doi: 10.13241/j.cnki.pmb.2014.19.047

混合胶束作为药物载体的研究进展 *

李扬龚 沈园园△ 钱嫦云 陆 菲 徐晓芬

（上海交通大学药学院 上海 200240）

摘要： 许多抗肿瘤药物因为水溶解性差，在临床上的应用受到了很大影响。胶束可将药物包载到疏水核，可显著提高药物的水溶解性，是一种极具潜力的新型给药体系。然而胶束也面临着一系列问题，比如说需要提高其在体内的动力学稳定性和热力学稳定性等。与此同时，如果想要在单一的胶束体系上实现多种功能，需要对载体材料进行繁杂的修饰，也是一个难题。由不同嵌段聚合物、聚合物 / 表面活性剂自组装成的混合胶束或聚离子复合物胶束，相对于单一嵌段聚合物形成的胶束而言，物理稳定性和载药能力都得到了提高。同时，通过将具有不同官能团的聚合物制备成混合胶束，可以直接方便得到多功能复合的体系。本文对混合胶束载体系统的药剂学进展进行了综述。

关键词： 混合胶束；聚离子复合物胶束；嵌段聚合物；表面活性剂

中图分类号： R917 **文献标识码：** A **文章编号：** 1673-6273(2014)19-3784-02

Progress of Mixed Micelles in Drug Delivery*

LI Yang-gong, SHEN Yuan-yuan△, QIAN Chang-yun, LU Fei, XU Xiao-fen

(Shanghai Jiao Tong University School of Pharmacy, Shanghai, 200240, China)

ABSTRACT: Many antitumor drugs are restricted in clinic because of their low solubility in water. Micelles that can encapsulate the drug in their hydrohobic core to enhance the drug's solubilty in water, are of great potential in drug delivery. However, lots of problems must be solved such as their poor stability in vivo.At the same time, it is difficult to endow a single system with multpile functionalities, because of the synthetically challenging to modify functional groups into a sigle copolymer. Mixed micelles or polyion complex micelles formed by different copolymers or copolymers/surfactants, showed higher stability and higher drug loading capacity than micelles formed by sigle copolymer. Also, through selecting the right candidates, multi-functional micelles can be obtained easily and directly. This paper summarizes the progress of mixed micelles in drug delivery.

Key words: Mixed micelles; Polyion complex micelles; Block copolymers; Surfactants

Chinese Library Classification(CLC): R917 **Document code: A**

Article ID: 1673-6273(2014)19-3784-02

前言

胶束是一种新型的给药方式，两亲性嵌段共聚物胶束指的是两亲性嵌段共聚物在溶液中自组装形成 " 核 - 壳 " 结构的纳米载体，胶束的核能包封疏水性药物并保护它们不被降解，壳可以起到稳定的作用。胶束可将药物包载到疏水核，可显著提高药物的水溶解性，兼且可具有靶向作用[1-6]、增溶作用[7]、提高稳定性作用[5,8-11]、长循环作用[12]等，是一种极具潜力的新型给药体系。然而胶束也面临着一系列问题，比如说需要提高其在体内的动力学稳定性和热力学稳定性等。与此同时，如果想要在单一的胶束体系上实现多种功能，需要对载体材料进行繁杂的修饰，也是一个难题。由不同嵌段聚合物、聚合物 / 表面活性剂自组装成的混合胶束或聚离子复合物胶束，相对于单一嵌段聚合物形成的胶束而言，物理稳定性和载药能力都得到了提高。同时，通过将具有不同官能团的聚合物制备成混合胶束，可以直接方便得到多功能复合的体系。通过选择和混合适宜的聚合物，可以制备得到新型且多功能的胶束体系。按照组成，混合胶束大致可以分为三类：由两种或以上不同组成的嵌段共聚物制备得的混合胶束；由嵌段共聚物和小分子表面活性（包括阳离子型表面活性剂、阴离子型表面活性剂和非离子型表面活性剂）制备得的混合胶束；由既含有带正负电荷基团又含有不带电荷水溶性段的不同聚合物在水中通过静电结合自发形成。本文就这三个方面对混合胶束载体系统的药剂学进展进行了综述。

1 嵌段共聚物混合胶束

Ning Kang[13]等发现，将等量的 PEG-PLLA 和 PEG-PDLA 放在水中，可以形成单分散的立体复合嵌段共聚物胶束，这些胶束拥有部分结晶的核，且显示出了要优于单一聚合物胶束的动力学稳定性和再分散性。Wei Zhang[14]等以普洛尼克 -F127、普洛尼克 -P123 和修饰有叶酸集团的普洛尼克 -F127 制备载了紫杉醇的多功能混合胶束，相对单一胶束而言提高了细胞的

* 基金项目：国家自然科学基金项目(81171439/H1816)

作者简介：李扬龚（1988-），男，硕士研究生，主要研究方向：聚合物胶束

△通讯作者：沈园园，电话：+86(21) 3420-4793，E-mail: shenyuanyuan@sjtu.edu.cn

（收稿日期：2013-09-28 接受日期：2013-10-26 ）

摄取,有更好的体内外抗肿瘤活性,可以大大提高紫杉醇的生物利用度,且可以用于治疗多药耐药肿瘤。Vipin Saxena[15]等将两种 P- 糖蛋白抑制剂泊洛沙姆 407 和 D-α- 生育酚聚乙二醇 1000 琥珀酸酯制备成载藤黄酸混合胶束,通过在细胞内形成高浓度的 P- 糖蛋白抑制剂来达到治疗多药耐药的肿瘤的目的。Liyan Zhao[16]等以薄膜分散法制备了载姜黄素的普洛尼克 -P123 和普洛尼克 -F68 的混合胶束,混合胶束粒径为 68.2 nm,姜黄素的包封率和载药量分别为为 86.93%和 6.99%。该混合胶束可在体内缓慢释放姜黄素,且可以表现出很好的体外抗肿瘤活性。Kanwaldeep K. Gill[17]等制备了聚乙二醇 2000- 二硬脂酰磷脂酰乙醇胺和维生素 E- 聚乙二醇琥珀酸酯的混合胶束,同时载紫杉醇和白菊两种药物,研究混合胶束对紫杉醇敏感 A549 细胞和耐紫杉醇的 A549-T24 非小细胞肺癌细胞。研究结果表明载双药混合胶束显著提高了这两种药物的抗肿瘤效果。

2 嵌段聚合物 / 表面活性剂混合胶束

Yujun Wang[18]等将聚山梨酯 80 与聚己内酯 - 聚乙二醇 - 聚己内酯三嵌段聚合物制备成混合胶束用于紫杉醇给药。他们发现,混合胶束可以改变紫杉醇在大鼠体内的分布模型,同时显著提高了紫杉醇在脑中的分布。提示通过制备聚山梨酯 80 与聚己内酯 - 聚乙二醇 - 聚己内酯聚合物胶束,可以提高紫杉醇的脑靶向效果,该种胶束体系有潜力用于脑肿瘤化疗。Hui-jun Liang[19]等制备了吐温 80 和大豆磷脂 80 的载紫杉醇混合胶束,实验表明混合胶束比临床用紫杉醇制剂泰素有更好的抗稀释稳定性,对 HeLa 和 A549 细胞的抑制效果也要强于泰素,动物实验表明混合胶束提高了紫杉醇的生物利用度。J.S.Nambam[6]等研究和普洛尼克 -F108 与阴离子表面活性剂十二烷基硫酸钠(SDS)、阳离子型表面活性剂十六烷基三甲基溴化铵(CTAB)、非离子型表面活性剂壬基酚乙氧基化物(NP9)制备得混合胶束,研究表面活性剂的加入对胶束的粒径、zeta 电位、流变学特性的影响,结果发现,通过加入不同浓度的表面活性剂,可以调节普洛尼克胶束的微观结构和弹性性质等,从而达到调节药物释放的目的。

3 聚离子复合物胶束

聚离子复合物胶束,是由既含有带正负电荷基团又含有不带电荷水溶性段的不同聚合物在水中通过静电结合自发形成。Masao Kamimura[20]等把带负电荷的聚乙二醇 - 聚 4- 乙烯基苄基磷酸聚合物和带正电荷的阳离子表面活性剂十二烷基三甲基溴化铵(DTAB)、十二烷基三甲基溴化铵(HTAB)、十二烷基氯化铵(C12Py)、西吡氯铵(C16Py)等通过电荷作用形成了嵌段离聚复合物(block ionomer complexes),这些复合物在水中自发自组装形成了 40-60 nm 的粒子。表面活性剂的疏水基团构成了胶束的疏水内核而聚乙二醇 - 聚 4- 乙烯基苄基磷酸聚合物的聚乙二醇段构成了水溶性的外壳。用这些嵌段离聚体包载阳离子抗肿瘤药物多柔比星阿霉素,具有很高的载药量和包封率。与此同时,阿霉素嵌段离聚体有很强的抗稀释稳定性和抗离子强度能力。该系统中阿霉素在正常 pH 下的释放非常缓慢,在模拟体内核内体 / 溶酶体微环境的酸性 pH 中,阿霉素则释放很快。其亦能有效提高阿霉素在 MCG-7 胸腺癌细胞的摄取,具有很强的抗肿瘤活性。

4 总结和讨论

在最近的十年,胶束给药系统的研究已经取得了飞速进展。但是仍有一些问题啓待解决。混合胶束给药系统,相对单一胶束而言具备更高的载药能力、更好的稳定性、更强的抗肿瘤活性,同时可以方便简单得实现多种功能比如说提高靶向等,引发了越来越多的关注。随着各项研究的不断深入,相信混合胶束给药体系会发展得日益完善,从而在临床治疗上发挥重大作用。

参 考 文 献(References)

[1] Jiao Z., Wang X., Chen Z. Folate-conjugated methoxy poly (ethylene glycol)/poly (l-alanine) amphiphilic block copolymeric micelles for targeted delivery of paclitaxel[J]. Drug Deliv, 2011, 18(7): 478-484

[2] Park E. K., Kim S. Y., Lee S. B., et al. Folate-conjugated methoxy poly (ethylene glycol)/poly (epsilon-caprolactone) amphiphilic block copolymeric micelles for tumor-targeted drug delivery [J]. J Control Release, 2005, 109(1-3): 158-168

[3] Liu Y., Sun J., Cao W., et al. Dual targeting folate-conjugated hyaluronic acid polymeric micelles for paclitaxel delivery [J]. Int J Pharm, 2011, 421(1): 160-169

[4] Zhan C., Li B., Hu L., et al. Micelle-based brain-targeted drug delivery enabled by a nicotine acetylcholine receptor ligand [J]. Angew Chem Int Ed Engl, 2011, 50(24): 5482-5485

[5] Yoncheva Krassimira, Calleja Patricia, Agü eros Maite, etc. Stabilized micelles as delivery vehicles for paclitaxel [J]. International Journal of Pharmaceutics, 2012, 436(1-2): 258-264

[6] Nambam J. S., Philip J. Effects of interaction of ionic and nonionic surfactants on self-assembly of peo-ppo-peo triblock copolymer in aqueous solution [J]. J Phys Chem B, 2012, 116(5): 1499-1507

[7] Kim S., Shi Y., Kim J. Y., et al. Overcoming the barriers in micellar drug delivery: Loading efficiency, in vivo stability, and micelle-cell interaction [J]. Expert Opin Drug Deliv, 2010, 7(1): 49-62

[8] Nederberg F., Appel E., Tan J. P., et al. Simple approach to stabilized micelles employing miktoarm terpolymers and stereocomplexes with application in paclitaxel delivery [J]. Biomacromolecules, 2009, 10 (6): 1460-1468

[9] Pool R., Bolhuis P. G. The influence of micelle formation on the stability of colloid surfactant mixtures [J]. Phys Chem Chem Phys, 2010, 12(44): 14789-14797

[10] Su W., Luo X. H., Wang H. F., et al. Hyperbranched polycarbonate-based multimolecular micelle with enhanced stability and loading efficiency[J]. Macromol Rapid Commun, 2011, 32(4): 390-396

[11] Miller T., Rachel R., Besheer A., et al. Comparative investigations on in vitro serum stability of polymeric micelle formulations [J]. Pharm Res, 2012, 29(2): 448-459

[12] 曾昭武,肖人钟,王小丽,等. 聚乙二醇 - 聚乳酸嵌段共聚物纳米粒的研究进展 [J].现代生物医学进展, 2012, 12(1): 179-182
Zeng Zhao-wu , Xiao Ren-zhong, Wang Xiao-li, et al. Study Progress of Polyethylene Glycol-Polylactic Acid Block Copolymer Nanoparticles[J]. Progress in Modern Biomedicine, 2012, 12(1): 179-182

(下转第 3783 页)

protein (CRP)--no association with sleep duration or sleep disordered breathing[J]. Sleep, 2007, 30: 991-996

[37] Carpen O, Pallai P, Staunton DE, et al. Association of intercellular adhesion molecule-1 (ICAM-1) with actin-containing cytoskeleton and alpha-actinin[J]. J Cell Biol, 1992, 118: 1223-1234

[38] Ohga E, Nagase T, Tomita T, et al. Increased levels of circulating ICAM-1, VCAM-1, and L-selectin in obstructive sleep apnea syndrome[J]. J Appl Physiol, 1999, 87: 10-14

[39] El-Solh AA, Mador MJ, Sikka P, et al. Adhesion molecules in patients with coronary artery disease and moderate-to-severe obstructive sleep apnea[J]. Chest, 2002, 121: 1541-1547

[40] Dyugovskaya L, Lavie P, Lavie L. Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients[J]. Am J Respir Crit Care Med, 2002, 165: 934-939

[41] Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s[J]. Nature, 1993, 362: 801-809

[42] Chin K, Nakamura T, Shimizu K, et al. Effects of nasal continuous positive airway pressure on soluble cell adhesion molecules in patients with obstructive sleep apnea syndrome [J]. Am J Med, 2000, 1 09: 562-567

[43] Price DT, Loscalzo J. Cellular adhesion molecules and atherogenesis [J]. Am J Med, 1999, 107: 85-97

[44] Howard EF, Chen Q, Cheng C, et al. NF-kappa B is activated and ICAM-1 gene expression is upregulated during reoxygenation of human brain endothelial cells[J]. Neurosci Lett, 1998, 248: 199-203

[45] Lattimore JD, Wilcox I, Nakhla S, et al. Repetitive hypoxia increases lipid loading in human macrophages-a potentially atherogenic effect [J]. Atherosclerosis, 2005, 179: 255-259

[46] Dempsey JA, Veasey SC, Morgan BJ, et al. Pathophysiology of sleep apnea[J]. Physiol Rev, 2010, 90: 47-112

[47] Saarelainen S, Seppala E, Laasonen K, et al. Circulating endothelin-1 in obstructive sleep apnea[J]. Endothelium, 1997, 5: 115-118

[48] Zamarron-Sanz C, Ricoy-Galbaldon J, et al. Plasma levels of vascular endothelial markers in obstructive sleep apnea [J]. Arch Med Res, 2006, 37: 552-555

[49] Arnaud C, Dematteis M, Pepin JL, et al. Obstructive sleep apnea, immuno-inflammation, and atherosclerosis[J]. Semin Immunopathol, 2009, 31: 113-125

[50] Jelic S, Lederer DJ, Adams T, et al. Vascular inflammation in obesity and sleep apnea[J]. Circulation, 2010, 121: 1014-1021

[51] Phillips BG, Narkiewicz K, Pesek CA, et al. Effects of obstructive sleep apnea on endothelin-1 and blood pressure[J]. J Hypertens, 1999, 17: 61-66

[52] Trakada G, Marangos M, Spiropoulos K. Mechanisms of endothelin-1 elevation in chronic obstructive pulmonary disease patients with nocturnal oxyhemoglobin desaturation [J]. Respiration, 2001, 68:134-139

[53] Ito H, Hirata Y, Adachi S, Tanaka M, et al. Endothelin-1 is an autocrine/paracrine factor in the mechanism of angiotensin II-induced hypertrophy in cultured rat cardiomyocytes[J]. J Clin Invest, 1993, 92: 398-403

[54] Grimpen F, Kanne P, Schulz E, et al. Endothelin-1 plasma levels are not elevated in patients with obstructive sleep apnoea[J]. Eur Respir J, 2000, 15: 320-325

(上接第 3785 页)

[13] Kang N., Perron M. E., Prud'homme R. E., et al. Stereocomplex block copolymer micelles: Core-shell nanostructures with enhanced stability [J]. Nano Lett, 2005, 5(2): 315-319

[14] Zhang Wei, Shi Yuan, Chen Yan-zuo, et al. Multifunctional pluronic p123/f127 mixed polymeric micelles loaded with paclitaxel for the treatment of multidrug resistant tumors [J]. Biomaterials, 2011, 32 (11): 2894-2906

[15] Hussain M. Delwar, Saxena. Poloxamer 407/tpgs mixed micelles for delivery of gambogic acid to breast and multidrug-resistant cancer [J]. International Journal of Nanomedicine, 2012: 713

[16] Zhao Liyan, Du Jianchao, Duan Yuwei, et al. Curcumin loaded mixed micelles composed of pluronic p123 and f68: Preparation, optimization and in vitro characterization [J]. Colloids and Surfaces B: Biointerfaces, 2012, 97: 101-108

[17] Gill Kanwaldeep K., Kaddoumi Amal, Nazzal Sami. Mixed micelles of peg2000-dspe and vitamin-e tpgs for concurrent delivery of paclitaxel and parthenolide: Enhanced chemosenstization and antitumor efficacy against non-small cell lung cancer (nsclc) cell lines [J]. European Journal of Pharmaceutical Sciences, 2012, 46 (1-2): 64-71

[18] Wang YuJun, Wang Cheng, Gong ChangYang, etc. Polysorbate 80 coated poly (□ -caprolactone)-poly (ethylene glycol)-poly (□ -caprolactone) micelles for paclitaxel delivery [J]. International Journal of Pharmaceutics, 2012, 434(1-2): 1-8

[19] Liang Huijun, Yang Qiuxia, Deng Li, et al. Phospholipid-tween 80 mixed micelles as an intravenous delivery carrier for paclitaxel [J]. Drug Development and Industrial Pharmacy, 2011, 37(5): 597-605

[20] Kamimura M., Kim J. O., Kabanov A. V., et al. Block ionomer complexes of peg-block-poly(4-vinylbenzylphosphonate) and cationic surfactants as highly stable, ph responsive drug delivery system [J]. J Control Release, 2012, 160(3): 486-494