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Research Article

Liposomal Gel Of Ciprofloxacin For Better Treatment Of Periodontal Disease

Ekta Malik* , Nazneen Dubey, Shubhangi Nema , Bharti Choudhary

Shri Ram Institute of Technology-Pharmacy Jabalpur Madhya Pradesh India Pin code -482001

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ABSTRACT

Periodontal disease, a prevalent oral health issue, is characterized by inflammation and infection of the supporting structures of the teeth, often leading to tooth loss if untreated. Traditional treatments, including systemic antibiotics, may not achieve adequate local concentrations at the site of infection, leading to suboptimal therapeutic outcomes. This study explores the development of a liposomal gel formulation of ciprofloxacin, aimed at enhancing localized delivery and improving treatment efficacy for periodontal disease. Ciprofloxacin, a broad-spectrum fluoroquinolone antibiotic, was encapsulated in liposomes to enhance its stability, bioavailability, and penetration into periodontal tissues. The liposomal gel was characterized for its physicochemical properties, including particle size, zeta potential, drug loading capacity, and release kinetics. In vitro studies demonstrated controlled release profiles, indicating sustained drug availability over time. Viability assays and in vivo evaluations were conducted to assess the safety and efficacy of the formulation. The results indicated significant antibacterial activity against periodontal pathogens, with improved patient compliance due to the gel's ease of application. Stability studies confirmed the formulation's robustness under various storage conditions. This innovative liposomal gel of ciprofloxacin presents a promising alternative for the treatment of periodontal disease, potentially leading to enhanced therapeutic outcomes and improved patient adherence to treatment regimens. Further clinical trials are warranted to validate these findings and establish the formulation's effectiveness in a clinical setting.

INTRODUCTION

Periodontal disease:-

Periodontal disease, also known as gum disease, is a set of inflammatory conditions affecting the tissues surrounding the teeth. In its early stage, called gingivitis, the gums become swollen and red and may bleed. It is considered the main cause of tooth loss for adults worldwide. In its more serious form, called periodontitis, the gums can pull away

***Corresponding Author:** Ekta Malik
Address: *Shri Ram Institute of Technology-Pharmacy Jabalpur Madhya Pradesh India Pin code -482001*
Email : mallu.sha007@gmail.com
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from the tooth, bone can be lost, and the teeth may loosen or fall out. Bad breath may also occur. (Niemiec B.A at.,al2008) Periodontal disease is generally due to bacteria in the mouth infecting the tissue around the teeth. Factors that increase the risk of disease include smoking, diabetes, HIV/AIDS, family history, and certain medications. Diagnosis is by inspecting the gum tissue around the teeth both visually and with a probe and X-rays looking for bone loss around the teeth. (Niemiec B.A at.,al2008) Treatment involves good oral hygiene and regular professional teeth cleaning. Recommended oral hygiene include daily brushing and flossing. In certain cases antibiotics or dental surgery may be recommended. Clinical investigations demonstrate that quitting smoking and making dietary changes enhance periodontal health. Globally 538 million people were estimated to be affected in 2015 and has been known to affect 10-15% of the population generally. In the United States nearly half of those over the age of 30 are affected to some degree, and about 70% of those over 65 have the condition. Males are affected more often than females. (Highfield J. at.,al2009)

Symptoms of periodontal disease:-

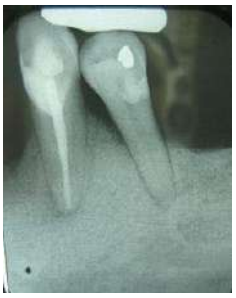
In the early stages, periodontitis has very few symptoms, and in many individuals the disease has progressed significantly before they seek treatment.

Symptoms may include:

Redness or bleeding of gums while brushing teeth, using dental floss or biting into hard food (e.g., apples) (though this may also occur in gingivitis, where there is no attachment loss gum disease) Gum swelling that recurs Spitting out blood after brushing teeth Halitosis, or bad breath, and a persistent metallic taste in the mouth Gingival recession, resulting in apparent lengthening of teeth (this may also be caused by heavy-handed brushing or with a stiff toothbrush) (Highfield J. at.,al2009) Deep pockets between the teeth and the gums (pockets are sites where the attachment has been gradually destroyed by collagen-destroying enzymes, known as collagenases) Loose teeth, in the later stages (though this may occur for other reasons, as well) Gingival inflammation and bone destruction are largely painless. Hence, people may wrongly assume painless bleeding after teeth cleaning is insignificant, although this may be a symptom of progressing periodontitis in that person

Causes of periodontal disease:-

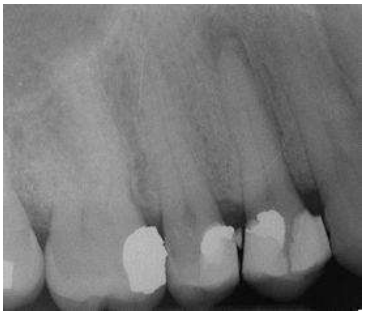
Periodontitis is an inflammation of the periodontium, i.e., the tissues that support the teeth. The periodontium consists of four tissues: gingiva, or gum tissue, cementum, or outer layer of the roots of teeth, alveolar bone, or the bony sockets into which the teeth are anchored, and periodontal ligaments (PDLs), which are the connective tissue fibers that run between the cementum and the alveolar bone.



This X-ray film displays two lone-standing mandibular teeth, the lower left first premolar and canine, exhibiting severe bone loss of 30–50%. Widening of the periodontal ligament surrounding the premolar is due to secondary occlusal trauma.

The primary cause of gingivitis is poor or ineffective oral hygiene, which leads to the accumulation of a mycotic and bacterial matrix at the gum line, called dental plaque. Other contributors are poor nutrition and underlying medical issues such as diabetes. Diabetics must be meticulous with their homecare to control periodontal disease. New finger prick tests have been approved by the Food and Drug Administration in the US, and are being used in

dental offices to identify and screen people for possible contributory causes of gum disease, such as diabetes. (Kinane DF.at.,al2000) In some people, gingivitis progresses to periodontitis – with the destruction of the gingival fibers, the gum tissues separate from the tooth and deepened sulcus, called a periodontal pocket. Subgingival microorganisms (those that exist under the gum line) colonize the periodontal pockets and cause further inflammation in the gum tissues and progressive bone loss. Examples of secondary causes are those things that, by definition, cause microbic plaque accumulation, such as restoration overhangs and root proximity.



The excess restorative material that exceeds the natural contours of restored teeth, such as these, are termed "overhangs", and serve to trap microbic plaque, potentially leading to localized periodontitis. Smoking is another factor that increases the occurrence of periodontitis, directly or indirectly, and may interfere with or adversely affect its treatment. It is arguably the most important environmental risk factor for periodontitis. Research has shown that smokers have more bone loss, attachment loss and tooth loss compared to non-smokers. This is likely due to several effects of smoking on the immune response including decreased wound healing, suppression of antibody production, and the reduction of phagocytosis by neutrophils (Kinane DF.at.,al2000) Ehlers–Danlos syndrome and Papillon–Lefèvre syndrome (also known as palmoplantar keratoderma) are also risk factors for periodontitis. If left undisturbed, microbial plaque calcifies to form calculus, which is commonly called tartar. Calculus above and below the gum line must be removed completely by the dental hygienist or dentist to treat gingivitis and periodontitis. Although the primary cause of both gingivitis and periodontitis is the microbial plaque that adheres to the tooth surfaces, there are many other modifying factors. A very strong risk factor is one's genetic susceptibility. Several conditions and diseases, including Down syndrome, diabetes, and other diseases that affect one's resistance to infection, also increase susceptibility to periodontitis. Periodontitis may be associated with higher stress. Periodontitis occurs more often in people from the lower end of the socioeconomic scale than people from the upper end of the socioeconomic scale. Genetics appear to play a role in determining the risk for periodontitis. It is believed genetics could explain why some people with good plaque control have advanced periodontitis, whilst some others with poor oral hygiene are free from the disease. Genetic factors which could modify the risk of a person developing periodontitis include:

Defects of phagocytosis: person may have hypo-responsive phagocytes. Hyper-production of interleukins, prostaglandins and cytokines, resulting in an exaggerated immune response. Interleukin 1 (IL-1) gene polymorphism: people with this polymorphism produce more IL-1, and subsequently are more at risk of developing chronic periodontitis. Diabetes appears to exacerbate the onset, progression, and severity of periodontitis. Although the majority of research has focused on type 2 diabetes, type 1 diabetes appears to have an identical effect on the risk for periodontitis. The extent of the increased risk of periodontitis is dependent on the level of glycaemic control. Therefore, in well managed diabetes there seems to be a small effect of diabetes on the risk for periodontitis. However, the risk increases exponentially as glycaemic control worsens. Overall, the increased risk of

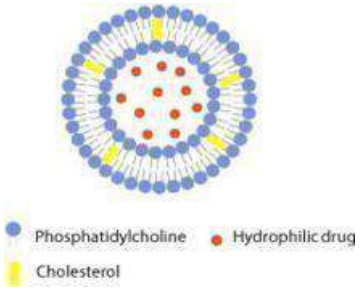
periodontitis in diabetics is estimated to be between two and three times higher. So far, the mechanisms underlying the link are not fully understood, but it is known to involve aspects of inflammation, immune functioning, neutrophil activity, and cytokine biology.

Liposomal drug delivery system:-

Liposomes are microscopic spherical vesicles. These vesicles have a great impact when it comes to the field of medicine. Liposomes have been used as a way of delivering drugs, which could possibly make it the way of the future. However, there are some risks that may prevent it from achieving that potential. A liposome containing a certain drug, or genetic material, can be delivered past the cellular lipid bilayer by fusing with the cell's bilayer. To do this both membranes need to come in very close contact of each other. The liposome fuses with the outer layer of the plasma membrane, then the two fused membranes unite as the inner layers of both membranes get closer to each other as the drug is delivered as both layers fuse. (Allen TM, at.,al2013)

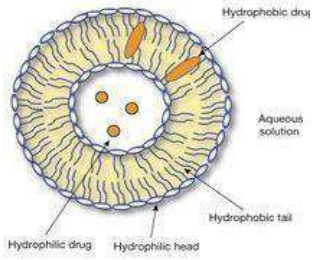
Structure of liposomes:-

The outer part of a liposome, the membrane, is composed of a phospholipid bilayer enclosing in an aqueous volume. Phospholipids are the main building block of liposomes. They have tubular shape and two acyl chains attached to a polar head, which with hydration results in a bilayer, with a hydrophilic head and two hydrophobic tails. This combination means that liposomes are amphiphilic. Liposomes can either be naturally derived phospholipids or of pure surfactant components like DOPE. Cholesterol is important for liposomes as it is used as a membrane additive to fill up the empty spaces between the phospholipids. Cholesterol increases the fluidity of the cell's membrane and provides an increase in the order of the bilayer as it anchors the components of the bilayer more strongly. This increases the transition temperature of the system and provides stability. (Allen TM, at.,al2013)



Types of liposomes:-

Depending on the molecule we wish to use, drugs can either be introduced into an aqueous space or intercalated into the lipid bilayer. This depends on whether the molecule is hydrophobic or hydrophilic. Unilamellar vesicles, which are liposomes with one lipid bilayer, are optimally used with water soluble drugs as they contain the largest aqueous core. However, when lipid soluble drugs are introduced, a multilamellar vesicle is used, as it can passively entrap the drug between its multiple lipid bilayers structured like an onion skin.



Hydrophobic and hydrophilic drug placement inside the liposome

Liposomes containing a certain drug, or genetic material can be delivered past the cellular lipid bilayer by fusing with the cell's bilayer. To do this, both membranes need to come in very close contact of each other. The liposome fuses with the outer layer of the plasma membrane, then the two fused membranes unite as the inner layers of both membranes get closer to each other, the drug is delivered as both layers fuse. Schematic drawing for the fusion of liposome with plasma membrane of a cell

The method of preparing liposomes varies depending on the intended use, and the type of drug being used. A general method of preparation includes hydrophilic materials, which are entrapped to be used as the hydrating fluid. More simply, the drug could be added during some stage of the lipid formation the lipophilic materials are solubilized in an organic solution pertaining to the lipid. The solvent is evaporated, leaving behind the solute. It is then dispersed it into an aqueous solution for hydration. It is somewhere during these stages that the drug is introduced. However, remote loading of ionizable groups can be introduced to the lipid. Finally, the resulting liposome is purified and analyzed. Also, liposomes of varying sizes be used to target certain endocytosis events. This way, the drug is delivered once the

ADVANTAGES AND DISADVANTAGES:-

The versatility of liposomes makes them great for various therapeutic applications in immunology, tumor therapy, gene delivery, antiviral therapy and most importantly to deliver drugs and proteins. In addition, given the fact that liposomes are vesicles made of phosphates, hence a phospholipid bilayer. This could give rise to several advantages in its clinical and preclinical use. The first being the increase in intracellular drug delivery, since the liposome can fuse with the cell's external bilayer and hence more efficiently deliver the drug. This method is more efficient than pinocytosis for instance, and could increase the drug's theraputical effect against both intracellular and extracellular pathogens. Liposomes are used as carriers for controlled drug delivery, which decreases toxic effects of drugs in the body; the drug will be protected from the external environment, and hence won't target unintended tissues. Liposomes are composed of biocompatible and biodegradable material, which makes it a safe way of drug delivery. On the other hand, there are certain disadvantages associated with this delivery system. For example, liposomes could be quite physicochemically unstable. The ester bond in the bilayer could be hydrolyzed and/or the drug can be leaked due to the fusion of liposomes to form larger particles. In addition, liposomes could be rapidly cleared out of the circulation system to the work of the reticuloendothelial system. Also, it is hard to sterilize liposomes since phospholipids' bilayer is sensitive to heat. Other disadvantages may include a high production cost. (Feng T, at.,al2017)

GENERAL METHOD OF PREPRATION AND DRUG LOADING

Liposomes are manufactured in majority using various procedures in which the water soluble (hydrophilic) materials are entrapped by using aqueous solution of these materials as hydrating fluid or by the addition of drug/drug solution at some stage during manufacturing of the liposomes. The lipid soluble (lipophilic) materials are solubilized in the organic solution of the constitutive lipid and then evaporated to a dry drug containing lipid film followed by its hydration. These methods involve the loading of the entrapped agents before or during the manufacturing procedure.

MECHANICAL DISPERSION METHODS

PREPARATION OF LIPOSOMES BY LIPID FILM HYDRATION

When preparing liposomes with mixed lipid composition, the lipids must first be dissolved and mixed in an organic solvent to assure a homogeneous mixture of lipid. Usually this process is carried out using chloroform : menthol mixture. Once the lipids are thoroughly mixed in the organic solvent, the solvent is removed to yield a lipid film.

SOLVENT DISPERSION METHOD

Ether injection methods A solution of lipids dissolved in diethyl ether or ether/methanol mixture is slowly injection to an aqueous solution of the material to be encapsulated at 55- 65% or

under reduce pressure. The subsequent removal of ether under vacuum leads to the formation of liposomes. The main drawback of the method are population is heterogeneous [70-90nm] and the exposure of compounds to be encapsulated to organic solvents or high temperature Ethanol injection method A lipid solution of ethanol is injection to a vast excess of buffer. The MLVs are immediately formed. The drawback of the method are that the population is heterogeneous [30-110nm], liposomes are very dilute, it is difficult to remove all ethanol because it forms azeotrope with water. Reverse phase evaporation method First water in oil emulsion is formed by brief sonication of a two phase system containing phospholipids in organic solvent (diethylether or isopropylether or mixture of isopropyl ether and (chloroform) and aqueous buffer. The organic solvents are removed under reduced pressure, resulting in the formation of viscous gel. The liposomes are formed when residual solvent is removed by continued rotary evaporation under reduced pressure. With this method high encapsulation efficiency up to 65% can be obtained. (Robson AL, at.,al2018) French pressure cell method the method involves the extrusion of MLV at 20,000 psi at 4 degree salacious through a small orifice. The method has several advantages over sonication method. The method is simple sonication method. The method is simple, rapid, reproducible and involves gentle handling of unstable material [Hamilton and Guo 1984]. The resulting liposomes are somewhat larger than sonicated SUVs

APPLICATION

Topical drug delivery:-

The application of liposomes on the skin surface has been proven to be effective in drug delivery into the skin. Liposomes increase the permeability of skin for various entrapped drugs and at the same time diminish the side effect of these drugs because lower doses are now required. (Robson AL, at.,al2018)

Treatment of human immunodeficiency virus :-

Several antiretroviral nucleotide analogues have been developed for the treatment of patients suffering from the acquired immunodeficiency syndromes (AIDS). These include antisense oligonucleotide which is a new antiviral agent that has shown potential therapeutic application against HIV-1.

Enhanced antimicrobial efficacy/ safety :-

Antimicrobial agents have been encapsulated in liposomes for two reasons. First, they protect the entrapped drug against enzymatic degradation

TOPICAL APLLICATION OF LIPOSOMES

The major obstacle for topical drug delivery is the low diffusion rate of drugs across the stratum corneum. Several methods have been proposed to increase the permeation rate of drugs temporarily. One of the most promising approaches is the application of drugs in vesicle-based formulation. Vesicles in dermal and transdermal delivery system can be used as:

- Delivery the entrapped drug into or through skin Act as penetration enhancers
- Delivery dermal active compounds in forms of a depot system
- Be as a rate limiting membrane barrier and modulate the
- systemic absorption.

Liposomes can be employed as a drug carrier, or they can act as penetration enhancers that increase the transport rate of drug across the skin. (David AL. at.,al2021) The exact mechanism of liposomal action as penetration enhancers is still not agreed on, namely some of the authors believe that when liposomes containing drugs are applied onto the skin, they disrupt the lipids which causes skin partitioning and the drug dissolves in skin cells. Another possibility would be that liposomes becomes one part of the skin layer and release drug into the skin. In brief, three ways that liposomes can penetrate through skin can be described as:

- Lateraldiffusion of liposomes in the stratum corneum
- Via a trans-epidermal osmotic gradient
- Via the pilosebaceous units

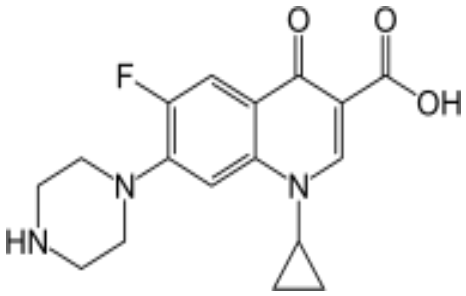
LIPOSOMAL HYDROGELS

Liposomal gels have the advantages that they enhanced the skin retention of drugs, provide higher and sustained concentrations of drug in skin and at the same time do not enhance the systemic absorption of drugs. They can also serve as a drug reservoir that provides a localized and controlled drug delivery and it is also possible to delivery sufficient amount of drugs into skin by using liposomal gels. Lipids composition of liposomes and the lipid concentration of liposomes incorporated into hydrogels are two most important factors that influence the rheological properties of gels. In the case of hydrophilic drugs, release is not affected by the amount of lipid loaded in gels, but can be affected by the amount of rigid membrane liposomes that are used. For lipophilic drugs, lipid concentration added in the gel has a strong affect on the drug release and rigidity of membranes is not important Carbopol hydrogels as vehicles for liposomes have ability to enhanced local delivery of drugs in the vagina. The release of drugs is controlled by degradation of hydrogel matrix. One can control release rate of drug by tailoring the hydrogel degradation. Beukelman et al, (2008) developed liposomal hydrogel containing PVP-ILH. The hydrogel had both the moistening effect and an anti-infection effect. Moistening effect was contributed to carbomer based hydrogels and antiinfective effect was a result of PVP-ILH. (David AL. at.,al2021) Methotrexate (MTX) that can be used for treatment of psoriasis has been administrated mainly via oral route. Mohamed Ali et al. (2008) prepared photosensitive liposomes containing MTX for treatment of localized psoriasis via topical administration. Liposomal MTX was incorporated in 2% carbomer 974NF gel. Gel was applied once a day and followed by 80-J laser session 3 times weekly.

DRUG PROFILE

Introduction of ciprofloxacin :-

Ciprofloxacin is a fluoroquinolone antibiotic used to treat a number of bacterial infections. This includes bone and joint infections, intra abdominal infections, certain types of infectious diarrhea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections, among others. For some infections it is used in addition to other antibiotics. It can be taken by mouth, as eye drops, as ear drops, or intravenously. Common side effects include nausea, vomiting, and diarrhea. Severe side effects include an increased risk of tendon rupture, hallucinations, and nerve damage. In people with myasthenia gravis, there is worsening muscle weakness. Rates of side effects appear to be higher than some groups of antibiotics such as cephalosporins but lower than others such as clindamycin. Studies in other animals raise concerns regarding use in pregnancy. No problems were identified, however, in the children of a small number of women who took the medication. It appears to be safe during breastfeeding. It is a second- generation fluoroquinolone with a broad spectrum of activity that usually results in the death of the bacteria. Ciprofloxacin was patented in 1980 and introduced in 1987. It is on the World Health Organization's List of Essential Medicines. The World Health Organization classifies ciprofloxacin as critically important for human medicine. It is available as a generic medication. In 2020, it was the 132nd most commonly prescribed medication in the United States, with more than 4 million prescriptions.



Ciprofloxacin

Ciprofloxacin for systemic administration is available as immediate-release tablets, extended-release tablets, an oral suspension, and as a solution for intravenous administration. When administered over one hour as an intravenous infusion, ciprofloxacin rapidly distributes into the tissues, with levels insome 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. The serum half-life of ciprofloxacin is about 4–6 hours, with 50–70% of an administered dose being excreted in the urine as unmetabolized drug. An additional 10% is excreted in urine as metabolites. Urinary excretion is virtually complete 24 hours after administration. Dose adjustment is required in the elderly and in those with renal impairment. Ciprofloxacin is weakly bound to serum proteins (20–40%). It is an inhibitor of the drug-metabolizing enzyme cytochrome P450 1A2, which leads to the potential for clinically important drug interactions with drugs metabolized by that enzyme. Ciprofloxacin is about 70% orally available when administered orally, so a slightly higher dose is needed to achieve the same exposure when switching from IV to oral administration. The extended release oral tablets allow once-daily administration by releasing the drug more slowly in the gastrointestinal tract. These tablets contain 35% of the administered dose in an immediate- release form and 65% in a slow-release matrix. Maximum serum concentrations are achieved between 1 and 4 hours after administration. Compared to the 250- and 500-mg immediate-release tablets, the 500-mg and 1000-mg XR tablets provide higher Cmax, but the 24-hour AUCs are equivalent. Ciprofloxacin immediate-release tablets contain ciprofloxacin as the hydrochloride salt, and the XR tablets contain a mixture of the hydrochloride salt as the free base.

Chemical properties :-

Ciprofloxacin is 1-cyclopropyl-6-fluoro-1,4-dihydro-4- oxo- 7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is C17H18FN3O3 and its molecular weight is 331.4 g/mol. It is a faintly yellowish to light yellow crystalline substance. Ciprofloxacin hydrochloride (USP) is the monohydrochloride monohydrate salt of ciprofloxacin. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8 g/mol. Its empirical formula is C17H18FN3O3HCl•H2O.

Mechanism Of Action :-

Ciprofloxacin is a broad-spectrum antibiotic of the fluoroquinolone class. It is active against some Gram-positive and many Gram-negative bacteria. It functions by inhibiting a type II topoisomerase (DNA gyrase) and topoisomerase IV, necessary to separate bacterial DNA, thereby inhibiting cell division. Bacterial DNA fragmentation will occur as a result of inhibition of the enzymes.

Adverse effect :-

Adverse effects can involve the tendons, muscles, joints, nerves, and the central nervous system. Rates of adverse effects appear to be higher than with some groups of antibiotics such as cephalosporins but lower than with others such as clindamycin. Compared to other antibiotics some studies find a higher rate of adverse effects while others find no difference. In clinical trials most of the adverse events were described as mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment. Some adverse effects may be permanent. Ciprofloxacin was stopped because of an adverse

event in 1% of people treated with the medication by mouth. The most frequently reported drug-related events, from trials of all formulations, all dosages, all drug-therapy durations, and for all indications, were nausea (2.5%), diarrhea (1.6%), abnormal liver function tests (1.3%), vomiting (1%), and rash (1%). Other adverse events occurred at rates of <1%.

Toxicity:-

Cipro toxicity leads to toxic aldehyde formation, peroxynitrite formation, leading to oxidative stress and cell death, thus making these antibiotics toxic to every organ in the body including the brain, musculoskeletal system, heart, kidneys, lungs, nervous system, and connective tissue.

Side Effects-

Muscle weakness, pain or swelling in your joints or tendons. This often begins in the ankle or calf, but could also be in your shoulder, arms or legs. It can happen in the first 2 days of taking ciprofloxacin or even several months after stopping. It is more common in children

MATERIAL AND METHODS

Pre-Formulation Studies Organoleptic Propertes

Organoleptic properties of Ciprofloxacin were observed by visual observation. The organoleptic studies of Ciprofloxacin like general appearance like color, odor, state, etc. were performed.

Solubility study

Qualitative solubility of Ciprofloxacin in differe nt solvents was determined according to USP NF, 2007. Approximately 1 mg of Ciprofloxacin was weighed and transferred into a 10 ml test tube and dissolved in the respective solvents (1 ml each of methanol, ethanol, DMSO, chloroform and water) (Jain and Verma 2020).

Melting Point

Melting point was analyzed by open Capillary method using Thiele's tube. Few quantity of the Ciprofloxac in was placed in a thin walled capillary tube 10-15 mm long, about 1mm inside diameter, and closed at one end. Liquid paraffin oil was filled in the thieles tube and placed in the contact of flame. The capillary was suspended into the thiele's tube and heat the sample slowly; thermometer was attached to check the temperature. The temperature at which the sample starts to melt was taken as the melting point of the sample (Chowk, M. I. 2020).

pH determination

pH was determined by Electrochemical method. Digita l pH meter is used to determine the pH of Ciprofloxac in. After the meter has been turned on, allowed to stabilize as necessary and properly calibrated, begin by rinsing the probe with deionized or distilled water and blotting the probe dry with lint-free tissue paper. Immerse the sensing tip of the probe in the sample and record the pH reading and Rinse the probe, blot dry and repeat step 2 on a fresh portion of sample. The two readings should agree to within the accuracy limits of the meter.

Determination of Lambda max and calibration curve:

Preparation of standard stock solution:

About 5mg of Ciprofloxacin was weighed and transferred into 5ml volumetric flask. The volume was made up to 5ml using methanol to obtain a solution that has a concentration 1000 µg/ml. 1ml of this stock solution was taken and then diluted up to 10 ml using methanol to obtain a solution that has a concentration 100 µg/ml which is standard stock solution.

Lambda max

From the above stock solution 2 ml of sample was transferred into a 10 ml volumetric flask and the volume was made up to mark with methanol to prepare a concentration of 20 µg/ml. The sample was scanned by Double beam UV-VIS Spectrophotometer (Shimadzu - 1700) in the range of 200- 400 nm, using methanol as a blank. The maximum absorbance (λmax) of the sample was noted (Kumbhar and Salunkhe 2013).

Linearity (Calibration curve)

Aliquots of 2, 4, 6, 8, 10 and 12µg/ml were prepared from the solution of 100 µg/ml Ciprofloxacin working standard stock solution were accurately transferred into a series of 5 ml calibrated flask and volume was made up to the mark with methanol. Calibration curve was prepared by plotting the absorbance vs concentration of drug. Seven points calibration curve were obtained in a concentration range from 2-12µg/ml of Ciprofloxac in (Behera et al., 2012).

Fourier transmission Infra-Red Spectroscopy

FT-IR spectrum of Ciprofloxacin was recorded over the range of 4000 to 400 cm−1 by KBr pelet method using a FT-IR spectrophotometer. The KBr disc was prepared using 1 mg of each Ciprofloxacin in 100 mg of spectroscopic grade KBr which has been dried using IR lamp. Both KBr and drug was mixed and subjected to hydraulic pressure to form disc. This disc was placed in FT-IR chamber. Infrared spectrum was recorded in the 4000 - 400 cm-1 region.

Formulation and optimization of vesicle system (Liposomes)

Several parameters influence the final properties of liposomes. Major variables in the liposome properties include cholesterol and lecithin amounts and sonicatio n time. Five different formulations with low and high values of cholesterol (50 to 300 mg), lecithin (50 to 300 mg), and sonication time (10 to 60 minutes) were used to prepare liposomal formulations. Liposomes were prepared by thin film method. Briefly, differe nt concentrations of soya lecithin and cholesterol (Table 4) were dissolved in the chloroform-methanol (1:1) and 100 mg Ciprofloxacin was added to the solution, then the mixture was evaporated in a rotary evaporator when the thin film was formed in the round- bottoms flask, it was hydrated with phosphate buffer (pH 7.4). The suspension was agitated by vortex for 30 minutes and then sonicated for ten to sixty minutes (Moghimipour et al., 2015

Table 1: Composition of liposome formulation

S.	Ingredients	Formulation code				
		LS 1	LS 2	LS 3	LS 4	LS 5
1.	Ciprofloxacin (drug)(mg)	100	100	100	100	100
2.	Lecithin (mg)	50	100	150	200	250
3.	Cholesterol (mg)	250	200	150	100	50
4.	Chloroform- methanol (1:1) (ml)	10	10	10	10	10
5.	Pbs (7.4) (ml)	10	0	10	10	10
6.	Sonication time (min.)	10	20	30	40	50

Evaluation parameter of liposome formulation

Particle size and poly-dispersibility

The measurement of particle size and poly-dispersibi lity were done on Zetasizer at 25°C. The analysis was done by the software provided by Malvern Instrume nts. Before analysis samples were placed in refrigera tor maintained at 4°C (Ahmed et al., 2021).

Zeta potential

The formulation of liposome was tested for zeta potential using Malvern Zetasizer instrument. The analysis was carried out at 25°C (Kumar et al., 2018, Penjuri et al., 2016)..

Entrapment efficiency

To calculate the entrapment efficiency accurately weighed the quantity of liposome (10 mg) with 5

ml of methanol in a volumetric flask was shaken for 1 min using vortex mixer. The volume was made up to 10 ml. Then the solution was filtered and diluted. The concentration of Ciprofloxacin was determined spectrophoto metrically at 272.0 nm (Solunke et al., 2019).

Loading efficiency = Actual drug content in liposomes / Theoretical drug content × 100

Scanning Electron Microscopic (SEM)

The electron beam from a scanning electron microscope was used to attain the morphological features of the optimized Ciprofloxacin loaded liposome were coated with a thin layer (2–20 nm) of metal(s) such as gold, palladium, or platinum using a sputter coater under vaccum. The pre-treated specimen was then bombarded with an electron beam and the interaction resulted in the formation of secondary electrons called auger electrons. From this interaction between the electron beam and the specimen's atoms, only the electrons scattered at 90° were selected and further processed based on Rutherford and Kramer's Law for acquiring the images of surface

topography (Anwer et al., 2019).

Formulation of liposomal gel

Initially, carbopol-934 was immersed in 50 mL of warm water (A) for 2 hours and homogeneously distributed using a magnetic stirrer at 600 rpm. In a separate container, carboxymethyl cellulose and methyl paraben were mixed with 50 ml of warm water (B) and agitated continuously to form a hard gel. Both the mixtures A and B were mixed with the continuous stirring. Then tri-ethanol amine (Drop wise) was added to neutralize the pH and liposomes of optimized formulation were incorporated into the dispersion to obtained Gel. At this stage, permeation enhancer (Propylene glycol) was added. The final dispersion was agitated until smooth gel was formed without lumps (Silpa et al., 2021, Eswaraiah et al., 2020).

Table 2: Composition of gel formulation

S. No	Excipients	Quantity
1.	Carbopol 934	1.00 gm
2.	Carboxymethyl cellulose	1.00 gm
3.	Propylene glycol	0.5 ml
4.	Methyl paraben	0.2 ml
5.	liposome	10 ml
6.	Tri-ethanolamine	q.s
7.	Water	100 ml

Characterization of Liposomal gel formulation

Physical appearance

The prepared Gel formulation was evaluated for appearance, Color, Odor, and homogeneity by visual observation (Kumar and Eswaraiah 2020).

pH

The meter was allowed to stabilize as needed before being calibrated. Rinse the probe with de-ionized or distilled water and blot it dry with lint-free tissue paper. Immerse the sensor tip of the probe in the sample and record the pH reading. Rinse the probe, blot it dry, and repeat step 2 with a fresh sample. The two readings should accord within the meter's accuracy limitatio ns. The samples were examined in triplicate. If tiny differences in pH were noticed, it was corrected to skin pH by adding tri-ethanolamine solution drop by drop (McGlynn, W. 2003).

Viscosity

The viscosity of the gel formulations was measured using a Brookfield viscometer with spindle number 61 at 100 rpm and a temperature of 250C (Monica and Gautami 2014).

Spreadability

An ideal topical gel should have a high spreading coefficient when applied or rubbed over the skin's surface. This was assessed by placing approximately 1g of formulation on a glass slide. Another glass slide of the same length was placed above it, and a 50 mg mass was placed on it, sandwiching the gel between the two glass slides and spreading at a specific distance. The time taken for the gel to travel the distance from the place of its position was noted down. Spreadability was determined by the following formula

S= M*L/T

Where, S-Spreadability, g.cm/s M-Weight placed on the upper glass L-Length of glass slide T is the time it takes to distribute gel in seconds (Sandeep, D. S. 2020).

In-vitro drug release study

The in-vitro drug release study of drug loaded liposoma l gel formulation was studied by dialysis bag diffus ion method. Ciprofloxacin loaded liposomal gel was dispersed into dialysis bag and the dialysis bag was then kept in a beaker containing 100 ml of pH 7.4 phosphate buffer. The beaker was placed over a magnetic stirrer and the temperature of the assembly was maintained at 37 ± 2 °C throughout the experiment. During the experiment rpm was maintained at 100 rpm. Samples (2 ml) were withdrawn at a definite time intervals and replaced with equal amounts of fresh pH 7.4 phosphate buffers. After suitable dilutions the samples were analyzed using UV–Visible spectrophotometer. To analyze the in vitro drug release data various kinetic models were used to describe the release kinetics. To analyze the in vitro release data various kinetic models were use to describe the release kinetics. The zero order rate Eq. (2) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (3) describes the release from system where release rate is concentration dependent. Higuchi described drug release from insoluble matrix as a square root of time dependent process based on Fickian diffusion. The results of in vitro release profile obtained for all the formulation were plotted in modes of data treatment.

Zero - order kinetic model – Cumulative % drug released versus time.

First – order kinetic model – Log cumulative percent drug remaining versus time. Higuchi's model –

Cumulative percent drug released versus square root of time. Korsmeyer-Peppas model - log cumulative % drug release vs log time (Kors-meyer–Peppas model)

First order kinetics

First-order release could be predicted by the following equation:

$LogC=logC_0–K_t/2.303$ (3)

Where,

C=Amount of drug remained at time't'

C0=Initial amount of drug.

K=First-order rate constant (hr-1).

When the data is plotted as log cumulative percent medication remaining vs time, a straight line appears, showing that the release follows first-order kinetics. The constant 'K1'can be obtained When the data is plotted as log cumulative percent medication remaining vs time, a straight line appears, showing that the release follows first-order kinetics. The constant 'K1' is obtained by multiplying 2.303 by the slope value.

Higuchi's Model

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation:

$Q= [DЄ /\tau (2A–ЄCs) Cst]1/2$ eq (4)

Where,

Q= Amount of drug release at time't'

D= Diffusion coefficient of the drug in the matrix.

A= Total amount of drug in unit volume of matrix.

Cs= Solubility of drug in the matrix

Є= Porosity of the matrix. τ= Tortuosity.

t= Time (hrsat which q amount of drug is released. Above equation can be simplified as if we assume, that 'D', 'Cs' and 'A' are constant. Then equation: becomes. Korsmeyer-Peppas model

Korsmeyer et al. (1983) A simple relationship describing drug release was obtained from a polymeric system equation. (5). To find out the mechanism of drug release

$$Mt / M\infty = Ktn \quad (5)$$

Where Mt / M∞ are a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize differe n release for cylindrical shaped matrices.

RESULTS AND DISCUSSION

Organoleptic properties- An evaluation of the API's organoleptic qualities, including Appearance, color, odor, and state, was conducted. Ciprofloxacin was discovered to have a White color to it when tested. Ciprofloxacin has an odorless and has a solid state powder form, according to research conducted on it. Ciprofloxacin exhibited the same appearance, color, odor and state as the I.P. requirements for these characteristics. Result show in Table

Drug	Solvents	Observation/Inference
Ciprofloxacin	Water	Slightly soluble
	Ethanol	Soluble
	Methanol	Freely soluble
	Chloroform	Soluble
	DMSO	Freely soluble

Solubility study-

The solubility of Ciprofloxacin was determined in various non-volatile or volatile liquid vehiclessuch as Dimethyl sulfoxide, methanol, ethanol, chloroform, and water shown in Table 7. From the results, it was observed that the drug is freely soluble in Dimethyl sulfoxide, and methanol and slightly soluble in water.

Melting point-

The capillary method is used to determine the melting point of a substance. The melting point of the Ciprofloxacin was found to be 297ºC, which is well within the limits of the drug specification. The digital pH meter used to determine the pH of a substance. The pH of the Ciprofloxacin was found to be 6.1, which is well within the limits of the drug specification.

Calibration curve of Ciprofloxacin-

The linearity of the proposed method was established by least squares linear regression analysis of the calibration curve. The regression equation for Ciprofloxacin was obtained by plotting absorbance versus concentration of Ciprofloxacin in the range of 1-12 µg/mL.

Six points calibration curve were obtained in a concentration range from 1-12 µg/ml for drug. The response of the drug was found to be linear in the investigation concentration range and the linear regression equation was y = 0.1006x + 0.0534 with correlation coefficient R^2 = 0.9766.

Drug	Organoleptic properties	Observation
Ciprofloxacin	Color	White
	Odor	Odorless
	Appearance	Powder
	State	Solid powder
	Organoleptic properties	Observation

Table 3: Calibration curve

Concentration n (µg/ml)	Absorbance
2	0.285
4	0.412
6	0.662
8	0.812
10	1.159
12	1.215

Mean	0.7575

Characterization of Liposomes

Particle Size-

The particle size is one of the most important parameter for the characterization of liposomes. The average particle size of the prepared drug loaded liposomes was measured using Malvern zeta sizer. Particle size analysis showed that the average particle size of drug loaded liposomes was found to be range 210.3 nm to 469.7 nm.

Zeta potential –

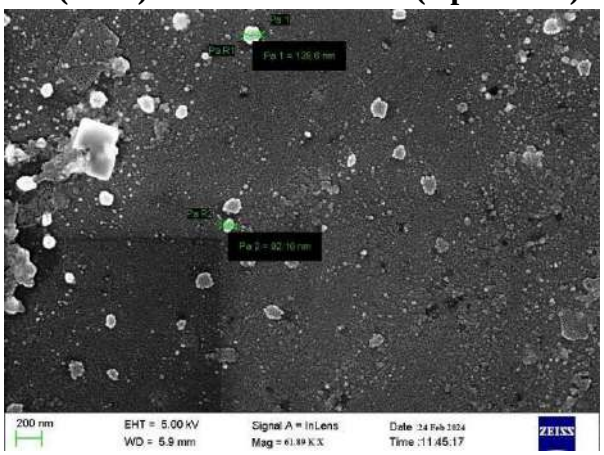
Zeta potential analysis is carried out to find the surface charge of the particles to know its stability during storage. If the particles in liposomes have a large positive zeta potential then they will tend to repel each other and there will be no tendency for the particles to come together. However, if the particles have low zeta potential values then there will be no force to prevent the particles coming together and floccula t ing for liposomes. Zeta potential of all formulations was found to be range -10.8 mV to -21.2 mV with peak area of 100% intens ity. These values indicate that the formulated liposomes are stable.

Entrapment efficacy-

This might be due to the fact that the variation in entrapment efficiency was due to the changes in the polymer concentration and difference in the degree of cross linking. The prepared liposomes possess drug entrapment range (80.33 to 94.30). The F4 liposomes possess high drug entrapment efficiency and were found to be in the range of 94.30 %.

S. No.	Formulations (F1-F5)	Entrapment efficacy(%)
1.	liposomes F1	80.33
2.	liposomes F2	81.03
3.	liposomes F3	92.32
4.	liposomes F4	94.30
5.	liposomes F5	93.81

Scanning electron microscope (SEM) of F4 Formulation (Optimized)



SEM analysis was used to determine the microscopic characteristics (shape and morphology) of the manufactured liposomes. Liposomes were made and thoroughly dried to reduce moisture content, and images were captured using scanning electron microscopy. A scanning electron micrograph of the manufactured liposomes at 61.89 KX magnification revealed that they were porous, had a smooth

S. No	Formulationcode	Particle size(nm)	PI Value
1.	liposomes F1	469.7 nm	0.388
2.	liposomes F2	299.8 nm	0.349
3.	liposomes F3	211.7 nm	0.428
4.	liposomes F4	210.3 nm	0.293
5.	liposomes F5	362.5 nm	0.820

surface morphology, and were spherically shaped. The porous nature of liposomes was readily visible in SEM pictures.

Characterization of liposomal gel

Physical appearance- An evaluation of the gel, including colour, odor, appearance and homogene ity, was conducted. Gel was discovered to have a dark brown

S. No	Formulation Code	Zeta potential
1.	liposomes F1	-14.5 mV
2.	liposomes F2	-18.3 mV
3.	liposomes F3	-21.2 mV
4.	liposomes F4	-13.7 mV
5.	liposomes F5	-10.8 mV

colour to it when tested. Gel does not have a distinct ive odor and has a Yellowish colour appearance, according to research conducted on it. Viscosity of Gel-The viscosity was measured by the Brookfield viscometer spindle no. 61 at 100rpm. The result was shown in the table 16. The viscosity of Gel was found to be 6518 centipoise respectively.

pH determination-

The pH of the gel formula t ion was found to be 6.5, which lies in the normal pH range of the skin and would not produce any skin irritation. There was no significant change in pH values as a function of time. The physicochemica l properties of prepared gel formulation were in good agreement.

Spreadability-

One of the essential criteria for a Gel is that it should possess good spreadability. Spreadability depends on the viscosity of the formulation and physical characteristics of the polymers used in the formulat io n. A viscous formulation would have a lower spreadabilit y. Spreadability is a phrase used to describe the area across which the gel rapidly spreads when applied to the skin. The medicinal efficacy of a formulation is also determined by its spreading value. The spreadability of Gel formulation is found to be 12.09 g.cm/s.

In-vitro drug release

The data of percentage drug release formulation were shown in Figure. 16 to 19. For kinetic study follow ing plots were made: cumulative % drug release vs. time (zero order kinetic models); log cumulative % drug remaining vs time (first order kinetic model); cumula t ive % drug release vs square root of time (Higuchi model); log cumulative % drug release vs log time (Korsmeyer– Peppas model). All Plots are shown in Figure. 16 to19 and results are summarized in Table 20. Zero order kinetic models refer to the process of constant drug release from a drug delivery device independent of the concentration. The zero order graph of optimized formulation showed the constant drug release from the gel, the results of the zero order model was found to be y = 5.4767x + 17.738 R2 = 0.925. The first order kinetic model describes the release from system where release rate is concentration dependent. The results of first order kinetic model was found to be y = -0.1451x + 2.2566 R^2 = 0.851. The Higuchi model is used to describe the limits for transport and drug release. The Higuchi model of formulation was found to be, y= 24.001x - 0.5449 R^2 = 0.996. And the results of Korsmeyer peppas kinetic model was found to be y = 1.0414x + 0.869 R^2 = 0.601. In-vitro drug diffusion studies were carried out using dialysis bag method. In the above table R2 is correlation value. On the basis of best fit with the highest correlation (R2) value it is concluded that in the optimized formulation of Gel follow the Higuchi kinetic model.

Table 4 Release kinetics study of gel formulation

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drugreleased

0	0	100	0.000	2.000	0.000	0.000
1	23.18	76.82	1.000	1.885	0.000	1.365
2	36.09	63.91	1.414	1.806	0.301	1.557
4	43.63	56.37	2.000	1.751	0.602	1.640
6	57.6	42.4	2.449	1.627	0.778	1.760
8	66.13	33.87	2.828	1.530	0.903	1.820
10	77.56	22.44	3.162	1.351	1.000	1.890
12	82.45	17.55	3.464	1.244	1.079	1.916
16	96.13	3.87	4.000	0.588	1.204	1.983

Table 4: Correlation value (R2 value)

Formulation	Model	Kinetic parametervalues
Gel	Zero Order	R^2 = 0. 0.9253
	First Order	R^2 = 0.8512
	Higuchi	R^2 = 0.9961
	Korsmeyerpep pas	R^2 = 0.6015

SUMMARY AND CONCLUSION

Ciprofloxacin was discovered to have a White color to it when tested. Ciprofloxacin has an odorless and has a solid state powder form, according to research conducted on it. Ciprofloxacin exhibited the same appearance, color, odor and state as the I.P. requireme nts for these characteristics. From the solubility study results, it was observed that the drug is freely soluble in Dimethyl sulfoxide, and methanol and slightly soluble in water. The melting point of the Ciprofloxacin was found to be 297ºC, which is well within the limits of the drug specification. The pH of the Ciprofloxacin was found to be 6.1, which is well within the limits of the drug specification. Double beam UV visible spectrophotometer (Shimadzu- 1700) was used to determine the lambda max (absorption maxima) of a substance. The lambda max of the Ciprofloxacin was found to be 272.0 nm. Formulation was carried out by thin film method. Trial batches indicated that polymers are suitable for the liposomal gel formulat io n. Cholesterol and soya lecithin were selected for further studies. A scanning electron micrograph of the generated liposome at 61.89 KX magnification revealed that they were porous with smooth surface morphology and a spherical form. The porous nature of liposome was readily visible in SEM pictures. The Malvern Zeta sizer determined particle size and zeta potential. The particle size analysis confirmed that the prepared sample was within the nanoscale range. The average particle size found for formulations F1 to F5 ranged from 210.3 to 469.7 nm. Zeta potential values of liposome indicated that the formulated liposomes are stable. The amount of drug entrapped in liposome was calculated, and all generated liposomes demonstrated extremely high entrapment efficiency (80.33 to 94.30). The viscosity of liposomes loaded gel is found to 6835±0.32cps. The ph of microsphere loaded gel is 6.6 and spreadability is 13.09, indicating that liposomes loaded gel has high release and permeability. Therefore, in this study drug loaded in liposome formulation to improve solubility and bioavailability. This can be solved by developing nanotechnology-based formulations like as liposomes, which have the potential to boost bioavailability. Through the different evaluatio n parameters the formation of liposomes confirmed and via drug release study as well as solubility study proven the enhancement of the bioavailability of the drug. The development of liposomes has become a key step toward overcoming some challenges such as drug toxicity,

low bioavailability, and predictable drug release because they can accept both hydrophilic and hydrophobic drugs. Liposomes have a porous structure in nature that has the unique capacity to entrap drug moieties and provide a benefit of desired release. In-vitro drug diffusion studies were carried out using dialysis bag method. In the above table R2 is correlation value. On the basis of best fit with the highest correlation (R2) value it is concluded that in the optimized formulation of Gel follow the Higuchi kinetic model

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