口服大分子药物靶向递送研究进展

郑 正[1,2,3], 张雅文[2,3], 宋永波[1*], 范武发[2,3*]

(1. 沈阳药科大学生命科学与生物制药学院, 辽宁 本溪 117000; 2. 中国医学科学院 北京协和医学院, 药物研究所, 天然药物活性物质与功能国家重点实验室, 北京 100050; 3. 中国医学科学院 北京协和医学院, 药物研究所, 药物传输技术及新型制剂北京市重点实验室, 北京 100050)

摘要: 大分子药物因其高特异性与良好生物活性, 在疾病治疗中具有重要价值。口服给药途径以其优良的患者依从性和较高的安全性, 成为大分子药物递送的理想选择。然而, 胃肠道中的多种生物屏障严重限制了大分子药物的口服生物利用度及其靶向递送效率。现有研究多聚焦于单一屏障突破或单一载体设计, 本文系统地论述了口服大分子药物靶向递送过程中面临的多重生物屏障, 概况了适应于大分子药物口服靶向递送的各类纳米载体, 并深入探讨了器官特异性靶向策略的最新进展, 为口服大分子药物的精准治疗提供了新视角。此外, 还结合了多肽、蛋白质、核酸等大分子药物的应用实例, 为提升大分子药物的口服递送效率提供了理论依据与研究思路。

关键词: 大分子药物; 口服递送; 纳米递药系统; 生物屏障; 生物利用度

中图分类号: R943 **文献标识码**: A **文章编号**: 0513-4870(2026)05-1560-13

Research progress in oral targeted delivery systems for macromolecular drugs

ZHENG Zheng[1,2,3], ZHANG Ya-wen[2,3], SONG Yong-bo[1*], FAN Wu-fa[2,3*]

(*1. College of Life Sciences and Biopharmaceuticals, Shenyang Pharmaceutical University, Benxi 117000, China; 2. State Key Laboratory of Active Substances and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China; 3. Beijing Key Laboratory of Drug Delivery Technology and Novel Formulation, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China*)

Abstract: Macromolecular drugs, due to their high specificity and excellent biological activity, play a crucial role in disease treatment. The oral administration route, with its advantages of high patient compliance and safety, is considered an ideal approach for delivering macromolecular drugs. However, various biological barriers in the gastrointestinal tract significantly limit the oral bioavailability and targeted delivery efficiency of macromolecular drugs. Existing research has primarily focused on overcoming single barriers or designing single carriers, this paper systematically addresses the multiple biological barriers encountered during the targeted delivery of orally administered macromolecular drugs. It provides an overview of various nanocarriers suitable for the targeted oral delivery of macromolecular drugs and delves into the latest advances in organ-specific targeting strategies, offering new perspectives for the precision treatment of orally administered macromolecular drugs. Furthermore, it incorporates examples of applications involving macromolecular drugs such as peptides, proteins, and nucleic acids, providing theoretical insights and research directions for enhancing the oral delivery efficiency of macromolecular drugs.

收稿日期: 2025-11-11; 修回日期: 2026-01-05.

基金项目: 国家自然科学基金青年项目 (82304396); 中国医学科学院中央级公益性科研院所基本科研业务费 (2023-RC350-01).

*通讯作者 Tel: 15566181109, E-mail: Songyongbo@syphu.efu.cn;

Tel: 13693524103, E-mail: fanwufa@imm.ac.cn

DOI: 10.16438/j.0513-4870.2025-1333

Key words: macromolecular drug; oral delivery; nanoscale drug delivery system; biological barrier; bioavailability

大分子药物 (也称生物制品) 是指利用基因工程、细胞工程、蛋白质工程等现代生物技术制备的、具有特定生物活性的高分子化合物。其分子质量通常超过 1 000 Da, 主要包括蛋白质、多肽、核酸、疫苗及细胞因子等[1]。与传统小分子药物相比, 大分子药物在治疗方面展现出显著优势[2]。首先, 其生物活性高, 能够精准识别并结合体内的蛋白质和核酸等靶标, 从而高效发挥药理作用[3]; 其次, 大分子药物与生物靶点之间的相互作用具有高度特异性, 可显著降低脱靶毒性与毒副作用[4]; 此外, 此类药物在体内代谢缓慢、半衰期较长, 能够维持稳定持久的血药浓度, 从而进一步增强治疗效果[5]。因此, 大分子药物已成为现代生物医药领域的核心组成部分。

口服给药因其操作简便和患者依从性高等优势, 已成为目前最常用的给药方式。口服大分子药物递送系统是指通过口服给药途径将大分子药物安全、高效地输送至特定病变部位, 从而实现精准治疗并降低全身毒性[6]。近年来, 科研人员围绕口服大分子药物递送开展了广泛研究, 并取得了显著进展。然而, 口服大分子药物递送系统仍面临诸多瓶颈 (图 1)[7]。例如, 胃肠道内的强酸性环境及丰富的消化酶极易导致大分子药物发生降解或结构破坏[8]; 肠上皮细胞的紧密连接和黏液层的屏障作用严重限制了药物的跨膜吸收[9]; 即便大分子药物成功进入血液循环, 如何规避免疫系统的清除并精准靶向至病变组织, 仍是亟待攻克的关键难题[10]。因此, 梳理和总结口服大分子药物递送领域的研究进展, 对推动该领域的技术创新与临床转化具有重要意义。

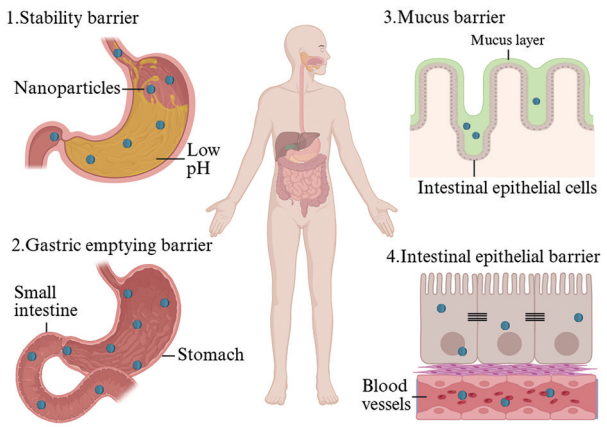


Figure 1　Biological barriers of oral targeted delivery systems for macromolecular drugs

1　口服靶向递送的生物屏障

1.1　稳定性屏障　药物稳定性是指药物维持其化学结构、生物活性及治疗效能的能力。大分子药物在口服给药后, 首先面临胃酸与酶的破坏。胃部强酸性环境可诱导蛋白质变性及多肽水解, 而胃肠道中的蛋白酶和核酸酶则通过特异性切割肽链和核酸链, 导致药物完全失活[11]。为解决这一问题, 目前已开发出多种策略, 例如使用胃酸调节剂改善胃内的低 pH 值环境, 利用酶抑制剂抑制胃肠道内酶的活性, 从而提高药物载体的稳定性[12]; 此外, 耐酸及耐酶稳定性材料也已被应用于口服药物递送载体[13]。载体技术在提升药物稳定性方面已展现出显著潜力, 但在复杂胃肠道环境中, 药物的长期稳定性仍面临严峻挑战, 也可能导致其靶向效率下降, 未来仍需开展系统深入的研究。

1.2　胃排空屏障 (胃肠道滞留屏障)　胃排空屏障 (又称胃肠道滞留屏障) 指的是在胃肠道特有的节律性运动与排空机制共同作用下, 药物滞留时间受限的现象。作为口服药物进入体内的第二道屏障, 胃通过周期性的容受性舒张与蠕动收缩, 将内含药物按生理节律逐步推送至小肠。胃排空速率受多种因素的调控, 包括药物本身的理化性质、胃内环境及机体生理状态, 因而具有高度变异性[14]。这种不可控的排空行为导致药物在胃肠道内的滞留时间短暂且波动显著, 若药物停留时间不足, 难以与吸收部位充分接触, 从而导致其生物利用度下降[15]。为克服该屏障, 当前常采用黏膜黏附的策略, 以增强纳米制剂与胃肠道黏膜的相互作用。例如, 在纳米载体表面修饰聚乙二醇黏附性配体, 可借助配体与黏膜层黏蛋白的特异性结合, 使纳米颗粒牢固锚定于肠壁, 抵抗胃蠕动带来的机械清除, 从而延长其在靶向吸收区域的滞留时间, 为后续的跨膜吸收与靶向转运奠定基础[16]。尽管如此, 胃排空屏障依然是限制大分子药物口服递送的重要因素, 未来在载体设计、材料创新与靶向策略等方面仍需开展更系统深入的研究。

1.3　黏液屏障　黏液屏障主要由杯状细胞分泌的黏蛋白构成, 其本质是一种由蛋白质、碳水化合物、脂质、无机盐及细胞碎片等构成的水凝胶, 厚度通常为 50～500 μm。其生理功能是通过黏附作用与空间位阻效应来捕获肠内容物, 防止病原体及毒素渗透侵入黏膜上皮细胞。然而, 这一天然保护机制同时也会阻碍药物载体的扩散与吸收, 对大分子药物口服递送造成严

重限制[17]。黏蛋白分子富含半胱氨酸, 整体呈负电荷, 这使得表面疏水性或带正电荷的药物载体易借助静电作用、范德华力等与黏蛋白发生相互作用, 从而显著降低其在黏液中的扩散和渗透能力[18]。因此, 对药物载体表面进行亲水性修饰成为当前突破黏液屏障和保障靶向递送的重要研究方向。常用修饰材料包括聚乙二醇 (polyethylene glycol, PEG) 及甜菜碱型两性离子聚合物等, 它们可通过在载体表面形成稳定的水合层, 有效削弱其与黏蛋白之间的非特异性相互作用, 从而提高载体在黏液中的渗透性与迁移速率[19]。黏液屏障目前依然是口服大分子药物递送系统中亟待突破的关键瓶颈, 未来需开发更高性能的载体材料及功能化表面修饰策略, 以实现更高效、更精准的黏液渗透, 从而优化靶向效率[20]。

1.4 肠上皮屏障 肠组织主要由肠上皮细胞构成, 还包含少量的杯状细胞和微褶皱细胞 (microfold cells, M细胞)。肠上皮屏障是指肠上皮细胞之间通过紧密连接形成一道重要的生理屏障, 其功能是防止肠道内的有害物质进入血液循环, 但同时也对外源药物的口服吸收构成严重限制。由于细胞间的缝隙极小, 仅有少量疏水性小分子可经细胞旁路途径被动扩散吸收, 而亲水性小分子及大分子药物则难以跨越该屏障[21]。此外, 药物载体通常具有较大粒径, 进一步导致其通过细胞旁路的吸收效率极低[22]。为克服这一障碍并提升靶向效率, 研究者常利用化学促渗剂暂时、可逆地调节肠上皮细胞, 以提升药物或载体经细胞旁路的转运量, 但该策略在增强吸收的同时, 也可能破坏上皮完整性, 导致肠道内容物异常渗透并增加感染风险[23]。近年来, 研究者尝试采用上皮细胞自身的转胞吞机制, 通过对药物载体进行表面功能化修饰, 可有效诱导其通过转胞吞途径跨越上皮屏障, 提高靶向特异性[24]。此外, 利用M细胞特有的高效吞噬与跨膜转运能力, 构建靶向M细胞的递送系统, 也可显著提高大分子药物的口服靶向递送效率[25]。

2 大分子口服靶向递药系统的分类

近年来, 大分子药物的口服靶向递送策略受到了广泛关注, 相关研究取得了显著进展 (图2, 表1[26-43])。

2.1 脂质类纳米粒 脂质类纳米粒是一类由天然或合成脂质构成的、粒径在纳米级别的球形载药系统。其核心是利用脂质材料良好的生物相容性和可降解性, 将大分子药物 (如蛋白质、多肽、核酸等) 包封于内部或吸附于其表面, 从而构建一种用于口服给药的纳米递送载体[44]。首先, 脂质纳米粒的脂质双分子层能有效隔绝胃肠道中苛刻的生化环境 (如低pH环境和消化酶), 避免大分子药物在抵达吸收部位前失活或降解[45]。Wei等[46]设计了一种负载微RNA (miR-200) 的脂质纳米粒, 该系统能够在胃酸环境中保持结构稳定, 并经口服途径靶向肠道上皮细胞, 从而促进肠道干细胞的增殖与上皮再生 (图3); 其次, 脂质纳米粒可通过被动靶向与主动靶向实现其精准递送功能。被动靶向依赖于载体自身的理化特性, 利用机体的生理学特征实现药物在特定部位的富集。例如, Li等[47]评估了不同粒径的脂质纳米粒口服递送的能力, 结果表明, 粒径为100 nm的脂质纳米粒表现出更强的黏液渗透能力和更高的递送效率, 其口服生物利用度较其他组提高1.22和1.80倍。主动靶向则是通过将特异性的靶向配体修饰于脂质纳米粒表面, 使其能够识别并结合靶细胞表面过度表达的特定受体, 从而显著提升递送的细胞选择性。例如Suri等[48]开发了一种可同时递送多种核酸有效载荷的口服脂质纳米平台, 在阳离子类脂 (C12-200) 为基础的脂质体 (lipid nanoparticle, LNP) 中引入阳离子脂质体可显著提高其在生理相关培养基中的稳定性, 并在体外与体内均表现出优异的siRNA和mRNA递送疗效。综上所述, 脂质纳米粒凭借其良好的安全性、生物可降解性及易于规模化制备的优势, 在口服胰岛素、疫苗及siRNA等大分子药物的递送研究中展现出广阔的应用前景与发展潜力[49]。

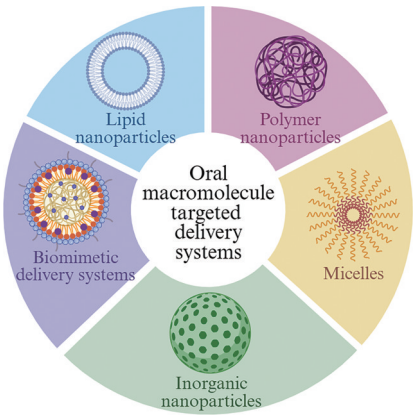


Figure 2 Summary of oral macromolecule targeted delivery systems

2.2 聚合物纳米粒 聚合物纳米粒是指由天然或合成的高分子聚合物通过物理或化学方法自组装、聚合或沉淀形成的、粒径在10～1 000 nm之间的纳米级载药系统。其结构通常分为两类——纳米胶囊 (药物被包裹于聚合物外壳形成的腔室内) 和纳米球 (药物通过吸附、镶嵌或分散于聚合物形成的固体基质中)[50]。聚合物纳米粒主要通过主动靶向与刺激响应性靶向策略实现精准药物递送。主动靶向常通过表面修饰特异性配体, 借助配体−受体相互作用识别并结合靶细胞表面过度表达的特定受体, 从而显著提升载体的细胞

Table 1　Summary of oral targeted macromolecule delivery systems

Drug carry	Drug	Disease	Characteristics	Ref.
Lipid nanoparticles	IL-12 mRNA	Inflammatory bowel disease	Improving colon targeting by modifying ginger-derived lipid ligands	[26]
	Gcgr siRNA	Hyperglycemia	Improving glucose homeostasis through targeted delivery of siRNA	[27]
	Insulin	Diabetes	Improving intestinal absorption of insulin with lectin-mediated targeted delivery	[28]
	Elcatonin	Osteoporosis	Improving the oral bioavailability and intestinal mucosal retention of calcitonin with submicron-sized, chitosan-coated liposomes	[29]
	Leuprolide	Prostate cancer	Enhancing gastrointestinal stability and improving oral peptide delivery by linking to palmitoyl chains and utilizing it to modify scleroglucan-coated nanostructured lipid carriers	[30]
Polymer nanoparticles	NF-κB mRNA	Inflammatory arthritis	Enhancing oral bioavailability and macrophage-mediated targeting delivery of antisense oligonucleotide to NF-κB by albumin microencapsulation	[31]
	Ovalbumin	Human immunodeficiency virus	Improving antigen immunogenicity and dendritic cell targeting by ovalbumin-loaded polyelectrolyte multilayer capsules functionalized with CpG oligonucleotides	[32]
	STAT3 siRNA	Colorectal carcinoma	Improving bioavailability and therapeutic efficacy of STAT3 siRNA by cRGD-9R-PAss hydrogel nanocapsules for colorectal carcinoma	[33]
	INFα-2b	Human jymphotropic-T virus	Enhancing IFNα solubility, stability, and therapeutic impact by chitosan nanoparticle encapsulation for oral administration	[34]
Micelles	Anti-RelA siRNA	Ulcerative colitis	Alleviating ulcerative colitis by multifunctional peptide carrier-modified polymer micelles for oral siRNA delivery	[35]
	TY1 RNA	Myocardial infarction	Exploiting the presence of macrophage-specific uptake mechanisms by the preparation of casein-chitosan (C2) micelles for oral RNA delivery	[36]
	Insulin	Diabetes mellitus	Exploiting the presence of goblet cell receptors by the preparation of CSKSSDYQC peptide	[37]
Inorganic nanoparticles	Bcl-2 siRNA	Oral cancer	Mediating nanoparticle-enhanced siRNA delivery through magnetic targeting and polycationic complexation for oral cancer gene therapy	[38]
	Influenza split vaccine	Seasonal influenza	The large pore structure in the core of mesoporous silica nanoparticles facilitates stable vaccine encapsulation and intestinal absorption, affording enhanced mucosal immunity	[39]
	Insulin	Diabetes mellitus	Moiety modification in the core mesoporous structure enables pH-responsive crosslinking with enteric polymers to afford stable insulin encapsulation and targeted intestinal release	[40]
Biomimetic delivery systems	Dmt1 siRNA	Hereditary hemochromatosis	Binding to intestinal folate receptors and releasing siRNA affinity-driven reaction to silence iron transporters	[41]
	Semaglutide	Type 2 diabetes mellitus	Exhibiting negligible adverse effects and superior anti-diabetic outcomes and enhancing oral bioavailability *via* self-adapting surface properties	[42]
	ZFP-362 mRNA	Acquired immunodeficiency syndrome	Offering the system broad biodistribution and brain-targeting capacity by engineering exosomes with surface modifications for enhanced blood-brain barrier penetration	[43]

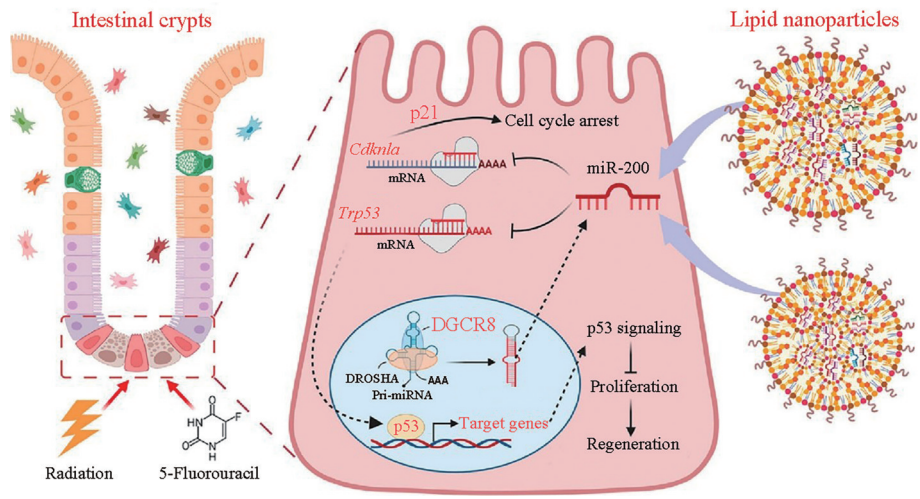


Figure 3　Schematic illustration demonstrates the role of lipid nanoparticles carrying miR-200 in promoting intestinal regeneration following acute injury in mice. Reprinted with permission from Ref. 46, copyright 2023 ACS Nano

选择性摄取效率。例如Ruiz-Gatón等[51]构建的聚乙二醇化聚酸酐纳米颗粒 (PEG-PA) 在模拟胃酸环境中孵育 2 h, 药物泄漏率仅 3.2%, 在模拟肠液中 6 h 累积释放率达 78%, 表明该载体对胃蛋白酶具有良好的耐受性及控释性能。此外, 通过选用具有不同降解速率和环境响应特性的聚合物, 可实现药物在肠道特定部位的时空可控释放, 从而有效提高局部药物浓度与治疗效果。Yu等[33]开发了一种响应型聚丙酰胺纳米颗粒中含有可被结肠高谷胱甘肽浓度还原的二硫键结构, 结肠病灶处可快速降解, 药物释放率高达 91% (图 4)。如Steinbach等[52]设计的细胞穿模肽修饰聚乳酸−羟基乙酸共聚物 (poly lactic-*co*-glycolic acid, PLGA) 纳米粒, 能够通过网格蛋白介导的内吞途径进入肠上皮细胞, 其摄取效率较未修饰组提高 26 倍, 且能有效避免溶酶体降解。总之, 聚合物纳米粒通过其可设计的智能特性, 为实现大分子药物的高效、精准口服递送提供了强大而多样的平台。

2.3 胶束 胶束是由两亲性分子在水溶液中自组装形成的纳米级聚集体, 其粒径通常在 10～1 000 nm 之间。两亲性分子兼具亲水基团和疏水基团, 在水溶液中疏水基团相互聚集以避免与水接触, 而亲水基团则朝向水相, 从而自发形成具有核−壳结构的稳定胶束

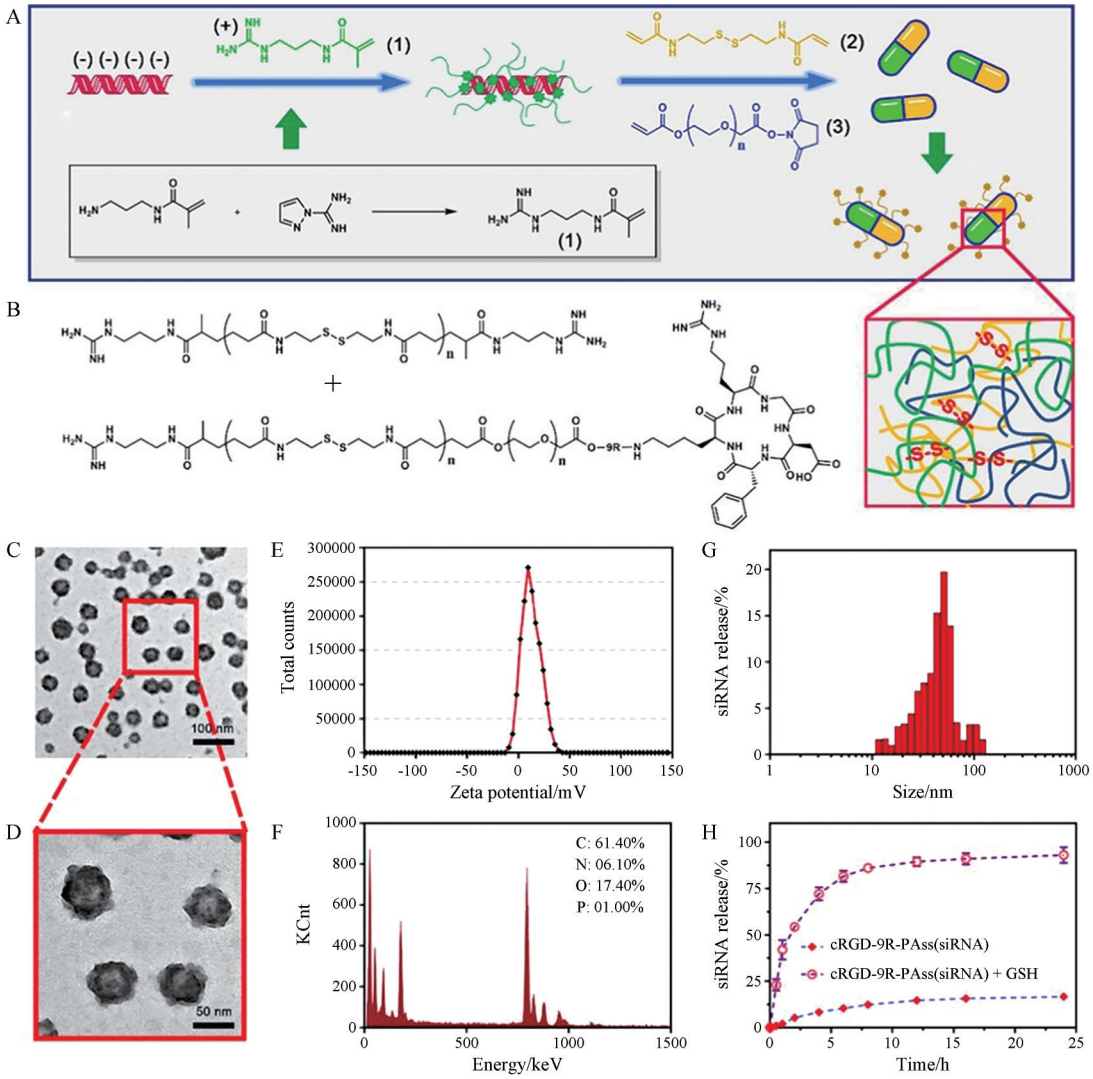


Figure 4 Preparation and characterization of cRGD-9R-PAss (siRNA) hydrogel nanocapsules. A: Illustration of cRGD-9R-PAss (siRNA) nanosphere preparation; (1) acrylate guanidine, (2) cystamine bis (acrylamide), and (3) acryl-PEG2000-NHS; B: The potential structure of the GSH-responsive hydrogel nanocapsule; C, D: Transmission electron microscope (TEM) images of cRGD-9R-Pass (siRNA) with negative staining; E: ζ-Potential of cRGD-9R-Pass (siRNA); F: Elemental analysis of cRGD-9R-Pass (siRNA) by HRTEM + EDS; G: Size distribution of cRGD-9R-Pass (siRNA); H: *In vitro* siRNA release behavior of cRGD-9R-PAss (siRNA). The release studies were performed at pH 7.4 and 37 ℃ in the presence or absence of 1 mmol·L^{-1} GSH. Reprinted with permission from Ref.33, copyright 2024 ACS Applied Nano Materials

体系。该结构赋予胶束优异的药物包载能力、生物相容性与结构稳定性[21]。胶束主要通过被动靶向与主动靶向两种策略实现药物的精准递送。被动靶向依赖于胶束的纳米尺寸效应及其表面性质, 通过增强的渗透性和滞留效应在病理组织富集。两亲性聚合物材料可使胶束在胃肠道复杂环境下保持结构完整, 并高效携带大分子药物穿越肠道黏液屏障及肠上皮细胞, 实现有效吸收。例如, Fan等[53]开发了基于三级胺氮氧结构 (OPDEA-PCL) 的两亲性聚合物胶束, OPDEA片段形成具黏液穿透能力的亲水外壳, PCL片段形成疏水内核, 可同时突破黏液与上皮屏障, 与其他给药组相比, 相对生物利用度分别提高了4.62和11.82倍。此外, 而主动靶向则通过在胶束表面共价缀合特异性靶向配体, 使其能够识别并结合靶细胞表面过度表达的特定受体, 从而显著提升递送系统的细胞选择性摄取效率。例如Lu等[54]在胶束表面共价修饰叶酸分子, 实现了对叶酸受体高表达的海拉细胞 (HeLa) 的主动靶向递送。实验结果表明HeLa细胞中该胶束的细胞吸收率分别比空白胶束组和游离药物组高4.3和1.7倍, 并且有效提高药物在病灶部位的富集浓度并增强治疗效果。此外, Wang等[55]设计了一种基于透明质酸的肿瘤靶向及氧化还原双响应型聚合物胶束, 通过透明质酸靶向肿瘤细胞表面高表达的CD44受体。此胶束在荷瘤小鼠模型中显示出59.45%的肿瘤抑制率, 体现了优异的靶向性和治疗效能。胶束凭借其优异的药物包载能力及灵活的靶向功能化设计, 已成为实现大分子药物高效、精准口服递送的重要平台, 展现出广阔的临床转化前景。

2.4　无机纳米粒　无机纳米粒是由无机材料构成的, 具有精确可控的尺寸与结构特征和独特的理化性质, 可为大分子药物口服递送提供了高稳定性的功能化平台。常用无机材料具有极高的化学稳定性和机械强度, 为包载的核酸、多肽、蛋白质等大分子药物提供坚实保护, 确保药物以活性形式稳定抵达吸收部位[56]。无机纳米粒可通过被动靶向、主动靶向及刺激响应性靶向等多种策略实现药物的精准递送。被动靶向依赖于纳米粒自身的理化特性, 利用机体的生理学特征实现药物在特定部位的富集。例如, Hu等[40]设计了一种表面为pH敏感涂层的介孔二氧化硅纳米粒, 其孔径大小控制在5～10 nm之间, 能高效装载胰岛素 (载药量达35%)。该纳米粒在胃部酸性环境中保持稳定, 在肠道中性环境中迅速释放药物, 实现了胰岛素的精准肠道递送。此外, 主动靶向则通过在无机纳米粒表面共价修饰特异性配体, 使其能够识别并结合靶细胞表面过度表达的特定受体, 从而显著提升递送系统的细胞选择性摄取效率。Yang等[57]开发了一种pH响应型的纳米颗粒, 表面共价修饰了可拉伸穿膜肽 (Pep) 与肝靶向配体 (Gal)。该纳米粒在胃酸环境中, 穿膜肽可呈现病毒样伸展构象, 显著增强其跨越肠道上皮屏障的能力; 而在肠道生理pH环境中, 穿膜肽折叠回缩, 使肝靶向配体暴露, 从而实现从肠道至肝脏的药物递送。尽管无机纳米粒的生物安全性仍需深入评估, 但其兼具高结构稳定性、高载药量及多功能表面修饰潜力, 为实现大分子药物的高效、智能化口服递送提供了极具前景的研究方向[58]。

2.5　仿生载体　仿生载体是一类受生物体系启发或基于生物源性成分构建的纳米药物递送系统。其核心设计理念是通过模拟天然生物结构 (如细胞、病原体) 的组成、结构及功能, 以克服口服递送过程中的多重生理屏障, 实现大分子药物的高效与精准递送[59]。仿生载体主要通过主动靶向、同源靶向和微环境响应性靶向等策略实现精准递送。主动靶向是通过修饰或天然表达特异性配体识别肠道上皮或病灶区域高表达的相应受体, 从而促进载体的胞吞转运。例如, Gu等[60]构建了一种仿生胆碱磷酸–聚乳酸羟基乙酸共聚物杂化纳米粒 (图5)。该纳米粒通过引入槐糖脂, 赋予其优异的胃肠道物理稳定性及快速黏液穿透能力, 显著增强了药物载体的上皮细胞内吞效率与生物利用度。而同源靶向是利用源自特定细胞的膜结构所保留的源细胞表面抗原与黏附分子, 使其能够识别并结合同类型细胞。Kaur等[61]设计了一种名为“Bacterioboat”的创新仿生载体, 将代谢活跃的罗伊氏乳杆菌包覆于介孔无机纳米颗粒表面, 在口服递送中表现出优良的肠道黏附与定植能力, 并实现了药物的持续释放与局部作用维持。此外, 微环境响应性靶向利用病灶区域特有的信号实现药物的智能释放。例如, Weng等[62]通过减毒活细菌包被纳米颗粒, 构建了一种创新型口服DNA疫苗递送系统。该系统不仅显著提升了细菌在胃肠道环境下的耐酸性与存活率, 还促进了其在口服后的全身迁移与免疫系统激活反应。总体而言, 仿生载体代表了口服递药系统设计理念的重要转变, 为实现大分子药物的高效与精准口服给药提供了极具前景的解决方案。

3　基于器官靶向的递送策略

各类递药系统通过自身结构设计与功能修饰, 为器官特异性口服靶向递送提供了基础载体平台。基于不同器官的生理特征与病理微环境, 设计适配的靶向策略, 可进一步提升大分子药物的递送精准度与治疗效果 (图6)。

3.1　结肠靶向　结肠靶向递送是一种将大分子药物特异性递送至结肠部位以实现局部精准治疗的递药策

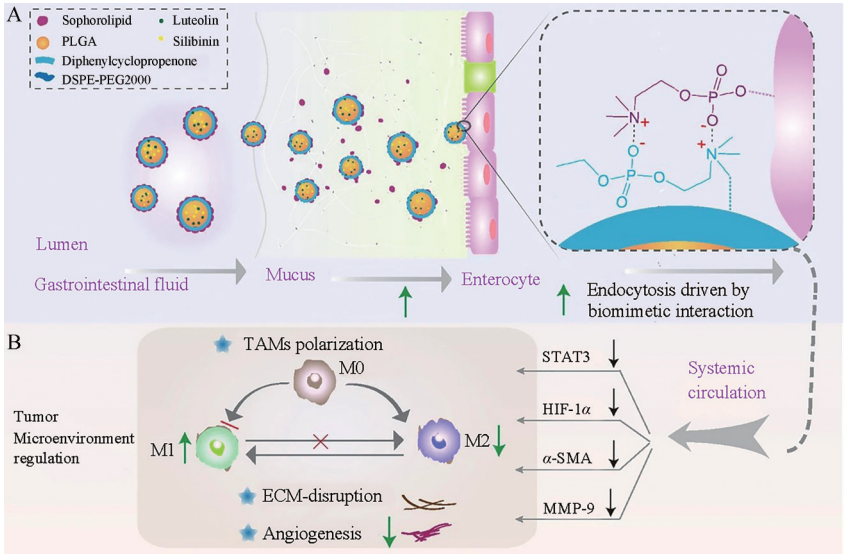


Figure 5 Schematic illustration of the sophorolipid-associated membrane-biomimetic choline phosphate-poly (lactic-*co*-glycolic) acid hybrid nanoparticle. A: Schematic illustration of physical stability in the gastrointestinal tract, rapid mucus diffusion, and improved endocytosis, driven by the dipalmitoyl choline phosphate-phosphatidyl choline interaction; B: Regulation of the conversion of tumor-associated M2 macrophages into the M1 phenotype and the matrix barrier, as well as the reduction of angiogenesis in the tumor microenvironment. Reprinted with permission from Ref. 60, copyright 2023 Journal of Nanobiotechnology

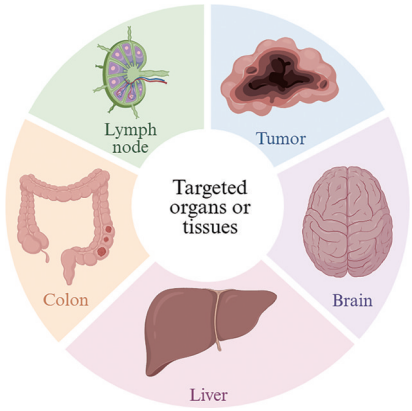


Figure 6 Summary of organs targeted by oral macromolecule delivery systems

略。其设计核心在于利用结肠独特的生理环境作为药物释放的触发信号, 构建具有智能响应特征的递送系统。该系统能够使药物在消化道中保持其结构稳定与生物活性, 仅在到达结肠后启动释放程序, 从而实现精准控释与靶向递药[63]。研究者常利用结肠的pH值作为触发机制, 以提高药物在结肠区域的分布。Huang等[64]设计了一种名为RNACap的胶囊装置, 用于将白细胞介素10 (IL-10) mRNA纳米制剂口服递送至胃肠道。借助外层pH敏感涂层, RNACap能在消化道环境中保持稳定, 而在结肠中性环境下降解, 其结肠富集率可达60%～80%, 从而实现mRNA的结肠靶向递送。该策略机制相对成熟, 但易受个体饮食或病理状态影响, 导致靶向准确性下降。此外, 结肠炎症区域常存在高浓度活性氧 (reactive oxygen species, ROS), 可被用于构建ROS响应型递药系统, 实现炎症部位的特异性药物释放。Wilson等[65]提出了一种硫酮醛纳米颗粒siRNA递送系统, 在炎症部位的释放率可达80%。该策略的优势在于能特异性响应病变微环境, 提升治疗效果并减少对正常组织的影响, 但其有效性高度依赖于炎症的严重程度。另一方面, 结肠内丰富的微生物菌群可分泌多种独特酶, 选用酶特异性降解的多糖类材料构建载体, 可实现基于酶响应的结肠靶向释药。Mohanta等[66]研发了美沙拉嗪−苹果多糖迷你片剂, 并将其与益生菌联合给药。其片剂中的尤特奇S100可以实现药物在结肠部位的特异性释放。

3.2 肠系膜淋巴结靶向 淋巴结 (lymph nodes, LNs) 作为人体免疫系统的重要中枢器官, 是启动与调控适应性免疫应答的关键场所。淋巴结靶向递送是指将大分子药物高效输送至淋巴结内部, 并在特定免疫细胞亚群中实现精准富集的一种新型递送策略[67]。目前, 实现淋巴结靶向的递送主要依赖于纳米载体的尺寸设计和表面修饰。首先, 基于粒径调控的被动靶向策略是指采用粒径在10～100 nm范围内的纳米载体。Ye等[68]开发了绿原酸 (chlorogenic acid, CHA) 封装的自微乳化药物递送系统 (CHA-SME), 用于靶向递送至肠系膜淋巴结。该系统通过增强药物跨肠上皮的渗透能力并利用淋巴转运通路, 显著提升了CHA在MLN内

的蓄积与生物利用度, 分别达到了5.1和9.5倍。其次, 基于配体修饰的主动靶向策略是在纳米载体表面修饰可与免疫细胞表面特异性受体结合的分子配体, 以实现对淋巴结中特定免疫细胞群体的主动识别与高效靶向。例如, Wan等[69]开发了一种由甘露糖修饰的脂质纳米颗粒 (mLNP), 包裹环状RNA疫苗 (circRNA-G), 口服给药靶向至淋巴结的效率对比游离mRNA提升了46.61%。此外, 仿生纳米载体介导的淋巴靶向递送策略近年来也受到广泛关注。Attili-Qadri等[70]开发了一种嵌入微粒结构中的多西紫杉醇纳米胶囊口服制剂, 其表面吸附的脂蛋白与磷脂分子可介导药物穿越肠上皮细胞, 并经淋巴系统转运进入体循环, 使得多西紫杉醇的口服生物利用提升了6.2倍。淋巴结靶向策略通过粒径控制、配体优化及仿生设计协同提升药物淋巴富集效率, 为免疫治疗和肿瘤转移防治提供了关键技术支撑, 但各策略均需进一步优化靶向精度与临床转化可行性。

3.3　肝靶向　肝脏靶向是指将口服大分子药物选择性地富集于肝脏组织或特定肝细胞, 以实现高效治疗并降低全身毒副作用的递送技术。肝脏作为人体的代谢与解毒中枢, 具有独特的解剖学与生理学特征, 包括显著的首过效应、丰富的血窦结构、数量众多的吞噬细胞 (Kupffer细胞) 及肝细胞膜上高密度分布的特异性受体[71]。口服肝脏靶向递送系统旨在充分利用这些特性, 通过主动或被动靶向机制, 引导药物克服胃肠道屏障, 经肠黏膜吸收后经门静脉系统精准作用于肝脏。首先, 通过在载体表面修饰能够与肝细胞特异性受体结合的配体, 可实现对Kupffer细胞或肝窦内皮细胞的主动靶向递送。例如, He等[72]开发了一种甘露糖修饰的三甲基壳聚糖–半胱氨酸 (mannose-modified trimethyl chitosan-cysteine, MTC) 偶联纳米颗粒, 用于口服递送肿瘤坏死因子α (TNF-α) siRNA。实验结果显示, MTC偶联物的口服生物利用度对比游离药物提升了6.5倍, 从而显著减轻了急性肝损伤小鼠的炎症反应。其次, 通过调控纳米载体的粒径、表面电荷及疏水性, 可促进其被肝脏网状内皮系统选择性摄取与内吞, 实现被动肝靶向效应。Shashni等[73]构建了短链脂肪酸 (short-chain fatty acid, SCFA) 前药递送系统, 通过酯键与丙酸或丁酸偶联, 自组装形成小粒径聚合物纳米粒 ($Nano^{SCFA}$)。$Nano^{SCFA}$经口服后在肠黏膜中富集, 并持续释放SCFA长达数小时, 其口服生物利用度增加了4.38倍。同时, 该体系可部分逃避单核吞噬细胞系统的清除, 从而显著提高其体内生物利用度与滞留时间。此外, 利用具有肝趋向性的天然载体 (如乳糜微粒类似物或肝细胞靶向外泌体), 通过模拟内源性物质的转运途径, 将药物高效递送至肝细胞。Gao等[74]从黑桑叶中分离提取了天然外泌体样脂质纳米颗粒, 该类天然载体富含糖脂、功能性蛋白及活性分子。研究表明, 其可通过半乳糖受体介导的内吞作用, 肝肿瘤细胞的摄取效率提高了7.1倍。总体而言, 肝脏靶向需兼顾克服胃肠道稳定性屏障、肠上皮渗透屏障及肝靶向特异性等多重挑战。未来通过融合主动靶向、刺激响应性设计与仿生策略的复合型递送系统, 有望进一步提升口服肝靶向递送的精准性与临床转化潜力。

3.4　脑靶向　脑靶向是指使口服大分子药物能够跨越多重复杂生物屏障, 最终选择性富集于脑组织以发挥治疗作用的递送过程。其中, 血脑屏障 (blood-brain barrier, BBB) 是该过程中的核心障碍, 其由脑微血管内皮细胞紧密连接、星形胶质细胞及基底膜共同构成, 几乎完全阻隔了大分子及亲水性药物的跨膜通透[75]。目前的研究重点主要聚焦于载体的功能化与表面工程化设计, 以欺骗BBB的防御系统, 实现药物的高效入脑递送。首先, 可借助受体介导的转胞运作用, 通过在载体表面修饰与BBB内皮细胞高表达受体特异结合的配体, 激活受体介导的跨膜内吞转运通路。Zhang等[76]构建了一种基于聚乳酸–聚乙二醇 (PLA-PEG2000) 的口服脑靶向抗miR-21脂质–聚合物胶束系统, 并对其进行脑肽载体 (Ang-2) 修饰。Ang-2是一种特异性多肽配体, 能够优先结合于BBB及神经胶质瘤细胞中高表达的低密度脂蛋白受体相关蛋白1。该系统可有效激活内吞转运途径, 对比游离药物组, 其脑靶向效率与抗瘤活性分别提高了4.6和6.3倍。其次, 仿生合成载体因其优异的生物相容性与跨屏障能力, 已成为提升药物入脑效率的重要方向。Yang等[77]基于*D*-氨基酸逆转–反转异构化设计原理, 合成了一种DSP肽, 并将其修饰于脂质体表面, 构建出DSP-sLip仿生脂质体系统。研究结果表明, 与普通脂质体相比DSP-sLip的肝脏与脾脏蓄积率提升了约3倍, 显著增强了脑部药物的靶向递送效率与分布特异性。各类脑靶向策略的靶向效率因设计而异, 但也普遍存在制剂复杂性高、个体差异影响靶向一致性及长期安全性待验证等局限性, 未来仍需进一步提升脑靶向递送的精准性与临床转化前景。

3.5　肿瘤靶向　肿瘤靶向是指通过特异性递送策略使口服大分子药物克服多重生理屏障, 选择性富集于肿瘤组织并高效进入肿瘤细胞内部发挥药理作用的一项前沿递送技术。其靶向机制主要基于两种原理——被动靶向与主动靶向[78]。首先, 被动靶向依赖于肿瘤组织独特的病理生理特征。由于肿瘤组织内血管生成紊乱、血管通透性增强且淋巴回流受限纳米级药物载体可通过增强型渗透与滞留效应 (enhanced permeability

and retention, EPR) 在肿瘤间质中被动富集。Yang等[79]证实, 巨噬细胞膜包被的纳米粒可利用EPR效应被动蓄积于口腔鳞状细胞癌组织。当粒径调控在100～150 nm范围内时, 药物在肿瘤部位的滞留量较游离药物提高约6倍, 显著增强了局部治疗效果。主动靶向则通过在载体表面修饰能够与肿瘤细胞膜上或肿瘤微环境中特异性分子结合的配体, 以显著提升药物的递送效率与组织选择性, 降低系统性脱靶毒性。Kübler等[80]通过数据挖掘与蛋白组学筛选发现, 前列腺癌与乳腺癌细胞中多种G蛋白偶联受体高表达。据此设计了特异性配体修饰的纳米载体, 通过受体介导的内吞作用, 药物细胞摄取量提升4.3倍, 脱靶毒性降低约70%, 显著增强了治疗靶向性与安全性。此外, 可基于肿瘤微环境 (tumor microenvironment, TME) 特征设计具备刺激响应功能纳米载体, 实现条件触发式药物释放, 从而进一步提高肿瘤治疗的精准度与疗效。例如, Gooneh-Farahani等[81]开发了一种牛血清白蛋白稳定的石墨烯−壳聚糖pH敏感复合载体, 其在肿瘤弱酸性环境 (pH ≈ 6.5) 下的药物释放率高达84%, 而在血液中仅为14%, 表现出优异的酸敏响应特性与选择性药物释放能力。肿瘤靶向递送策略通过被动富集、主动识别及智能响应等多重机制的整合, 显著提升了药物在肿瘤组织的富集效率与治疗精准性, 但各策略均需进一步优化其靶向稳定性、穿透深度及临床转化可行性。

4 大分子药物的分类

4.1 多肽药物 多肽药物是指由多个氨基酸通过肽键连接而成的一类大分子药物, 其相对分子质量通常介于1 000～10 000 Da, 在分子大小和结构上介于传统小分子化学药物和蛋白质药物之间[82]。为提高其口服吸收效率, 可采用吸收促进来增强肠上皮的旁路通透性或促进跨细胞转运[83]。此外, 借助脂质体、聚合物纳米粒 (如PLGA) 或多糖基纳米颗粒等载体系统包封多肽, 不仅可有效屏蔽胃酸与蛋白酶的降解作用, 还能通过表面功能化修饰特异性靶向配体, 实现对肠道吸收与组织分布的精确调控。Xue等[84]开发出了一种新型硅氧烷脂质纳米颗粒。研究结果表明, 引入硅氧烷基团可显著增强载体的细胞摄取能力与内质网逃逸效率, 从而实现对肝脏、肺及脾脏的选择性富集与高效递送。该研究为多肽药物的器官特异性靶向提供了一种可行且具有创新性的递送策略。

4.2 蛋白质药物 蛋白质药物是指由氨基酸通过肽键连接形成、具有特异性空间构象和生物学活性的高分子生物制剂, 其分子质量通常大于10 000 Da[85]。然而, 由于蛋白质药物分子体积大、亲水性强、化学结构不稳定, 且易在胃肠道的酸性环境及蛋白酶作用下发生变性或降解失活, 因此其口服递送面临严峻挑战。目前, 递送蛋白质药物可以采用表面活性剂 (如胆汁盐)、螯合剂或特殊渗透增强分子 (salcaprozate sodium, SNAC), 以可逆方式调节上皮紧密连接或提高细胞膜通透性。值得注意的是, SNAC技术已在口服索马鲁肽 (肽类药物) 中获得成功应用[86]。其次, 采用可生物降解的高分子材料 (如聚乳酸−羟基乙酸共聚物、PLGA、壳聚糖) 进行包封或功能化修饰, 可有效提高其递送效率与稳定性[87]。例如, Wu等[88]制备了多孔聚乳酸−乙醇酸共聚物 (PLGA) 微球, 用于负载胰岛素, 结果表明, 该载体的药物负载率为2.83%, 包封效率达82.6%。该系统在糖尿病智能化控释药物递送平台中显示出显著的应用潜力。另外, 利用pH敏感型材料构建递送系统, 可有效保护蛋白质免受酶解。例如, Eweje等[89]开发了一种基于弹性蛋白 (elastin-like polypeptide, ELP) 的纳米颗粒, pH响应性胶束结构能够有效封装核酸, 并在转运至酸性环境后分解。研究结果表明, 该系统可将蛋白质递送效率提高约48%, 并在鼻内给药模型中实现对小鼠肺上皮细胞的有效编辑, 展现出跨屏障给药的应用潜力。最后, 通过将蛋白质与穿膜肽或靶向受体 (如转铁蛋白受体) 的配体偶联, 可借助主动转运机制促进其跨细胞吸收。例如, Sand等[90]基于新生儿Fc受体 (neonatal Fc receptor, FcRn) 介导的跨膜转运机制, 成功实现了免疫球蛋白G (IgG) 类抗体从母体向胎儿或新生儿的转运, 并有效保护IgG免受细胞内降解代谢, 为蛋白质药物口服递送的生物学途径设计提供了新的启示。

4.3 核酸药物 核酸药物是以脱氧核糖核酸 (DNA) 或核糖核酸 (RNA) 为基础, 通过调控基因表达或修饰信号通路以实现疾病治疗目的的新型生物大分子药物。该类药物的分子质量通常为几千至几百万道尔顿, 并带有高密度负电荷与显著的亲水性, 因此其在体内稳定性差, 易被核酸酶降解, 难以穿越生物屏障[91]。实现核酸口服递送的关键在于构建能够有效保护核酸分子、高效穿透肠道屏障并实现胞内靶向递送的载体系统。近年来, 研究者致力于发展多种递送策略以应对上述挑战。一方面, 利用纳米载体包封核酸, 以提供物理保护并优化其体内的药代动力学行为。通过在载体表面引入特异性靶向配体, 可进一步促进siRNA/mRNA跨越胃肠屏障并增强上皮细胞摄取能力。例如, Zhang等[92]设计了一种半乳糖化巯基化壳聚糖纳米载体, 其表面半乳糖配体可特异识别结肠活化巨噬细胞表面的半乳糖受体, 而巯基介导的黏附作用可显著延长载体在肠道中的滞留时间, 从而促进肠道上皮修复并改善局部炎症微环境。另一方面, 可借助带正电材

通过静电作用与核酸形成复合物, 以显著增强其黏膜黏附性并促进细胞摄取。例如, Jin等[93]设计了一种内表面带正电的截短型铁蛋白载体 [tHFn(+)], 其可通过静电作用负载mRNA, 形成具有弱酸响应特性的复合结构。该载体在内体酸性环境中可自发解聚, 诱导溶酶体逃逸, 并在口服后能穿越肠道屏障并通过肠–脑轴靶向递。

5　总结与展望

本文综述了大分子药物口服递送系统的研究进展, 重点分析了胃肠屏障、黏液屏障及上皮屏障等限制因素, 并总结了脂质纳米粒、聚合物纳米粒、无机纳米粒及仿生递送系统等不同载体的应用。随着生物材料与纳米技术的快速发展, 多种功能化载体在药物保护、跨膜吸收及靶向递送方面取得显著进展。然而, 脂质纳米粒可能面临长期稳定性问题, 聚合物纳米粒的生物降解性需优化, 无机纳米粒的生物安全性尚待评估。此外, 虽然多肽、蛋白质和核酸等大分子药物在多种疾病治疗中展现出独特优势, 但其口服递送仍受稳定性差和吸收效率低等问题制约。

未来, 加强材料科学、生物医学、纳米技术等多学科的交叉合作将成为突破关键, 通过开发新型载体材料和探索新的靶向机制, 为口服大分子药物靶向递送提供创新性解决方案。同时, 个性化医疗与多组学技术的发展将促进口服大分子递药系统向个体化与临床转化方向迈进。尽管多数研究尚处于临床前研究阶段, 但随着高效载体和跨屏障策略的不断优化, 大分子药物由注射向口服的转变有望成为现实, 为精准治疗开辟新的途径。

作者贡献: 郑正、宋永波负责文章资料收集与初稿撰写; 郑正、张雅文和范武发负责文章的选题建议与修改; 宋永波和范武发为该文章的共同负责人。所有作者阅读并认可终稿。

利益冲突: 本文所有作者声明不存在利益冲突关系。

References

[1] Greish K, Fang J, Inutsuka T, et al. Macromolecular therapeutics: Advantages and prospects with special emphasis on solid tumour targeting [J]. Clin Pharmacokinet, 2003, 42: 1089-1105.

[2] Wang Z, Lai RZ, Wang XP, et al. Targeted penetrating motif engineering of BH3 mimetic: Harnessing non-canonical amino acids for coinhibition of MCL-1 and BCL-xL in acute myeloid leukemia [J]. Adv Sci (Weinh), 2025, 12: e2503682.

[3] Li C, Zhan WQ, Yang ZL, et al. Broad neutralization of SARS-CoV-2 variants by an inhalable bispecific single-domain antibody [J]. Cell, 2022, 185: 1389-1401.e18.

[4] Simmons JK, Burke PJ, Cochran JH, et al. Reducing the antigen-independent toxicity of antibody-drug conjugates by minimizing their non-specific clearance through PEGylation [J]. Toxicol Appl Pharmacol, 2020, 392: 114932.

[5] Wang ZR, Guo JW, Liu XY, et al. Temperature-triggered micellization of interferon alpha-diblock copolypeptide conjugate with enhanced stability and pharmacology [J]. J Control Release, 2020, 328: 444-453.

[6] Ji KF, Wei XQ, Kahkoska AR, et al. An orally administered glucose-responsive polymeric complex for high-efficiency and safe delivery of insulin in mice and pigs [J]. Nat Nanotechnol, 2024, 19: 1880-1891.

[7] Xia Y, Li YM, Huang JX, et al. Chimeric collagen-like proteins with tunable structural heterogeneity for precise control and targeted doxorubicin delivery [J]. J Control Release, 2025, 386: 114131.

[8] Fein KC, Gleeson JP, Newby AN, et al. Intestinal permeation enhancers enable oral delivery of macromolecules up to 70 kDa in size [J]. Eur J Pharm Biopharm, 2022, 170: 70-76.

[9] Lamson NG, Fein KC, Gleeson JP, et al. The strawberry-derived permeation enhancer pelargonidin enables oral protein delivery [J]. Proc Natl Acad Sci U S A, 2022, 119: e2207829119.

[10] Zang WQ, Gao D, Yu MR, et al. Oral delivery of gemcitabine-loaded glycocholic acid-modified micelles for cancer therapy [J]. ACS Nano, 2023, 17: 18074-18088.

[11] Xiao B, Zhang C, Zhou JX, et al. Design of SC PEP with enhanced stability against pepsin digestion and increased activity by machine learning and structural parameters modeling [J]. Int J Biol Macromol, 2023, 250: 125933.

[12] Zhang M, Wang MR, Mi YM, et al. Enhanced enzyme stability at the interphase of water-oil for continuous-flow olefin epoxidation [J]. Nat Commun, 2025, 16: 8087.

[13] Fu Y, Liu WJ, Jiang LH, et al. Core-shell hydrogel with synergistic super absorption and long-term acid resistance stability: A novel gastric retention drug delivery carrier [J]. J Mater Chem B, 2025, 13: 2457-2468.

[14] Sharma S, Prasad B. Meta-analysis of food effect on oral absorption of efflux transporter substrate drugs: Does delayed gastric emptying influence drug transport kinetics? [J]. Pharmaceutics, 2021, 13: 1035.

[15] Mehrdadi S. Lipid-based nanoparticles as oral drug delivery systems: Overcoming poor gastrointestinal absorption and enhancing bioavailability of peptide and protein therapeutics [J]. Adv Pharm Bull, 2024, 14: 48-66.

[16] Tong T, Wang LY, You XR, et al. Nano and microscale delivery platforms for enhanced oral peptide/protein bioavailability [J]. Biomater Sci, 2020, 8: 5804-5823.

[17] Li YM, Mao MQ, Yuan X, et al. Natural gastrointestinal stable pea albumin nanomicelles for capsaicin delivery and their effects for enhanced mucus permeability at small intestine [J]. Biomater Res, 2024, 28: 0065.

[18] Tafech B, Rokhforouz MR, Leung J, et al. Exploring mecha-

nisms of lipid nanoparticle-mucus interactions in healthy and cystic fibrosis conditions [J]. Adv Healthc Mater, 2024, 13: e2304525.

[19] Chen YM, Lin SS, Wang L, et al. Reinforcement of the intestinal mucosal barrier *via* mucus-penetrating PEGylated bacteria [J]. Nat Biomed Eng, 2024, 8: 823-841.

[20] Wang ZH, Chu MY, Yin N, et al. Biological chemotaxis-guided self-thermophoretic nanoplatform augments colorectal cancer therapy through autonomous mucus penetration [J]. Sci Adv, 2022, 8: eabn3917.

[21] Han XF, Liu Y, Xie JB, et al. Zwitterionic micelles efficiently deliver oral insulin without opening tight junctions [J]. Nat Nanotechnol, 2020, 15: 605-614.

[22] Chen GY, Kang WR, Li W, et al. Oral delivery of protein and peptide drugs: From non-specific formulation approaches to intestinal cell targeting strategies [J]. Theranostics, 2022, 12: 1419-1439.

[23] Li C, Yuan LW, Zhang XH, et al. Core-shell nanosystems designed for effective oral delivery of polypeptide drugs [J]. J Control Release, 2022, 352: 540-555.

[24] Hameedat F, Pizarroso NA, Teixeira N, et al. Functionalized FcRn-targeted nanosystems for oral drug delivery: A new approach to colorectal cancer treatment [J]. Eur J Pharm Sci, 2022, 176: 106259.

[25] Song JG, Lee SH, Han HK. Development of an M cell targeted nanocomposite system for effective oral protein delivery: preparation, *in vitro* and *in vivo* characterization [J]. J Nanobiotechnology, 2021, 19: 15.

[26] Sung J, Alghoul Z, Long DP, et al. Oral delivery of IL-22 mRNA-loaded lipid nanoparticles targeting the injured intestinal mucosa: A novel therapeutic solution to treat ulcerative colitis [J]. Biomaterials, 2022, 288: 121707.

[27] Neumann UH, Ho JSS, Chen S, et al. Lipid nanoparticle delivery of glucagon receptor siRNA improves glucose homeostasis in mouse models of diabetes [J]. Mol metab, 2017, 6: 1161-1172.

[28] Zhang N, Ping QN, Huang GH, et al. Investigation of lectin-modified insulin liposomes as carriers for oral administration [J]. Int J Pharm, 2005, 294: 247-259.

[29] Takeuchi H, Matsui Y, Sugihara H, et al. Effectiveness of submicron-sized, chitosan-coated liposomes in oral administration of peptide drugs [J]. Int J Pharm, 2005, 303: 160-170.

[30] Carafa M, Marianecci C, Annibaldi V, et al. Novel *O*-palmitoylscleroglucan-coated liposomes as drug carriers: Development, characterization and interaction with leuprolide [J]. Int J Pharm, 2006, 325: 155-162.

[31] Uddin MN, Patel NJ, Bhowmik T, et al. Enhanced bioavailability of orally administered antisense oligonucleotide to nuclear factor kappa B mRNA after microencapsulation with albumin [J]. J Drug Target, 2013, 21: 450-457.

[32] De Geest BG, Willart MA, Lambrecht BN, et al. Surface-engineered polyelectrolyte multilayer capsules: Synthetic vaccines mimicking microbial structure and function [J]. Angew Chem Int Ed, 2012, 51: 3862-3866.

[33] Yu S, Zheng J, Xie H, et al. Biocompatible hydrogel nanoparticles with lysosomal escape properties for the delivery of siRNA for the gene therapy of colorectal carcinoma [J]. ACS Appl Nano Mater, 2024, 7: 6626-6635.

[34] Cánepa C, Imperiale JC, Berini CA, et al. Development of a drug delivery system based on chitosan nanoparticles for oral administration of interferon-α [J]. Biomacromolecules, 2017, 18: 3302-3309.

[35] Ibaraki H, Hatakeyama N, Takeda A, et al. Multifunctional peptide carrier-modified polymer micelle accelerates oral siRNA-delivery to the colon and improves gene silencing-mediated therapeutic effects in ulcerative colitis [J]. J Drug Delivery Sci Technol, 2022, 73: 103481.

[36] Yamaguchi S, Miyamoto K, Jones XM, et al. Oral bioavailability of a noncoding RNA drug, TY1, that acts on macrophages [J]. J Extracell Biol, 2025, 4: e70081.

[37] Zhang PW, Xu YN, Zhu X, et al. Goblet cell targeting nanoparticle containing drug-loaded micelle cores for oral delivery of insulin [J]. Int J Pharm, 2015, 496: 993-1005.

[38] Jin LL, Wang QY, Chen JY, et al. Efficient delivery of therapeutic siRNA by Fe_3O_4 magnetic nanoparticles into oral cancer cells [J]. Pharmaceutics, 2019, 11: 615.

[39] Liu Z, Lu HY, Li S, et al. Size effect of mesoporous silica nanoparticles on regulating the immune effect of oral influenza split vaccine [J]. Colloids Surf B Biointerfaces, 2024, 238: 113920.

[40] Hu D, Li Y, Teng W, et al. pH-responsive mesoporous silica nanorod for high load and oral delivery of insulin [J]. J Drug Delivery Sci Technol, 2024, 91: 105256.

[41] Wang XY, Zhang MZ, Woloshun RR, et al. Oral administration of ginger-derived lipid nanoparticles and Dmt1 siRNA potentiates the effect of dietary iron restriction and mitigates pre-existing iron overload in *Hamp* KO mice [J]. Nutrients, 2021, 13: 1686.

[42] Xiao PF, Wang HX, Liu HB, et al. Milk exosome-liposome hybrid vesicles with self-adapting surface properties overcome the sequential absorption barriers for oral delivery of peptides [J]. ACS Nano, 2024, 18: 21091-21111.

[43] Shrivastava S, Ray RM, Holguin L, et al. Exosome-mediated stable epigenetic repression of HIV-1 [J]. Nat Commun, 2021, 12: 5541.

[44] Hou X, Zaks T, Langer R, et al. Lipid nanoparticles for mRNA delivery [J]. Nat Rev Mater, 2021, 6: 1078-1094.

[45] Gao Q, Gao YX, Cao YG, et al. Reinforced plant-derived lipid nanoparticles for oral precise epigenome editing in colonic diseases [J]. Sci Adv, 2025, 11: eadw9275.

[46] Wei XY, Yu SC, Zhang TH, et al. MicroRNA-200 loaded lipid nanoparticles promote intestinal epithelium regeneration in

canonical microRNA-deficient mice [J]. ACS Nano, 2023, 17: 22901-22915.

[47] Li HP, Chen ML, Su ZG, et al. Size-exclusive effect of nano-structured lipid carriers on oral drug delivery [J]. Int J Pharm, 2016, 511: 524-537.

[48] Suri K, Pfeifer L, Cvet D, et al. Oral delivery of stabilized lipid nanoparticles for nucleic acid therapeutics [J]. Drug Deliv Transl Res, 2025, 15: 1755-1769.

[49] Chu CX, Deng YX, Liu HB, et al. *In situ* rearranged multifunctional lipid nanoparticles *via* synergistic potentiation for oral insulin delivery [J]. Int J Pharm, 2023, 636: 122811.

[50] Zu MH, Ma Y, Cannup B, et al. Oral delivery of natural active small molecules by polymeric nanoparticles for the treatment of inflammatory bowel diseases [J]. Adv Drug Deliv Rev, 2021, 176: 113887.

[51] Ruiz-Gatón L, Espuelas S, Larrañeta E, et al. Pegylated poly (anhydride) nanoparticles for oral delivery of docetaxel [J]. Eur J Pharm Sci, 2018, 118: 165-175.

[52] Steinbach JM, Seo YE, Saltzman WM. Cell penetrating peptide-modified poly (lactic-*co*-glycolic acid) nanoparticles with enhanced cell internalization [J]. Acta Biomater, 2016, 30: 49-61.

[53] Fan WF, Wei QY, Xiang JJ, et al. Mucus penetrating and cell-binding polyzwitterionic micelles as potent oral nanomedicine for cancer drug delivery [J]. Adv Mater, 2022, 34: e2109189.

[54] Lu Q, Yi MJ, Zhang MC, et al. Folate-conjugated cell membrane mimetic polymer micelles for tumor-cell-targeted delivery of doxorubicin [J]. Langmuir, 2019, 35: 504-512.

[55] Wang XY, Zhang H, Li CX, et al. Tumor-targeting and redox dual-responsive hyaluronic acid-based polymeric micelles loaded with celastrol for breast cancer treatment [J]. Int J Biol Macromol, 2025, 327: 147365.

[56] Cao YX, Janjua TI, Qu Z, et al. Virus-like silica nanoparticles enhance macromolecule permeation *in vivo* [J]. Biomater Sci, 2023, 11: 4508-4521.

[57] Yang TT, Wang AH, Nie D, et al. Ligand-switchable nanoparticles resembling viral surface for sequential drug delivery and improved oral insulin therapy [J]. Nat Commun, 2022, 13: 6649.

[58] Liong M, Lu J, Kovochich M, et al. Multifunctional inorganic nanoparticles for imaging, targeting, and drug delivery [J]. ACS Nano, 2008, 2: 889-896.

[59] Sang ZT, Xu L, Ding RY, et al. Nanoparticles exhibiting virus-mimic surface topology for enhanced oral delivery [J]. Nat Commun, 2023, 14: 7694.

[60] Gu XY, Zhang RG, Sun YW, et al. Oral membrane-biomimetic nanoparticles for enhanced endocytosis and regulation of tumor-associated macrophage [J]. J Nanobiotechnology, 2023, 21: 206.

[61] Kaur P, Ghosh S, Bhowmick A, et al. Bacterioboat-a novel tool to increase the half-life period of the orally administered drug [J]. Sci Adv, 2022, 8: eabh1419.

[62] Weng LT, Wu L, Guo RJ, et al. Lactobacillus cell envelope-coated nanoparticles for antibiotic delivery against cariogenic biofilm and dental caries [J]. J Nanobiotechnology, 2022, 20: 356.

[63] Tang SC, Wang WC, Wang YJ, et al. Sustained release of 5-aminosalicylic acid from azoreductase-responsive polymeric prodrugs for prolonged colon-targeted colitis therapy [J]. J Nanobiotechnology, 2024, 22: 468.

[64] Huang XG, Liu C, Sharma SN, et al. Oral delivery of liquid mRNA therapeutics by an engineered capsule for treatment of preclinical intestinal disease [J]. Sci Transl Med, 2025, 17: eadu1493.

[65] Wilson DS, Dalmasso G, Wang LX, et al. Orally delivered thioketal nanoparticles loaded with TNF-α-siRNA target inflammation and inhibit gene expression in the intestines [J]. Nat Mater, 2010, 9: 923-928.

[66] Mohanta S, Singh SK, Kumar B, et al. Efficacy of co-administration of modified apple polysaccharide and probiotics in guar gum-Eudragit S100 based mesalamine mini tablets: A novel approach in treating ulcerative colitis [J]. Int J Biol Macromol, 2019, 126: 427-435.

[67] Che YJ, Ren XH, Wang ZW, et al. Lymph-node-targeted drug delivery for effective immunomodulation to prolong the long-term survival after heart transplantation [J]. Adv Mater, 2023, 35: 2207227.

[68] Ye J, Gao Y, Ji M, et al. Oral SMEDDS promotes lymphatic transport and mesenteric lymph nodes target of chlorogenic acid for effective T-cell antitumor immunity [J]. J Immunother Cancer, 2021, 9: e002753.

[69] Wan JW, Wang ZM, Wang LL, et al. Circular RNA vaccines with long-term lymph node-targeting delivery stability after lyophilization induce potent and persistent immune responses [J]. mBio, 2024, 15: e0177523.

[70] Attili-Qadri S, Karra N, Nemirovski A, et al. Oral delivery system prolongs blood circulation of docetaxel nanocapsules *via* lymphatic absorption [J]. Proc Natl Acad Sci U S A, 2013, 110: 17498-17503.

[71] Jiang K, Tian KS, Yu YF, et al. Kupffer cells determine intrahepatic traffic of PEGylated liposomal doxorubicin [J]. Nat Commun, 2024, 15: 6136.

[72] He CB, Yin LC, Tang C, et al. Multifunctional polymeric nanoparticles for oral delivery of TNF-α siRNA to macrophages [J]. Biomaterials, 2013, 34: 2843-2854.

[73] Shashni B, Tajika Y, Ikeda Y, et al. Self-assembling polymer-based short chain fatty acid prodrugs ameliorate non-alcoholic steatohepatitis and liver fibrosis [J]. Biomaterials, 2023, 295: 122047.

[74] Gao Q, Chen NX, Li BY, et al. Natural lipid nanoparticles extracted from *Morus nigra* L. leaves for targeted treatment of hepatocellular carcinoma *via* the oral route [J]. J Nanobiotechnology, 2024, 22: 4.

[75] Miao YB, Chen KH, Chen CT, et al. A noninvasive gut-to-brain oral drug delivery system for treating brain tumors [J]. Adv Mater, 2022, 34: e2202282.

[76] Zhang C, Zhao X, Zhang J, et al. Dual-modified brain-targeting lipid polymer micelle delivery of anti-miRNA-21 for achieving oral treatment of glioma [J]. J Drug Delivery Sci Technol, 2024, 96: 105721.

[77] Yang Y, Chu YX, Li C, et al. Brain-targeted drug delivery by *in vivo* functionalized liposome with stable D-peptide ligand [J]. J Control Release, 2024, 373: 240-251.

[78] Kandimalla R, Aqil F, Alhakeem SS, et al. Targeted oral delivery of paclitaxel using colostrum-derived exosomes [J]. Cancers (Basel), 2021, 13: 3700.

[79] Yang L, Li HJ, Luo AH, et al. Macrophage membrane-camouflaged pH-sensitive nanoparticles for targeted therapy of oral squamous cell carcinoma [J]. J Nanobiotechnology, 2024, 22: 168.

[80] Kübler E, Albrecht H. Large set data mining reveals overexpressed GPCRs in prostate and breast cancer: Potential for active targeting with engineered anti-cancer nanomedicines [J]. Oncotarget, 2018, 9: 24882-24897.

[81] Gooneh-Farahani S, Naghib SM, Naimi-Jamal MR, et al. A pH-sensitive nanocarrier based on BSA-stabilized graphene-chitosan nanocomposite for sustained and prolonged release of anticancer agents [J]. Sci Rep, 2021, 11: 17404.

[82] Hossain S, Kneiszl R, Larsson P. Revealing the interaction between peptide drugs and permeation enhancers in the presence of intestinal bile salts [J]. Nanoscale, 2023, 15: 19180-19195.

[83] Li L, Yang LQ, Li MM, et al. A cell-penetrating peptide mediated chitosan nanocarriers for improving intestinal insulin delivery [J]. Carbohydr Polym, 2017, 174: 182-189.

[84] Xue LL, Zhao G, Gong NQ, et al. Combinatorial design of siloxane-incorporated lipid nanoparticles augments intracellular processing for tissue-specific mRNA therapeutic delivery [J]. Nat Nanotechnol, 2025, 20: 132-143.

[85] Lamson NG, Berger A, Fein KC, et al. Anionic nanoparticles enable the oral delivery of proteins by enhancing intestinal permeability [J]. Nat Biomed Eng, 2020, 4: 84-96.

[86] Srinivasan SS, Alshareef A, Hwang AV, et al. RoboCap: Robotic mucus-clearing capsule for enhanced drug delivery in the gastrointestinal tract [J]. Sci Robot, 2022, 7: eabp9066.

[87] Zhu SQ, Chen SX, Gao Y, et al. Enhanced oral bioavailability of insulin using PLGA nanoparticles co-modified with cell-penetrating peptides and engrailed secretion peptide (Sec) [J]. Drug Deliv, 2016, 23: 1980-1991.

[88] Wu JZ, Williams GR, Li HY, et al. Insulin-loaded PLGA microspheres for glucose-responsive release [J]. Drug Deliv, 2017, 24: 1513-1525.

[89] Eweje F, Ibrahim V, Shajii A, et al. Self-assembling protein nanoparticles for cytosolic delivery of nucleic acids and proteins [J]. Nat Biotechnol, 2025. DOI: 10.1038/s41587-025-02664-2.

[90] Sand KMK, Bern M, Nilsen J, et al. Unraveling the interaction between FcRn and albumin: Opportunities for design of albumin-based therapeutics [J]. Front Immunol, 2014, 5: 682.

[91] Tan XY, Jia F, Wang P, et al. Nucleic acid-based drug delivery strategies [J]. J Control Release, 2020, 323: 240-252.

[92] Zhang J, Tang C, Yin CH. Galactosylated trimethyl chitosan-cysteine nanoparticles loaded with Map4k4 siRNA for targeting activated macrophages [J]. Biomaterials, 2013, 34: 3667-3677.

[93] Jin YL, Zhang BL, Li JR, et al. Bioengineered protein nanocarrier facilitating siRNA escape from lysosomes for targeted RNAi therapy in glioblastoma [J]. Sci Adv, 2025, 11: eadr9266.