10. Conclusion

The three drugs under investigation—cisplatin, methotrexate, and vincristine—interact readily with the bilayer. However, the extent and nature of interaction vary. Cisplatin shows a strong surface interaction compared to methotrexate and vincristine. The order of surface interaction of the three drugs is:

\[
\text{Cisplatin} > \text{vincristine} \geq \text{methotrexate}
\]

All three drugs show limited transport across the lipid bilayer, which is consistent with the clinical reports. However, the drugs are able to perturb the lipid bilayer to different extents, which results in a disorganization of the lipid packing in the bilayer. The perturbation is dose dependent and increases with increasing drug doses. The extent of perturbation of the lipid bilayer by the three drugs is in the order:

\[
\text{Cisplatin} < \text{methotrexate} < \text{vincristine}
\]

Since membrane perturbation is related to the toxic effects of the drugs, it is obvious that the relative toxicities of the three drugs under investigation also follow the same order. The magnitude of perturbation by methotrexate is significant only at extremely high aqueous concentrations unlike vincristine. The perturbation of the bilayer by cisplatin is also dose-dependent.

As the three drugs are able to perturb the lipid bilayer significantly in the absence of any proteins, it could be assumed that such interactions could also take place in the biological systems, though on a smaller scale. The results indicate that the neurotoxic
side effects associated with these drugs could be partly due to such non-specific interactions on the lipid bilayer. The lipid bilayer core being the common construct in all cells suggests that the drugs could interact with the lipid bilayer even in the absence of specific transport systems. The probability of interacting with the lipid bilayer is more significant in nerve membranes as the lipid content of these membranes is extremely high. The lipid-drug interactions might also result in changes in the conformation of membrane-associated proteins and alter the permeability characteristics of the membrane. The presence of proteins and other molecules in the complex biological system might mask these non-specific actions, but it cannot be eliminated completely. The inferences made from the experimental results show a reasonably good correlation with clinical reports of neurotoxic manifestations of these drugs suggesting that the non-specific interaction of the drugs on the lipid bilayer of membranes is a key factor in determining the extent of neurotoxic effects. The greater the time of exposure of the drug to the lipid bilayer, greater would be the damage caused. Hence, patients undergoing chemotherapy with these drugs also exhibit a delayed neurotoxicity.

The doses of the drugs used in the present study are quite high and are not usually used in therapeutic practice. The high doses used in the present study are to magnify the changes produced in the electrical characteristics of the membrane so that the changes could be followed. The experiments also gave an insight into the type of interaction of the drugs with the purely lipoidal bilayer. These drugs even in lesser doses would exhibit similar mechanisms of action. The biological system is extremely sensitive to even minute changes in the ionic environment. Therefore, even the slightest perturbing action of these drugs on the lipid bilayer architecture of biological membranes would be
magnified and could alter the extremely fragile ion balance in the cell. This could trigger undesired reactions that could possibly result in the observed toxicities.

The frontiers of research are infinite. The present study is a small but definite step in trying to understand the possible mechanisms of neurotoxic side effects of some cancer drugs. The results point to a possible explanation for the still unknown molecular level interactions occurring between the drug and the bilayer construct of the membrane. The study can be extended to in vitro and in vivo systems to confirm the non-specific action of these drugs on lipid bilayers. Then, possible solutions to avert such type of interactions could be worked out. Finally, a successful chemotherapy regimen sans the undesired neurotoxic side effects could be designed. Let us hope that day is not far away.