# Development of Lipid-based Nano Formulations of Miriplatin against Lung Cancer

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## Background

**Lung cancer claims the highest mortality and the second most new cases in the US. Cisplatin, the first platinum-based anticancer drug, has the highest potency against lung cancer but carries many severe adverse effects. Miriplatin was discovered with a higher lipophilicity and approved in Japan for the treatment of hepatocellular carcinoma (HCC). Nanocarriers provide a promising platform to overcome the physiochemical barrier of solid tumors and to reduce the toxicity of anticancer drugs.**

**In this study, miriplatin is formulated into various lipid-based nanocarriers (micelles and solid lipid nanoparticles (SLNs)) by a scale-up preparation method to evaluate the anticancer activities against lung cancer.**

## METHODS

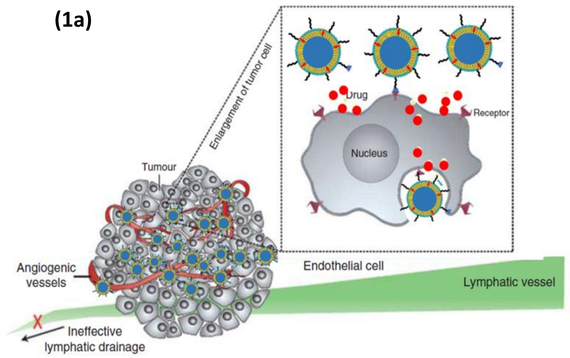
**Miriplatin-loaded nano formulations were prepared by a scale-up method (co-solvent slow evaporation). (Figure 2)**

**Selected miriplatin-loaded formulations prepared by co-solvent slow evaporation method were characterized by sizes, polydispersity index (PDI), platinum recovery and morphology using transmission electron microscopy (TEM).**

**A three-dimensional multicellular spheroid (3D MCS) model of A549-iRFP cells was well established for in vitro evaluation of the nano formulations' anticancer activity against lung cancer. The A549-iRFP 3D MCS were treated by 3-day exposure to miriplatin-loaded nano formulations and 4-day drug-free growth.**

**Figure 1:** Proposed mechanism of action of miriplatin-loaded nano formulations. (a) The passive targeting of miriplatin-loaded nano formulation to lung solid tumor; (b) The cellular uptake of miriplatin-loaded nano formulation in lung solid tumor cells.

(1a)




(1b)

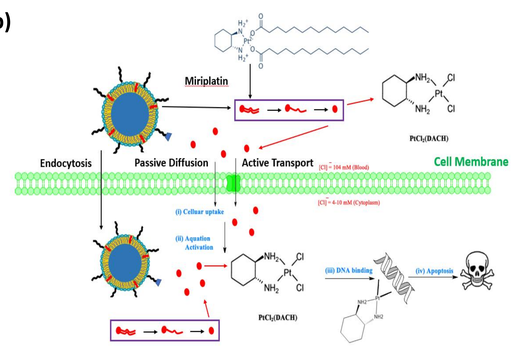



**Figure 2:** Schematic of preparation of miriplatin-loaded nano formulations by co-solvent slow evaporation method.

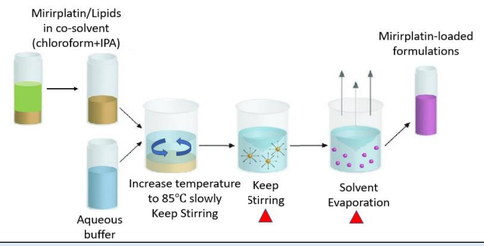
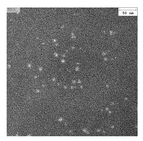



**Figure 3:** Composition, size, PDI and Pt recovery of selected miriplatin-loaded nano formulations (table), and morphology of miriplatin-loaded micelles (3a) and SLNs (3b).

| Formulations | Size (nm) | PDI | Pt Recovery |
|---|---|---|---|
| **Micelle:** 100%PEG+20%miriplatin | 11.90 | 0.247 | 80.8% |
| **Micelle:** 100%PEG+20%miriplatin+**10%PTX** | 11.71 | 0.254 | 77.7% |
| | | | |
| **SLN:** 90%TM/10%PEG+20%miriplatin | 109.2 | 0.801 | 76.2% |
| **SLN:** 90%TP/10%PEG+20%miriplatin | 143.6 | 0.948 | 86.3% |
| **SLN:** 90%TM/10%PEG+20%miriplatin+**10%PTX** | 138.1 | 0.872 | 83.2% |
| **SLN:** 90%TP/10%PEG+20%miriplatin+**10%PTX** | 82.08 | 1.000 | 74.4% |

(3a)



(3b)

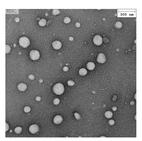
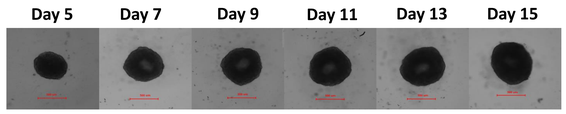
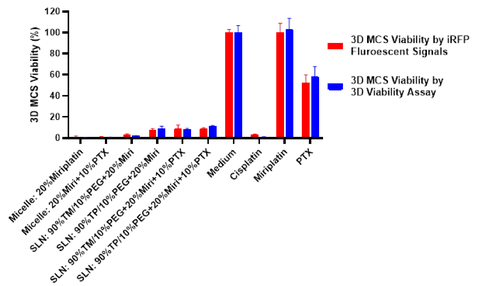


**Figure 4:** Morphology of A549-iRFP 3D MCS (4a). Cell viability (4b) and fluorescent signals change (4c) of A549-iRFP 3D MCS after exposure to miriplatin-loaded nano formulations.

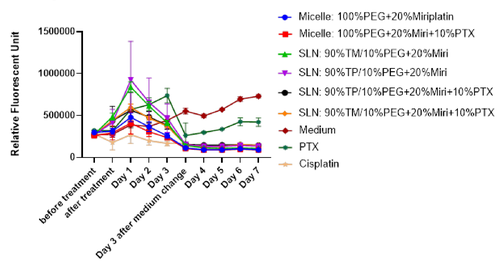
(4a)




(4b)




(4c)




## RESULTS

**Figure 2 shows that the miriplatin-loaded nano formulations (both micelles and SLNs) were successfully prepared by the co-solvent slow evaporation method.**

**Figure 3 compares the two types of nano formulations, micelles were much smaller (~10 nm in diameter) and more homogeneous (PDI < 0.3), while SLNs were bigger (~ 100 nm in diameter) and more heterogeneous (PDI ~0.8). Both nano formulations showed high platinum recovery (>75%). The TEM images shows that micelles had a morphology of spherical dots at around 10 nm in diameter, while SLNs showed spherical structures with a size distribution from 50 to 150 nm.**

**Figure 4 highlights that a 3D MCS model of A549-iRFP cells with fluorescent signals was successfully established. Selected miriplatin-loaded nano formulations showed substantial anticancer activity against A549-iRFP 3D MCS, which is comparable to cisplatin, a first line drug against lung cancer. The fluorescent signals indicated that the cancer cells did not relapse after the clearance of the anticancer agents after three-day exposure.**

## CONCLUSION

**A co-solvent slow evaporation method has been established as a pharmaceutically viable scale-up method to prepare nano formulations with good reproducibility.**

**The miriplatin-loaded nano formulations carrying favorable physiochemical properties (smaller size, high platinum drug recovery and round morphological features) could enhance the anticancer activities of platinum drugs against lung cancer.**