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Gatifloxacin detection in the nanoscale: a review exploring current biosensing technologies and future opportunities

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Addressing the United Nations Sustainable Development Goals (SDGs), particularly SDG 3 (good health and well-being), SDG 6 (clean water and sanitation), SDG 9 (industry, innovation, and infrastructure), and SDG 15 (life on land) necessitates robust and accessible diagnostic tools for effective healthcare management and combating global health threats. Antimicrobial resistance (AMR) poses a formidable challenge to global health, with fluoroquinolones, a critical class of broad-spectrum antibiotics, facing increasing resistance. Gatifloxacin, a widely used fourth-generation fluoroquinolone, is a prime example of a drug whose efficacy is threatened by emerging resistance mechanisms. This review delves into the growing concern of gatifloxacin resistance and highlights the urgent need for innovative strategies to combat this escalating public health crisis. The necessity of rigorous healthcare monitoring for fluoroquinolones, including precise Therapeutic Drug Monitoring (TDM), is emphasized to optimize patient outcomes and mitigate the development of further resistance. Traditional monitoring techniques, such as chromatography and immunoassay, while effective, often suffer from limitations in terms of cost, complexity, and real-time applicability for routine clinical settings. This review provides a comprehensive overview of the current landscape of gatifloxacin detection, focusing on the significant advancements in electrochemical and optical sensor technologies at the nanoscale. We critically evaluate the underlying principles, performance characteristics, and limitations of existing sensor platforms. Furthermore, a detailed analysis of prevailing research gaps is presented, specifically highlighting the nascent exploration of advanced biosensing platforms like immunosensors, aptasensors, and FET-based devices for gatifloxacin. The absence of integrated Lab-on-Chip, microfluidic, and MEMS-based solutions, alongside the underutilization of next-generation materials such as MXenes, Transition Metal Dichalcogenides (TMDs), and rare earth metal oxides, is critically discussed. The untapped potential of Artificial Intelligence and Machine Learning (AI/ML) integration for enhanced sensor performance and the glaring lack of clinically validated point-of-care (POC) devices for TDM, particularly those adhering to USFDA Bioanalytical Device guidelines, are identified as critical avenues for future research. This review concludes by outlining the future prospects for developing cutting-edge, nanotechnological biosensors that are sensitive, selective, rapid, and cost-effective, ultimately contributing to better management of gatifloxacin therapy and bolstering global efforts against antimicrobial resistance.

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1. Introduction to quinolones and fluoroquinolones

Antibiotics are chemical compounds which are designed to either kill or inhibit bacterial activity. Antibiotics became a reality by the discovery of Penicillin in 1928 by Sir Alexander Fleming. When classified on the basis of molecular structures, the main categories of antibiotics are beta-lactams, macrolides, tetracyclines, quinolones, aminoglycosides, sulphonamides, glycopeptides and oxazolidinones.[1]

Quinolones are synthetic antibacterial agents characterized by their bicyclic core structure. The first-generation quinolone was in the form of nalidixic acid which did not prove to be effective due to its narrow antibacterial spectrum, poor tissue penetrability, rapid emergence of bacterial resistance, and frequent adverse central nervous system effects.[2] Second-generation quinolones introduced a fluorine atom at position C-6, a piperazine ring at R-7, and a cyclopropyl group at R-1. These became known as fluoroquinolones, offering enhanced Gram-negative and some Gram-positive activity but initially limited by bioavailability.[3] Third-generation fluoroquinolones

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further broadened their spectrum through additional substitutions at R-7 and R-8 (*e.g.*, methoxy, amino, chloro groups), providing better Gram-positive and atypical pathogen coverage. Fourth-generation agents added further structural modifications at multiple positions (R-1, R-5, R-7, and R-8), resulting in activity that extended to anaerobes as well.[4] In contrast to previous generation quinolones, fluoroquinolones have a stronger antibacterial effect and a wider range of activity because they have a fluorine atom added at position six and a nitrogen atom substituted for the eighth carbon atom in the backbone.[5] Fluoroquinolones are a class of antibiotics which has wide-spectrum of antibacterial activity and are designed to fight against bacteria by the inhibition of DNA gyrase and topoisomerase IV.[6] They have good bioavailability and tissue penetration capabilities.[6] They are now widely used to treat a variety of urogenital, respiratory, gastrointestinal, skin and urinary tract infections.[7] Ciprofloxacin, levofloxacin, cinoxacin, norfloxacin, ofloxacin, temafloxacin,[1] sparfloxacin, enoxacin, trovafloxacin, grepafloxacin, moxifloxacin and gatifloxacin[6] are some of the widely used fluoroquinolones. Topoisomerase is the primary target of quinolones in Gram-positive bacterial action while DNA gyrase is the secondary target. On the other hand, the quinolones' ability to combat Gram-negative bacteria is mostly due to their ability to first target DNA gyrase and then topoisomerase.[2,6] The evolution from first-generation quinolones to fluoroquinolones is marked by specific structural modifications—most importantly fluorination at C-6 and other substitutions at R-1, R-7, and R-8—which have progressively broadened their antimicrobial spectrum and clinical utility (Fig. 1).

2. Anti-microbial resistance to fluoroquinolones

Resistance to fluoroquinolones (FQs) in several bacterial species has been on the rise for a couple of decades due to their excessive administration in humans and animals. If this issue persists, fluoroquinolones will eventually become useless. Hence it is necessary to prevent inappropriate usage of such drugs. In certain European countries, usage of FQs is suggested only if specific narrow spectrum agents have failed to do the job.[5] Changes in access to the drug target enzymes (DNA-gyrase and topoisomerase IV) and mutations in the chromosomal genes encoding both subunits of DNA gyrase (gyrA and gyrB) or topoisomerase IV (parC and parE) cause resistance to quinolones.[7–10] Resistance also may occur through the action of efflux pumps. Bacterial resistance to quinolones, such as those used to treat infections caused by *Staphylococcus aureus* and *Streptococcus pneumoniae*, can arise through the increased activity of efflux pumps (Fig. 2).[11] These pumps, like NorA in *S. aureus* and PmrA in *S. pneumoniae*,[10] are cellular transporters that actively expel the antibiotic from the bacterial cell. Enhanced expression of these efflux pumps leads to reduced intracellular drug concentrations, thereby diminishing the effectiveness of the quinolone and contributing to antibiotic

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resistance. Resistance to ciprofloxacin increased slowly from 1.2% in 1998 to 2.5% in 2001. However, the NAUTICA (North American Urinary Tract Infection Collaborative Alliance) study revealed that ciprofloxacin resistance increased to 5.5% in 2004. The resistance rates in *E. coli* and *K. pneumoniae* increased from less than 2% in 1996 to greater than or equal to 20% in 2009.[7] In 1995, data from Thailand showed 83% resistance to fluoroquinolones in *campylobacter* species.[9] In Beijing within the years 1997-8, 50 to 60% resistance in *E. coli* was observed. Readings taken from Japan during the years 1993 to 1997, signified high AMR up to 62% towards ciprofloxacin in Neisseria gonorrhoeae.[9] *Among Staphylococcus aureus*, ciprofloxin was found to have above 95% AMR in Brazil and Europe.

3. Gatifloxacin: the drug of the hour

Gatifloxacin (gatifloxacin) is an 8-methoxy fluoroquinolone with a 3-methylpiperazinyl substituent at C-7 (Fig. 3a).[13] The drug has high oral bioavailability (96%), and, therefore, oral and intravenous formulations are bioequivalent and interchangeable. Gatifloxacin has a large volume of distribution (-1.8 L kg^{-1}), low protein binding ($\sim$20%), and broad tissue distribution and is

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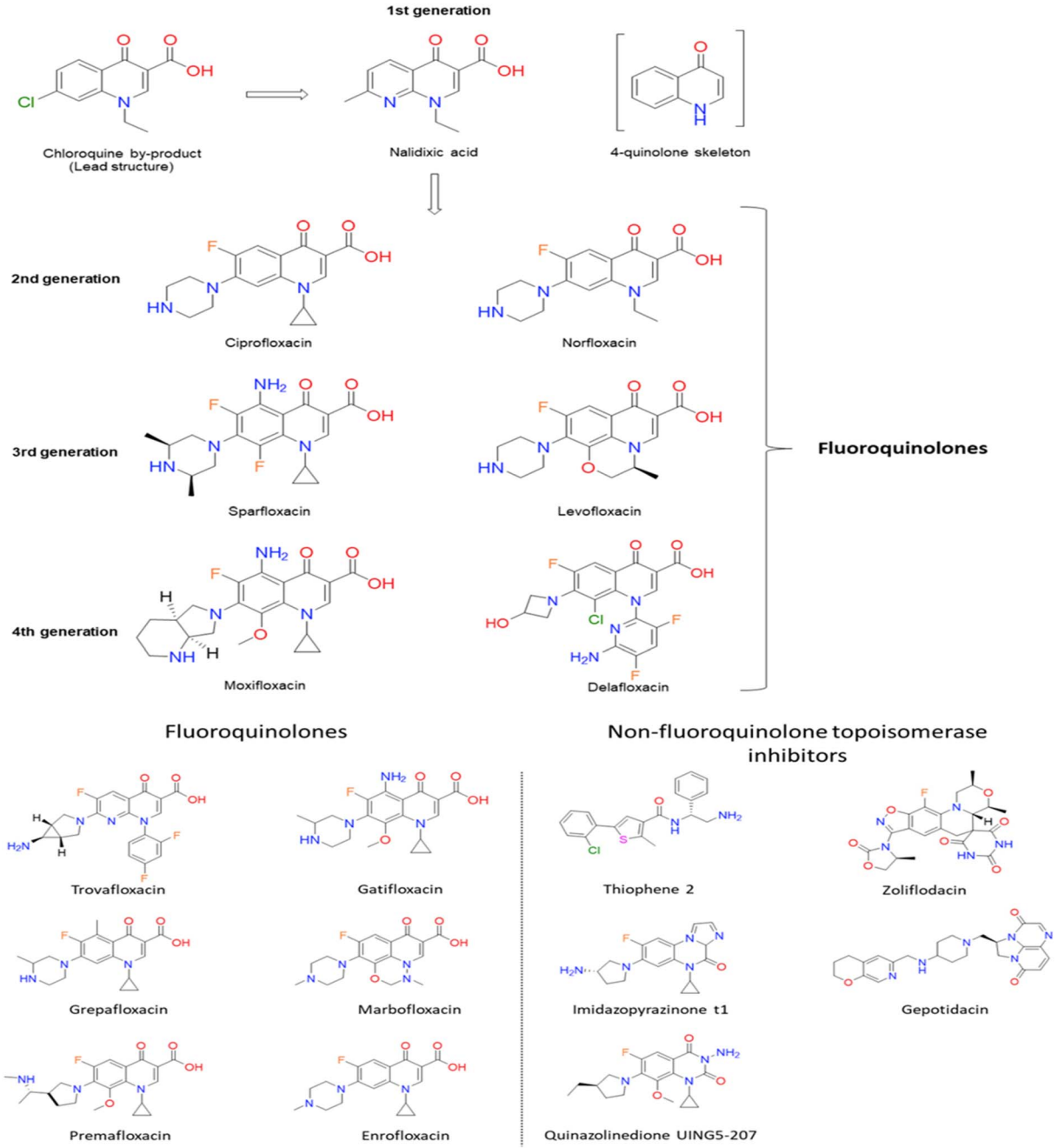

Fig. 1 Chemical structures of fluroquinolones.[8]

primarily excreted unchanged in the urine (180%).[14] Gatifloxacin, a fourth-generation fluoroquinolone, has been cleared to treat a variety of respiratory diseases, including community-acquired pneumonia, acute sinusitis, and chronic bronchitis.[15] It is usually prescribed to patients with several ocular infections. When it comes to Gram-positive bacteria, especially penicillin resistant *Streptococcus pneumoniae*, gatifloxacin exhibits superior *in vitro* activity than the more established fluoroquinolones ciprofloxacin and levofloxacin.[16] Also gatifloxacin is twice as active as levofloxacin. DNA gyrase and topoisomerase IV are necessary for both DNA replication and the division of replicated chromosomal DNA.[17] A key benefit of this drug is its ability to inhibit multiple enzymes. This makes it harder for bacteria to develop resistance. If a mutation occurs in one enzyme, the drug can still target the other, preventing significant resistance from developing. However, if mutations occur in both enzymes, resistance could still emerge.[18] Gatifloxacin is primarily excreted in the urine unchanged *via* glomerular filtration.[14] The plasma elimination half-life was found to be approximately 8 hours in individuals with normal renal function.[13,17] It is minimally altered by the body's metabolic processes.[13] gatifloxacin was a mainstay fluoroquinolone of the shorter MDR-TB regimen until a global shortage of quality-assured formulations of the medicine occurred following safety concerns. Clinicians had to replace

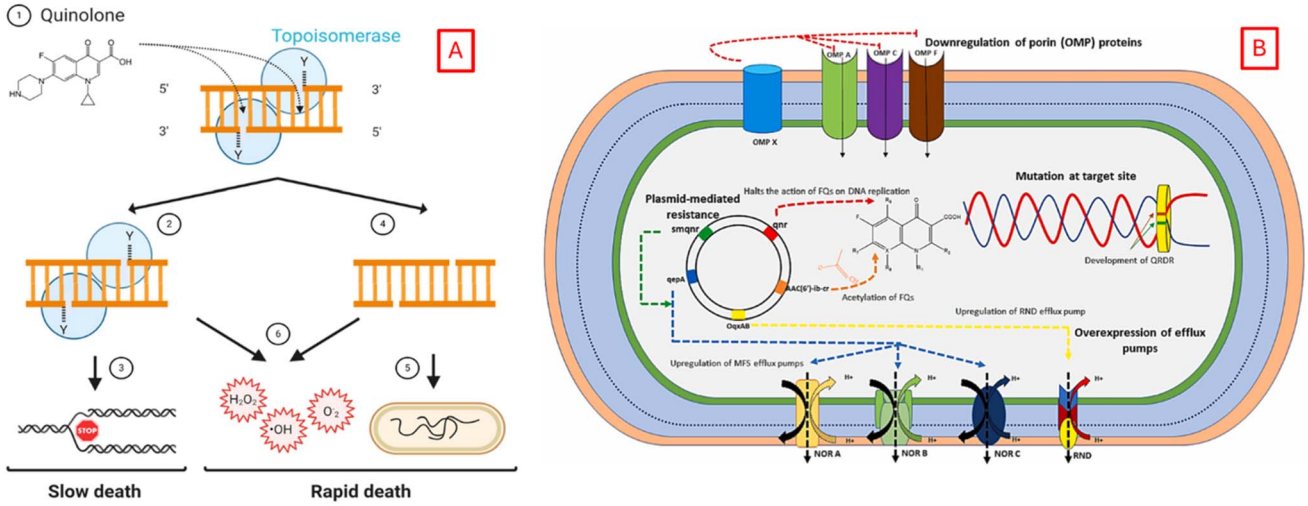

Fig. 2 (A) Mode of action of quinolones and fluroquinolones;[8] (B) mechanism of antimicrobial resistance imposed from fluroquinolones.[12]

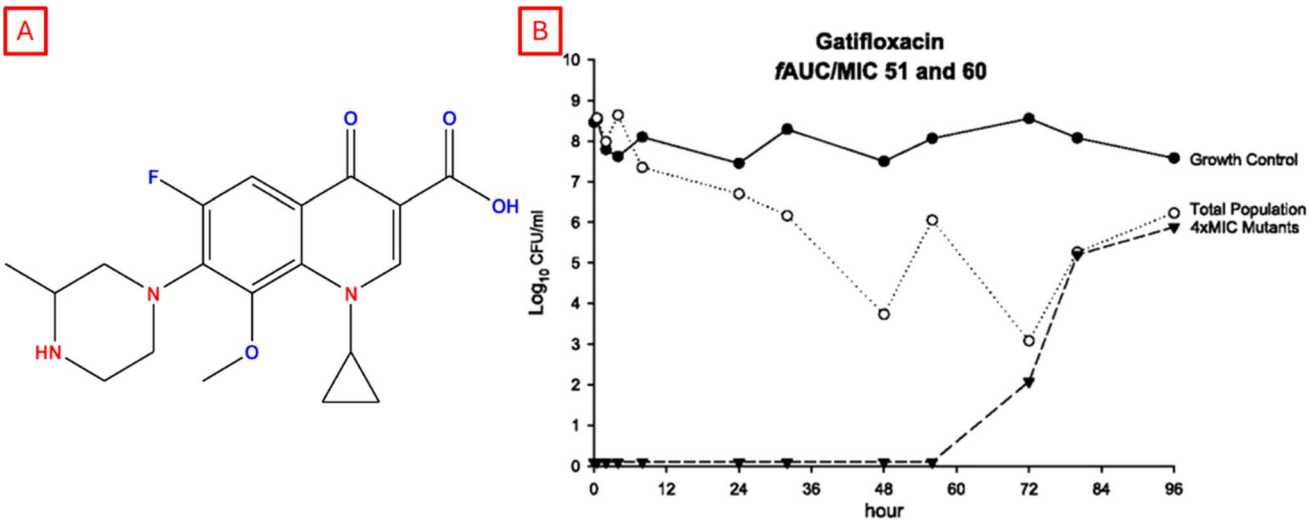

Fig. 3 (A) 2D Chemical structure of gatifloxacin;[50] (B) time-kill assessment and resistance development at *fAUC*/MIC of gatifloxacin *versus* wild-type *Streptococcus pneumoniae* (BSP2443 and ATCC 49619).[51]

gatifloxacin with other later-generation fluoroquinolones in both shorter and longer MDR-TB regimens. Given that gatifloxacin is cheaper to manufacture than other later-generation fluoroquinolones, the inclusion of gatifloxacin on the EML should encourage pharmaceutical manufacturers to produce this medicine. In 2017, the Expert Committee did not recommend listing of gatifloxacin in the World Health Organization's List of Essential Medicines as a reserve second-line drug for multidrug-resistant tuberculosis was not recommended, as the available evidence did not show it to have a superior benefit-harm ratio compared with alternative fluoroquinolones included on the list.[19]

4. Pharmacokinetics and pharmacodynamics of gatifloxacin

Gatifloxacin is a synthetic broad-spectrum fluoroquinolone antibiotic, and its pharmacokinetics describe how the body absorbs, distributes, metabolizes, and eliminates the drug. Gatifloxacin is well-absorbed from the gastrointestinal tract after oral administration. Its absolute bioavailability is high, typically around 96%, meaning a large proportion of the administered dose reaches the systemic circulation. Peak plasma concentrations are generally achieved within 1 to 2 hours after oral dosing. Food does not significantly affect the extent of absorption, although it may slightly delay the time to peak concentration. Gatifloxacin is widely distributed throughout the body, with concentrations in tissues and bodily fluids often exceeding those in plasma. It penetrates well into various tissues, including respiratory tract secretions, lung tissue, blister fluid, and gynaecological tissues. Approximately 20% of gatifloxacin is bound to plasma proteins. Gatifloxacin undergoes limited biotransformation in humans. Less than 1% of the administered dose is excreted in the urine as ethylenediamine and methyl ethylenediamine metabolites. This

minimal metabolism suggests that drug interactions based on cytochrome P450 enzyme inhibition or induction are unlikely to be clinically significant.[20–22]

Pharmacodynamics describes the effects of gatifloxacin on the body, particularly its mechanism of action and the relationship between drug concentration and its antimicrobial effects. Gatifloxacin exerts its bactericidal action by inhibiting two essential bacterial enzymes: DNA gyrase (topoisomerase II) and topoisomerase IV. These enzymes are crucial for bacterial DNA replication, transcription, repair, and recombination. In Gram-negative bacteria, DNA gyrase is the primary target. This enzyme is responsible for introducing negative supercoils into bacterial DNA, which is necessary for DNA replication and transcription. Gatifloxacin binds to the DNA-gyrase complex, preventing the enzyme from resealing the DNA breaks it creates, leading to fragmentation of the bacterial chromosome and cell death. In Gram-positive bacteria, topoisomerase IV is often the primary target. This enzyme is involved in separating replicated bacterial DNA chromosomes (decatenation) before cell division. Gatifloxacin inhibits topoisomerase IV, preventing the separation of daughter DNA strands, thereby blocking bacterial cell division. The dual targeting of both DNA gyrase and topoisomerase IV contributes to gatifloxacin's broad spectrum activity and helps to reduce the frequency of resistance development compared to earlier fluoroquinolones that primarily targeted only one enzyme. Gatifloxacin is a broad-spectrum antibiotic active against a wide range of Gram-positive and Gram-negative bacteria, as well as atypical pathogens. Its activity includes common respiratory pathogens such as Streptococcus pneumoniae (including penicillin-resistant strains), Haemophilus influenzae, and Moraxella catarrhalis.[23,24]

The primary route of gatifloxacin elimination is renal, with approximately 70% of an orally administered dose excreted unchanged in the urine. The mean terminal half-life of gatifloxacin ranges from 7 to 14 hours, allowing for once-daily dosing. Dosage adjustments are typically required for patients with impaired renal function to prevent drug accumulation. Standard dosages of gatifloxacin typically vary depending on the type and severity of the infection. It is commonly available in oral tablet and intravenous (IV) formulations. For Community-Acquired Pneumonia (CAP), Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB), Acute Sinusitis, and Uncomplicated Skin and Skin Structure Infections: Typically, it is administered as 400 mg orally or intravenously once daily. The treatment duration varies depending on the infection, often ranging from 5 to 10 days. For Uncomplicated Urinary Tract Infections (UTIs), a shorter course, such as 400 mg orally once daily for 3 days, is followed. For Complicated Urinary Tract Infections (UTIs) and Acute Pyelonephritis, a standard regime of 400 mg orally or intravenously once daily for a longer duration, often 7 to 14 days. Gatifloxacin is also available as an ophthalmic solution (*e.g.*, 0.3% or 0.5%) for bacterial conjunctivitis. The dosage typically involves instilling one drop into the affected eye(s) several times a day, with frequency potentially decreasing over the course of treatment.[25,26]

A comparative pharmacokinetic/pharmacodynamic (PK/PD) profiling of gatifloxacin with other fluoroquinolones may be incorporated to better delineate its unique therapeutic advantages and limitations. Pharmacokinetic parameters such as oral bioavailability, plasma elimination half-life, volume of distribution, and tissue penetration profiles can be systematically compared with agents like moxifloxacin, levofloxacin, and ciprofloxacin.[27,28] Pharmacodynamic indices, including the ratio of the area under the concentration–time curve to the minimum inhibitory concentration (AUC/MIC) and peak plasma concentration to MIC ratio (Cmax/MIC)—may also be contrasted to assess bactericidal potential and resistance suppression capacity.[29–31] Gatifloxacin has been shown to achieve high and sustained tissue concentrations, particularly within ocular tissues and the respiratory tract. Its intermediate elimination half-life permits once- or twice-daily dosing schedules, offering dosing flexibility.[32,33] MIC values for key Gram-positive and Gram-negative pathogens are often lower compared to ciprofloxacin and levofloxacin, allowing pharmacodynamic targets to be attained at standard dosing regimens.[34] Limitations have been identified, including the risk of dysglycemia, which has been reported with greater frequency relative to other fluoroquinolones, thereby restricting systemic use in certain patient populations such as those with diabetes mellitus.[35,36] Moreover, regional surveillance data have demonstrated increasing resistance rates, reducing its empiric utility in high-prevalence settings.[37,38] By presenting these comparative PK/PD data in tabular or narrative form, a clearer understanding can be provided of those clinical scenarios in which gatifloxacin, based on its pharmacological characteristics, may be preferred, as well as those in which alternative fluoroquinolones may exhibit superior efficacy or safety. In this manner, the inclusion of such a profile would facilitate evidence-based antimicrobial selection while aligning with antimicrobial stewardship objectives.[39]

5. Global outlook and regional surveillance

According to data from the World Health Organization's GLASS program and regional networks, resistance to fluoroquinolones, including gatifloxacin, has been rising in key pathogens such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Salmonella* species.[40,41] In several Asian countries, the susceptibility of *E. coli* and *K. pneumoniae* to gatifloxacin is reported to be below 30%, with similar trends in parts of Africa and Latin America. In India and Southeast Asia, surveillance between 2021 and 2024 shows declining gatifloxacin efficacy against common uropathogens and *Salmonella enterica* (typhoid). In China and Bangladesh, increased resistance among *E. coli* isolates to gatifloxacin has been documented in hospital and outpatient settings, often exceeding 40% non-susceptibility rates post-2022. In a hospital-based study spanning 2014 to 2024, resistance to gatifloxacin among ocular bacterial isolates showed a marked increase in certain bacterial species during and post the COVID-19 pandemic.[42–44] For example, resistance in *Staphylococcus* rose from 15.2% pre-COVID-19 to 32.7% during the pandemic and remained high at 29.7% post-pandemic. *Streptococcus* resistance similarly increased from 12.0% to over 40% during the same period. *Corynebacterium* resistance also nearly doubled, reaching 46.4% post-pandemic. Conversely, *Pseudomonas* resistance rates remained relatively

stable, around 6–11%. These data point to a reduced utility of gatifloxacin for empiric therapy in areas with high resistance and reinforce the necessity for local susceptibility testing and antimicrobial stewardship to guide prescribing. They also underline the importance of monitoring resistance trends to fluoroquinolones as a class and adapting treatment guidelines accordingly.[45]

6. Mechanism of resistance development to gatifloxacin

In a study conducted by Laplante *et al.*, about resistance in two fluoroquinolone-susceptible strains of *S. pneumoniae*, MICs reported for ATCC 49619 and BSP2443 were 0.19 and 0.25 mg L^{-1} for gatifloxacin.[10] Simulated free gatifloxacin exposure at fAUC/MICs of 51 and ≤60 led to first-step parC (S79Y, S52G, and N91D) and second-step gyrA (S81Y and S114G) mutations for the BSP2443 and ATCC 49619 strains, respectively (Fig. 3b).[10] The fAUC/MIC ratios of 62 and ≥66 with gatifloxacin for the BSP2443 and ATCC 49619 strains, prevented the development of first-step parC and second-step gyrA mutations.[10] However, there was no evidence of efflux-mediated resistance following gatifloxacin exposure. It is suggested that, in patients with respiratory infections caused by *S. pneumoniae*, the emergence of resistance may be reduced by using a fluoroquinolone like gatifloxacin that surpasses the pharmacodynamic breakpoint for resistance development. Ince *et al.*, did a comparison study of resistance to gatifloxacin and drugs like AM-1121 and ciprofloxacin in *S. aureus* and found that single mutation in gyrA of DNA gyrase had very little impact on MICs of these FQs. But in double mutants with gyrA and either grlA or grlB mutations, the MICs of gatifloxacin increased 32- to 64-fold (to 4.0 g mL^{-1}), while the MICs of ciprofloxacin and AM-1121 increased 128- to 256-fold (to 32 g mL^{-1}). Effect of over-expression of the NorA efflux pump on the MIC of gatifloxacin was negligible.[46] Another resistance mechanism proposed was the interaction of efflux transporters.[15] It has been already stated that gatifloxacin is prescribed for ocular infections. It is highly effective against many bacterial species, with a very low minimum inhibitory concentration (MIC) of 0.1 g mL^{-1}. However, its use in treating eye infections is limited due to systemic toxicity. One major challenge is that certain drug-resistant mechanisms, such as efflux pumps, can reduce its effectiveness. These pumps actively push the drug out of cells, preventing it from reaching therapeutic levels in the corneal aqueous humor and iris-ciliary body. Increasing the dosage to overcome this issue may lead to harmful side effects. ATP-binding cassette transporters are one of the primary pumps that drive drug molecules out of the target cell, which essentially limits the drug concentration at target cell.[15] Antimicrobial resistance surveillance programs have been established in various parts of the world to assess the threat. One such program named SENTRY, 1997 investigated the potency and spectrum of gatifloxacin against over 23 000 clinical isolates collected from different parts of America. Jones *et al.*, evaluated the antimicrobial activity of gatifloxacin using data from the SENTRY Antimicrobial Surveillance Program. Gatifloxacin demonstrated strong potency against a wide range of bacterial pathogens, showing similar effectiveness to other fluoroquinolones such as levofloxacin, sparfloxacin, and trovafloxacin.[47] Gatifloxacin was particularly effective against Enterobacteriaceae (94.8% susceptible at ≤2 mg L^{-1}), *Acinetobacter* spp. (77.2%), *Stenotrophomonas maltophilia* (75.1%), *Streptococcus pneumoniae* (99.8%), and various *Staphylococcus* species (79.2–100%).[47] Trovafloxacin was the most similar in terms of spectrum and potency. Studies indicate that high-level resistance is often associated with specific mutations at positions 87 and 91 of the gyrA gene, which can lead to increased minimum inhibitory concentrations (MICs) for gatifloxacin.[48] Another study investigated resistance to gatifloxacin, moxifloxacin, and balofloxacin in *Staphylococcus epidermidis* strains isolated from patients with ocular infections, including endophthalmitis, corneal ulcers, and conjunctivitis. Scientists reported that 13.6% of the tested strains were quinolone-resistant, with higher resistance rates in endophthalmitis cases (21.4%) compared to corneal ulcers (14.2%) and conjunctivitis (4.3%). The resistance mechanism was linked to mutations in the *gyrA* and *parC* genes, specifically Ser84Phe in *gyrA* and Ser80Phe in *parC*, which are known to cause quinolone resistance. It should be noted that gatifloxacin had little effect on the expression levels of these genes, suggesting that genetic alterations rather than overexpression of genes are the main cause of resistance. The results emphasize the necessity of taking into account alternate treatments for ocular infections caused by *Staphylococcus epidermidis* because fluoroquinolone resistance is growing.[49]

7. Combating AMR to gatifloxacin

To combat AMR, optimizing treatment regimens is crucial. High dose gatifloxacin regimens have shown improved cure rates even in the presence of low-level resistance, suggesting that appropriate dosing can mitigate resistance development.[52] In the context of multidrug-resistant tuberculosis (MDR-TB), gatifloxacin has been associated with lower rates of treatment failure and relapse compared to other fluoroquinolones, indicating its potential role in effective treatment strategies.[53] Additionally, the use of gatifloxacin in combination with other antibiotics may enhance its efficacy and reduce the likelihood of resistance.[54] Results from a study conducted by Liu *et al.*, revealed the advantage of using gatifloxacin ophthalmic gel rather than ophthalmic solution, which improved the drug concentration in aqueous humor of cataract patients.[55] Furthermore, the formulation of bio-adhesive gels containing gatifloxacin for localized delivery in periodontal treatments illustrates a strategy to enhance drug concentration at infection sites while minimizing systemic exposure and potential resistance.[56]

Clinical guidelines emphasize that the use of gatifloxacin should be considered when local antimicrobial susceptibility data indicate favourable sensitivity patterns, particularly in regions where resistance to older fluoroquinolones or other antibiotic classes is prevalent. Furthermore, the safety profile of gatifloxacin, including its relatively lower risk of certain adverse effects compared to other fluoroquinolones, may influence its

selection, especially in populations at higher risk of drug-related toxicities.[57–61] Therapeutic choice is also influenced by the patient's underlying conditions, comorbidities, and previous antibiotic exposure, which can affect the risk of resistance and adverse events. The drug's pharmacokinetics, including good bioavailability and extensive tissue distribution, are considered to optimize dosing regimens tailored to infection site and severity. In clinical decision-making, the selection of gatifloxacin over other fourth-generation fluoroquinolones is generally guided by specific infection characteristics, pathogen susceptibility profiles, pharmacokinetic and pharmacodynamic properties, and safety considerations. Gatifloxacin is often preferred in the treatment of ocular infections such as bacterial conjunctivitis and keratitis, where its broad-spectrum activity against both Gram-positive and Gram-negative bacteria, including resistant strains, has been demonstrated. The drug's high ocular tissue penetration and sustained intraocular concentrations contribute to its clinical efficacy in this context. Additionally, gatifloxacin exhibits potent activity against certain respiratory pathogens and atypical organisms, which may inform its use in respiratory tract infections when susceptibility is confirmed or strongly suspected.[62–67] Hence, gatifloxacin is widely selected over as an alternative fourth-generation fluoroquinolones primarily based on infection type, documented or anticipated pathogen susceptibility, favourable pharmacological properties, and an acceptable safety margin, all of which are integrated into evidence-based clinical guidelines to maximize therapeutic outcomes while minimizing resistance development.

Several clinical trials have been conducted or are ongoing that illustrate gatifloxacin's safety, efficacy, and potential roles in therapy amid resistance challenges. Trials in bacterial conjunctivitis have demonstrated the safety and clinical superiority of gatifloxacin ophthalmic solutions compared to placebo or vehicle, supporting its use in ocular infections where local drug delivery can limit systemic resistance pressure.[68] In respiratory infections, randomized controlled trials have compared once-daily oral gatifloxacin to standard treatments like co-amoxiclav and ceftriaxone, showing comparable clinical efficacy and safety, which underscores its therapeutic value in community-acquired pneumonia and enteric fever.[69] Notably, a large randomized controlled trial in Vietnam compared gatifloxacin (10 mg kg per day) for 7 days with azithromycin in typhoid fever patients, finding similar rates of fever clearance and treatment failure in multidrug-resistant (MDR) and nalidixic acid-resistant strains.[70] This trial highlighted gatifloxacin's role in combating resistant pathogens, although concerns about emerging high-level resistance influenced treatment recommendations. Completed Phase IV trials have assessed formulations of gatifloxacin eye drops with additives like benzalkonium chloride, aiming to improve local drug concentrations and reduce resistance development.[71–73] While direct ongoing clinical trials specifically targeting AMR to gatifloxacin are limited, many existing studies and trials have focused on optimizing dosing regimens, evaluating combination therapies, and improving formulations to curb resistance emergence.

8. Beyond the prescription does fluoroquinolone use demand our continuous supervision?

Gatifloxacin can have several harmful effects on the environment, primarily due to its widespread use in human and veterinary medicine and its subsequent release into aquatic and terrestrial ecosystems. While some studies suggest its degradation in the environment, particularly through photolysis, its continuous introduction can still pose risks. Gatifloxacin, being water-insoluble and not readily volatile, tends to partition into the aquatic environment. It has been detected in municipal wastewater, surface waters (rivers, lakes), and even groundwater. Conventional wastewater treatment plants can only partially remove fluoroquinolone antibiotics like gatifloxacin, leading to their release into receiving water bodies. Studies have shown gatifloxacin to have toxic effects on aquatic organisms. For instance, acute and chronic toxicity tests on *Daphnia magna* (a freshwater cladoceran often used as a model organism) demonstrate adverse effects on their growth, survival, and reproduction at certain concentrations.[74–76] As an antibiotic, gatifloxacin can disrupt the natural microbial communities in aquatic systems. This can affect nutrient cycling and overall ecosystem health. While gatifloxacin undergoes photodegradation (degradation by light), some of its photodegradation products can retain comparable or even higher antibacterial activity than the parent compound.[77] This means that even after partial breakdown, the transformed compounds can still exert selective pressure on bacteria, potentially contributing to antibiotic resistance. Research on zebrafish has indicated that gatifloxacin exposure can induce morphological and functional abnormalities in their cardiovascular system.[78] The presence of gatifloxacin in the environment, even at low concentrations, can create a selective pressure that favours the survival and proliferation of antibiotic-resistant bacteria.[79,80] This is a major global health concern, as it can lead to the emergence of "superbugs" that are difficult to treat with existing medications. Environmental reservoirs of antibiotics can facilitate the transfer of antibiotic resistance genes among different bacterial species, further exacerbating the problem. Gatifloxacin is primarily excreted unchanged in urine and faeces by humans and animals and enters the environment through the improper disposal of unused medications. This can lead to its introduction into soil through sewage sludge application or direct contamination. Similar to aquatic environments, gatifloxacin can affect the delicate balance of microbial communities in soil, which are crucial for soil fertility and ecosystem services. While studies on its biodegradation in soil specifically are less abundant, general principles suggest that antibiotics can persist and impact soil microbiology. While gatifloxacin is somewhat water-soluble, there is a potential for it to be taken up by aquatic organisms and potentially transferred up the food chain. This bioaccumulation could lead to higher concentrations in top predators, though specific data on gatifloxacin's accumulation in wildlife needs further extensive research. Pharmaceuticals, including antibiotics, can be taken up by

plants grown in contaminated soil or irrigated with contaminated water. This raises concerns about their entry into the food chain and potential impacts on plant health and consumers.[80]

WHO assists countries in designing and executing Antimicrobial Stewardship Programs (ASPs) to enhance antimicrobial use, improve patient care, and combat antimicrobial resistance (AMR). Implementing robust antimicrobial stewardship programs is essential to curb the misuse of gatifloxacin and other antibiotics. The indiscriminate use of fluoroquinolones in clinical settings has been linked to rising resistance rates,[81] particularly in ocular infections.[82] In 725 Gram-positive bacteria, the resistance of ciprofloxacin, ofloxacin, gatifloxacin, and moxifloxacin was 55.9%, 42.7%, 47.6%, and 45.6% respectively. In 266 Gram-negative bacteria, the resistance of ciprofloxacin, ofloxacin, gatifloxacin, and moxifloxacin was 57.9%, 56.0%, 59.9%, and 74.3% respectively.[83] Educating healthcare providers on appropriate prescribing practices and the importance of susceptibility testing[81] can help mitigate the emergence of resistant strains.[82]

9. Environmental impact of gatifloxacin: quantitative evidence on ecological risks

The environmental presence and impact of gatifloxacin, a widely used fourth-generation fluoroquinolone antibiotic, have become a growing concern due to its persistence, bioaccumulation potential, and ecological toxicity. Quantitative data from recent studies provide a robust evidence-based perspective on the environmental risks associated with gatifloxacin exposure in aquatic ecosystems, particularly through wastewater contamination.

Gatifloxacin residues have been consistently detected in wastewater treatment plant (WWTP) influents, effluents, and associated sludge, underscoring its incomplete removal during conventional treatment processes.[84,85] Concentration measurements in raw sewage have been reported around 229.30–1595.73 μg L^{-1}. Sludge concentrations are substantially higher, indicating a strong affinity for sorption to biosolids rather than complete biodegradation.[86] The detection efficiencies of gatifloxacin in WWTPs vary but are generally moderate, averaging around 96.97% with considerable variability depending on treatment technologies and operational conditions. This incomplete removal leads to the continuous release of gatifloxacin into receiving surface waters, where it can exert selective pressure on microbial communities. The bioaccumulation potential of gatifloxacin in aquatic organisms is an important factor in ecological risk. Though bioaccumulation factors (BAFs) or bioconcentration factors (BCFs) specific to gatifloxacin are less frequently published than for other fluoroquinolones, related research indicates that fluoroquinolones tend to accumulate preferentially in tissues with high lipid and phospholipid content, such as the liver and viscera of fish and invertebrates.[87] This retention is influenced not only by hydrophobicity but also by environmental pH and the compound's ionizable nature. Experimental exposures in model fish species reveal differential accumulation across tissue types, and for fluoroquinolones in general, BCF values can range widely, often within 10–62.37 ng g^{-1} depending on concentration and species. Gatifloxacin's structure, particularly substitutions at R-7 and R-8, may influence its accumulation patterns similarly, though direct BCF quantifications for gatifloxacin remain limited in reported literature.

Ecotoxicological assays have demonstrated that gatifloxacin at environmental concentrations can induce significant negative effects on aquatic organisms. For example, studies on cyanobacteria such as Microcystis aeruginosa report 96-hour EC50 toxicity values of approximately 25.30 μg L^{-1} for gatifloxacin, indicating moderate toxicity that can impair photosynthesis, induce oxidative stress, and promote the release of harmful microcystin.[88] Such effects threaten aquatic primary producers, potentially disrupting entire food webs. Similarly, photodegradation studies of gatifloxacin reveal that while sunlight can partially degrade the molecule with half-lives ranging from minutes to hours under sunlit conditions, the breakdown products may retain or even exceed the parent compound's antibacterial activity, prolonging ecological risks.[89] Recent advances in wastewater treatment, such as ozonation and activated peroxymonosulfate processes, have shown promise in degrading gatifloxacin residues effectively under optimized conditions.[90,91] However, these treatments need to be carefully managed as some transformation products may still exhibit residual antimicrobial or toxic effects. Such treatment improvements could reduce environmental loading and consequent selective pressure for resistance development.

In summary, quantitative environmental data highlight the persistence of gatifloxacin in aquatic environments, moderate removal in WWTPs, propensity for bioaccumulation, and measurable ecological toxicity at environmentally relevant concentrations. These findings underscore the need for continued monitoring, improved treatment technologies, and collaborative efforts to mitigate the ecological risks posed by gatifloxacin contamination. Integrating these quantitative metrics into environmental risk assessments provides a more evidence-based foundation to support policy decisions and sustainable antibiotic use practices.

10. Therapeutic drug monitoring: an important aspect of human healthcare

The process of periodic measurement of drug concentration in a patient's bloodstream is termed as Therapeutic Drug Monitoring (TDM).[92,93] This analysis is used to study the pharmacokinetics upon the administration of a drug. Keeping the drug concentration within the target concentration range is advised. This is to ensure that inadequate dosage as well as excess administration of drug can be prevented. The amount of drug required the way each patient's body reacts or eliminates a particular drug will be different.[92] The dosage required after a certain period in therapy will be different from the initial dosage. In clinical settings, TDM tests are done by chromatographic techniques or immunoassays.[94] However, these

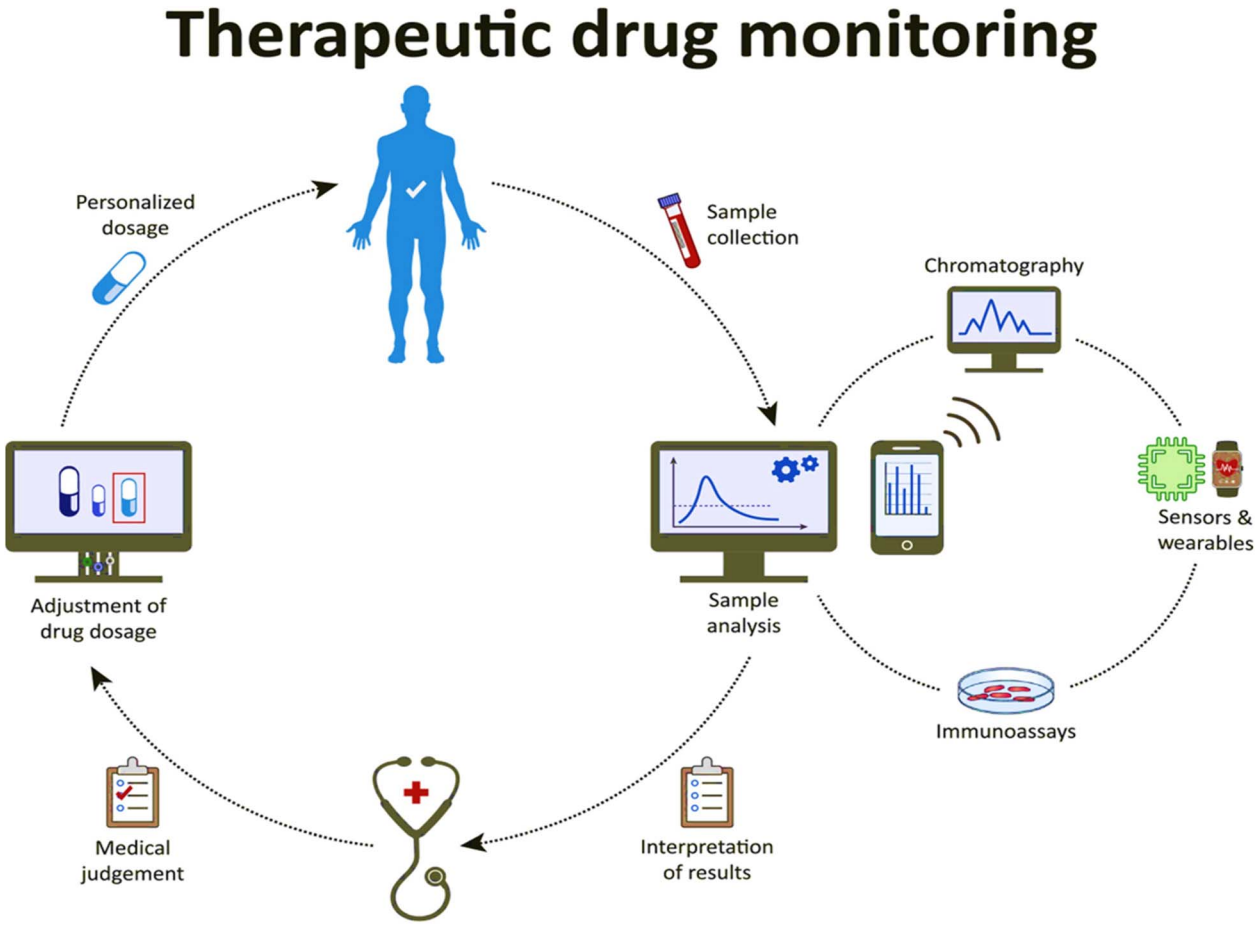

Fig. 4 Overview of therapeutic drug monitoring.[97]

techniques are complex and cumbersome. Also, the instruments are expensive and need expert handling. For medications with narrow therapeutic indices, TDM is crucial for optimizing drug therapy because it keeps drug concentrations within a target range, maximizing efficacy while avoiding toxicity.[95,96] Since AMR to gatifloxacin has been spiking, appropriate tracking of its usage is necessary (Fig. 4).

11. Monitoring techniques for gatifloxacin detection

11.1. Chromatography

Chromatography is a well-established tool for separation of components in a mixture. Basically, the analyte is carried by the mobile phase through the stationary phase. Mobile phase can either be gas or liquid. Similarly, stationary phase can be solid, or liquid adsorbed on a solid surface. The rate at which each component in the sample moves will be different. Corresponding to their movement, there will be a specific retention time for each element. Thus, on the chromatogram we can differentiate between various components because each one will have peaks at varied retention times. Though chromatography was initially designed to separate constituents in a sample, eventually it became a tool for quantitative analysis too. Detectors coupled with the chromatography system does the identification of each component that has been separated. Detectors based on UV absorbance, IR spectroscopy, MS (mass spectrometry), refractive index changes, electrochemical reactions have been used successfully. Several chromatographic techniques, such as gas chromatography (GC),[98] liquid chromatography (LC),[98] thin layer chromatography, affinity chromatography and high-performance liquid chromatography (HPLC),[99] have been developed for practical applications. Even though gas chromatography is a relatively easy method, it can only be used for about 20% of chemical compounds. This is because, compounds which are unstable or highly reactive cannot be separated using GC. Another limitation is that it needs to be heated to 300 to 400 °C during the process. For the examination of volatile and semi-volatile substances, GC is still a crucial method, especially in metabolic, toxicological, and forensic investigations. GC allows for the quick separation of analytes according to their volatility and affinity for a liquid or solid stationary phase by using a gaseous mobile phase. By providing high resolution, selectivity, and structural elucidation of complex biochemical profiles, including fatty acids and steroid hormones, the combination of GC with mass spectrometry (GC-MS) has boosted its value for diagnosis.

The versatility of these techniques allows for the precise quantification of various compounds including fluoroquinolones. HPLC has proved its worth in effective and precise therapeutic drug monitoring (TDM) in matrices like pharmaceutical formulations, biological fluids, and environmental samples. The development of HPLC methods for gatifloxacin has been extensively documented. Lopez *et al.* proposed a reverse phased HPLC for the estimation of gatifloxacin, which gave results in 2 hours.[100] The choice of mobile phase and column type is critical in HPLC method development. For example, a study by Razzaq *et al.*, employed a C8 stationary phase with a phosphate buffer and methanol, achieving good separation of gatifloxacin from degradation products.[101] In addition to pharmaceutical applications, HPLC has been utilized to analyze gatifloxacin in biological matrices. For instance, Ding *et al.*, employed HPLC to compare drug concentrations in human aqueous humor after administering gatifloxacin ophthalmic formulations.[102] This study illustrates the relevance of HPLC in pharmacokinetic studies, providing insights into the drug's distribution and efficacy in therapeutic applications. Several studies have developed and validated HPLC methods for the simultaneous determination of gatifloxacin and other compounds. Santoro *et al.* used HPLC with minor variations in wavelengths to determine four different fluoroquinolones quantitatively.[99] Reverse phase HPLC was utilized by Sultana *et al.*, for determination of gatifloxacin in pharmaceutical formulations and human plasma. It had a linear range of 0.1–25 μg mL^{-1}.[103]

11.2. Immunoassays

Immunoassays are used to quantify biomolecules. When an antigen binds with a suitable antibody, it causes a reaction which can be observed *via* several methods. The most widely applied immunoassay is enzyme-linked immunosorbent assay (ELISA). In addition to that, assays such as Lateral flow immune assay (LFIA), Fluorescence immunoassay (FIA), Surface plasmon resonance (SPR) immunoassay and Electrochemical immunoassay have been developed.[104]

FIA utilizes fluorescent labels for signal detection, offering higher sensitivity compared to colorimetric methods. FIA enables real-time monitoring and quantitative analysis, with the ability to detect low concentrations of quinolones. Fluorophores such as quantum dots and certain metal ions enhance the assay's performance.

Electrochemical Immunoassay combines immunoassay principles with electrochemical detection, using electrodes to measure changes in current, potential, or impedance upon antigen–antibody binding. This format allows for miniaturization, rapid analysis, and integration into portable devices.

Analytes can be antigens, antibodies or haptens. Small molecular weight compounds such as antibiotics, pesticides, toxins, hormones[105] *etc* are non-immunogenic by themselves but will react to a suitable antibody. Such compounds are called haptens. Only when haptens are bound to carrier proteins can they trigger an immune response.[106] For quinolone detection, polyclonal antibodies (pAbs), monoclonal antibodies (mAbs) and newly developed recombinant antibodies (rAbs) are being used. Other recognition elements like aptamers, DNA and molecularly imprinted polymers (MIPs) are also tried in studies.

11.3. Sensors

Sensors are analytical devices that detect and quantify samples using a recognition element and a transducer. Other than chromatography and immunoassay, this is the most promising quantification technique for antibiotics. There are various types of sensors such as electrochemical, optical, thermal and piezoelectric sensors classified on the basis of transducers. Owing to their large surface area to volume ratio, nanomaterials show supreme capabilities in sensing applications. When the recognition element is a biomolecule, the sensor can be called a biosensor. Enzymes, antibodies, DNA/RNA aptamers, or molecularly imprinted polymers (MIPs) are usually the recognition elements in biosensors.[107]

11.3.1. Electrochemical sensors. One of the first studies about detection of Gatifloxacin (along with Moxifloxacin and Sparfloxacin) was published in 2010.[108] The Glassy Carbon Electrode (GCE) was modified with double-stranded calf thymus DNA and then used for DPV study. According to the CV, there is no reduction of the FQs at bare GCE. DPV in the presence and absence of DNA was done in Phosphate Buffer Solution (PBS) of pH 7. Oxidation peaks of guanine (G) and adenine (A) were identified, and it was observed that the anodic peaks of FQs were affected by G and A. Results from electrochemical studies were compared and confirmed with direct spectrophotometry at 290 nm. A good linear range of 0.2 to 1.4 μM was achieved with a limit of detection as low as 0.05 μM.[108]

Brahman *et al.*, in 2012 also utilized calf thymus DNA for the voltametric detection of gatifloxacin.[109] Instead of GCE, they used multi-walled carbon nanotube paste electrode as the working electrode. They prepared an electrode with DNA immobilized on it, and did DPV to understand the interaction of varying concentrations of the drug (gatifloxacin) with DNA in acetate buffer. It primarily demonstrates how the drug intercalates between the helical strands of DNA in solution. This setup gave a linear range of 21.3 to 170 μM and a detection limit of 0.0045 μM.[109] In another approach, the electrode is first pretreated with the drug on the electrode surface. Then, when DNA is introduced, subsequent changes in the electrochemical behaviour of the DNA (such as shifts in oxidation peaks of guanine and adenine) reveal how the anchored drug interacts with the incoming DNA molecules. This method provides an alternate perspective, confirming the binding mechanism observed with the DNA-modified electrode.

In 2013, Zhang *et al.*, prepared a P-β-CD-L-arg/CPE based on electro-polymerization of β-cyclodextrin (β-CD) and L-arginine (L-arg) on carbon paste electrode[110] *via* 10 cycles CV in PBS. EIS showed decrease in charge transfer resistance on the addition of β-cyclodextrin and L-arginine polymer. Compared with CV of P-β-CD/CPE and P-L-arg/CPE, P-β-CD-L-arg/CPE showed superior charge transfer kinetics and thereby increased current density. β-CD was chosen because its inner cavities may prevent fluoroquinolones from forming stable host–guest inclusion

complexes.[110] Also, the guanidyl group of L-arg was expected to form electrostatic interactions with negatively charged carboxylate ions of the FQs. The prepared electrode was then used for successful electrocatalytic sensing of fluoroquinolones namely ciprofloxacin, ofloxacin, norfloxacin and gatifloxacin.

Another research focused on the development of cysteic acid modified carbon paste electrode (cysteic acid/CPE) for simultaneous detection of ofloxacin and gatifloxacin.[111] The working electrode was prepared by electrochemical oxidation (20 cycles CV) of L-cysteine on CPE. It had a wide linear response, ranging from 0.02 to 200 μM.

A sensor based on β-cyclodextrin (β-CD) and reduced-graphene oxide (rGO) modified GCE[112] proved to be one of the most successful electrochemical sensing tool for gatifloxacin. rGO increased the conductivity and β-CD provided more surface area for adsorbing the analyte. EIS was employed to study the electrical resistance of the solution while CV and DPV were done to find out the performance of the proposed sensor. With a decent sensitivity of 0.33 μA μM^{-1} and a linear range of 0.05 to 150 μM, this sensor could detect gatifloxacin in tablets and human urine samples.[112]

One study compared Graphene modified CPE, Cu-GR/CPE (copper nanoparticle-graphene modified CPE), and CTAB-Cu-GR/CPE (Cetyltrimethylammonium bromide-Cu NPs-GR modified CPE) to find their effectiveness in detection of gatifloxacin and pefloxacin simultaneously. Drop casting was done for graphene modified CPE and then further modifications were done by amperometry. CTAB-Cu-GR composite gave highest current response possibly due to electro-catalytic activity and large surface area.[113] 0.02 to 40 μM concentration of gatifloxacin could be assessed linearly with LOD (limit of detection) equal to 0.0021 μM.[113] These results were confirmed in shrimp and animal serum.

Screen printed electrodes (GSPs) were also be used for gatifloxacin determination.[114] They are easily disposable, manipulation on the surface can be done with great ease and are fit for *in situ* analysis. By comparing with solid contact glassy carbon ion selective electrode (GSC), it can be ascertained that GSP can sense gatifloxacin equally well. In the work done by Abd El-Rahman *et al.*, 2021, potentiometric method was used to find the linearity and LOD for gatifloxacin using GSP and GSC. Both showed almost similar linear range, 1 to 10 000 μM for GSP and 10 to 10 000 for GSC. Still GSP had the edge over GSC because of its longer shelf life and lower detection limit.[114]

Abdel-Gawad *et al.*, developed another two sensors based on potentiometry. Ion selective electrodes (ISEs) were prepared by formation of membranes on glassy carbon electrodes. The membranes were formed using sodium tetraphenylborate (TPB) and another with phosphotungstic acid (PTA).[115] Both the electrodes worked in a wide range of 1 to 10^4 μM, but the stability was limited to only twenty-one days. Satisfactory response was observed for pH 1 through 5. To determine the method's repeatability, robustness and ruggedness[115] were also thoroughly assessed and all the results were remarkable.

Terbium doped copper oxide nanoflowers also proved to be efficient in determination of gatifloxacin in real samples. CuO:Tb^{3+} nanoflowers synthesized by hydrothermal method was drop-casted on GCE for the voltametric studies LSV and DPV. Ofloxacin, pefloxacin and gatifloxacin tested gave distinct peaks for each one as observed from DPV. Fluroquinolone abuse being primarily in cattle and livestock, detection of these from milk sample is deemed necessary. The CuO:Tb^{3+}/GCE succeeded in the determination of gatifloxacin in milk and human serum with a LOD of 0.0012 μM.[116]

Of all these studies, lowest detection limit for gatifloxacin was observed for *p*-aminobenzoic acid (*p*-ABA) and nicotinamide (NA) dual functional monomers electropolymerized with gatifloxacin as template molecule. This sort of molecularly imprinted polymer (MIP) based electrochemical sensor works on the principle of lock and key.[117] The analyte serves as the template for MIPs. Once the electro polymerization is done, template molecule is washed out which makes space for the analyte at the time of detection. A staggering LOD of 2.61×10^{-9} was achieved by Huang *et al.*, in 2023.[117] In the same work, MIP-*p*-ABA sensor and MIP-NA sensor performance was studied and it gave satisfactory results, but the MIP-dual sensor was found to be the best with a huge response range of 10^{-8}–0.1 μM.

Metal organic frameworks were also tried for determination of gatifloxacin in real samples. UiO-66 and carboxylate multi-walled nano tube nanocomposites solution drop-casted on GCE was used in this case. UiO-66 is a metal–organic framework (MOF) that's made of zirconium clusters and 1,4-benzenedicarboxylate linkers. It can have very high surface area to volume ratio and is thus excellent for this application. Detection in effluent, milk, serum, and eye drops was also confirmed using LSV. The proposed UiO-66/MWCNT-COOH/GCE sensor showed an ultrahigh sensitivity of 18.7 μA μM^{-1} (ref. 118) which is much higher than all the other sensors made for gatifloxacin and was stable for almost 49 days.

Another utilization of MWCNT-COOH, due to its high electrical conductivity, was done by Li *et al.*, in 2024 for sensing of gatifloxacin. $ZnCo_2O_4$/MWCNT-COOH/GCE was prepared by drop-casting a dispersion solution of $ZnCo_2O_4$ nanoparticles and MWCNT-COOH onto the surface of GCE and then the usual drying process. It had a fairly decent sensitivity of 29.64 μA μM^{-1} along with a good response range of 0.01 to 10 μM.[119] EIS analysis showed fast electron transport between the electrode and the analyte. Hydrogen bonding between the carboxyl group and the analyte is thought be the reason for higher current response than when only MWCNT was present. The importance of optimization of accumulation parameters, pH, scan rate,[119] and mass ratio of nanoparticles and nanotube is clear throughout the study.

In a study by Yao *et al.*, 2024, gatifloxacin detection was verified for two separate linear ranges, low concentration (0.2 to 20 μM) and high concentration (20 to 250 μM), with the same device. LSV has been done to find out whether interference from other contaminants will affect the gatifloxacin determination. Silver sulfide and reduced graphene oxide composite mixed with chitosan and chloroform, coated on a GCE was used for sensing purpose. As in other publications, a two-electron transfer process is thought to happen during the oxidation of gatifloxacin.[120]

Moxifloxacin (MOX) and gatifloxacin, both having very close oxidation potential was determined by DPV done with Cu-TCPP/rGO/GCE. Cu-TCPP (copper porphyrin complex) or rGO alone could not provide sufficient current, but copper porphyrin complex coated on rGO/GCE significantly improved the performance. DPV done by keeping MOX constant and varying gatifloxacin and *vice versa* was used to study accuracy of the proposed sensor. The device had a sensitivity of 2.360 μA μM^{-1} and shows good selectivity and repeatability.[121] Also there were no superposition of MOX and gatifloxacin oxidation curves (Fig. 5a).

Most recent research on the voltammetric determination of gatifloxacin was done using molecularly imprinted poly(pyrrole) membrane with Ag-nanoparticle-functionalized black phosphorus nanosheets (MIP/BPNS-AgNPs) coated on a GCE.[125] The vacancies left behind by the gatifloxacin template serves as a highly selective binding area for the analyte. Response range for the low concentration varied from 0.001–1 μM had a sensitivity of 9.965 μA μM^{-1} whereas the high concentration response range (1 to 50 μM) had a comparatively low sensitivity of 0.5378 μA μM^{-1}.[125] LSV was done in eye drops, milk and human serum to test its efficacy (Fig. 5c).

Radi *et al.* investigated the electrochemical oxidation of three fluoroquinolone drugs: gatifloxacin (GTF), moxifloxacin (MXF), and sparfloxacin (SPF), using both bare and DNA-modified glassy carbon electrodes *via* voltammetric techniques.[126] It was observed that all three fluoroquinolones exhibited a single, irreversible oxidation peak within the potential range of 0.85–0.91 V *vs.* Ag/AgCl in a pH 7.0 phosphate buffer. Differential pulse voltammetry (DPV) and UV-absorption spectroscopy were employed to characterize the interaction between these fluoroquinolones and calf thymus double-stranded DNA (ds CT-DNA). Electrochemical data revealed binding constants of 3228 M^{-1} for gatifloxacin, 2596 M^{-1} for moxifloxacin, and 2857 M^{-1} for sparfloxacin with DNA. Based on these electrochemical and spectroscopic findings, a combined mode of binding involving both intercalation and electrostatic interaction was concluded for the fluoroquinolone-DNA interaction. Finally, a preconcentration and DPV determination method utilizing a dsDNA-modified glassy carbon electrode (DNA/GCE) was proposed for the trace determination of these analytes, which was successfully applied to their detection in pharmaceutical formulations. A list of nanomaterial based electrochemical sensors demonstrating different parameters is provided in Table 1.

11.3.1.1. Electrochemical oxidation of gatifloxacin and its pH dependency. The electrochemical oxidation of gatifloxacin is a complex process that typically involves the irreversible transfer of electrons from the gatifloxacin molecule to the electrode surface, leading to its degradation. This process is highly dependent on various factors, with pH being a critical parameter that significantly influences the reaction pathway and kinetics.

The electrochemical oxidation of gatifloxacin, like other fluoroquinolones, is generally initiated at specific electroactive sites within its molecular structure. The primary sites for oxidation are often the piperazine ring and/or the quinolone core. The exact mechanism can vary depending on the electrode material, applied potential, and solution conditions.

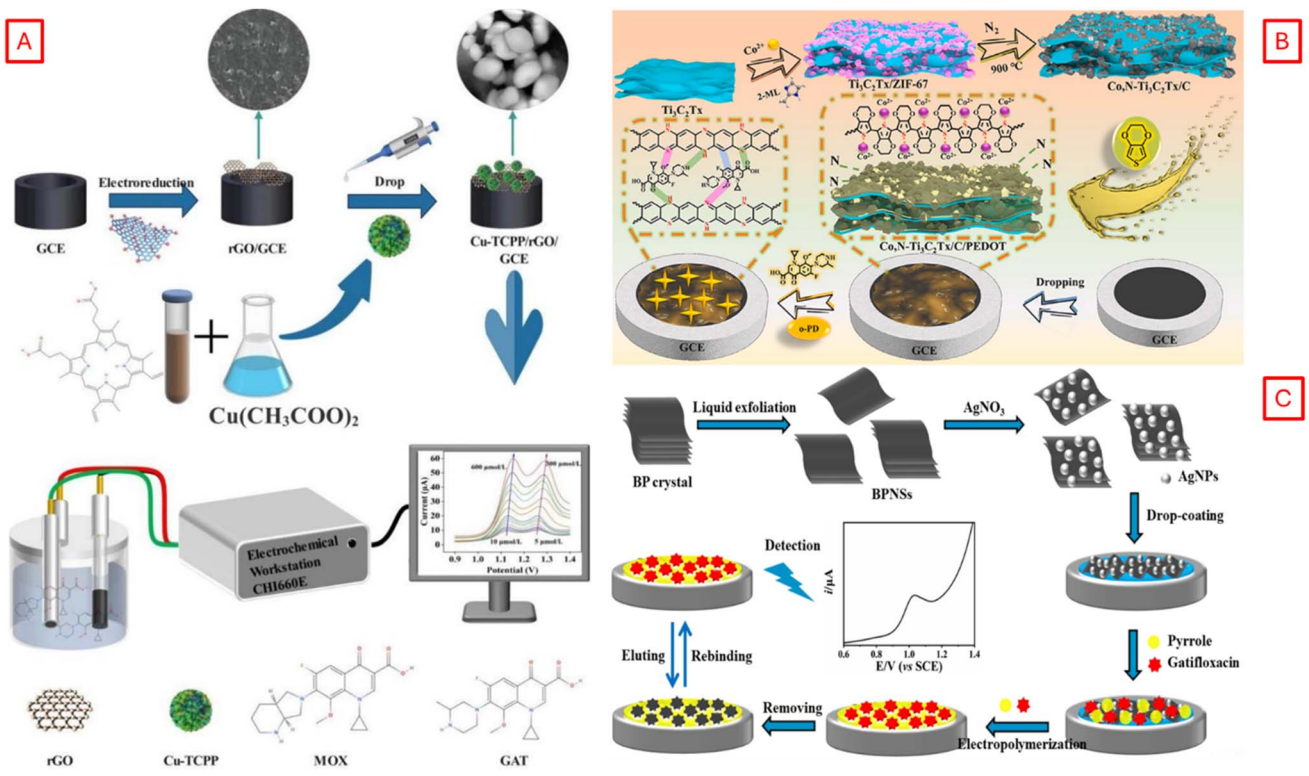

Fig. 5 Electrochemical detection of gatifloxacin based on (A) Cu-TCPP/rGO;[122] (B) defect-rich Co, N-doped $Ti_3C_2T_x$/Cpoly (3,4-ethylenedioxy thiophene);[123] (C) BPNS-AgNP/GCE based molecularly imprinted sensors.[124]

Table 1 Advancements in nanomaterial-based electrochemical (Bio)sensors for gatifloxacin detection

Electrodes	Methods	Linear response range (μM)	Limit of detection (μM)	Sensitivity (μA μM^{-1})	Matrix	References
β-CD/rGO/GCE	EIS, CV, DPV	0.05–150	0.02	0.33	Tablet, human urine	112
A_2S/RGO/GCE	LSV	0.2–20; 20–250	0.0667	0.072; 0.097	Shrimp, fish, chicken meat	120
Cu-TCPP/rGO/GCE	DPV	10–300	0.59	2.360	Lake water	121
(P-L CuO: Tb^{3+} NS/GCE	LSV, DPV	0.01–800	0.0012		Tablet, human serum, milk	116
$ZnCo_2O_4$/ MWCNT-COOH/GCE	CV, LSV	0.01–10	0.002	29.64	Pond effluent, tap water, eye drops	119
CTAB-Cu-GR/CPE	CV, DPSV	0.02–40	0.0021		Shrimp, blood serum	113
Cysteic acid/CPE	EIS, CV, DPV	0.02–200	0.01		Tablet, human serum	111
P-β-CD-L-arg/CPE	EIS, CV, DPV	0.06–100	0.02		Tablet, human serum	110
UiO-66/ MWCNT-COOH/GCE	CV, LSV	0.05–10	0.0075	18.7	Effluent, milk, serum, eye drops	118
MW-CNT-PE	CV, DPV	21.3–170	0.0045		Serum, plasma, urine	109
MIP/BPNS-AgNP/GCE	CV, LSV	0.001–1; 1–50	0.0002	9.965; 0.5378	Pharmaceutical formulations, milk, human serum	125
MIP-dual/ MWCNT-ZIF8/GCE	CV, DPV	10^{-8}–0.1	2.61×10^{-9}		Pond water, tap water	117
GSP ISE	Potentiometry	1–10 000	1		Tablet, urine	114
GSC ISE	Potentiometry	10–10 000	10		Tablet, urine	114
DNA modified GCE	CV, DPV	0.2–1.4	0.05		Tablet	108
TPB/GCE	Potentiometry	$1–10^4$	0.24 μg mL^{-1}		Industrial wastewater effluents	115
PTA/GCE	Potentiometry	$1–10^4$	0.24 μg mL^{-1}		Industrial wastewater effluents	115

Initially, gatifloxacin molecules are typically adsorbed onto the electrode surface. This adsorption is often described as an adsorption-controlled process, meaning the rate of the electrochemical reaction is limited by how quickly the molecules can accumulate on the electrode. Upon application of a sufficient anodic potential, electrons are transferred from the adsorbed gatifloxacin molecules to the electrode. This electron transfer is commonly accompanied by the loss of protons (H+). The specific sites where electrons are lost are typically the nitrogen atoms in the piperazine ring, particularly the secondary amine, or potentially the phenolic hydroxyl group if it is present and deprotonated, or the quinolone ring itself.[127–129] The oxidation is generally irreversible, indicating that the products formed are not easily reduced back to the original gatifloxacin molecule under the experimental conditions. The initial electron transfer and proton loss lead to the formation of highly reactive radical intermediates. These radicals are inherently unstable and undergo further chemical reactions. The radical intermediates can either undergo further electron transfer steps at the electrode (direct oxidation) or react with other species in the solution, such as water or hydroxyl radicals (indirect oxidation, especially in the presence of strong oxidants generated electrochemically). These subsequent reactions lead to the formation of various degradation products, which may include ring opening, cleavage of bonds, and eventually, if oxidation is complete, mineralization to simpler inorganic compounds like carbon dioxide, water, and nitrogen-containing species. The specific degradation pathways and products are influenced by the functional groups present in gatifloxacin and the oxidative power of the electrochemical system.[130–132]

The electrochemical oxidation of gatifloxacin is significantly influenced by the pH of the supporting electrolyte solution. This dependency arises primarily from two factors protonation state of gatifloxacin and the nature of oxidizing species/environment/electrolyte.

Gatifloxacin is an amphoteric molecule, possessing both basic (piperazine nitrogen) and acidic (carboxylic acid) functional groups.[133] Its protonation state changes with pH. At low pH values, the basic sites (*e.g.*, the piperazine nitrogen) are protonated. This protonation can make it more difficult to oxidize these sites as a positive charge would need to be created or an existing positive charge would need to be eliminated, requiring higher oxidation potentials. The oxidation peak potential is often observed to shift to more positive values as the pH decreases, indicating that more energy is required for the oxidation to occur. In acidic conditions, the oxidation may preferentially occur at the quinolone ring itself, which might become more accessible for electron transfer due to protonation of other parts of the molecule.[134] As the pH increases, the acidic groups (*e.g.*, the carboxylic acid) become deprotonated, existing in their anionic form. Simultaneously, the basic sites become deprotonated. The deprotonated forms are generally easier to oxidize because the removal of an electron is facilitated by the presence of electron-donating groups or by the absence of a positive charge. Therefore, the oxidation peak potential typically shifts to more negative (less positive) values with increasing pH. This suggests that the oxidation process often involves the loss of both electrons and protons. The slope of the peak potential *versus* pH plot can provide insight into the number of protons and electrons involved in the rate-determining step of the oxidation. A slope close to 59 mV pH^{-1} unit at 25 °C for a 1-electron, 1-proton process, or multiples thereof, is often observed. At neutral pH, a zwitterionic form may exist, where both the acidic and basic groups are ionized. The electrochemical behaviour at neutral pH will reflect a balance of these protonation states.

Table 2 Overview of optical sensor applications in gatifloxacin detection using different techniques

Materials	Methods	Linear response range ($\mu g\ mL^{-1}$)	Limit of detection ($\mu g\ mL^{-1}$)	Sandell's sensitivity ($\mu g\ cm^{-2}$/0.001A)	Matrix	References
NAC–CdTe QDs	Ratiometric fluorescence	0.00085–3.6 μM	0.00026 μM		Milk, drinking water, fish-farming water	135
y-CDs	Fluorometry	0.1–10 μM	0.0125 μM		Milk, eggs	136
Carbon dots-copper(II)	Ratiometric fluorometry	0.01877–105.1	0.04995		Human serum	150
BCG	Extractive spectrophotometry	2.0–20	0.285	0.01052	Tablet	138
BCP	Extractive spectrophotometry	2.0–14	0.252	0.02391	Tablet	138
BPB	Extractive spectrophotometry	2.0–16	0.312	0.01065	Tablet	138
BTB	Extractive spectrophotometry	2.0–16	0.232	0.01411	Tablet	138
KMnO4–$SO3^{2-}$-Tb(III)-GFLX	Chemiluminescence spectrophotometry	0.05–8 μM	0.0032 μM		Capsule, tablet, urine, serum	141
Co(II)-HGAT	Spectrophotometry	18.77–150.16	2.05	0.077	Ophthalmic formulations	139
Ni(II)-HGAT	Spectrophotometry	18.77–131.39	2.21	0.103	Ophthalmic formulations	139
La(III)-HGAT	Spectrophotometry	18.77–112.62	1.08	0.044	Ophthalmic formulations	139
Methanol*	First-derivative spectrophotometry	10–70	0.632	0.00375	Eye drops	151
Eu(III) doped in sol–gel matrix	Fluorometry	0.0024–32 μM	0.00016 μM		Tablet, eye drops, serum	152
Tb(III) doped in sol–gel matrix	Fluorometry	0.05–8 μM	0.2 μM		Tablet, eye drops, serum	152
Tb^{3+} doped In Sol–gel matrix	Fluorometry	0.005–1 μM	0.00165 μM		Tablet, serum	153
Eu^{3+} sensitized GFLX	Fluorometry	0.05–1.2 μM	0.016 μM		Tablet, eye drops, serum	154
GTFX-MIPCH		1×10^{-6}–1 μM	1×10^{-8} μM		Lake water, tap water	155
Ag^{+}/GSH-AuNCs	Ratiometric fluorometry	0.3–9 μM	0.13 μM		Ophthalmic gel	140
Eriochrome black-T	Extractive spectrophotometry	3–18	0.42	0.02	Eye drops	156
In PBS	Spectrophotometry	1–18	0.103	0.0143	Tablet, injection, ophthalmic solution	137
In HCl	Spectrophotometry	1–14	0.099	0.0114	Tablet, injection solution, ophthalmic solution	137
Al^{3+} sensitized GFLX	Fluorometry	0.0561–15 μM	0.0561 μM		Milk, injection solution	157
Sodium dodecyl sulphate–-gatifloxacin	First-derivative fluorometry	0.001–1	0.0002305		Tablet	158

The process of direct oxidation involves the rate and pathway of direct electron transfer from gatifloxacin to the electrode can be directly affected by its protonation state, as mentioned above. In some electrochemical oxidation systems, highly reactive species, such as hydroxyl radicals (˙OH), are generated from water oxidation at the anode. The production and reactivity of these species can also be pH dependent. For instance, the oxidation potential of water to form hydroxyl radicals is influenced by pH. In acidic media, hydroxyl radicals are potent oxidizers, readily attacking organic molecules. In alkaline media, the nature of reactive oxygen species might change (*e.g.*, formation of O_2-), potentially influencing the degradation efficiency and pathways. For example, some studies suggest that the first ozone attack on gatifloxacin can occur at the carboxylic group under alkaline conditions, while at the piperazinyl ring under acidic conditions. The pH of the solution thus plays a crucial role by altering the protonation state of gatifloxacin, which directly impacts the ease of electron transfer and the preferred sites of oxidation, leading to observable shifts in oxidation potentials and variations in degradation pathways and efficiencies.

11.3.2. Optical sensors. Generally, optical sensing is done using spectrophotometry (usually UV-vis absorbance) or fluorometry (Table 2). It is to be noted that quantifying low concentration of analyte with spectrophotometry is difficult because the absorbance is calculated from the difference in transmittance of the sample containing analyte and a blank reference sample. Fluorometry has significant advantages over spectrophotometry, in finding quantification and detection limits. Fluorescence is the emission of light with a longer wavelength than the incident one, upon excitation by a light beam. In fluorometry, only the intensity of light emitted perpendicular to the excitation light beam is measured and not the transmitted light. This enables fluorometry to have higher signal to noise ratio. The only limitation is that not every material exhibit fluorescence. Fluorescent markers or probes have been developed to mitigate this issue.

Gatifloxacin possesses a fluoroquinolone core, which exhibits native fluorescence when excited at specific wavelengths, often in the UV region (*e.g.*, excitation at ~280–290 nm, emission at ~450–480 nm) (Fig. 6). The intensity of this native fluorescence can be directly correlated to the concentration of gatifloxacin. However, this method can be affected by matrix interferences. Gatifloxacin molecules absorb photons at an excitation wavelength, promoting electrons to a higher energy state. These excited electrons then return to a lower energy state by emitting photons at a longer wavelength (fluorescence). The intensity of this emitted light is directly proportional to the concentration of gatifloxacin in the sample, following Beer–Lambert law under dilute conditions.

A point-of-care device based on ratiometric fluorescence have been developed by Ye *et al.*, using (NAC)-coated CdTe

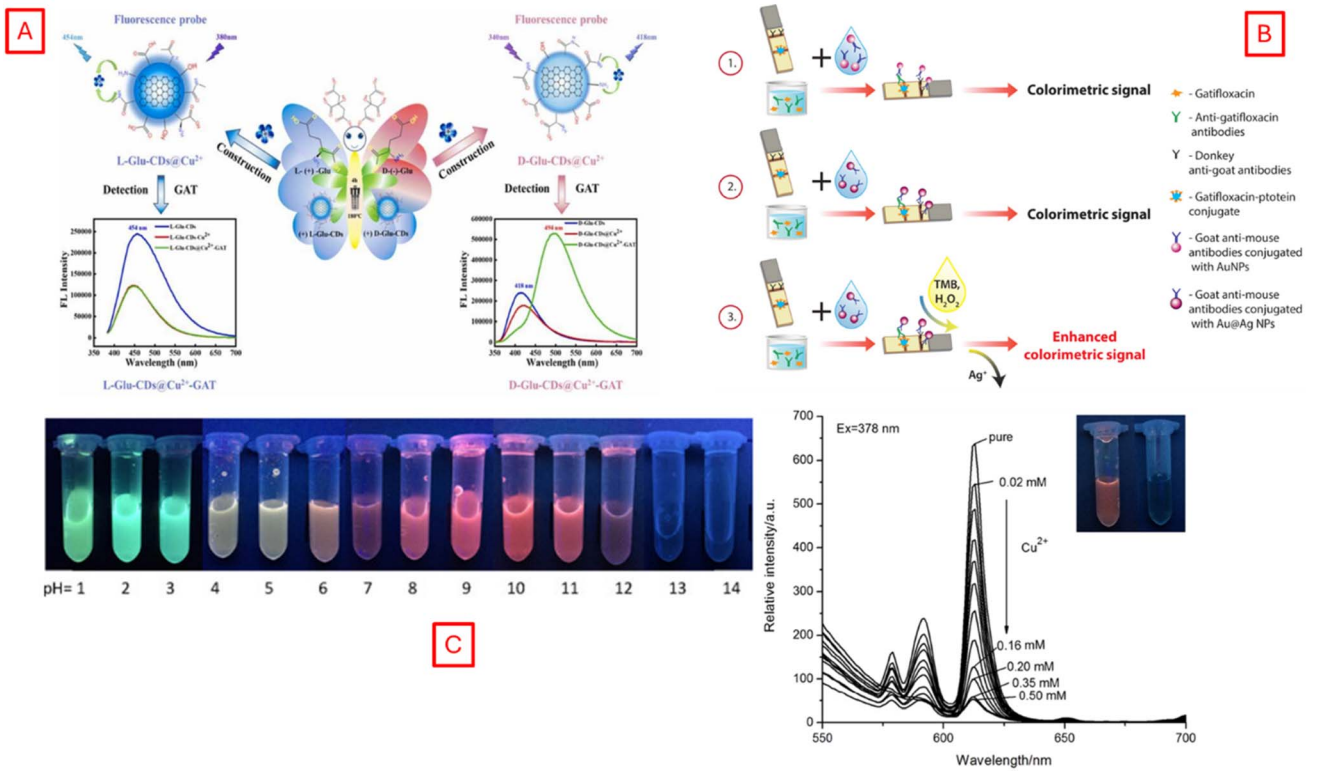

Fig. 6 (A) A chiral fluorescent probe (D-Glu-CDs@Cu^{2+}) was designed using Cu^{2+} as a medium for fluorescence resonance energy transfer which was used for the rapid and effective detection of gatifloxacin;[144] (B) lateral flow Immunoassays performed in this study: AuNP-based LFIA (1), common Au@Ag NP-based LFIA (2), and enhanced Au@Ag NP-based LFIA (3);[145] (C) Eu^{3+}-gatifloxacin complex (0.5 mM) in Tris-buffer solution at consecutive pH values and excited by UV light at 365 nm with Luminescence response curves of Eu^{3+}-gatifloxacin complex at different concentrations of Cu^{2+} in Tris-buffer solution of pH 7.[146]

quantum dots as markers. Photoinduced electron-transfer (PET) process resulted in fluorescent quenching of QDs as the concentration of gatifloxacin increased. Excitation wavelength of 365 nm by a UV lamp gave way for 557 nm fluorescence emission which was then turned to 448 nm blue fluorescence. These wavelengths were used for ratiometric analysis. The device had a linear range of 0.85 nM to 3.6 μM with a detection limit of 0.26 nM.[135] The results were confirmed in milk, drinking samples and fish-farming water. Another ratiometric sensor, which was made using carbon dots-copper(II) system, for quantification of gatifloxacin based on fluorescence resonance energy transfer (FRET) was proposed by Chen *et al.*, in 2022. It had a linear response range of 0.01877–105.1 μg mL^{-1} and a detection limit of 0.04995 μg mL^{-1}. Li *et al.*, proposed a fluorescence enhancement (turn-on) sensor by excitation tuning strategy of yellow carbon dots (y-CDs).[136] 355 nm was chosen as the excitation wavelength for simultaneous detection of norfloxacin and gatifloxacin. 0.0125 μM was found to be the LOD for gatifloxacin. Venugopal *et al.*, put forth a simple method of UV-spectrophotometric analysis of gatifloxacin. Analysis was done at 286 nm in hydrochloric acid and at 292 nm in phosphate buffer.[137] The limit of quantification was found to be 0.312 μg mL^{-1} in the phosphate buffer and 0.3 μg mL^{-1} hydrochloric acid medium, respectively. The results were confirmed in tablets, injection and ophthalmic solutions.

An extractive spectroscopic analysis method for gatifloxacin was designed for detection in pharmaceutical dosage forms by Amin *et al.*, in 2006. The foundation is the creation of yellow ion–pair complexes in phthalate buffer between the drug's basic nitrogen and sulphone-phthalein acid dyes: bromocresol green (BCG), bromocresol purple (BCP), bromophenol blue (BPB), and bromothymol blue (BTB).[138] The absorption spectra gave satisfying results for each complex and linear range was found using Beer's law. Spectrophotometric analysis of gatifloxacin (HGAT) *via* its interaction with metal ions was investigated by Mostafa *et al.*[139] The observed sample followed Beer's law in the range of 18.77 to 150.16 μg mL^{-1}, 18.77 to 131.39 μg mL^{-1}, and 18.77 to 112.62 μg mL^{-1} for Co(II)-HGAT, Ni(II)-HGAT, and La(III)-HGAT respectively. In a study conducted by Madni *et al.*, gatifloxacin was analyzed using the aggregation induced emission (AIE) behavior of glutathione stabilized gold nanoclusters (GSH-AuNCs) activated by silver (Ag^{+}) ions.[140] It was based on the fluorescence enhancement by the interaction of silver ions on GSH-AuNCs.

In addition to that chemiluminescence properties have been employed for sensing purposes. Flow injection system was used to pump gatifloxacin (GFLX) to a stream of sulphite and then mixed with Tb(III) and $KMnO_4$ (ref. 141) for the production of a chemiluminescent signal. The intensity difference observed from the blank and analyte solution was proportional to the GFLX concentration. The response range was found to be 0.05 to 8.0 μM and LOD was 0.0032 μM. But this method is rather complicated for practical use. Studies have shown that some fluorescent materials exhibit a decrease in fluorescence intensity in the presence of fluoroquinolones. For example, 1,4-dihydroxyanthraquinone (1,4-DHAQ) has been reported to be quenched by gatifloxacin, norfloxacin, ofloxacin, and ciprofloxacin, providing a simple and sensitive detection method.[142] The change in fluorescence intensity is then inversely proportional to the gatifloxacin concentration. Gatifloxacin, acting as a quencher, interacts with the excited state of the fluorophore. This interaction can occur *via* several mechanisms. Dynamic quenching involves collisional encounters between gatifloxacin and the excited fluorophore lead to non-radiative deactivation of the excited state. Static quenching involves non-fluorescent complex is formed between gatifloxacin and the fluorophore in the ground state. If gatifloxacin absorbs light at the excitation or emission wavelength of the fluorophore, it can reduce the effective light reaching or emitted by the fluorophore, leading to an apparent decrease in fluorescence intensity which maybe also referred to as Inner Filter Effect (IFE). Some nanomaterials (nanozymes) possess intrinsic enzyme-like catalytic activity. This activity can be modulated by the presence of gatifloxacin, leading to a colour change in the presence of a chromogenic substrate. A nanozyme (*e.g.*, metal oxide nanoparticles) catalyses a reaction that produces a coloured product. Gatifloxacin might inhibit or enhance this catalytic activity, leading to a quantifiable change in the colour intensity. This mechanism has been reported for other antibiotics like tetracyclines with nano enzymes (Cu-BL) co-modified by L-lysine and 2-amino terephthalic acid, where a dual-mode colorimetric and fluorescent sensor was developed.[143]

Gold or silver nanoparticles exhibit a phenomenon called Localized Surface Plasmon Resonance (LSPR). This refers to the collective oscillation of conduction electrons in response to incident light. The LSPR band is highly sensitive to the size, shape, aggregation state, and the refractive index of the surrounding medium. In many colorimetric assays for gatifloxacin, specific ligands or recognition elements are functionalized onto the surface of AuNPs. In the absence of gatifloxacin, these nanoparticles remain dispersed, exhibiting a characteristic wine-red colour (due to the LSPR band around 520 nm). Upon the addition of gatifloxacin, the drug can interact with the functionalized nanoparticles, leading to their aggregation. This aggregation causes a red-shift and broadening of the LSPR band, resulting in a visible colour change from wine-red to blue or purple. The extent of this colour change is proportional to the gatifloxacin concentration. While direct examples for gatifloxacin with standard AuNP aggregation assays are not as widely highlighted as for other antibiotics like ciprofloxacin or moxifloxacin, the principle is transferable. For instance, ammonium thioglycolate-functionalized AuNPs have been used as a colorimetric chemosensor for moxifloxacin and ciprofloxacin based on aggregation, which changes the colour from wine-red to blue-grey.[147] A similar mechanism could be envisioned for gatifloxacin due to its structural similarities.

In SPR based biosensors, a recognition element (*e.g.*, an antibody, aptamer, or molecularly imprinted polymer) that can selectively bind gatifloxacin is immobilized on the gold surface of the SPR sensor chip. When a sample containing gatifloxacin flows over the surface, gatifloxacin binds to the immobilized recognition element. This binding event causes an increase in the mass and local refractive index at the sensor surface. The change in refractive index alters the conditions for SPR, leading

to a shift in the SPR angle. This shift is directly proportional to the amount of gatifloxacin bound to the surface, allowing for its quantification. SPR offers real-time monitoring of binding events, label-free detection, and high sensitivity. While specific published SPR biosensors exclusively for gatifloxacin are less prominent in general reviews compared to other small molecules or proteins, the principle is well-established for antibiotic detection (*e.g.*, chloramphenicol) and holds significant potential for gatifloxacin.[148,149]

12. Research gap and future prospect

Notable progress in the development of both electrochemical and optical sensors for gatifloxacin detection exists in current technology. However, certain research gaps still persist, particularly concerning the translation of promising laboratory-scale methods into practical, clinically relevant applications and the exploration of cutting-edge materials and technologies.

Despite advancements in sensor sensitivity and selectivity, a significant proportion of reported electrochemical sensors utilize costly, non-renewable, or potentially toxic materials such as noble metals (gold, platinum), rare metal oxides, and certain synthetic nanomaterials.[159] Comprehensive assessment and development of environmentally benign, economically feasible electrode materials remain lacking. This gap underscores the need for systematic exploration of green sensor design, including the adoption of renewable biomass-derived carbon materials, biodegradable polymers, and waste-derived components that maintain analytical performance while minimizing environmental and economic burdens.[160–162]

Although MIP sensors show promise for selective gatifloxacin detection, current discussions insufficiently address the regeneration and reusability of the imprinted sites. There is limited evidence on the long-term operational stability of these sensors, their capacity for repeated use without loss of sensitivity or selectivity, and the mechanisms to restore binding site functionality after analyte extraction. Investigation into durable MIP formulations and robust regeneration protocols is essential for translating these sensors into practical, cost-effective analytical tools.

While detection performance metrics are often detailed in the literature, validation of sensor reproducibility across multiple fabrication batches is rarely reported. This constitutes a critical gap, as batch-to-batch variability can impair reliability and commercial viability.[163] Rigorous evaluation of fabrication consistency, including the influence of nanocomposite synthesis parameters on sensor performance reproducibility, is required to establish the robustness of these technologies.[164,165]

The electrochemical oxidation of gatifloxacin involves complex processes influenced by pH-dependent protonation states and electrode conditions. However, comprehensive experimental verification of this mechanism, correlating electrochemical parameters such as peak potential shifts with specific molecular structural transformations using complementary techniques like voltammetry and spectroelectrochemistry, remains insufficiently addressed. Such studies are critical to elucidate detailed reaction pathways and improve sensor design and interpretation.

While highly selective biosensing platforms like immunosensors and aptasensors have shown immense potential for other analytes, their application for gatifloxacin detection remains conspicuously scarce in the reported literature. The scarcity of high-affinity antibodies or aptamers specifically targeting gatifloxacin limits the development of extremely selective immunosensors or aptasensors. Generating robust biorecognition elements that maintain stability and specificity within complex biological matrices requires extensive selection and validation, which can be technically challenging and time-consuming. Efficiently immobilizing biorecognition molecules onto sensor transducers while preserving their activity and preventing nonspecific binding is difficult, particularly in miniaturized formats. Ensuring long-term stability under varying environmental conditions and repeated use poses additional hurdles.

Field-Effect Transistor (FET) based sensors, renowned for their ultra-high sensitivity, label-free detection, and miniaturization capabilities, have seen limited to no dedicated reports for gatifloxacin quantification.[166,167] Their potential for real-time monitoring and integration into portable devices remains largely untapped for this specific antibiotic. Despite the growing trend towards miniaturized analytical systems for rapid and multiplexed analysis, the development of gatifloxacin sensors integrated into Lab-on-Chip, microfluidic, or Micro-Electro-Mechanical Systems (MEMS) platforms is critically underdeveloped.[168,169] Such integration is crucial for reducing sample volume, reaction time, and cost, paving the way for truly portable diagnostic tools. Several technical challenges may arise in realizing smart, miniaturized devices for gatifloxacin detection, especially when employing advanced biosensing platforms such as immunosensors, aptasensors, FET-based sensors, and integrated microfluidic or MEMS systems. Biological fluids such as blood, urine, or saliva present complex matrices with abundant interfering substances that may affect sensor selectivity and accuracy. Miniaturized devices must incorporate effective antifouling coatings, sample preparation modules, or signal amplification strategy FET-based sensors require precise and reproducible fabrication of nanoscale semiconducting channels and gate electrodes functionalized with selective receptors. Achieving consistent performance, avoiding device-to-device variability, and maintaining sensitivity at nanoscale while preserving low noise levels are significant challenges to overcome these interferences without significantly increasing device complexity. Incorporating fluid handling, mixing, separation, and multi-analyte detection capabilities into compact microfluidic platforms demands sophisticated design and fabrication techniques. Balancing device complexity with user-friendliness, minimizing sample volume, and ensuring reliable fluid flow control are critical considerations. Miniaturized smart sensors generate complex data that require onboard or cloud-based processing algorithms. Implementing compact, low-power electronics capable of real-time signal processing, AI/ML-based noise reduction, and predictive analytics without compromising battery life or device size involves technical

trade-offs. Transitioning from laboratory prototypes to mass-produced devices necessitates reproducible fabrication methods compatible with scalable, cost-effective materials and processes. Ensuring batch-to-batch consistency in nanoscale features and bioreceptor immobilization is challenging and impacts commercial viability.[170]

The vast potential of emerging two-dimensional (2D) materials[171,172] and novel nanomaterials, such as MXenes and its derivatives, Transition Metal Dichalcogenides (TMDs), for enhanced sensor performance (*e.g.*, higher surface area, improved conductivity, unique optical properties, and catalytic activity) remains largely unexplored for gatifloxacin sensing. Existing literature predominantly relies on conventional nanomaterials (*e.g.*, graphene, carbon nanotubes, gold/silver nanoparticles), overlooking the superior properties that these newer materials could offer in terms of sensitivity, selectivity, and stability.[173,174] MXenes and TMDs can be engineered at the nanoscale to create highly reactive and selective surfaces by tailoring their composition, defect sites, and surface chemistry for optimal interaction with gatifloxacin molecules.[175] These materials can serve as the transduction element in electrochemical, optical, or fluorescence-based sensors, providing increased signal-to-noise ratios due to their superior conductivity and catalytic properties. Integration with biomimetic recognition elements such as molecularly imprinted polymers or aptamers on 2D material surfaces can further enhance selectivity. The high surface-to-volume ratio of 2D materials leads to amplified electronic or optical responses when gatifloxacin binds or reacts on the sensor surface. This produces rich, multidimensional datasets encompassing subtle signal variations in currents, potentials, spectroscopic signatures, or impedance profiles. Such complex datasets are well suited for analysis using AI/ML tools that can decipher intricate patterns compared to conventional methods.

The application of Artificial Intelligence (AI) and Machine Learning (ML) algorithms for optimizing sensor design, processing complex sensor data, enhancing selectivity through pattern recognition, or predicting gatifloxacin concentrations in complex matrices is rarely reported in the context of gatifloxacin sensors. Incorporating AI/ML could significantly improve data interpretation, reduce false positives, and enable the development of "smart" sensors with enhanced analytical capabilities.[176,177] Machine learning algorithms, including supervised learning (*e.g.*, support vector machines, random forests), deep learning (*e.g.*, convolutional neural networks), and ensemble methods can be trained using datasets generated by 2D material-based sensors to recognize unique signal fingerprints of gatifloxacin in complex biological or environmental matrices. This facilitates improved selectivity by distinguishing target analyte signals from interfering substances and reducing false positives or negatives. AI-enabled models can continuously learn from sensor outputs and environmental/contextual parameters to recalibrate sensors in real time, compensating for drift, matrix effects, or temperature fluctuations. Predictive analytics can estimate precise gatifloxacin concentrations even in low-signal or noisy conditions, supporting reliable therapeutic drug monitoring or environmental surveillance. Advanced miniaturized electronics and edge computing units can embed AI/ML models alongside 2D material-based sensor arrays for real-time on-site analysis, eliminating dependence on centralized labs. Wireless connectivity to mobile devices or cloud platforms allows data visualization, remote monitoring, and integration with electronic health records or stewardship programs. Utilizing advanced nanomaterials with high biocompatibility, stability, and eco-friendly profiles can improve sensor robustness. Coupling sensors with machine learning algorithms or artificial intelligence for data processing enhances accuracy, compensates for biological variability, and provides predictive analytics, supporting individualized dosing regimens.

A significant void exists in the development of dedicated point-of-care devices for Therapeutic Drug Monitoring (TDM) of gatifloxacin. While gatifloxacin's therapeutic window and potential for adverse effects (*e.g.*, QT interval prolongation, dysglycemia) underscore the need for precise individual dosing, there are no readily available or reported POC devices for real-time or near real-time TDM in clinical settings. These limits personalized medicine approaches for gatifloxacin administration.

Crucially, there are virtually no reports of gatifloxacin sensors (of any type) undergoing rigorous clinical trials or validation studies in accordance with stringent regulatory guidelines such as those set by the USFDA Bioanalytical Device guidelines. This indicates a substantial translational gap, where promising laboratory-scale sensor prototypes fail to progress towards real-world clinical applicability, lacking the necessary validation for accuracy, precision, robustness, and stability in clinically relevant samples (*e.g.*, blood, urine). To accelerate the clinical validation and regulatory approval of gatifloxacin sensors for therapeutic drug monitoring (TDM), several strategic approaches can be adopted to bridge the translational gap between laboratory prototypes and real-world clinical applications.[176,178] From the outset, sensor development should align with established regulatory frameworks such as the USFDA Bioanalytical Device guidelines and ISO standards for *in vitro* diagnostic devices.[179,180] This alignment ensures that critical performance characteristics, including accuracy, precision, sensitivity, specificity, linearity, robustness, and stability, are rigorously assessed using clinically relevant biological matrices (*e.g.*, blood, plasma, urine). Adherence to Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) throughout validation phases is essential for smooth regulatory submissions. Comprehensive validation must be conducted in stages: beginning with analytical validation under controlled laboratory conditions, followed by verification in spiked biological samples, and culminating in clinical validation involving real patient samples. Clinical studies should be designed as prospective trials, preferably multicentric, incorporating diverse patient populations to evaluate sensor performance in variable physiological and pathological states. Key endpoints should include comparison against gold-standard methods (*e.g.*, LC-MS/MS), reproducibility across batches, sensor stability over time, and influence of potential interferents. Translating sensor technology into intuitive, portable, and rapid point-of-care

(POC) devices will increase clinical uptake. Integrating microfluidics, automated sample preparation, and wireless data transmission to electronic health records or mobile apps can facilitate real-time decision-making. User-centric design, ease of calibration, low maintenance, and minimal training requirements are critical features to ensure acceptance by healthcare providers. Active dialogue and policies with regulatory agencies during sensor innovation accelerates feedback cycles and clarifies requirements. Engagement with clinicians, pharmacologists, and patient advocacy groups ensures that developed devices meet real clinical needs and facilitates the design of relevant clinical trial protocols. Developing and adopting standardized testing protocols and reference standards for gatifloxacin measurement will facilitate inter-laboratory comparability and regulatory acceptance. Collaborative efforts between academic, industrial, and regulatory entities enable the creation of recognized benchmarks. Post-approval phased pilot testing in clinical environments can identify practical challenges and generate real-world evidence on device performance, safety, and user satisfaction. Preparing post-market surveillance plans, including monitoring sensor longevity and adverse events, supports sustained regulatory compliance and iterative improvements.

In essence, while foundational electrochemical and optical principles have been applied to gatifloxacin detection, the field is yet at a proof-of-concept level for innovation through the incorporation of advanced biosensing architectures, next-generation materials, intelligent data processing, and, most critically, a dedicated focus on developing clinically validated, point-of-care solutions for therapeutic drug monitoring. Addressing these gaps is paramount for developing gatifloxacin sensors that are truly impactful in clinical diagnostics, environmental monitoring, and pharmaceutical analysis. Accelerating clinical validation and regulatory approval of gatifloxacin sensors in modern era requires a multidisciplinary effort emphasizing regulatory alignment, rigorous validation, user-friendly design, advanced materials and algorithms, proactive regulatory communication, standardization, and real-world performance monitoring. Addressing these strategies collectively will propel innovative gatifloxacin TDM devices from proof-of-concept to impactful clinical tools enabling personalized antibiotic therapy and improved patient outcomes.

13. Conclusion

The escalating global challenge of antimicrobial resistance, particularly against widely used fluoroquinolones like gatifloxacin, underscores an urgent imperative for advanced and accessible detection methodologies. As explored throughout this review, gatifloxacin, once a frontline agent, faces increasing resistance, necessitating vigilant monitoring to preserve its efficacy and inform therapeutic strategies. The critical need for precise healthcare monitoring of fluoroquinolones, coupled with the growing importance of TDM for individualized dosing and minimizing adverse effects, highlights a significant demand for robust analytical tools. While traditional techniques such as chromatography and immunoassay have long served as gold standards, their inherent limitations, including lengthy analysis times, high operational costs, and the requirement for specialized instrumentation and trained personnel often hinder their utility in rapid, decentralized settings. This review has meticulously detailed the comprehensive landscape of nanoscale-enabled electrochemical and optical biosensors, demonstrating their transformative potential in overcoming these challenges. These innovative sensing platforms, leveraging the unique properties of nanomaterials, offer remarkable advantages in terms of sensitivity, selectivity, speed, and miniaturization, positioning them as powerful alternatives for gatifloxacin detection.

However, despite these advancements, significant research gaps remain that must be diligently addressed to unlock the full potential of biosensing for gatifloxacin. The current literature reveals a conspicuous absence of sophisticated immunosensors and aptasensors, which offer unparalleled specificity. Furthermore, the integration of gatifloxacin sensing into miniaturized systems such as FET-based sensors, Lab-on-Chip, microfluidics, and MEMS-based devices is severely underrepresented. The exploration of next-generation materials like MXenes, Transition Metal Dichalcogenides (TMDs), and novel rare earth metal oxides is also in its nascent stages for this application, despite their demonstrated superior analytical capabilities. Critically, the integration of Artificial intelligence and Machine Learning for enhanced data analysis and predictive capabilities remains largely untapped. Perhaps the most significant impediment to real-world impact is the glaring lack of point-of-care (POC) devices specifically designed for gatifloxacin TDM applications. The journey from laboratory prototype to clinical utility is fraught with challenges, as evidenced by the virtual absence of clinical trials adhering to stringent regulatory frameworks like the USFDA Bioanalytical Device guidelines. In summary, overcoming these challenges requires multidisciplinary approaches combining advances in nanofabrication, biochemistry, materials science, microfluidics, and data analytics. Addressing the incomplete development of specific biorecognition elements for gatifloxacin, enhancing device robustness against complex matrices, and integrating user-friendly fluidics and electronics are essential steps toward realizing practical, portable smart sensors for this antibiotic.

Looking ahead, the future of gatifloxacin detection in the nanoscale is contingent upon a concerted effort to bridge these identified gaps. Future research should prioritize the development of highly integrated, multiplexed, and automated biosensing platforms, leveraging novel nanomaterials and incorporating AI/ML for intelligent data processing. Smart miniaturized devices must undergo rigorous validation for stability, reproducibility, and accuracy under varied environmental and storage conditions. Meeting regulatory standards for clinical or environmental diagnostics involves extensive testing, documentation, and quality control protocols. The ultimate goal must be the translation of these cutting-edge technologies into validated, user-friendly POC devices that can facilitate real-time TDM, optimize antibiotic stewardship, and ultimately contribute to more effective patient management in the global fight against AMR. This interdisciplinary endeavour,

combining materials science, nanotechnology, bioengineering, and clinical validation, holds the key to safeguarding the efficacy of essential antibiotics like gatifloxacin for future generations.

Conflicts of interest

The authors have no conflict of interest among themselves.

Data availability

As a review article, this manuscript did not generate any new or original data. All data and information presented herein were obtained from previously published studies, which are appropriately cited and referenced within the manuscript.

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