Application of Lecithin (PL90) and Poloxamer 188 in Permeability and P-gp/BCRP-Mediated Drug Interaction Studies in Caco-2 Cells

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Abstract

Highly lipophilic compounds typically exhibit poor aqueous solubility and high non-specific binding. These properties can make conventional *in vitro* permeability and P-gp/BCRP-mediated drug interaction studies infeasible at intended concentrations. Additionally, high non-specific binding may compromise experimental accuracy, potentially leading to the premature discontinuation of promising candidates. To address these challenges, two pharmaceutical excipients, lecithin (PL90) and poloxamer 188, were selected, which demonstrated effective solubility enhancement and non-specific binding reduction capabilities for highly lipophilic compounds.

Objective

The objective of this study was to apply PL90 and poloxamer 188 in permeability and P-gp/BCRP-mediated drug interaction studies in Caco-2 cells to improve solubility and reduce non-specific binding for highly lipophilic compounds.

Methods

- The monolayer integrity of Caco-2 cells was evaluated using the Lucifer Yellow rejection assay with PL90 tested at 0.01, 0.100, and 1.00 mM, and poloxamer 188 tested at 0.02%, 0.2%, and 2%.
- The effects of the two excipients on P-gp and BCRP functions were evaluated in Caco-2 cells in the presence of 0.01, 0.100, and 1.00 mM PL90, and 0.02%, 0.2%, and 2% poloxamer 188.
- To assess the impact of excipients on drug permeability, a bidirectional permeability study was conducted in Caco-2 cells using 27 commercially available drugs with varying %Human Absorption (Fa) values in the absence and presence of 1.00 mM PL90 and 2% (w/v) poloxamer 188.
- Verapamil (P-gp inhibitor), along with novobiocin (BCRP inhibitor), were used to examine the effects of 1.00 mM PL90 and 2% poloxamer 188 on their IC_{50} values on P-gp and BCRP, with digoxin and estrone 3-sulfate serving as the probe substrates, respectively.

Results

1. The Lucifer Yellow rejection assay confirmed that PL90 (0.01, 0.100, and 1.00 mM) and poloxamer 188 (0.02%, 0.2%, and 2%) did not compromise the monolayer integrity of Caco-2 cells, as all measured %Lucifer yellow values were below the cut-off value of 1.0 (Figure 1).
2. In the presence of 0.01, 0.100, and 1.00 mM PL90 and 0.02%, 0.2%, and 2% poloxamer 188, the transport activity ratios with and without excipients were all greater than 83.0% (> the cut-off value of 70%), indicating that PL90 up to 1.00 mM and poloxamer 188 up to 2% did not affect P-gp and BCRP activities (Figure 2).

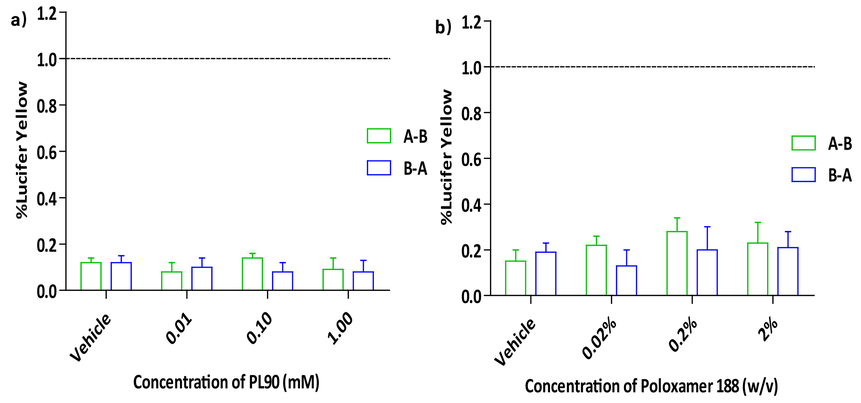

Figure 1. Impact of PL90 and Poloxamer 188 on Caco-2 Cell Monolayer Integrity

3. For these 27 commercially available drugs, the P_{app} (A-B) values in the absence and presence of PL90 and poloxamer 188 showed good correlations, with R^2 values of 0.98 and 0.98 (Figure 3a and Figure 3b), respectively, and the logarithm of P_{app} (A-B) values in the presence of excipients showed good correlation with %Fa values through Boltzmann nonlinear analysis, with R^2 values of 0.85 and 0.86, respectively (Figure 3c and 3d).

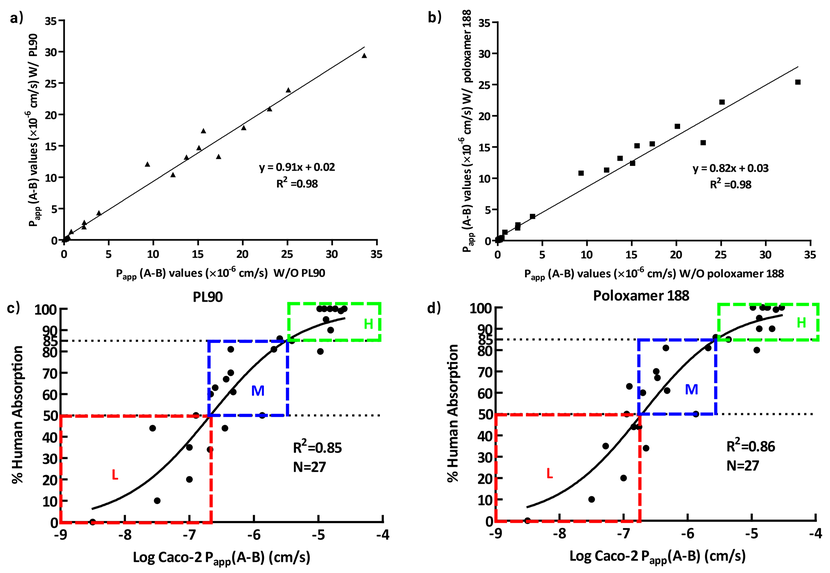

Figure 3. Correlation of the P_{app}(A-B) values in the absence and presence of 1.00 mM PL90 (a) and 2% poloxamer 188 (b), and the Log P_{app}(A-B) values in the presence of 1.00 mM PL90 (c) and 2% poloxamer 188 (d) with %Fa values

Conclusion

PL90 at concentrations up to 1.00 mM and poloxamer 188 at concentrations up to 2% (w/v) can be applied in permeability and P-gp/BCRP-mediated drug interaction studies in Caco-2 cells to improve solubility and reduce non-specific binding for highly lipophilic compounds.

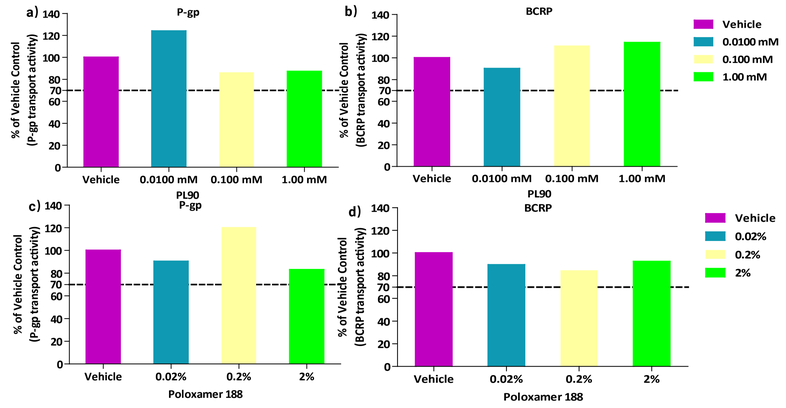

Figure 2. Impact of PL90 (0.01, 0.10, 1.00 mM) and poloxamer 188 (0.02%, 0.2%, 2% w/v) on P-gp and BCRP Activities in Caco-2 Cells

4.The IC_{50} values of verapamil and novobiocin on P-gp and BCRP showed no significant differences ($p > 0.05$) in the absence or presence of the two excipients (Figure 4).

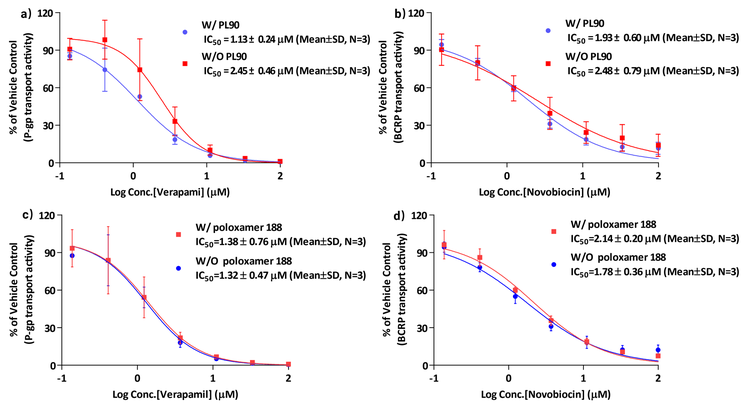

Figure 4. Impact of 1.00 mM PL90 (a, b) and 2% poloxamer 188(c, d) on P-gp and BCRP inhibition

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