第 7 卷◆第 1 期◆版本 1.0◆2025 年
文章类型：论文丨刊号（ISSN）：2705-1102(P) / 2705-1110(O)

纳米药物递送系统在眼科的应用与发展

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DOI:10.12238/bmtr.v7i1.11803

[摘　要] 眼部解剖结构的特殊性和多种生理屏障(如角膜、血-视网膜屏障等)的存在是导致药物眼内生物利用度低,治疗效果差的重要原因之一。促进药物眼内转运,提高眼内有效药物浓度和延长药物作用时间是改善眼病药物治疗效果亟需攻克的难关。随着药学、材料学和生物医学等多种学科的交叉融合,“新型药物递送系统”这一概念应运而生。其中,基于纳米技术开发的药物递送载体,可显著提高药物的转运能力、靶向性和安全性等,为眼病的药物治疗带来新的机遇。
[关键词] 新型药物递送系统；纳米技术；眼部用药
中图分类号：R453　文献标识码：A

Application and development of drug delivery system based on nanotechnology in ophthalmology

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[Abstract] Due to the distinctive anatomy and various physical barriers (such as cornea, blood retina barrier) of eyes, the bioavailability of drugs and their therapeutic efficacy of eye diseases is limited. Promoting intraocular transport, elevating effective concentrations, and prolonging duration of action are the key points to improve the drug curative effect of ocular diseases. Novel drug delivery system is a combination of pharmacy, materials science, and biomedical science. Notably, drug delivery system based on nanotechnology, which can improve the permeation, targeting and safety of drugs, presents novel opportunities for the pharmacological treatment of ocular diseases.
[Key words] novel drug delivery system; nanotechnology; drug treatment of ocular diseases

药物治疗是眼科疾病治疗中的一大重要板块,减少泪液冲刷、鼻泪管引流等作用造成的药物损失,攻克角膜、血-房水屏障、血-视网膜屏障等对药物转运的阻碍,降低给药频率,提高药物的有效性和安全性,是目前眼科药物治疗关注的重点。随着药学、材料科学和生物医学的交叉融合,新型药物递送系统应运而生。其中,基于纳米技术的药物递送系统在眼病的防治研究中发挥了重要作用。基于纳米颗粒独特的理化性质和生物特性,其作为载体可提高药物高角膜渗透性,影响药物体内过程,增强药物的特异性和选择性,减少不良反应的发生,提供高效、低毒、靶向、可控的治疗方案[1]。本综述主要探讨不同类型的纳米药物递送载体的特点及其在眼科的应用进展,以期为眼部药物递送系统的开发提供一些新的思考。

1 脂质体(Liposome)

脂质体是药物递送系统构建过程中使用最广泛的纳米载体[2]。它是由磷酸酯分子自组装形成的具有亲脂壳和亲水核心的脂性微球,可负载极性、非极性等多种类型的药物,促进药物体内转运与吸收,提高药物的组织靶向性和生物利用度[3]。

由于角膜表面含有丰富的带负电荷的糖蛋白,相较于阴离子脂质体,阳离子脂质体表现出更优异的角膜吸附力和渗透力[4],以及更高的细胞内化速率[5],更低的体内清除速率[6],和更长的药物释放时长[7]。有研究表明,在合成配方中添加蛋黄卵磷脂酰胆碱等阳离子脂质可获得具有更高角膜上皮亲和力的阳离子脂质体,以提高虾青素的干眼症治疗效果[8]。此外,使用带正电荷的生物粘附剂包裹脂质体,也是赋予脂质体正电荷的一种有效手段。其中,壳聚糖作为最常见的一种包封剂,可通过氢键结合与静电吸附双重作用增强脂质体的角膜亲和力和角膜渗透性[9],同时还可提高脂质体的药物封装效率,延长药物释放时间[10]。但大分子生物黏附剂会对药物的流体力学特性和粒径大小造成影响,导致药物粒度和粘性增加,用作滴眼液时可能诱发眼部的不适感。而使用小分子正电荷添加剂改变脂质体表面电荷可避开这一缺陷[11],但目前这一策略尚未在眼部药物递送方面得到广泛应用,其有效性和安全性仍待进一步的验证。

脂质体还可通过与靶向配体(如小分子化合物、肽、单克隆抗体等)结合,实现药物的位点特异性递送。在干眼症的治疗模型中,利用唾液酸靶向肽修饰的脂质体递送环孢菌素A和铁死亡抑制剂,可选择性抑制角膜组织的p53-SLC7A11-GSH通路,阻断铁死亡和TNF-α相关炎症级联反应,恢复泪液分泌,改善角膜缺损[12]。利用特异性抗体片段对脂质体进行表面修饰,可获得用于递送化疗药物的靶向免疫脂质体,能有效定位并清除癌细胞,减少化疗药物对周围健康组织的损伤[13]。此外,经聚乙二醇修饰后,还可获得对吞噬细胞不可见的“隐形”脂质体,从而逃避机体免疫系统的识别清除作用,增加了药物在靶标部位的富集浓度,增强药理活性[14]。

脂质纳米颗粒(Lipid Nanoparticles,LNP)是一类没有亲水腔的脂质体特殊子集,其免疫原性和体内捕获性低,可逃避单核-巨噬细胞系统的识别与清除,是良好的基因递送载体,可保护寡聚核苷酸免于酶降解作用[15]。且相较于病毒载体,LNP的组织特异性更高、细胞毒性更低,可作为遗传性眼病基因编辑治疗的理想载体[16]。

然而,脂质体生产成本高、载药量低、稳定性和组织选择性差。革新脂质体制备工艺,降低生产成本,提高其稳定性和载药量,增强靶向性和刺激响应性,是未来脂质体药物递送系统研发的一个重要方向。

2 聚合物纳米颗粒(PNPs)

聚合物纳米颗粒(Polymer Nanoparticles,PNPs)是直径为1-1000nm的胶体颗粒,相较于脂质体而言,其制备工艺更简单,稳定性更好,靶向性更高。同时,通过操纵聚合物载体化学键的合成/断裂,可调节体内药物释放动力学以实现药物控释[17]。常见的PNPs包括聚乳酸-羟基乙酸共聚物、多孔配位聚合物、壳聚糖、海藻酸盐和白蛋白等。

2.1聚乳酸-羟基乙酸共聚物(PLGA)。聚乳酸-羟基乙酸共聚物(Poly(lactic-co-glycolic acid),PLGA)是一种生物降解产物无毒、安全性高的药物控释载体[18],被广泛应用于小分子药物、免疫活性物质、蛋白质等的递送。利用PLGA微胶囊封装外泌体,可成功构建“伪细胞”,模拟细胞旁分泌机制用于治疗视网膜缺血再灌注损伤,一次玻璃体内注射可维持超一个月的释放时长,有效促进损伤视网膜的修复[19]。相比于直接输入干细胞或免疫细胞,PLGA构建的“伪细胞”活性不受机体病理状态或肿瘤微环境等的影响,疗效更加稳定。

PLGA还具有良好的刺激响应性,经叶酸修饰后可负载吲哚菁绿和化疗药物,用作光声成像双模态造影剂,探测并靶向定位肿瘤,并联合光热治疗发挥抗癌作用。同时,吲哚菁绿在光照条件下产生的热量可触发纳米载体的药物释放“开关”,精准投递化疗药物,进一步增强抗癌效果[20,21]。

2.2壳聚糖。壳聚糖是一种天然的多糖,其体内代谢产物无毒,可被人体完全吸收,也是一种良好的药物载体[22]。壳聚糖具有很强的生物黏附特性,可在角膜、结膜表面附着4小时以上[23],并可有效提高药物的角膜渗透性,促进药物眼内转运[24]。壳聚糖还能够打开细胞间的紧密连接蛋白,促进药物眼后段转运[25]。有研究表明,结膜下注射壳聚糖包被的贝伐珠单抗可获得较玻璃体内注药更高的生物利用度[26]。此外,壳聚糖还具有一定的抗菌活性,包封利奈唑胺后可发挥协同抗菌作用,使药物抗菌效果较前提高1.6倍,减少了微生物耐药的发生[27]。因此,壳聚糖负载抗生素有望为感染性眼病的治疗提供更好的选择。

提高壳聚糖溶解度和稳定性是相关载药系统构建过程中需攻克的难关。目前,可通过乙酰化、羟甲基化、季铵化等修饰来提高壳聚糖溶解度,但化学修饰对载体性能的影响还有待更多的研究。

2.3金属有机骨架(MOF)。金属有机骨架(Metal Organic Framework,MOF)属于多孔配位聚合物家族中的一员,具有孔隙大,载药率高,生物降解性好等优点[28]。与其他纳米载体相比,MOF的另一大特点在于其具有一定的催化活性。有研究证实,通过卤素配位调节MOF的空间构型和电子结构,可赋予其优异的超氧化物歧化酶样活性,用于减轻角膜化学烧伤后的氧化应激损伤[29]。刺激响应型MOF还可用于智能释药系统的设计。pH响应型MOF在生理条件下表现出良好的稳定性,但可捕获肿瘤等疾病导致的微小pH变化,实现精准药物释放[30]。

然而,MOF可影响细胞中儿茶酚胺等神经递质的代谢[31],诱导氧化应激损伤,释放金属离子启动细胞自噬[32],产生组织细胞毒性。因此,未来MOF药物递送系统的开发应重点关注其生物安全性。

3 水凝胶(Hydrogel)

水凝胶作为当下材料学领域的研究热点之一,具有优异的生物相容性、生物降解性和对光、热、pH等理化因素的刺激性响应性,可实现药物靶向、持续释放[33]。目前,基于水凝胶研发的软性隐形眼镜、人工晶状体、玻璃体替代物等已进入临床。

基于其高载药量的特性,水凝胶可作为缓释药物库用于玻璃体内给药,降低眼内注射频率,以减少眼内感染、视网膜血管炎等并发症的发生概率[34]。一项兔眼模型研究显示,注射入玻璃体内的水凝胶可维持约4个月稳定释药时长,且不会导致免疫排斥、眼压升高和视网膜损伤等[35]。值得注意的是,用于玻璃体内药物递送的水凝胶在合成过程中需考虑其透明性和密度,避免发生玻璃体混浊和水凝胶沉积导致的视网膜损伤。

水凝胶还可制备成类似隐形眼镜的载药角膜植入物,作为促进角膜再生的支架和药物释放载体治疗炎性角膜病等[36]。由于水凝胶孔隙率高,相比于载药式隐形眼镜,前者载药量更大,但因存在溶蚀作用,其释药时长相对较短。

此外,水凝胶对外部刺激敏感,可用于制备“智能”或“环境响应性”载药系统,以捕获眼内微小环境的变化,触发水凝胶解交联并释放负载药物,治疗玻璃体视网膜病等[37]。

4 其他纳米载体

纳米金属颗粒也是一种理想的药物载体,高比表面积和尺寸可定制的特点赋予其优异的表面滞留性、可修饰性和生理屏障透过性[38]。现有研究已成功制备以金纳米颗粒作为载体的心

房利钠肽滴眼液，用于治疗大鼠视网膜母细胞瘤[39]，这为眼后段疾病的无创治疗开辟了一条新的道路。介孔二氧化硅是一种表面积大、孔径分布均匀、孔径体积大的无机纳米材料，可负载他克莫司、丝裂霉素、5-氟尿嘧啶等药物[40-42]，提高靶向性和生物利用度的同时，降低了这类药物的细胞毒性。磁性纳米颗粒是一种可通过磁共振成像进行追踪的纳米粒子，负载药物后，在磁场引导下可靶向视网膜组织，定位追踪病变并提供磁热治疗，为视网膜病的诊治提供了更多的可能[43,44]。

眼药制剂的研发一直以来都是制药技术领域中的一大热点。随着纳米技术的飞速发展，眼药的开发与应用也进入了一个新的纪元。纳米药物递送系统充分利用了纳米颗粒的小尺寸效应、体积效应、表面效应和量子效应等特性，在改善眼药理化性质，提高其靶向性和生物利用度的同时，减少药物不良反应，使得眼病的药物治疗更加安全有效。未来纳米药物递送系统的开发除关注其疗效外，还应聚焦于纳米颗粒的眼内过程，平衡纳米载体的理化特性与眼内组织细胞毒性的关系，以期获得更加安全、高效的治疗。此外，与使用单一药物递送系统相比，多系统协作是否能获得更好的药理活性和更小的毒副作用也是一个值得思考的新方向。

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