Advances in Clinical Medicine 临床医学进展, 2025, 15(6), 1472-1479
Published Online June 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.1561875

Hans汉斯

超声响应聚合物微粒在骨修复领域的研究进展

袁小焱[1,2,3]，吴小红[1,2,3*]

[1]重庆医科大学附属口腔医院口腔修复科，重庆
[2]口腔疾病与生物医学重庆市重点实验室，重庆
[3]重庆市高校市级口腔生物医学工程重点实验室，重庆

收稿日期：2025年5月23日；录用日期：2025年6月16日；发布日期：2025年6月25日

摘　要

骨修复过程复杂，需要先进的药物递送系统来满足骨微环境的复杂性、精准治疗和多阶段治疗的需求。传统缓释系统存在药物突释与后期释放不足的矛盾，且缺乏对修复过程中动态生物学需求的响应能力。刺激响应型药物载体为解决这些问题提供了新思路，其中超声触发系统因具有非侵入性、深层组织穿透性和精确时空控制特性而备受关注。低强度脉冲超声(LIPUS)不仅能促进骨愈合，还在软组织再生方面有一定效果，但单独使用治疗深部病变存在局限性。聚合物基药物递送系统可实现药物靶向递送和可控释放，聚合物微粒在药物递送中具有诸多优势。超声介导的药物递送增强效应源于力学效应与热效应，涉及微气泡、纳米气泡、聚合物囊泡/胶束、聚合物水凝胶和压电聚合物基复合材料等多种载体。目前超声响应材料在药物/基因递送中的研究多处于体外和动物实验阶段，未来需更多临床试验进行验证，超声控释与压电结合也为智能响应材料局部疗法的精细控制开辟了新方向。

关键词

超声响应，聚合物微粒，药物递送系统

Research Progress of Ultrasound-Responsive Polymeric Microparticles in the Field of Bone Repair

Xiaoyan Yuan[1,2,3], Xiaohong Wu[1,2,3*]

[1]Department of Restorative Dentistry of Stomatological Hospital of Chongqing Medical University, Chongqing
[2]Chongqing Key Laboratory of Oral Diseases and Biomedical Sciences, Chongqing
[3]Chongqing Municipal Key Laboratory of Oral Biomedical Engineering of Higher Education, Chongqing

*通讯作者。

文章引用: 袁小焱, 吴小红. 超声响应聚合物微粒在骨修复领域的研究进展[J]. 临床医学进展, 2025, 15(6): 1472-1479. DOI: 10.12677/acm.2025.1561875

Received: May 23rd, 2025; accepted: Jun. 16th, 2025; published: Jun. 25th, 2025

Abstract

Drug delivery systems are designed to meet the needs of the complexity of the bone microenvironment, precise treatment, and multi-stage treatment. Traditional sustained-release systems have the contradiction of rapid drug release at the beginning and insufficient release in the later stage, and lack the ability to respond to the dynamic biological needs during the repair process. Stimuli-responsive drug carriers provide new ideas for solving these problems. Among them, the ultrasound-triggered system has attracted much attention due to its non-invasive nature, deep tissue penetration, and precise spatiotemporal control characteristics. Low-intensity pulsed ultrasound (LIPUS) can not only promote bone healing but also has certain effects in soft tissue regeneration. However, its use alone has limitations in treating deep-seated lesions. Polymeric drug delivery systems can achieve targeted drug delivery and controlled release, and polymeric microparticles have many advantages in drug delivery. The enhanced effect of ultrasound-mediated drug delivery originates from its mechanical and thermal effects, involving various carriers such as microbubbles, nanobubbles, polymeric vesicles/micelles, polymeric hydrogels, and piezoelectric polymer-based composites. Currently, the research on ultrasound-responsive materials in drug/gene delivery is mostly at the *in vitro* and animal experiment stages. More clinical trials are needed for verification in the future. The combination of ultrasound-controlled release and piezoelectricity also opens up a new direction for the fine control of local therapies with intelligent responsive materials.

Keywords

Ultrasound Response, Polymeric Microparticles, Drug Delivery System

1. 引言

骨修复过程不仅涉及骨组织的再生，还依赖于骨微环境的支持。骨微环境包括细胞外基质、生物化学因子、局部血液循环网络和神经分布等，这些因素共同影响干细胞的生长和分化[1]。骨修复同时也是一个多阶段的过程，包括炎症期、修复期和重塑期。每个阶段对药物的需求不同，例如，早期可能需要抗炎药物，而后期则需要促进骨再生的药物[2]。因此骨修复过程需要更先进的药物递送系统，以满足骨微环境的复杂性、精准治疗的需求、多阶段治疗的要求。近年来，局部药物递送系统因其可降低全身毒副作用、延长治疗窗口期等优势备受关注[3] [4]。然而，传统缓释系统普遍存在两大瓶颈：其一，为了达到所需的药物治疗浓度并在特定时间内保持药物浓度，递送剂由两部分组成。药物的第一部分应包含负荷剂量，第二部分应为维持剂量。药物的预期反应是通过负荷剂量实现的(初始爆发剂量导致药理作用的快速发作)，并且药物的维持剂量释放以缓慢而稳定的速率(遵循零级动力学)给药以维持药物的药理作用[5]。由于被动扩散机制导致的药物突释与后期释放不足的矛盾，许多药物释放产品不能被视为理想的递送系统[6]；其二，缺乏对修复进程中动态生物学需求的响应能力，难以实现治疗因子的精准时序递送[7]。刺激响应型药物载体为解决上述问题提供了新思路，其中超声触发系统因其非侵入性、深层组织穿透性和精确时空控制特性展现出独特优势[8] [9]。

低强度脉冲超声(LIPUS)作为机械波，可以在骨缺损处提供额外的机械刺激，它可以直接影响骨愈合过程中涉及的一系列细胞信号变化。Ikeda 等人[10]的研究表明，LIPUS 干预能够显著上调成骨相关转录因子 Runx2 的蛋白表达水平，并通过双重信号通路调控促进细胞外信号调节激酶(ERK1/2)和 p38 丝裂原活化蛋白激酶的磷酸化激活。机制研究发现，该刺激模式可使血管内皮生长因子 A (VEGF-A) mRNA 表达量显著提升，作为血管生成的关键调控因子，这一变化为后续新骨形成提供了必要的血供基础。在软骨修复方面，LIPUS 处理组显示出显著的促增殖效应，伴随软骨特异性基质成分(II 型胶原蛋白、糖胺聚糖)合成量增加，同时新生骨组织的矿化程度和成熟度均优于对照组，提示其可能通过加速软骨内骨化进程促进组织修复[11]。值得注意的是，LIPUS 的抗炎调控机制也逐渐被揭示，Nakamura 等人[12]通过滑膜细胞模型发现，低强度脉冲超声能够剂量依赖性地下调促炎介质 COX-2 和 PGE2 的表达水平，同时显著上调透明质酸合成酶 2 (HAS2)和 HAS3 的基因转录，这种双向调节作用为其在炎症性关节疾病中的应用提供了理论依据。这些信号通路和分子机制的证实也促成了进一步在动物模型和临床治疗的验证，它被证明可以促进新鲜骨折、骨不连和延迟愈合的恢复[13] [14]。它的应用不仅仅限于骨愈合的治疗，LIPUS 还在软组织再生方面显示出有效性，如肌腱、韧带和软骨等[15]-[17]。因此，低强度脉冲超声(LIPUS)作为一种机械能量形式可直接或间接地激活相关细胞增殖和涉及特殊蛋白质的不同目标信号通路，也可以用于临床治疗。并且。然而，一些研究表明，单独的 LIPUS 治疗并不能治疗所有骨缺损，尤其是深部部位的病变，导致治疗时间延长和预后不满意[18] [19]。

聚合物基药物递送系统(Polymeric Drug Delivery Systems, PDDS)在近年来取得了显著进展，并在药物递送领域展现出独特的优势。聚合物基系统可以通过功能化修饰实现药物的靶向递送，将药物精准递送至病变部位，减少对健康组织的副作用[20] [21]。例如，通过 pH 响应或酶响应聚合物，可以在特定环境下释放药物[22] [23]。使用不同的给药途径或不同方式封装活性分子，可以降低毒性、实现有效且准确的长期控制，无法自理的人群(如儿童和特殊需求人群)能够方便使用。聚合物材料还可以通过选择其化学和分子特性(如分子量(Mw)、单体组成、结晶度、玻璃化转变温度(Tg)和固有粘度)来实现药物的可控释放[24] [25]。术语“微粒”的定义是尺寸为 1 μm 至 2 mm 的球形颗粒，其中包含由一个或多个膜或壳包围的核心物质，是 PDDS 的其中一种形式。微粒可以根据其内部结构进一步分为微球和微胶囊。微球通常由均质基质形成，其中不可能分离核心和膜，而靶向活性药物成分(API)以小团聚或分子形式分散在聚合物基质中。而微胶囊是由含有 API 的中心液体、固体或半固体核心构成的制剂，单独或与赋形剂联合构成，周围环绕着膜或连续聚合物涂层[26]。如果需要达成以下目的：保持封装活性成分的稳定性；获得最佳药物负荷；实现了高封装效率和产率；获得所需的药物释放曲线，初始释放量低；产生自由流动且注射性好的颗粒；建立一个简单、可扩展且可重复的流程。聚合物微粒便能派上用场[27]。超声刺激和药物释放机制的联合应用可以相互增强，从而进一步提高组织生长和修复的效果。超声刺激能够增加细胞对药物的吸收和反应，并提高药物在病损区域的作用时间[28]-[30]，而药物释放系统可以提供持续的药物浓度，使治疗效果更持久和稳定。

2. 超声诱导聚合物微粒药物输送的机制

超声介导的药物递送增强效应主要源于其双重声学作用机制，包括力学效应与热效应。力学效应的核心是空化现象，根据作用强度差异可分为稳态空化与惯性空化两种模式。前者表现为微气泡在低强度超声场中作周期性振荡而不破裂，后者则发生在高强度声场下，气泡经历剧烈膨胀–坍塌循环，伴随冲击波、局部高温(约 5000 K)及自由基生成，这种非线性空化过程常被称为瞬态空化或崩溃空化[31]。惯性空化通过两种途径促进药物释放：一方面，微泡破裂产生的剪切应力可直接破坏载体结构；另一方面，空化诱导的细胞膜局部穿孔(声孔效应)使细胞膜通透性提升[32]。此外，超声热效应通过声能–热能转换

机制，可使靶区组织温度升高 3℃~5℃，这种温和的热刺激通过改变膜脂流动性和血管内皮间隙，进一步增强药物渗透效率[33] [34]。

2.1. 微气泡

超声微泡作为兼具诊断与治疗功能的复合载体，在医学领域展现出独特优势。这类载体的典型尺寸范围为 1~5 μm，气体核心由水溶性低的惰性气体构成，如全氟化碳等。通过高分子聚合物外壳设计可显著延长体内循环时间，并提供更高的配体负载能力以实现精准靶向[35]。相较于第一代微泡的脂质外壳，聚合物外壳比脂质包被的微泡更稳定，并且能够携带更多的有效载荷[36]。有研究超声合成了亲脂性药物递送的新型聚合物微胶囊，在具有高药物载量和明确的声学激活阈值，展现了在超声图像引导下具有超声触发亲脂性药物局部递送的巨大潜力[37]。Raffaella Villa 等人建立了一种将抗癌剂阿霉素靶向递送到肝癌细胞的负载有阿霉素且基于 PVA 的微泡与半乳糖基化壳聚糖复合物，实现对过表达乙酰半乳糖胺蛋白受体的 HepG2 肝癌细胞的定位和药物递送[38]。

2.2. 纳米气泡

鉴于微泡受限于血管内空间且尺寸较大难以穿透血管壁的局限性，药物在脉管系统部位的输送可能会受到阻碍[39]。基于这类问题，研究人员也开发了微泡向纳米泡转化的体系。因此纳米气泡在癌症诊断和治疗的药物/基因递送中显示出巨大的潜力，因为它们可以在肿瘤组织中积累并直接与肿瘤细胞相互作用[40]。Wu 及其团队构建了基于 PLGA 的纳米气泡递送平台，该系统以全氟丙烷(C_3F_8)为气体内核负载抗癌药物紫杉醇，并通过表面修饰技术将 A10-3.2 适配体锚定在载体表面，从而实现对前列腺癌细胞膜特异性抗原的靶向识别[41]。

2.3. 聚合物囊泡/胶束

聚合物囊泡和胶束通常由两亲性嵌段共聚物自组装，当共聚物浓度超过称为临界胶束浓度(CMC)的临界值时，嵌段共聚物胶束是通过两亲性嵌段共聚物分子在水性环境中自组装形成的。疏水嵌段形成胶束核心，而亲水嵌段(通常为 PEG)形成胶束电晕(或壳) [42]。尽管聚合物胶束在体外和动物研究中取得了相当大的成功，但到目前为止，他们的临床试验令人失望[43]。由于胶束的形成是热力学驱动的，因此如果共聚物浓度降至 CMC 以下，胶束会解离成单个分子(单体)。这可能导致药物在到达其肿瘤靶点之前过早释放到循环中。在临床试验中，胶束 DOX 制剂 NK911 [44]和 SP 1049C [45]表现出与游离 DOX 相同的副作用谱。

2.4. 聚合物水凝胶物

高分子水凝胶是一类具有三维网络结构的软物质材料，通过物理交联或化学交联形成微米级多孔架构，表现出独特的高含水率特性[46]，相较于传统超声响应性载体系统(多用于小分子药物负载)，三维水凝胶体系凭借其可控的溶胀行为和生物相容性，在生物大分子药物递送领域展现出显著优势[47]。目前有超声反应性聚合物水凝被报道[48] [49]，但也需要更深入的研究来实现未来的临床转变。

2.5. 压电聚合物基复合材料

聚合物与具有高介电常数的陶瓷填料结合通常是为了改造单独的聚合物低介电常数的特质并兼具其具有良好加工性能以及机械性能。有文献报道了超声介导调节压电聚合物复合材料药物释放动力学的初步证据，并证明了所涉及的主要机制是机械和电气机制，而热效应似乎没有发挥重要作用[50]。超声作为机械应力源，在四方相钛酸钡(T-BTO)催化体系中可诱导活性氧(ROS)生成[51]，其作用机制表现为：超声

振动通过压电效应促使材料内部产生电子－空穴对分离，形成内部强电场，进而驱动原位催化反应生成羟基自由基(·OH)和超氧阴离子自由基($\cdot O_2^-$) [52]。有研究发现，钛酸钡内部会发生基于压电效应的载流子分离过程。这种电子－空穴能够显著促进有机污染物的降解反应[53]。另外 PLGA 骨架上的极性基团极有可能在微电场的作用下进行了重新排布，可能对聚合物的结构形态产生了一定的影响[54] [55]。尽管目前还没有文献直接探究钛酸钡纳米颗粒与聚合物体外释放与降解之间的相关关系以及可能存在的机制，但是上述的文献提供了多种理论支持，这说明 US 和压电纳米颗粒之间存在调节药物释放动力学的可能，值得进行进一步的深入探究。

3. 未来发展与展望

3.1. 多模态响应系统的开发

当前单一超声响应系统难以满足骨修复多阶段需求(如炎症期抗炎、修复期成骨、重塑期血管化) [56]建议设计多重敏感响应载体，例如：超声触发早期药物突释以抗炎，局部酸性微环境(炎症期特征)触发中期成骨因子释放，酶(如基质金属蛋白酶)响应激活后期血管生成因子[57]。

3.2. 智能化精准递送与监控

引入人工智能(AI)算法优化超声参数与载体设计，通过机器学习预测不同骨缺损模型下的最佳释药模式。同时，开发超声成像－药物递送一体化系统，利用微泡的超声造影特性实时追踪载体分布与药物释放效率，解决现有技术中“递送－监控分离”的难题。

3.3. 临床转化的关键挑战

尽管动物实验显示超声响应材料的有效性，并且良好生物相容性得到了完善的证明[15] [18]，但临床转化需突破的瓶颈是：对于植入物长期安全性的评估。现有研究多使用短期毒性数据[58] [59]缺乏长期植入后的生物相容性评价[60]。因此可以考虑延长实验周期。

基金项目

重庆医科大学附属口腔医院新技术新项目，项目编号：QYYL2024X009；重庆市医学领军人才项目，项目编号：YXLJ202401。

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