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University of Al-Mustansiriyah
College of Pharmacy

Formulation and Characterization of Ciprofloxacin Hydrochloride Emulgel with The Attempt to Synthesis New Derivatives of Ciprofloxacin

A Thesis

Submitted to the Department of Pharmaceutics and the Committee of Graduate Studies of the College of Pharmacy / University of Al - Mustansiriyah in Partial Fulfillment of the Requirements For the Degree of Master of Science in Pharmacy

"Pharmaceutics"

BY

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(B.Sc. Pharmacy 2008)

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بسم الله الرحمن الرحيم

(وَأَنزَلَ اللَّهُ عَلَيْكَ الْكِتَابَ وَالْحِكْمَةَ وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا)

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[سورة النساء: 113]

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We certify that this thesis, **"Formulation and Characterization of Ciprofloxacin Hydrochloride Emulgel with the attempt to synthesis new derivatives of Ciprofloxacin"**, was prepared under our supervision at the University of Al-Mustansiriyah, College of Pharmacy as a partial fulfillment of the requirements for the degree of Master of Science in Pharmacy (Pharmaceutics).

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Dedication

To ….

My father for his endless support.

My mother for encouraging me to fight hard for what I believe.

My wife for her support, patience and understanding.

My brother Ali and sisters for supporting me all the time.

My son Yaseen, always you are the hope

I dedicate my thesis with love

Ahmed

2015

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AHMED ALSHAREA

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Abbreviations

CMC	Carboxymethylcellulose
CF	Ciprofloxacin
CP	Carbopol
CO	Coconut oil
LP	Liquid Paraffin
SCMC	Sodium Carboxymethylcellulose
nm	Nanometer
rpm	Rotation per minute
USP	United States Pharmacopeia
λmax	Wave length with maximum absorbance

Abstract

The present study is to develop and evaluate an emulgel formulation of ciprofloxacin (CF-HCl).It aims to provide a topical treatment fr many bacterial infections that affect the skin. Administration of medications topically having the facility of delivering a high concentration of the drug to the skin than would be possible with systemic therapy. Also the study involves chemical synthesis of two CF derivatives so as to get rid of bacterial resistant to the drug, as well as looking forward to the production of derivatives that wider spectra of antimicrobial efficacy and have better chemical and physical properties than the original drug.

Thirty-six emulgel formulas of CF (0.5% w/w) were prepared containing equal quantities of gel and emulsion portions. The gel portion of the emulgel prepared by dissolving certain quantities of three gelling agents (separately): Sodium Carboxymethylcellulose (SCMC), Carboxy methyl cellulose (CMC) and Carbopol 940 in water .The composition of emulsion are liquid paraffin or coconut oil as an oil phase, tween 20 and span 20 as emulsifying agents, and propylene glycol was used to improve the solubility and as penetration enhancer through the skin. The influence of type and concentration of both gelling agent and oil phase on drug release were studied. All the prepared formulas were characterized physically in term of colour , bio adhesion , pH , drug content and rheological properties (viscosity) Furthermore , drug release performance, kinetics , sensitivity and stability study were achieved.

The appearance of most of the formulas prepared were homogenous with smooth appearance, easily distributed over skin and the pH values of all the prepared

formulas ranged from 5.44 to 7.6, which is considered to be acceptable to avoid the risk of irritation upon application to the skin ,since adult skin pH is 5.5.The optimized formula was (F25),that has no skin irritation and 94% cumulative drug release at the end of experiment. (F25) contains 0.75% w/w (CMC) and 6% w/w coconut oil. The expiry date calculated to be three years. CF-Glycine amide and CF-Chitosan amide were synthesized and separated. Although UV , FTIR , TLC subjected the synthesized new derivatives to characterization, solubility and anti-microbial studying, further purification and identification like ^{1}HNMR , ^{13}C-NMR , CHN and mass spectroscopy are potentially required to optimize the characterization of new derivatives.

Chapter One

Introduction

1. INTRODUCTION

1.1Topical Dosage Forms

Topical drug delivery systems allow localized administration of the drug anywhere in the body through ophthalmic, vaginal, skin and rectal routes [1]. Topical formulations encompass a wide variety of formulations intended for cosmetic or dermatological application, to healthy as well as diseased skin. These formulations range in physicochemical nature from solid through semisolid to liquid [2]. Drug substances are infrequently administered alone, but rather as part of a formulation, in combination with one or more non-medicated agents that serve varied and specialized pharmaceutical function. [3]

Drug absorption through the skin is enhanced if the drug substance is in solution, if it has a favorable lipid/water partition coefficient and if it is a nonelectrolyte [4]. For the most part, pharmaceutical preparations applied to the skin are intended to serve some local action and as such are formulated to provide prolonged local contact with minimal systemic drug absorption. Drugs that applied to the skin for their local action include antiseptics, antifungal agent, skin emollient, anti-inflammatory, analgesic and protectant [5].

1. 2 Skin

Skin is the biggest organ in the body and it is considered as an external defense system [6]. it covers the outside of the body a has other functions beside the defense mechanism it serve as a mechanical barrier between the inner part of the body and the external world [7].

1. 3 Physiology of Skin and Penetration of Topical Medications

The skin of an average adult body covers a surface area approximately $2m^2$ and receives about one third of the blood circulating through the body [8]. An average of every square centimeters of the human skin surface is known to contain, on the average 40-70 hair follicles and 200-300 sweat ducts [9]. Skin surface is slightly acidic and the pH of the skin varies from (4 to 5.6). Sweat and fatty acid secretions influences the pH of the skin surface [10].

The skin can be considered to have three distinct layers of tissue that is epidermis, dermis and subcutaneous connective tissue as shown in figure. (1-1)

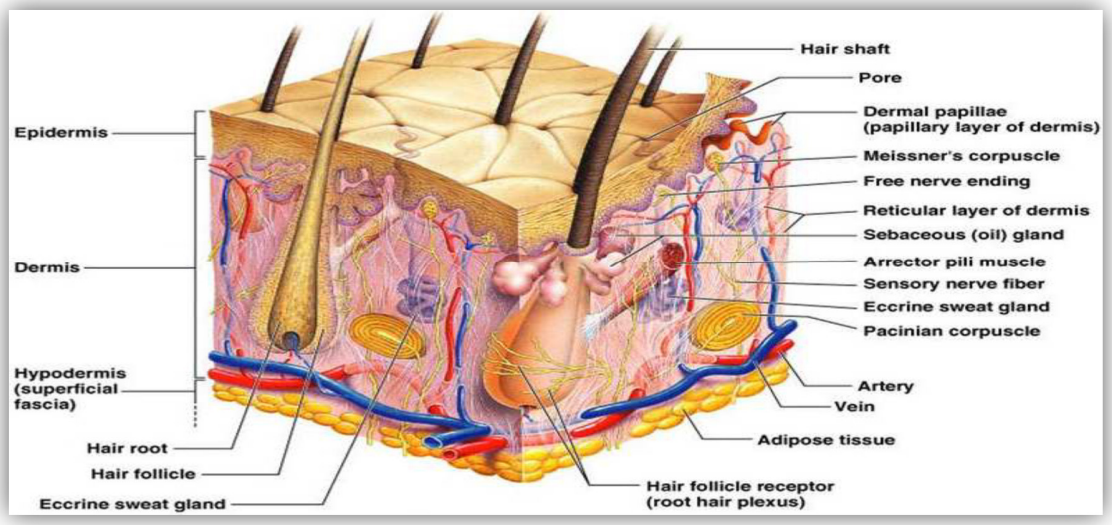


Figure (1-1): Skin structure [11, 12].

1.4 Advantages and Disadvantages of Topical Drug Delivery System

Topical drug delivery system have many advantages like local treatment and direct effectiveness of medications like antifungal, anti-bacterial ,acne preparation and other medications that used for different purposes[13]. It is characterized by avoidance of gastrointestinal incompatibility and avoidance of first pass metabolism. Also, more selective to a specific site, improve patient compliance and suitability for self-medication. Moreover, we have ability to easily terminate medication when needed however, local drug administration has some disadvantages like skin irritation or possibility of allergenic reactions. Other disadvantage is low penetration of drugs of large particle size, which means not easily to be absorbed through the skin [14].

1.5 Factors Affecting Topical Absorption of Medications

A-Physiological Factors of Skin *(15)*

- Skin thickness
- Lipid content and part of skin.
- Density of sweat glands.
- skin pH.
- Blood flow.
- Hydration of skin.
- Disease state and inflammation of skin

B-Physiochemical Factors of Drug *(16)*

- Distribution coefficient.
- Molecular weight (<400 Dalton).
- Degree of ionization (unionized drugs gets absorbed well).
- Effect of excipients

1.6 Pathway of Transdermal Permeation

Permeation can occur by diffusion via:

A-Transdermal permeation, through the stratum corneum.

B-Intercellular permeation, between cells of the stratum corneum.

C-Trans appendage permeation, via the hair follicle, sebaceous and sweat glands [17]. Most molecules penetrate through skin via intercellular micro route (figure (1-2)) and therefore many enhancing techniques aim to disrupt or bypass its elegant molecular architecture has developed.

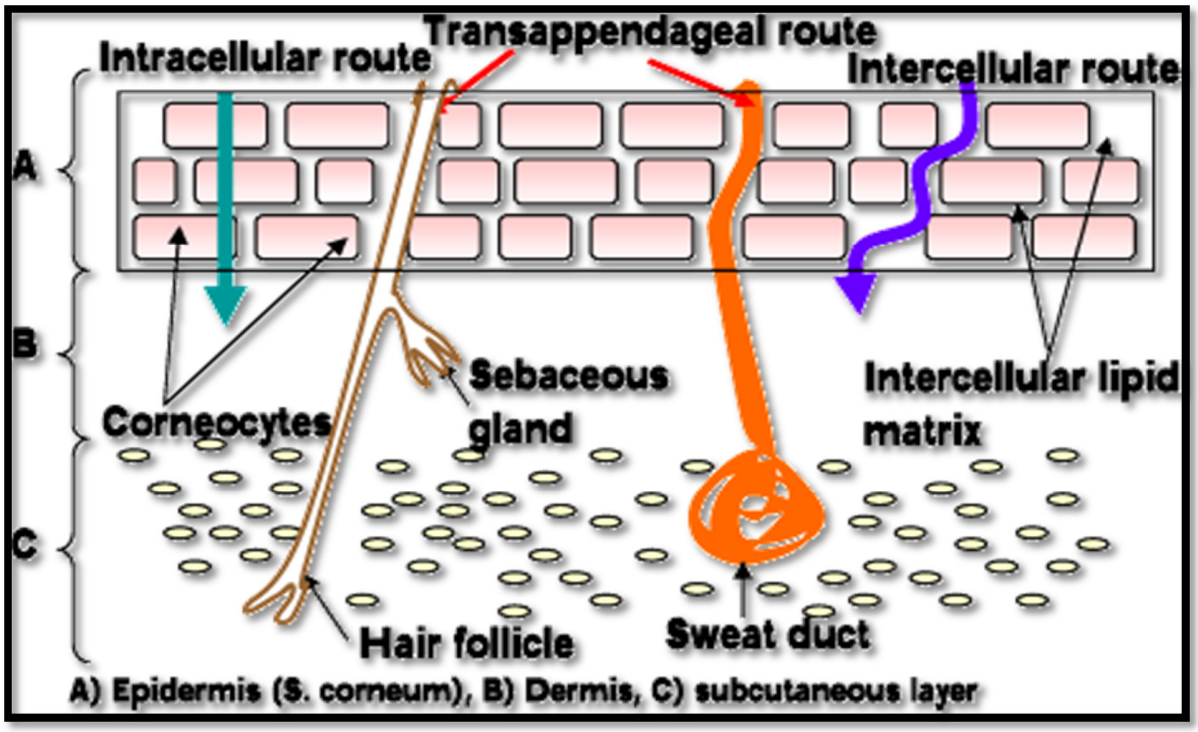


Figure (1-2): Simplified representation of skin showing routes of penetration (18)

1.7 Types of Topical Drug Delivery Systems

1.7.1Conventional Topical preparations

Many types of conventional topical preparations are shown in table (1-1) [19]:

Table (1-1): Conventional Topical Preparations

Liquid preparations	Semi-solid preparations	Solid preparations
Liniments	Ointments	Topical powders
Lotions	Creams	Poultices
Paints	Pastes	Plaster
Topical solution	Gels	
Topical tinctures		

1.7.2 Advanced Topical Delivery System

These formulations have been shown to be superior for cutaneous delivery compared with other conventional vehicles. [20].

1.7.2.1 Micro Emulsions

Micro emulsions droplets has a particle size (> 0.5 μm). In addition, they are spontaneously produced in a narrow range of oil-water-surfactant composition. They are dynamic systems with continuously fluctuating interfaces. Their good dermal and transdermal delivery properties could be attributed to their excellent solubilizing properties [21].

1.7.2.2 Nano Emulsions/Sub micro Emulsions/Mini Emulsions

These are oil-in-water emulsions with an average droplet size ranging from 100 to 500 nm. They have very good stability and they do not undergo phase separation during storage. They have a liquid lipophilic core and are appropriate for lipophilic compound transportation [22]. Nanoemulsion viscosity is very low, which is interesting because they can be produced as sprays. [23]

1.7.2.3 Multiple Emulsions

Multiple emulsions are novel carrier system which are complex and poly dispersed in nature where both w/o (water/oil) and o/w (oil/water) emulsion exists simultaneously

In a single system. Lipophilic and hydrophilic surfactants are used for stabilizing these two emulsions respectively [24]. The droplets of the dispersed phase contain even smaller dispersed droplets themselves, therefore also called as “emulsions of

emulsions". Each dispersed globule in the double emulsion forms a vesicular structure with single or multiple aqueous compartments separated from the aqueous phase by a layer of oil phase compartments [25].

1.7.3 Vesicular Carriers Dermal Drug Delivery System

1.7.3.1 Liposomes

Liposomes are defined as lipidic vesicles containing water. Conventional liposomes are composed of phospho-lipids, mostly phosphatidylcholine from soybean or egg yolk, with or without cholesterol [26]. Liposomes are accepted as ideal dermal drug carriers due to their ability to alter the bio distribution profile of incorporated drugs. Liposomes can be adsorbed on the skin surface or may go into defused into skin. Fusion of liposomes may facilitate dermal penetration of the drug [27].

1.7.3.2 Niosome

A niosome is a non-ionic surfactant-based liposome. Niosome are formed mostly by cholesterol incorporation as an excipient. Niosome have more penetrating capability than liposomes. They are structurally similar to liposomes in having a bilayer, however, the materials used to prepare niosome make them more stable and thus niosome offer many more advantages over liposomes. [28].

1.7.3.3 Transfersomes

Transfersomes are highly deformable or elastic liposomes. They are composed of phospholipids and a surfactant, which gives flexibility to the liposome structure. Transfersomes have been successfully assessed as topical and transdermal carriers for drugs and have been shown to be effective carriers for genetic material and vaccines [29].

1.7.3.4 Ethosomes

These are liposomes with high alcohol content capable of enhancing penetration to deep tissues and systemic circulation. It is proposed that alcohol fluidizes the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate [30].

1.7.3.5 Aquasomes

These are nano particulate carrier systems but instead of being simple nanoparticles these are three layered self-assembled structures, comprised of a solid phase monocrystalline core coated with oligomeric film to which biochemically active molecules conected. Aquasomes are one of the most recently developed delivery system for bioactive molecules like peptide, protein, hormones, antigens and genes to specific sites and they are adsorbed with or without modification. [31].

1.8 Rationale of Emulgel as a Topical Drug Delivery System

When gel and emulsion are used in combination form, the dosage form is referred to as "emulgel". Emulgel is having major advantages on novel vesicular systems as well as on conventional systems in various aspects:

Being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance .[32] Emulgel dosage form is used for steroids, some antibiotics and it was extended to analgesics and antifungal drugs [33].

Topical agents such as ointment, cream, lotion have many disadvantages. They are sticky and causing uneasiness to the patients, also have lesser spreading coefficient, and need to be applied sometimes with rubbing. They exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparations, the use of transparent gel has expanded both in cosmetics and in pharmaceutical preparation [34]. However, despite of offering several benefits, gels a colloid system shows major limitations like delivery of hydrophobic drugs. In order to overcome this problem an emulsion-based approach is being used so that even hydrophobic therapeutic moiety can be successfully incorporated and delivered through gel mixtures [35]. Emulgel structure was showed in figure (1-3)

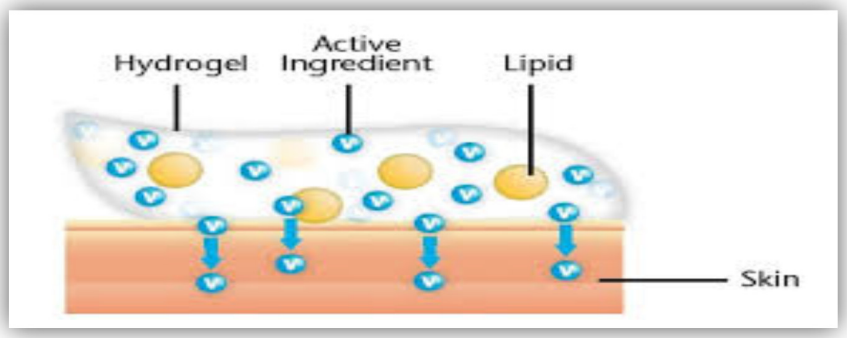


Figure (1-3): Emulgel structure

1.8.1 Method of preparation of Emulgel:

The method-involved preparation of an o/w emulsion after incorporation of the drug into either oil or aqueous phase depending on the solubility, formation of gel base then mixing the emulsion with the gel base at ratio of 1:1. [36]. These steps are showed in figure (1-4)

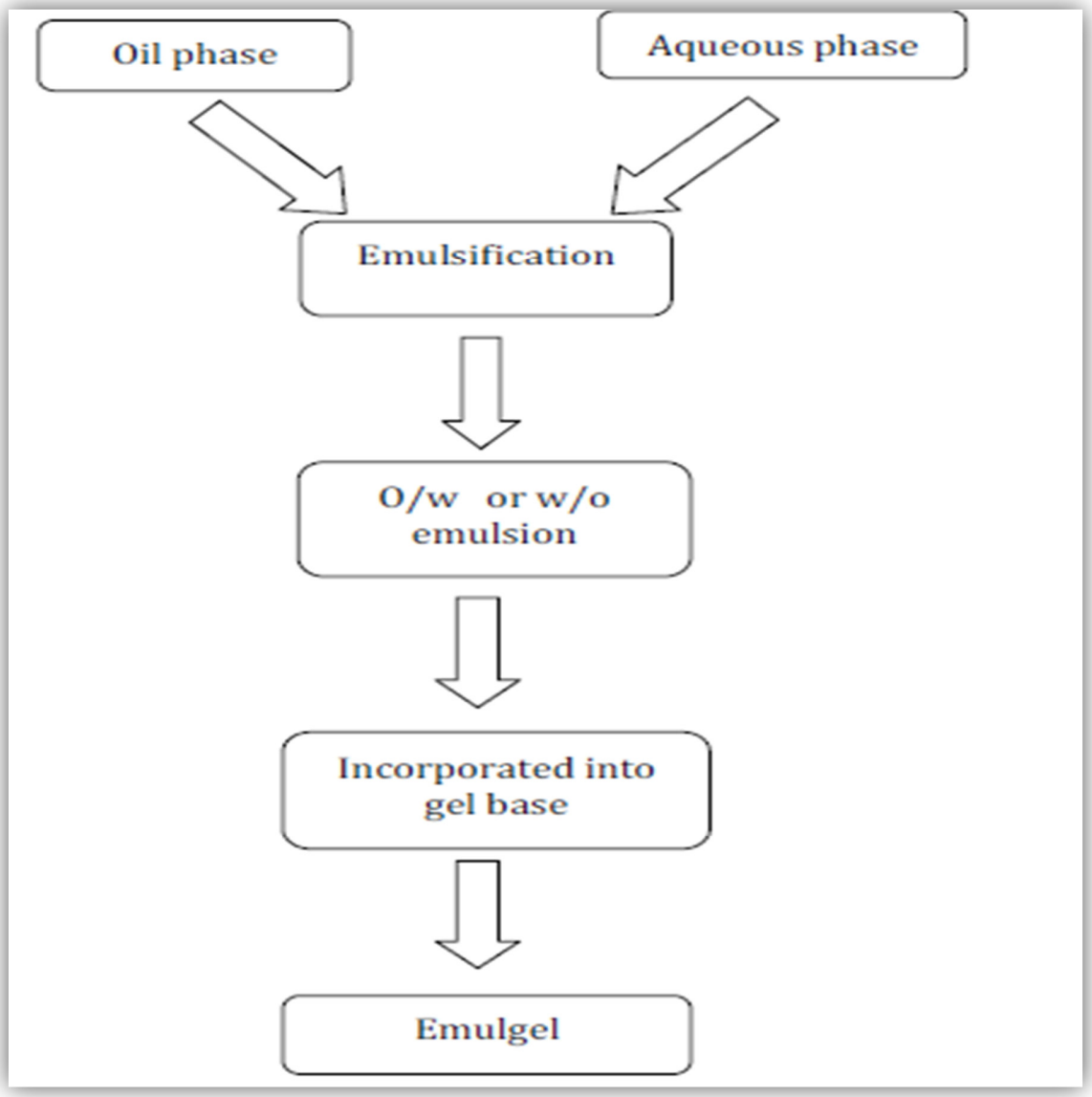


Figure (1-4): Scheme of emulgel preparation [37]

1.8.2 Important Constituents of Emulgel Dosage form

1.8.2.1 Aqueous Material

This forms the aqueous phase of the emulsion, commonly used agents are water and alcohols. (38)

1.8.2.2 Oils

Mineral oils, either alone or combined with soft or hard paraffin's, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics. (39) Widely used oils are castor oil, fish liver oils or various fixed oils of vegetable origin (e.g., a rachis, cotton seed, and maize oils). (40)

1.8.2.3 Emulsifiers

Emulsifying agents are used to promote emulsification between oil phase and water phase at the time of manufacture of emulsion and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations. Examples of emulsifiers are polyethylene glycol (40) stearate, polysorbate 40 (Polyoxyethylene (20) sorbitan monopalmitate) (41)

1.8.2.4 Gelling Agents

These are thickening agents used to increase the consistency of any dosage form [42], there are many gelling agents. Some of the common ones are acacia, alginic acid, bentonite, Carbopol®, Carboxymethylcellulose. ethyl cellulose, gelatin, hydroxyethylcellulose, hydroxypropyl cellulose, magnesium aluminum silicate (Veegum®), methylcellulose, poloxamers (Pluronics®), polyvinyl alcohol, sodium alginate, tragacanth, and xanthan gum. The gelling agents are usually used in low concentrations (0.5 w/w-5% w/w) when used to prepare gels [42].

1.8.2.4. A Carbopol

Carbopol polymers are acrylic acid cross-linked with poly alkenyl ethers or divinyl glycol. It also known as carbomers. Carbomers polymers are cross-linked together and form a micro gel structure that makes them optimal to be used as a drug vehicle for dermatological purposes. They can be used in cases when drug delivery in a controlled manner is desired. These polymers are anionic polymers that need naturalization to become jellified. Organic amines like triethanol amine can be used to naturalize these polymers in liquids [43].

Carbopol has high viscosity at low concentrations, wide concentration interval and characteristic flow behavior .Also it is characterized by wonderful compatibility with many active ingredients also; it has a good bio adhesive properties and good thermal stability

Carbopol is available in several modified structures like carbopol 910, carbopol 934, carbopol 940, etc. [44] Table (1-2).

They differ in their chemical substitution and their physicochemical properties. Figure (1-5) shows the basic chemical structure of carbopol.

Table (1-2): Some examples of Carbopol gelling agents.

Polymer Name	Viscosity (centipoise)*	Properties
Carbopol® 910	3,000 - 7,000	Effective in low concentrations and will provide a low viscosity formulation.
Carbopol® 934	30,500 - 39,400	Effective in thick formulations such as emulsions, suspensions, sustained-release formulations, transdermal, and topical. Forms clear gels with water.
Carbopol® 934P	29,400 - 39,400	Same properties as 934, but intended for pharmaceutical formulations. "P" = highly purified product
Carbopol® 940	40,000 - 60,000	Effective in thick formulations, very good clarity in water or hydro alcoholic topical gels. Forms clear gels with hydro alcoholic systems.
Carbopol® 941	4,000 - 11,000	Produces low viscosity gels, very good clarity.

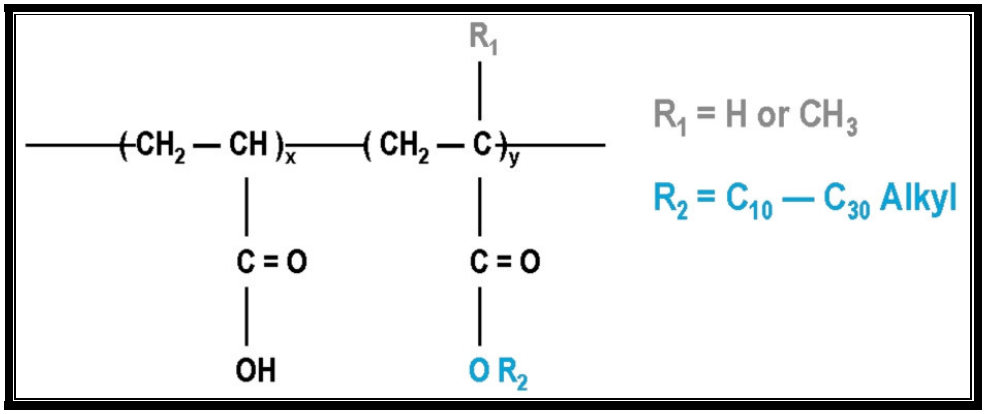


Figure (1-5): Basic chemical structure of carbopol.

1.8.2.4. B Carboxy Methyl Cellulose

Carboxy methylcellulose or cellulose gum is a cellulose derivative with carboxymethyl groups (-CH2-COOH) bound to some of the hydroxyl groups of the glucopyranose monomers that make up the cellulose backbone. [45]

The functional properties of CMC depend on the degree of substitution of the cellulose structure (i.e., how many of the hydroxyl groups have taken part in the substitution reaction), as well as the chain length of the cellulose backbone structure and the degree of clustering of the carboxymethyl substituents. CMC has many different uses, beside its use as thickening agent; it also used filler, dietary fiber, anti-clumping agent and emulsifier. It is similar to cellulose, Micro granular CMC is used as a cat ion-exchange resin in ion-exchange chromatography for purification of proteins. [46]

Figure (1-6) show the chemical structure of carboxy methylcellulose.

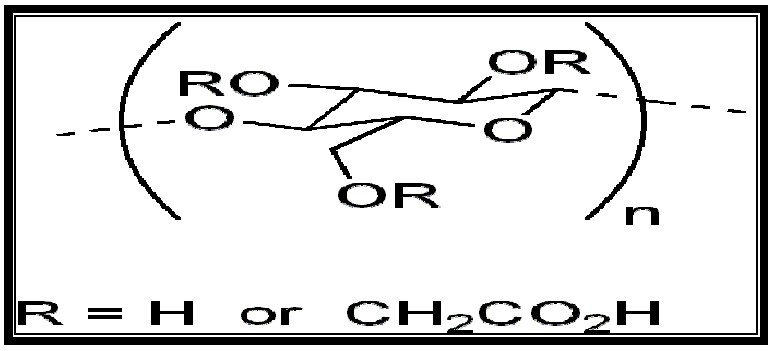


Figure (1-6): Chemical structure of carboxy methylcellulose

1.8.2.4. C Sodium Carboxy Methyl Cellulose

Sodium carboxy methylcellulose is a cellulose-derived ester, originated by the reaction of cellulose with sodium mono-chloro acetate in the presence of sodium hydroxide, which results in a long chain of anhydrous glucose, which in turn generates a highly hygroscopic and viscous polymer, nontoxic to humans. [47]

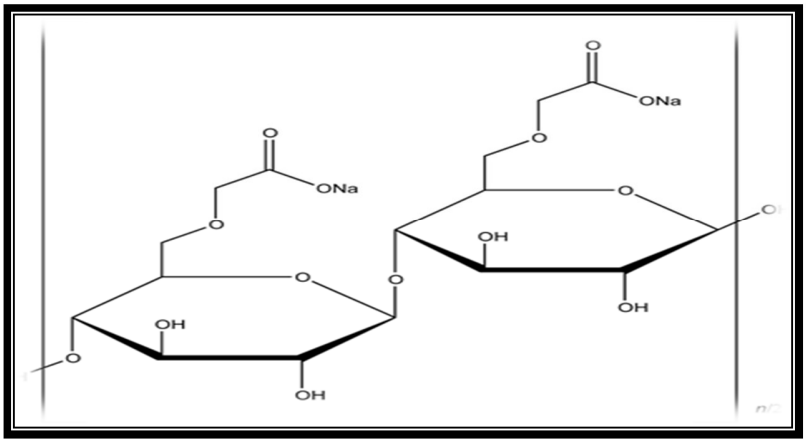


Figure (1-7): Chemical structure of sodium carboxy methylcellulose

1.8.2.5 Permeation Enhancers

These agents interacts with skin constituents to induce a temporary and reversible increase in skin permeability [48]. Like propylene glycol.

Penetration enhancers may act by one or more of the following three main mechanisms:

- Disruption of the highly ordered structure of stratum corneum lipid.
- Interaction with intercellular protein.
- Improved partition of the drug, co enhancer or solvent into the stratum corneum. [49]

1.8.3 Advantages of Emulgel

Beside the properties mentioned that emulgel helps in the incorporation of hydrophobic drugs into the oil phase, and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. Emulsion can be mixed into gel base, emulgel may provide better stability and release of drug than simply incorporating drugs into gel base and it have better loading capacity. Furthermore, preparation of emulgel comprises of simpler and short steps, which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgel. Moreover, materials used are easily available and cheap. Hence, decreases the production cost Emulgel can be also used to prolong the effect of drugs having shorter half-life (t 0.5), increases the stability of formulation and increases the contact time and mean residence time of the drug. In addition, they introduce dual release of drug from emulsion and gel. Finally emulgel used even for cosmetic purposes. [50]

1.9 Drug under Investigation; Ciprofloxacin Hydrochloride

Ciprofloxacin hydrochloride (CF-HCl) is an antibiotic useful for the treatment of a number of bacterial infections. It is a second-generation fluoroquinolone [51]. Its spectrum of activity includes most strains of bacterial pathogens responsible for respiratory, urinary tract, gastrointestinal, and abdominal infections, including gram-negative bacteria like (Escherichia coli, Haemophilus influenzae, Klebsiella pneumonia, Legionella pneumophila, Moraxella catarrhalis, Proteus mirabilis, and Pseudomonas aeruginosa) [52].

Additionally it is highly effective against gram-positive bacteria like (Staphylococcus aureus, Streptococcus pneumonia, Staphylococcus epidermises, Enterococcus faecalis, and Streptococcus pyogenes). (CF-HCl) and other fluoroquinolone are valued for their broad spectra of activity, excellent tissue penetration, and for their availability in both oral and intravenous formulations [53].

1.9.1 Chemical Name and Structure

(CF-HCl) is the monohydrochloride monohydrate salt of ciprofloxacin. It is a white powdery substance with a molecular weight of 385.8 g/mol. Its empirical formula is $C_{17}H_{18}FN_3O_3HCl{\bullet}H_2O$. [54] Figure (1-8) show the chemical structure of (CF-HCl)

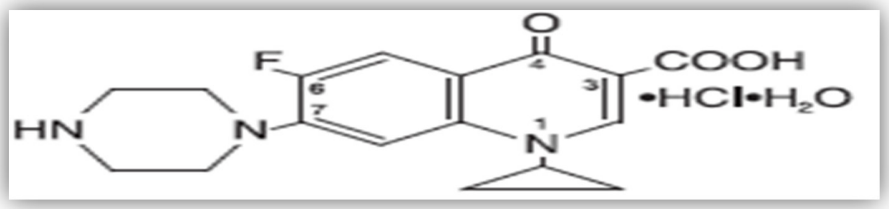


Figure (1-8): Chemical structure of ciprofloxacin hydrochloride

1.9.2 Mechanism of Action

Quinolones in general are bactericidal and inhibit DNA *Topoisomerases* II, specifically DNA *Gyrase*. These enzymes are responsible for negative super-coiling of DNA, which is important in the packing of DNA as well as replication and transcription [55].

1.9.3 Indication and Use

(CF-HCl) is a broad-spectrum bactericidal anti-infective agent of the fluoroquinolone class [56]. It is approved for the treatment of several diseases like urinary tract infections such as acute uncomplicated cystitis and chronic bacterial prostatitis, and lower respiratory infections and many other infectious diseases of various body organs [57]. The most frequent adverse reactions of the drug are nausea, vomiting, diarrhea, abdominal pain, rash, headache, and restlessness [58].

1.9.4 Dissociation Constants

(CF-HCl) is a zwitter ion molecule containing two proton-binding sites values of pKa1 and pKa2 are 6.2 and 8.59, respectively [59]

1.9.5 Partition Coefficient

The (n-Octanol/pH 7.0 buffered solution) partition coefficient (log P) of (CF-HCl) was reported to be 1.45 at 37˚C [60].

1.9.6 Solubility

(CF-HCl) as a salt is sparingly soluble in water, slightly soluble in methanol, very slightly soluble in ethanol, practically insoluble in acetone, ethyl acetate and

methylene chloride [60]. As other fluoroquinolone compounds, ciprofloxacin base exhibits a ''U'' shaped pH-solubility profile, with high solubility at pH values below 5 and above 10, and minimum solubility near the isoelectric point. [61].

Data on solubility, oral absorption, and permeability conclusively show ciprofloxacin to be BCS Class IV. [62]

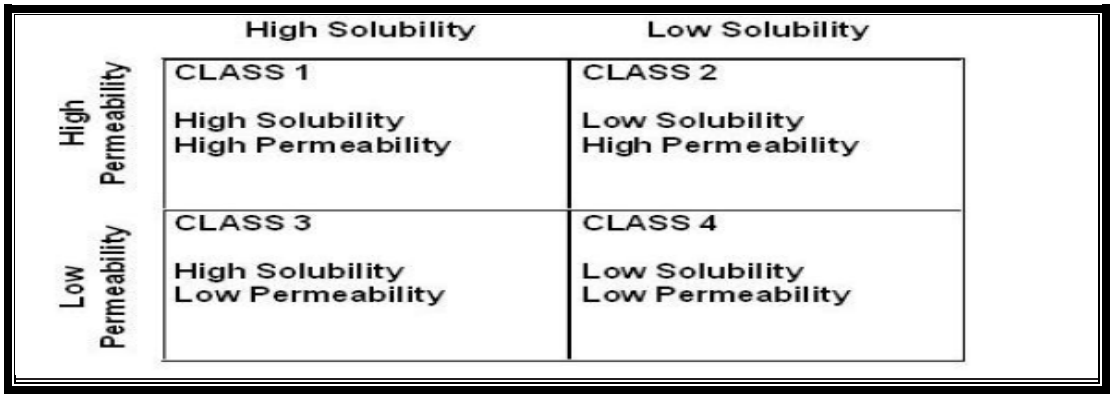


Figure (1-9): Biopharmaceutical solubility classification system [63, 64]

1.9.7 Pharmacokinetics

When (CF-HCl) administered over one hour as an intravenous infusion, it is rapidly distributes into the tissues, with levels in some tissues exceeding those in the serum. Penetration into the central nervous system is relatively modest, with cerebrospinal fluid levels normally less than 10% of peak serum concentrations [65]. The serum half-life of (CF-HCl) is about 4–6 hours, with 50-70% of an administered dose being excreted in the urine as an un-metabolized drug. An additional 10% is excreted in urine as metabolites. Urinary excretion is virtually completed within 24

hours after administration. Dose adjustment is required in the elderly and in those with renal impairment.

(CF-HCl) is about 70% orally available, so a slightly higher dose is needed to achieve the same exposure when switching from I.V. to oral administration [66].

1.9.9 Bacterial Resistance to Ciprofloxacin

There were two basic strategies that bacteria could adopt to circumvent the action of quinolones. The first strategy is alterations in DNA Gyrase (the target of the quinolones) [67] and the second strategy is mutations that lead to reduced access of quinolones to DNA Gyrase [68] ,the mutation strategy involves either efflux system, which is found in both Gram-positive and Gram-negative bacteria, or alterations in the outer membranes of Gram-negative bacteria. A study shows a graphical representation of resistance pattern of clinical isolates against Ciprofloxacin; figure (1-10) [69]

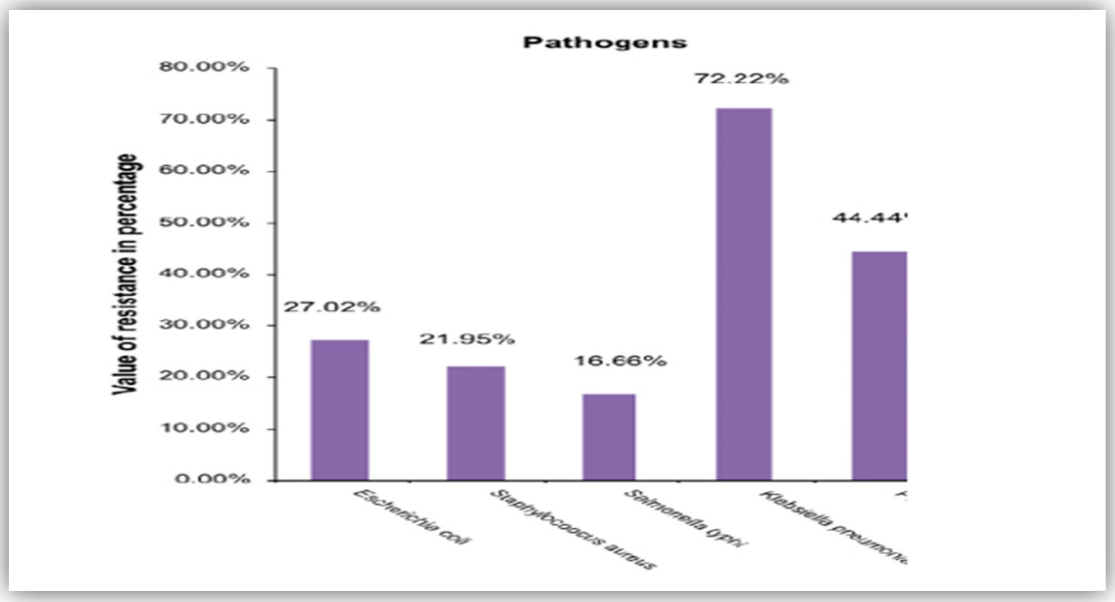


Figure (1-10): Resistance pattern of clinical isolates microorganism against ciprofloxacin [70].

1.9.10 Ciprofloxacin HCl Dosage Forms

Ciprofloxacin available as tablets in a 250 mg ,500 mg or 750 mg, suspension available 250 mg /5ml , intravenous infusion (as lactate) 2mg/ml in sodium chloride 0.9%.Also its marketed as eye drop and otic drop in 0.3% w/v. Eye ointment is available as 0.3% w/v of ciprofloxacin HCl. In addition, it is supplied as cream available in 0.5% w/w of ciprofloxacin HCl, otic ointment in combination with ketoconazole and triamicn and 0.227% w/w of ciprofloxacin.

1.10 Structural Modifications of Medicinal

Several natural and synthetic medicinal exert their biological activity at different potencies. Rational medicinal modifications on medicinal can improve its physicochemical properties, which in turn it is pharmacological, and biopharmaceutical characters. Numerous investigations needed including studying structure-activity relationship of medicinal and also to design rational modification position on its chemical skeleton, which includes the preparation of numerous derivatives and study their effectiveness and choose the most effective with least collateral side effects

Among structural modifications the concept of drug was introduced which signify pharmacologically inactive chemical derivatives that could be used to alter the physicochemical properties of drugs, in a temporary manner, to increase their usefulness or to decrease their toxicity. [71] Figure (1-11) shows a simplified representative illustration of the dervative concept.

The chemically modified versions of the pharmacologically active agent (pro-drug) must undergo transformation *in vivo* to release the active drug .Dervative system is an important strategy to improve the physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically potent compounds, and thereby increase the development ability and usefulness of a potential drug [72]. For example, derivatives provide possibilities to overcome various barriers to drug formulation and delivery such as poor aqueous solubility, chemical instability, insufficient oral absorption, rapid pre-systemic metabolism and prolonged action. Other benefits it aids in overcoming inadequate brain penetration, toxicity and local irritation .finally, derivatives can also improve drug targeting [73].

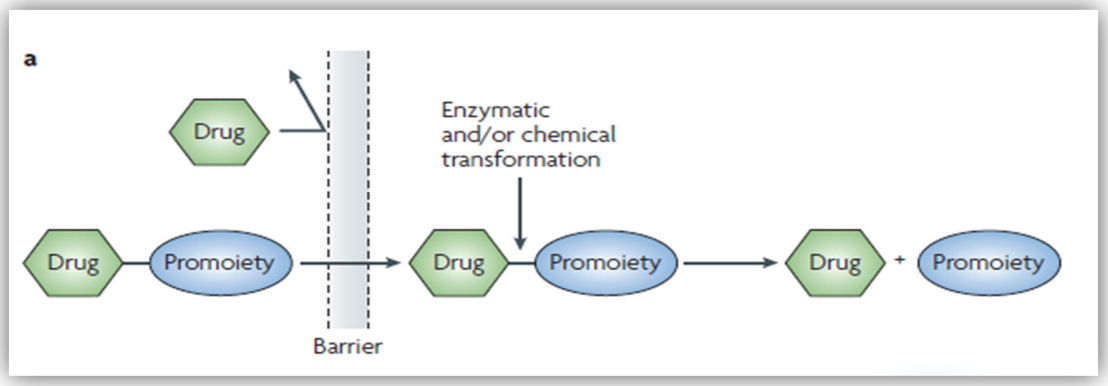


Figure (1-11): A Simplified representative illustration of the derivative concept (73).

1.10.1 Functional Groups Responsive to Derivative Design

The most common functional groups that are amenable to derivative design are carboxyl, hydroxyl, amine, phosphate and carbonyl groups [74]. Dervatives typically produced via the reaction and modification of these groups presented in the active constituent and includes the formation of esters, carbonates, carbamates, amides, phosphates and oximes. [75]. The dervative structures for the most common functionalities are illustrated in figure 1-12 and discussed below.

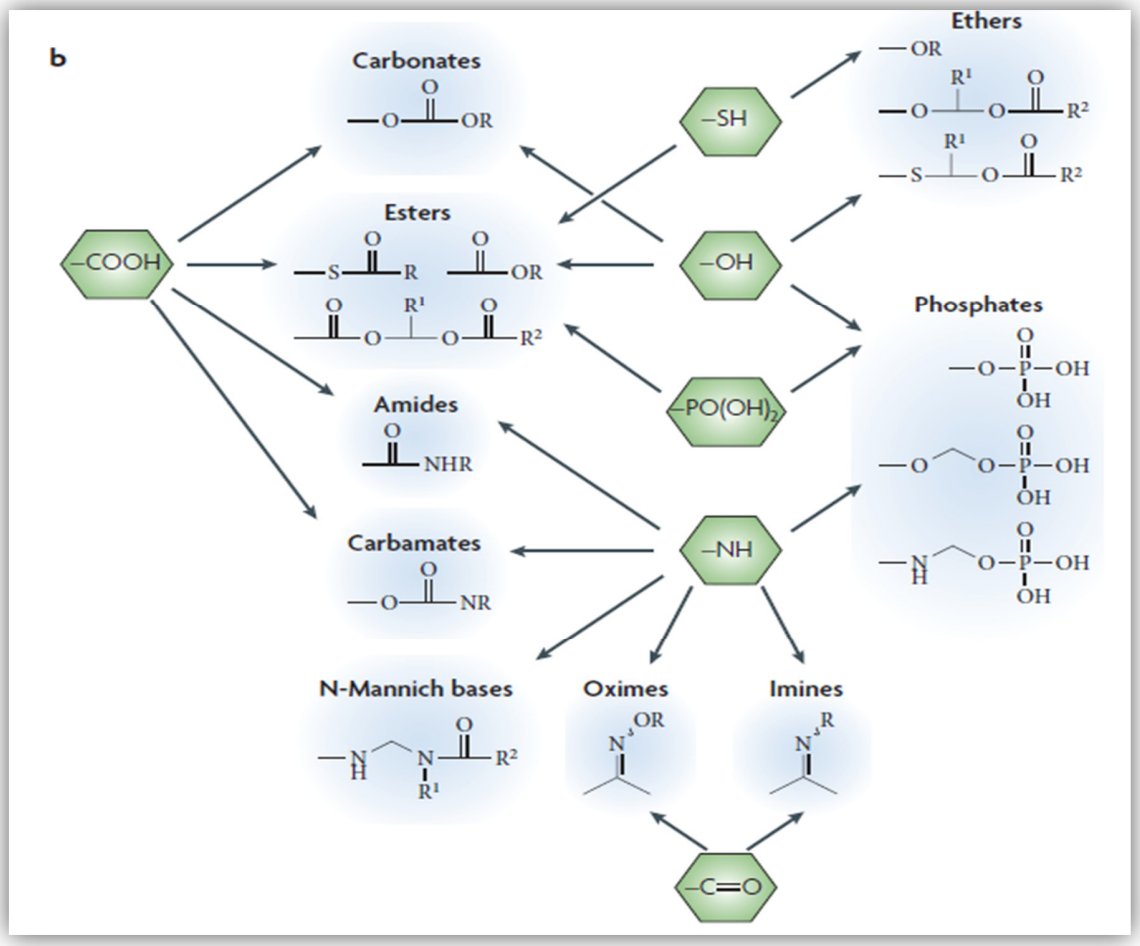


Figure (1-12): Common functional groups on parent drugs that is flexible to derivative design (shown in green) [(77)].

1.10.1.1 Esters as derivatives of Carboxyl, Hydroxyl and Thiol Functionalities

Esters are the most common derivatives used. It is estimated that approximately 50% of ester derivatives are activated by enzymatic hydrolysis while others are chemically hydrolyzed [(78)]. Ester derivatives are most often used to enhance the lipophilicity, and thus enhances the passive membrane permeability, of water-soluble drugs by masking charged groups such as carboxylic acids and phosphates [(79)].

1.10.1.2 Phosphate Esters as Derivatives of Hydroxyl or Amine Functionalities

Phosphate ester derivatives are typically designed for hydroxyl and amine functionalities of poorly water-soluble drugs [80]. The main purpose was to enhance their aqueous solubility thus to allow a more favorable oral or parenteral administration of phosphate derivatives [81].

1.10.1.3 Carbonates as Derivatives of Carboxyl with Hydroxyl

Carbonates differ from esters by the presence of an oxygen or nitrogen on both sides of the carbonyl carbon. Carbonates are derivatives of carboxylic acids and alcohols. The bioconversion of many carbonate derivatives requires esterase for the formation of the parent drug. However, they are often enzymatically more stable than the corresponding esters but are more susceptible to hydrolysis than amides. [82]

1.10.1.4 Amides as Derivatives of Carboxylic Acids and Amines

Amides are derivatives of amine and carboxyl functionalities of a molecule. In derivative design, amides are characterized by their relatively high enzymatic stability *in vivo* [83]. An amide bond is usually hydrolyzed by ever-present carboxyl esterase's, peptidases or proteases . Amides are often designed for enhanced oral absorption by manufacturing substrates of specific intestinal uptake transporters [84]

1.11 Examples of Chemical Substances Used as Conjugation Moieties in Derivative Synthesize:

1.11.1 Glycine

Glycine is the simplest amino acid; its side chain consists of just a single hydrogen atom. It is an abundant amino acid and is not considered essential. Supplementation with glycine, however, has been shown to support healthy kidney and liver function as well as nervous system health [85].The structure of glycine is shown in figure (1-13).

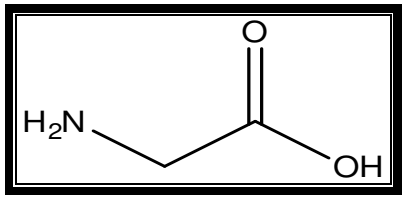


Figure (1-13): Chemical structure of glycine

1.11.2 Chitosan

Is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine.The molecular weight of commercially produced chitosan is between 3800 and 20,000 Daltons. Chitosan exhibits excellent biological and economical properties for drug delivery systems [86]. It is non-toxic, biocompatible, and biodegradable and the source of its precursor, chitin is renewable, widely available material. Moreover, chitosan itself possesses bioactivity, such as antioxidant and antibacterial activities. [87]

It has mucoadhesive moreover, chitosan showed to have a good hepatoprotective activity. It may be useful in bandages to reduce bleeding it can also be used to help deliver drugs through the skin. More controversially, chitosan has

been asserted to have use in limiting fat absorption, which would make it useful for dieting, but recently there is evidence against this recently, water - soluble O - carboxymethyl and N-succinylchitosan derivatives attracted attention as biodegradable drug carriers in antibacterial and anticancer therapy [88]. Figure (1-14) shows the chemical structure of chitosan.

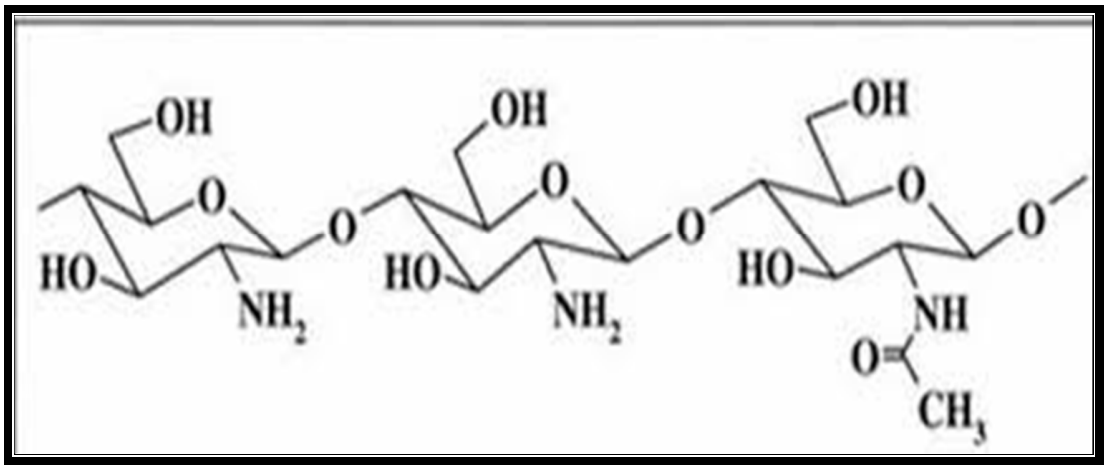


Figure (1-14): Chemical structure of chitosan.

1.12Literature Review on Experiments on Preparation of Ciprofloxacin Conjugates

Several researches studied structural modification of (CF-HCl) as derivative aiming to increase its pharmacological activity, imitated its bacterial resistance besides getting specialized dosage forms

Dong Choa, [89] and his coworkers prepared antibacterial-modified cellulose fiber by covalently bonding β-cyclodextrin (β-CD) with cellulose fiber via citric acid as crosslinking agent, followed by the inclusion of ciprofloxacin hydrochloride ((CF-HCl)) as antibiotic. They found that the loading amount of (CF-HCl) into grafted cellulose fibers increased remarkably, and the release of (CF-HCl) from the grafted cellulose fibers was prolonged. Considerably longer bacterial activity against *Escherichia* coli and *Staphylococcus aureus* was observed for grafted fibers loading (CF-HCl) compared to virgin ones.

In another study, successful synthesis of ZnO nanoparticles under microwave assisted condition followed by functionalization with ciprofloxacin, using EDC/NHS chemistry. Where EDC (1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide) is a zero-length crosslinking agent used to couple carboxyl or phosphate groups to primary amines and in order to increase the stability of this active ester, N-hydroxysuccinimide (NHS) is used . Successful conjugation of ciprofloxacin was detected by FTIR spectra. Ciprofloxacin-conjugated ZnO nanoparticles (ZN-CIP) exhibited an excellent antibacterial activity against clinically isolated multidrug resistant bacterial strains of Escherichia coli; Staphylococcus aureus and Klebsiella sp. (ZN-CIP) were small with particle size distribution of 18–20 nm as obtained from transmission electron microscope . A concentration of 10 µg/mL of ZN-CIP was a standard concentration. During evaluation of minimum

inhibitory concentration (MIC) values, similar concentration of antibiotic was incapable of producing such antibacterial activity [90]

Likewise. Novaca [91] ,and his colleagues success in the synthesis and characterization of gellan gum derivatives containing quaternary ammonium groups, with the purpose of obtaining particulate controlled release systems for ciprofloxacin. Degree of quaternization was determined by 1H NMR spectroscopy. *In vitro* transdermal release tests of ciprofloxacin from loaded particles were carried out on rat skin in isotonic phosphate buffer solution (pH = 7.43). Ciprofloxacin was released up to 24 h, confirming quaternized gellan–chitosan particles' potential as controlled release systems for topical dermal applications.

A novel method was developed and optimized to measure the in vitro release of two liposomal ciprofloxacin formulations under development to treat lung infection. The release agent, bovine serum, has components that interact with liposomes to cause the encapsulated drug to be released. The precision and accuracy of the method were characterized. The method has a nearly linear release phase initially, which then approaches a plateau value after 2-4 h. The method success in producing (CF-HCl) liposomes of preferable release properties and maximum stability over extended time of storage temperatures at buffered pH. [92]

Another study was designed for synthesis of a series of novel ciprofloxacin derivatives with remarkable improvement in lipophilicity by introducing a substituted benzyl moiety to the N atom on the C-7 of (CF-HCl). Ant mycobacterial and antibacterial activity of the newly synthesized compounds was evaluated. Results revealed that the synthesized compound has good *in vitro* activity against all of the tested gram-positive strains (MICs: 0.06–32 μg/mL) which is two to eightfold more potent than or comparable to the parent drug (CF-HCl) (MICs: 0.25–128

μg/mL).For gram-negative bacteria P. aeruginosa (MICs: 0.5–4 μg/mL) and M. tuberculosis (MIC: 1 μg/mL). [93]

Aim of the Study

The main objectives of this study are:

1-To develop and evaluate a sustained release topical emulgel drug delivery system of (CF-HCl) using different types of gelling polymers (CMC, SCMC and Carbopol 940) in addition to liquid paraffin or coconut oil as oil phase of the emulsion.

2- Improve the pharmaceuticals and microbiological properties of (CF-HCl) through synthesis of new (CF-HCl) derivatives .Then incorporation of these derivatives in the optimum selected emulgel formula.

Chapter Two

Experimental Work

2. Experimental

2.1 Materials

The materials used in this study and their manufacturers are listed in table (2-1).

Table (2-1) Materials Used in This Study

Material	Supplier
Ciprofloxacin HCl	MSN pharmachem .(India)
Carbapol 940	Hi-media. (India)
Carboxy methyl cellulose Low density	Hi-media. (India)
Chitosan (medium molecular weight)	Hi-media. (India)
Chloroform	BDH.(UK)
Citric acid	Thomas Beaker. (India)
Coconut oil	Thomas Beaker.(India)
Diethyl amine	BDH.(UK)
Dioxane	Thomas Beaker.(India)
Ethanol (99.8%) absolute	Scharlab. (Spain)
Glycine	Fluka AG.(Switzerland)
Lactic acid	Mscclesfield, Cheshire.(UK)
Liquid paraffin	Hi-media .(India)
Methanol	BDH.(UK)
Methyl paraben	Hi-media .(India)

Potassium di hydrogen orhto phosphate	Thomas Beaker. (India)
Propyl paraben	Hi-media. (India)
Propylene glycol	Mscclesfield, Cheshire. (UK)
Silica gel F254 aluminum sheets	Merck.(Germany)
Sodium carboxy methyl cellulose High density	Hi-media. (India)
Span 20	Carlo Erba. (Spain)
Thionyl chloride	Fluka AG.(Switzerland)
Toluene	BDH.(UK)
Triethanolamine	Cheshire. (UK)
Triethylamine	(BDH.(UK
Tween20	Carlo Erba. (Spain)

2.2 Instruments

The instruments used in this study and their manufacturers are listed in table (2-2).

Table (2-2) Instruments Used in This Study

Instrument	Manufacturer
Brookfield viscometer	Sanjay biotech solutions (DV-II +) , (Germany)
Electrical melting point apparatus	Stuart.(England)
Electronic Balance	Denever instrument,(Japan)
Fourier Transform Infrared System (FT-IR)	Shimadzu FTIR 8000.(Japan)
Hot plate Magnetic stirrer	Coply Scientific.(U.K)
Oven	Memmert.(Germany)
pH Meter	Ohaus Corporation. (USA)
Ultrasonic Cleaner	Scientific labo. (Italy)
USP dissolution apparatus	Minhua pharmaceutical machinery CO. LTD. (India)

UV-Visible Spectrophotometer	Biotech Engineering management CO.LTD.(UK)

2.3 Methods

2.3.1Characterization of Ciprofloxacin HCl

2.3.1.1 Determination of Ciprofloxacin HCl Melting point

The melting point was determined by inserting a small quantity of the drug powder into a capillary tube. The tube was sealed from one side by flame, then put in Stuart electrical melting point [94]

2.3.1.2 Fourier Transform Infrared Spectroscopy (FTIR)

Sample of (CF-HCl) powder mixed with potassium bromide and pressed in the form of disc. The disc was analyzed by Shimatzu FTIR spectroscopy from (4000-400) cm^{-1}.

2.3.1.3 Determination of Ciprofloxacin HCl λ Max

10 mgs of (CF-HCl) was dissolved in 100ml of phosphate citrate buffer (pH 5.5), which is within the pH range of human skin. Until it is completely dissolve then diluted to reach 5µg/ml concentration and scanned with UV spectrophotometer from 200-400 nm and the result was recorded [94, 95].

2.3.2 Calibration Curve of Ciprofloxacin HCl

Calibration curves of (CF-HCl) in phosphate citrate buffer (pH 5.5) were constructed by preparing a series of dilute solutions with different concentrations of (CF-HCl) from stock solution containing 1mg/ml. The absorbance was then measured at the λ_{max} of the drug. The measured absorbances were plotted against the respective concentrations [95].

2.3.2.1 Determination of Ciprofloxacin HCl Solubility

The solubility of (CF-HCl) was estimated in phosphate citrate buffer (pH 5.5). An excess amount of the drug was putted in 50 ml volumetric flask. The flask shaken by sonicator for 30 min then kept for 24 hrs. at room temperature then filtered and diluted, the concentration of the filtrate was determined by analyzing the sample spectrophotometrically at the λ_{max} of the drug. [94]

2.4 Preparation of Ciprofloxacin HCl Emulgel formulas

Thirty-six emulgel formulas were prepared and each emulgel formula was prepared by mixing equal quantities of a gel and emulsion portions.

Preparation of the gel portion was done by dispersing and dissolving different amounts of polymers (SCMC, CMC, or Carbopol 940) within 50 ml of deionized water with constant stirring at a moderate speed and the system was heated until we have a homogenous gel base, then the gel was leaved to cool down and homogenization for 48 hrs**.** Triethanolamine was added as neutralizing agent to formulas containing CP 940 as gelling agent

The oil phase of the emulsion was prepared by mixing certain quantity of Span 20 with certain amounts of light liquid paraffin or coconut oil. While the aqueous phase of the emulsion was prepared by dissolving estimated quantity of Tween 20, Propylene glycol in appropriate volume of deionized water. Methyl paraben and propyl paraben as preservatives were added at 0.3% w/w and 0.1% w/w concentration in the final formulas respectively.

(CF-HCl) was dissolved in ethanol, Then incorporated in this aqueous portion of the emulsion. Both the oily and aqueous portions of the emulsion were separately heated to 70º- 80º C; then the oily phase was added to the aqueous phase gradually with continuous stirring until getting homogenous emulsion and then cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio to obtain the final emulgel product. [96]

Table (2-3) represent quantitative composition of all the prepared thirty-six (CF-HCl) emulgel formulas

Table (2-3) The Main Composition of (CF-HCl) Emulgel Formulas

Gelling agent			Emul /oil phase			Emulsifier		Emul /aqueous phase
Formula NO.	CF-) (HCl)(gm.)	SCMC (gm.)	CMC (gm.)	CP 940 (gm.)	Liquid Paraffin (gm.)	Coconut oil (gm.)	Span 20 (gm.)	Tween 20 (gm.)	DW (ml) Qs.
F1	0.5	0.75	-	-	6	-	2.5	1.5	100
F2	0.5	1	-	-	6	-	2.5	1.5	100
F3	0.5	1.25	-	-	6	-	2.5	1.5	100
F4	0.5	0.75	-	-	9	-	2.5	1.5	100
F5	0.5	1	-	-	9	-	2.5	1.5	100
F6	0.5	1.25	-	-	9	-	2.5	1.5	100
F7	0.5	-	0.75	-	6	-	2.5	1.5	100
F8	0.5	-	1	-	6	-	2.5	1.5	100
F9	0.5	-	1.25	-	6	-	2.5	1.5	100
F10	0.5	-	0.75	-	9	-	2.5	1.5	100
F11	0.5	-	1	-	9	-	2.5	1.5	100
F12	0.5	-	1.25	-	9	-	2.5	1.5	100
F13	0.5	-	-	0.25	6	-	2.5	1.5	100
F14	0.5	-	-	0.5	6	-	2.5	1.5	100
F15	0.5	-	-	0.75	6	-	2.5	1.5	100
F16	0.5	-	-	0.25	9	-	2.5	1.5	100
F17	0.5		-	0.5	9	-	2.5	1.5	100
F18	0.5		-	0.75	9	-	2.5	1.5	100
F19	0.5	0.75	-	-	-	6	2.5	1.5	100
F20	0.5	1	-	-	-	6	2.5	1.5	100
F21	0.5	1.25	-	-	-	6	2.5	1.5	100
F22	0.5	0.75	-	-	-	9	2.5	1.5	100
F23	0.5	1	-	-	-	9	2.5	1.5	100
F24	0.5	1.25	-	-	-	9	2.5	1.5	100
F25	0.5	-	0.75	-	-	6	2.5	1.5	100
F26	0.5	-	1	-	-	6	2.5	1.5	100
F27	0.5	-	1.25	-	-	6	2.5	1.5	100
F28	0.5	-	0.75	-	--	9	2.5	1.5	100
F29	0.5	-	1	-	-	9	2.5	1.5	100
F30	0.5	-	1.25	-	-	9	2.5	1.5	100
F31	0.5	-	-	0.25	-	6	2.5	1.5	100
F32	0.5	-	-	0.5	-	6	2.5	1.5	100
F33	0.5	-	-	0.75	-	6	2.5	1.5	100
F34	0.5	-	-	0.25	-	9	2.5	1.5	100

F35	**0.5**	**-**	**-**	**0.5**	**-**	**9**	**2.5**	**1.5**	**100**
F36	**0.5**	**-**	**-**	**0.75**	**-**	**9**	**2.5**	**1.5**	**100**

2.5 Evaluation of the Ciprofloxacin Emulgel

2.5.1 Physical Properties of the Emulgel

The prepared emulgel formulations were inspected visually for their color, Homogeneity, consistency, and phase separation. [97]

2.5.1.2 Measurement of pH

An emulgel solution prepared by dissolving 1gm of emulgel in 100 ml of deionized water and it was left for 2 hrs. Then pH of the prepared emulgel solution was measured using digital pH meter. The measurement of pH of each formulation was done in triplicate and average values were calculated [98].

2.5.3 Viscosity Measurements

The viscosity of different emulgel formulation was determined at 37 ºC using a Brookfield viscometer (Brookfield DV II+ viscometer). The samples were rotated using spindle 6 at 3, 5,10,20,30 50 and 100 rpm and the viscosities were measured. With 30 seconds between these successive speeds [99].

2.5.4 Drug Content Determination

One gram of emulgel was dissolved in 100 mls of phosphate citrate buffer (pH 5.5), filtered to obtain clear solution. The absorbance of the

solution is determined using UV spectrophotometer at (CF-HCl) λ_{max} (dilution is performed when needed). Concentration and drug content was determined by using the same standard plot. The drug content was determined using following formula [100,101].

Drug Content = (Concentration × Dilution Factor × Volume taken)

2.5.5 Dissolution Study

Three gm of emulgel samples (15 mg CF) were putted in a small glass beaker of 2.5 cm in diameter .Then the mouth of the beaker was covered with a filter paper, which was kept in place with rubber band. Then inverted then immersed to about 0.5-cm of surface of the dissolution media (500 ml) of phosphate citrate buffer (pH 5.5) that present in a dissolution jar of the dissolution apparatus with stirring rate of 50 rpm. The study was carried out at 37±0.5°C.Samples of 5 ml were withdrawn after (15, 30, 45, 60, 90, 120 and 180….720 minutes) and filtered through 0.45µm millipore filter and replaced with an equal volume of fresh buffer. The samples were analyzed spectrophotometrically at λ_{max} of the drug. [102]

2.5.6 Ex–vivo Bio-Adhesive Strength Measurement

Modified method was used for the measurement of bio adhesive strength. The apparatus consist of two-arm balance. Both the ends are tied to glass plates using strings. One side contains two glass plates. Other side contains single glass plate for keeping weight. The right and left pans were balanced by adding extra weight on the left hand pan. The balance was kept in this position for 5 minutes. Accurately was weighed 1 gm of emulgel, placed between these two slides containing feathers fresh chicken skin pieces, and extra weight from the left pan was removed to sandwich the

two pieces of glass and some pressure was applied to remove the presence of air.

The balance was kept in this position for 1 minutes. Weights were added slowly to the left hand pan until the two glass slides were detached from each other. The weight (gram force) required to detach the emulgel from the glass surface gave the measure of bio adhesive strength of the emulgel. The bioadhesive strength is calculated by using following: Bioadhesive Strength = Weight required (in gm.) / Area (cm2). [103, 104]

2.5.7 Kinetics of Drug Release

The cumulative amount of (CF-HCl) released from the selected formulas at sequential time intervals were fitted to zero order, first order kinetics, Higuchi and Korsmeyer–Peppas models to characterize drug release kinetics and propose a mechanism of drug release. [105]

A-Zero Order Kinetic

It describes the system in which the drug release rate is independent on its concentration i.e. a constant amount is released per unit time.

$$Q_t = Q_o - K_o t \quad \text{..... Eq (2-1)}$$

Where Q_t is the amount of drug remained unreleased in time t, and the Q_o is the total amount of drug in the sample and K_o is the zero order release constant. If the zero order drug release kinetic is obeyed, then a plot of ($Q_o - Q_t$) versus t will give a straight line with a slope of K_o and an intercept at zero. [106]

B-First order Kinetic

It describes the drug release from the systems in which the release rate is concentration dependent i.e a constant ratio is released per unit time.

$$\log Q_t = \log Q_o - k_1 t / 2.303 \quad \text{..... Eq (2-2)}$$

Where Q_t is the amount of drug remained unreleased in time t, Q_o is the initial amount of drug in the sample and k_1 is the first order release constant. If the first order drug release kinetic is obeyed, then a plot of log (Q_o- Q_t) i.e.Drug released versus t will give a straight line with a slope of (k_1 / 2.303) and an intercept at t = 0 of log Q_o

C-Higuchi Model

It describes the fraction of drug release from a matrix is proportional to square root of time.

$$\boldsymbol{Q_t / Q\infty = k_H t^{1/2}} \ldots\ldots\ldots\ldots \text{ Eq (2-3)}$$

Where $\boldsymbol{Q_t}$ and $\boldsymbol{Q\infty}$ are cumulative amounts of drug release at time t and infinite time respectively, and k_H is the higuchi dissolution constant that reflect formulation characteristics. If the higuchi model of drug release (i.e. Fickian diffusion) is obeyed, then a plot of $\boldsymbol{Q_t / Q\infty}$ versus $t^{1/2}$ will produced a straight line with slope of k_H .[107]

D-Korsmeyer-Peppas Model

The Korsmeyer-Peppas model law describes the drug release from the polymeric system in which the release deviates from fickian diffusion, as expressed in following equation:-

$$\boldsymbol{Q_t / Q\infty = K_{KP} t^{n}} \ldots\ldots\ldots\ldots \text{ Eq (2-4)}$$

$$\boldsymbol{\log [Q_t / Q\infty] = \log K_{KP} + n \log t} \ldots\ldots\ldots\ldots \text{ Eq (2-5)}$$

Where $\boldsymbol{Q_t}$ and $\boldsymbol{Q\infty}$ are cumulative amounts of drug release at time t and infinite time (i.e. fraction of drug release at time t), K_{KP} is the constant incorporating structural and geometrical characteristics of controlled release device, and **n** is a diffusional release exponent indicative of the mechanism of drug release. To characterize the release mechanism, the dissolution data [Q_t / $Q\infty$ < 0.6] are evaluated. A plot of log [Q_t / $Q\infty$] versus log t will be linear with slope of n and intercept gives the value of

log K_{KP}. Antilog of log K_{KP} gives the value of K_{KP}. Peppas used the **n** value in order to characterize different release mechanisms.

----When **n** = 0.5 indicates Fickian diffusion controlled drug release.

----While **n** = 1 mean erosion controlled drug release.

---- A value of **n** between 0.5 and 1 can be regarded as an indicator for the superposition of both phenomena (anomalous transport).[108,109]

------and a value of **n** higher than 1 indicating super case II transport. [110]

2.6 Selection of Optimum Formula

The prepared emulgel formulas were evaluated for their physical appearance, pH determination, in vitro drug release, skin irritation, and stability studies.

2.6.1Skin Irritation Test

This test was conducted to evaluate the irritancy of the prepared formulation on the intact skin of animals. The formulation containing the lowest effective strength was tested on three lab animals (rabbits) as follows: Each animal was kept in a different cage and supplied with fresh food and water during the test period (24 hours) prior to test, that the hair from the spine region was shaved to expose sufficient large test area. The test site was cleaned with surgical spirit, and then 5g from (CF-HCl) selected optimum formula and from the prepared CF-derivatives emulgel, dosage forms were applied to test area. The test site was observed for erythema and edema for 6, 12, 18 and 24 hours after application. [111]

2.6.2 Stability Studies

The selected optimum formula of the prepared emulgel formulas was subjected to accelerated stability studies at 30°C, 40°C and 50°C for a period of 3 months. Samples were withdrawn at 15-day time intervals. In addition, evaluated for physical appearance, pH, rheological properties and drug content. [112]

2.7 Synthesis and Characterization of CF-Derivatives

2.7.1 Synthesis of CF-Glycine Amide Derivative

(2 gm, 5.19 mmole)of ciprofloxacin was converted to its acyl chloride using (0.6 ml 8.2 mmole , excess) of Thionyl chloride, the mixture was heated about 2hr .the excess of Thionyl chloride was distilled off. Then a (0.389 gm., 5.19 mmole) of glycine which was dissolved in 5 ml of dioxane. with vigorously stirred about 2hr, the reaction mixture was heated at 40C° for 1hr.the final product was formed, washed with 5%of sodium bicarbonate solution, dried at 50C° under vacuum oven. [113]

2.7.2 Synthesis of CF-Chitosan Amide Derivative

To the ciprofloxacin acyl chloride, which was prepared according to the procedure mentioned in section (2.7.1), we added (2.735 g , 5.2 mmole) of chitosan which was dissolved in (5ml) of (1% v/v) of acetic acid. 5 mls of dioxane with 3ml of triethyl amine was added, and then the mixture was stirred for 2 hrs. with heat (50 °C) .We filtered to remove the triethyl ammonium salt. The solvent was evaporated and the final product was washed two times with 10 mL of diethyl ether, then dried in an oven at 50 °C. [113]

2.8 Statistical Analysis

Statistical analysis was done by using the student t- test. In addition, a powerful program named DDSolver was used for estimating drug dissolution/release similarity. The difference is statistically significant when ($P < 0.05$).

Chapter Three

Results and Discussion

3. Results and Discussion

3.1Characterization of Ciprofloxacin HCl

3.1.1 Melting Point

The measured melting point of (CF-HCl) was found to be 321˚C. This result is the same as reported in references, which indicates the purity of the drug powder used in the study [94, 95].

3.1.2 FTIR Study

The FTIR spectrum of (CF-HCl) is shown in figure (3-1). It showed that, functional group band frequencies of (CF-HCl) were in resemblance to the reported range of standard (CF-HCl) that authenticated that the obtained sample of (CF-HCl)was pure [93, 94].

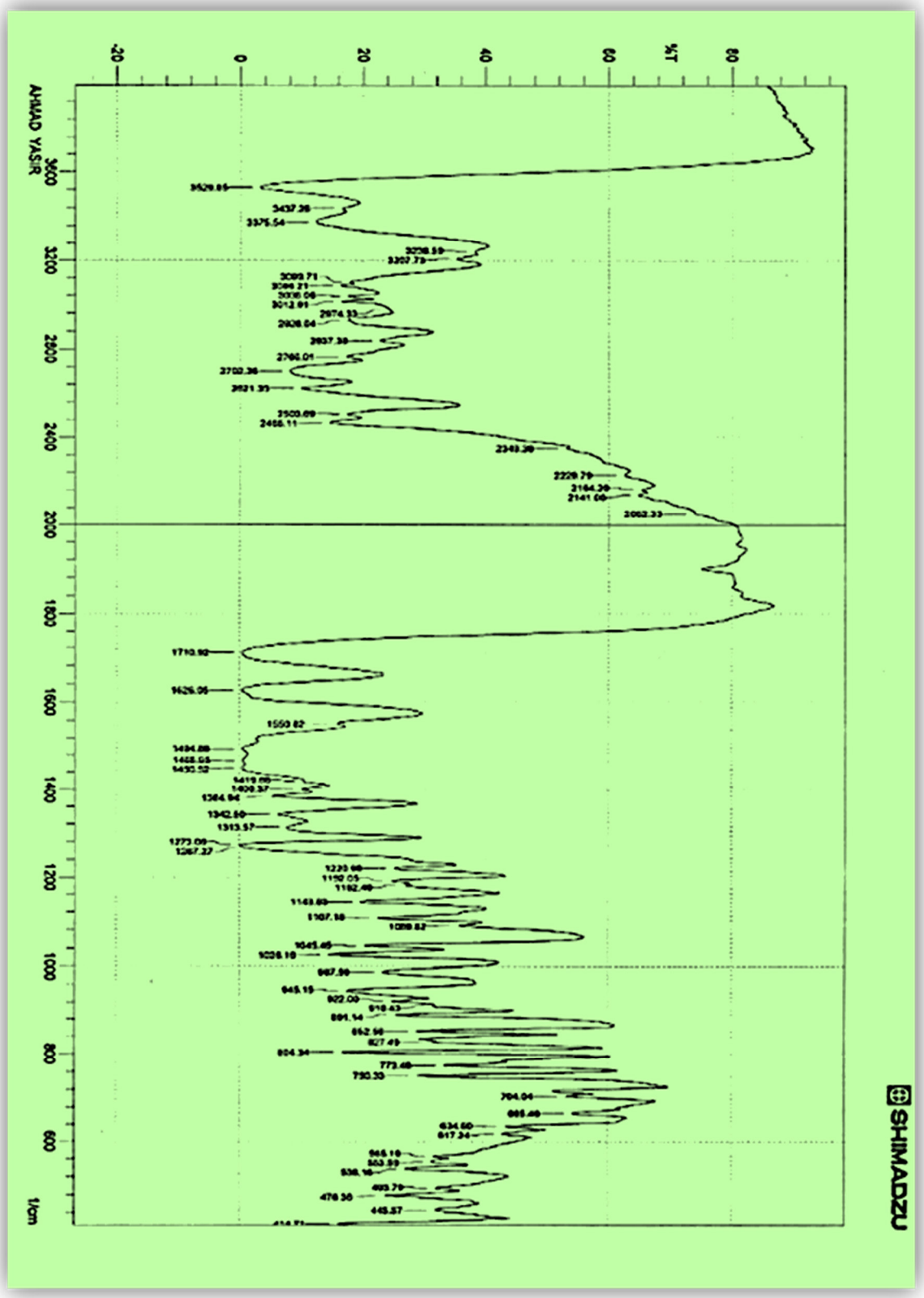


Figure (3-1): FTIR spectroscopy of CF

3.1.3 Determination of λ Max

Scanning of (CF-HCl)solution (5 µg/ml) in phosphate citrate buffer (pH 5.5) by UV spectrophotometer at 200-400 nm gave the spectrum shown in figure (3-2) .The maximum absorbance (λ max) found to be 278 nm, which is similar to standard references [94, 95]

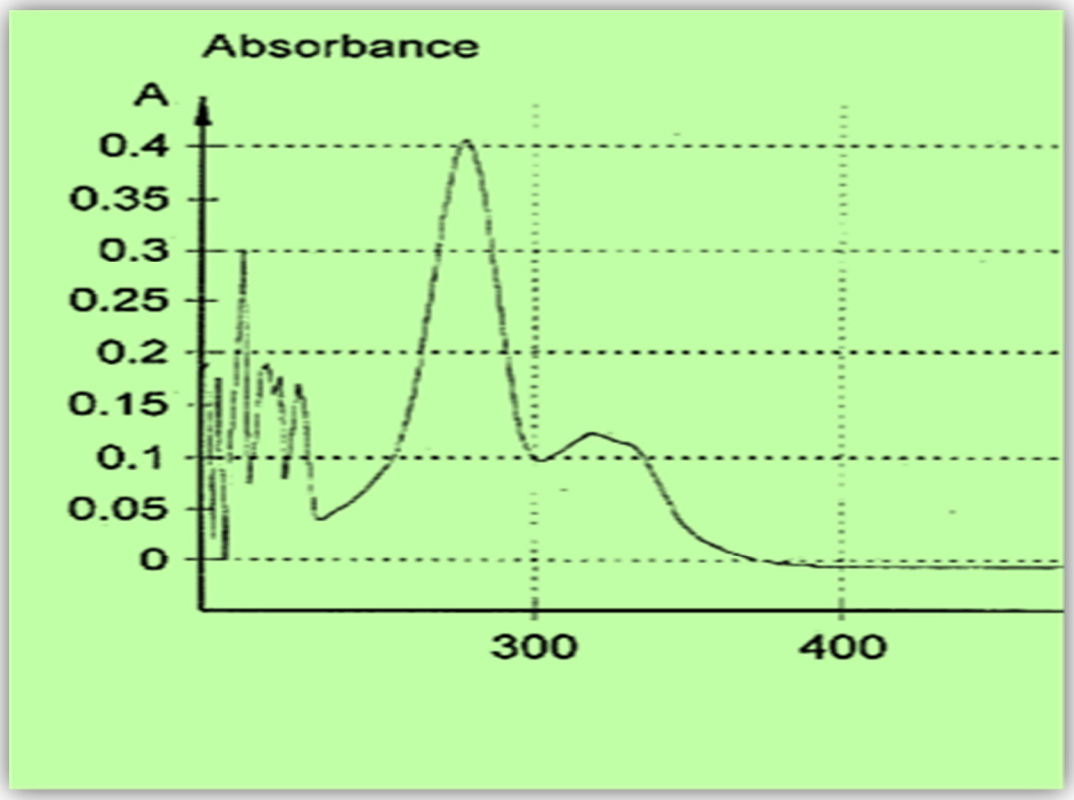


Figure (3-2): The UV Spectrum of (CF-HCl)in phosphate citrate buffer (pH 5.5)

3.2 Ciprofloxacin HCl Calibration Curve and Solubility Studies

Figure (3-3) shows the calibration curve of (CF-HCl)in phosphate citrate buffer (pH 5.5); a straight line was obtained by plotting the absorbance versus concentration. This indicates that the calibration curve within this range of concentration obeys Beer-Lamberts law at λ max 278 nm

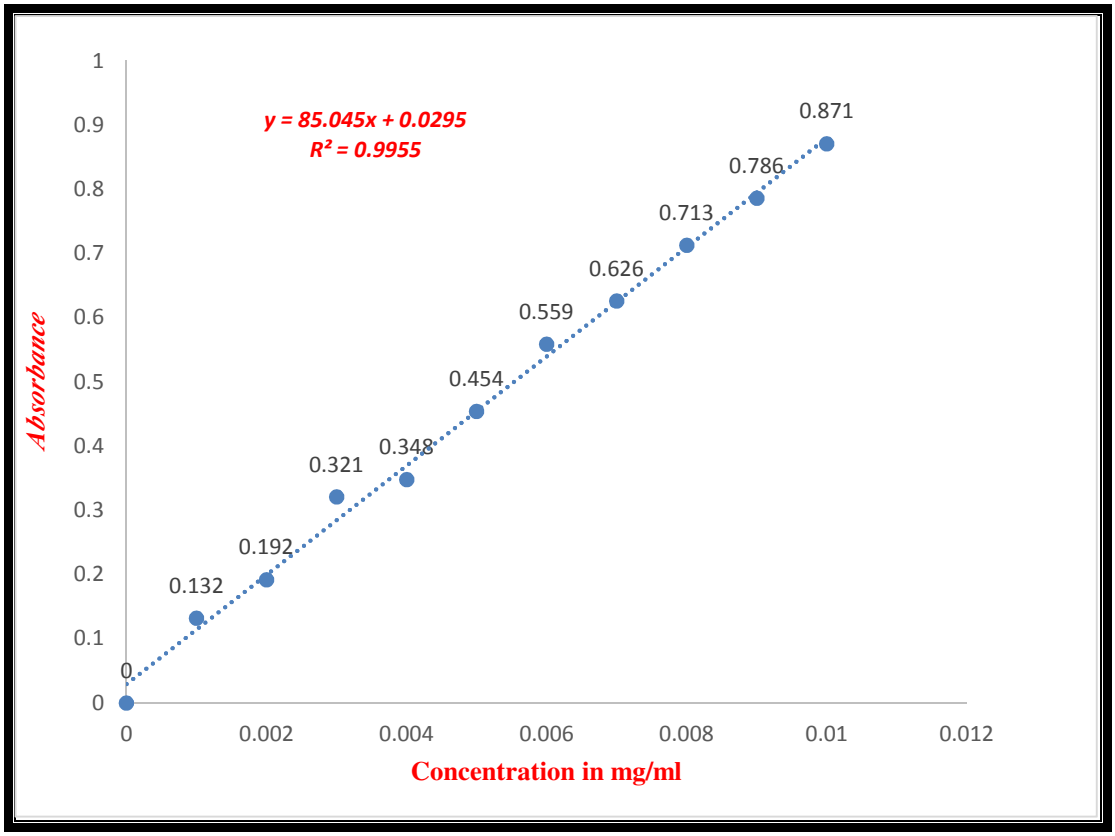


Figure (3-3): Calibration curve of (CF-HCl) in phosphate citrate buffer (pH 5.5) at 37ºC

Regarding the solubility of CF, saturated solubility of (CF-HCl) was calculated in phosphate citrate buffer (pH 5.5) at 37 ºC; and the maximum solubility found to be 0.176 mg/ml.

3.3 Evaluation of the prepared Ciprofloxacin HCl Emulgel Formulas

3.3.1 Physical properties and pH

Ciprofloxacin HCl emulgel formulas are prepared using CMC, or SCMC, or CP 940 as the polymers of the gel moiety and most of the prepared formulas found to be creamy white homogenous with smooth appearance, except the formulas containing CP 940 found to be light pink in color. The prepared formulas are easily distributed over skin. Their pH values ranged from 5.44 to 7.6, which are considered to be acceptable to avoid the risk of irritation upon application to the skin, since skin pH is about (5.5) [114].

The physical properties of the prepared emulgel formulas are shown in table (3-1)

Table (3-1): Physical Properties of Prepared (CF-HCl) Emulgel Formulas

Formula. No	Polymer%. Oil %	Color	Homogeneity and Consistency	pH
F1	SCMC 0.75 %.LP 6%	White	Excellent	5.5
F2	SCMC 1%.LP 6 %	White	Excellent	5.6
F3	SCMC1.25%.LP 6%	White	Excellent	5.6
F4	SCMC0.75%.LP 9%	White	Excellent	5.48
F5	SCMC 1%. LP 9%	White	Excellent	5.7
F6	SCMC 1.25%LP 9%	White	Excellent	5.93
F7	CMC0.75 %.LP 6%	White	Excellent	5.5
F8	CMC1%.LP 6%	White	Excellent	5.5
F9	CMC1.25%.LP 6%	White	Excellent	5.57
F10	CMC0.75%.LP 9%	White	Excellent	5.84
F11	CMC1 %.LP 9%	White	Excellent	5.7
F12	CMC1.25%.LP 9%	White	Excellent	5.9
F13	CP 940 0.25% LP 6%	Faint pink	Excellent	5.44

F14	**CP 940 0.5%.LP 6%**	**Faint pink**	**Excellent**	**5.45**
F15	**CP 940 0.75 %LP 6%**	**Faint pink**	**Excellent**	**5.44**
F16	**CP 940 0.25.% LP 9%**	**Faint pink**	**Excellent**	**6.9**
F17	**CP 940 0.5%.LP 9%**	**Faint pink**	**Excellent**	**7.55**
F18	**CP 940 0.75% .LP 9%**	**Faint pink**	**Excellent**	**7.6**
F19	**SCMC0.75% .CO 6%**	**White**	**Excellent**	**5.46**
F20	**SCMC1%. CO 6%**	**White**	**Excellent**	**5.88**
F21	**SCMC1.25% .CO 6%**	**White**	**Excellent**	**6.02**
F22	**SCMC 0.75%.CO 9%**	**White**	**Excellent**	**5.74**
F23	**SCMC 1%.CO 9 %**	**White**	**Excellent**	**5.87**
F24	**SCMC1.25%.CO 9%**	**White**	**Excellent**	**5.91**
F25	**CMC 0.75%.CO 6%**	**White**	**Excellent**	**5.74**
F26	**CMC 1%.CO 6%**	**White**	**Excellent**	**5.84**
F27	**CMC 1.25%.CO 6%**	**White**	**Excellent**	**6.10**
F28	**CMC 0.75%.CO 9%**	**White**	**Excellent**	**5.76**
F29	**CMC1 %. CO 9%**	**White**	**Excellent**	**5.94**

F30	**CMC1.25%.CO 9%**	**White**	**Excellent**	**5.86**
F31	**CP 940 0.25 %.CO 6 %**	**pink**	**Excellent**	**7.50**
F32	**CP 940 % 0.5%.CO6**	**pink**	**Excellent**	**7.55**
F33	**CP 940 0.75%.CO 6%**	**pink**	**Excellent**	**7.60**
F34	**CP 940 0.25%.CO 9%**	**pink**	**Excellent**	**7.1**
F35	**CP 940 0.5%.CO 9%**	**pink**	**Excellent**	**7.4**
F36	**CP 940 0.75%.CO 9%**	**pink**	**Excellent**	**7.6**

3.3.2 Multi-Speed Viscosity Measurement

Figures (3-4) presents the viscosity of emulgel formulas (F1-F18) where the oil phase is liquid paraffin .Figure (3-5) presents the viscosity of emulgel formulas (F19-F36) where the oil phase is Coconut oil.

Statistically, the viscosity of formulas containing the gelling agent CP 940 was significantly higher than that containing SCMC and CMC, ($P < 0.05$) and this was found in all in both liquid paraffin and Coconut oil as an oil phase.

The maximum viscosity was observed in F18, that contains CP 940 (0.75 %) and LP (9 %) , this could be explained by the higher molecular weight of the CP 940 in comparison with the other two polymer and also refer to the addition of the neutralizing agent Triethanolamine in CP 940 formulas . The second higher viscosity values was obtained with the formulas containing SCMC and then CMC respectively [115].

In gel systems, consistency depends on the ratio of solid fraction, which produces structure, to liquid fraction. [116] The profiles showed that as the share stress increased, the normally arranged molecules align their long axes in direction of flow orientation reduce the internal resistance of material and hence decrease viscosity [117].The results showed that within each type of polymer the viscosity increased as the concentration of polymer increased.

Most of the prepared formulations are of good acceptable rheological profile ranged mentioned in many literatures, which is 7100-83144 cps [118]. However, the attentiveness of viscosity increases with the understanding of the extent of increased viscosity on drug release retardation and stability of formulas prepared [119].

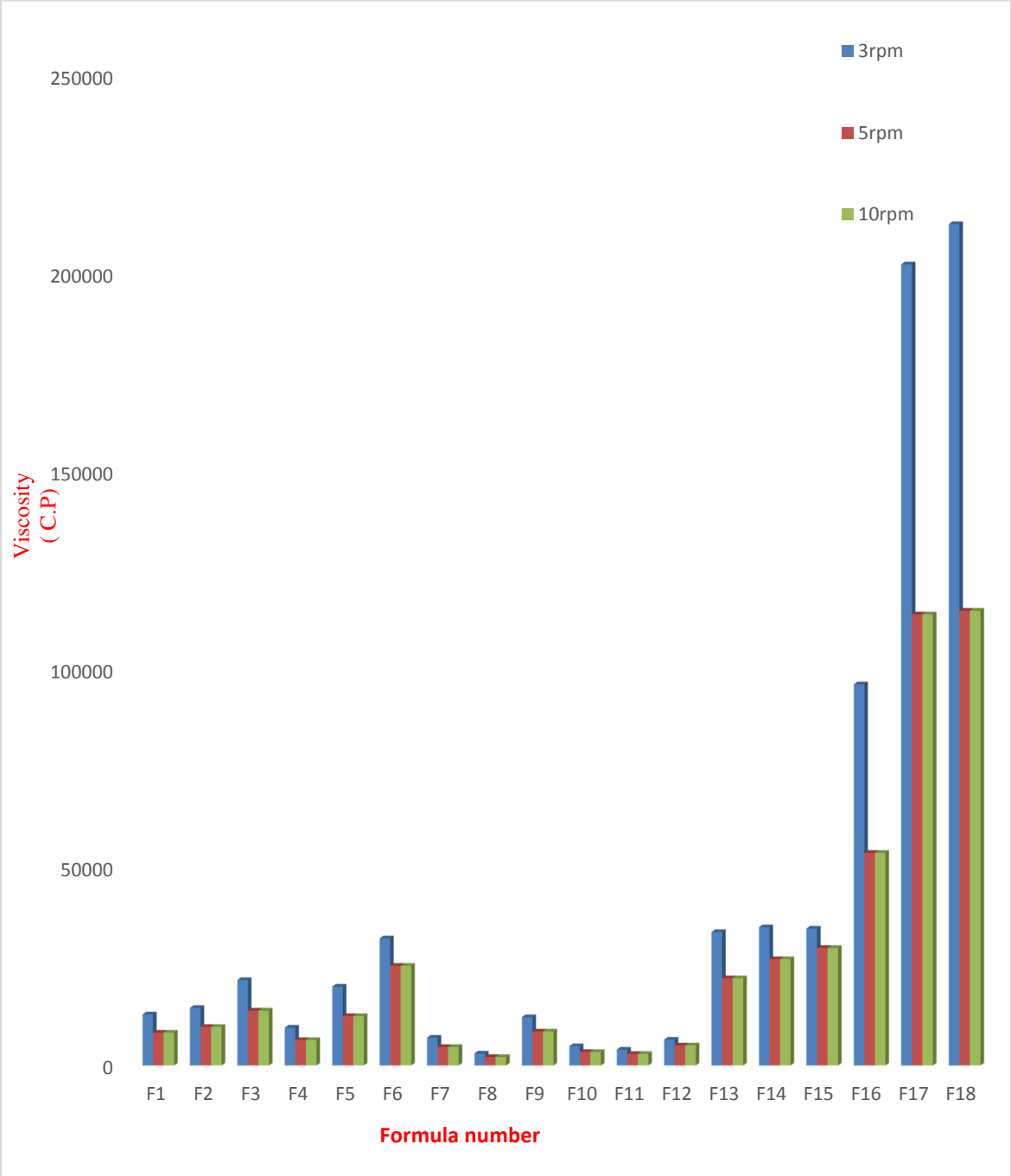


Figure (3-4): Emulgel formulas (F1-F18) viscosity (C.F) at 37 ˚C at different rotation per minute (rpm)

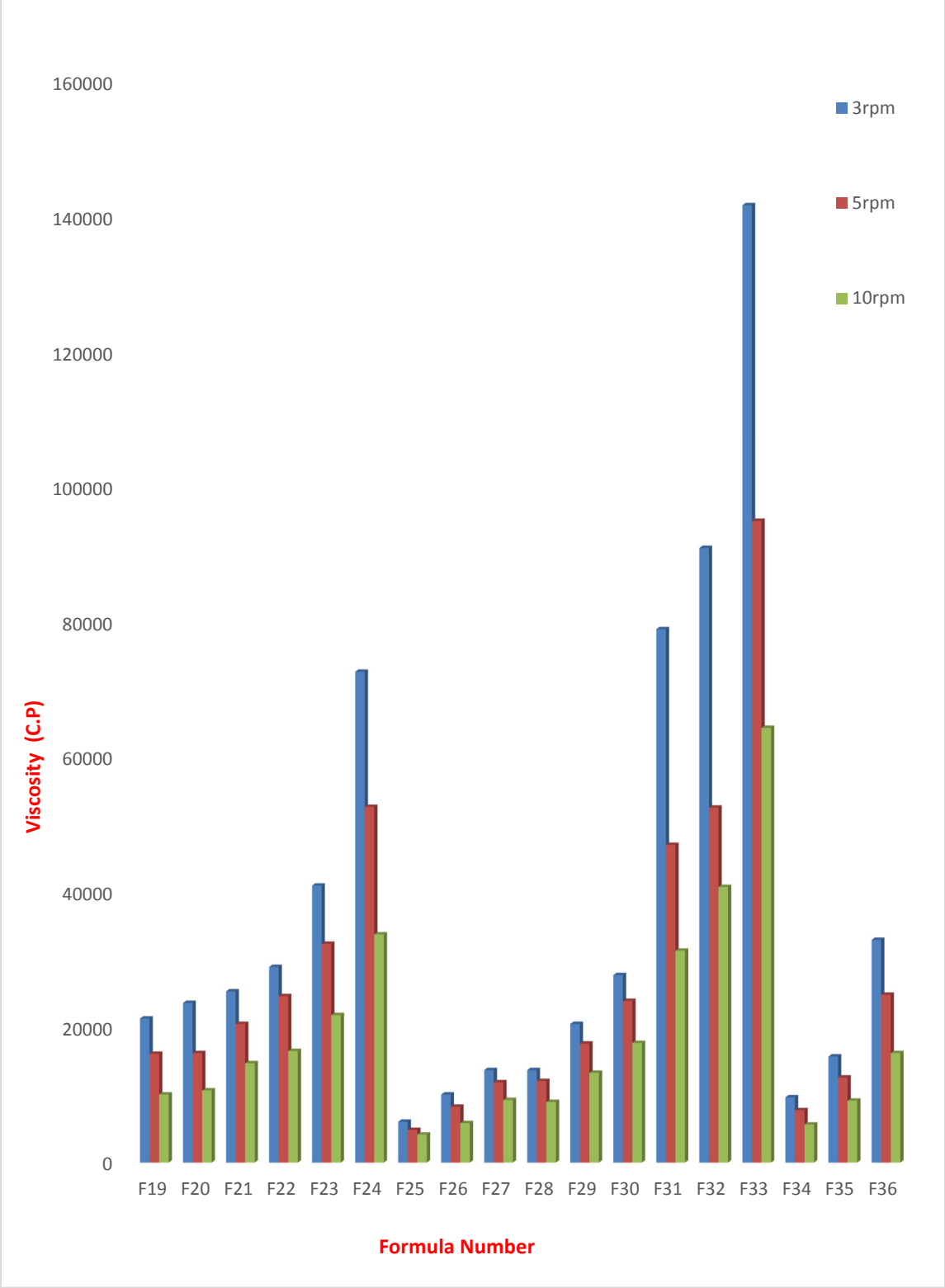


Figure (3-5): Emulgel formulas (F19-F36) viscosity (C.F) at 37 ˚C at different rotation per minute (rpm)

3.3.3 Drug content

The drug content of the formulated emulgel was estimated spectro photo metrically at 278 nm. The results were presented in figure (3-6) and they were within the official limits [120].

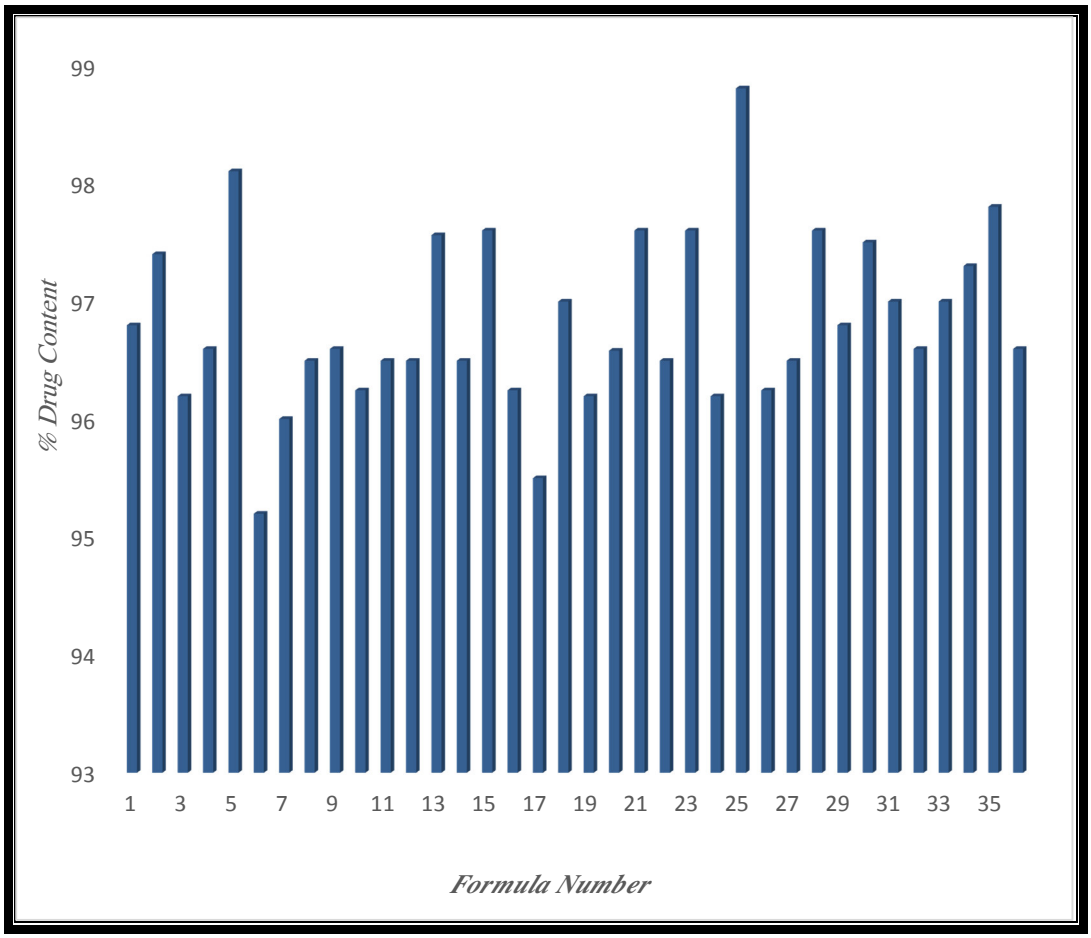


Figure (3-6): (CF-HCl) content (percentage) of formulas from (1-36)

3.3.4 InVitro Drug Release Profile

3.3.4.1 The Effect of the Gelling Agent Concentration on (CF-HCl) Release Profile

Figure (3-7) showed the release profiles of formulas, F1-F6 that prepared to study the effect of gelling agent concentration SCMC on drug release at 6 % and 9 % w/w concentration of liquid paraffin as the oil phase. We found that the sequence of magnitude of maximum % drug release at the end of the experiment is as follows F1 >F2 > F3 > F4 > F5 > F6 .The maximum percent of (CF-HCl)release within this group was with F1 which contains the smallest amount of the polymer SCMC (0.75 %) SCMC at the lower concentration of the oil phase LP (6 %) .Within this set of formulas the release percent of (CF-HCl) was decreased as the concentration of the gel base increased in both case of 6 % or 9 % oil phase concentration. The low concentration of the release retardant thickener (SCMC) accounts for the maximum release profile of (CF-HCl) from formula F1.

The same order for figure (3-8), that showed formulas F7-F12 which prepared to study the effect of gelling agent concentration CMC on drug release at 6 % , 9 % w/w liquid paraffin as an oil phase. The formulas can be arranged as follows: F7 > F8> F9> F10 >F11 >F12. The highest percent of release over 12 hr. was the formula with the lower concentration F7 (0.75) CMC at 6 % liquid paraffin as an oil phase and the release percent was always decreased when the concentration of the gel base increased in both case of 6 % or 9 % oil phase concentration.

Similarly, figure (3-9) showed formulas F13-F18 when three different concentrations of the gelling agent CP used at 6 % and 9 %w/w

LP as an oil phase. The highest percent of release over 12 hr. was also with the lowest polymer concentration formula F13 (0.25) CP 940 at 6 % liquid paraffin as an oil phase. The release percent also decreased when the concentration of the gel base increased in both cases of 6 % or 9 % oil phase concentration and the magnitude of total drug release at the end of experiment was as follows:F13 > F14 > F15 > F16 > F17 > F18.

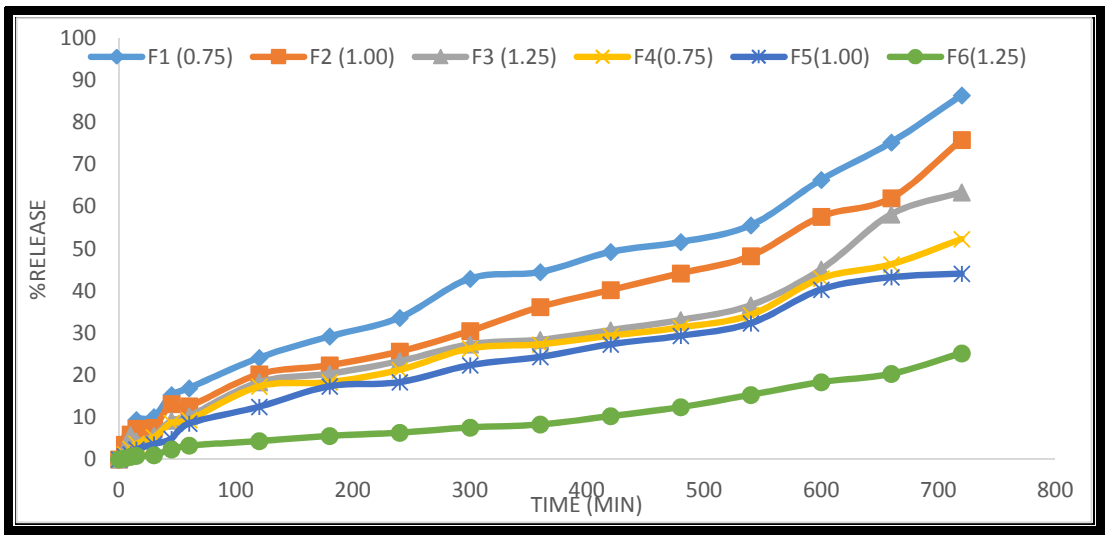


Figure (3-7): Release profile of (CF-HCl) at pH 5.5 and 37 ºC of formulas F1- F6 (SCMC is the gelling agent and LP is the oil phase)

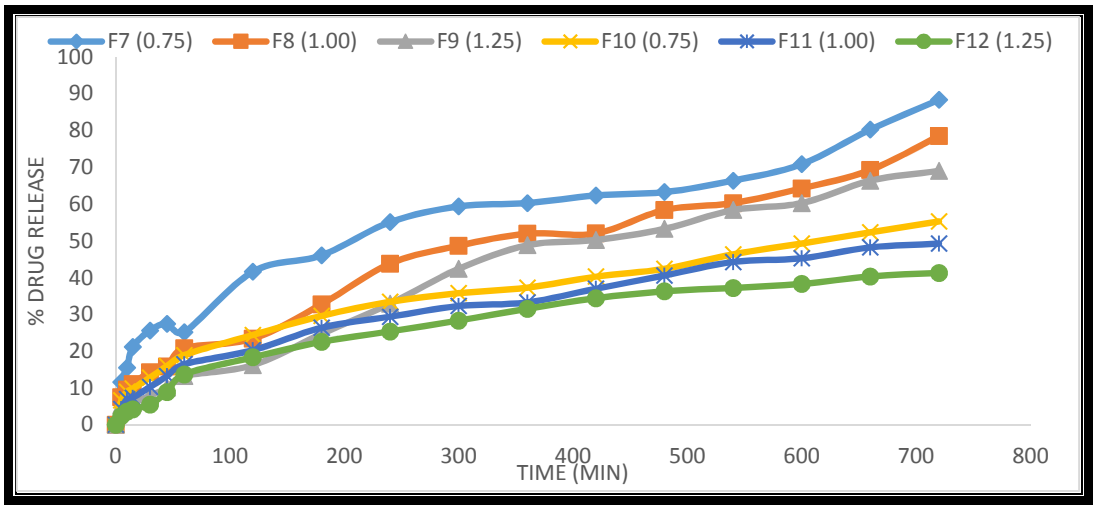


Figure (3-8): Release profile of (CF-HCl)at pH 5.5 and 37 ºC of formulas F7- F12 (CMC is the gelling agent and LP is the oil phase)

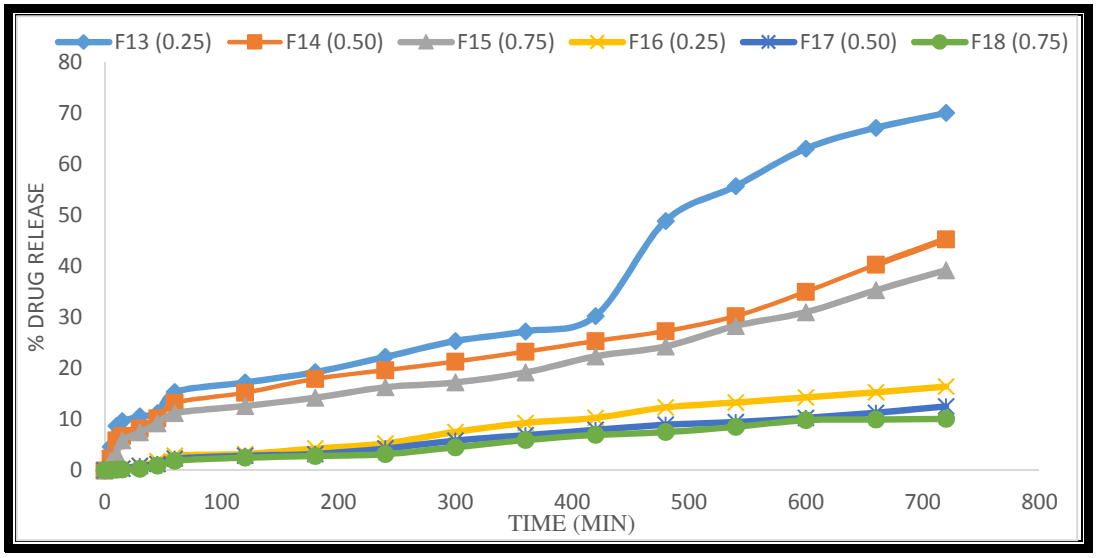


Figure (3-9): Release profile of (CF-HCl) at pH 5.5 and 37 ° C of formulas F13-F17, and F18 (CP940 is the gelling agent and LP is the oil phase)

Furthermore, figure (3-10) presents release profile of (CF-HCl) from formulas F19-F24 that prepared using SCMC at 6 % and 9 % Coconut oil as an oil phase. We can detect that the maximum release of (CF-HCl) at the end of experiment is with the following sequence F19 > F20 > F21 > F22 > F23 > F24 and that approximately similar to the result of liquid paraffin formulas. The formula with lowest concentration was F19 that contains the lowest concentration of the gelling agent SCMC (0.75 %) and 6 % Coconut oil. In addition, the release percent was decreased when the concentration of the gel base increased in both case of 6 % or 9 % Coconut oil concentration.

Figure (3-11) showed the release profile of (CF-HCl) from formulas F25-F30 that prepared using various concentrations of CMC at 6 % and 9 % w/w Coconut oil as oil phase. The following results of maximum release was obtained: F25 > F26 > F27 > F28 > F29 > F30.The highest percentage of release over 12 hours was obtained the formula of the lowest concentration of the polymer F25 (0.75 %) CMC at 6 % Coconut oil as an

oil phase and the release percent was similarly decreased when the concentration of the gel base increased in both cases of 6 % or 9 % oil phase concentration.

Finally, figure (3-12) showed the release profile of (CF-HCl)from formulas F31-F36 that was prepared using different concentration on drug release using CP 940 at 6 %, and 9 %w/w Coconut oil as oil phase. We found that, the following order of the formula F31> F32 > F33> F34 > F35 > F36, the highest percent of release over 12 hr. was also with the lowest concentration formula F31 (0.25) CP 940 at 6 % Coconut oil as an oil phase. The release percent was decreased when the concentration of the gel base increased in both cases of 6 % or 9 % oil phase concentration.

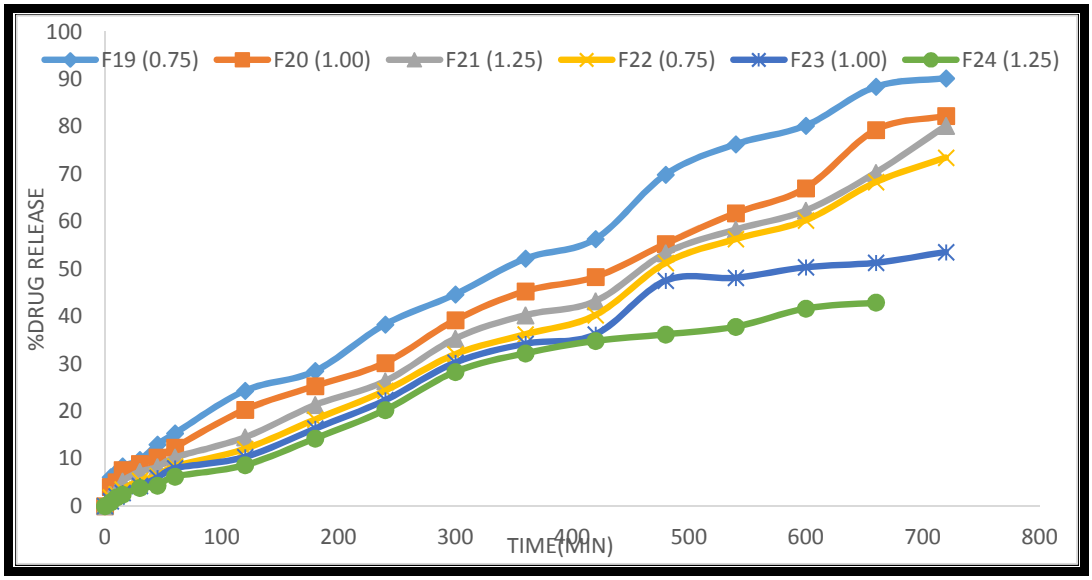


Figure (3-10): Release profile of (CF-HCl) at pH 5.5 and 37 °C of formulas F19- F24 (SCMC is the polymer and CO is the oil phase)

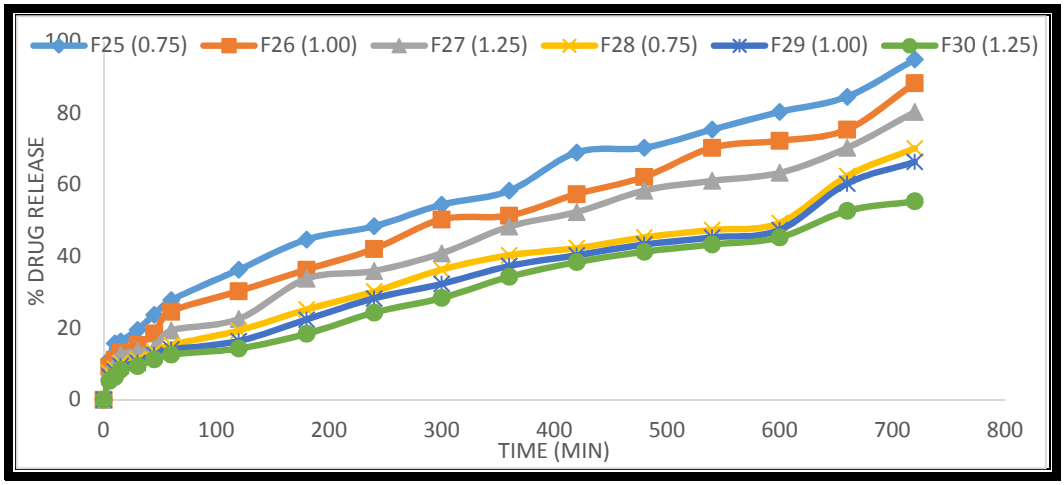


Figure (3-11): Release profile of (CF-HCl) at pH 5.5 and 37 ºC of formulas F25- F30 (CMC is the polymer and CO is the oil phase)

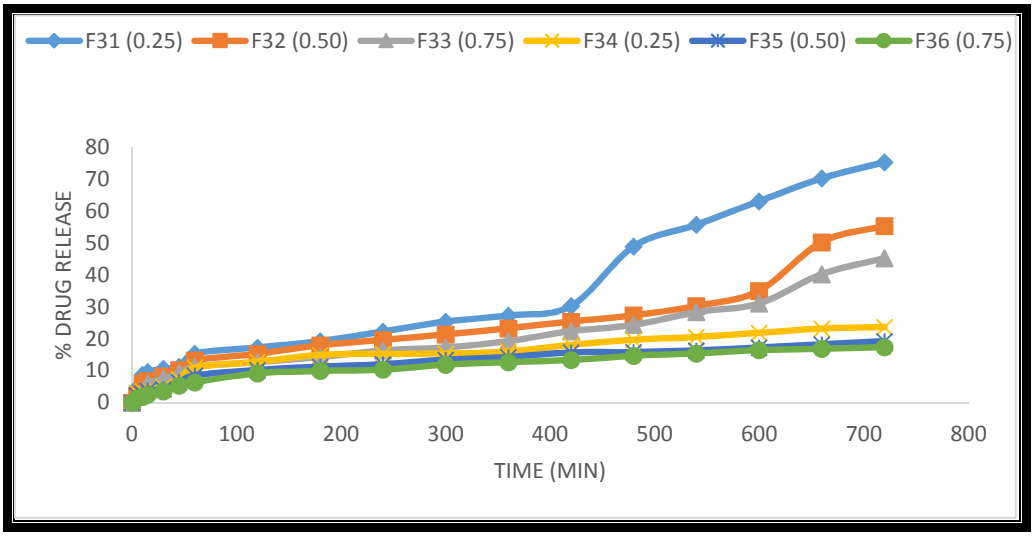


Figure (3-12): Release profile of (CF-HCl) at pH 5.5 and 37 ºC of formulas F31-F36 (CP 940 is the polymer and CO is the oil phase)

The higher concentration of gelling agents is always associated with increment in the viscosity that represent a mechanical barrier of drug release.

These results agreed with findings of several studies like that issued by Singla Vika .*etal*.[120]. and, Dignesh M.*et.al*[121].

All previous discussion have proved that in the group of formulas containing different concentrations of the same polymer we found that the largest drug release was clearly statistically significantly higher when the polymer concentration is lowest ($p < 0.05$)

3.3.4.2 The Effect of Oil Concentration on (CF-HCl) Release Profile

The effect of oil phase concentrations on drug release at constant concentrations of other variable are presented in figure (3-14).By comparing the opposite formulas that contain the same ingredients, except the concentration of oil phase we get the following results:

We observe the maximum release of (CF-HCl)from (F1 > F4), (F7 > F10), (F13 > F16), (F19 > F22), (F25 > F28), and (F31 > F34) finally release of (CF-HCl)was statistically significantly higher ($P < 0.05$) from formulas of 6 % w/w of the oil phase in comparison to that of formula of 9 % w/w oil phase when other variables is the same. These results were observed with both liquid paraffin and Coconut oil .These results may be explained according to the concept of escaping tendency of drugs [122].

It was suggested that according to the relative (hydrophobic-hydrophilic) characteristics of CF, the drug has an increased desire towards interaction with the oil phase. Therefore, with increasing the concentration of the oil the entrapment of the drug increased with subsequent reduction in drug release rate and extent [123]. These results agreed with El-Bary who proved that an increase in liquid paraffin concentration on chloramphenicol emulgel formulation lead to retardation of drug release [124].

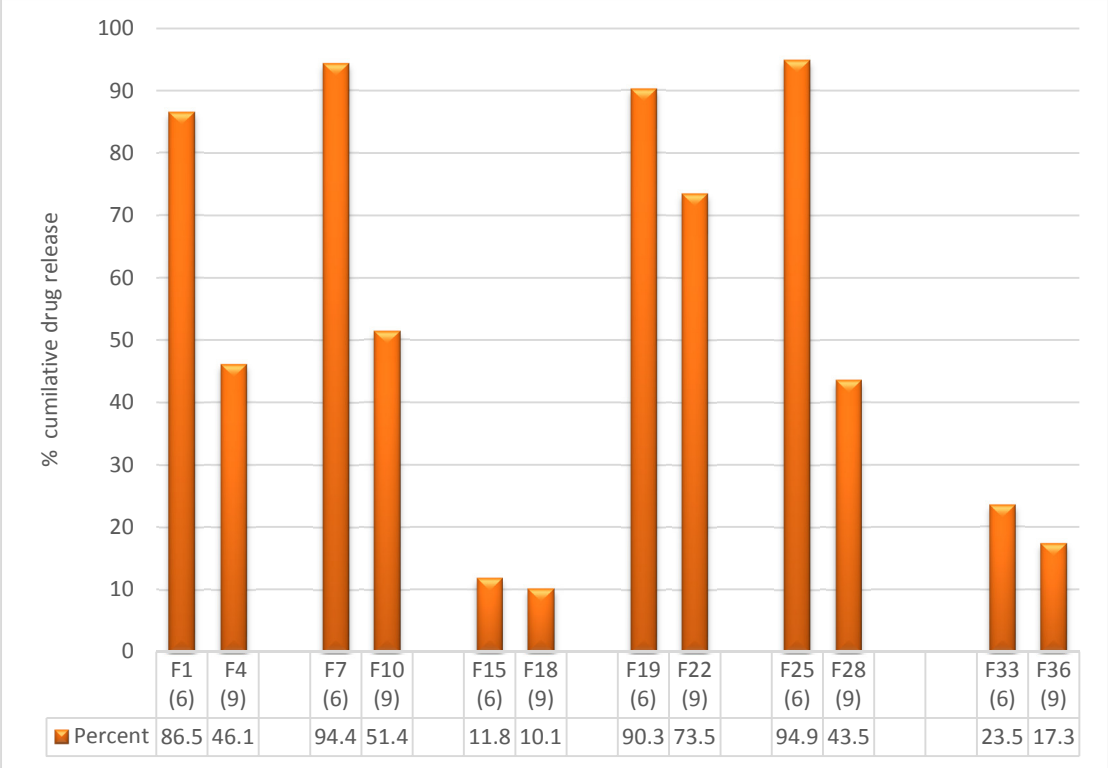


Figure (3-13): Effect of oil phase concentration (6 % vs. 9 %) on the maximum release profile of (CF-HCl) in emulgel formulas*.*Selected Formula are of Minimum Concentration of Gelling Polymer

3.3.4.3 The Effect of Gelling Agents Type on (CF-HCl) Release Profile

Figure (3-14) showed formulas F1, F7, and F15 that utilized to study the effect of gelling agent's type of the three polymers SCMC, CMC. CP 940 at (0.75 % w/w) concentration on the release of (CF-HCl)when the oil phase is liquid paraffin (6 %).The result indicates that the maximum release of (CF-HCl)follows the following sequence: F1 (CMC)>F7 (SCMC) > F15 (CP 940).

The same sequence was obtained with the higher concentration of the oil phase , figure (3-15) present release profile of (CF-HCl)from formulas F4, F10, and F18 that were utilized to study the effect of gelling agent's type (at 0.75 % w/w) on the release of drug when liquid paraffin (9 %) was the oil phase. We got the same results, but with more retarding that related to increasing the concentration of the oil phase but still we have the same sequence of final maximum release of the drug (CF): F10 (CMC)> F4(SCMC) > F18(CP 940) .The maximum release of the drug within this group was obtained also when the gelling agent is CMC.

On the other hand, figure (3-16) showed formulas F33, F19, and F25 that utilized to study the effect of gelling agent type (at 0.75 % w/w) on the release of (CF-HCl)using coconut oil (6 %) as an oil phase. According to this figure, the following sequence of maximum release of the drug was obtained: F25 (CMC) >F19 (SCMC) >F33 (CP 940). That means, when the gelling agent used was CMC (0.75 % w/w) we got the highest percent of drug release formula followed by that of SCMC (0.75 % w/w) and significant retarding effect obtained with CP 940 (0.75 % w/w)

The results of the last group are presented in figure (3-17). The three formulas are F33, F19, and F25 which was utilized to study the effect of

gelling agent type (at 0.75 % w/w) on the release of (CF-HCl) using coconut oil (9 %) as an oil phase. The final maximum release sequence of (CF-HCl)was as follows: F28 (CMC) >F22 (SCMC) >F36 (CP940).

Statistically, although the release percent of the drug from CMC containing formulas was higher than that of SCMC formulas, but its statistically non-significant ($p > 0.05$). This could be related to its lower degree of substitution (0.7) compared to the cationic polymer SCMC with large degree of substitution. The degree of substitution increased the capability of formation of long chain polymer. This increase will lead to progression in viscosity that caused a decrease in the release rate of the drug. On the other hand, CMC special structural network makes it compatible with most water-soluble nonionic solutions over a wide range of concentrations. All these features makes CMC more hydrophilic and more compatible as a hydrogel with the emulsion that consist of w/o portion [(125)].

Formulas containing SCMC polymer showed a cumulative percent drug release as second highest release polymer that is lower than that of CP940. This may be due to the low viscosity of mixture containing SCMC in comparison to that of CP940, which in turn facilitates the penetration of the dissolution media, as a result, the release will be increase.

Regarding formulas containing CP 940, It showed that as the concentration of CP 940 increased the drug release was reduced significantly($p < 0.05$) (.These results may be due to the acid weakening inductive effect of ionized carboxylate residues of CP 940 that affects the ionization potential of the neighboring groups. This may results in high coiling and proximity of carboxylic groups (compare with linear polymer) which lead to intermolecular hydrogen bonding.

Triethanolamine is a cross-linking agent added to CP 940 system, the cross linking leads to entrapment of the drug inside the cross-linked network of the polymer. Several literatures agree with our results like that findings of Lubna A.et.al [122].

Regarding the viscosity, the higher viscosity of emulgel formulas containing CP 940 compared with that containing CMC or SCMC may results in a more retarding effect of the gel.

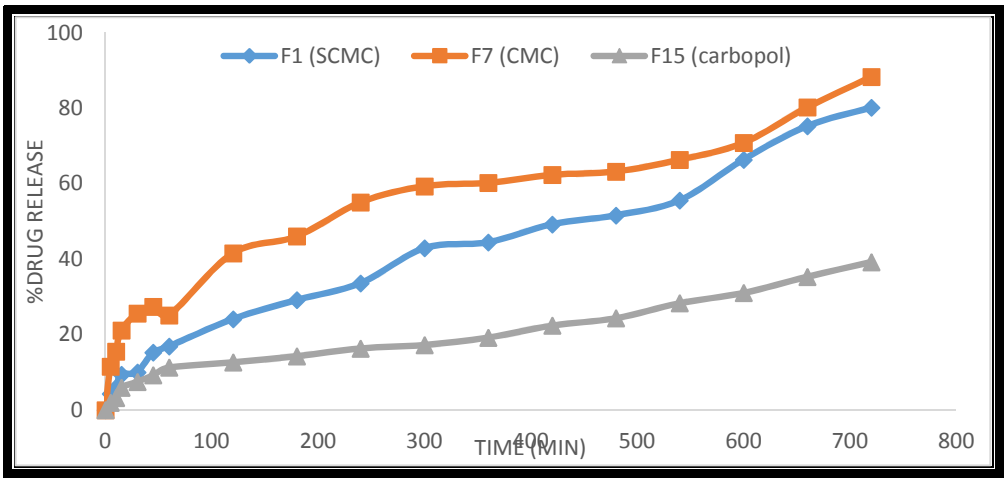


Figure (3-14): Release profile of (CF-HCl) studying the effect of polymer type at 6 %w/w liquid paraffin oil

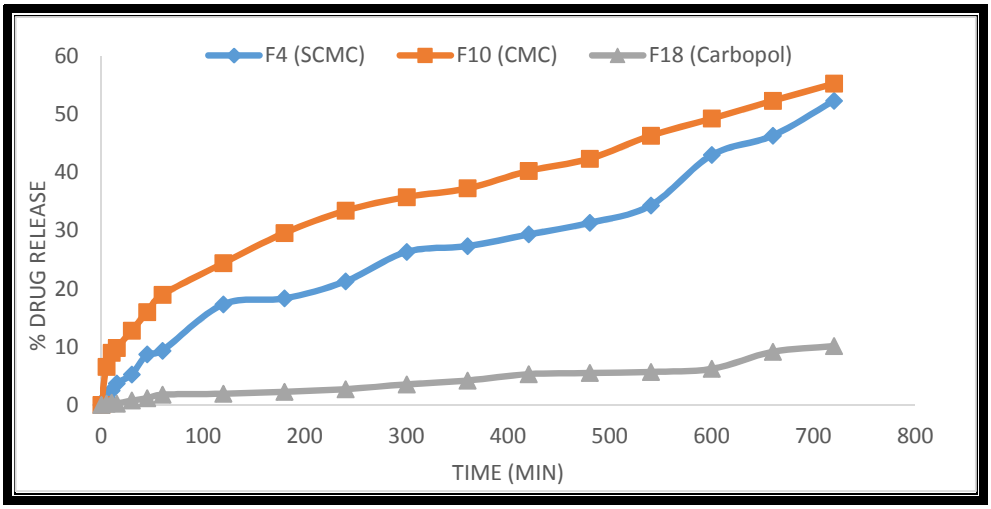


Figure (3-15): Release profile of (CF-HCl) studying the effect of polymer type at 9 %w/w liquid paraffin oil

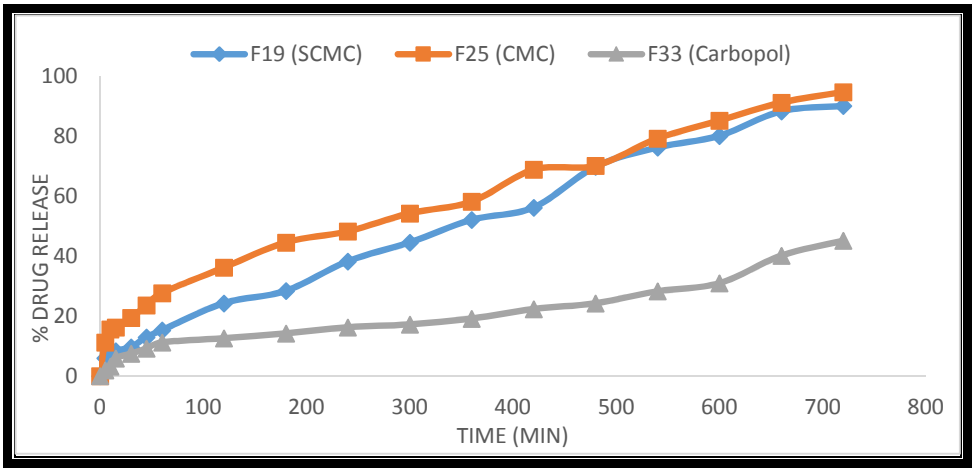


Figure (3-16): Release profile of (CF-HCl) studying the effect of polymer type at 6 %w/w Coconut oil

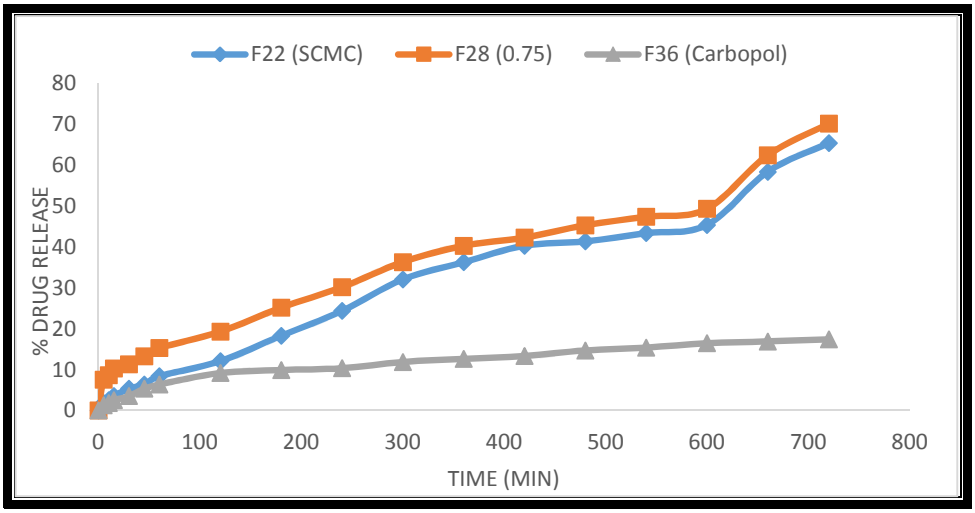
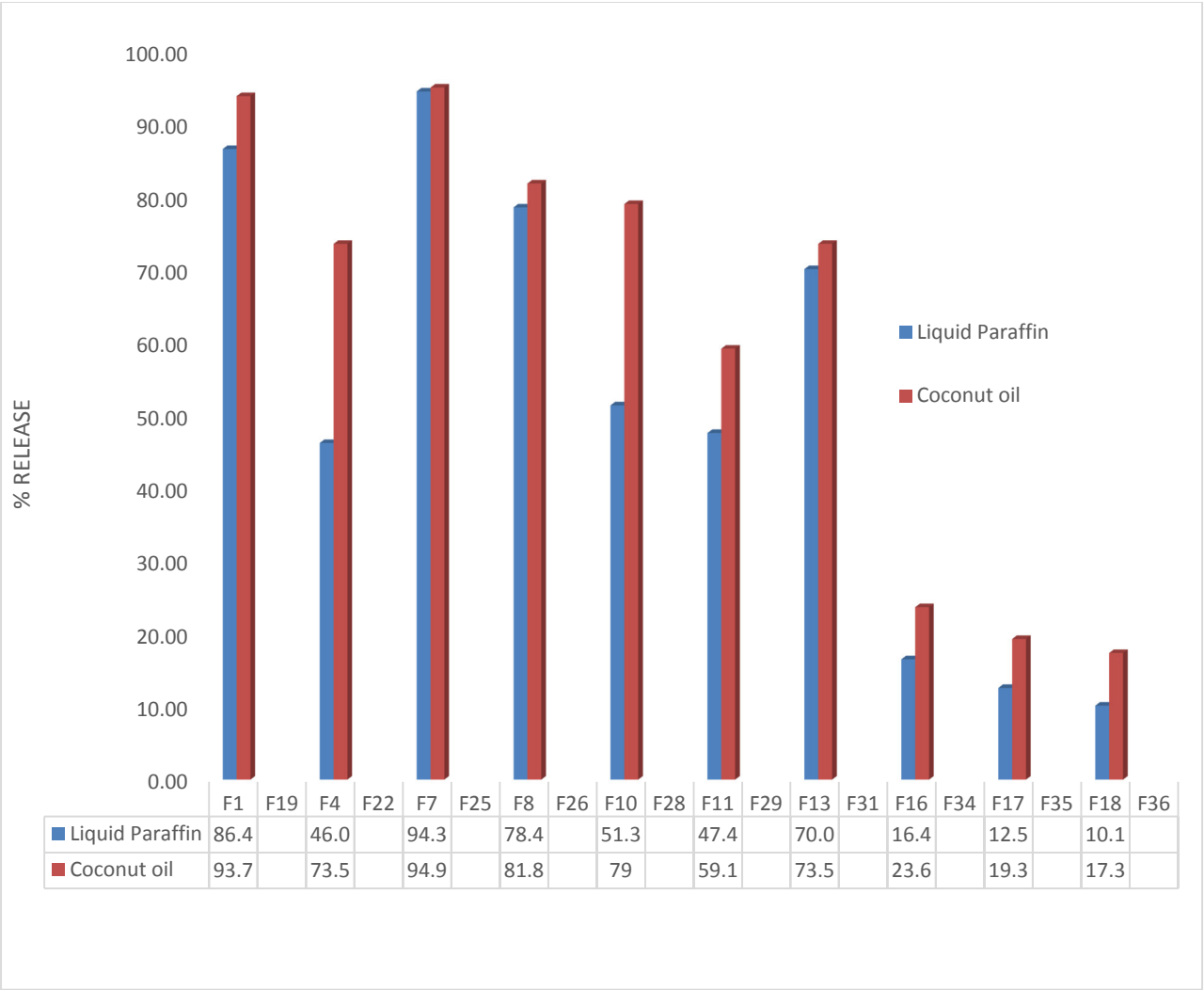


Figure (3-17): Release profile of (CF-HCl) studying the effect of polymer type at 9 % w/w Coconut oil

3.3.4.4 Effect of the Oil Types on the (CF-HCl) Release Profile

Figure (3-18) showed the difference in maximum drug released from formulas of different oil phase type at constant kind and concentration of other constituents. From these results, we found that statistically, the release of (CF-HCl) was significantly higher from formulas containing CO as an oil phase. compared to opposite formulas of LP ($p < 0.05$) .The reason behind this result may be explained by the short chain of fatty acid that form the back bone of CO compare with the long chain of hydrocarbons in the LP . In addition, the specific gravity of LP is (0.9999) which is higher than that of CO (0.9131).

This property manifested by the compaction of LP molecules that are closely packed and the molecule of CO are loosely packed and that explain the more retarding effect of LP [126].



	F1	F19	F4	F22	F7	F25	F8	F26	F10	F28	F11	F29	F13	F31	F16	F34	F17	F35	F18	F36
Liquid Paraffin	86.4		46.0		94.3		78.4		51.3		47.4		70.0		16.4		12.5		10.1	
Coconut oil	93.7		73.5		94.9		81.8		79		59.1		73.5		23.6		19.3		17.3	

Figure (3-18): Effect of oil type on maximums HCl release from emulgel

3.2.5 Ex–Vivo Bio adhesive Strength Measurement

The bio-adhesive strength of various emulgel formulas is presented in fig. (3-19).The results was mostly dependent on the concentration of gelling agents, CMC, SCMC and CP 940.The difference in mucoadhesion characteristics affected by several properties like polymer chain flexibility , ability to form hydrogen bonds and the extent of swelling of polymers [(127)]. The maximum bio-adhesion obtained was with formula F9 that contains 1.25 % CMC and 6 % LP and the lowest bio-adhesion obtained with formula F4 that contains 0.75 % SCMC and 9 % LP.

For all topical medications, the time of persistence of drug on its site of absorption (skin) is important in getting the appropriate time enough to get the highest liberation of the drug, which reflected, in more amount of the drug absorbed through the skin. All the prepared formulas are within the acceptable range [(128).]

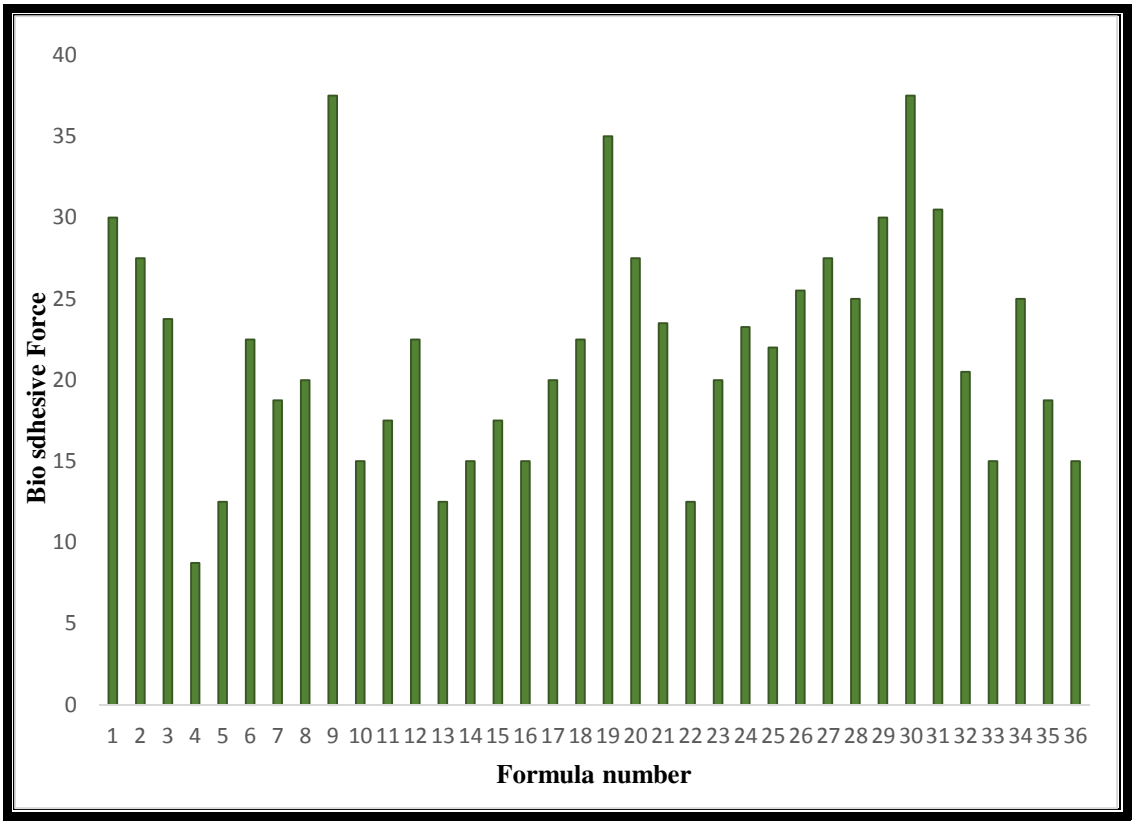


Figure (3-19) Bio adhesive strength of prepared emulgel formulas

3.3.6 Mathematical Analysis of Mechanism and Kinetics of Drug Release

In-vitro release data were fitted to various mathematical models such as Zero order, First order, Higuchi and Korsmeyer- Peppas model in order to understand the mechanism of drug release and the release rate from dosage forms.

Table (3-2) illustrated the correlation of dissolution data to different models of release kinetic. Most of the formulations follows higuchi kinetics and few others follows first order while formulas that best fit to favorable zero order model are the followings: (F6,F13,F16.F17,F18,F20,F21,F25), indicated by highest regression value (R^2).

For Korsmeyer-Pappas model, the value of release exponent (n) defines the release mechanism; the n value of formulas F20, F21, and F25 are between 0.45 to 0.89 indicating anomalous (non–Fickian) transport, which refers to combination of drug diffusion, and matrix erosion mechanism drug release

On the other hand, formulas F6, F13, F16, F17, and F18 shown n values more than 0.89 indicating super case II transport, where the drug release involves polymer relaxation and chain disentanglement [129].

Table (3-2): (CF-HCl) Release Kinetic from All the prepared Emulgel Formulas

Formula Number	Zero Order		First Order		Higuchi		Korsmeyer Pappas		
	K_O (h^{-1})	R^2	K_1 (h^1)	R^2	K_H ($h^{1/2}$)	R^2	n	K_{KP} ($h^{1/3}$)	R^2
F1	0.090	0.8937	0.002	0.9932	1.926	0.7506	1.500	0.004	0.9150
F2	0.108	0.9093	0.002	0.8936	2.409	0.9706	0.615	1.197	0.9834
F3	0.101	0.8588	0.002	0.9405	2.119	0.9780	0.539	1.793	0.9915
F4	0.078	0.8631	0.00105	0.9362	1.762	0.9846	0.559	1.234	0.9882
F5	0.072	0.8421	0.001	0.9132	1.629	0.9876	0.535	1.318	0.9892
F6	0.018	0.5156	0.00019	0.5031	0.368	0.3584	5.792	7.60E-	0.8767
F7	0.141	0.6228	0.002	0.9622	3.240	0.9293	0.397	6.036	0.9465
F8	0.122	0.8831	0.002	0.9622	2.737	0.9837	0.569	1.797	0.9890
F9	0.114	0.9456	0.002	0.9879	1.926	0.7506	0.698	0.759	0.9868
F10	0.080	0.5892	0.001	0.7218	1.863	0.9548	0.387	3.692	0.9828
F11	0.082	0.6610	0.001	0.7883	1.880	0.9749	0.417	3.108	0.9886
F12	0.071	0.5186	0.001	0.6470	1.651	0.9027	0.383	3.354	0.9340
F13	0.095	0.9157	0.001	0.8705	2.057	0.8051	1.164	0.034	0.9202

F14	**0.020**	**0.7685**	**0.00020**	**0.7714**	**0.438**	**0.8420**	**0.536**	**0.351**	**0.8430**
F15	**0.017**	**0.6536**	**0.003**	**0.8101**	**0.395**	**0.8570**	**0.410**	**0.679**	**0.8683**
F16	**0.015**	**0.8776**	**0.000**	**0.8696**	**0.324**	**0.6958**	**1.812**	**0.000**	**0.9361**
F17	**0.011**	**0.8233**	**0.00011**	**0.8168**	**0.228**	**0.6436**	**2.166**	**0.000**	**0.9176**
F18	**0.012**	**0.9553**	**0.00012**	**0.9535**	**0.269**	**0.8558**	**1.031**	**0.010**	**0.9555**
F19	**0.133**	**0.9565**	**0.002**	**0.9624**	**2.939**	**0.9401**	**0.744**	**0.663**	**0.9810**
F20	**0.118**	**0.8855**	**0.002**	**0.8557**	**2.592**	**0.8480**	**0.744**	**0.663**	**0.9810**
F21	**0.118**	**0.9795**	**0.002**	**0.9673**	**2.574**	**0.9117**	**0.867**	**0.272**	**0.9840**
F22	**0.129**	**0.6980**	**0.002**	**0.8893**	**2.950**	**0.9825**	**0.428**	**4.568**	**0.9921**
F23	**0.092**	**0.7303**	**0.001**	**0.8624**	**2.119**	**0.9815**	**0.455**	**2.784**	**0.9850**
F24	**0.074**	**0.7877**	**0.001**	**0.8747**	**1.689**	**0.9897**	**0.486**	**1.842**	**0.9900**
F25	**0.1083**	**0.9607**	**0.0014**	**0.5394**	**0.0431**	**0.6975**	**0.467**	**3.958**	**0.9812**
F26	**0.146**	**0.7873**	**0.003**	**0.9632**	**3.323**	**0.9708**	**0.503**	**3.268**	**0.9708**
F27	**0.096**	**0.6527**	**0.001**	**0.8005**	**2.205**	**0.9728**	**0.408**	**3.855**	**0.9898**
F28	**0.131**	**0.7873**	**0.002**	**0.9365**	**2.983**	**0.9966**	**0.476**	**3.447**	**0.9975**
F29	**0.101**	**0.7632**	**0.002**	**0.8804**	**2.302**	**0.9775**	**0.470**	**2.760**	**0.9788**
F30	**0.092**	**0.6161**	**0.001**	**0.7754**	**2.137**	**0.9694**	**0.395**	**4.029**	**0.9929**
F31	**0.038**	**0.7675**	**0.000**	**0.8096**	**0.228**	**0.6436**	**0.475**	**1.005**	**0.9855**

F32	**0.037**	**0.7218**	**0.000**	**0.7590**	**3.508**	**0.6461**	**0.431**	**1.267**	**0.9760**
F33	**0.036**	**0.9723**	**0.000**	**0.9837**	**0.791**	**0.9509**	**0.752**	**0.170**	**0.9965**
F34	**0.040**	**0.6270**	**0.000**	**0.6820**	**0.916**	**0.9598**	**0.399**	**1.686**	**0.9808**
F35	**0.031**	**0.6420**	**0.000**	**0.6859**	**0.723**	**0.9591**	**0.404**	**1.291**	**0.9771**
F36	**0.029**	**0.5166**	**0.000**	**0.5631**	**0.682**	**0.9385**	**0.354**	**1.648**	**0.9907**

3.4 Selection of Optimum Formula

All the prepared formulas are subjected to characteristic's analysis. Stability on standings in order to select the optimum formula , Formula (F25) was selected as an optimum formula since it has the maximum release profile (94.9 %) after 12 hrs., sufficient bio-adhesive strength (22.27gm), in addition to pH value of (6.00) which is within the range of healthy skin pH, so, there is no irritation would be expected from this formula. Additionally (F25) has an acceptable physical properties, homogeneity, consistency, drug content and viscosity. In addition, for the selected formula (F25), the release fitted mostly on zero order kinetics. Since, the correlation coefficient value is largest in case of zero order equation. (Figures (3-20), (3-21), (3-22)) The release rate is independent of the concentration of the drug. Their lease exponent value of Korsmeyer Peppas equation (n) was 0.467 i.e. this suggests that the emulgel follows case anomalous (non-Fickian) diffusion ($0.45< n<0.89$).The zero order kinetics, is considered a very desirable in drug release systems. Consequently, this formula was subjected to further studies like stability, expiration date and comparable release profiles with formulas containing the synthesized (CF-HCl) derivative compounds

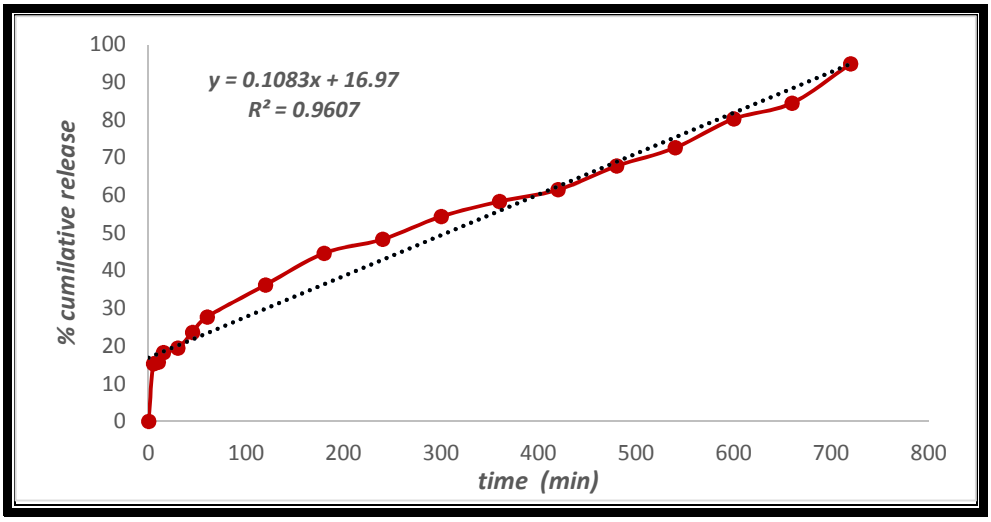


Figure (3-20): Zero order release plot of (CF-HCl) from formula F25

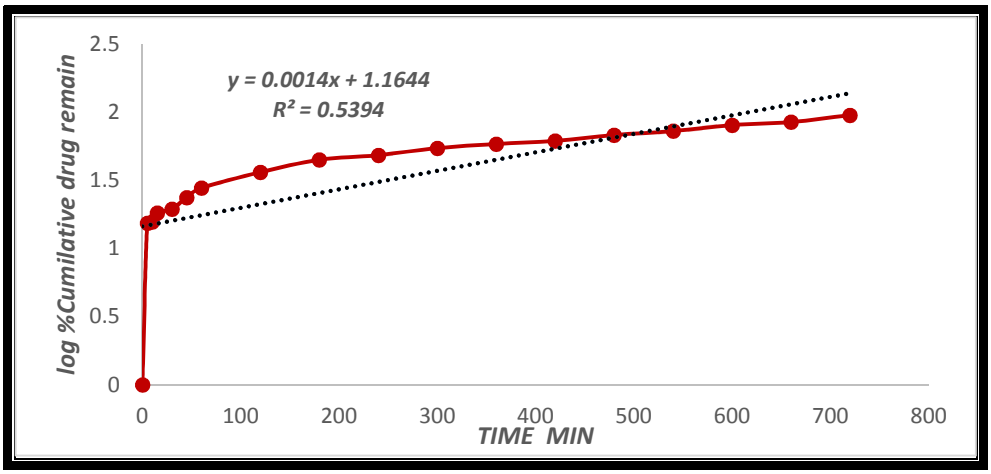


Figure (3-21): First order release plot of (CF-HCl)from formula F25

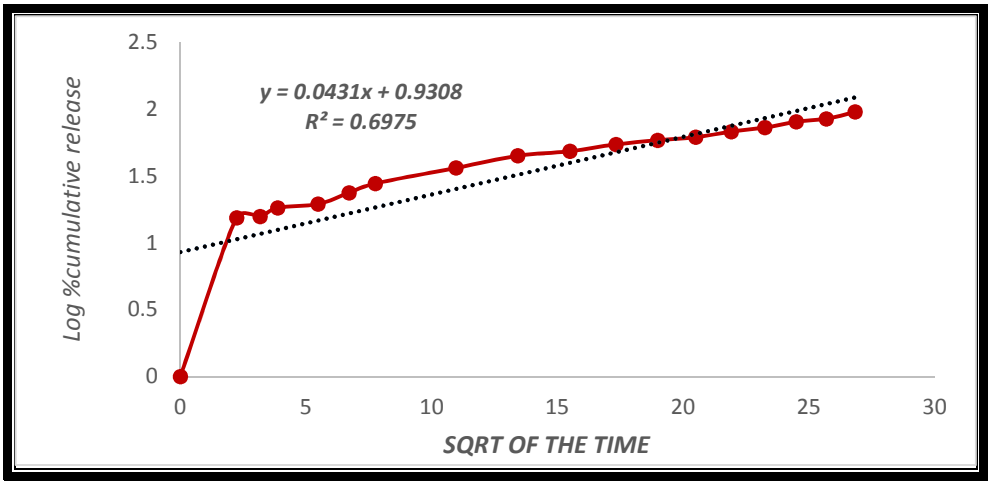


Figure (3-22): Higuchi release plot of (CF-HCl)from formula F25

3.4.1 Determination the Stability and Expiration date of Ciprofloxacin HCl

Expiration date or shelf life is the time at which the drug loses 10% of its potency. Studying the stability of a dosage form at accelerated temperature is one way to estimate the expiration date at room temperature. [129]

The stability of (CF-HCl) selected formula (F25) was studied at three different temperatures 30 ºC, 40 ºC and 50 ºC for four months. Samples the emulgel was taken at one month interval and was studied for drug content .The degradation of (CF-HCl) follows first order kinetics (Eq.3-1), since straight lines were obtained when the logarithm of percent remaining of (CF-HCl)was plotted versus time as illustrated in figure (3-23). The degradation rate constants (K_1) at 30ºC, 40 ºC and 50ºC were calculated from the slopes of the lines using equation (3-1), as shown in table (3-3).

$$\text{Log } Q_t = \log Q_0 - K_1 t / 2.303 \quad \ldots\ldots\ldots \text{ Eq. (3-1)}$$

Where Q_t = concentration remaining at time t

Q_0 = initial concentration

K_1 = 1st order degradation rate constant

t = time

To determine the expiration date ($t_{90\%}$) at 25 ºC, Arrhenius plot was utilized to predict the degradation rate constants (k_1) at 25 ºC for (CF-HCl)as represented in figure (3-24) and it was found to be 11.6×10^{-5} day^{-1}.

The expiration date was calculated according to the following, equation (3-2):

$$t_{90\%} = 0.105 / k_{25} \quad \text{..... Eq. (3-2)}$$

The calculated expiration date for (CF-HCl)was 2.9 years, which is considered very satisfactory for the emulgel dosage form.

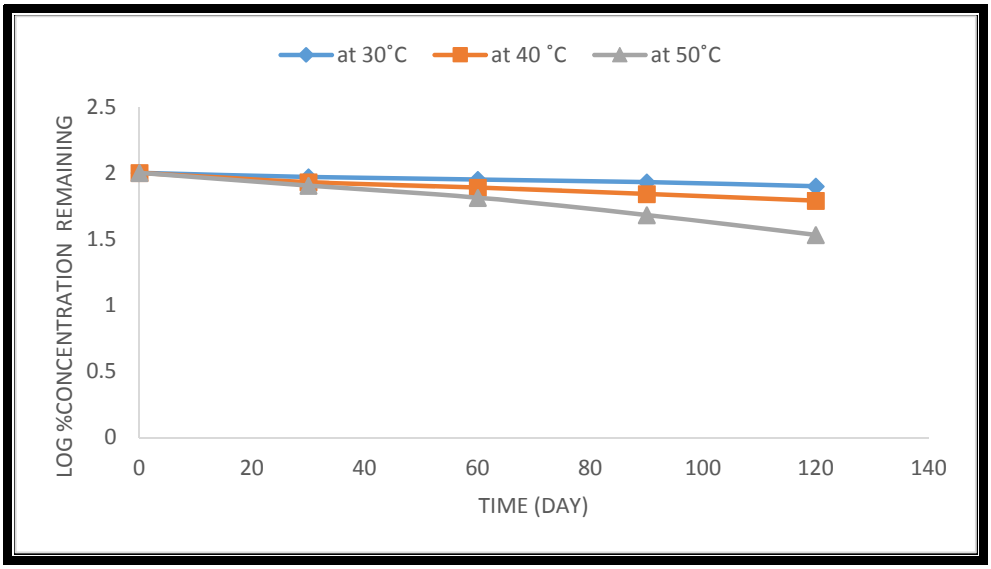


Figure (3-23): Degradation curve of ciprofloxacin HCl (F25) at 30 °C, 40 °C and 50 °C.

Table (3-3): Degradation Rate Constants (K) for (CF-HCl)at Different Temperatures (30, 40 and 50 °C).

Temperature (° C)	K (day $^{-1}$)
30	12.5 x 10 -5
40	16 x 10 -5
50	23 x 10 -5

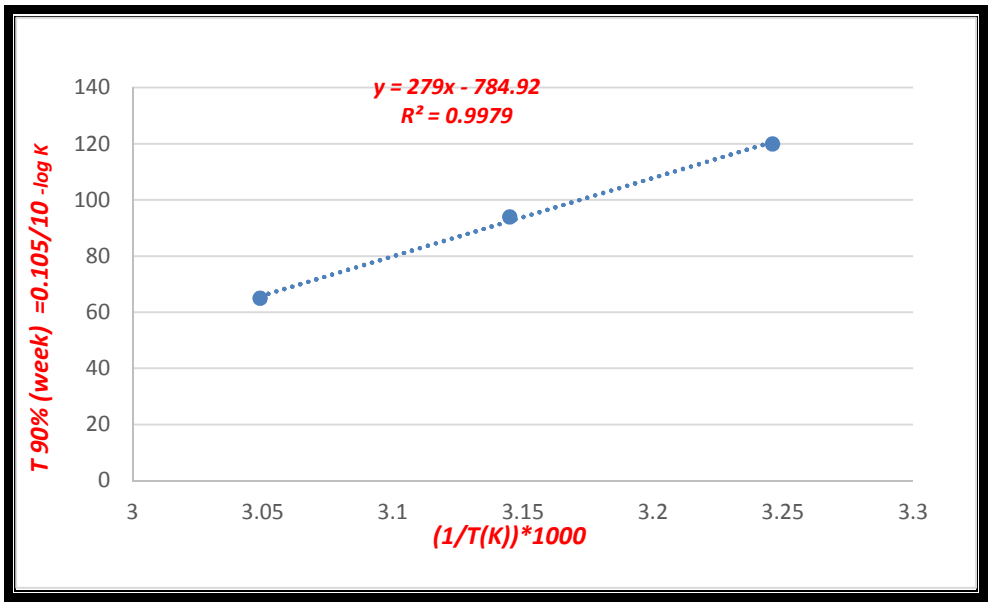


Figure (3-24): Modified Arrhenius plot and K_{25} ° C of Ciprofloxacin HCl Stability Study of F25.

3.5 Skin Irritation Test

This test was conducted for (F25) to evaluate the irritancy of the prepared formulations on the intact skin of animal's. There are no signs of irritation or erythema in the applied area for 24 hr. That mean there is no irritation.

3.6 The synthesize CF derivatives

CF-Glycine amide and CF-Chitosan amide were synthesized and separated. Although the synthesized new derivatives were subjected to characterization by UV, FTIR, TLC, solubility and anti-microbial studying, further purification and identification like ^{1}HNMR, ^{13}C-NMR, CHN and mass spectroscopy are potentially required to optimize the characterization of new derivatives.

Chapter Four

Conclusion

Conclusion and Further studies

4.1 Conclusion

On the basic of the preceding findings we can concluded the followings:

1- Ciprofloxacin was successfully incorporated into the different topical emulgel preparations.

2- Nearly all the developed 36 formulations showed acceptable physicochemical properties and the formula F25 which was CMC-based emulgel with coconut oil in low level shows the finest bio-adhesion, viscosity, and optimum drug release properties. Also, stability upon storage for 3 month at room temperature , where no significant change was observed in the parameters evaluated like color, consistency ,pH, rheological properties , skin permeability , and drug release pattern.

3- Ciprofloxacin conjugates could be prepared using chitosan or glycine and the attachment was through amide linkage.

4- Therefore, it was concluded that ciprofloxacin emulgel formula could be very promising topical alternative for the treatment of skin infections. However, further preclinical and clinical studies are required.

4.2 Future studies

1- We could synthesize other new chemical entities of natural constituents and synthetics compounds to prepare a lot of CF-HCl derivatives.

2- We could complete additional studies such as *in vivo* animal bioavailability for the prepared CF-HCl emulgel formula .

3- We also could formulate emulgel formulas with different oil phases and /or different polymers.

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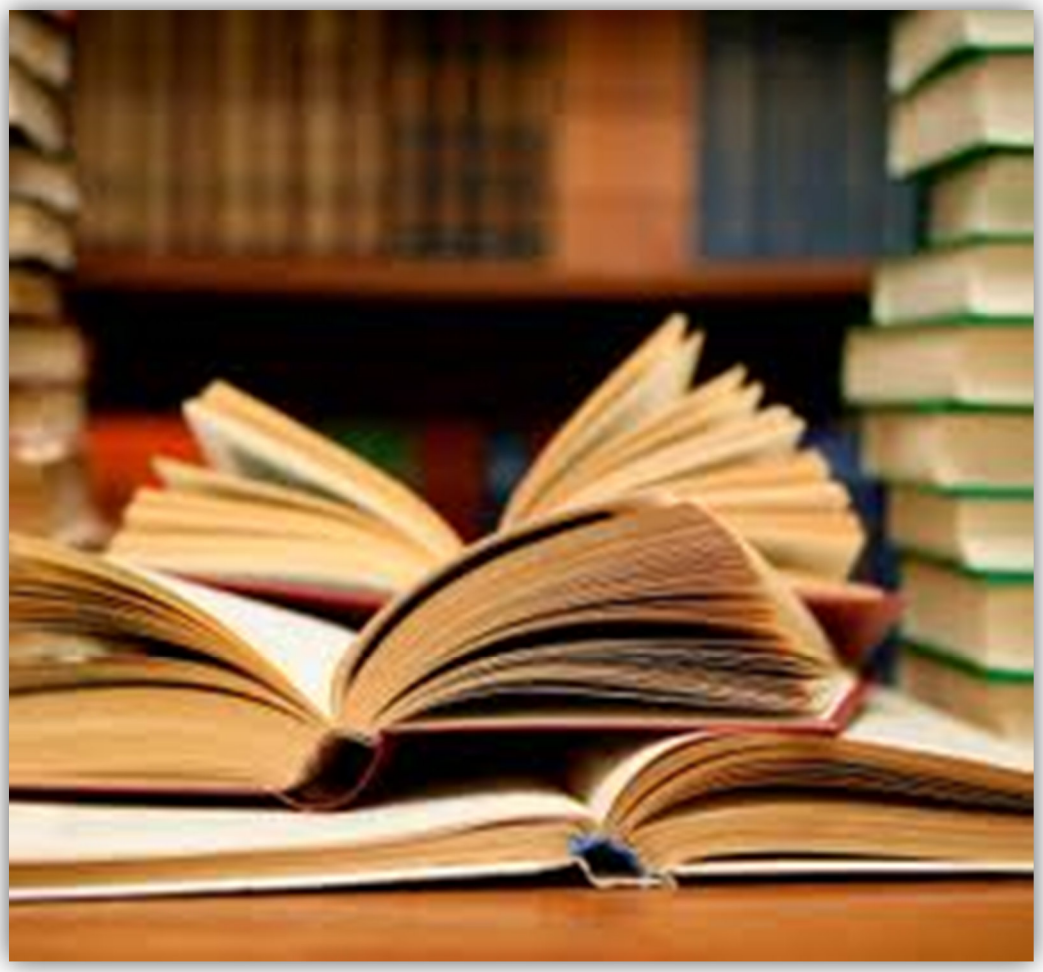

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الخلاصة

تهدف هذه الدراسة الى تطوير وتقييم وتصييغ جل مستحلب (املجل) من دواء الخلاصة

هذه الدراسة اجريت لتطوير وتقييم وصياغة" املجل Emulgel" من عقار سيبروفلوكساسين هيدروكلورايد (CF) بهدف توفير الدواء موضعيا لعلاج العديد من الالتهابات البكتيرية التي تصيب الجلد.

ان استخدام الأدوية موضعيا ينتج عنه تسليط الدواء بتركيز عالي على الجلد اكثر بكثير مما سيصله عند أخذه عن طريق الجسم.

كما تتضمن الدراسة تحضير تركيبين كيميائين اثنين من مشتقات CF وذلك للتخلص من مقاومة البكتيريا للدواء، وكذلك نتطلع إلى إنتاج مشتقات ذات أطياف واسعة من فعالية الدواء المضادة للميكروبات ولها أفضل الخصائص الفيزيائية والكيميائية بالمقارنة مع الدواء الأصلي.

تم إعداد ستة وثلاثون صيغة املجل emulgel من مادة السبروفلوكساسين بتركيز (0.5%) تحتوي الخلطات على كميات متساوية من هلام ومستحلب. جزء الهلام من الاملجل تم تحضيره عن طريق إذابة كميات معينة من ثلاث بوليمرات مختلفة (بصورة منفصلة) بالماء والبوليمرات هي كاربوكسي مثيل سيليلوز،صوديوم كاربوكسي مثيل سيليلوز و كاربوبول 940.

اما مكونات جزء المستحلب فهي البارافين السائل أو زيت جوز الهند ، توين 20 و سبان 20 كعوامل استحلاب، كذلك استخدمنا البروبيلين غليكول لتحسين قابلية الذوبان وكعامل مساعد لتغلغل العقار من خلال الجلد.

تم دراسة تأثير نوع وتركيز كل من المادة الصمغية والزيت بمسألة تحرر الدواء.كل الصيغ المحضرة تم دراستة خصائصها فيزيائيا من حيث اللون،الالتصاق،درجة الحامظية،كمية الدواء واللزوجة. وعلاوة على ذلك، تم التحقق من أداء تحرر الدواء، وحركيتة، ودراسة استقرار الخلطة وحساسيتها. تم تحضير مركبين اثنين من اتحاد عقار السبروفلوكساسين مع الشيتوزان البوليمر والجلايسين الحامض الأميني بشكل منفصل.

وكان مظهر معظم الصيغ المعدة متجانسا ناعما، وزعت بسهولة على الجلد وتراوحت قيم الرقم الهيدروجيني لجميع الصيغ من 5.44 حتى 7.6، والتي تعتبر مقبولة لتجنب خطر تهيج الجلد عند استخدام المستحضرحيث ان درجة حموضة الجلد للبالغين هي 5.5.

كانت الصيغة المختارة الامثل هي صيغة F25 حيث انها متفوقة في خصائص تحرر الدواء (حوالي 94%) في نهاية التجربة وأنه لم تظهر أي قوة تهيج الجلد جنبا إلى جنب مع العديد من الخصائص الإيجابية الأخرى.

الصيغة مختارة (F25) تتألف من 0.75%(CMC) كمادة صمغية و 6% من زيت جوز الهند باعتبارها المادة الزيتية.

اما حركية تحرر الدواء فإنها تبعت صيغة الرتبة "صفر" وكان تاريخ انتهاء المفعول حوالي ثلاث سنوات.

جمهورية العراق
وزارة التعليم العالي
والبحث العلمي
جامعة المستنصرية
كلية الصيدلة

تصييغ وتقييم سبروفلوكساسين هيدروكلورايد كمستحلب هلامي مع محاوله تصنيع مشتقات جديده لعقار السبروفلوكساسين

رسالة مقدمة الى فرع الصيدلانيات والى

لجنة الدراسات العليا في كلية الصيدلة / الجامعة المستنصرية كجزء من

متطلبات الحصول على درجة الماجستير في علوم الصيدلة (الصيدلانيات)

من قبل

أحمد ياسين الشرع

(بكالوريوس صيدلة عام 2008)

بإشراف

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الدكتور فراس عزيز راهي

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