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论文

肿瘤趋向性*N*-(2-羟丙基)甲基丙烯酰胺聚合物-米托蒽醌接合物研究肿瘤趋向性*N*-(2-羟丙基)甲基丙烯酰胺聚合物-米托蒽醌接合物研究

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摘要:

目的制备*N*-(2-羟丙基)甲基丙烯酰胺(HPMA)聚合物-米托蒽醌(DHAQ)接合物以提高DHAQ在实体瘤中的分布。方法采用DHAQ与四肽间隔基连接,再与HPMA进行自由基沉淀聚合反应的方法,合成目标接合物;考察了接合物在不同介质中的稳定性及荷瘤小鼠体内的分布情况。结果合成的接合物经UV,HPLC和FPLC鉴定为目标化合物。其总DHAQ含量为132.4 mg·g^{-1}接合物,游离DHAQ含量为3.5 mg·mg^{-1}接合物。摩尔质量19 000 g·mol^{-1},分子量分布1.4。在不同pH磷酸盐缓冲液及血浆中较稳定,在肿瘤中的释药明显加快。与原药相比,接合物在荷瘤小鼠体内的分布明显不同。肿瘤中AUC为游离药物3倍;血液循环时间延长;在心脏中的分布明显减少。表明接合物具有一定的肿瘤趋向性,并能降低原药对心脏的毒性。结论将具有仲氨基的DHAQ连接于HPMA聚合物,能提高DHAQ在肿瘤中的分布,为实体瘤靶向高分子给药系统的研究提供新的思路。

关键词: *N*-(2-羟丙基)甲基丙烯酰胺聚合物 米托蒽醌 抗肿瘤药物 肿瘤趋向

Selective tumor-accumulation of HPMA copolymer-mitoxantrone conjugates

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Abstract:

AimTo increase the accumulation of mitoxantrone in solid tumor by synthesis and characterization of *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymer-mitoxantrone conjugate (p-DHAQ). MethodsHPMA copolymer-mitoxantrone conjugate was prepared by free radical precipitation copolymerization method. The *in vitro* stability of conjugate was investigated under different conditions. Biodistribution was examined in mice bearing Ehrlich solid tumor. ResultsThe p-DHAQ conjugate was characterized by UV, HPLC and size exclusion chromatography. The conjugate was stable in buffers of different pH and in mice plasma while the rate of drug liberation was faster in tumor. It appeared that the circulation lifetime of HPMA copolymer-bound mitoxantrone were three times more than that of the drug in free form. The AUC of p-DHAQ was three times more than the AUC of free drug. The p-DHAQ level in heart was five times lower than free drug. This reduces the possibility of toxicity to the heart. ConclusionHPMA copolymer-mitoxantrone conjugate was successfully synthesized and characterized. The biodistribution results showed the possibility of targeting anticancer drug-mitoxantrone with secondary amino residue to the tumor tissue by HPMA copolymer as carrier.

Keywords: mitoxantrone anti-cancer drug selective tumor-accumulation HPMA copolymers

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