

Fluoroquinolones: a Pharmaceutical Review

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ABSTRACT: Since the introduction of the fluoroquinolones for clinical use in the late 1980s, they have been used successfully for a large number of clinical situations. The quinolones inhibit bacterial DNA replication by inhibiting DNA gyrase and topoisomerase IV. Careful clinical studies are needed to establish the efficacy of once daily use of fluoroquinolones, to determine that clinical efficacy is equivalent to multiple doses, and that once-daily dosing does not result in development of resistant bacteria. Single-dose therapy with quinolones would be an improvement in cost and patient compliance.

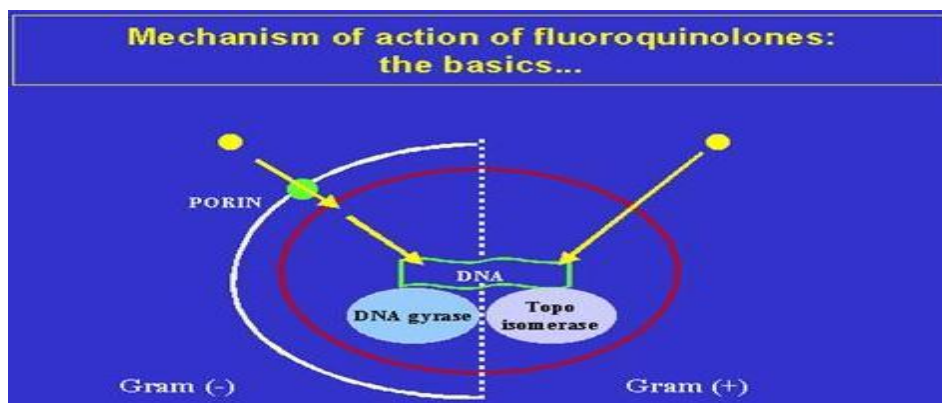
KEY WORDS: Fluoroquinolones, Active Pharmaceutical Ingredient, Crystallization

I. INTRODUCTION

The fluoroquinolones are a family of synthetic, broad-spectrum antibacterial agents with bactericidal activity. The parent of the group is nalidixic acid, discovered in 1962 by Lescher and colleagues. The first fluoroquinolones were widely used because they were the only orally administered agents available for the treatment of serious infections caused by gram-negative organisms, including *Pseudomonas* species. The newer fluoroquinolones have a wider clinical use and a broader spectrum of antibacterial activity including gram-positive and gram-negative aerobic and anaerobic organisms. The discovery of the fluoroquinolones (FQs) during the 1980s improved the treatment of infectious diseases, due to their fewer toxic side effects when compared with the existing drugs. Overall these compounds have enhanced pharmacokinetics properties and extensive and potent activity against various parasites, bacteria, and mycobacteria, including bacterial strains resistant to other antimicrobial agents. According to the medical literature, FQs are to be considered the first-line therapy for complicated urinary tract infection and diarrhea, considering the bacterial etiology. They are also alternative agents for the treatment of many sexually transmitted diseases, as well as osteomyelitis, wound infection and respiratory infections. After the discovery of the fluoroquinolone norfloxacin, structure-activity relationships (SAR) analysis of the fluoroquinolonic nucleus led to the development of new derivatives with better solubility, higher antimicrobial profile, prolonged serum half-life, fewer adverse side effects, and allowing for both oral and parenteral routes of administration.

II. MECHANISM OF ACTION OF FLUOROQUINOLONE'S

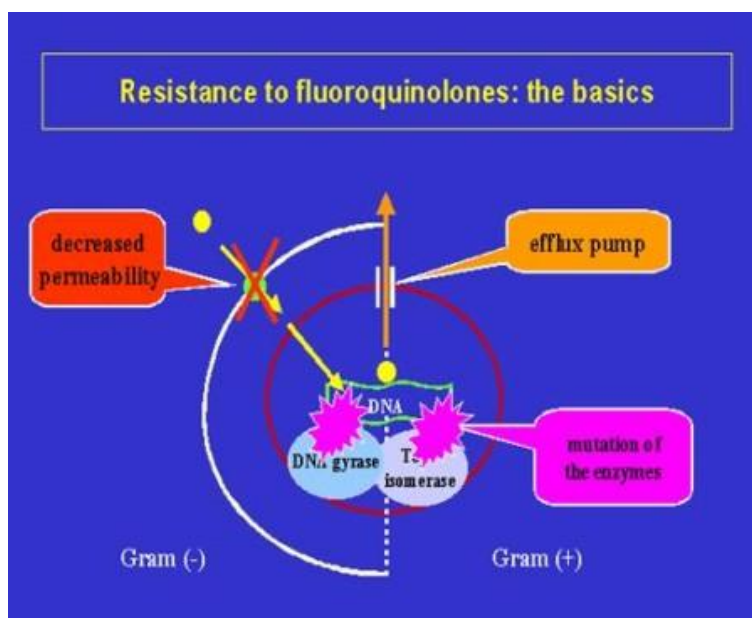
The mechanism of action of quinolones is through the inhibition of bacterial gyrase, an enzyme involved in DNA replication, recombination and repair. By interfering with gyrase, quinolones arrest bacterial cell growth. The affinity of quinolones to metal ions seems to be an important prerequisite of their antibacterial activity: probably, quinolones bind to the DNA-gyrase-complex via a magnesium ion.



Mechanism of action of Fluoroquinolones

III. BACTERIAL RESISTANCE OF FLUOROQUINOLONES

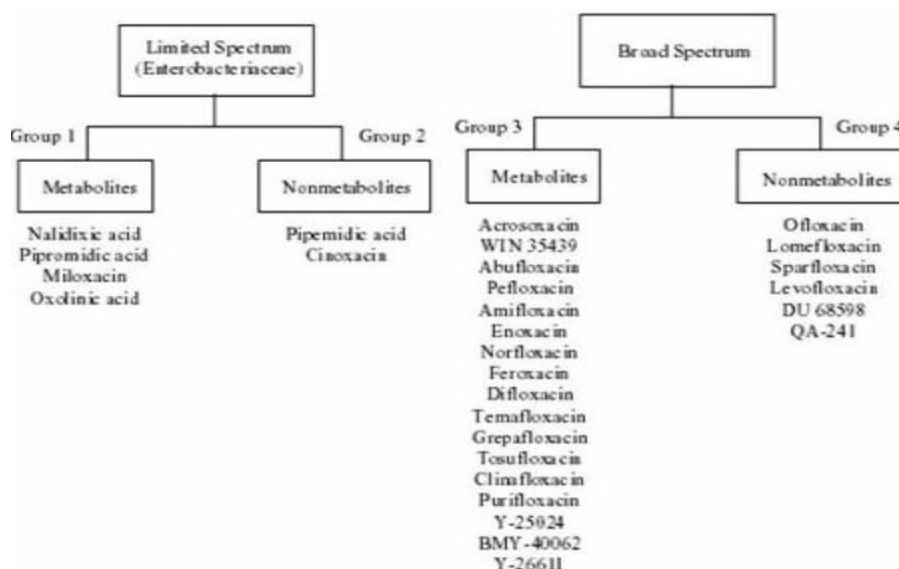
Gram-positive and gram-negative bacteria have been reported to be resistant to quinolones. This resistance appears to be the result of one of three mechanisms: alterations in the quinolone enzymatic targets (DNA gyrase), decreased outer membrane permeability or the development of efflux mechanisms. The accumulation of several bacterial mutations (DNA gyrase and bacterial permeability) has been associated with the development of very high minimum inhibitory concentrations to ciprofloxacin in isolates of *Staphylococcus aureus*, *Enterobacteriaceae* species and *P. aeruginosa*. Resistance to quinolones can also develop because of alterations in bacterial permeability and the development of efflux pumps. This resistance mechanism is shared with antimicrobial agents structurally unrelated to the quinolones, such as the betalactams, tetracyclines and chloramphenicol (Chloromycetin). Cross-resistance among the quinolones is expected, but the extent to which the minimum inhibitory concentration is affected varies from agent to agent. Therefore, the bacterial susceptibility and pharmacokinetic profiles of each quinolone should be considered in determining the effectiveness of specific agents.



Bacterial resistance to fluoroquinolones

CLASSIFICATION OF FLUOROQUINOLONES

Biological classification of Fluoroquinolones



IV. Classification On The Basis Of Activity

Class and agent	Half-life*	Route of administration	Dosage adjustment required	Significant adverse effects†	Significant Drug interactions‡
<u>First Generation</u>					
Nalidixic acid (NegGram)	60 to 90 min	Oral	Renal impairment		Warfarin (Coumadin)
Cinoxacin (Cinobac)	1.1 to 2.7 hours	Oral	Renal impairment	Hypersensitivity	
<u>Second Generation</u>					
Norfloxacin (Noroxin)	2.3 to 5.5	Oral	Renal		Warfarin, cyclosporine
Lomefloxacin (Maxaquin)	7 to 8.5 hours	Oral	Renal impairment	Phototoxicity, headache	
Enoxacin (Penetrex)	3.3 to 7 hours	Oral	Renal or hepatic impairment	Phototoxicity	Warfarin, ranitidine.
Ofloxacin (Floxin)	5 to 8 hours	Oral, intravenous	Renal or hepatic impairment	Insomnia	Warfarin
Ciprofloxacin (Cipro)	3 to 5.4 hours	Oral, intravenous	Renal impairment	Nausea, vomiting.	Warfarin, theophylline, caffeine.
<u>Third Generation</u>					
Levofloxacin (Levaquin)	6 hours	Oral, intravenous	Renal impairment	Headache, diarrhea	
Sparfloxacin (Zagam)	21 hours	Oral	Renal impairment	Phototoxicity QT-interval prolongation.	Drugs that prolong the QT interval,
Gatifloxacin (Tequin)	7 hours	Oral, intravenous	Renal impairment		Same as for sparfloxacin
Moxifloxacin (Avelox)	12 hours	Oral	Hepatic impairment	QT-interval prolongation	Same as for sparfloxacin
<u>Fourth Generation</u>					
Trovafloxacin (Trovan)	7.8 hours	Oral, Intravenous	Hepatic impairment	Dizziness severe hepatotoxicity	Morphine, citric acid

*—Half-lives are significantly increased for renally eliminated compounds.

†—All quinolones cause nausea, insomnia, headache and dizziness (3 percent or more of recipients); tendon rupture and cartilage damage are considered a possible effect of any quinolone.

‡—All quinolones interact with sucralfate (Carafate), antacids containing aluminum or magnesium, iron, calcium and zinc.

V. STRUCTURE ACTIVITY RELATIONSHIP

Position 1: Earlier study indicated that substitution at N-1 position is important for Anti-bacterial activity.

QSAR analysis of a set of N-1 allyl and alkyl derivatives suggested an optimum STERIMOL length of 0.42 nm, corresponding approximately to an ethyl group.



STERIMOL is a program that calculates a set of five parameters characterizing size and shape of a substituent. STERIMOL length is defined as length of substituent along the axis of bond between the substituent and the parent molecule.

Subsequently, the discovery of potent quinolones with N-1 phenyl and N-1 cyclopropyl substitutions indicated that with respect to an N-1 substituent, in addition to steric bulk, there are other factors such as electronic- π donation and ideal spatial effects that also have a great influence on their biological activities.

Introduction of a t-butyl group at N-1 produced quinolones with enhanced activity against gram positive bacteria with minor reduction of activity against gram negative bacteria.

In general, cyclopropyl group appears to be optimum for activity. e.g Ciprofloxacin.

Position 3: Position 3 and 4, having a link between the carboxylic acid group and the keto group are generally considered necessary for binding of quinolones to DNA gyrase.



Classical studies have produced no active quinolone with a significant modification of C-3 carboxylic acid group, with exception of groups which are converted *in vivo* to carboxylic group.

Position - 4: Position - 4 has not been extensively explored and replacement of 4- keto group with other groups has generally produced inactive or weakly active compounds.

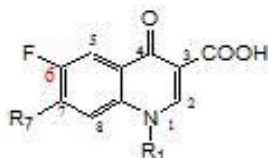
Position - 5:



Compounds with small substituents such as nitro, amino, halo, alkyl groups have been synthesized. Among them, C-5 amino group enhances absorption and / or tissue distribution. e.g Sparfloxacin .

The incidence of photo toxicity of Sparfloxacin is the lowest of the fluoroquinolones , because of the presence of the 5- amino group , which counteracts the effect of the 8- fluoro substituent .

Position - 6:

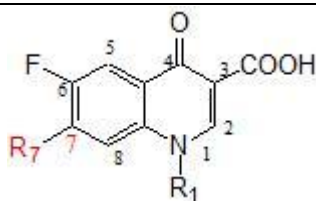


Of various C-6 substituents, H, Cl, Br, F, CH₃, S-CH₃, CO-CH₃, CN, NO₂ etc the addition of a fluorine atom resulted in a dramatic increase in anti-bacterial potency .

Fluoro group at C-6 seems to improve both the DNA gyrase complex binding (2 to 17 folds) and cell penetration (1 to 70 folds) of the corresponding derivatives with no substitution 6.

Position - 7: C-7 piperazinyl group in addition to C-6 fluorine substituent has anti-bacterial potency for superior to that of earlier classical quinolones against both gram-positive and gram-negative bacteria.

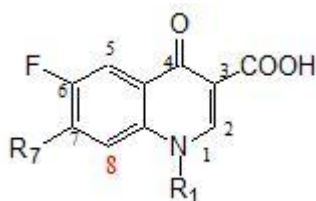
In general, quinolones with small or linear C-7 substituents (H, Cl, CH₃, NH₂-CH₂-CH₂-NH₂, NH-CH₃, NH-NH₂) possess moderate to weak anti-bacterial activities .



Various substitutions tried at C-7 position are -
 substituted piperazinyl
 substituted pyrrolidinyl
 substituted morpholinyl

In general, the substitution of methyl at C-4 position of the piperazinyl group enhances gram-positive antibacterial activity with slight decrease in gram-negative activity.

Position - 8: C-8 fluoro or chloro derivatives are more active in-vivo, owing to better oral absorption.



Oxygen substituent at C-8 position, where substituent is part of ring system has been shown to have better in vivo efficacy.

C-8 methoxy or ethoxy group appears to increase the spectrum of activity.

C-8 methoxy (e.g. Gatifloxacin) has been shown to contribute significant activity against anaerobes .

VI. DESIGNING THE DOSAGE FORM

In designing the dosage form, one major factor controlling their physicochemical properties is solid forms of the drug powder. Crystal engineering has evolved in such a manner that it is now synonymous with the paradigm of supramolecular synthesis, that is, it invokes self-assembly of existing molecules to generate a wide range of new solid forms without the need to break or form covalent bonds. A variety of surface specific techniques have been used to determine the face-specific structure, chemistry, and wettability of model pharmaceutical crystals. Crystallization is often employed for purifying a drug substance. Use of different solvents and processing conditions may change the crystal habit, besides altering the polymorphic state. Furthermore, altered habit may result from crystal growth during storage. Hence, there is a need to understand the factors influencing crystal habit and to evaluate critically, its role in the performance of dosage forms. Establishing the physic-technical properties of different habits of a drug will help to recognize lot-to-lot variations in raw materials and to ensure reproducibility of dosage for performance. One of the most important physical property which affects bio availability and therapeutic efficacy of a drug is existence of the active Pharmaceutical ingredient (API) in various crystal forms having different internal structure and physico chemical properties

Many solids may be prepared in a particular crystal form via appropriate change in conditions of crystallization e.g. (nature of solvent, solvent change, solvents with additives, temperature, rate of cooling etc). These crystal forms of a given API differ from each other with respect to their physical properties such as melting point, solubility, crystal shape, wettability, true density compaction behaviour and flow properties & dissolution rate etc. A crystal form having improved solubility / dissolution rate is useful in improving bio availability of a drug substance from an immediate release drug delivery system. The use of co-crystals in the pharmaceutical industry provides a great opportunity to enhance physicochemical properties of compounds with either poor solid state properties or poor solubility.

VII. CONCLUSION

The fluoroquinolones are important antimicrobial agents that have demonstrated activity against a wide range of Gram-positive and Gram-negative organisms and have proved useful against micro-organisms that are resistant to other antibacterial agents. Some examples include ofloxacin, ciprofloxacin, perfloxacin, levofloxacin and norfloxacin with newer ones entering the scene almost every five years. It is a well known fact now that all the clinically useful quinolones bear a fluorine group at the C-6 position and such quinolones which are

described as fluoroquinolones are produced by laboratory synthesis. They have excellent pharmacokinetic profile and attain appreciable concentrations well above their MICs in biological tissues .

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