微球载药系统的前沿进展和临床转化

吴其泷[1,2], 兰文悦[2,4], 崔明杰[2,3], 王珺珏[1,2], 程文豪[2], 于海军[1,2,3,4*]

(1. 南京中医药大学, 江苏 南京 210023; 2. 中国科学院上海药物研究所, 上海 201203;
3. 沈阳药科大学, 辽宁 沈阳 110016; 4. 中国科学院大学, 北京 100049)

摘要: 微球载药系统具有药物缓释和控释功能, 可提高药物稳定性, 临床应用前景广阔, 已成为创新制剂开发的前沿和热点领域。近年来, 科研人员发展了基于乳化溶剂挥发、高压均质、膜乳化和微流控等技术平台的载药微球制备方法, 并将微球载药系统应用于恶性肿瘤、精神分裂症、神经退行性疾病等重大疾病的临床治疗, 取得了良好的经济和社会效益。本文系统总结了微球载药系统的制备方法和临床应用情况, 同时讨论了新型微球载药系统临床转化方面的挑战, 希望进一步推动微球载药系统的开发和临床转化。

关键词: 微球载药系统; 制备方法; 局部药物递送; 药物储库; 临床转化

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Advances and clinical transformation of microsphere drug delivery systems

WU Qi-long[1,2], LAN Wen-yue[2,4], CUI Ming-jie[2,3], WANG Jun-jue[1,2], CHENG Wen-hao[2], YU Hai-jun[1,2,3,4*]

(*1. Nanjing University of Chinese Medicine, Nanjing 210023, China; 2. Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China; 3. Shenyang Pharmaceutical University, Shenyang 110016, China; 4. University of Chinese Academy of Sciences, Beijing 100049, China*)

Abstract: The microsphere drug delivery systems have been extensively exploited for providing controllable drug release kinetics, enhancing drug stability and localized drug delivery. In past decade, dozens of microsphere drug delivery systems have been developed for clinical therapy of cancer, schizophrenia and neurodegenerative diseases (e.g., Alzheimer's disease and Parkinsonism). In this review article, we comprehensively summarized the fabrication methods of drug delivery systems and highlighted their advances for clinical application. Furthermore, we analyzed the potential and the challenges for clinical translation of the drug delivery systems.

Key words: microsphere drug delivery system; fabrication method; localized drug delivery; drug deposit; clinical translation

载药微球通常是指将药物分散或吸附在高分子材料中形成的微小球状实体, 粒径一般在1～250 μm之间, 可用于静脉注射、口服、腔道局部给药或皮下埋植等不同给药途径[1,2]。将药物封装在微球中, 可改善药物溶解度、增加药物稳定性、实现药物缓释/控释及减少给药次数。此外, 微球可通过靶向策略定位到特定组织或细胞 (例如, 基于微球的粒径和表面电荷等理化性质实现被动靶向; 利用配体受体识别效应实现主动靶向; 利用磁场诱导实现物理靶向), 从而减少药物对机体健康组织的毒副作用, 改善疗效[3-6]。

特别是, 微球载药系统可利用自身优势实现小分子药物、多肽、蛋白质等大分子药物和工程化细胞的局部递送 (图1)。例如, 微球可促进骨髓间充质干细胞 (bone marrow mesenchymal stem cells, BMSCs) 的黏附

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*通讯作者 Tel: 86-21-68077900, E-mail: hjyu@simm.ac.cn
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和增殖, 将微球植入骨缺损部位可促进骨形成[7]; 用于经肝动脉化疗栓塞术 (transcatheter arterial chemoembolization, TACE) 时, 可根据血管直径和治疗要求按需制备微球, 以达到更精确的栓塞效果[8]; 将微球制备成多孔、多层结构, 负载不同内容物的同时在体内形成长效药物储库[9,10]; 利用不同材料降解速率的差异实现序贯或梯度释药[11]。微球制剂在医疗领域的应用已取得了显著进展, 多款产品成功上市, 为多种疾病提供了创新治疗策略。

1 载药微球制备方法

载药微球的制备流程通常包括分散、固化、洗涤和干燥4个步骤。分散是指通过乳化、控制溶质的溶解度等方法将药物均匀分布到聚合物基质中形成微球结构, 固化则是通过物理方法 (如溶剂挥发、温度变化) 或化学方法 (如交联反应) 等固定微球的形态和结构, 再经过洗涤干燥去除杂质, 得到可供保存的微球颗粒。本文根据不同的制备方法对载药微球进行了分类, 分析了各类方法的核心工艺, 并将其各自的特点归纳如表1[12-32]。

2 微球载药系统的临床应用

2.1 用于恶性肿瘤的局部治疗 恶性肿瘤 (癌症) 是威胁我国社会安定和经济发展的重大疾病。2022年, 我国约有480万新发癌症病例和250万癌症死亡病例[33]。目前临床使用的抗肿瘤药物主要包括分子靶向药物[34]、化疗药物[35]、免疫治疗药物[36]和细胞疗法[37]等。用微球包载抗肿瘤药物不仅可以延缓释放速率, 持续杀伤肿瘤细胞, 克服耐药性的发生和给药次数, 而且可通过局部或原位给药策略降低不良反应[38,39]。Xi等[40]用双乳液法和溶剂萃取法制备多孔聚乳酸 (polylactic acid, PLA) 微球。利用PLA的自愈合特性[41], 通过温和的红外光照射导致温度升高, 使PLA从玻璃态转变为橡胶态, 并触发聚合物链的自发重排, 该多孔微球会发生愈合, 将抗原分子装载在该微球中达到缓释效果。

微球还可以包载各种造影剂在体内实现可视化。Zhang等[10]将静电纺丝、均质化和电喷雾技术相结合, 制备了透明质酸功能化载药纤维微球。其中螯合在微球上的Gd^{3+}可实现对肿瘤的核磁共振成像 (至少5天)。

为防治实体肿瘤切除术后转移和复发, 术后常使用化疗或放疗等辅助治疗。但化疗药物全身给药后到达靶器官的浓度有限, 达到一定药物浓度需要较大剂量, 这会导致全身毒副作用。Zhong等[11]利用微流控法和电喷雾法制备包载多个甲基丙烯酰化明胶 (gelatin methacryloyl, GelMA) 微球的海藻酸钙微球 (图2A)。该海藻酸钙微球原位填充在肿瘤切除部位, 海藻酸钙微球的迅速降解使内容物多柔比星快速释放杀灭残余肿瘤细胞, 而GelMA微球缓慢降解, 持续释放包载的肝脏再生促进剂, 并且GelMA微球可作为肝细胞再生支架, 用于促进肝脏再生。

近年来, 嵌合抗原受体T细胞疗法 (chimeric antigen receptor T cells, CAR-T) 在治疗血液瘤方面产生了有效且持久的临床反应, 有望改变血液瘤治疗现状[42]。但目前CAR-T疗法对实体瘤效果有限, 这主要是因为实体瘤致密的细胞外基质和异常的血管系统限制了CAR-T细胞的肿瘤浸润。受淋巴结中T细胞增殖的生理过程启发, Liao等[43]通过微流控法制备了PLGA微球–人工淋巴结支架, 用于负载CAR-T细胞, 并同时封装了多种细胞因子, 模拟了抗原提呈细胞 (antigen-presenting cells, APCs) 提供的激活T细胞的关键信号

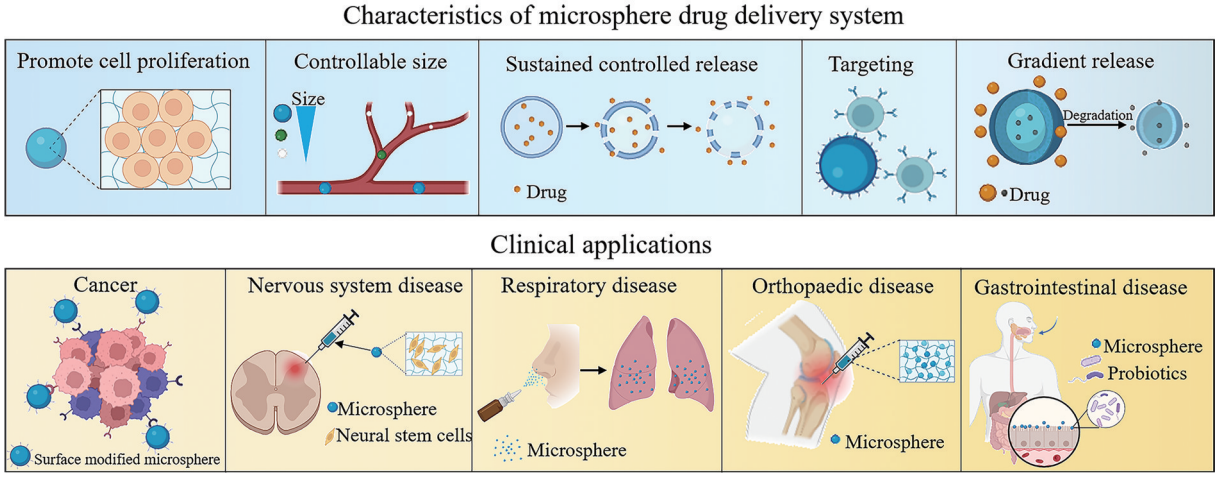

Figure 1 The advantages of microsphere drug delivery systems: promote cell proliferation, controllable size, sustained controlled release, targeting and gradient release. The main clinical applications of microsphere drug delivery system: tumor, nervous system disease, respiratory disease, orthopedic disease and gastrointestinal disease. Picture was created with BioRender.com

Table 1 The characteristics and core technology of methods to fabricate drug-loaded microspheres

Fabrication method	Encapsulation efficiency	Characteristic	Core technology	Ref.
Emulsion solvent evaporation	85.30%−97.58%	Simple operation and low cost Large amount of organic solvent used and non-uniform particle size	The organic phase containing drug is added into aqueous phase to emulsify by mechanical force	[12−14]
High-pressure homogenization	91.00%	Uniform particle size, simple operation, and suitable for continuous production Not suitable for encapsulating thermolabile drugs	The organic phase containing drug is added to aqueous phase, and colostrum prepared by high-shear mixing. The final emulsion is obtained by high-pressure homogenization	[15,16]
Membrane emulsification	85.10%	Uniform particle size with controllable distribution and good reproducibility High requirements for membrane material and hydrophilic drugs escape to external aqueous phase	The coarse single emulsion containing drug is extruded through the micro membrane with uniform pores	[17,18]
Microfluidic	98.94%	Uniform particle size with controllable distribution and good reproducibility Difficulties in equipment cleaning and susceptibility to clogging in microchannels	Continuous phase and dispersed phase form microspheres through microchannels of microfluidic chip	[19−21]
Phase separation	80.00%	Simple operation and suitable for large-scale production Relatively high residual level of organic solvents and microspheres aggregate easily,	Add non-solvent substance to the emulsion containing drug to reduce the solubility of the polymer	[22−24]
Supercritical fluid	50.40%−88.12%	Mild fabrication condition and low residual levels of organic solvents High costs and time-consuming fabrication process	Mix the drug and polymer in the supercritical fluid solution Reduce the solubility of the polymer by adjusting the temperature and pressure to form microsphere structure	[25,26]
Hot melt extrusion	46.50%−92.24%	No organic solvents required and high yield Not suitable for encapsulating expensive or thermolabile drugs	Polymeric materials and drug are heated and melted in a hot melt extrusion apparatus Then extruded through a screen, and cooled to form strip-like solids, which are subsequently pulverized into microspheres	[22,27]
Spray drying	82.00%−89.00%	High encapsulation efficiency and suitable for large-scale production Not applicable for the preparation of protein or peptide-based microspheres	The polymer solution containing drug is atomized through a nozzle and injected into hot air The atomized droplets are transformed into microspheres by solvent evaporation	[23,28]
Spray freeze drying	85.60%−95.50%	The microspheres are porous and suitable for encapsulating thermolabile drugs Costly equipment	A solution containing drug and polymer is sprayed through a nozzle into a freezing environment to form tiny ice crystals The ice crystals are sublimed in a freeze dryer to obtain dried microspheres	[29,30]
Electrospray	65.72%−74.14%	Controllable particle size distribution and low residual byproduct generation Low production efficiency and microspheres aggregate easily	A certain voltage is applied between nozzle and collecting substrate to generate a high-pressure difference The ejected polymer solution containing drug forms droplets and further atomize into particles	[31,32]

分子 (图2B)。

2.2 用于治疗骨缺损修复等骨科疾病 骨损伤微环境具有炎症、酸性和活性氧 (reactive oxygen species, ROS) 高表达等特征[44]。药物如细胞因子在骨缺损修复中起着关键作用, 但在复杂机体环境中细胞因子不能长期保持活性而限制了其应用。微球可以为其提供稳定的微环境, 能够长期保留其活性并达到缓释效果。并且微球的可注射性使其可植入患者体内填补不规则的骨缺损区域。Song等[45]用PLGA微球负载二氧化锰 (MnO_2) 纳米颗粒和骨形态发生蛋白-2 (bone morphogenetic protein-2, BMP-2), 使用低频超声技术实现了药物的响应性按需释放。

虽然骨组织具有一定再生能力, 对于超出骨组织自愈能力的较大骨缺损, 通常需要骨移植物植入才能达到有效的治疗效果[46]。Hao等[7]利用微流控法制备包封了脱钙骨基质 (decalcified bone matrix, DBM) 粉末和血管内皮生长因子的GelMA/甲基丙烯酰化透明质酸 (hyaluronic acid methacryloyl, HAMA) 微球, 并将

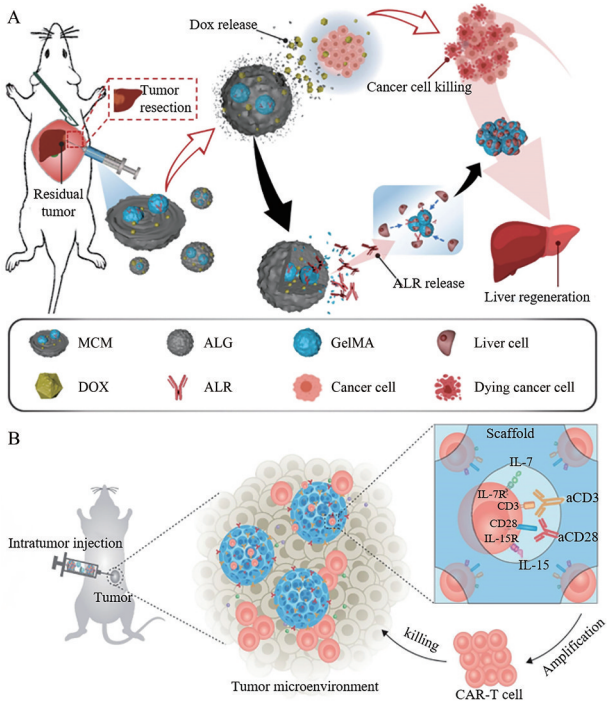

Figure 2 A: Schematic diagram of the multicomponent microspheres composed of DOX-loaded ALG shell and ALR-loaded GelMA cores for postsurgical liver cancer treatment and liver regeneration; B: Schematic of the artificial lymph node-like scaffold. The scaffold is constructed with the aCD3 and aCD28 antibodies-loaded porous microspheres for providing stimulatory and co-stimulatory signals for T-cell expansion. MCM: Multicomponent microspheres; DOX: Doxorubicin; ALG: Alginate; ALR: Augmenter of liver regeneration; GelMA: Gelatin methacryloyl; CD3: Cluster of differentiation 3; aCD3: Anti-cluster of differentiation 3 antibody; IL-7: Interleukin-7; IL-7R: Interleukin-7 receptor; CAR-T: Chimeric antigen receptor T cells. Adapted from Ref. 11 with permission. Copyright © 2024 Elsevier. Adapted from Ref. 43 with permission. Copyright © 2024 Oxford University Press

该微球装载在DBM支架中再植入骨缺损处。相比于块状水凝胶, 负载在微球表面的细胞可以与细胞外基质充分接触, 微球的孔隙也保证了营养的渗透和运输, 同时微球间的空隙有利于血管的生成, 可有效促进BMSCs黏附、增殖和成骨分化。

2.3 用于治疗脊髓损伤等中枢神经系统疾病 神经损伤包括中枢神经损伤和周围神经损伤, 这两种损伤在临床治疗和功能恢复方面都存在挑战, 尤其是与脊髓相关的损伤[47]。在世界范围内, 每百万人口中约有40例脊髓损伤 (spinal cord injury, SCI) 患者, 若没有得到有效治疗, 脊髓损伤往往会导致患者终身残疾[48]。

目前, 在SCI部位移植神经干细胞 (neural stem cells, NSCs) 被认为是一种很有前景的治疗策略。但受病理微环境的影响, 移植的细胞存活率和分化效率较低[48,49]。Wu等[50]制备了血小板衍生生长因子 (platelet-derived growth factor, PDGF) 模拟肽微球, 该微球由PDGF序列残基159～163之间的五肽VRKKP与萘乙酸–苯丙氨酸–苯丙氨酸–甘氨酸结合, 生成自组装水凝胶微球。其中五肽VRKKP可模拟PDGF功能, 包括防止神经元死亡、增加NSCs分化效率等, 从而提高NSCs移植存活率, 发挥协同作用。

2.4 用于治疗新型冠状病毒感染等呼吸系统疾病 严重急性呼吸系统综合征冠状病毒2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) 是一种高度传染性和致病性病毒, 会引起新型冠状病毒感染 (corona virus disease 2019, COVID-19), 造成急性呼吸道感染[51]。目前疫苗往往需要接种多针才可充分激活免疫系统。而微球载药系统具有提高药物稳定性和长效缓释药物的作用, 并且可包载一些响应性材料如氧化铁纳米颗粒从而具有靶向性, 可将疫苗精准地递送至APCs, 达到更好的免疫效果。

Chen等[52]通过双光子聚合3D激光光刻技术制造了GelMA微球, 用于DNA疫苗递送 (图3A)。改变激光功率可以调整该微球的交联水平, 从而可控制药物的释放。再通过在磁性骨架上制造GelMA微球赋予其可操作性和靶向性, 用于将DNA疫苗递送至树突状细胞和原代细胞, 以减小脱靶效应, 实现有针对性的疫苗递送。

Wang等[53]制备了一种用于治疗COVID-19的微球吸入气雾剂, 该气雾剂主要包含由巨噬细胞膜和过表达血管紧张素转化酶2 (angiotensin converting enzyme 2, ACE2) 受体的细胞膜包被的双重伪装的HAMA微球 (图3B), 通过抑制SARS-CoV-2与机体组织细胞的ACE2受体结合, 显著降低了其感染呼吸系统的能力, 且该气雾剂还可中和促炎细胞因子, 抑制细胞因子风暴。

2.5 用于调节肠道菌群 研究表明, 肠道微生物群在炎症性肠病乃至整个免疫系统中发挥重要作用[54]。口服益生菌可通过调节肠道菌群来治疗胃肠道疾病[55]。但胃肠道环境条件 (如胃酸及各种消化酶的存在) 导致口服益生菌存活率低且定植不足, 极大限制了其应用。Yang等[56]将甲基丙烯酸酯引入葡聚糖和单宁酸 (tannic acid, TA) 中, 并将两种溶液混合后通过可见光 (405 nm) 固化, 制成的水凝胶微球用来包封大肠杆菌Nissle 1917和吲哚-3-丙酸 (图4)。该微球综合了葡聚糖在胃和小肠的稳定性和富含邻苯三酚基团的TA在肠道中具有黏附性的特点, 将该微球用于小鼠结肠炎模型可以减少肠道炎症并恢复肠道屏障功能。

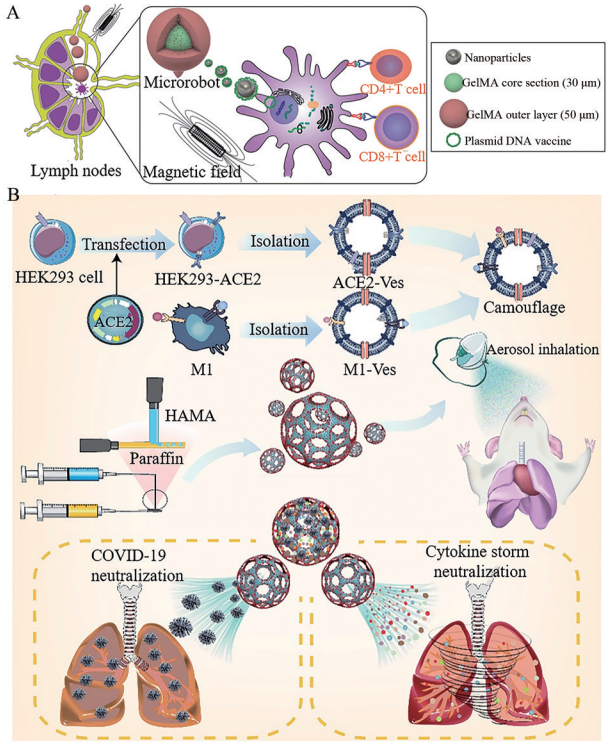

Figure 3 A: Schematic representation of DNA vaccine delivery and immunization strategy using the magnetically controlled GelMA microrobots; B: Schematic illustration of the inhaled ACE2-engineered microfluidic microsphere for neutralization of COVID-19 and calming of the cytokine storm. ACE2: Angiotensin converting enzyme 2; Ves: Vesicles; M1: Classically activated macrophages; HAMA: Hyaluronic acid methacryloy; COVID-19: Corona virus disease 2019. Adapted from Ref. 52 with permission. Copyright © 2024 Elsevier. Adapted from Ref. 53 with permission. Copyright © 2024 John Wiley and Sons Ltd

3 微球载药系统的市场份额分析

2021年12月, 国务院发布了《“十四五”医药工业发展规划》, 该政策鼓励使用先进制剂技术, 包括靶向、长效缓释/控释等复杂制剂。在国内政策的支持下, 微球载药系统由于具有延长药物半衰期、提高患者依从性等特点[57], 被广泛用于长效缓释/控释制剂开发, 市场前景广阔。

目前, 国内已上市的微球制剂主要用于恶性肿瘤、心血管疾病等慢性病领域。根据联合国《2022年世界人口展望》[58], 世界老年人口比例逐年增长, 而慢性病高发于老年群体中。根据《2022中国卫生健康统计年鉴》[59], 我国慢性病患病率逐年上升, 从2008年的157.4‰增长到2018年的342.9‰, 恶性肿瘤患病率从2008年的2.0‰增长到2018年的5.0‰, 高血压患病率从2008年的54.9‰增长到2018年的181.4‰, 对相关治疗药物的需求巨大。

4 载药微球产品分析

国内制备载药微球产品的企业有齐鲁制药、丽珠医药、绿叶制药和圣兆药物等 (表2), 国外的企业有Biocompatibles、BioSphere和武田制药等。

第一代注射用利培酮微球制剂由杨森制药公司开发, 该产品的制备过程包括几个步骤: ① 制备含有聚乙烯醇 (polyvinyl alcohol, PVA) 的水相及含有PLGA和利培酮的有机相; ② 有机相在水性连续相中乳化; ③ 通过静态混合形成液滴; ④ 通过筛分对微球进行分离。此药在首次注射后有约3周的释药延迟期, 因此在注射后前3周必须同时口服抗精神病药补充治疗, 增加了患者用药负担。而绿叶制药有限公司研制的利培酮缓释微球注射制剂, 通过改良的药物释放方式, 可缩短初始的释药延滞期, 在起始用药无需同时补充利培酮口服剂的情况下快速起效[60,61]。

栓塞微球主要用于TACE治疗肝癌。目前国内外上市的栓塞微球产品有DC bead载药微球[62]、CalliSpheres载药微球[63]、HepaSphere栓塞微球[63]、TheraSphere Y-90玻璃微球[64]、SIR-Spheres Y-90树脂微球和睿渊DiaSphere微球[65]等。通常情况下, 栓塞微球结合动脉微栓塞和化疗的作用杀死肿瘤细胞, 其中微球主要通过离子交换和吸附的方式负载化疗药物, 如DC bead

Table 2 Certain drug-loaded microsphere formulations that have been marketed or entered IND phase in China in recent years. IND: Investigational new drug; PVA: Polyvinyl alcohol

Generic name	Primary indication	Manufacturing company	Market approval date or clinical phase (nmpa.gov.cn, chinadrugtrials.org.cn)
Risperidone microspheres for injection (II)	Schizophrenia	Luye Pharmaceutical	2021
Triptorelin acetate microspheres for injection	Prostate cancer	Livzon	2023
Octreotide acetate microspheres for injection	Acromegaly	Qilu Pharmaceutical	2023
Goserelin microspheres for injection	Breast cancer	Luye Pharmaceutical	2023
PVA embolized microspheres	Liver cancer	Cardiolink Science	2023
Rotigotine microspheres for injection	Parkinsonism	Luye Pharmaceutical	2024
Alarelin acetate microspheres for injection	Endometriosis	Livzon	Phase I clinical trials
Ropivacaine microspheres for injection	Postoperative analgesia	Humanwell Pharmaceutical	Phase II clinical trials
Triptorelin acetate extended-release microspheres for injection	Prostate cancer	Luye Pharmaceutical	Phase III clinical trials

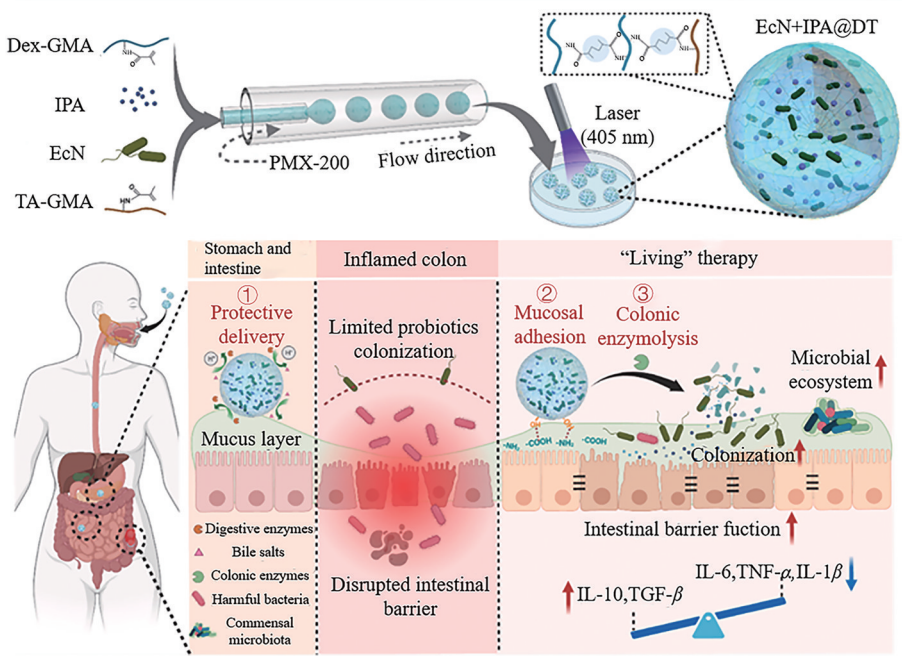

Figure 4 The microspheres composed of dextran, tannic acid, probiotic (EcN) and postbiotic (IPA) prepared based on microfluidic technology have the ability of protected delivery, enhanced mucosal adhesion and colon-targeted enzymolysis ability, thus promoting probiotic colonization and positively regulating microbial ecosystem. Dex-GMA: Dextran-glycidyl methacrylate; EcN: *Escherichia coli* Nissle 1917; IPA: Indole-3-propionic acid; TA-GMA: Tannic acid-glycidyl methacrylate; PMX: Polydimethylsiloxane; TGF-β: Transforming growth factor-β; TNF-α: Tumor necrosis factor-α. Adapted from Ref. 56 with permission. Copyright © 2024 Elsevier

微球通过表面带负电荷的磺酸基团吸附正电荷药物, 同体积结构中磺酸基团数量越多, 载药量越大[62]。而TheraSphere玻璃微球和SIR-Spheres树脂微球均用钇90标记, 注入肝动脉后通过间质性高剂量放疗和动脉微栓塞联合作用, 产生高剂量的辐射杀死肿瘤细胞, 而对周围的健康组织的辐射较小, 减少了不良反应。特别是使用SIR-Spheres Y-90树脂微球的患者在治疗第2天即可出院[66]。栓塞微球还可负载一些显影剂实现体内可视化, 提升了治疗成功率和目标血管的闭塞效果[67]。

虽然近年来陆续有微球制剂产品上市, 但载药微球制剂临床转化仍面临诸多挑战。微球载药系统的药物释放速度受到多种因素影响, 如载体材料、药物性质和制备工艺等, 因此很难精确控制药物释放速度。微球制剂产品的释药周期常需要数周至数月。长周期会导致微球的体外释药曲线与体内血药浓度曲线不一致, 从而需要反复且长期的动物实验验证。这使得研发时间和成本大幅增加。目前制备载药微球的设备一般为自主研发或改进的设备, 缺少标准化的设备。这些挑战构成了该领域的技术壁垒, 同时也对研发人员和医药设备企业提出较高的要求。

5 结论与展望

本文系统总结了微球载药系统的制备方法和临床应用情况, 同时讨论了新型微球载药系统临床转化方面的挑战。现有载药微球制备方法如乳化溶剂挥发法、相分离法等虽然存在粒径分布不均一、使用大量有机溶剂等缺点, 但其在成本上更具优势, 且更适合大规模生产。膜乳化法、微流控法、超临界流体法等由于具有粒径均一且分布可控、环境友好等优点而逐渐成为研究热点。为了获得更优性能的载药微球或满足特定的应用需求, 可以结合不同的微球制备技术。

对于不同适应症, 可结合微球的优势和疾病病理特征, 改善现有药物的不足。微球通常可负载多种药物, 利用微球结构的特点实现不同药物的同步、梯度等多种释放策略。同时微球也可结合其他结构的载体如块状水凝胶、骨再生支架 (脱钙骨基质) 等弥补彼此机械强度、细胞接种效率的不足, 或者对制备材料进行修饰以引入新的性能, 如在微球材料上修饰Gd^{3+}可实现肿瘤可视化成像。

虽然微球载药系统的临床转化面临着诸多挑战, 如难以精确控制药物释放速度、缺少标准化设备等, 但通过药学、材料学等跨学科合作共同解决载药微球工艺放大过程中的难题并不断优化载药微球制备工艺, 可以加速微球载药系统的研发和转化。随着研究的深入和技术进步, 药物研发人员有望设计开发出缓释/控释效果更好、生产工艺更完备的载药微球产品。

作者贡献: 吴其泷和兰文悦负责文稿撰写和编排; 崔明杰和王珺珏协助收集和整理相关文献; 程文豪负责审校; 于海军负责整体指导和文稿审阅。

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