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REVIEW ARTICLE

Chiral separation and modeling of quinolones on teicoplanin macrocyclic glycopeptide antibiotics CSP

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Abstract

New chiral high-performance liquid chromatography (HPLC) method for the enantiomeric resolution of quinolones is developed and described. The column used was Chirobiotic T (150 × 4.6 mm, 5.0 μm). Three mobile phases used were MeOH:ACN:Water:TEA (70:10:20:0.1%), (60:30:10:0.1%), and (50:30:20:0.1%). The flow rate of the mobile phases was 1.0 mL/min with UV detection at different wavelengths. The values of retention, resolution, and separation factors ranged from 1.5 to 6.0, 1.80 to 2.25, and 2.86 to 6.0, respectively. The limit of detection and quantification ranged from 4.0 to 12 ng and 40 to 52 ng, respectively. The modeling studies indicated strong interactions of R-enantiomers with teicoplanin chiral selector than S-enantiomers. The supra molecular mechanism of the chiral recognition was established by modeling and chromatographic studies. It was observed that hydrogen bondings and π-π interactions are the major forces for chiral separation. The present chiral HPLC method may be used for enantiomeric resolution of quinolones in any matrices.

KEYWORDS

chiral separation, macrocyclic glycopeptide antibiotics CPS, modeling, quinolones, teicoplanin

1 | INTRODUCTION

Quinolones; anti-bactericidal agents; unwind bacterial DNA[1] due to the attack on topoisomerase enzymes. The most commonly used quinolones are primaquine, tafenoquine, flumequine, lomefloxacin, ofloxacin, and qunacrine (Figure 1) because of their unique pharmaceutical properties. Most quinoles are racemic and, hence, are separated because only one enantiomer is pharmaceutically active, while the other may be toxic, ballast, or inactive.[2-20] Therefore, to avoid the toxicities, side effects, and other problems, these quinolones should be administered in the form of pharmaceutically active pure enantiomers. The scientists, clinicians, industrialists, and government authorities are asking data on the chiral resolution of biologically important molecules including quinolones. The United States Food and Drug Administration, European Committee for Proprietary Medicinal Products, Health Canada, and Pharmaceutical and Medical Devices Agencies of Japan formulated the guidelines for the production and control of racemic drugs to ensure their safety.[21-29] Besides, the clinical and pharmaceutical applications of the quinolones require chiral analytical methods for the pharmacodynamic and pharmacokinetic studies and the industrial quality control.

Once the importance of chirality in bioactivities of quinolone-based drugs was recognized, the efforts are made to develop analytical techniques to quantify their enantiomeric composition. A thorough search of literature on the enantiomeric resolution of quinolones was carried out through Scifinder, Scopus, and Science direct and peer reviewed Journals.[30-34] It was observed that there are only

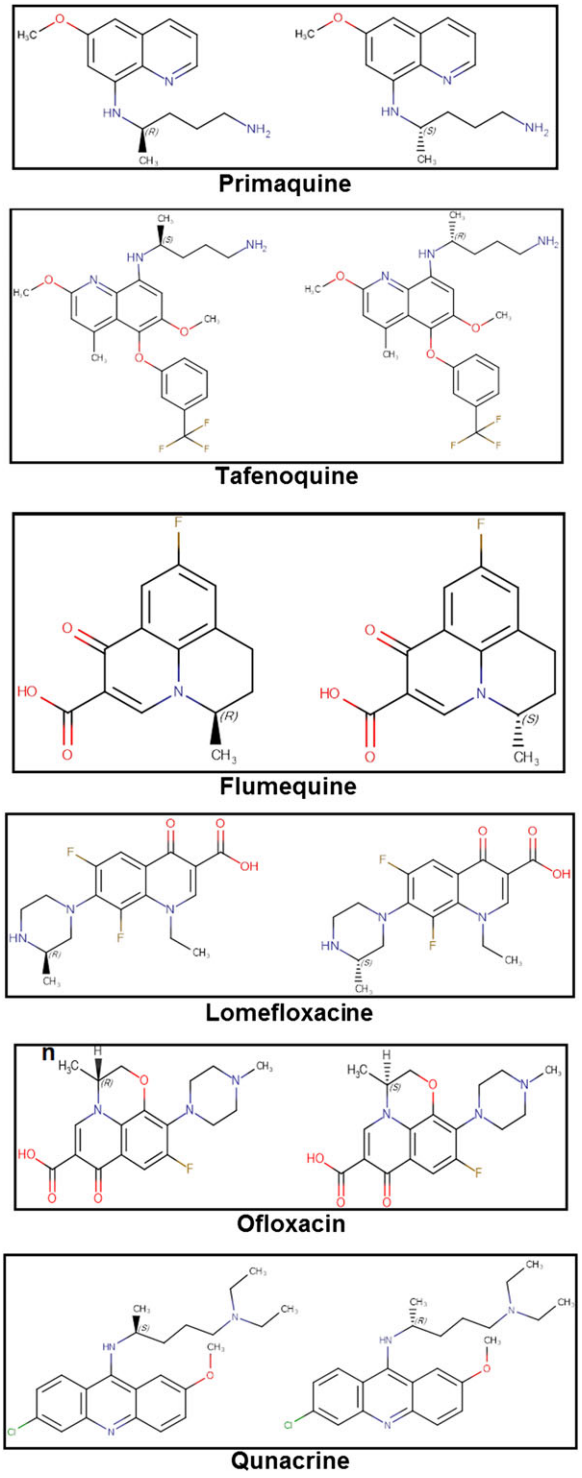


FIGURE 1 Chemical structures of quinolones

few methods available of the chiral separation of these drugs on chiral cwon ether, proteins, and polysaccharide, but there is no paper on the most effective macrocyclic glycopeptides antibiotics Chiral Stationary Phase (CSPs). In view of these facts, the efforts were made to develop fast, reproducible, and effective high-performance liquid chromatography (HPLC) methods using macrocyclic glycopeptides antibiotics CSPs. The chiral recognition mechanism is one of the important aspects in chiral chromatography and, hence, the attempts were made to study the chiral recognition mechanism via modeling.

2 | MATERIALS AND METHODS

2.1 | Chemicals and reagents

The racemic mixtures of primaquine, tafenoquine, flumequine, lomefloxacin, ofloxacine, and qunacrine were purchased from Sigma Aldrich Chem Co, USA. Methanol and acetonitrile of HPLC grade and triethyl amine of AR grade were supplied by Merck, Mumbai, India. Purified water was prepared using a Millipore Milli-Q (Bedford, Massachusetts) water purification system. The solutions (100 μg/mL) of the quinolones were prepared in methanol.

2.2 | Instrumentation

The experiments were carried out on an HPLC system of Shimadzu, Japan, consisting of solvent delivery pump (LC-10 AT VP), manual injector, UV-Visb. detector (SPD-10A), and Class-VP software. The column used was Chirabiotic T and obtained from Sigma Aldrich Chem Co, USA.

2.3 | High performance liquid chromatography

The experiments were carried out using an HPLC system as mentioned above. A total of 20.0 μL of each solution of quinolones was injected into HPLC system. The mobile phases used were three combinations of MeOH:ACN: Water:TEA, ie, (70:10:20:0.1%), (60:30:10:0.1%), and (50:30:20:0.1%). The flow rate was 1.0 mL/min with detection of primaquine, lomefloxacin, ofloxacin, tefnoquine, flumequine, and quinacrine at 530, 248, 351, 290, 296, and 450 nm, respectively. The column used was Chirobiotic T (150 × 4.6 mm, 5.0 μm), obtained from Supelco-Sigma-Aldrich, Bellefonte, USA. The working temperature was 25 ± 1°C for all the mobile phases. Mobile phases were filtered and degassed daily before use. The mobile phases were filtered through nylon membrane of 25-mm diameter and 0.45-μm pore size. The retention (k), separation (α), and resolution (R_s) factors were calculated.

2.4 | System suitability test

System suitability test was performed with replicate injections (n = 5) of the standard solution into the chromatographic system. The tailing factor, resolution, %RSD of

the peak area, and retention times were calculated, and the results are summarized in Table SI1. These results showed low RSD values, <1% for peak area and < 1% for retention time. The tailing factors of primaquine, tafenoquine, flumequine, lomefloxacin, ofloxacine, and qunacrine were 0.88, 0.80, 0.90, 0.95, 0.90, and 0.82, respectively.

2.5 | Specificity

Specificity study was conducted for the interference of any other peak at the retention time of the principal peaks in blank solution. Diluent was injected as blank solution. No peaks were detected from blank solution at the retention time of the principal peaks.

2.6 | Linearity

The linearity curves were plotted with peak area vs. different concentration for the quinolones. The linearity was plotted and the slope, y-intercepts, correlation coefficient (r), and regression coefficient (r^2) were determined. The detailed descriptions of regression curves are summarized in Table SI1. Good linearity was observed for all the quinolones. The regression coefficient (r^2) ranged from 0.9952 to 0.9993.

2.7 | Limit of detection and quantification

The limit of detection (LOD) and limit of quantification (LOQ) were considered for the analytes with a signal to noise ratio of 3 and 10, respectively. The LOD and quantification ranged from 4.0 to 12 ng and 40 to 52 ng, respectively. The values were summarized in Table SI1.

2.8 | Intraday and interday precision

Intraday and interday precision was carried out as per the standard procedure. The intraday precision was carried out within a single day, whereas the interday precision was carried out on the other day. The % assay for intraday precision was calculated for primaquine, tafenoquine, flumequine, lomefloxacin, ofloxacine, and qunacrine. These values were in the range of 99.88 to 99.99. On the other hand, the % assay for interday precision was 98.30 to 99.35, respectively.

2.9 | Robustness

Robustness of the method was evaluated by slight altering one parameter at a time while keeping the others constant and observing the changes in the chromatograms, which may affect the performance of the method. The variations in retention time (Rt) and peak area were < 1, which confirmed the robustness of method.

2.10 | Simulation studies

The interactions of stereomers of the quinolones with teicoplanin (Figure 2) were evaluated by simulation studies. The results obtained were used to establish chiral recognition mechanism.

2.10.1 | Methodology

Docking studies were performed by Intel dual CPU (1.86 GHz) with Windows XP operating system. The 3D structures of ligands were drawn by using Marwin sketch. The so obtained 3D structure was converted to the pdb file format. Ligand preparation was done by assigning Gastegier charges, merging nonpolar hydrogens, and saving it in PDBQT file format using AutoDock Tools[35] (ADT) 4.0. X-ray crystal structure of teicoplanin (PDB ID: 3MGB) was obtained from the Protein Data Bank (http://www.rcsb.org/pdb). Using AutoDock Tools (ADT) 4.0, the receptors were saved in PDB file format leaving heteroatoms (water). Gastegier charges were assigned to receptor and saved in PDBQT file format using ADT. Preparation of parameter files for grid and docking was done using ADT. Docking was performed with AutoDock 4.0 (Scripps Research Institute, USA) considering all the rotatable bonds of ligand as rotatable and receptor as rigid.[36] Grid box size of 60 × 80 × 114 Å with 0.375 Å spacing was used that included the whole DNA. Docking to macromolecule was performed using an

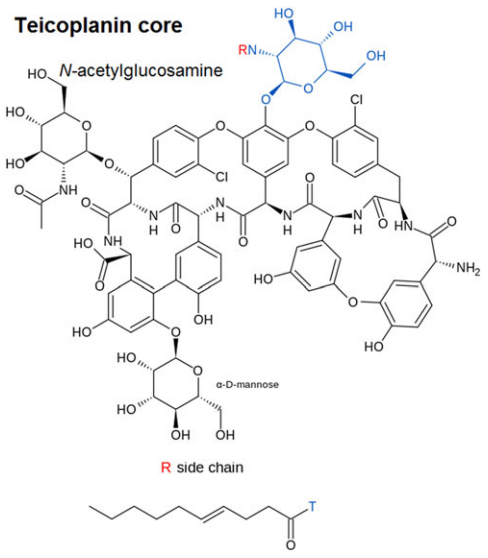


FIGURE 2 Chemical structure of teicoplanin macrocyclic glycopeptides CSP.Chromatograms of quinolones in three solvent systems I, II, and II

empirical-free energy function and Lamarckian Genetic Algorithm, with an initial population of 150 randomly placed individuals, a maximum number of 2 500 000 energy evaluations, a mutation rate of 0.02, and crossover rate of 0.80. Fifty independent docking runs were performed for each ligand and teiecoplanin-ligands adducts for lowest free energy of binding conformation from the largest cluster and saved in PDBQT format. The molecular docking, virtual screening, and binding site analysis were performed. Moreover, Ligplot software was used for the evaluation of hydrophobic interactions. Fifty independent docking runs were applied for each enantiomer (stereomer) and teicoplanin for the lowest free energy of binding conformation from the largest cluster.

3 | RESULTS AND DISCUSSION

3.1 | Chromatography

The chromatographic parameters such as retention (k), separation (α), and resolution (Rs) factors were calculated for the stereomers of quinolones on teicoplanin column (Chirobiotic T). Three solvent system used were MeOH: ACN:Water:TEA, ie, (70:10:20:0.1%), (60:30:10:0.1%), and (50:30:20:0.1%). The values of retention, resolution, and separation factors for the resolved enantiomers of quinolones are given in Table 1. These values ranged from 1.5 to 6.0, 1.80 to 2.25, and 2.86 to 6.0, respectively. All the values were greater than 1.0 indicating complete resolution of all the enantiomers of the quinolones. The chromatograms of the resolved enantiomers are shown in Figure 3. Furthermore, a critical perusal of chromatographic parameters and chromatograms confirmed good chiral resolution of all the enantiomers of the quinolones. S-enantiomers of all the quinolones eluted first followed by R-enantiomers.

3.2 | Chiral HPLC method optimization

To optimize the chromatographic conditions, the different combinations of mobile phases were tried in the mobile phase methanol:acetonitrile:water:triethyl amine. As a result of extensive experimentation, the best combinations were (70:10:20:0.1%), (60:30:10:0.1%), and (50:30:20:0.1%). It is interesting to mention here that the peaks were broad without triethyl amine, showing pH dependent resolution. Without triethylamine, pH was 5.0 (acidic), while with triethylamine, pH was 7.7. The changes in flow rates were

TABLE 1 Chromatographic parameters for chiral resolution of quinolones on teicoplanin macrocyclic glycopeptides antibiotic CSP

Sl. No.	Racemates	k_1	k_2	α	R_s
Solvent System I: MeOH:ACN:Water:TEA (70:10:20:0.1%)					
1.	Primaquine	1.5	3.5	2.33	2.86
2.	Tafenoquine	2.75	6.0	2.18	5.90
3.	Flumequine	-	-	-	-
4.	Lomefloxacin	-	-	-	-
5.	Ofloxacine	-	-	-	-
6.	Qunacrine	2.5	6.25	2.5	6.00
Solvent System II: MeOH:ACN:Water:TEA (60:30:10:0.1%)					
1.	Primaquine	-	-	-	-
2.	Tafenoquine	-	-	-	-
3.	Flumequine	2.5	4.5	1.8	3.20
4.	Lomefloxacin	-	-	-	-
5.	Ofloxacine	-	-	-	-
6.	Qunacrine	-	-	-	-
Solvent System III: MeOH:ACN:Water:TEA (50:30:20:0.1%)					
1.	Primaquine	-	-	-	-
2.	Tafenoquine	-	-	-	-
3.	Flumequine	-	-	-	-
4.	Lomefloxacin	2.0	4.5	2.25	3.57
5.	Ofloxacine	3.0	5.5	1.83	3.57
6.	Qunacrine	-	-	-	-

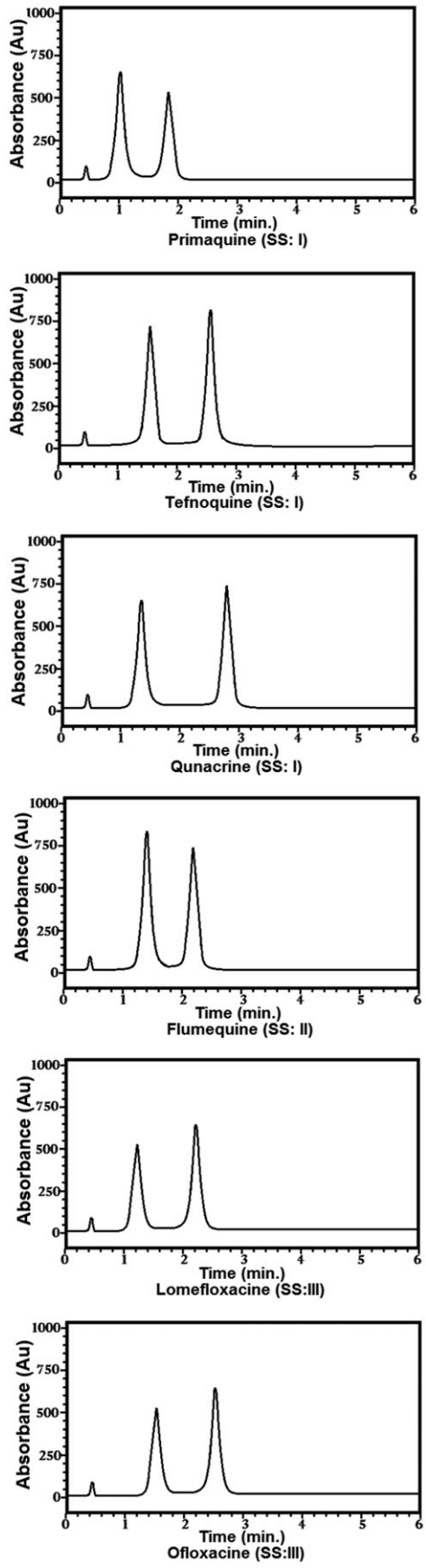


FIGURE 3 Chromatograms of quinolones in three solvent systems I, II and II

varied from 0.5 to 1.5 mL/min, and the best flow rate was found to be 1.0 mL/min. The detection wavelengths were varied from 220 to 600 nm. The amounts of injection were 5 to 25 μL. The optimization was ascertained by controlling temperature from 10 to 50°C.

3.3 | Simulation study of quinolone enantiomers with teicoplanin CSP

The simulation study is one of the most important tools for determining the bindings of stereomers to the chiral selector. Therefore, the attempts have been made to determine the stereomeric interactions on chiral stationary phase. The simulation studies of the stereomers of the quinolones, viz, primaquine, tafenoquine, lomefloxacin, ofloxacin, flumequine, and qunacrine with teicoplanin were performed as described above. The results are given in Tables SI2. The representative interactions of one chiral centered quinolones with teicoplanin are shown in Figures 4–6

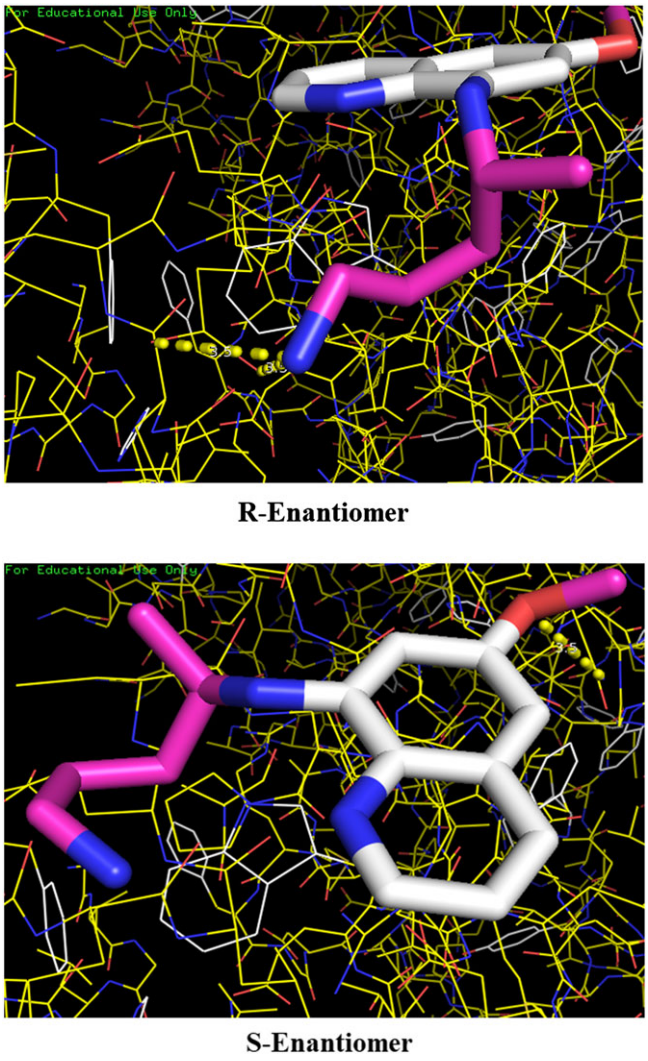
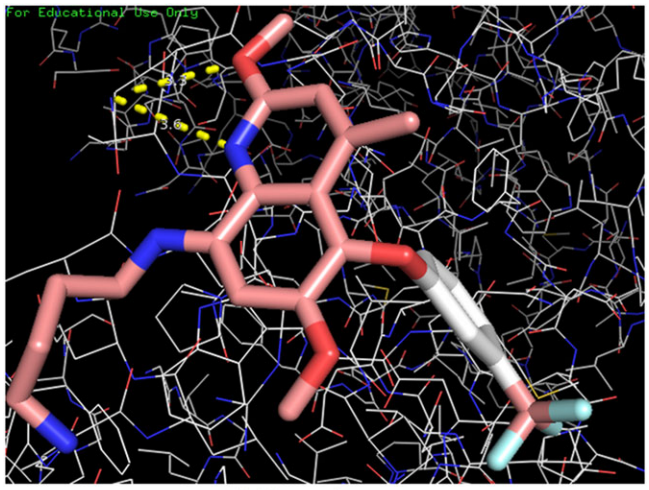
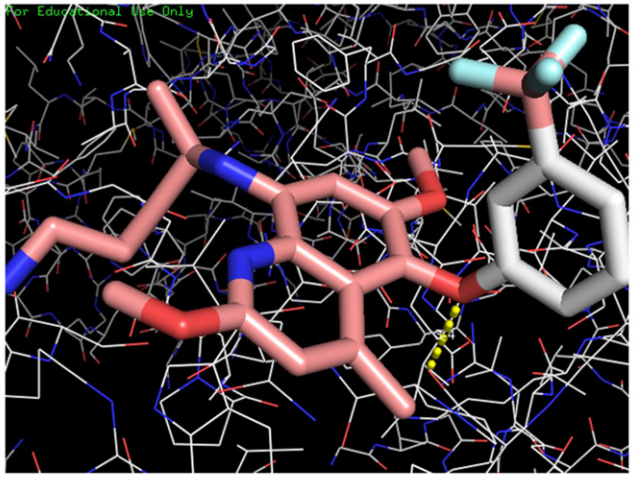


FIGURE 4 Simulation studies of primaquine enantiomers with teicoplanin antibiotic CSP

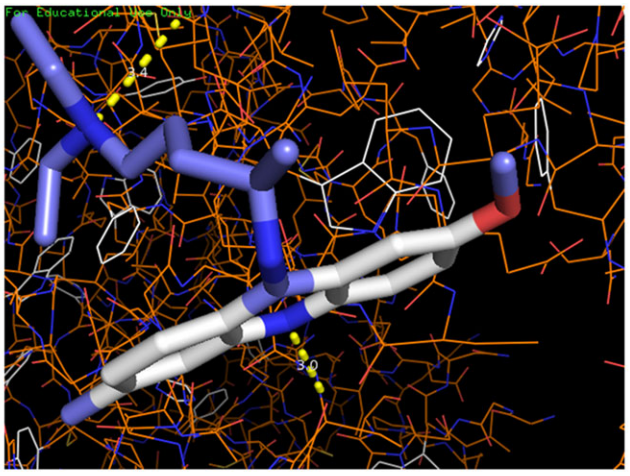


R-Enantiomer

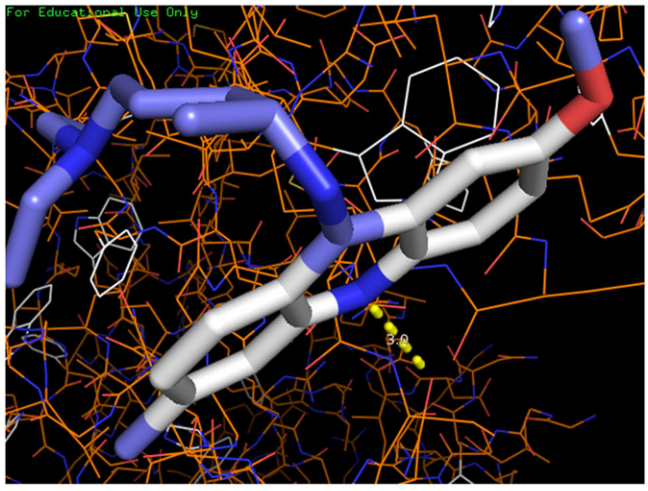


S-Enantiomer

FIGURE 5 Simulation studies of tafenoquine enantiomers with teicoplanin antibiotic CSP



R-Enantiomer



S-Enantiomer

FIGURE 6 Simulation studies of qunacrine enantiomers with teicoplaninantibiotic CSP

(Figures SI1-SI3). It is clear from these figures that the stereomers interacted in the different fashion with teicoplanin. The binding affinities of the stereomers of the quinolones with teicoplanin ranged from −2.1 to −3.4 kcal/mol. In case of R-primaquine 2 H bonds, R-tefnoquine 2 H bonds, R-lomefloxacin 2 H bonds, R-ofloxacin 1 H bond, R flumequine 1 H bond, and R-qunacrine 2 H bonds were formed. In case of S-primaquine 1 H bond, S-tefnoquine 1 H bond, S-lomefloxacin 1 H bond, S-ofloxacin 2 H bonds, S flumequine 2 H bonds, and S-qunacrine 1 H bond were formed. Additionally, hydrophobic interactions were also seen. Fifty free docking runs were applied for each stereomer and teicoplanin for smallest free energy of binding conformation from the largest cluster. The common residues involved were Ala 30, Ala214, Arg214, Gln217, Gln 32, Gln210, Glu210, Lys213, Lys29, NE2, NZ, N, and OE1. The different binding affinities of the stereomers of the reported one chiral centered quinolones with teicoplanin were examined because of their different stereochemical structures.

The simulation studies indicated that the interactions among the stereomers and teicoplanin were due to hydrogen bonding and hydrophobic interactions. Approximately, R-stereomers of one chiral centered quinolones interacted with teicoplanin stronger than S-stereomers. The different binding affinities of the stereomers of the reported quinolones with teicoplanin were seen because of their different stereochemical structures. These are the reasons that the R-(-)-stereomers of the reported one chiral are more active than S-(-)-stereomers.

3.4 | Mechanisms of resolution at supramolecular level

The chiral recognition mechanism may be explained by considering the docking results and the elution order. Literature survey and our experience indicate that teicoplanin

is a good chiral selector.[3,4,6,26,37-39] Teiocoplanin has 23 chiral centers with three cavities. The hydrogen donners and acceptors sites are readily available close to the ring structure. The molecule also has a hydrophobic acyl site chain attached to a 2-amino-2-deoxy-β-D-glucopyranosyl moiety, which activates its surface and enables the formation of micellar aggregates. All these features made this molecule chiral and highly stereospecific in nature. Teicoplanin molecule provides the stereoselective hydrogen bondings, inclusion complexation, diploe interactions, steric interactions, and anionic and cationic bondings to the enantiomers of quinolones. The enantiomers of quinolones have oxygen and nitrogen atoms, which interacted with teicoplanin via hydrogen bondings. Therefore, hydrogen bonding are the major controlling factors. However, the other forces as mentioned above are also playing crucial role in the chiral recognition of the enantiomers of the reported quinolones. Finally, the stereomers of these quinolones are fixed stereospecifically at various extents. As per the modeling results, R-enantiomers interacted strongly in comparison to S-enantiomers. The flow of mobile phase is pushing these enantiomers out of the column. As a result of these competitive interactions, S-enantiomers eluted first followed by R-enantiomers.

4 | CONCLUSION

The reproducible, accurate, inexpensive, and effective chiral HPLC methods are described for the chiral resolution of quinolones on teicoplanin column. The LOD and quantification ranged from 0.20 to 0.26 and 2.0 to 2.62 μg/mL, respectively. The modeling studies indicated strong interactions of R-enantiomers with teicoplanin chiral selector than S-enantiomers. The supramolecular mechanism of the chiral recognition was established by modeling and chromatographic studies. It was observed that hydrogen bondings and π-π interactions are the major forces for chiral separation. The present chiral HPLC method may be used for enantiomeric resolution of quinolones in any matrices.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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