

## Effect of Wheat Germ Agglutinin- and Lactoferrin-Grafted Catanionic Solid Lipid Nanoparticles on Targeting Delivery of Etoposide to Glioblastoma Multiforme

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**Abstract :** Catanionic solid lipid nanoparticles (CASLNs) with surface wheat germ agglutinin (WGA) and lactoferrin (Lf) were formulated for entrapping and releasing etoposide (ETP), crossing the blood-brain barrier (BBB), and inhibiting the growth of glioblastoma multiforme (GBM). Microemulsified ETP-CASLNs were modified with WGA and Lf for permeating a cultured monolayer of human brain-microvascular endothelial cells (HBMECs) regulated by human astrocytes and for treating malignant U87MG cells. Experimental evidence revealed that an increase in the concentration of catanionic surfactant from 5  $\mu\text{M}$  to 7.5  $\mu\text{M}$  reduced the particle size. When the concentration of catanionic surfactant increased from 7.5  $\mu\text{M}$  to 12.5  $\mu\text{M}$ , the particle size increased, yielding a minimal diameter of WGA-Lf-ETP-CASLNs at 7.5  $\mu\text{M}$  of catanionic surfactant. An increase in the weight percentage of BW from 25% to 75% enlarged WGA-Lf-ETP-CASLNs. In addition, an increase in the concentration of catanionic surfactant from 5 to 15  $\mu\text{M}$  increased the absolute value of zeta potential of WGA-Lf-ETP-CASLNs. It was intriguing that the increment of the charge as a function of the concentration of catanionic surfactant was approximately linear. WGA-Lf-ETP-CASLNs revealed an integral structure with smooth particle contour, displayed a lighter exterior layer of catanionic surfactant, WGA, and Lf and showed a rigid interior region of solid lipids. A variation in the concentration of catanionic surfactant between 5  $\mu\text{M}$  and 15  $\mu\text{M}$  yielded a maximal encapsulation efficiency of ETP at 7.5  $\mu\text{M}$  of catanionic surfactant. An increase in the concentration of Lf/WGA decreased the grafting efficiency of Lf/WGA. Also, an increase in the weight percentage of ETP decreased its encapsulation efficiency. Moreover, the release rate of ETP from WGA-Lf-ETP-CASLNs reduced with increasing concentration of catanionic surfactant, and WGA-Lf-ETP-CASLNs at 12.5  $\mu\text{M}$  of catanionic surfactant exhibited a feature of sustained release. The order in the viability of HBMECs was ETP-CASLNs  $\square$  Lf-ETP-CASLNs  $\square$  WGA-Lf-ETP-CASLNs  $>$  ETP. The variation in the transendothelial electrical resistance (TEER) and permeability of propidium iodide (PI) was negligible when the concentration of Lf increased. Furthermore, an increase in the concentration of WGA from 0.2 to 0.6 mg/mL insignificantly altered the TEER and permeability of PI. When the concentration of Lf increased from 2.5 to 7.5  $\mu\text{g/mL}$  and the concentration of WGA increased from 2.5 to 5  $\mu\text{g/mL}$ , the enhancement in the permeability of ETP was minor. However, 10  $\mu\text{g/mL}$  of Lf promoted the permeability of ETP using Lf-ETP-CASLNs, and 5 and 10  $\mu\text{g/mL}$  of WGA could considerably improve the permeability of ETP using WGA-Lf-ETP-CASLNs. The order in the efficacy of inhibiting U87MG cells was WGA-Lf-ETP-CASLNs  $>$  Lf-ETP-CASLNs  $>$  ETP-CASLNs  $>$  ETP. As a result, WGA-Lf-ETP-CASLNs reduced the TEER, enhanced the permeability of PI, induced a minor cytotoxicity to HBMECs, increased the permeability of ETP across the BBB, and improved the antiproliferative efficacy of U87MG cells. The grafting of WGA and Lf is crucial to control the medicinal property of ETP-CASLNs and WGA-Lf-ETP-CASLNs can be promising colloidal carriers in GBM management.

**Keywords :** catanionic solid lipid nanoparticle, etoposide, glioblastoma multiforme, lactoferrin, wheat germ agglutinin

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