光响应聚倍半硅氧烷纳米载体及其光控药物释放性能

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摘要 设计并合成了氨基甲酸-*N,N*-双[3-(三甲氧基硅基)丙基]-(2-硝基苯基)甲酯(BS)光响应性桥联硅烷单体, 采用 ^1H NMR、 ^{13}C NMR、 ^{29}Si NMR和质谱对其进行了表征, 硅烷的邻硝基苄基桥联结构单元具有光响应性能, 在254 nm光照射下会发生光致断裂. 通过溶胶-凝胶过程, 利用BS桥联硅烷制备了具有光响应性能的聚倍半硅氧烷纳米粒子(BPS), 其平均直径为127 nm, 粒径分布窄(PDI=0.167). 在254 nm光照射下BPS有机桥联结构发生光致断裂反应, 表面电荷性质发生由负(-28.20 mV)到正(+22.86 mV)的翻转, BPS纳米粒子通过静电相互作用能够高效装载阿霉素药物, 并具有光控药物释放行为. 体外释放实验表明, 在254 nm光照射下药物的释放率与光照强度和光照时间正相关, 可对药物实现定时、定位和定量地精确控制释放, 最高药物释放率达到82.9%, 该研究为目标分子的控制释放提供了一种新的聚倍半硅氧烷可控释放体系, 具有重要应用价值.

关键词 聚倍半硅氧烷, 光响应, 桥联, 纳米载体, 可控释放, 阿霉素

光响应性聚合物能在光作用下发生物理或化学性质的变化, 如聚合物材料的形状、表面性质(电荷、亲疏水性)、交联解交联以及孔隙结构等^[1-3]. 光作为一种调控手段具有高效可控和非接触性特点^[4], 通过调节光照波长、光照强度、光照时间和位置等参数可以实现聚合物性能的变化. 接枝香豆素基团的聚乙烯在光照条件下发生可逆的光致聚合和光致断裂反应, 改变了聚乙烯表面润湿性, 从而赋予材料光控抗污性能^[5]. 以偶氮苯基团为有机桥的桥联聚倍半硅氧烷材料利用偶氮苯的光致异构化反应改变分子内构象, 实现材料光控自愈合行为^[6]. 邻硝基苄基位于主链的两亲性共聚物具有光控降解行为, 其光致断裂反应使聚合物主链发生降解, 从而实现光控释放目标分子的目的^[7].

光的易调控性在目标分子释放体系中具有重要应

用价值, 可采用非接触方式, 通过调节光的参数实现对光响应释放体系中的目标分子的释放速率、释放位置和释放浓度进行有效控制, 达到时间和空间的同时可控释放. Karthik等人^[8,9]将药物苯丁酸氮芥通过化学共价键的方法分别连接在修饰有喹啉和香豆素的二氧化硅纳米粒子表面, 利用光反应进行光控释放. 类似地, 赵一兵课题组^[10]通过共价方式构建光响应型控制释放体系, 在二氧化硅纳米粒子表面接枝光响应基团的药物分子. 朱麟勇课题组^[11]将香豆素基苯丁酸介氮与氨基硅氧烷共价连接, 经过水解缩合反应得到的介孔二氧化硅纳米粒子具有光控释放药物行为. 这些研究体系都是以二氧化硅材料为载体, 并通过共价键的方式将带有光响应基团的二氧化硅载体与受控释放分子连接起来, 其制备过程复杂, 共价键的连接会影响目标分子的化学活性.

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聚硅氧烷是一种主链为-Si-O-的高分子材料,具有耐高低温、耐候性、生理惰性和生理相容性好等优点,在药物载体、生物成像和抗菌涂层等领域具有应用前景^[11~14]. 桥联聚倍半硅氧烷属于聚硅氧烷,具有 $[-A-SiO_{1.5}]_n$ -化学组成的高分子交联网络结构. 这里, A为有机桥联基团,如甲基、乙基、苯基或其他功能性有机基团等,有机桥联基团具有可设计性和可调控性,因此可以得到不同性能的桥联聚倍半硅氧烷材料,具备无机和有机聚合物材料的性能特征^[15~19]. 由桥联硅烷制备的聚倍半硅氧烷纳米粒子^[20~23],其粒径大小可以通过水解缩合反应有效调控、纳米粒子比表面积大、易功能化设计、生物相容性好,因此在刺激响应释放体系、光学传感器、生物成像等领域具有重要应用价值.

本研究设计合成了含光敏基团邻硝基苄基的桥联硅烷,经水解缩合反应制备了具有光触发电荷翻转特性的桥联聚倍半硅氧烷纳米粒子,邻硝基苄基桥联基团在254 nm光照射下发生光致断裂反应,使得纳米粒子的表面电荷性质发生由负到正的翻转. 利用静电相互作用,将具有正电荷性质的药物阿霉素分子结合到带负电荷性质的桥联聚硅氧烷纳米载体上. 光照后,纳米粒子表面电荷发生翻转,药物受到静电斥力作用从纳米载体表面脱离释放,通过改变光的照射强度和照射时间,能够精确调控药物阿霉素的释放量. 本工作研究了一种基于邻硝基苄基桥联聚倍半硅氧烷纳米粒子的光响应型药物控制释放体系,对发展光控目标分子释放体系具有重要意义.

1 实验

(i) 原料与试剂. 2-硝基苄醇(分析纯)、二(三氯甲基)碳酸酯(分析纯)、*N,N*-二异丙基乙胺(DIPEA, 分析纯)、二(三甲氧基硅烷丙基)胺(分析纯)、盐酸、无水硫酸钠、三乙胺、乙酸乙酯、正己烷、石油醚、二氯甲烷、丙酮均购自国药集团化学试剂有限公司,盐酸阿霉素(doxorubicin·HCl, DOX, 分析纯)购自上海麦克林生化科技有限公司.

(ii) 仪器与方法. 使用Tensor-27型傅里叶变换红外光谱仪(Bruker, 德国)采集样品的红外吸收光谱(FTIR),将干燥后的样品与色谱纯溴化钾混合研磨后压片,频率收集范围为 $500\sim 4000\text{ cm}^{-1}$,分辨率为 4 cm^{-1} ,采样32次. 使用Bruker型超导傅立叶变换核磁共振仪(瑞士)检测样品的核磁谱图(NMR),将干燥后的样品溶于氘代氯仿中,对样品进行氢谱、碳谱和硅谱

测试,测试温度为298 K. 使用Agilent Cary 5000型紫外-可见-近红外分光光度计(Agilent, 美国)检测其紫外-可见光谱(UV-vis),将3 mL样品溶液置于比色皿中,测试温度为室温,波长范围为200~800 nm,扫描速度为1 nm/s. 将样品均匀地分散在乙醇中,滴于洁净的硅片上,干燥后喷金,使用SU8010型高分辨场发射扫描电子显微镜(SEM, Hitachi, 日本)对样品的形貌进行观察. 将样品均匀地分散于去离子水中,浓度为0.1 mg/mL,使用NanoZS型纳米粒度电位仪(Malvern Panalytical, 英国)检测其粒径大小和zeta电位,每个样品测定12次,每组样品测试3次,取平均值计算粒径和zeta电位.

(iii) 2-硝基苄基氯甲酸酯的合成. 将3.80 g 2-硝基苄醇(24.8 mmol)和3.71 g DIPEA(28.7 mmol)溶于25 mL二氯甲烷中,逐滴加入10 mL二(三氯甲基)碳酸酯(9.58 mmol)的二氯甲烷溶液. 将反应混合物在0~4℃冰水浴下搅拌30 min,除去冰水浴,室温下继续搅拌2 h. 反应结束后,分别用30 mL蒸馏水洗涤粗产物3次,再用30 mL二氯甲烷萃取溶液,收集所有有机层,用无水硫酸钠干燥,抽滤、蒸发溶剂浓缩后,经柱层析(二氯甲烷/石油醚体积比为3:1)提纯,得到2-硝基苄基氯甲酸酯黄色固体产物(3.08 g, 57.8%). ^1H NMR(400 MHz, CDCl_3) δ 8.09(d, 1H), 7.71(d, 1H), 7.67(t, 1H), 7.54(t, 1H), 5.01(s, 2H).

(iv) 氨基甲酸-*N,N*-双[3-(三甲氧基硅基)丙基]-(2-硝基苄基)甲酯(BS)的制备. 将3.51 g二(三甲氧基硅基)胺(10.3 mmol)和1.26 g三乙胺(12.5 mmol)溶解在60 mL二氯甲烷中. 在室温条件下逐滴加入的20 mL 2-硝基苄基氯甲酸酯(10.3 mmol)的二氯甲烷溶液,滴加完毕后,继续反应4 h. 反应结束后,抽滤除去三乙胺盐酸盐化合物,澄清的滤液经蒸发浓缩后,采用柱层析(乙酸乙酯/正己烷体积比为4:7)提纯,得到黄色油状物BS(3.05 g, 56.9%). ^{13}C NMR(100 MHz, CDCl_3) δ 155.47, 147.51, 133.62, 133.32, 128.69, 128.39, 124.90, 63.59, 50.51, 50.29, 49.54, 21.96, 20.90, 6.19; ^{29}Si (99.25 MHz, CDCl_3) δ -42.5; MS(ESI): 521.2042[M⁺].

(v) 光响应性聚倍半硅氧烷纳米粒子(BPS)的制备. 将8 mL蒸馏水、0.5 mL氢氧化钠溶液(0.1 mol/L)、1 mL氟化钾溶液(0.1 mol/L)和0.5 mL异丙醇加入至25 mL圆底烧瓶中,在80℃将0.05 mL光响应桥联硅烷BS逐滴加入至上述混合溶液中,搅拌反应8 h,离心收集下层固体,分别用乙醇和蒸馏水洗涤3次,

60°C烘箱中干燥得到白色粉末状桥联聚倍半硅氧烷纳米粒子BPS, 收率为90.3%。

(vi) 载药纳米粒子的制备. 分别配制0.5 mg/mL的DOX水溶液和0.5 mg/mL的BPS水分散悬浊液. 取一定量的DOX水溶液与磷酸缓冲溶液(BPS)溶液混合, 用PBS调节溶液pH为7.4, 室温下磁力搅拌24 h, 离心分离, 用pH 7.4的PBS磷酸缓冲液洗去物理吸附在粒子表面的DOX, 反复洗3遍, 得到的载药纳米粒子DOX@BPS, 同时保留上清液, 制备了4种药物与载体投料比(R)分别为0.1、0.2、0.5和1.0的载药纳米粒子。

载药率和包封率通过检测上清液中DOX的含量计算得到, 载药率和包封率计算公式如下:

$$\text{载药率} = (\text{载药纳米粒子中药物的质量} / \text{载药纳米粒子的总质量}) \times 100\%, \quad (1)$$

$$\text{包封率} = (\text{载药纳米粒子中药物的质量} / \text{投药量}) \times 100\%. \quad (2)$$

(vii) BS和BPS的光反应. 将100 mL BS的四氢呋喃溶液(80 $\mu\text{g/mL}$)置于光源下方5 cm处, 使用254 nm光(200 mW/cm^2)进行照射, 每隔10 min取样6 mL进行UV-vis测试以监测反应进程. 利用吸光度的变化($A_t - A_0$)/ A_0 来判断反应程度。

将100 mL BPS纳米粒子的悬浊液(1 mg/mL)置于

光源下方5 cm处, 使用254 nm光(200 mW/cm^2)进行照射, 每隔10 min取样6 mL对其进行离心分离, 上层清液用于UV-vis测试, 下层固体用水洗涤后再次分散于水中用于zeta电位测试。

2 结果与讨论

2.1 光响应桥联硅烷BS的制备及其光响应性能

光响应桥联硅烷BS的合成路线如图1所示. 首先邻硝基苄基醇和二(三氯甲基)碳酸酯经过取代反应得到化合物2-硝基苄基氯甲酸酯, 继续与二(三甲氧基硅烷丙基)胺发生取代反应, 光响应基团邻硝基苄基通过酯基与硅烷共价键相连, 得到光响应桥联硅烷BS. 图2(a)是该单体的核磁氢谱, 苯环上的4个氢质子 H_a 、 H_b 、 H_d 和 H_c 的化学位移分别为7.99、7.57、7.50和7.40, 苄基氢质子 H_e 的化学位移为5.44, 烷氧基上氢质子 H_f 的化学位移为3.49, 主链亚甲基上氢质子 H_g 、 H_h 和 H_i 的化学位移分别为3.16、1.61和0.53, BS的质子峰化学位移能一一归属, 各质子峰积分面积比例与理论值相同. 图2(b)为光响应桥联硅烷BS的红外谱图, 2940~2840 cm^{-1} 为饱和C-H伸缩振动峰, 1530 cm^{-1} 为硝基反对称伸缩振动峰, 1350 cm^{-1} 为硝基对称伸缩振动峰, 1082 cm^{-1} 为Si-O强伸缩振动峰峰, 963 cm^{-1} 为C-N伸缩振动峰,

图1 光响应桥联硅烷(BS)和光响应性聚倍半硅氧烷纳米粒子(BPS)的合成路线

Figure 1 Synthesis route of photoresponsive 2-nitrobenzyl bridged silane (BS) and polysilsesquioxane nanoparticles (BPS)

图2 光响应桥联硅烷(BS)的氢核磁谱图(a)和红外谱图(b)

Figure 2 ^1H NMR (a) and FTIR (b) spectra of photoresponsive 2-nitrobenzyl bridged silane (BS)

812 cm^{-1} 为苯环C-H弯曲振动峰, 1705 和 1196 cm^{-1} 分别为酰胺键的C=O和C-N特征伸缩振动峰。

BS中桥联有机基团2-硝基苄基甲酸酯在光照下会发生光致断裂反应, 产生二(三甲氧基硅烷丙基)胺、邻亚硝基苯甲醛和二氧化碳(图3(a)), 采用UV-vis光谱监测BS在四氢呋喃溶液中的光响应行为过程(图3(b)). BS溶液在 300 nm 处的吸收峰为邻硝基苄基酯的 $n\rightarrow\pi^*$ 电子跃迁, 在 224 nm 吸收峰为苯环的 $\pi\rightarrow\pi^*$ 电子跃迁行

为. 在 254 nm 光照条件下, BS溶液在 300 nm 处吸收峰随着光照时间增加吸光度逐渐增大, 在 224 nm 处的光吸收峰随光照时间的增加逐渐红移至 231 nm 处. BS在 254 nm 光照下, 随着光解反应的进行, BS中硝基苄基酯基团被逐渐消耗, 光解反应产生的邻亚硝基苯甲醛浓度逐渐增加, BS中光吸收基团硝基苄基酯逐渐演变成了游离的邻亚硝基苯甲醛, 光解前后光吸收基团发生了变化^[24]. BS单体的光反应程度可通过在 300 nm 处的吸

图3 光响应桥联硅烷BS的光反应(a)、UV-vis跟踪的光响应桥联硅烷BS四氢呋喃溶液光反应过程(光照波长为 254 nm)(b)、以及光响应桥联硅烷BS的光反应程度(c)

Figure 3 Photolysis of 2-nitrobenzyl bridged silane (a), photoresponsive behavior of 2-nitrobenzyl bridged silane in tetrahydrofuran under 254 nm light monitored by UV-vis spectrum (b), and photoreaction degree of 2-nitrobenzyl bridged siloxane (c)

光度的变化 $(A_t - A_0)/A_0$ 来判断, A_0 为未光照时BS的处吸光度值, A_t 为光照后溶液的吸光度值. 图3(c)表明在光照70 min时, 70%的BS发生了光致断裂反应.

2.2 BPS的制备及其光响应性能

在强力搅拌作用下, 光响应桥联硅烷BS分散在水相中形成微小的液滴, 初始阶段单体是以悬浮液滴的形式分散. 随着单体在油/水相界面水解反应的进行, 形成了大量硅羟基, 产生自乳化效果. 因此单体液滴会变得很小, 最后形成的是纳米级颗粒, BS演变成BPS的整个化学过程是一个基于水解-缩合机理的溶胶-凝胶过程, 得到具有网状交联结构的桥联聚倍半硅氧烷纳米粒子. 图4(a)为BPS纳米粒子的SEM图, 制备的BPS为球状形貌, 其形状规则、大小均匀, 平均粒径为127 nm(图4(b)), 分散性良好(PDI=0.167). BPS纳米粒子在水相的分散液在254 nm光下进行照射, 水相分散液经离心后, 检测其上层清液的UV-vis吸收光谱. 如图4(c)所示, 光反应后的溶液在305 nm处出现吸收峰, 随着光照时间增加吸光度逐渐增大, 表明BPS纳米粒

子也发生了与BS类似的光解反应, BS有机桥联结构被引入到BPS纳米粒子中(图1). 有机桥联结构中的邻硝基苄基酯键在254 nm光下发生同样的光致断裂反应, 在水溶液中释放出光解产生的邻亚硝基苯甲醛, BPS纳米粒子表现出光响应性能.

BPS纳米粒子是由含有机桥联烷氧基硅烷经过水解缩聚制备的, 表面存在大量的硅羟基. 硅羟基在水相体系中会发生水解电离反应, 析出氢质子, 粒子表面呈现负电荷特征, 粒子表面zeta电位是-28.20 mV(图4(d)). BPS纳米粒子的水分散体系经254 nm光照10 min后, BPS纳米粒子的zeta电位变为+22.86 mV, 光照100 min后zeta电位达到+40.92 mV, 水相中的BPS纳米粒子在254 nm光照射下表面电荷性质发生由负到正的翻转. 在光照条件下, 光响应基团2-硝基苄基甲酸酯发生光致断裂反应, 产生的二级胺会与硅羟基电离出的氢质子发生了质子化反应, 改变了BPS纳米粒子表面电荷性质, 表现为BPS的zeta电位由负到正的翻转. 实验观察到, BPS纳米粒子悬浊液的水相颜色在光照前后也发生了明显的变化, 由无色逐渐变为浅黄色, 光照后逐渐

图4 性能表征. 制备的聚倍半硅氧烷纳米粒子SEM图(a)和粒径分布图(b); 纳米粒子发生光致断裂反应后溶液的UV-vis吸收光谱(c)和纳米粒子表面zeta电位(d)

Figure 4 Performance characterization. SEM images (a) and size distribution (b) of synthesized polysilsesquioxane nanoparticles; UV-vis spectra of solutions (c) and zeta potential (d) of polysilsesquioxane nanoparticles under 254 nm light

产生的邻亚硝基苯甲醛小分子给水相溶液带来了颜色上的变化,制备的BPS纳米粒子表现出光响应行为。

2.3 DOX@BPS载药纳米粒子

聚倍半硅氧烷基BPS纳米粒子界面在水相环境的硅羟基电离使粒子表面呈现负电荷特征,带正电荷的药物DOX与BPS通过粒子表面的静电相互作用结合在一起,得到DOX@BPS载药纳米粒子。这种吸附行为一般都符合Langmuir模型,属于单层吸附^[25-28]。图5为4种不同投药比 R ($R=w(\text{DOX}):w(\text{BPS})$)下得到的DOX@BPS载药纳米粒子的SEM图片。载药后的纳米粒子仍为球形形貌,与未载药的纳米粒子相比,表面变得粗糙。4种不同投药比制得的纳米粒子在表面形态上没有很大的差异。表1是制备DOX@BPS载药纳米粒子时投药比 R 与载药率和包封率,随着投药比 R 的增加,载药率也逐渐增加,当BPS纳米粒子和投入DOX的质量比为1:1时,制备的DOX@BPS载药纳米粒子载药率可达14.38%。该方法不仅制备过程简单,条件温和,而且载药率明显高于通过共价方法构建的硅基载药体系^[9,11]。

在一定范围内,包封率随着投药比增加而增加,由28.8%增加至67.3%。但是当投药比继续增加时,包封率下降为54.9%。当投药量较少时,纳米粒子能够提供足够的表面空间来静电吸附药物,因此投药量增加,载药量也随之增加;当投药量继续增加时,纳米粒子的吸附量达到饱和,不再吸附药物,过剩的药物只能保留在溶液中,包封率下降。该结果表明,选择合适的投药比以保证较高的载药量和适量的载药效率,因此在接下来的实验中,投药比保持1.0。

2.4 DOX@BPS载药纳米粒子的光控体外释放

体外药物释放研究在37°C的PBS(pH 7.4)缓冲溶液中进行。取1.0 mg DOX@BPS纳米粒子分散在10 mL磷酸缓冲溶液中,置于254 nm波长的光源下,分别在特定时间取样,并进行离心分离,用磷酸缓冲溶液洗涤分离后的纳米粒子,保留含有DOX的溶液,采用UV-vis分析法测定DOX@BPS纳米粒子光照后释放出的DOX。所有不同光照条件下的释放实验均重复3次,DOX的释药量取平均值,释药率根据下式计算:

$$\text{释药率} = \frac{\text{载药纳米粒子释放的药物质量}}{\text{载药纳米粒子的载药量}} \times 100\% \quad (3)$$

图6(a)是光照30 min后DOX@BPS载药纳米粒子的

图5 不同 R 值下的载药聚倍半硅氧烷纳米粒子的形貌(SEM)。 (a) $R=0.1$; (b) $R=0.2$; (c) $R=0.5$; (d) $R=1.0$

Figure 5 SEM images of DOX-loaded polysilsesquioxane nanoparticles with different feed ratios of doxorubicin. (a) $R=0.1$; (b) $R=0.2$; (c) $R=0.5$; (d) $R=1.0$

表1 不同投药比 R 值下制备的载药聚倍半硅氧烷纳米粒子DOX@BPS的载药率和包封率

Table 1 Drug loading content and efficiency of DOX-loaded polysilsesquioxane nanoparticles with different feed ratios of doxorubicin

R	载药量(%)	包封率(%)	粒径(nm)
0.1	6.11	28.8	182
0.2	9.16	38.3	194
0.5	12.8	67.3	203
1.0	14.4	54.9	198

形貌,区别于图5的载药纳米粒子($R=1.0$),其表面形貌更加粗糙,粒子间有黏附行为,DOX@BPS载药纳米粒子在光控释药后表面形貌发生了较明显的变化。图6(b)是DOX@BPS载药纳米粒子($R=1.0$)的体外释放行为,在未光照条件下DOX@BPS载药纳米粒子放置16 h后药物释放量仅为3.5%,DOX很好地负载在聚倍半硅氧烷纳米粒子表面,载药纳米粒子在未光触发条件下具有良好的稳定性。采用254 nm波长的光对DOX@BPS进行照射时,载药纳米粒子表现出药物释放行为,在光照前6 h内该载药纳米粒子没有出现突释行为,随着光照时间的增加,DOX@BPS的药物释放率也随之增加。光照强度为60和160 mW/cm^2 时,光照16 h后的载药释放率分别为21.9%和48.9%,当光照强度为200 mW/cm^2 时,光照16 h后的载药释放率可达82.9%。表2列出了几个不同时间点和不同光照强度下的载药纳米粒子释药率。可以看出,通过改变光照时长和光照强度可对药物的释放过程进行精准控制,制备的DOX@BPS载药纳

图 6 光照30 min后的DOX@BPS载药纳米粒子扫描电子显微镜图片(a)和DOX@BPS载药纳米粒子扫描电子显微镜图片的体外释放行为(b)
Figure 6 The SEM image of DOX@BPS upon irradiation over 30 min (a) and *in vitro* release of DOX@BPS (b)

表 2 不同光照时间和光照强度(254 nm)下DOX@BPS载药粒子的释药率

Table 2 The drug release of DOX-loaded polysilsesquioxane nanoparticles under 254 nm light with different irradiation intensity and irradiation time

光照时间(h)	释药率(%)		
	60 mW/cm ²	160 mW/cm ²	200 mW/cm ²
1	2.64	7.19	12.4
2	5.40	14.2	23.6
4	10.2	27.7	45.3
6	16.0	37.9	62.5
8	17.5	41.3	69.4
12	19.9	46.7	78.3
16	21.9	48.9	82.9

米粒子具有良好的光响应性能。

3 结论

基于邻硝基苄基酯的光致断裂反应, 设计合成了具有光响应性能的新型含邻硝基苄基团的光响应桥联硅烷单体。进一步采用溶胶-凝胶法成功制备了具有光响应性能的聚倍半硅氧烷纳米粒子, 其平均直径为127 nm, 粒径分布窄, 纳米粒子表面具有光触发电荷翻

转性能, 在254 nm光照射下纳米粒子表面电荷性质发生由负到正的翻转。该纳米粒子可以通过静电相互作用高效装载阿霉素药物, 载药率可达14.38%。该载药纳米粒子具有光控药物释放行为, 在254 nm光照射下, 由于纳米粒子表面电荷性质的翻转会释放出通过静电负载的阿霉素药物, 药物释放率为82.9%。该载药纳米粒子可对药物实现定时、定位和定量的精确控制释放, 该研究提供了一种新的目标分子可控释放体系。

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Summary for “光响应聚倍半硅氧烷纳米载体及其光控药物释放性能”

Light controlled release system based on photoresponsive bridged polysilsesquioxane nanocarriers

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Light-controlled release system plays an important role in the stimuli-responsive release application, due to light with its efficient controllability and non-contact. By adjusting the light irradiation of intensity, wavelength, time and location, the release behavior of the target molecule, such as the release rate, location and concentrations, can be performed by spatial and temporal control. Bridged polysilsesquioxanes have a $-\text{[A-SiO}_{1.5}]_n-$ molecular chain structure (A is an organic group) which show good mechanical properties and biocompatibility. Due to the wide designability and tunability of the A organic group, bridged polysilsesquioxane materials with different properties can be prepared. This kind of hybrid inorganic-organic materials have potential application values on stimulus-responsive release, optical sensors and biological imaging.

A novel photoresponsive controlled release system based on this material was designed and prepared in the present study. When target molecules are connected to nanocarriers with photoresponsive groups by a covalent bond, the covalently binding tends to affect the characteristics of the target molecules, and the chemical process of preparing the controlled release system is complex. Therefore, a photoresponsive controlled release system with simple preparation process and guaranteed target molecular characteristics is highly desired to be constructed. In the paper, a bridged silane containing 2-nitrobenzyl group (BS) was successfully prepared. First, 2-nitrobenzyl chloroformate was obtained by substitution reaction of 2-nitrobenzyl alcohol and triphosgene. Then, the photoresponsive bridged silane monomer BS was produced from 2-nitrobenzyl chloroformate and bis(trimethoxysilylpropyl)amine. The photoresponsive group 2-nitrobenzyl was covalently connected with the silane through an ester group. The synthesized BS was confirmed by nuclear magnetic resonance spectroscopies (^1H NMR, ^{13}C NMR, and ^{29}Si NMR), FTIR and mass spectrometry. UV-vis spectra showed that BS was photoresponsive under 254 nm light. The characteristic absorption peaks of the BS at 300 and 224 nm obviously changed during the period of irradiation. Furthermore, the maximum photoreaction conversion was 70% at the irradiation time of 70 min.

Further, photoresponsive bridged polysilsesquioxane nanoparticles (BPS) were prepared from BS using a sol-gel method. The prepared BPS nanoparticles were characterized by SEM and DLS. The results showed that the nanoparticles had a spherical morphology with an average particle size of 127 nm. The UV-vis spectra of BPS in an aqueous solution irradiated over different time testified the photoresponse property of BPS. More importantly, the surface charge of BPS nanoparticles could be reversed from negative (-28.20 mV) to positive ($+22.86$ mV) triggered by light. Upon irradiation, the secondary amine groups were exposed on the surface of BPS due to the photocleaved reaction of photosensitive groups. And the further protonation of amine groups in the aqueous solution increased the positive property of the surface of BPS. The properties indicated that the light-triggered charge reversal nanoparticles may be promising candidates for controlled drug release system.

Doxorubicin (DOX) as a widely used clinical anticancer drug was used to evaluate the concept of charge reversal. It was easily combined on the BPS nanoparticles by electrostatic interaction. The nanoparticles could efficiently load 14.8wt% of DOX. The strategy to prepare drug-loaded nanocarriers is simple, mild and high efficiency. *In vitro* release results showed that the loaded DOX release rate had positive correlation with irradiation intensity and irradiation time (254 nm). The release behaviors under different laser power (60, 160 and 200 mW/cm²) were performed in PBS buffer (pH 7.4) at 37°C over a period of 16 h. There was no obvious release without light. The loaded DOX release rate increased with the increasing irradiation intensity or irradiation time. The highest release rate was 82.9% under 200 mW/cm² irradiation over 16 h. Moreover, no sudden release behavior was found for the drug-loaded nanoparticles occurred within 6 h of irradiation. As a result, the drug release process can be precisely controlled by regulating the irradiation time and intensity. The prepared DOX@BPS drug-loaded nanoparticles exhibited good photoresponsive performance.

polysilsesquioxane, photoresponsive, bridged, nanocarriers, controlled release system, doxorubicin (DOX)

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