**The Use of Ambroxol Hydrochloride Loaded Gastro-Retentive Nanosuspension against Lung Cancer**

**Abstract:** This study aimed to develop gastro-retentive sustained-release ambroxol (ABX) nanosuspensions utilizing ambroxol-kappa-carrageenan (ABX-CRGK) complexation formulations. The complex was characterized by differential scanning calorimetry, powder x-ray diffractometer, and scanning electron microscopy. The prepared co-precipitate complex was used for the development of the sustained-release formulation to overcome the high metabolic and poor solubility problems associated with ABX. Furthermore, the co-precipitate complex was formulated as a suspension in an aqueous floating gel-forming vehicle of sodium alginate with chitosan, which might be beneficial for targeting the stomach as a good absorption site for ABX. The suspension exhibited rapid floating gel behaviour for more than 8 h, thus confirming the gastro-retentive effects. Particle size analysis revealed that the optimum nanosuspension (ABX-NS) had a mean particle size of 332.3 nm. Afterward, the ABX released by the nanoparticles would be distributed to the pulmonary tissue as previously described. Based on extensive pulmonary distribution, the developed nanosuspension-released ABX nanoparticles showed significant cytotoxic enhancement compared to free ABX in A549 lung cancer cells. However, a significant loss of mitochondrial membrane potential (MMP) also occurred. The level of caspase-3 was the highest in the ABX-NS-released particle-treated samples, with a value of 416.6 ± 9.11 pg/mL. Meanwhile, the levels of nuclear factor kappa beta, interleukins 6 and 1 beta, and tumour necrosis alpha (NF-kB, IL-6, IL-1\_, and TNF-\_, respectively) were lower for ABX-NS compared to free ABX (p < 0.05). In caspase-3, Bax, and p53, levels significantly increased in the presence of ABX-NS compared to free ABX. Overall, ABX-NS produced an enhancement of the anticancer effects of ABX on the A549 cells, and the developed sustained-release gel was successful in providing a gastro-retentive effect.