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FORMULATION AND EVALUATION OF TABLET DOSES FORM ALONG WITH ANTIMICROBIAL DRUG

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ABSTRACT
Antiinfective chemotherapy is the science of administering chemical agents to treat infectious diseases. The fluoroquinolone market is heavily dominated by norfloxacin, ofloxacin, ciprofloxacin, etc. The 6-fluoroquinolones (also known as 4-quinolones or quinolones are a series of synthetic antibacterial agents derived from, or related to, nalidixic acid and oxolinic acid. Pharmacology Fluoroquinolones inhibit the replication and transcription of bacterial DNA, which eventually culminate in cell death. A tension is created in this remaining double helix which must be relived in order to continue the process. This enzyme has an important role in partitioning of chromosomal DNA during bacterial cell division and may be the primary target of fluoroquinolone activity in Gram positive bacteria cell.

KEYWORDS: Antimicrobial Drug, Solid doses form, evaluation, formulation, FTIR.

INTRODUCTION
Anti-infective chemotherapy is the science of administering chemical agents to treat infectious diseases. This practice has proven to be one of the most successful of all pharmaceutical studies. Historically, the use of anti-infective agents can be credited with saving more human lives than any other area of medicinal therapy discovered to date. Antibacterial chemotherapy accounts for the majority of anti-infective agents in comparison to antifungal, antiviral and anti-parasitic agents. It is a highly valued medical science, which has shaped modern humanity in a phenomenal fashion Ehrlich successfully developed the first purely synthetic revolutionary antimicrobial drug salvarsan in 1910.[1]

Fluoroquinolones are today's blockbusters of the antibacterial and thus challenging the predominance of well- established β-lactam antibiotics which are becoming more prone to the resistant pathogenic bacteria. The fluoroquinolone market is heavily dominated by norfloxacin, ofloxacin, ciprofloxacin, etc. The benzopyridone nucleus (quinolone) proved to be more responsive to chemical manipulation in order to enhance antibacterial potency, and subsequent discovery of fluorine atom and piperazinyl ring on the quinolone ring revolutionized the chemistry and clinical importance of fluoroquinolones In Fourier Transform Infrared (FTIR) spectroscopy, the resulting spectrum represents the molecular absorption and transmission, creating a molecular fingerprint of the sample.[8] Fluoroquinolones antimicrobial agents are widely used inclinical practice as broad-spectrum antimicrobials with excellent bioavailability.[2]

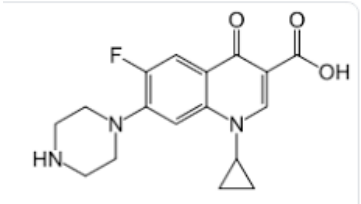
However, they have been reported to induce tendinopathies and, less often, arthralgia and myalgia (Jorgensen et al., 1991; Hayem and Carbon, 1995; Stahlmann and Lode, 2000; Stahlmann, 2002).[4] The main target is the Achilles tendon, where complete rupture can occur; other sites of involvement include the shoulders, knees, hand, and plantar fascia. More than 400 cases of FQ-induced tendinopathy have been reported (Ribard et al., 1992; Zabraniecki et al., 1996; Lewis et al., 1999; Vander Linden et al., 2001). Risk factors for fluoroquinolones-induced tendinopathy include older age, corticosteroid therapy and renal dysfunction. Achilles cause prolonged functional impairment. This pathology can be observed in patients only a few hours or days after receiving a single oral dose of FQ, and results in a serious source of invalidity (Stahlmann and Lode, 2000).[5]

These agents are also employed against bacterial enteric infections, prophylaxis in the immune compromise neutropenic host. New quinolones provide a valid alternative antibacterial therapy, especially in areas where the prevalence of pencillin resistant and macrolide resistant organisms exist.[6]

These fluoroquinolones share a great oral bioavailability in all monogastric species, a large volume of distributionand a low binding to plasma proteins that

allows them to cross membranes and reach the most remote parts of the body at concentrations above the minimum inhibitory concentrations (MIC's) of most pathogens. Tissues and sites demonstrating high concentrations following systemic administration include the kidney, liver and bile plus the prostate, female genital tract, bone and inflammatory fluids (Montay *et al*., 1984).[7] They are eliminated for the most part in the urine and reach the levels 100 to 300 times higher in the urine than in the serum (Montay *et al*., 1984). All the fluoroquinolones exhibit distributional and antimicrobial properties that make them potentially useful in veterinary medicine.[8]

CHEMISTRYMOLCEULAR STRUCTURE



Structure of fluoroquinolone.[9]

The 6-fluoroquinolones (also known as 4-quinolones or quinolones are a series of synthetic antibacterial agents derived from, or related to, nalidixic acid and oxolinic acid.

Position 1 is nitrogen in the bicyclical aromatic ring structure, with an alkyl group (ethyl or perhaps cyclopropyl) often attached there. Carboxylic acid at position 3 is required for antimicrobial activity, similarly like a keto group at position 4. Many improvements on these early quinolone carboxylic acids have been made based in systematic structure-activity studies.[10]

A fluorine atom at position 6 on the quinolone carboxylic acid nucleus enhances the efficacy of these compounds against gramnegative pathogens and broadens the spectrum of activity against gram-positive pathogens: a basic nitrogen-containing moiety enhances tissue penetration and reduces the central nervous system toxicity. Modifications of the basic structure at positions 2, 5 and 7 alter the pharmacokinetics of the compound. A carbon, nitrogen or oxygen atom occupies position 8 on the heterocyclic aromatic ring, depending on the quinolone. Nitrogen atoms at positions 1 and 8 produce naphthyridine carboxylic acids (eg.enoxacin or nalidixic acid), whereas nitrogen atoms at positions 1, 6 and 8 are called pyridopyrimidine carboxylic acids, which are not fluorinated at position 6 (e.g. pipemidic acid). Because of the presence of carboxylic acid and one or several basic amine functional groups, these antibacterial agents are amphoteric and considered zwitterionic: however, between the pKa of the acidic and the basic functional groups (between pH 6 and 8), these compounds are sufficiently lipid-soluble to be able to penetrate tissues. In octanol/water partition experiments conducted at pHs ranging from ciprofloxacin, norfloxacin and enoxacin did not pass significantly into octanol: though nalidixic acid showed an increasing passage into the lipid layer from pH 7.6 to 6.4. However, these classic study methods are unable.[11]

CLASSIFICATION

Fluoroquinolones are classified (Table 1) on the basis of their spectrum of activity and their pharmacokinetic.[12]

GENERATION	DRUG	CHARACTERISTIC FEATURES
First	Naldixic acid Oxolinic acid Pipemidic acid	Active against some Gram negative bacteria. Highly protein bound drugs. Short half life.
Second	Norfloxacin Enoxacin Ciprofloxacin Ofloxacin Lomefloxacin	Protein binding (50%). Longer half life than previous agents. Improved activity against Gram negative bacteria.
Third	Temafloxacin Sparafloxacin Grepafloxacin	Active against Gram negative bacteria. Also active against Gram positive bacteria.
Fourth	Clinafloxacin Trovafloxacin Moxifloxacin Gatifloxacin	Show extended activity against both strains of bacteria. Active against anaerobes and atypical bacteria.

MECHANISM OF ACTION

Pharmacolog Fluoroquinolones inhibit the replication andn transcription of bacterial DNA, which eventually culminate in cell death. They either inhibit the activity of DNA gyrase, an essential adenosine triphosphate-hydrolyzing topoisomerase II enzyme or/and prevent the detachment of gyrase from DNA. The topoisomerases exert their bactericidal activity by interacting with the DNA.[13]

During the processes of replication and transcription, enzymes called helicases unwind/uncoil the DNA double helix leading to excess supercoiling of the remaining DNA double helix. A tension is created in this remaining

double helix which must be relived in order to continue the process. The topoisomerase IIenzyme allows the relaxation of supercoiled DNA by breaking both strands of DNA chain, crossing them over, and then resealing them. Bacterial gyrase is different enough from mammalian topoisomerase so that quinolones and fluoroquinolones show about 1000 fold selectivity towards bacteria over the corresponding enzyme in humans.[14]

Thisenzyme has an important role in partitioning of chromosomal DNA during bacterial cell division and may be the primary target of fluoroquinolone activity in Gram positive bacteria. This mechanism is consistent with apoptosis rather than necrosis.[15]

MATERIALS AND METHODS

For the formulation of the drug the listed material is required.

Materials

S.No.	Material required	Amount
1	Ciprofloxacin	500mg
2	Levofloxacin	500mg
3	Moxiflxacin	400mg

Methods'

For the preparation of the tablet this method is required to be the follow The fluoroquinolones used were Ciprofloxacin 500mg, Levofloxacin 500mg and Moxiflxacin 400mg. 0.1N NaOH and 0.1 N HCl were accurately prepared. Freshly prepared distilled water was used throughout the study. Glass wares used are volumetric flasks, stirrer, beakers, pipette and measuring cylinder. All glass wares used were made up of Pyrex material. Initially they were rinsed with chromic acid then with water and finally washed with freshly prepared distilled water.

DRUG INTERACTIONS

Potentially hazardous interactions, which have been documented only in human studies of fluoroquinolones are limited. Absorption of fluoroquinolones by oral route of administration is drasticallydecreased by antacid containing magnesium, aluminum and other agents such as sucralfate.[16] Without exception, all of the new compounds interact with multivalent containing products. Ranitidine does not alter the oral absorption of ciprofloxacin, but it decreases the oral bioavailabilityof enoxacin, suggesting that the gastric pH affects the oral absorption of the some fluoroquinolones, perhaps through alteration in dissolution. These interactions of fluoroquinolones with antacids might be hazardous during the treatment of serious infections Concurrent administration of the non-steroidial anti-inflammatory agent fenbufen with enoxacin hasbeen associated with seizures in humans. Patients given other fluoroquinolones concurrently with nonsteroidal anti-inflammatory agents except fenbufen Some other significant drug interactions of fluoroquinolones are as follows:

- Elevated serum levels of cyclosporine have been reported with concomitant use of fluoroquinolones.
- Serum concentration of antineoplastics decrease due to the interaction with ciprofloxacin.[48]
- Ciprofloxacin and norfloxacin serum concentrations increase and decrease in their clearance asdid not develop seizures.[17]

PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetic and pharmacodynamic properties of different antimicrobial compounds depend on the dosage form and dose of drug required for inhibiting the viability of pathogens. This differencein absorption, distribution, metabolism and excretion of quinolones may affect the endophthalmitis(ocular complication) incidences after cataract surgery Fluoroquinolones, however, kill pathogens in a concentration dependent manner. Consequently, it is their peak concentration that is important and not the time above the minimum inhibitory concentration. Their longer serum half life permits the once daily dosing and greater maximum plasma concentration offers more extensive coverage above the minimum inhibitory concentration. Fluoroquinolones are distributed rapidly and extensively in tissues except for the brain. It was hypothesized that P-glycoprotein at the blood brain barrier may play a role in this fact.[18]

ADSORPTION

Fluoroquinolones are readily absorbed but their complete absorption is not always achieved following oral administration.[19] The oral bioavailability varies with the individual compounds of the class. The bioavailability of new fluoroquinolones after oral doses is equal to or greater than that of ciprofloxacin, ranging from a low of 70% with grepafloxacin to a high of 99% with levofloxacin. Although drug food interactions may prolong the time required to reach maximum plasma concentration (tmax) and thus affect the area underthe concentration-time curve, this does not significantlyalter the bioavailability of the drugs.[20]

DISTRIBUTION

Distribution of fluoroquinolones to tissues is superior to that of most other drugs because there islittle binding to plasma proteins. After oral administration, fluoroquinolones have good penetrationinto various fluids and tissues of body except central nervous system (CNS). A remarkable drug levelis achieved in kidney, prostate gland, liver and lung. The penetration into the cerebrospinal fluid is poor, except when the meninges are inflamed. Their urinary drug concentration is higher than minimuminhibitory concentration and thus fluoroquinolones are mainly used in urinary tract infections.[21]

METABOLISM AND ELIMINATION

The fluoroquinolones differ greatly in the degree to which they are eliminated by metabolism in liver or by renal excretion. Their metabolism is inactivating and is primarily by glucuronides conjugation at the 3-carboxylic group. The piperazine ring is readily metabolized resulting in decreased antimicrobial activity. Thus, in patients with renal impairment and in geriatrics, dosage adjustment is required. The secondary route of excreation is *via* the lever. They are poorly cleared by both peritoneal dialysis and hemodialysis.[22]

ANTIBICROBIAL SPECTRUM

Many studies have been reported on the activity of the fluoroquinolones. The newer and developmental fluoroquinolones are distinguished by their enhanced spectrum of antimicrobial activity against clinically important pathogens such as *S.pneumoniae*, Enterococcus spp, *S. pyrogenes, S.aureus*, and multidrug resistant isolates.[23] general, these agents have an excellent activity against Enterobacteriaceae, fastidious Gram negative bacteriaand *Pseudomonas aeruginosa*, moderate activity against staphylococci, mycobacteria, chlamydia, mycoplasma and ureaplasma, less activity againststreptococci (particularly group D. streptococci), and anaerobic bacteria. The term ìpost antibioticeffect describes the continuous suppression of anorganismís growth after short exposure to an antibacterialagent such that there is an inhibitory effectin the absence of the antibiotic. Such an effect of fluoroquinoloneshas been shown to be of 4-8 hoursagainst *E. coli, Klebsiella, Serratia* and *Pseudomonas aeruginosa*.[24]

ACTIVITY AGAINST GRAM POSITIVE ORGANISMS

Streptococcus pneumoniae is the commonestcause of community-acquired respiratory tract infection(RTI) and strains resistant to penicillins andmacrolides have become increasingly prevalent inall parts of the world. Activity against pneumococciwas lacking in the early 4-quinoloes and wasonly marginal in the first generation of fluoroquinolones. Their activity has improved steadilywith the newer compounds such as trovafloxacinand moxifloxacin.[25] Bauernfeind observedthat the enhanced activity of the newer fluoroquinolonesagainst Gram positive cocci is limited toagents whose chemical structure at position 7 of thebasic ring contains an azabicyclo, a 3-amino-pyrolidinyl, or a 3-methyl-piperazinyl ring. Fluoroquinolones are bactericidal compounds and a number of studies have shown their ability to kill pneumococci at concentration about 2 to 8 times higher than their minimum inhibitory concentration(MIC). Although resistance to this class of antibiotics in pneumococci is rare, however, recent reportsindicate that resistance to ciprofloxacin and of loxacin is increasing.[26] The newer compounds have greatly improvedactivity against *Streptococcus pyogenes*. The activity of earlier fluoroquinoloes is only modestagainst methicillin-sensetive *S. aureus* and *Staphylococcus epidermidis* strains, with minimuminhibitory concentration 0.5-1.0 mg/l.[27]

ACTIVITY AGAINST GRAM NEGATIVE ORGANISMS

In the development of newer analogs of fluoroquinolones, research work has been primarily focused on improving their potency against Gram positive organisms while retaining the favorable activity against Gram negative organisms.[28] Resistance to ciprofloxacin has been most often seen in strains of *Escherichia coli*, *Enterobacter*, and *Klebsiella* spp and also observed in some members of Enterobacteriaceae. Infectious Gram negative pathogens are mainly *P. eruginosa*, *Acinetobacter*, *Alcaligenes*, *Stenotrophomonas* and *Burkholderia* species. The activities of different fluoroquinolones considerably vary, particularly among strains of *P. aeruginosa*. Ciprofloxacin is generally more active than the newer analogs of this class against most species of *P. aeruginosa*.[29]

ACTIVITY AGAINST ATYPICAL PATHOGENS

A notable improvement in most of the neweranalogs of this class is their enhanced activity againstatypical respiratory tract pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumonia*, and *Legionella pneumophila*. These agents also showtheir significant activities against most of genitalpathogens. The findings regarding the performanceof the new quinolones in clinical studies of respiratory tract infections involving atypical pathogens have generally been favorable.[30]

TOXICITES AND ADVERSE EVENTS

With few exceptions, the adverse effects of fluoroquinolones are not too severe consequences when compared to the beneficial features they exhibit.Toxicity is mild at therapeutic doses, and is generally limited to gastrointestinal disturbances such as nausea,vomiting and diarrhea.[31] Recently, ciprofloxacin has been reported to be an effective therapeutic for anthrax; however, a large dose is needed due to bloodbrain barrier (BBB) and heavy use of ciprofloxacin insuch cases has been suspected to induce aseptic meningitis and arthritis damage and hence there is aneed to increase uptake by the brain.[32] These drugsare still effective as antibiotic prophylaxis for prostatebiopsies but there is an increase in infective complicationsand fluoroquinolones resistance (100). Newerdrugs of this class have greater epithelial toxicity thando the previous fluoroquinolones. In addition, there canbe a significant difference in toxicity between any twonewer fluoroquinolones.[33]

SOME FOCUSED ADVERSE EVENTS

- Skin photosensitivity reactions have been reported during treatment with fluoroquinoloneantibiotics. The incidence and severity of such reactions, however, appear to differ between differentdrugs.[34]
- The greatest concern with ciprofloxacin use in children is potential bone and joint damage.

● CNS effects are second most common type of adverse events associated with quinolone therapy. Dizziness, insomnia, and mood alterations have frequently been observed during treatment with fluoroquinolones. Seizures or hallucination have also been described.
● Unpleasant taste was reported fairly by greapafloxacin treated patients during the clinical trialsbut at a much lesser extent.[35]
● Rarely, anaphylaxis and agranulocytosishave been reported.

CLINICAL AND THERAPEUTIC ROLE

Numerous factors govern the selection of a specificantimicrobial agent, including severity of infection, likely pathogen or pathogens, pharmacokinetic profile, safety, dosing convenience, cost, and increasing patterns of antimicrobial resistance in particular community or hospital setting. Fluoroquinolones have many favorable properties including broad spectrum of activity (107), excellent bioavailability whengiven orally, good tissue penetrability and a relative low incidence of adverse and toxic effects.[36] Although fluoroquinolones have several clinical applications, yet few of important indications are as below,
● Effective against bacterial enteric infections, prophylaxis in the immuno compromised neutropenic Host.[37]
● Some fluoroquinolones are the drugs of firstchoice in prevention and treatment of diarrheal disease
● In the treatment of urinary tract infections and prostatitisThe fluoroquinolones are presently found to beeffective in tuberculosis, primarily in cases involvingresistance or intolerable to first line antituberculosistherapy. However, there is concern about the developmentof fluoroquinolone resistance in *Mycobacteriumtuberculosis*, particularly when administered asmonotherapy or as the only active agent in a failingmultidrug regimen. Important fluoroquinolonesalong with their structures, pharmacokinetics.[38]

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CONCLUSION

The multidisciplinary validation team must identified the product tablet dosage form validation should be part of a comprehensive validation program within an industry. & process characteristics that must be studied & incorporate specific validation tests to ensure that product will meet all quality, manufacturing & Continuous awareness of validation will produce reproducibility regulatory requirements.

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