPI or gelatin to improve their mechanical characteristics and diminish their solubility in aqueous solutions. It was noted that expanding the quantity of crosslinker rendered the samples more stiff and accelerated their aggregation; however, the swelling ratios diminished. This behaviour is natural, as the elevated crosslink density obstructs water infiltration into the polymeric network [107,108] . The findings indicated that the ideal added volume was 0.5 ml for both SPI and gelatin matrices, at which the samples attained the highest swelling ratio. This demonstrates that the crosslinking forces did not impede swelling, while the dimensional stability and integrity of the samples were preserved, as illustrated in Figure (3.7) . Interestingly, the gelatin-based matrices consistently demonstrated significantly higher swelling capacities than their SPI counterparts across all crosslinker concentrations. This can be attributed to gelatin's superior hydrophilicity and the abundance of reactive amine and carboxyl groups, which enhance water affinity and hydrogen bonding capability.

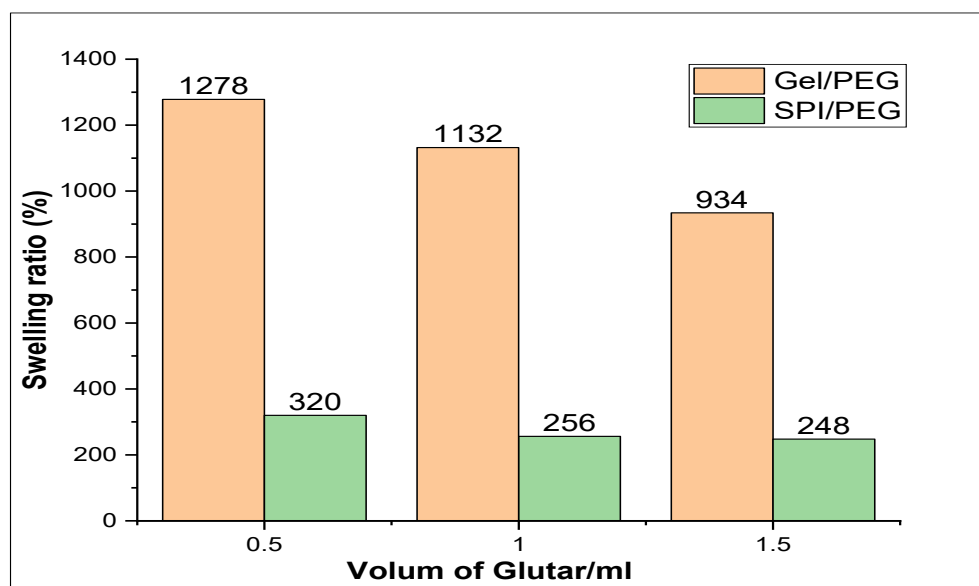


Figure (3.7) Impact of crosslinking agent on the swelling ratios of polymeric matrixs

3.5 Swelling Behavior of Polymeric Matrices in Simulated Gastrointestinal Conditions

To evaluate the pH-responsive behavior of the synthesized polymeric hydrogels, the swelling performance of both SPI/PEG and Gelatin/PEG (Gel/PEG) matrices was assessed in simulated gastric fluid (SGF, pH ~1.2) and simulated intestinal fluid (SIF, pH ~6.8). These media were selected to mimic the physiological conditions of the human gastrointestinal tract and assess the suitability of the hydrogels for oral drug delivery applications. The results, presented in Figure (3.8), reveal that both hydrogel systems exhibited marked pH-sensitive swelling, confirming their responsiveness to environmental pH variations.

The SPI/PEG hydrogel matrix demonstrated a swelling ratio of 140% in SGF and increased significantly to 274% in SIF. This trend reflects the pH-dependent ionization of amino and carboxyl groups within the SPI backbone. At lower pH, the polymeric network remains relatively compact due to protonation and increased hydrogen bonding, which limits water diffusion. In contrast, under neutral to slightly basic pH conditions, deprotonation of

functional groups enhances electrostatic repulsion and osmotic pressure within the matrix, promoting greater solvent uptake and expansion.

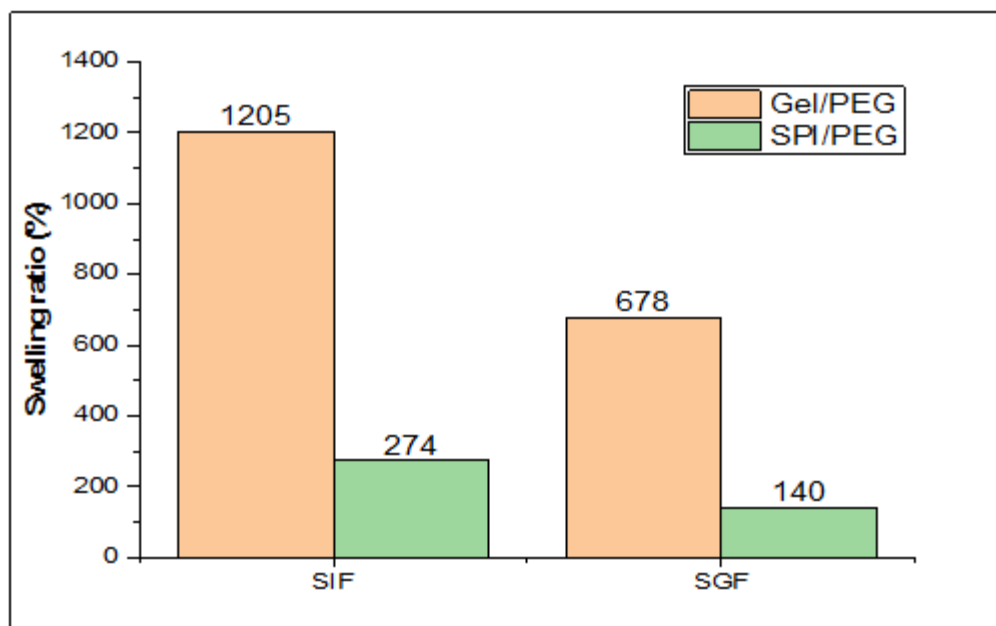


Figure (3.8) Swelling ratios of polymeric matrices in simulated gastric fluid and intestinal fluid

In comparison, the Gel/PEG matrix displayed a considerably higher swelling response across both media. In SGF, the swelling ratio reached 678%, and in SIF, it increased further to an impressive 1205%. The enhanced swelling behavior of the gelatin-based system is attributable to gelatin's highly hydrophilic nature and the abundance of ionizable functional groups (e.g., $-\text{COOH}$ and $-\text{NH}_2$), which exhibit strong hydration potential. Furthermore, gelatin flexible polymer chains and less compact network architecture compared to SPI allow for more efficient solvent penetration and matrix expansion.

The underlying mechanism of swelling in both hydrogel types involves the diffusion of solvent molecules into the polymeric network, where they interact with hydrophilic moieties on the polymer chains. Rather than dissolving completely, the hydrogel undergoes a phase transition into a gel-like state characterized by partial chain mobility and significant volumetric expansion [109]. These findings demonstrate that both SPI/PEG and Gel/PEG systems are capable of pH-triggered swelling, an essential feature for site-specific

drug delivery in the gastrointestinal tract. Notably, the Gel/PEG system showed superior responsiveness, positioning it as a more promising candidate for applications requiring high fluid uptake and rapid drug release in the intestinal environment.

3.6 Kinetic study of polymeric matrix swelling

The swelling behavior of hydrogel-based drug delivery systems is a critical determinant of their performance, as it directly influences both the rate of drug release and the degradation kinetics of the polymer matrix. The absorption of water by hydrogels causes them to swell, which facilitates drug diffusion through the hydrated polymer network. This process is closely governed by the physicochemical properties of the hydrogel, including crosslink density, porosity, and hydrophilicity, as well as environmental conditions such as pH and temperature.

To gain a deeper understanding of the water diffusion mechanisms in the prepared hydrogel matrices, kinetic modeling was employed. The time-dependent swelling process was evaluated using empirical models, including the power law model (Korsmeyer–Peppas equation) and the second-order swelling kinetic model.

The first model applied was a semi-empirical power law expression used to describe water diffusion into the hydrogel network[108]:

$$\ln \frac{W_t}{W_{max}} = \ln k + n \ln t \quad \dots\dots\dots(3.2)$$

Where:

W_t : is the amount of water absorbed at time t

W_{max} : is the equilibrium water uptake (maximum swelling),

K : is the swelling rate constant,

n : is the diffusional exponent, which characterizes the mode of water transport and provides insight into the underlying diffusion mechanism:

$n \leq 0.5$: Fickian diffusion, governed predominantly by solvent diffusion with minimal polymer relaxation.

$0.5 < n < 1$: Anomalous (non-Fickian) transport, involving a combination of diffusion and polymer relaxation.

$n = 1$: Case II transport, where the release is dominated by polymer chain relaxation rather than solvent diffusion.

This model is particularly suitable for analyzing initial swelling behavior and distinguishing between diffusion-limited and relaxation-controlled processes within the hydrogel matrix[101].

In addition to the power law model, a second-order kinetic model was employed to further evaluate the swelling dynamics, particularly for long-term behavior. The second-order swelling equation is expressed as[110,111]:

$$\frac{t}{W_t} = A + \frac{t}{W_\infty} \quad \text{.....(3.3)}$$

A is a constant defined by the following equation:

$$A = \frac{1}{kW_\infty^2} \quad \text{.....(3.4)}$$

Plotting the relationship between t/W_t and time yields a straight line with a slope of $1/W_\infty$. The constant k can be ascertained from the intercept of the linear equation, as per Equation (3.4). This model assumes that swelling is controlled by the availability of free water and the polymer's ability to absorb it over time [110,111].

3.6.1 Swelling Kinetic Study of SPI/PEG/ZnO polymeric Matrix

A comprehensive swelling study was performed on the SPI/PEG/ZnO hydrogel matrix to assess its water uptake behavior and model the swelling kinetics. The parameters evaluated over time included the swelling ratio, degree of swelling, and water content, as presented in Tables (3.1) and (3.2) and illustrated in Figures (3.9) and (3.10). The hydrogel samples were immersed in aqueous medium, and weight measurements were taken at defined intervals to determine the swelling characteristics. The swelling ratio showed a consistent increase over time, reaching a maximum of 274.26% at 360 minutes indicate that the SPI/PEG/ZnO hydrogel matrix possesses substantial water absorption capacity, a desirable feature for sustained drug delivery applications.

The experimental swelling data were fitted to kinetic models to elucidate the mechanism of water diffusion within the polymeric network. Application of the Korsmeyer–Peppas model yielded a diffusional exponent (n) value of 0.83702, indicating that the water transport mechanism follows a non-Fickian (anomalous) diffusion pattern [112, 113]. This type of behavior suggests that the swelling process is governed by a combination of Fickian diffusion and polymer relaxation dynamics, commonly observed in moderately crosslinked hydrogel systems.

Additionally, the swelling behavior showed good agreement with the second-order swelling kinetic model, as demonstrated by the linearity of the plot of t/W_t versus time. The second-order model fit suggests that swelling is dependent not only on diffusion gradients but also on the availability of water-binding sites within the polymer matrix, and the dynamic rearrangement of polymer chains over time.

Table (3.1) Swelling ratios, swelling degree and water content values of the SPI/PEG/ZnO polymeric matrix

Time (min)	Wt	swelling ratio	swelling degree Dh	water content	First order		Second order
		(Ws-Wd)/Wd*100	wet weight/dry weight	Ws-Wd	Ln Time(Ln t)	Ln(Wt/Wmax)	t/W
0	2.02						
30	2.65	31.19	1.31	0.63	3.40	-2.17	11.32
60	3.81	88.61	1.89	1.79	4.09	-1.13	15.75
90	4.55	125.25	2.25	2.53	4.50	-0.78	19.78
120	4.89	142.08	2.42	2.87	4.79	-0.66	24.54
150	5.33	163.86	2.64	3.31	5.01	-0.52	28.14
180	6.12	202.97	3.03	4.10	5.19	-0.30	29.41
240	6.98	245.54	3.46	4.96	5.48	-0.11	34.38
300	7.34	263.37	3.63	5.32	5.70	-0.04	40.87
360	7.56	274.26	3.74	5.54	5.89	0.00	47.62
390	7.56	274.26	3.74	5.54			51.59

Table (3.2) Rate constants and s Regression coefficient for the swelling kinetics of the SPI/PEG/ZnO polymeric matrix

Kinetic Model	R^2	k
First Order	0.94589	0.0088
Second Order	0.99087	0.0011

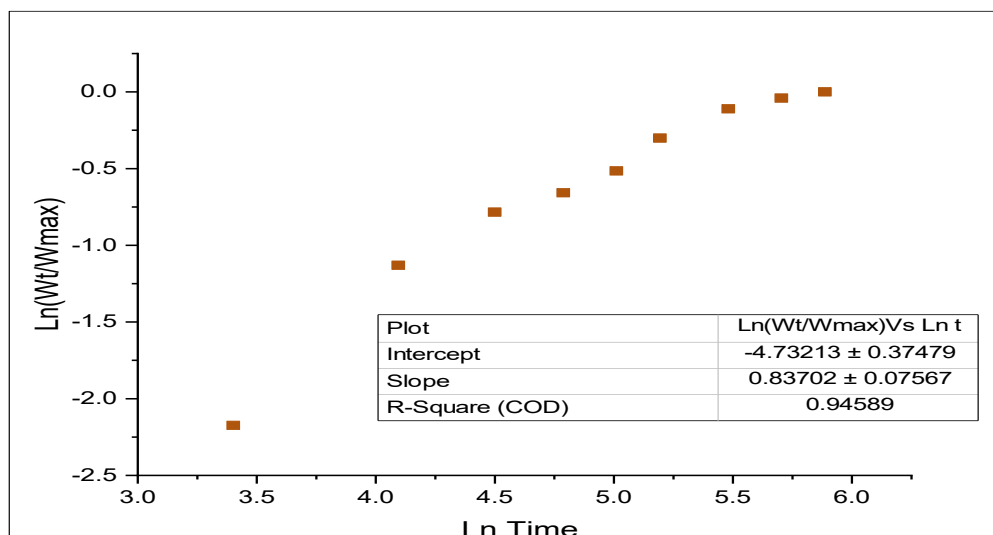


Figure (3.9) The First-order kinetic model for the swelling behavior of the SPI/PEG polymeric matrix

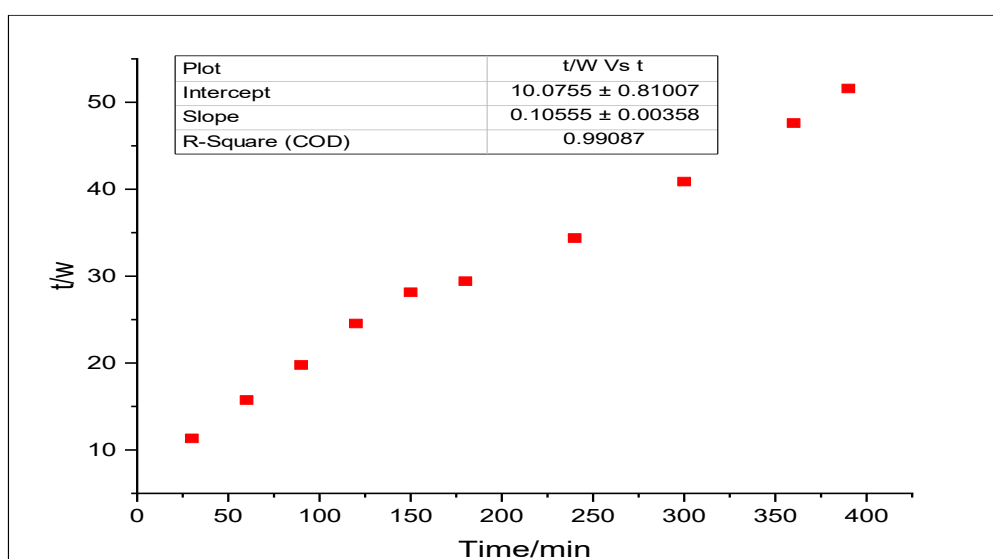


Figure (3.10) The second-order kinetic model for the swelling behavior of the SPI/PEG polymeric matrix

3.6.2 Swelling Kinetic Study of Gel/PEG/ZnO polymeric Matrix

A detailed kinetic study was conducted to assess the swelling behavior of the gelatin/polyethylene glycol hydrogel matrix loaded with ZnO nanoparticles. Over a period of 390 minutes, the swelling ratio was quantified at defined time intervals to evaluate the hydrogel fluid uptake capacity and hydration dynamics. The results are presented in Tables (3.3) and (3.4) and visualized in Figures (3.11) and (3.12)

The swelling ratio increased progressively over time, reaching a maximum of 1205.37% at 390 minutes, indicating a highly absorbent hydrogel structure with considerable swelling potential. These high values are consistent with gelatin's strong hydrophilic character and the open network structure of the matrix, which enables substantial solvent diffusion.

To further understand the kinetic mechanism governing this behavior, the experimental data were fitted to both first-order (Korsmeyer–Peppas power law model) and second-order swelling models, and the corresponding rate constants and regression coefficients (R^2) were determined (Table 3.4). The first-order kinetic model produced a regression coefficient of $R^2 = 0.96873$ with a rate constant of 0.003 min^{-1} , indicating a strong linear relationship and good model fit. In contrast, the second-order model yielded a much lower R^2 value of 0.65122, suggesting that it does not adequately describe the swelling dynamics of the Gel/PEG system.

The swelling mechanism evaluated using the Korsmeyer–Peppas power law model yielded a diffusional exponent (n) value of 1.00915, this value is nearly equivalent to the theoretical threshold for Case II transport ($n = 1$) [114-115], implying that the swelling process in the Gel/PEG/ZnO matrix is dominated not by diffusion alone, but by polymer chain relaxation dynamics. This mechanism is typical of hydrophilic polymer systems that undergo substantial volumetric expansion, where solvent uptake leads to a time-independent, constant-rate swelling phase.

Table (3.3) Swelling ratios, swelling degree and water content values of the Gel/PEG polymeric matrix

Time (min)	Wt	swelling ratio	swelling degree Dh	water content	First order		second order
		$(W_s - W_d)/W_d \times 100$	wet weight/dry weight	$W_s - W_d$	LN Time(Ln t)	LN(Wt/Wmax)	t/w
0	3.91						
30	8.64	120.97	2.21	4.73	3.40	-2.30	3.47
60	11.16	185.42	2.85	7.25	4.09	-1.87	5.38
90	15.35	292.58	3.93	11.44	4.50	-1.42	5.86
120	22.93	486.45	5.86	19.02	4.79	-0.91	5.23
150	29.21	647.06	7.47	25.30	5.01	-0.62	5.14
180	36.56	835.04	9.35	32.65	5.19	-0.37	4.92
240	42.93	997.95	10.98	39.02	5.48	-0.19	5.59
300	45.77	1070.59	11.71	41.86	5.70	-0.12	6.55
360	49.39	1163.17	12.63	45.48	5.89	-0.04	7.29
390	51.04	1205.37	13.05	47.13	5.97		

Table (3.4) Rate constants and Regression coefficient for the swelling kinetics of the Gel/PEG polymeric matrix

Kinetic Model	R^2	k
First Order	0.96873	0.003
Second Order	0.65122	1.43×10^{-5}

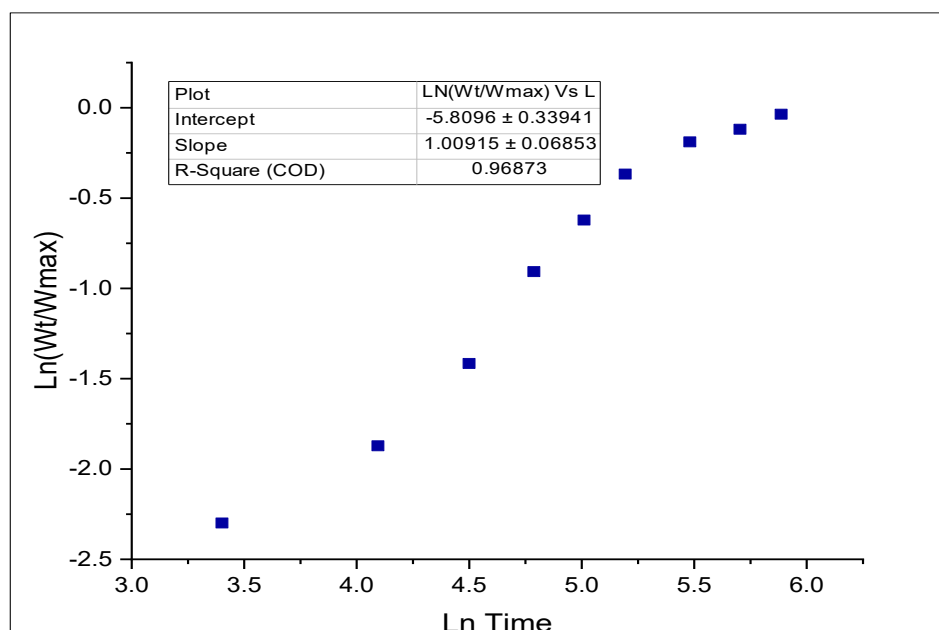


Figure (3.11) First-order kinetic model for the swelling behavior of the Gel/PEG polymeric matrix.

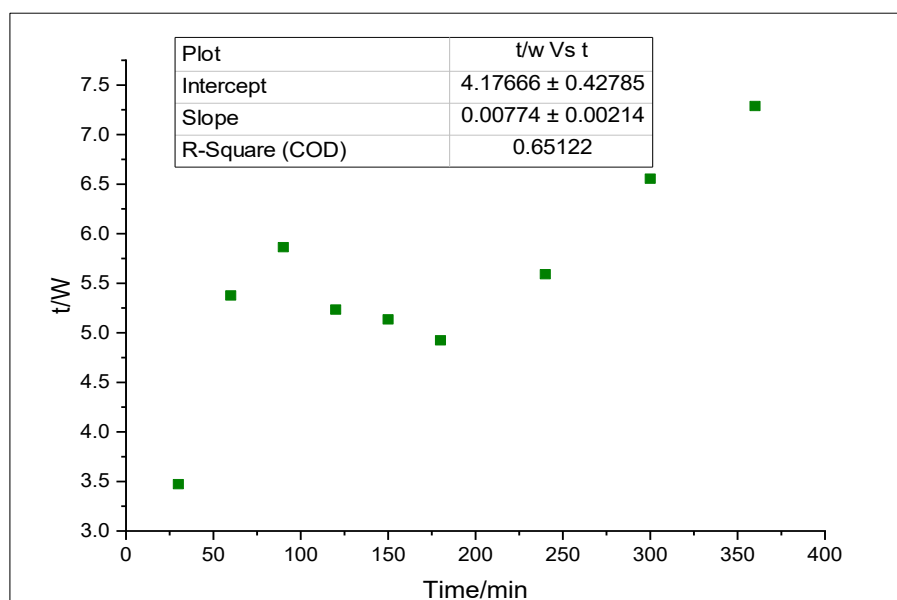


Figure (3.12) The second-order kinetic model for the swelling behavior of the Gel/PEG polymeric matrix

3.7 Kinetic Study for the Drug Release from the Polymeric Matrix

To elucidate the mechanism of drug release from the developed polymeric hydrogel matrices, kinetic modeling was employed using zero-order, first-order, and the Higuchi diffusion model. These models are commonly applied in pharmaceutical sciences to predict and interpret release profiles, optimize formulation parameters, and design controlled delivery systems.

The zero-order model assumes a constant drug release rate, independent of the concentration of the drug within the matrix. It is expressed by the following equation [116,117]:

$$x = k_0 t \dots\dots (3.5)$$

X denotes the value of the drug release at time t, K is the zero-order release rate constant.

The first-order kinetic model describes a release mechanism in which the rate is proportional to the concentration of the drug remaining in the matrix.

$$\ln C_t = \ln C_0 - k_1 t \dots\dots (3.6)$$

C₀ is the initial drug concentration, C_t is the concentration at time t and k₁ is the first-order release rate constant. In this model, the release rate decreases exponentially with time, often observed in systems where diffusion is concentration-dependent.

Additionally, the Higuchi model was applied to assess whether the drug release was controlled by diffusion through a porous matrix. The simplified form of the Higuchi equation is given by [118]:

$$f_t = Q = k_H t^{1/2} \dots\dots (3.7)$$

Q is the cumulative amount of drug released at time t, and k_H is the Higuchi release constant.

3.7.1 Examine the drug release from the polymeric matrix

The in vitro release behavior of cephalexin from the synthesized polymeric hydrogels was investigated under physiologically relevant conditions, specifically in simulated intestinal fluid SIF and simulated gastric fluid SGF. The results revealed a significantly enhanced drug release profile from the Gel/PEG/ZnO matrix compared to the SPI/PEG/ZnO counterpart, as shown in Figures 3.13 and 3.14 for gelatin and Figures 3.15 and 3.16 for SPI-based systems.

In the Gel/PEG system, cephalexin release extended over a period of 24 hours, with a cumulative release of 99.89% in SIF and 44.24% in SGF. The reduced release observed in SGF is attributed to the acidic gastric environment, which can suppress swelling in hydrophilic matrices and influence drug solubility. In contrast, the SPI/PEG matrix exhibited relatively lower release efficiency, achieving 89.34% in SIF and 38% in SGF over the same duration. These results highlight the influence of matrix composition and network swelling properties on the drug release kinetics.

The superior performance of the Gel/PEG matrix is associated with its higher swelling capacity, particularly under neutral to mildly basic conditions such as those simulated in SIF. Enhanced water uptake promotes polymer chain relaxation and facilitates diffusion of the encapsulated drug, resulting in nearly complete release. Conversely, the SPI/PEG matrix, with its lower swelling ratio and denser network structure, offers more resistance to water diffusion and drug migration, especially under acidic conditions.

A consistent trend was observed in both matrices, with drug release efficiency being lower in SGF than in SIF. This behavior confirms that the hydrogel matrices exhibit pH-sensitive characteristics. The acidic pH of SGF induces contraction of the polymer network or protonation of functional groups, limiting matrix expansion and drug diffusion. In contrast, the more alkaline environment of SIF promotes matrix relaxation, increased porosity, and higher drug mobility [119, 120].

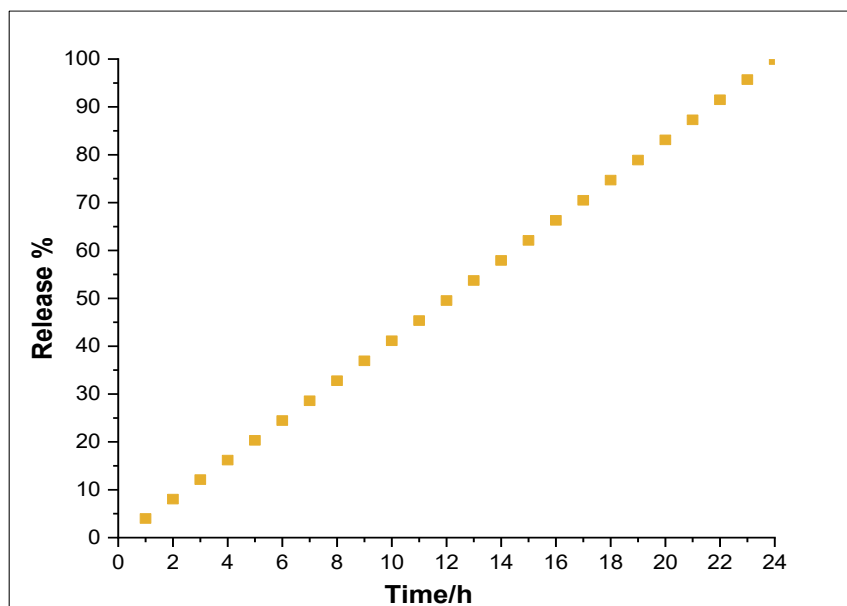


Figure (3.13) Release ratio of Gel/PEG-encapsulated cephalixin in SIF

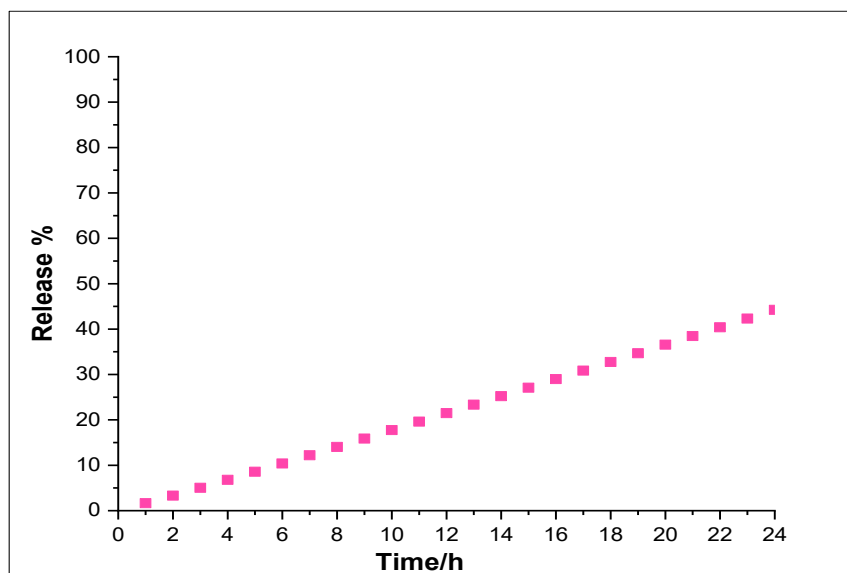


Figure (3.14) Release ratio of Gel/PEG-encapsulated cephalixin in SGF

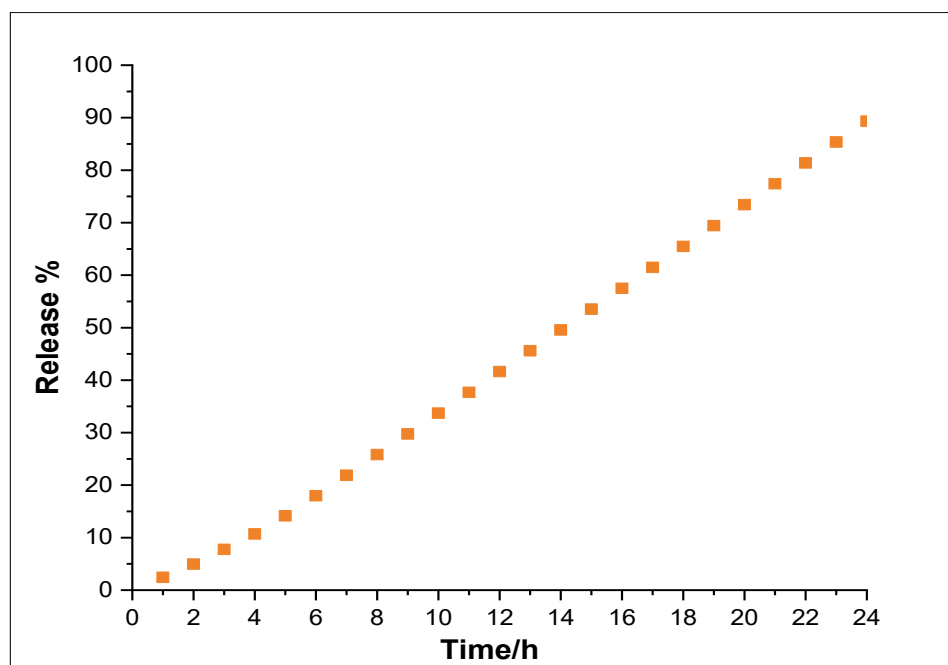


Figure (3.15) Release ratio of SPI/PEG-encapsulated cephalixin in SIF

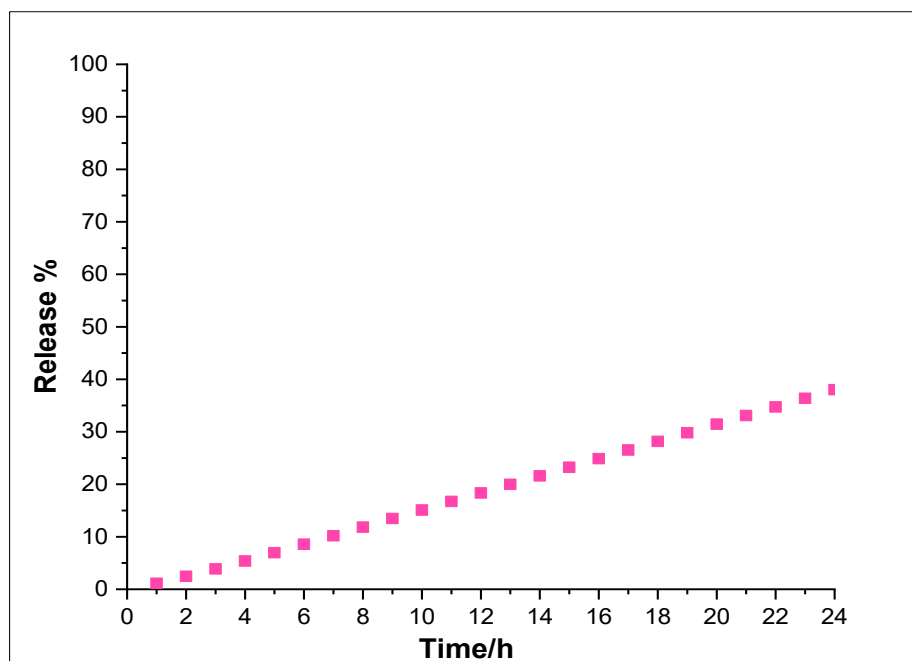


Figure (3.16) Release ratio of SPI/PEG-encapsulated cephalixin in SGF

3.7.2 Mechanism of Drug Release from the Polymeric Matrix

The primary mechanism governing drug release from the synthesized polymeric hydrogels in this study is diffusion-controlled transport. In such systems, drug molecules migrate from within the polymeric network into the surrounding release medium through a concentration gradient. This type of mechanism is particularly relevant for hydrogel-based delivery systems, where the polymer matrix acts as a physical barrier that modulates the rate and extent of drug release.

Diffusion occurs as the active compound moves through the hydrated, three-dimensional polymer structure, navigating between polymer chains that form the structural framework of the hydrogel. These polymer chains inherently limit the mobility of the drug due to physical entrapment, steric hindrance, and intermolecular interactions. As the matrix becomes hydrated, it swells and expands, creating aqueous channels that facilitate molecular diffusion toward the external environment.

Although swelling and matrix erosion are often concurrent processes in hydrogel-based systems, the drug release mechanism in the current study was predominantly swelling-controlled diffusion, with erosion being excluded. This conclusion is supported by post-release observations confirming that the polymeric matrices retained their structural integrity throughout the release period. No significant disintegration or fragmentation was observed, indicating that matrix erosion did not contribute to the release mechanism.

In this formulation strategy, the drug was uniformly dispersed within the polymer network, forming a homogeneous matrix system. Upon exposure to the release medium, the matrix absorbed fluid and swelled, which in turn facilitated drug diffusion through the swollen hydrogel network. As illustrated in Figure 3.17, the drug release process can be described as a two-step mechanism: initial swelling of the hydrogel followed by diffusion of the drug from the interior of the matrix into the external environment [119].

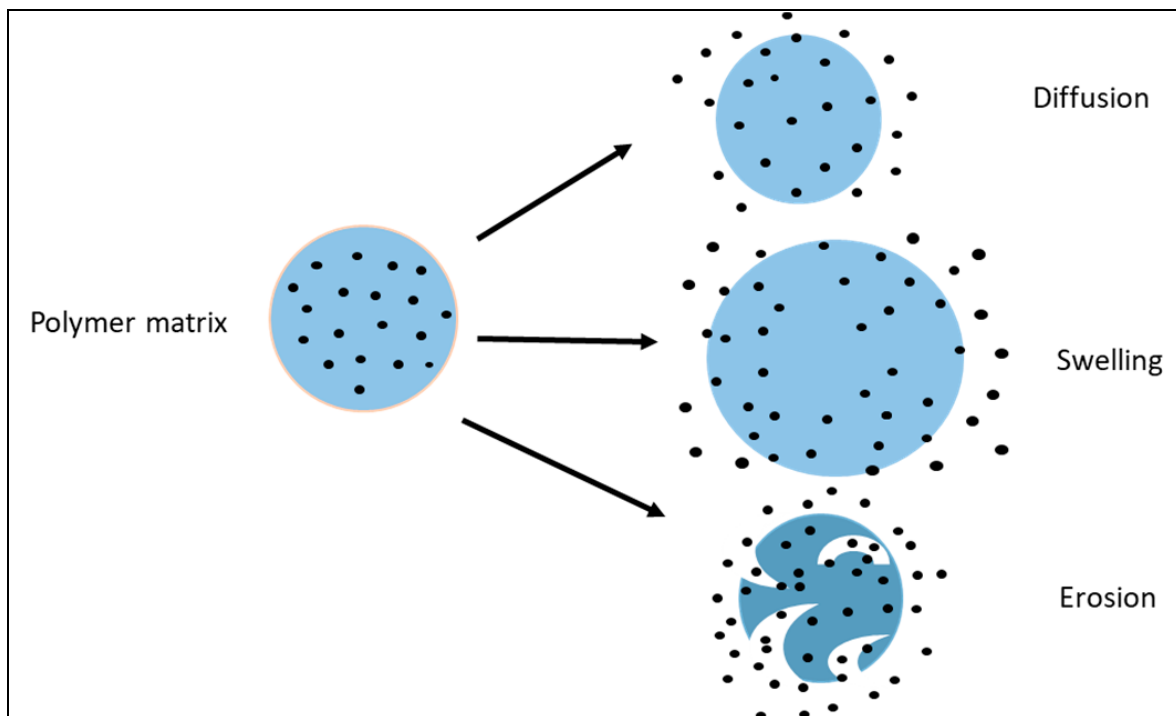


Figure (3.17) potential drug release mechanisms by diffusion, swelling, and erosion of the polymeric matrix[119]

3.7.3 Kinetic Analysis of Drug Release from the Polymeric Matrix

The release kinetics of cephalexin from the SPI/PEG polymeric matrix were examined in both simulated intestinal fluid (SIF) and simulated gastric fluid (SGF), providing insight into the release mechanisms under physiologically relevant conditions. The cumulative release data, along with calculated diffusion coefficients and rate constants, are presented in Tables 3.5 through 3.7, while Figures 3.18 to 3.23 illustrate the corresponding kinetic models.

In SIF, the release of cephalexin from the SPI/PEG matrix exhibited a gradual and sustained profile, with a total cumulative release reaching 89.34% after 24 hours. Among the three evaluated kinetic models zero-order, first-order, and Higuchi the Higuchi model displayed the best correlation, with a coefficient of determination (R^2) of 0.679 and a rate constant (k_H) of 0.3654. This model assumes that drug diffusion is the rate-limiting step and

follows a square root of time dependence, which was observed in the linear fit of the experimental data. The moderate fits for the zero-order ($R^2 = 0.5268$) and first-order ($R^2 = 0.485$) models suggest that release was not strictly concentration-dependent nor purely linear over time.

In contrast, the release profile in SGF was significantly reduced, with a maximum release of only 38.00% over the same period. The Higuchi model again yielded the highest correlation ($R^2 = 0.586$), although it was slightly lower than in SIF, with a corresponding rate constant (k_H) of 0.0844. The reduced release in SGF is attributed to the limited swelling of the polymeric matrix in acidic conditions, which restricts the formation of aqueous diffusion pathways necessary for effective drug transport. The zero-order and first-order models provided weaker fits ($R^2 = 0.427$ and 0.394 , respectively), further emphasizing the dominance of diffusion-based mechanisms in these hydrogel systems.

The linearity observed in Higuchi plots in both media confirms that cephalexin release from SPI/PEG matrices primarily occurs through a diffusion-controlled mechanism. This mechanism is facilitated by swelling of the matrix in aqueous environments, particularly at near-neutral pH levels. Additionally, the data suggest a homogeneous drug distribution within the polymer network and a relatively stable hydrogel structure during the release process, with minimal contribution from matrix erosion.

Table (3.5) Rate constants and Registration coefficients values for the release kinetics of cephalexin in SPI/PEG polymeric matrix in different media

Medium	Zero Order		First Order		Higuchi Model	
	R^2	k_0	R^2	k_1	R^2	k_H
SIF	0.5268	0.0511	0.485	0.0004	0.679	0.3654
SGF	0.427	0.1146	0.394	0.0001	0.586	0.0844

Table (3.6) Kinetic Parameters of Cephalexin Release from SPI /PEG Matrix in SIF

Time	Cumulative Drug Release (ppm)	Amount Released per Hour	Release%	First Order		Higuchi
		Q_t	$(C_t/C_i)*100\%$	$C_i/(C_i-C_t)$	$\ln C_i/(C_i-C_t)$	$t^{1/2}$
1	2.43	2.43	2.43	1.0249052	0.024600117	1
2	4.96	2.53	4.96	1.0259567	0.025625548	1.414213562
3	7.75	2.79	7.75	1.02870075		1.732050808
4	10.69	2.94	10.69	1.03029054	0.029840842	2
5	14.15	3.46	14.15	1.03584007	0.035212756	2.236067977
6	17.96	3.81	17.96	1.03960911	0.038844784	2.449489743
7	21.87	3.91	21.87	1.04069102	0.039884934	2.645751311
8	25.81	3.94	25.81	1.04101603	0.04019719	2.828427125
9	29.76	3.95	29.76	1.04112441	0.040301297	3
10	33.72	3.96	33.72	1.04123282	0.040405415	3.16227766
11	37.68	3.96	37.68	1.04123282	0.040405415	3.31662479
12	41.64	3.96	41.64	1.04123282	0.040405415	3.464101615
13	45.6	3.96	45.6	1.04123282	0.040405415	3.605551275
14	49.56	3.96	49.56	1.04123282	0.040405415	3.741657387
15	53.52	3.96	53.52	1.04123282	0.040405415	3.872983346
16	57.5	3.98	57.5	1.0414497	0.040613683	4
17	61.48	3.98	61.48	1.0414497	0.040613683	4.123105626
18	65.46	3.98	65.46	1.0414497	0.040613683	4.242640687
19	69.44	3.98	69.44	1.0414497	0.040613683	4.358898944
20	73.42	3.98	73.42	1.0414497	0.040613683	4.472135955
21	77.4	3.98	77.4	1.0414497	0.040613683	4.582575695
22	81.38	3.98	81.38	1.0414497	0.040613683	4.69041576
23	85.36	3.98	85.36	1.0414497	0.040613683	4.795831523
24	89.34	3.98	89.34	1.0414497	0.040613683	4.898979486

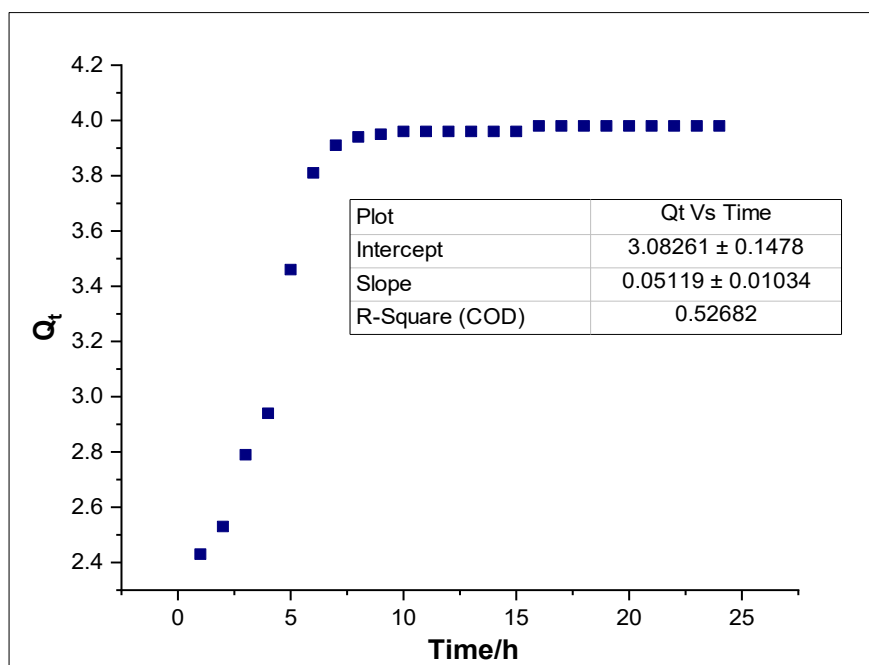


Figure (3.18) Zero-order kinetic model for the release of cephalixin from SPI/PEG in SIF

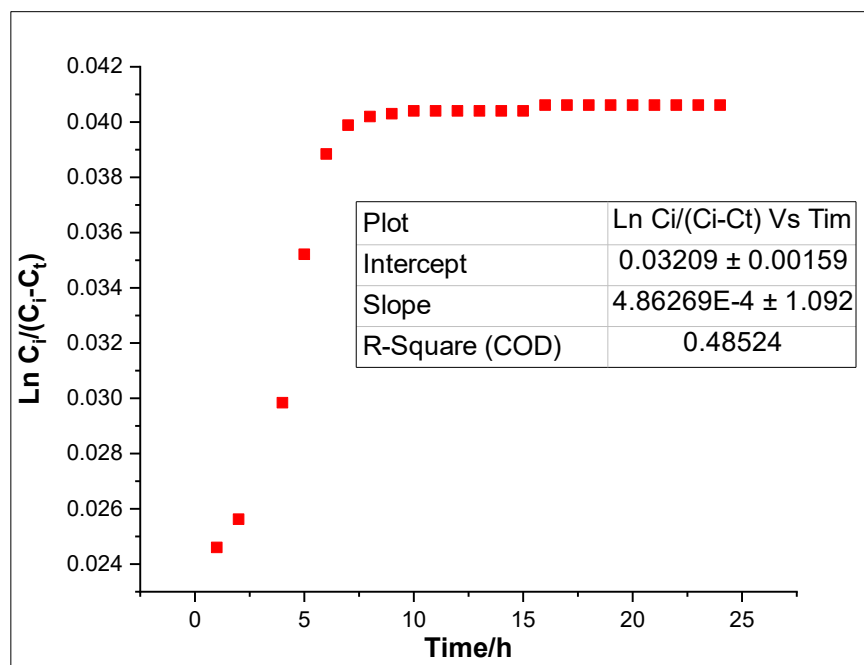


Figure (3.19) First-order kinetic model for the release of cephalixin from SPI/PEG into SIF

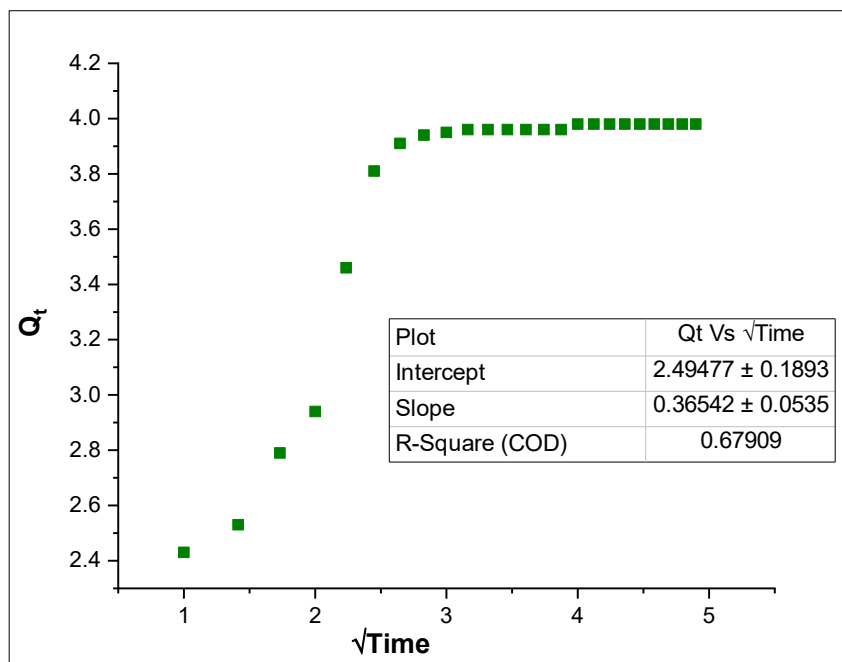


Figure (3.20) Higuchi-order kinetic model for the release of cephalexin from SPI/PEG into SIF

Table (3.7) Kinetic Parameters of Cephalexin Release from SPI/PEG Matrix in SGF

Time	Cumulative Drug Release (ppm)	Amount Released per Hour	Release%	First Order		Higuchi
		Q_t	$(C_t/C_i) \times 100\%$	$C_i/(C_i - C_t)$	$\ln C_i/(C_i - C_t)$	$t^{1/2}$
1	1.13	1.13	1.13	1.01142915	0.01136433	1
2	2.45	1.32	2.45	1.01337657	0.013287894	1.414213562
3	3.89	1.44	3.89	1.01461039		1.732050808
4	5.38	1.49	5.38	1.01512537	0.01501212	2
5	6.96	1.58	6.96	1.01605365	0.015926151	2.236067977
6	8.57	1.61	8.57	1.01636345	0.016231013	2.449489743
7	10.2	1.63	10.2	1.01657009	0.016434306	2.645751311
8	11.83	1.63	11.83	1.01657009	0.016434306	2.828427125
9	13.46	1.63	13.46	1.01657009	0.016434306	3
10	15.09	1.63	15.09	1.01657009	0.016434306	3.16227766
11	16.72	1.63	16.72	1.01657009	0.016434306	3.31662479

12	18.35	1.63	18.35	1.01657009	0.016434306	3.464101615
13	19.98	1.63	19.98	1.01657009	0.016434306	3.605551275
14	21.61	1.63	21.61	1.01657009	0.016434306	3.741657387
15	23.24	1.63	23.24	1.01657009	0.016434306	3.872983346
16	24.88	1.64	24.88	1.01667344	0.016535969	4
17	26.52	1.64	26.52	1.01667344	0.016535969	4.123105626
18	28.16	1.64	28.16	1.01667344	0.016535969	4.242640687
19	29.8	1.64	29.8	1.01667344	0.016535969	4.358898944
20	31.44	1.64	31.44	1.01667344	0.016535969	4.472135955
21	33.08	1.64	33.08	1.01667344	0.016535969	4.582575695
22	34.72	1.64	34.72	1.01667344	0.016535969	4.69041576
23	36.36	1.64	36.36	1.01667344	0.016535969	4.795831523
24	38	1.64	38	1.01667344	0.016535969	4.898979486

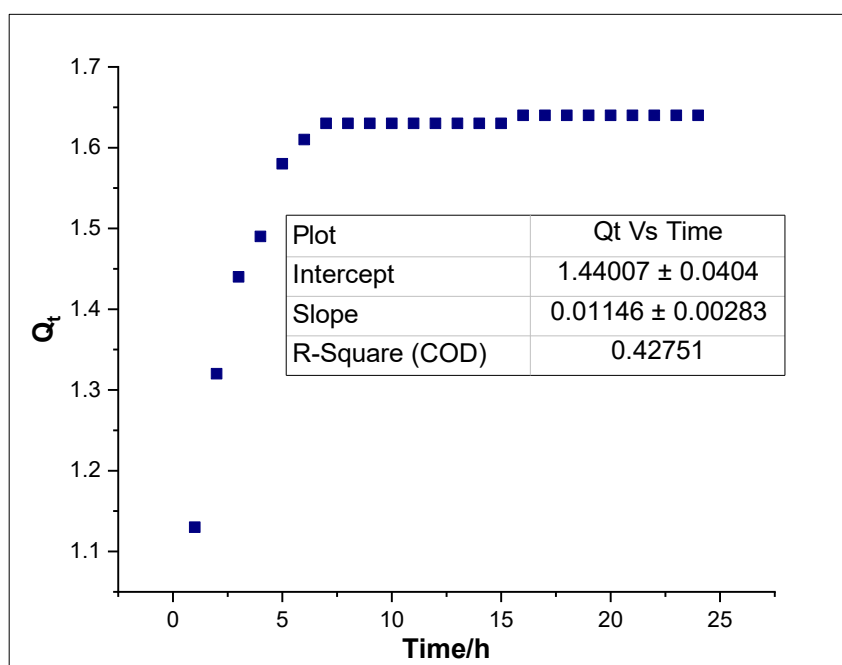


Figure (3.21) Zero-order kinetic model for the release of cephalixin from SPI/PEG into SGF

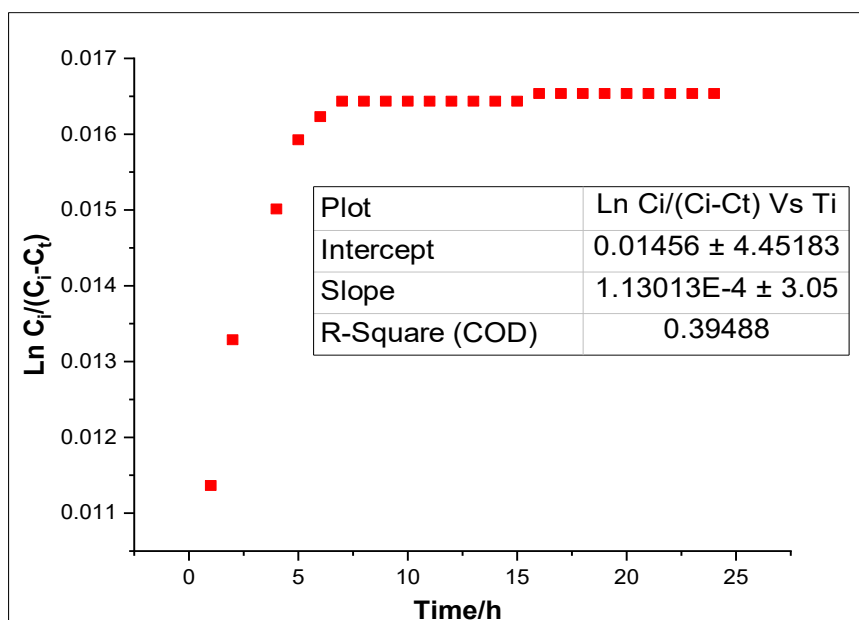


Figure (3.22) First-order kinetic model for the release of cephalexin from SPI/PEG into SGF

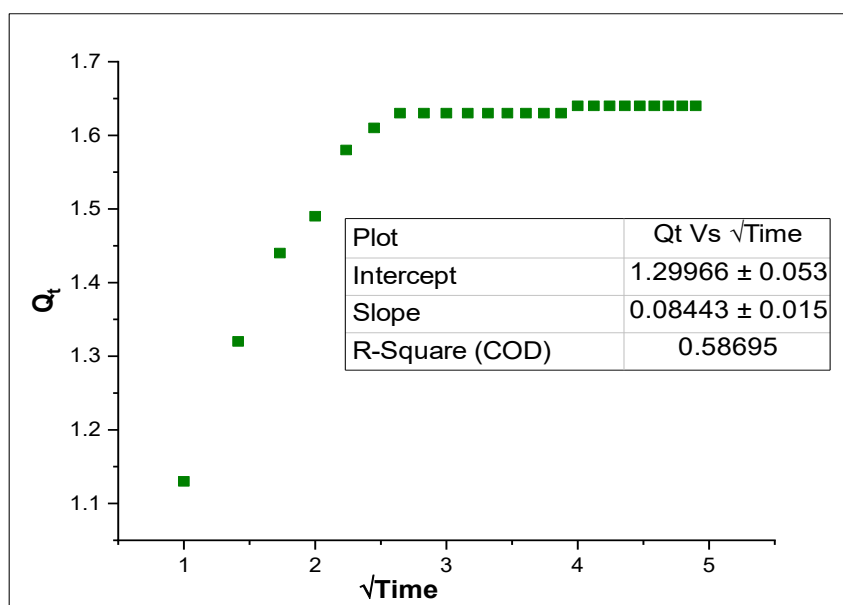


Figure (3.23) Higuchi-order kinetic model for the release of cephalexin from SPI/PEG into SGF

The release kinetics of cephalexin from the Gel/PEG polymeric matrix were systematically evaluated in both simulated intestinal fluid (SIF) and simulated gastric fluid (SGF). Tables 3.8 through 3.10 summarize the kinetic parameters calculated using three established models zero-order, first-order, and Higuchi while Figures 3.24 through 3.29 present the corresponding release profiles.

In SIF, the Gel/PEG/ZnO matrix exhibited an extended and nearly complete drug release, reaching a cumulative percentage of 99.89% within 24 hours. Among the applied models, the Higuchi model demonstrated the strongest correlation ($R^2 = 0.812$) with a diffusion constant (k_H) of 0.0466, indicating that diffusion through the hydrated matrix dominated the release process. The zero-order and first-order models provided lower correlation coefficients of 0.665 and 0.637, respectively, suggesting that the release rate was neither strictly constant nor directly dependent on drug concentration remaining in the matrix.

The superior alignment with the Higuchi model implies that cephalexin release from the Gel/PEG/ZnO system is predominantly governed by a diffusion-controlled mechanism. This behavior is typical of hydrophilic matrices, where drug molecules migrate through the swollen polymeric network into the external environment. The consistent release rate per hour (~ 4.2 ppm/h) throughout the 24 hour period supports the sustained and controlled release characteristics of the system.

In SGF, the matrix demonstrated a lower yet substantial release percentage of 44.24% over the same duration. Notably, the Higuchi model again exhibited the best fit, with a correlation coefficient (R^2) of 0.924 and a rate constant (k_H) of 0.066. This finding is indicative of diffusion-based release behavior even under acidic conditions, although at a slower rate due to reduced matrix swelling. The zero-order and first-order models yielded slightly lower correlation values ($R^2 = 0.817$ and 0.801, respectively), reinforcing the observation that release was primarily diffusion-controlled rather than erosion- or degradation-driven.

The results indicate that Gel/PEG hydrogels are highly responsive to environmental pH, with a significantly enhanced drug release profile in intestinal conditions. The strong correlation with the Higuchi model across both pH environments supports the hypothesis that drug release occurs through a swelling–diffusion mechanism. Furthermore, the high release efficiency and kinetic predictability of the Gel/PEG/ZnO matrix position it as a promising candidate for the development of sustained oral drug delivery systems.

Table (3.8) Rate constants and Registration coefficients values for the release kinetics of cephalixin in Gel/PEG polymeric matrix in different media

Medium	Zero Order		First Order		Higuchi Model	
	R ²	k ₀	R ²	k ₁	R ²	k _H
SIF	0.665	0.0061	0.637	0.00006	0.812	0.0466
SGF	0.817	0.0098	0.801	0.00009	0.924	0.066

Table (3.9) Kinetic Parameters of Cephalixin Release from Gel/PEG Matrix in SIF

Time	Cumulative Drug Release (ppm)	Amount Released per Hour	Release%	First Order		Higuchi
		Q _t	(C _t /C _i)*100%	C _i /(C _i -C _t)	Ln C _i /(C _i -C _t)	t ^{1/2}
1	3.99	3.99	3.99	1.04155817	0.040717833	1
2	8.03	4.04	8.03	1.04210088	0.041238748	1.414213562
3	12.11	4.08	12.11	1.04253545		1.732050808
4	16.2	4.09	16.2	1.04264415	0.041759934	2
5	20.31	4.11	20.31	1.04286161	0.041968485	2.236067977
6	24.45	4.14	24.45	1.04318798	0.042281392	2.449489743
7	28.6	4.15	28.6	1.04329682	0.042385716	2.645751311
8	32.77	4.17	32.77	1.04351456	0.042594398	2.828427125
9	36.95	4.18	36.95	1.04362346	0.042698755	3
10	41.14	4.19	41.14	1.04373239	0.042803122	3.16227766
11	45.33	4.19	45.33	1.04373239	0.042803122	3.31662479
12	49.52	4.19	49.52	1.04373239	0.042803122	3.464101615
13	53.71	4.19	53.71	1.04373239	0.042803122	3.605551275
14	57.9	4.19	57.9	1.04373239	0.042803122	3.741657387

15	62.09	4.19	62.09	1.04373239	0.042803122	3.872983346
16	66.29	4.2	66.29	1.04384134	0.042907501	4
17	70.49	4.2	70.49	1.04384134	0.042907501	4.123105626
18	74.69	4.2	74.69	1.04384134	0.042907501	4.242640687
19	78.89	4.2	78.89	1.04384134	0.042907501	4.358898944
20	83.09	4.2	83.09	1.04384134	0.042907501	4.472135955
21	87.29	4.2	87.29	1.04384134	0.042907501	4.582575695
22	91.49	4.2	91.49	1.04384134	0.042907501	4.69041576
23	95.69	4.2	95.69	1.04384134	0.042907501	4.795831523
24	99.89	4.2	99.89	1.04384134	0.042907501	4.898979486

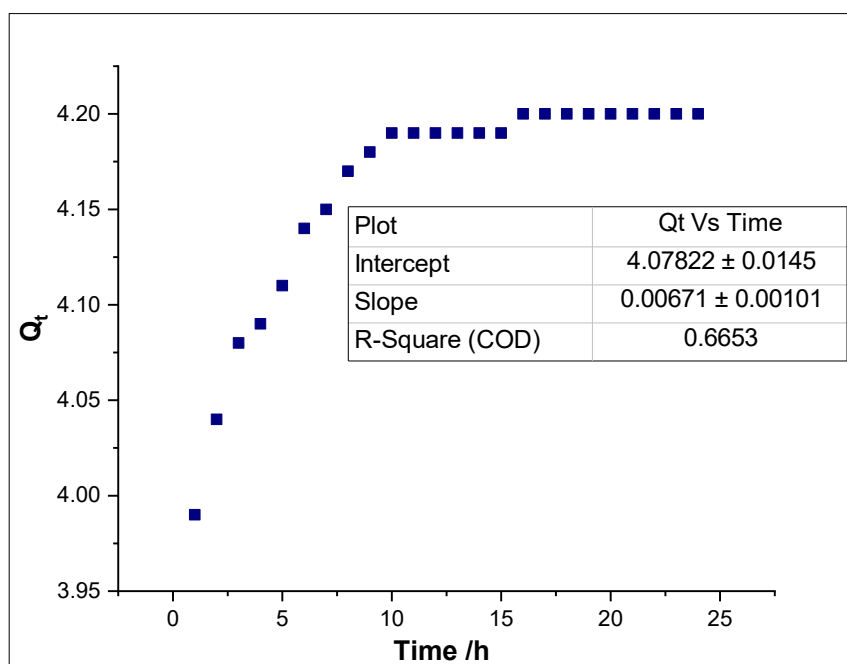


Figure (3.24) Zero-order kinetic model for the release of cephalexin from Gel/PEG into SIF

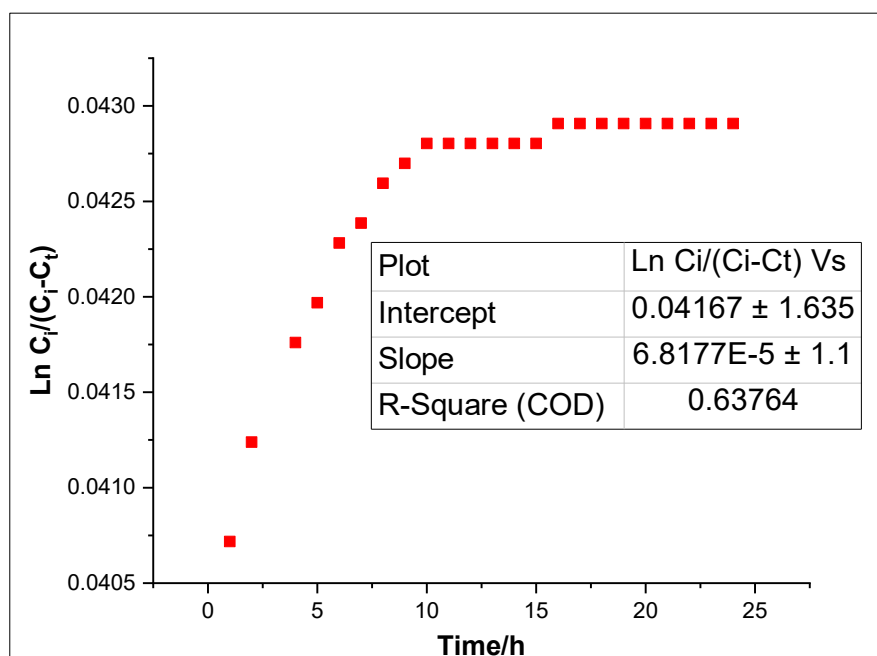


Figure (3.25) First-order kinetic model for the release of cephalixin from Gel/PEG into SIF

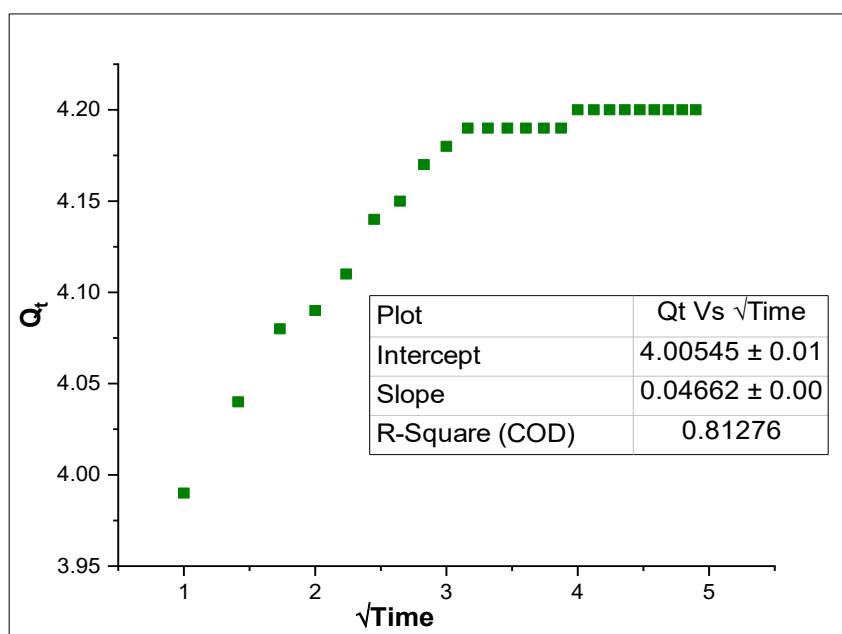


Figure (3.26) Higuchi-order kinetic model for the release of cephalixin from Gel/PEG into SIF

Table (3.10) Kinetic Parameters of Cephalexin Release from Gel/PEG Matrix in SGF

Time	Cumulative Drug Release (ppm)	Amount Released per Hour	Release%	First Order		Higuchi
		Q_t	$(C_i/C_t)*100\%$	$C_i/(C_i-C_t)$	$\ln C_i/(C_i-C_t)$	$t^{1/2}$
1	1.64	1.64	1.64	1.01667344	0.016535969	1
2	3.32	1.68	3.32	1.01708706	0.016942721	1.414213562
3	5.04	1.72	5.04	1.01750102		1.732050808
4	6.79	1.75	6.79	1.01781117	0.017654935	2
5	8.57	1.78	8.57	1.01812258	0.017960325	2.236067977
6	10.38	1.81	10.38	1.01843365	0.018265809	2.449489743
7	12.21	1.83	12.21	1.01864113	0.018469516	2.645751311
8	14.04	1.83	14.04	1.01864113	0.018469516	2.828427125
9	15.89	1.85	15.89	1.0188487	0.018673265	3
10	17.75	1.86	17.75	1.01895252	0.018775155	3.16227766
11	19.61	1.86	19.61	1.01895252	0.018775155	3.31662479
12	21.47	1.86	21.47	1.01895252	0.018775155	3.464101615
13	23.34	1.87	23.34	1.01905635	0.018877056	3.605551275
14	25.22	1.88	25.22	1.01916021	0.018978967	3.741657387
15	27.1	1.88	27.1	1.01916021	0.018978967	3.872983346
16	28.98	1.88	28.98	1.01916021	0.018978967	4
17	30.86	1.88	30.86	1.01916021	0.018978967	4.123105626
18	32.76	1.9	32.76	1.01936799	0.019182819	4.242640687
19	34.66	1.9	34.66	1.01936799	0.019182819	4.358898944
20	36.57	1.91	36.57	1.01947191	0.019284761	4.472135955
21	38.48	1.91	38.48	1.01947191	0.019284761	4.582575695
22	40.4	1.92	40.4	1.01957586	0.019386714	4.69041576
23	42.32	1.92	42.32	1.01957586	0.019386714	4.795831523
24	44.24	1.92	44.24	1.01957586	0.019386714	4.898979486

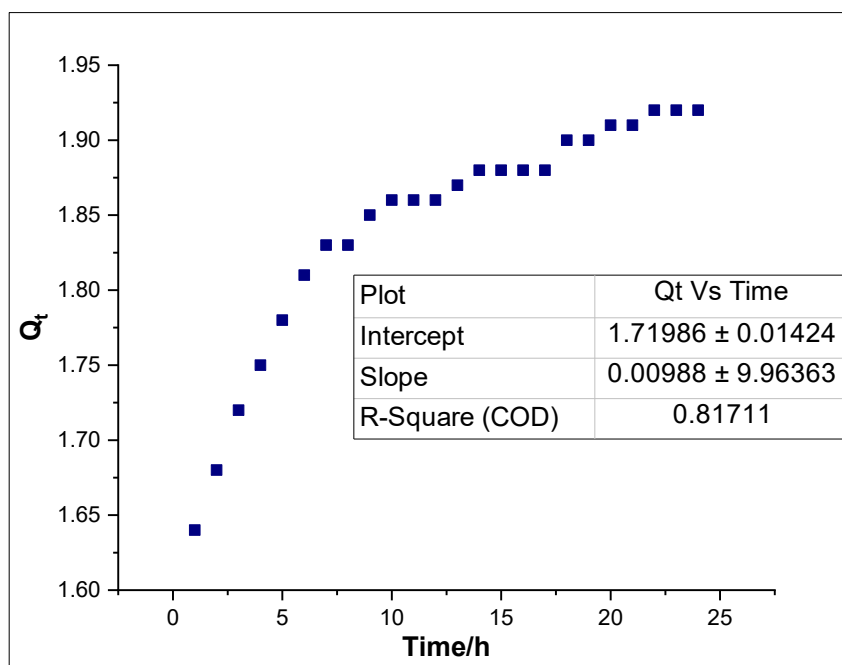


Figure (3.27) Zero-order kinetic model for the release of cephalexin from Gel/PEG into SGF

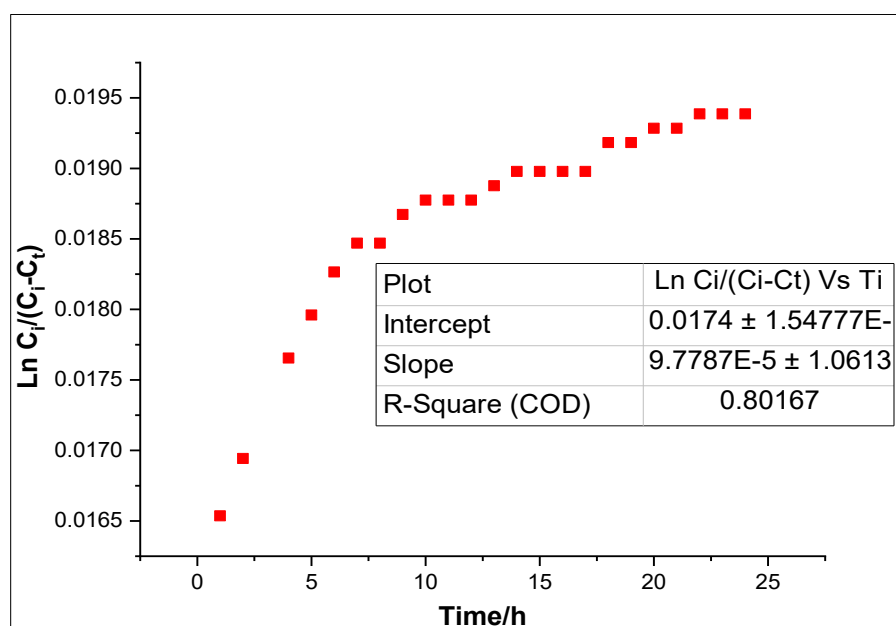


Figure (3.28) First-order kinetic model for the release of cephalexin from Gel/PEG into SGF

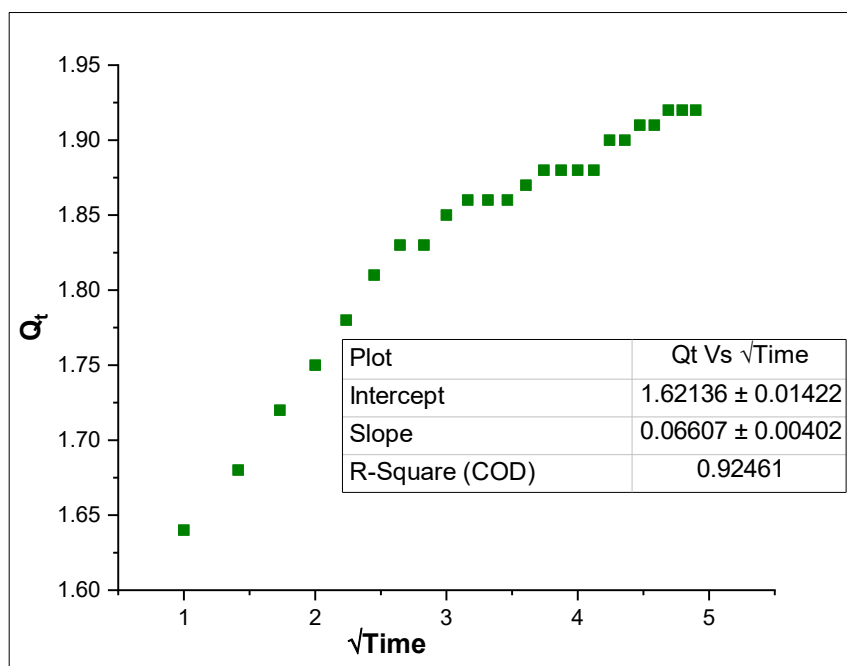


Figure (3.29) Higuchi-order kinetic model for the release of cephalixin from Gel/PEG into SGF

3.8 SEM Measurement for polymeric matrix

For the SPI/PEG/ZnO composite (Figure 3.30), SEM images reveal that prior to drug incorporation, the surface of the nanoparticles exhibited uniform, well-defined geometries with predominantly cubic or quasi-spherical morphology and narrow size distribution. This indicates a homogeneous and stable structure, suitable for drug delivery applications. Following drug loading, significant morphological changes were observed, including an increase in surface roughness and the appearance of nanoscale deposits or aggregates. These features are indicative of successful cephalexin attachment, likely through surface adsorption or weak physical interactions. The distinct surface modifications suggest the formation of a composite matrix in which cephalexin is distributed across or embedded within the polymeric framework[121, 122].

In the case of the Gel/PEG matrix (Figure 3.31), the SEM images prior to drug loading show a smooth and moderately aggregated surface with minimal topographical complexity. Post-drug loading, the morphology becomes notably more heterogeneous, with observable crystalline formations, irregular particle shapes, and increased surface roughness. These structural transformations imply effective drug integration into the matrix via either surface entrapment or internal encapsulation mechanisms. Such morphological shifts serve as strong indicators of successful drug loading and suggest enhanced interaction between the polymer and the cephalexin molecules [123 -125].

Overall, the evident morphological alterations in both matrices at the nanoscale provide visual confirmation of drug incorporation and further support the functionality of the SPI/PEG/ZnO and Gel/PEG systems as potential candidates for controlled drug delivery platforms.

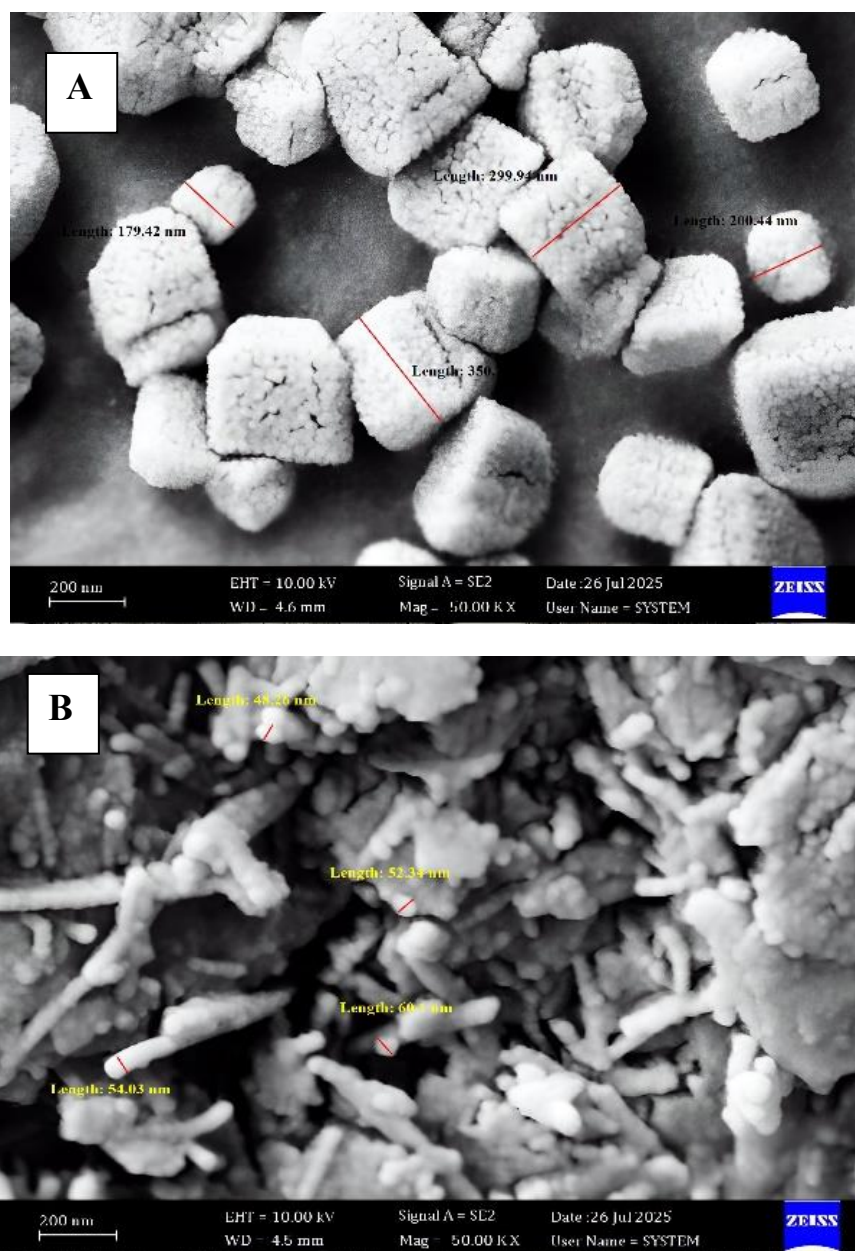


Figure 3.30: Scanning Electron Microscopy (SEM) micrographs of the SPI/PEG/ZnO polymer matrix at 200 nm magnification: (A) before drug loading (B) after drug loading

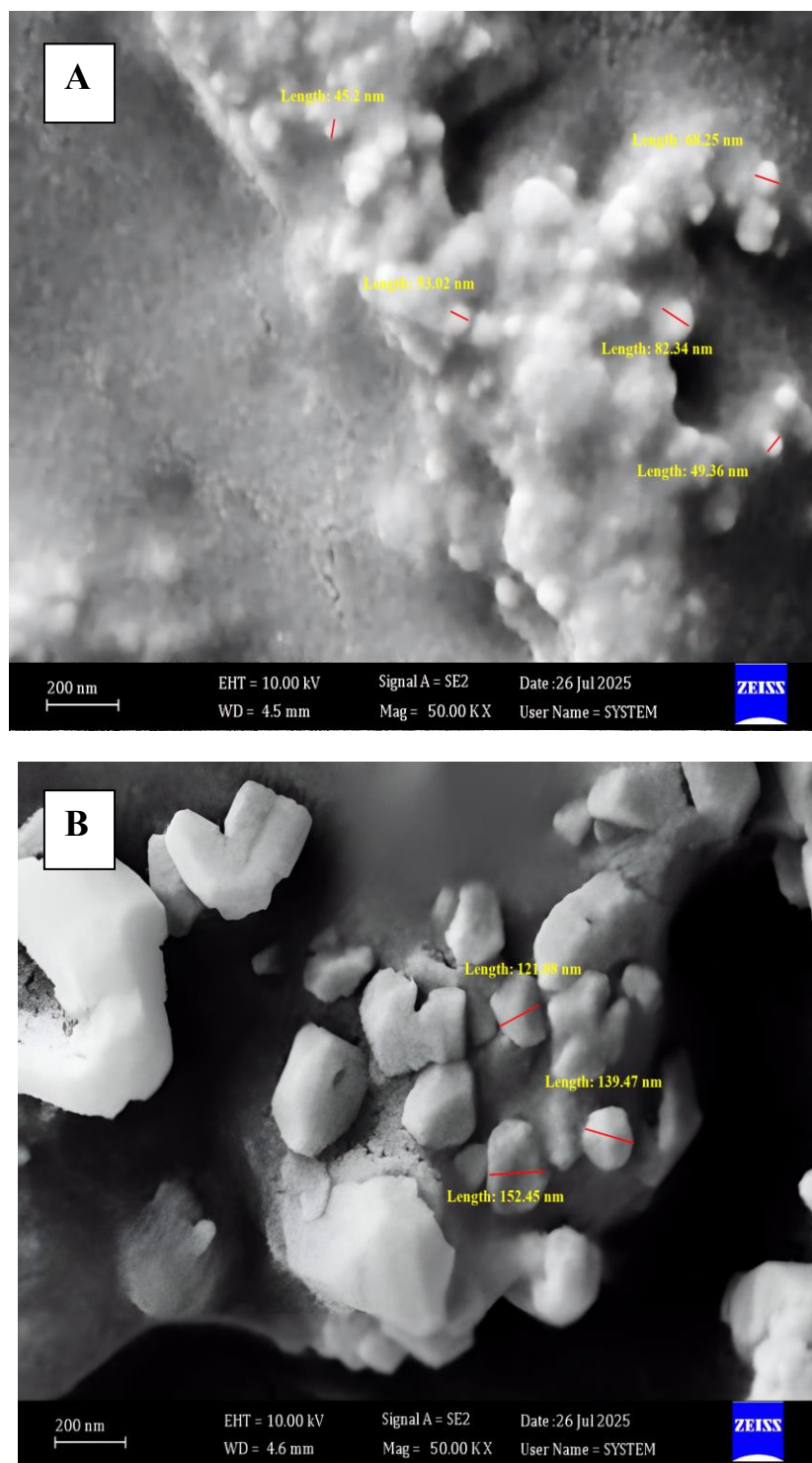


Figure 3.31: Scanning Electron Microscopy (SEM) micrographs of the Gel/PEG/ZnO polymer matrix at 200 nm magnification: (A) prior to drug loading (B) after drug loading

3.9 Antibacterial Activity Assessment of Gelatin-Based Polymeric Matrix

The antibacterial potential of gelatin-based nanocomposite systems was assessed using the agar well diffusion method, as illustrated in Figure 3.32. The antimicrobial evaluation focused on two bacterial strains: *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative). Three different sample formulations were prepared to examine the contribution of each component gelatin, polyethylene glycol (PEG), zinc oxide (ZnO) nanoparticles, and cephalixin toward antibacterial performance.

Bacterial suspensions were standardized to a concentration of 1.5×10^8 CFU/mL using sterile physiological saline and calibrated against the 0.5 McFarland turbidity standard for consistency. Mueller Hinton Agar (MHA) was autoclaved and poured into sterile Petri dishes under aseptic conditions. After the surface of the agar was inoculated with the test organisms, wells were created using sterile cork borers, and 100 μ L of each test formulation was introduced into the wells. Plates were incubated at 37°C for 24 hours, and the diameters of the zones of inhibition were measured in millimeters (mm) to determine antibacterial efficacy [126-129].

The formulations used in this study were:

1Gel: Gelatin + PEG + ZnO nanoparticles + Cephalixin

2Gel: Gelatin + PEG

3Gel: Gelatin + PEG + ZnO nanoparticles

The antimicrobial efficacy results are tabulated in Table 3.11:

Table (3.11) Inhibition zone diameters (mm) of gelatin-based nanocomposites against *S. aureus* and *E. coli*

	(S.a)	(E.c)
1Gel	20	-
2Gel	13	-
3Gel	10	-

As indicated in Table 3.11, antibacterial activity was only observed against *S. aureus*, with no inhibition recorded against *E. coli*. Among all samples, 1Gel exhibited the highest antibacterial effect, yielding a 20 mm inhibition zone. This can be attributed to the synergistic antibacterial mechanisms of ZnO nanoparticles and cephalexin. ZnO disrupts bacterial cell membranes and induces oxidative stress via reactive oxygen species (ROS), while cephalexin interferes with bacterial cell wall biosynthesis. Reduced inhibition in 2Gel and 3Gel underscores the necessity of both active agents for optimal antibacterial performance, as depicted in Figure 3.33.

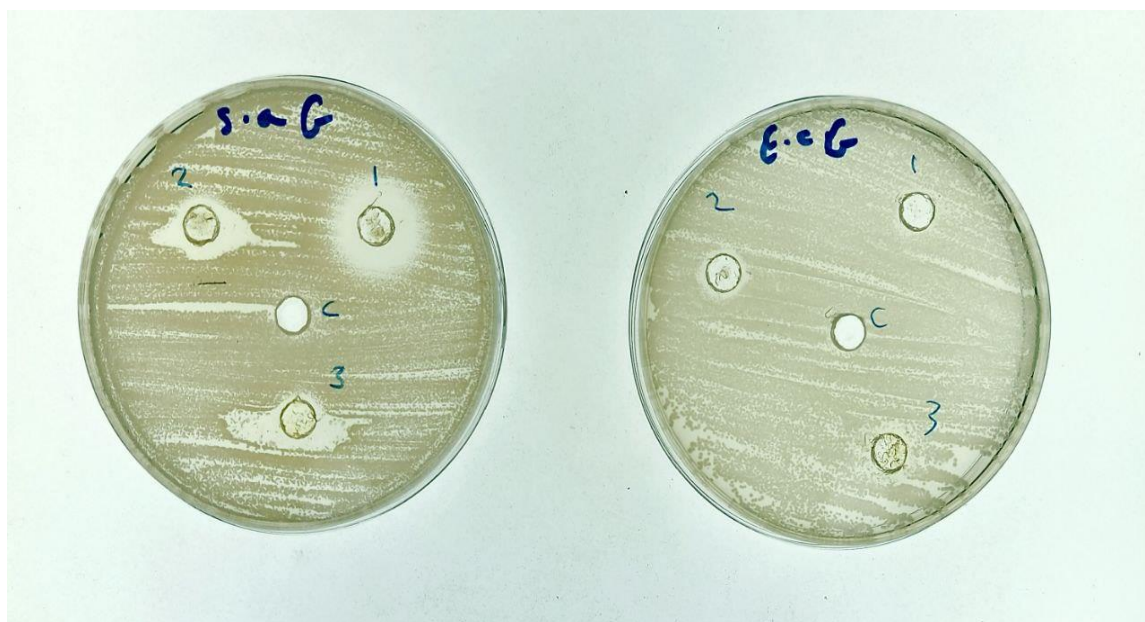


Figure (3.32) Antibacterial activity of gelatin-based polymeric nanocomposites against *Staphylococcus aureus* (left) and *Escherichia coli* (right) using the agar well diffusion method.

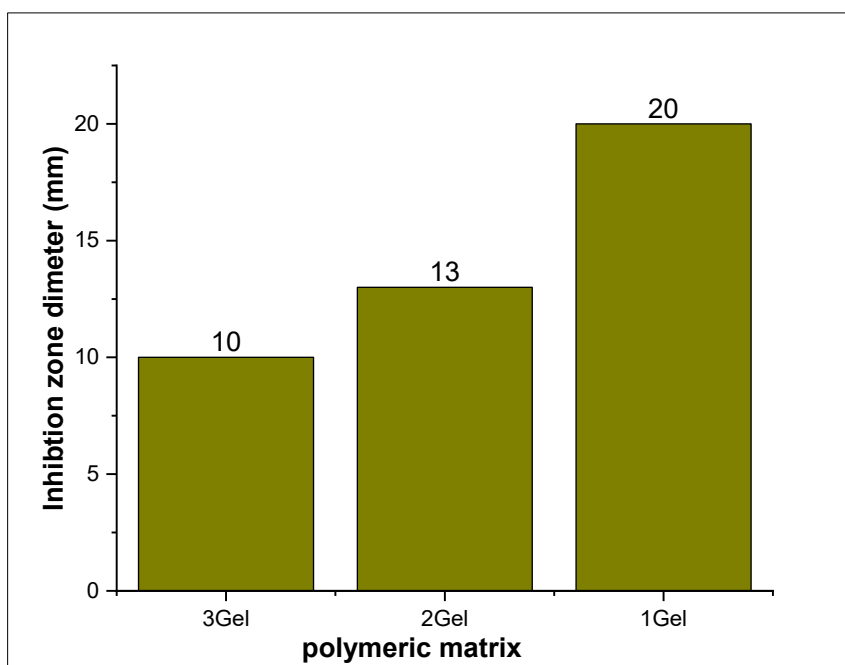


Figure (3.33) Comparative bar graph representing the inhibition zone diameters of gelatin-based samples against *Staphylococcus aureus* .

3.10 Conclusions

- 1- Two types of polymeric nanocomposite matrices (SPI/PEG/ZnO and Gel/PEG/ZnO) were successfully synthesized and crosslinked using glutaraldehyde, and their swelling behavior was found to be pH-dependent, with Gel/PEG exhibiting greater swelling ratios, particularly in simulated intestinal fluid.
- 2- FTIR spectroscopy confirmed the successful incorporation of cephalexin and highlighted key functional group interactions within the polymeric networks, while SEM analysis revealed significant surface morphological changes after drug loading, confirming successful encapsulation and interaction within the polymer structure.
- 3- Drug release kinetics followed a predominantly diffusion-controlled mechanism, best described by the Higuchi model, with the Gel/PEG matrix showing a more sustained and higher drug release profile compared to SPI/PEG, especially under intestinal conditions.
- 4- Antibacterial testing demonstrated that the Gel/PEG/ZnO nanocomposite had enhanced activity against *Staphylococcus aureus*, attributed to the combined effect of ZnO nanoparticles and cephalexin, and overall, the developed polymeric systems exhibit promising characteristics for use as controlled-release drug delivery platforms, particularly for oral antibiotic administration.

3.11 Future Work

1. Investigate the application of alternative biopolymers or natural materials (e.g., chitosan, alginate, or pectin) with functional attributes to improve hydrogel-based drug delivery systems.
2. Integrate other antibacterial nanoparticles (such as silver or copper oxide NPs) and evaluate their effects on medication release performance and antimicrobial efficacy in comparison to ZnO.
3. Assess the system in more intricate contexts, including actual biological fluids such as plasma, to evaluate its performance under physiological parameters.
4. Conduct in vivo animal model experiments to assess the biological performance and therapeutic potential of the cephalexin-loaded system in authentic biological situations.
5. Develop intelligent drug delivery systems that respond to various stimuli (such as temperature, enzymes, or magnetic fields) to improve targeted and regulated drug release.
6. Investigate the multi-drug loading potential of a singular hydrogel system for the treatment of chronic or comorbid illnesses, emphasizing the distinct regulation of release kinetics for each pharmaceutical agent.

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الخلاصة

ركزت هذه الرسالة على تحضير وتقييم مصفوفات هلامية بوليمرية قابلة للتحلل الحيوي تعتمد على بروتين الصويا المعزول (SPI) والجيلاتين (Gel)، والممزوجة ببولي إيثيلين غليكول (PEG) وجزيئات أكسيد الزنك النانوية (ZnO) من أجل الإطلاق المتحكم فيه لدواء السيفالكسين وتقييم النشاط المضاد للبكتيريا. تم تحسين التركيبات من خلال تغيير نسب البوليمرات وكميات عامل الربط المتصالب.

تم تصنيع المصفوفات الهلامية عبر الربط الكيميائي المتصالب باستخدام الغلوتارالدهيد، بتركيز مختلفة (٠,٥، ١,٠، و ١,٥ مل) لدراسة تأثيرها على الخصائص البنيوية والوظيفية للهيدروجيل. وُجد أن التركيبة المثلى تتكون من ٠,٧ غرام من SPI (أو الجيلاتين) و ٠,٣ غرام من PEG مع ٠,٥ مل من الغلوتارالدهيد، حيث أعطت أعلى نسبة انتفاخ.

تم تقييم سلوك الانتفاخ للهيدروجيل من خلال التحليل الحركي باستخدام نماذج الانتفاخ من الدرجة الأولى والثانية في سوائل تحاكي البيئة المعدية (SGF) والمعدية (SIF). أظهر هيدروجيل SPI/PEG نسب انتفاخ بلغت ٢٧٤٪ في SIF و ١٤٠٪ في SGF، في حين أظهر هيدروجيل Gel/PEG نسب انتفاخ أعلى بشكل ملحوظ وصلت إلى ١٢٠٥٪ في SIF و ٦٧٨٪ في SGF.

أثر الأس الهيدروجيني (pH) بشكل كبير على سلوك الانتفاخ، حيث كانت نسب الانتفاخ أعلى في السائل المعوي المحاكي (SIF, pH = 6.8) مقارنةً بالسائل المعدني المحاكي (SGF, pH = 1.2). ويُعزى ذلك إلى تأين المجموعات الوظيفية ضمن تركيب الهيدروجيل في البيئات المحايدة إلى القاعدية، مما يزيد من محبته للماء وقدرته على امتصاصه. في المقابل، يؤدي الوسط الحمضي إلى تثبيط عملية التأين، مما يقلل من ضغط الانتفاخ الأسموزي. ويؤكد هذا السلوك المعتمد على pH ملائمة الهيدروجيل لإطلاق الدواء الموجه في الأمعاء.

تم تحديد الطول الموجي الأعظمي لامتصاص السيفالكسين (λ_{max}) في الماء المقطر عند تركيز ١٠٠ جزء في المليون عند ٢٦١ نانومتر باستخدام مطياف الأشعة فوق البنفسجية - المرئية (UV-Vis). وقد توافقت نتائج إطلاق الدواء مع سلوك الانتفاخ: ففي SIF، أطلق Gel/PEG ما نسبته ٩٩,٨٩٪ من السيفالكسين خلال ٢٤ ساعة، بينما أطلق SPI/PEG نسبة ٨٩,٣٤٪. أما في SGF،

فقد انخفضت نسب الإطلاق إلى ٤٤,٢٤٪ و ٣٨٪ على التوالي. أظهر التحليل الحركي أن إطلاق الدواء يتبع نموذج Higuchi، مما يشير إلى آلية إطلاق تعتمد على الانتشار. وقد حقق Gel/PEG في SIF أفضل توافق مع النموذج ($R^2 = 0.812$ ، $KH = 0.0466$).

أكدت أطياف FTIR نجاح دمج الدواء وحدث عملية الربط المتصالب، بينما كشفت صور المجهر الإلكتروني الماسح (SEM) عن اختلافات واضحة في الشكل السطحي قبل وبعد تحميل الدواء، بما في ذلك زيادة الخشونة وتجمع الجزيئات. أما من ناحية النشاط المضاد للبكتيريا، فقد أظهرت اختبارات الحفر بالأجار أن التركيبة المكونة من Gel/PEG/ZnO/cephalexin أظهرت أكبر منطقة تثبيط (٢٠ مم) ضد بكتيريا *Staphylococcus aureus*. ويُعزى هذا التأثير القوي إلى التآزر بين نشاط جسيمات ZnO (التي تتلف أغشية البكتيريا) والسيفالكسين (الذي يمنع تكوين جدران الخلايا).



جمهورية العراق
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قسم الكيمياء

تطوير وتطبيق مصفوفة بروتين / بولي اثيلين كلايكول /او كسيد الزنك لأنظمة توصيل السيفالكسين

رسالة تقدم بها الطالب
أحمد كاظم حسين

الى مجلس كلية العلوم / جامعة القادسية
وهي جزء من متطلبات نيل درجة الماجستير في علوم الكيمياء

بإشراف
أ.د. اوراس عدنان حاتم

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١٤٤٧ هـ