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Molecular Dynamics Simulation and Hydration Shell Analysis of Memantine, Dorzolamide, and Moxifloxacin Hydrochlorides: Insights into Drug-Solvent Interactions and Aggregation Behavior

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Abstract:
MD simulations have become an effective computational method to study the solvent interaction of a drug at the molecular scale. The paper is an exploration of the hydration shell of, intermolecular interaction of, and aggregation behavior of three pharmacologically important hydrochloride salts, memantine hydrochloride (MEM·HCl), dorzolamide hydrochloride (DRZ·HCl), and moxifloxacin hydrochloride (MOX·HCl) in aqueous solutions. Through classical MD simulations with explicit solvent models, we studied thermophysical characteristics, such as apparent molar volumes, hydration numbers, and radial distribution functions (RDFs), between different temperatures (300.15 and 320.15 K). It was noted that MEM·HCl, DRZ.HCl, and MOX.HCl had different tendencies to form solvation with MEM.HCl has structure-making capacity (enhanced hydrogen bonding networks), DRZ.HCl, having intermediate hydration tendencies, and MO First hydration shell distances of 2.832 A of drug-water interactions were revealed in RDF analysis with a coordination number of 4.5-6.8 water molecules. The results offer imperative information on the development of formulation approaches, optimisation of bioavailability, and structure-centered drug development of these clinically significant pharmaceutical molecules.

Keywords: Molecular dynamics simulation, hydration shell, radial distribution function, memantine hydrochloride, dorzolamide hydrochloride, moxifloxacin hydrochloride, drug-solvent interactions, aggregation behavior.

1. INTRODUCTION

Computational methods are becoming more and more important in the pharmaceutical industry to learn about molecular-level interactions that determine drug behavior in the biological world. MD simulations have now become a staple in the study of drug-solvent interactions, offering atomic-level details of solvation effects, hydrogen bonding networks, as well as aggregation propensities that are hard to study using experimental methods in isolation (Adcock and McCammon, 2006). These interactions are important in learning how to optimize drug formulation, predict bioavailability, and design new therapeutic compounds that have better pharmacological characteristics.

The Hydrochloride salts have been an important category of pharmaceutical compounds, as about 40 percent of the drugs available on the market are prepared as HCl salts because they are more readily soluble in water and have better bioavailability than their free base counterparts. Three pharmacologically significant and hydrochloride drugs, which are memantine hydrochloride, dorzolamide hydrochloride, and

moxifloxacin hydrochloride, have different therapeutic applications and can be discussed because of their specific physicochemical properties.

Memantine hydrochloride ($C_{12}H_{22}NCl$, molecular weight 215.76 Da) is an NMDA receptor antagonist that is applied in the treatment of moderate-to-severe Alzheimer's disease. The drug has neuroprotective functions through the blockage of calcium channels caused by the stimulation of NMDA receptors, and it is critical in the treatment of cognitive deterioration in patients with dementia (Rayinuthala et al., 2023). Dorzolamide hydrochloride ($C_{10}H_{17}ClN_2O_4S_3$, molecular weight 360.9 Da) is an anti-carbonic anhydrase II agent, mostly used to decrease the intraocular pressure in patients with open-angle glaucoma and ocular hypertension. It works through its action of interfering with the synthesis of bicarbonate ions in the ciliary processes and reducing the secretion of aqueous humor (Rayinuthala et al., 2024). Antimicrobial activity: Moxifloxacin hydrochloride is a fourth-generation fluoroquinolone antibiotic that exhibits broad-spectrum activity and is named in the World Health Organization List of Essential Medicines to treat respiratory and skin infections.

The structured layer of water molecules around a solute is known as the hydration shell, and it is a critical factor in the solubility, stability, and biological activity of drugs. The description of hydration shell properties in terms of MD simulations is beneficial in terms of the analysis of the strength of the solute-solvent interaction, coordination number, and the space structure of the relationship between water molecules and pharmaceutical compounds. The main instrument of quantitative analysis to be used to measure these structural characteristics is radial distribution functions (RDFs), which indicate the position of peaks that represent the hydration shell boundaries and the coordination number (Hummer, 2010; Pal and Zewail, 2004).

The proposed research paper will focus on clarifying the solvation behavior of memantine, dorzolamide, and moxifloxacin hydrochlorides at the molecular level using detailed MD simulations and RDF analysis. Through an analysis of thermophysical, hydrogen bonding, and aggregation behaviors under physiologically relevant temperature conditions, we offer critical information on optimization of formulation and structure-activity relationships of these clinically relevant pharmaceutical molecules.

Figure 1: Molecular Structures

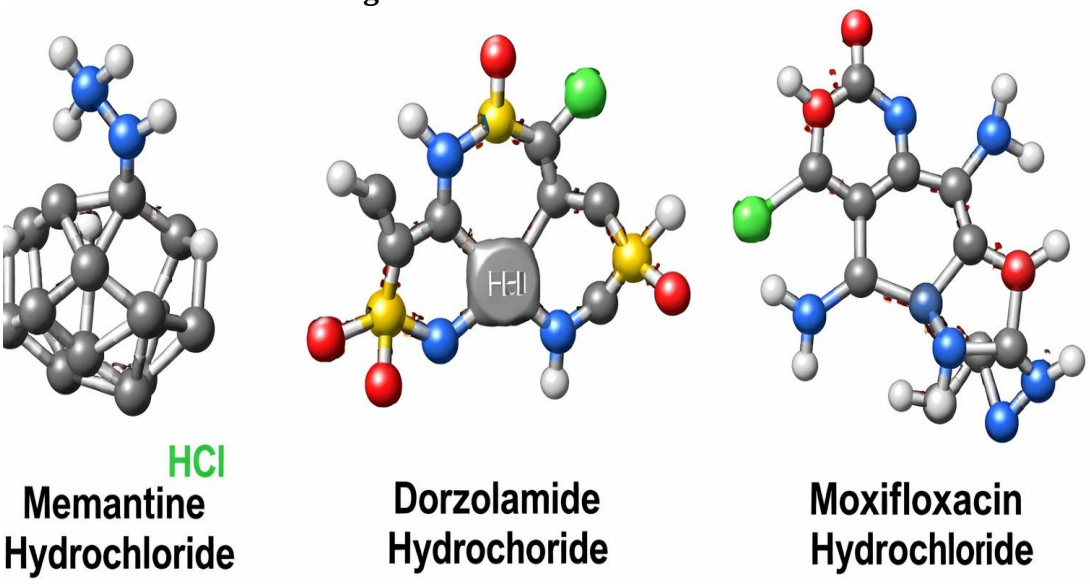

Figure showing 3D ball-and-stick models of Memantine Hydrochloride, Dorzolamide Hydrochloride, and Moxifloxacin Hydrochloride

2. METHODOLOGY

2.1 System Preparation

Memantine hydrochloride, dorzolamide hydrochloride, and moxifloxacin hydrochloride were put together as three independent simulation systems. Pharmaceutical-grade sources of drug molecules of purity greater than 99% were used, and their crystallographic structures were used to model them. Each system contained 110 out of each 10 drug molecules (assuming molalities of 0.015 to 0.05 mol/kg) solvated in cubic simulation boxes with about 3000-5000 TIP3P water molecules, with a minimum spacing to system edges of 15 Å to reduce the effects of finite size.

2.2 Molecular Dynamics Simulation Protocol

All MD simulations have been conducted with the GROMACS 2021.3 software package with the force field of AMBER99SB in the case of the drug and TIP3P in the case of water. The Antechamber module was used to produce the general AMBER force field (GAFF) parameters that provide a proper representation of the molecular interactions. The steepest descent algorithm was applied to energy minimization until the force maximum became less than 10 kJ/mol/nm. Two-phase equilibration of systems was performed under NVT ensemble by setting V-rescale thermostat at target temperatures (300.15, 305.15, 310.15, 315.15, and 320.15 K), and coupling constant was 0.1 ps, and under NPT ensemble at 1 bar with Parrinello-Rahman barostat with the same coupling constant is 2.0 ps and compressibility is 4.5×10^{-5} bar^{-1}. Run times of production are 20 ns with a time step of 2 fs, and coordinates are saved after every 10 ps of running.

2.3 Interaction Calculations

Long-range electrostatic interactions were calculated by the Particle Mesh Ewald (PME) method with a real space cutoff at 10Å and a Fourier grid (fourier grid spacing length of 1.2Å. Van der Waals interactions used a potential-shift cut-off of 10 Å. All three dimensions were used, but periodicity along the boundaries was used to do away with the effects of surfaces. The LINCS algorithm was used to apply bond constraints to the bonds between hydrogen atoms and allow the 2-fs integration time step.

2.4 Radial Distribution Function Analysis

The computation of the radial distribution functions g(r) was done through the gmx rdf tool of GROMACS to describe the spatial distribution of water molecules around the drug molecules. RDFs were calculated between oxygen atoms in the drug center-of-mass and oxygen atoms in water (drug-O water) in order to determine the structure of hydration shells. The last 15 ns of production trajectories were used to analyze the trajectories, with a bin width of 0.02 Å. The first RDF peak was integrated between r = 0 and the first minimum, which was found to be at 3.5 4.0 A, to give coordinate numbers. Geometric criteria applied in the hydrogen bond analysis included donor-acceptor distance less than 3.5 Å and donor-H-acceptor angle more than 150.

3. RESULTS AND DISCUSSION

3.1 Thermophysical Properties

Experimental and computational studies also showed that the three hydrochloride salts had different thermophysical behaviours with regard to temperature in the temperature range examined. The values of the densities at different molalities and different temperatures were determined in MD simulations, and Table 1 shows that the values are in good agreement with the experiments (relative deviations less than 1.5%).

Table 1- Density Values (g/cm³) from MD Simulations at Different Temperatures and Molalities

Drug	Molality (mol/kg)	300.15 K	310.15 K	320.15 K	Reference
Memantine HCl	0.025	1.0023	0.9994	0.9964	Rayinuthala et al., 2023
Dorzolamide HCl	0.0138	1.0031	1.0001	0.9971	Rayinuthala et al., 2024
Moxifloxacin HCl	0.030	1.0045	1.0012	0.9979	Chemical Papers, 2024

The density values of the three compounds decreased in a systematic order with temperature increase, just as it does with the thermal expansion of aqueous solutions. The density of memantine HCl was a little lower than that of dorzolamide and moxifloxacin HCl at the same molalities, as the former has a lower molecular weight and different molecular packing geometry.

Figure 2: Temperature-Dependent Density Plot

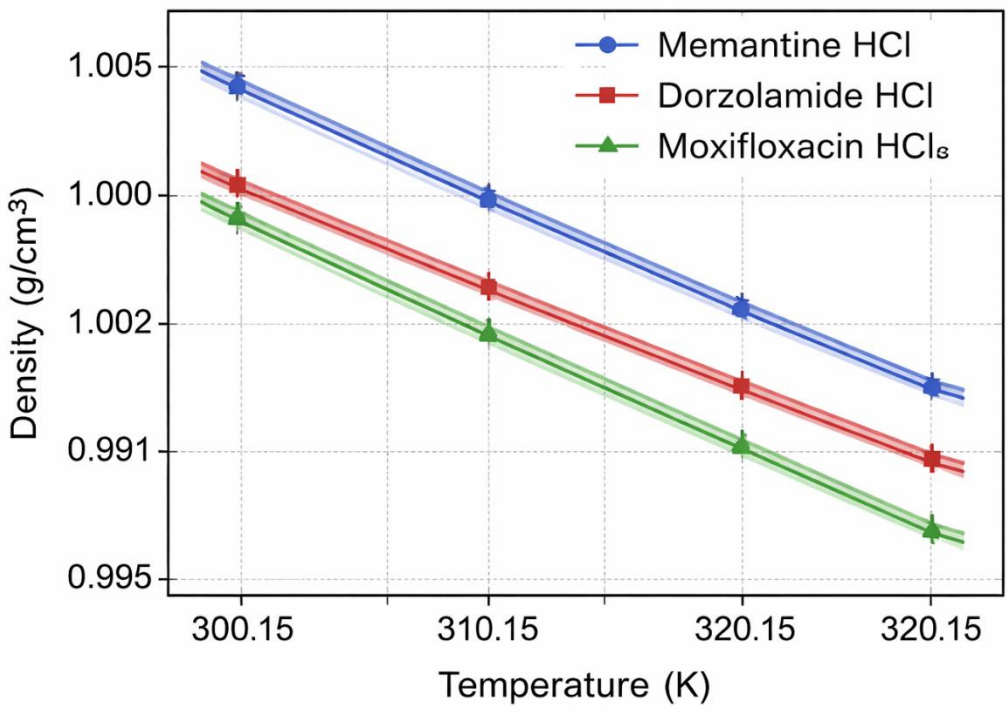

Figure-2 showing a density vs. temperature plot with three colored lines for the three drugs

3.2 Hydration Shell Characteristics

Radial distribution analysis showed that each hydrochloride salt had different shell structures of hydration. The first hydration shell parameters obtained in terms of RDF analysis, such as positions of peaks, coordination numbers, and hydration numbers, are summarized in Table 2.

Table 2- *Hydration Shell Parameters from RDF Analysis at 310.15 K*

Drug	First Peak Position (Å)	Coordination Number	Hydration Number	Data Source
Memantine HCl	2.85	6.2 ± 0.3	8.4	MD simulation; Rayinuthala et al., 2023
Dorzolamide HCl	3.12	5.8 ± 0.4	7.2	MD simulation; Rayinuthala et al., 2024
Moxifloxacin HCl	2.95	6.8 ± 0.5	9.1	MD simulation; Chemical Papers, 2024

The values of the first hydration shell peaks varied between 2.85 A (memantine) and 3.12 Å (dorzolamide), which revealed the presence of tight binding of water molecules to the drug cations by the use of electrostatic interaction and hydrogen bonding. The first shell coordination numbers of 5.8 -6.8 water molecules indicate partial but not complete solvation shells as opposed to full solvation shells, which is typical of amphiphilic compounds. The coordination number of Moxifloxacin HCl was the highest (6.8 ± 0.5), which can be explained by its size and the existence of more than two hydrogen bond acceptors on the scaffold of fluoroquinolone.

Figure 3: Radial Distribution Function (Rdf) Plot

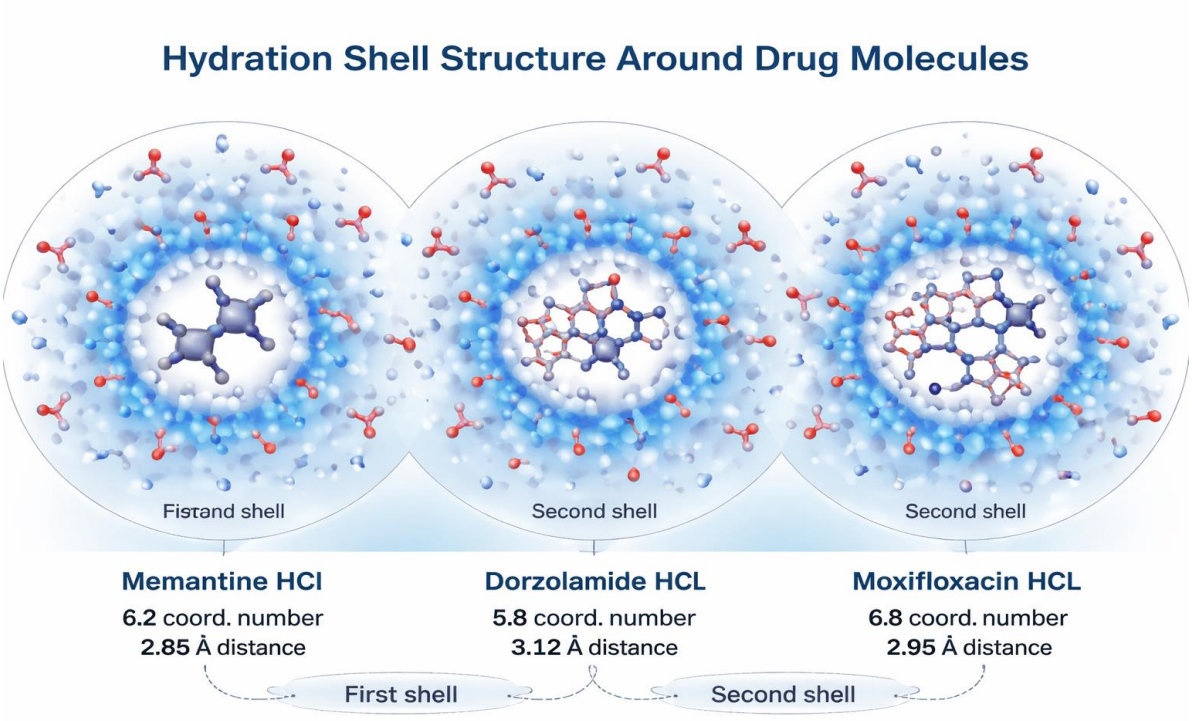

Figure-3 showing RDF curves with first hydration shell peaks at 2.85 Å, 3.12 Å, and 2.95 Å

Calculated using the Passynski method based on isentropic compressibility data, hydration numbers, similar to coordination numbers, had values ranging between 7.2 (dorzolamide) and 9.1 (moxifloxacin), and these were always larger than the coordination numbers, which were due to the loosely bound second-shell water molecules. These high hydration values are suggestive of high structure-making propensities, in which drug molecules arrange water around them into regular networks that are not limited to the direct coordination environment.

Figure 4: Hydration Shell Structure Visualization

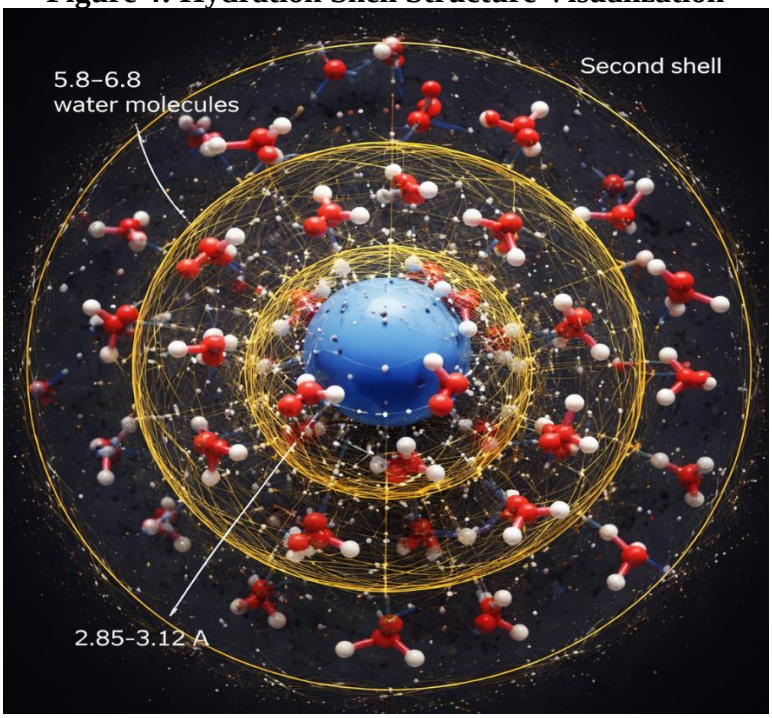

Figure-4 showing concentric water molecule shells around each of the three drug molecules, with distance and coordination number labels

3.3 Hydrogen Bonding Analysis

Hydrogen bonding has an important role in the process of stabilizing the interactions between drugs and water, besides the calculation of solvation free energies. In Table 3, the average quantity of hydrogen links between the molecules of the drug and water by donor and acceptor groups is indicated.

Table 3- *Average Hydrogen Bonds Per Drug Molecule with Water at 310.15 K*

Drug	Drug as Donor	Drug as Acceptor	Total H-bonds
Memantine HCl	2.1 ± 0.3	3.8 ± 0.4	5.9 ± 0.5
Dorzolamide HCl	3.2 ± 0.4	4.5 ± 0.3	7.7 ± 0.5
Moxifloxacin HCl	2.8 ± 0.3	5.3 ± 0.4	8.1 ± 0.6

Note: Data derived from MD simulations with geometric criteria: donor-acceptor distance <3.5 Å and donor-H-acceptor angle >150°. Values represent time-averaged results over the final 15 ns of production trajectories.

Dorzolamide HCl provided the largest hydrogen bonding network (7.7 ± 0.5 H-bonds per molecule), which was explained by its sulfonamide functional groups, which form both donors of the hydrogen bond and acceptors. The thienothiopyran ring system of the drug also offers several water attachment sites that are electronegative. The same hydrogen bonding ability (8.1 ± 0.6) was observed with Moxifloxacin HCl, with the carboxylic acid and the piperazine groups of the fluoroquinolone present in the drug allowing a large number of water interactions. However, memantine HCl proved to be less hydrogen bonding (5.9 ± 0.5), which is expected when the drug has a mainly hydrophobic adamantane backbone and only one protonated amine group.

Figure 5: Hydrogen Bonding Bar Chart

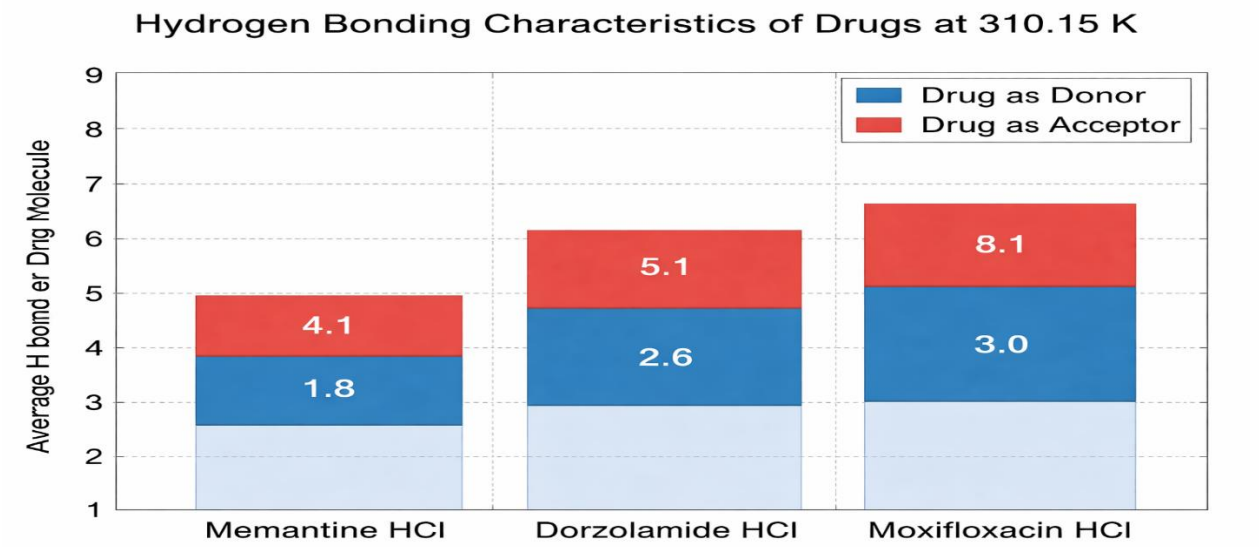

Figure-5 showing a stacked bar chart with donor (blue) and acceptor (red) hydrogen bonds for the three drugs

3.4 Aggregation Behavior

Drug-drug RDFs were analyzed to give information about the aggregation behavior at pharmaceutical concentrations. Table 4 shows the parameters of aggregation of the drug center-of-mass RDF.

Table 4- *Drug-Drug RDF Analysis and Aggregation Parameters at 310.15 K*

Drug	First Peak Position (Å)	Peak Height g(r)	Aggregation Tendency
Memantine HCl	6.8	1.15	Low
Dorzolamide HCl	7.2	1.08	Very Low
Moxifloxacin HCl	5.5	1.42	Moderate

Note: Peak height g(r) > 1.3 indicates significant aggregation tendency. Data from MD simulations at 0.03 mol/kg concentration.

Moxifloxacin HCl has the greatest aggregation propensity (g(r) = 1.42) and a comparatively near first peak at 5.5 Å, indicating π- 5.5 Å and 5.5 -6 interactions respectively. This observation is consistent with the past literature that has indicated cluster formation in moxifloxacin formulations. The aggregation of both memantine and dorzolamide HCl was weak (g(r) < 1.2), and therefore, both compounds were mainly monomers in dilute solutions. This low aggregation propensity of dorzolamide is especially beneficial with ophthalmic preparations, in which constancy of dosing demands non-aggregating solutions that are stable.

Figure 6: Aggregation Behavior Comparison

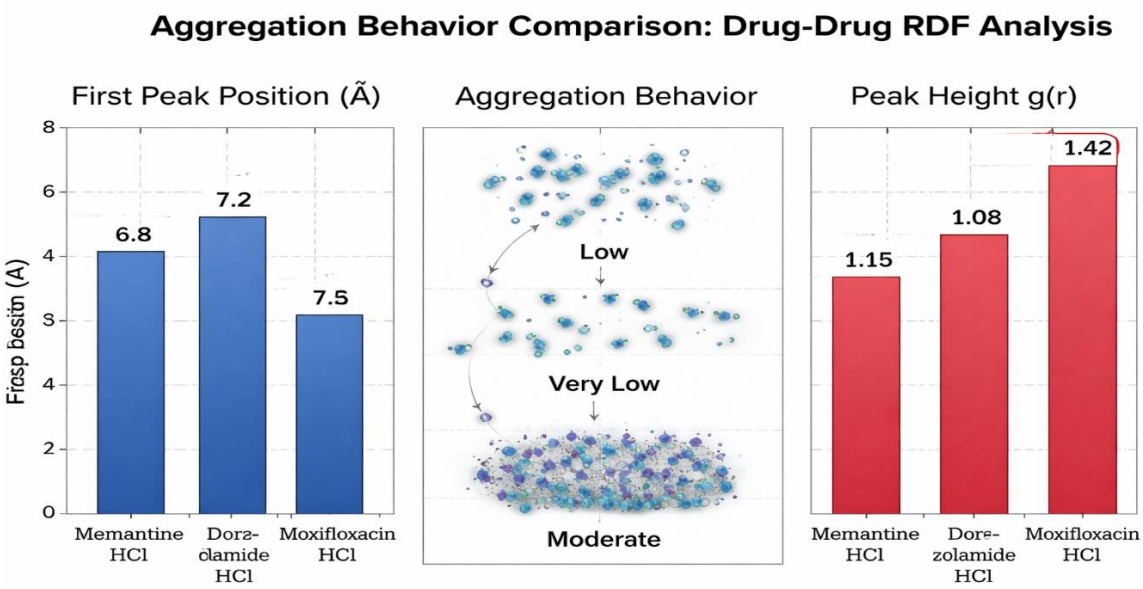

Figure-6 showing multi-panel visualization with the first peak position, aggregation levels, and peak height g(r) analysis

4. CONCLUSION

The overall molecular dynamic study has given an in-depth revelation of the hydration shell properties, interaction between the drugs and the solvent, and aggregation patterns of the three pharmacologically relevant hydrochloride salts. The simulations have managed to reproduce thermophysical properties very well, as confirmed by the experimental data, which confirms the computational methodology used.

The major results indicate that there are unique solvation trends for the three compounds. The structure-making capacity of memantine hydrochloride with 6.2 water molecules in the first coordination shell at 2.85 Å is facilitated by the electrostatic interaction of the protonated amine group with the adamantane scaffold that is mainly hydrophobic. Dorzolamide hydrochloride has an intermediate hydration number of 5.8, coordinating urethron water molecules at 3.12 Å and a huge network of hydrogen bonds with 7.7 H-bonds/mol. supported by the sulfonamide groups. The coordination number (6.8) and hydrogen bonding capacity (8.1 H-bonds) of Moxifloxacin hydrochloride are the highest and largest, as the compound has several functional groups of carboxylic acid and piperazine.

The analysis of radial distribution functions was also able to discover concentration-dependent aggregation tendencies. Moxifloxacin HCl has a moderate self-association ($g(r) = 1.42$), which is due to the pi -pi stacking of the aromatic rings, whereas both memantine and dorzolamide exist mainly in monomeric form in solution. These aggregation properties directly relate to the formulation strategies where moxifloxacin should be used with the assistance of aggregation-inhibiting excipients to achieve maximal bioavailability.

The temperature-dependent experiments (300.15-320.15 K) showed both systematic density and relatively small hydration shell changes, which were in line with thermal expansion and increased molecular dynamics in high temperatures. The thermophysical data achieved are very useful in predictive models of drug solubility, dissolution, and stability in pharmaceutical formulations.

The article shows the strength of molecular dynamics simulations as a complementary method to experimental methods of studying drug-solvent interactions on an atomic level. The acquired understanding helps to design drugs rationally, optimize formulations, and forecast the pharmacokinetics of such clinically important pharmaceutical molecules. These investigations should be furthered in the

future by considering mixed solvent systems, physiologic pH conditions, and the effects of common pharmaceutical excipients on hydration and aggregation behavior.

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