# HA-PLGA Nanoparticles As Novel Drug Carrier for Cancer Therapeutics

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**Statement of Purpose:** Hyaluronic acid (HA) is a biodegradable, biocompatible, non-immunogenic, and non-inflammatory linear polysaccharide [1]. Because of the excellent physicochemical properties, HA has been widely used for arthritis treatment, ophthalmic surgery, drug delivery, and tissue engineering. The biodegradable poly(lactic-*co*-glycolic acid) [PLGA] grafted with HA (HA-PLGA) has been used as a novel tissue engineering scaffold [2]. In this work, adipic acid dihydrazide grafted HA (HA-ADH) was synthesized and conjugated with PLGA. The HA-PLGA nanoparticle was characterized and assessed as a novel anti-cancer drug carrier with passive targeting effect.

**Methods:**

**Synthesis of HA-ADH:** HA-ADH was synthesized and purified as described elsewhere [3]. The degree of substitution by ADH was determined with $^1$H-NMR according to the analysis by Luo *et al.* [3].

**Conjugation of HA-ADH with PLGA:** PLGA was dissolved in dimethyl sulfoxide (DMSO, 5 ml). The addition of NHS and DCC in PLGA solution resulted in successful activation of functional end group of PLGA. Then, HA-ADH was dissolved in 5 mL of dimethyl sulfoxide (DMSO) and then mixed with activated PLGA resulting in successful conjugation of HA-PLGA. The ratio of PLGA to HA was changed from 1/4 to 1/40.

**Preparation of HA-PLGA nanopaticles:** HA-PLGA nanoparticles were prepared by the dialysis and freeze drying method.

**Characterization of HA-PLGA nanopaticles:** HA-PLGA copolymer was analyzed by $^1$H NMR and gel permeation chromatography (GPC). The particle size was measured by ELS-8000.

**Results/Discussion:** Figure 1 shows the schematic representation of HA-PLGA synthesis. Interestingly, the recovered HA-ADH with high degree of ADH modification was soluble in DMSO and used for the preparation of HA-PLGA. HA-ADH was conjugated to PLGA activated with NHS and DCC in DMSO. The mean particle size, which was in the range of 250 nm ~ 150 nm, could be controlled by changing the molar ratio of HA to PLGA and the molecular weight of PLGA. Figure 2 shows the particle size distributions of HA-PLGA nanoparticles in water according to the ratio of PLGA to HA. The novel HA-PLGA nanoparticle was used to incorporate paclitaxel in the core of HA-PLGA polymeric micelle system. The drug loading was higher than 70 wt%. As well known, a drug delivery system with a mean particle size of 100 nm ~ 200 nm can be selectively delivered by the EPR effect. In addition, HA has recently been reported to be degraded at the HA receptor of LYVE-1 on the lymphatic endothelial cells [4]. HA-PLGA polymeric micelle system may be successfully applied for tumor target delivery for cancer therapeutics.

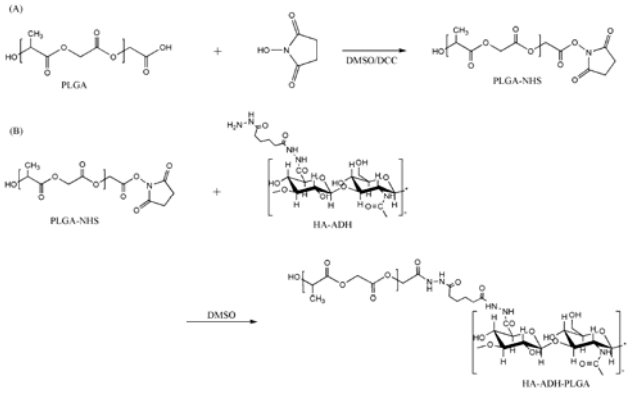


**Figure 1.** Schematic representation of HA–PLGA synthesis: (A) Activation of PLGA with NHS/DCC. (B) Conjugation of HA-ADH with the activated PLGA.

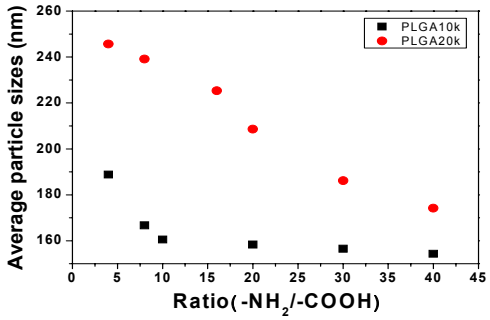


**Figure 2.** Size distribution of HA-PLGA according to the molar ratio of $-NH_2$ of HA-ADH to –COOH of PLGA.

**Conclusions:** A novel protocol for the preparation of HA-PLGA polymeric micelle system was successfully developed for tumor targeting cancer drug delivery applications. The mean particle size of HA-PLGA, which was in the range of 150 nm ~ 250 nm, could be controlled by changing reaction conditions. These novel HA-PLGA nanoparticles incorporating paclitaxel were thought to be a novel cancer drug delivery system with EPR effect. *In vivo* release test will be followed.

**References:**

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