Research in Pharmaceutical Sciences, 2012;7(5)
School of Pharmacy and Pharmaceutical Sciences
Isfahan University of Medical Sciences

Targeted drug delivery to cancer stem cells by hyaluronic acid-based drug conjugates: Synthesis and characterization

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Background and Aims: Combined eradication of both cancer stem cells (CSCs) and non-stem cancer cells may be the most appealing strategy for treatment of cancer [1,2]. The stem cell marker CD44 itself is a receptor for hyaluronic acid (HA) [3,4]. This research is aimed to develop a HA-based nanostructure delivery system to target breast cancer cells and CSCs via CD44 marker.
Methods: HA was conjugated directly or by the covalent attachment of adipic dihydrazide-functionalized HA (HA-ADH), as a carrier and targeting agent, with 2'-OH of docetaxel (DTX), which lead to fabrication of the conjugates with different molecular weights and degrees of substitution (DS). Their chemical structure of HA-DTX conjugates were investigated using 1HNMR, DSC, GPC and TEM. The release behavior of docetaxel is also studied.
Results: As a result of the controlled synthesis of HA-ADH, the HA-spacer-DTX conjugates, and HA-DTX direct conjugates with DS less than 35% was obtained which it retains CD44 targeting properties of hyaluronic acid. It was observed that dispersion of the amphiphilic conjugates in aqueous media, lead to formation of nanostructures with a particle size less than 250 nm. It was worthy of note that HA-DTX nanostructures improved the solubility of DTX in aqueous media.
Conclusions: Two-steps method in preparation of the conjugate leads to control the degree of substitution in hyaluronic acid, which in part maintain the active CD44 targeting ability of the prodrug. Although indirect conjugation of anticancer drug to HA backbone gives an oppurtunity to adjust DS, direct conjugates follow a less sophisticated method of preparation. The assembled nanostructures based on the HA–DTX conjugates shows a great potential as polymer prodrug for tumor therapy, and might achieve targeting of cancer stem cells and non-stem cancer cells in future cell culture and in vivo studies.

Keywords: Hylauronic Acid; Drug conjugate; Docetaxel; Cancer stem cells