Inhalable TPGS/DPPC Micelles Loaded with Curcumin and Icariin for Targeted Lung Cancer Therapy

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INTRODUCTION

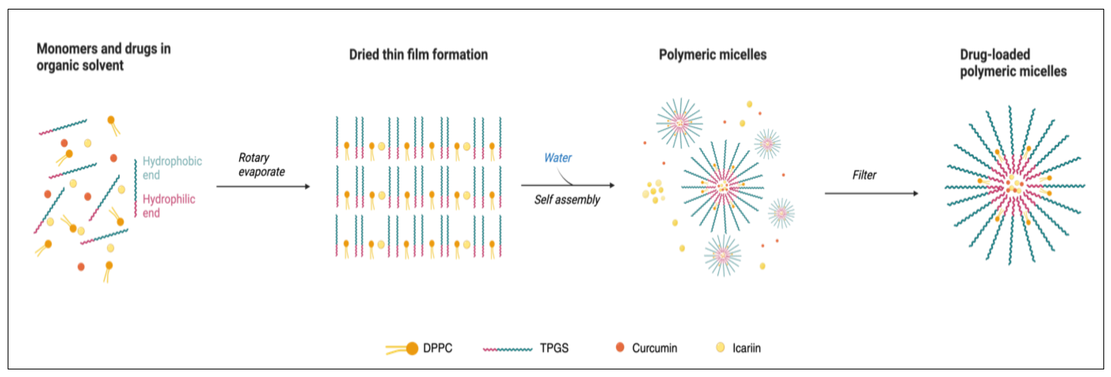
- Lung cancer, particularly NSCLC, poses a major therapeutic challenge due to drug resistance and the poor aqueous solubility of chemotherapeutic agents, limiting treatment efficacy[1].
- Curcumin (CUR), extracted from Curcuma longa, Icariin (ICA), isolated from Epimedium species. Both of them has anti-cancer properties by modulating multiple pathways, including the induction of apoptosis, inhibition of cell cycle progression, and suppression of metastasis.
- Nanoparticle-based drug delivery platforms provide an effective by improving solubility, prolonging systemic circulation, and enabling site-specific drug accumulation.

AIM

To develop an inhalable micelle formulation composed of D-α-tocopheryl polyethylene glycol succinate (TPGS) and lung surfactant component, DPPC. The target particle size for optimization ranges from 10 to 100 nm. Polymeric micelles aims to enhance the solubility of CUR and ICA and facilitate its efficient delivery to the lungs, thereby ensuring effective therapeutic outcomes.

METHODS

- **Preparation of Combination:** TPGS/DPPC micelles encapsulating CUR and ICA were prepared by a thin-film rehydration method.



- **Dynamic Light Scattering (DLS):** This technique measured the size of nano micelles in nano meters (nm).
- **Transmission Electron Microscopy (TEM):** This method determined the size and shape of the micelles.
- **Fourier-Transform Infrared Spectroscopy (FTIR):** This was used to check if the encapsulation of CUR and ICA in micelles was successful by comparing CUR, ICA, blank freeze-dried micelles, and CUR+ICA-loaded freeze-dried micelles.
- **X-Ray diffraction analysis (XRD):** This test provided insights into CUR+ICA's physical state inside the micelles.
- **Next Generation Impactor (NGI):** This device tested how CUR + ICA-loaded TPGS/DPPC micelles would deposit *in vitro.*
- **DPPH Assay:** This method checked free radical scavenging activity of CUR, ICA, CUR + ICA mixture, and CUR + ICA-loaded TPGS/DPPC
- **MTT Assay:** Cell viability of A549 cells was checked after exposure to CUR+ICA-loaded nano micelles to determine potential cytotoxicity.
- **Fluorescence Microscopy:** Fluorescence microscopy was employed to visually assess the uptake of nanomicelle by A549 cells .
- **Flow cytometry**: Cellular uptake of TPGS/ DPPC micelles by A549 cells was measured using flow cytometry utilizing coumarin-6 labeling.

RESULTS

- CUR + ICA-loaded TPGS/DPPC encapsulated CUR and ICA with high EE% and DL%. The 10:10:90:10 (w/w/w/w) yielded encapsulation efficiency (EE%) of 84 ± 3% of CUR, 92 ± 4% of ICA and the drug loading (DL%) was 17 ± 4%. The freshly prepared formulations for loaded micelles had mean diameters of 15.79 ± 1.7 nm, PDI of 0.21 ±0.06.
- The FT-IR spectra and XRD diffractograms provided conclusive evidence of successful encapsulation, confirming the presence of both CUR, ICA and TPGS/DPPC within the CUR +ICA/TPGS/DPPC micelles.

RESULTS (continued)

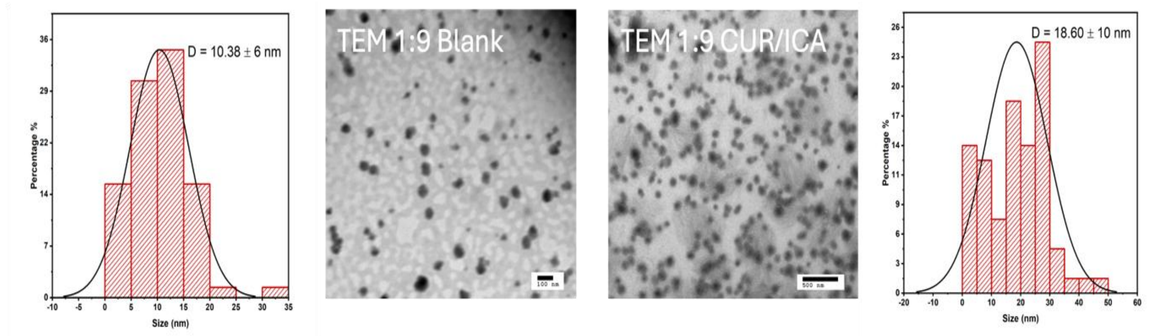


Figure. 2 Particle size and TEM image for blank and CUR + ICA-loaded TPGS/DPPC micelles

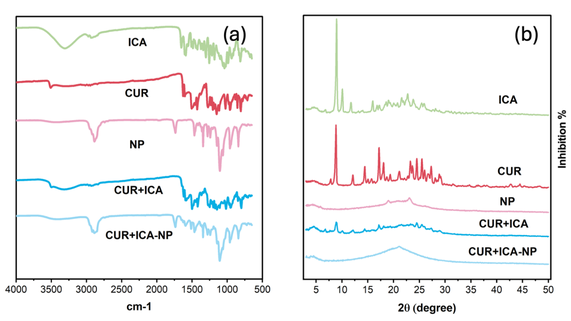


Figure. 3 (a) FTIR spectroscopy analysis (b) XRD patterns of CUR, ICA, blank TPGS/DPPC micelles, a physical mixture of CUR + ICA, and CUR + ICA-loaded TPGS/DPPC micelles.

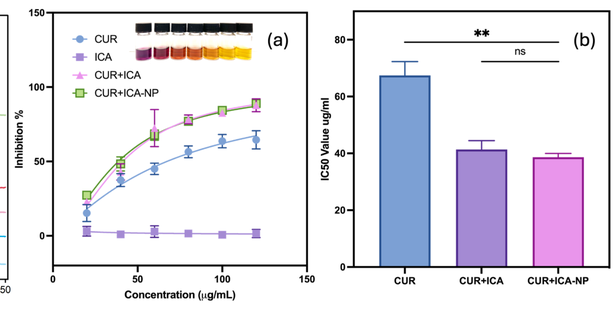


Figure. 4 Determination of DPPH radical scavenging activity of CUR, ICA, TPGS, CUR + ICA physical mixture, TPGS micelles, and CUR + ICA loaded TPGS/DPPC (9:1, w/w)

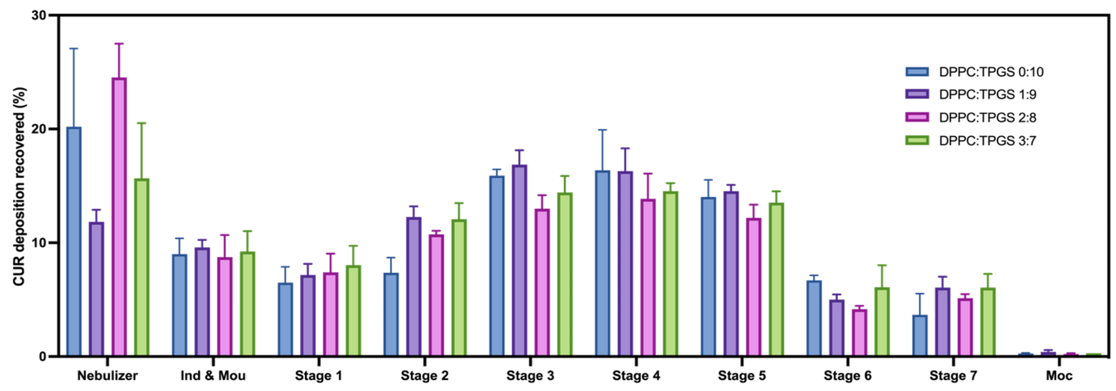


Figure. 4 NGI experimental results analyzing the airway deposition of CUR and ICA-loaded TPGS/DPPC micelles with varying TPGS/DPPC ratios. (a) Airway deposition profile, (b) cumulative particle size distribution measured by NGI, and (c) MMAD and GSD values calculated from the cumulative particle size distribution. Data are presented as mean ± SD, *n* = 3.

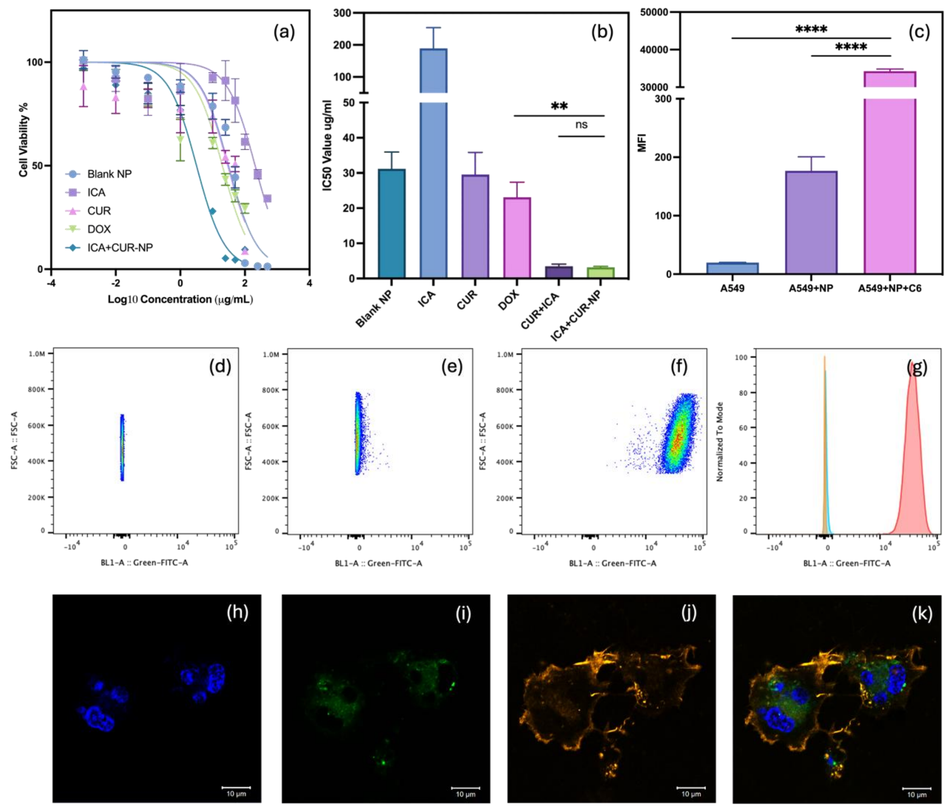


Figure. 5 (a) Cell viability dose–response curves.(b) IC50 values of blank TPGS/DPPC micelles, ICA, CUR, DOX, and CUR + ICA micelles.(c) MFI of untreated A549 cells, blank micelle-treated cells, and coumarin-6 micelle-treated cells (by flow cytometry).(d–f) Flow cytometry of blank micelle-treated and coumarin-6 micelle-treated cells.(g) Histogram comparing fluorescence intensity.(h–k) Confocal images showing cellular uptake:(h) Nuclei stained with Hoechst dye.(i) Coumarin-6-loaded TPGS/DPPC micelles.(j) Membranes stained with Cell Mask Orange Actin Stain.(k) Merged image of A549 cells.

CONCLUSION AND FUTURE WORK

- CUR and ICA-loaded TPGS/DPPC micelles enabled effective inhalation-based delivery of ICA and CUR, while enhancing their solubility, stability, and cellular uptake. The optimized 9:1 TPGS/DPPC formulation exhibited favorable particle size, high encapsulation efficiency, and stability, supporting its suitability for further investigation.
- Future work will focus on formulation optimization and *in vivo* drug anticancer efficacy evaluation.

References

[1] Wang, M.; Herbst, R. S.; Boshoff, C. Toward Personalized Treatment Approaches for Non-Small-Cell Lung Cancer. *Nat. Med.* **2021**, *27*, 1345, DOI: 10.1038/s41591-021-01450-2 There is no corresponding record for this reference.

CRS 2025 ANNUAL MEETING & EXPOSITION PHILADELPHIA, PA JULY 14-18, 2025