A machine learning approach to design a chitosan-doped LeciPlex nanosystem loaded with Resveratrol for nebulization in cancer therapy

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Background: Lung cancer remains a leading cause of cancer-related deaths, with non-small-cell lung cancer (NSCLC) being particularly lethal. Despite advancements in treatment options, prognosis for many patients remains unsatisfactory. The employment of a novel nanoformulation for non-toxic active agents can be a solution. Methods: A novel, chitosan-doped lecithin-based nanocarrier (LeciPlex) was developed to enhance the solubility and anticancer efficacy of Resveratrol. Results: Using a machine learning regression model, LP5 (composed of lecithin, Peceol®, and chitosan) was identified as the optimal formulation. LP5 exhibited spherical particles of 59 nm, an encapsulation efficiency of 89%, a mean release time of 2.75 hours, and strong mucoadhesion. Cascade impactor studies demonstrated its potential for deep lung deposition after nebulization. Safety assessments on WISH cells confirmed the non-toxicity of both Resveratrol suspension and LP5. In vitro studies against the A549 cell line revealed that LP5 significantly enhanced the anticancer activity of Resveratrol compared to the drug suspension, with an IC50 value of 1.708 µg/ml. This represented a 63.2-fold increase in efficacy and a higher selectivity index (>5.51). Cellular uptake studies showed that A549 cells took up LP5 40,000 times more efficiently than the drug suspension. Moreover, LP5 markedly induced apoptosis in A549 cells reaching 73.1%. Conclusion: These findings highlight the improved lung anticancer efficacy, reduced toxicity, and increased selectivity of Resveratrol-loaded LeciPlex compared to the drug suspension. This study presents a promising nanocarrier system for the nebulization of Resveratrol in the treatment of lung cancer.

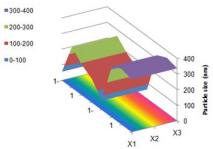
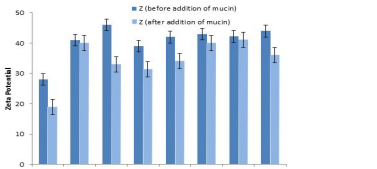


Figure 1. 3D surface response plot of Y1



.Figure 2. Zeta potential of the LP batches before and after the addition of mucin

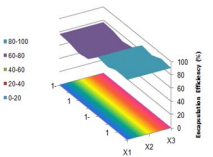


Figure 3. 3D surface response plot of Y3

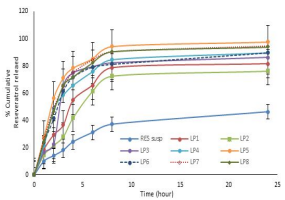


Figure 4. Release profiles of RES from the chitosan-doped LP

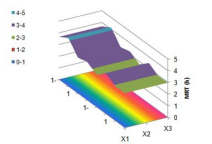


Figure 5. The 3D surface response plot of Y5

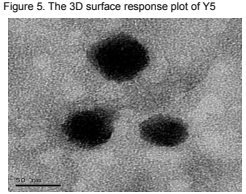
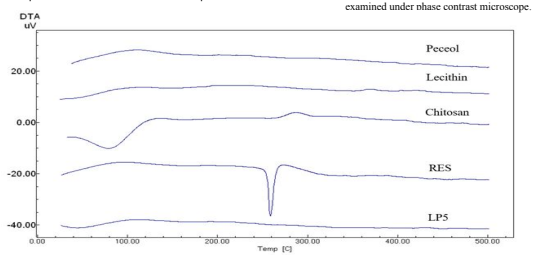


Figure 6. TEM photography of the selected formula (LP5)



.Figure 7. DTA thermograms of Peceol, lecithin, chitosan, the drug (RES), and the selected formula (LP5)

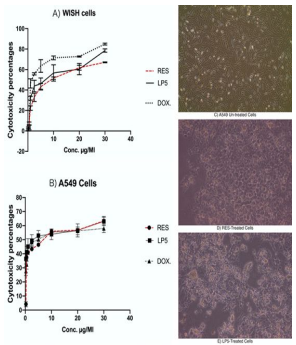


Figure 8. Safety assay and anticancer effects of RES and PL5. A)Safety assay on WISH cell line B) The anticancer effects against A549 cell line the morphological features of untreated A549 cells lines C) and after RES D) and LP5 E) treatments were examined under phase contrast microscope.

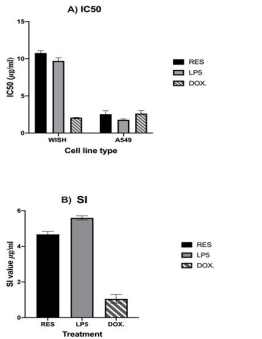


Figure 9. IC50 values of RES and LP5 on WISH and A549 cell line (A) and the treatment selectivity index on A549 cell line (B).

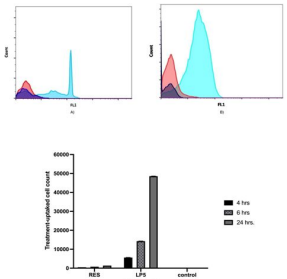


Figure 10. RES suspension and LP5 cellular uptake of A549 cell line. Flow cytometric analysis of RES (A) and LP5 uptake (B) by A549 cell line and their counts (C).

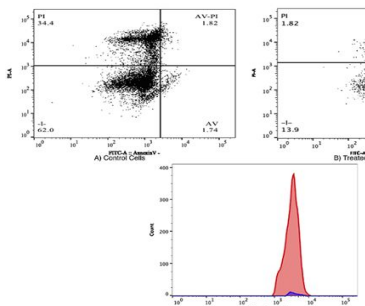


Figure 11. Apoptosis detection of untreated A549 cells (A) and LP5-treated cells (B). The untreated A549 cells are plotted against LP5 treated one (C).

Conclusion

This study presents the novel self-assembled lecithin-based cationic nanocarrier (LeciPlex) as an approach for overcoming low drug solubility. Using on a machine learning method based on regression analysis, LP5 (composed of lecithin, Peceol® and chitosan) was selected as the optimized one. LP5 was successfully nebulized to target the lungs. Cell biology study showed the enhanced anticancer effects, lower toxicity, and higher selectivity of the selected Resveratrol-loaded LeciPlex against lung cancer cell line compared to the drug suspension. The designed nano-vesicular formula seems to be a successful pulmonary delivery system for Resveratrol which can be a viable option for the treatment of lung cancer. This provides a rationale for further in-vivo investigations.