Abstract: Hydroxylated oxime ether lipids (OELs) have previously been reported to efficiently deliver functional Dicer substrate siRNAs (DsiRNAs) in cells. Here, we explored *in vivo* utility of these OELs, using OEL4 as a prototype and report that surface modification of the OEL4 formulations was essential for their *in vivo* applications. These surface modified OEL4 formulations were developed by inclusion of various PEGylated lipids. The vesicle stability and gene knock-down were dependent on the PEG chain length. OEL4 containing DSPE-PEG350 and DSPE-PEG1000 (but not DSPE2000) promoted gene silencing in cells. *In vivo* studies demonstrated that OEL4 vesicles formulated using 3 mol% DSPE-PEG350 accumulate in human lung cancer (A549-luc2) tumors in mice xenografts and exhibit significant increase in tumor to liver ratios. These vesicles also showed a statistically significant reduction of luciferase signal in tumors as compared to untreated mice. Taken together, OEL4:DSPE-PEG350 formulation serves as a novel candidate for delivery of RNAi therapeutics.