渗透增强剂在口服肽类药物中的应用

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摘要: 肽类药物具有高效性、高特异性、低毒性, 被广泛应用于多种疾病的临床治疗。由于肽类药物胃肠道渗透性低, 易被酶降解, 加之诸多生理屏障, 口服生物利用度极低, 通常采用注射给药。但与便利性更高、患者依从性更好的口服给药相比, 注射给药的依从性较差, 易出现不良反应。近年大量研究集中于基于渗透增强剂 (penetration enhancers, PEs) 的促渗技术以提高肽类药物的口服生物利用度。本文综述了常用的PEs包括表面活性剂 (辛酸钠、癸酸钠、烷基糖苷、胆盐)、螯合剂、壳聚糖、细胞穿透肽等的作用机制及临床应用情况, 并总结了相关专利技术 (Eligen™、TPE™、GIPET™、POD™、Peptelligence™), 促进口服肽类制剂的研发和临床转化。

关键词: 口服肽类药物; 渗透增强剂; 作用机制; 临床应用; 专利技术

中图分类号: R943 **文献标识码**: A **文章编号**: 0513-4870(2026)06-2108-15

Application of penetration enhancers in oral peptide drugs

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Abstract: Peptide therapeutics are characterized by high potency, exquisite specificity, and low toxicity, and have therefore been widely adopted for the clinical management of diverse diseases. However, their inherently low gastrointestinal permeability, rapid enzymatic degradation, and multiple physiological barriers collectively result in extremely low oral bioavailability, necessitating parenteral administration. Compared with the more convenient and patient-compliant oral route, chronic injection is associated with poor adherence and an increased incidence of adverse reactions. In recent years, extensive research has focused on permeation enhancers (PEs) based strategies to improve the oral bioavailability of peptide drugs. This review systematically summarizes the mechanisms of action and clinical applications of representative PEs-including surfactants (sodium caprylate, sodium caprate, alkyl glycosides, bile salts), chelating agents, chitosan and cell-penetrating peptides. It also summarizes related patented technologies (Eligen™, TPE™, GIPET™, POD™, Peptelligence™) to facilitate the development and clinical translation of oral peptide formulations.

Key words: oral peptide drug; permeation enhancer; mechanisms of action; clinical application; proprietary technology

肽类药物生物活性高、特异性强、生物相容性好, 常用于多种疾病的治疗, 如糖尿病、短肠综合征、骨质疏松症等。口服肽类药物相较于注射剂具有高便利性, 高依从性, 但因其自身理化性质及胃肠道生理屏障的影响, 口服生物利用度极低。渗透增强剂 (penetration enhancers, PEs) 能促进药物穿越细胞膜进入细胞, 提升药物在肠黏膜中的渗透和吸收, 目前已在胰岛素、奥曲肽、鲑鱼降钙素等肽类药物中有了较多的应用。

收稿日期: 2025-09-02; 修回日期: 2026-01-08.

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DOI: 10.16438/j.0513-4870.2025-1042

本文介绍了口服肽类药物所面临的问题, 渗透增强剂的促渗机制及临床应用情况, 并总结了相关专利技术(Eligen™、TPE™、GIPET™、POD™、Peptelligence™), 为PEs在口服肽类制剂的研发和临床转化提供新的认识。

1 口服肽类药物的优势及面临的挑战

1.1 口服肽类药物的优势

多肽通常是由2～50个氨基酸组成的具有特定空间结构的化合物, 具有生物活性高、特异性强、毒性低、免疫原性低[1,2]等优点, 被应用于多种疾病的治疗。目前全球市场上有80多种肽类药物, 临床开发150多种肽和临床前研究约600种肽[3]。然而, 肽类药物胃肠道渗透性低且易被酶降解, 通常采取注射给药, 但是患者的依从性较差[1]。对于需要长期重复给药的患者, 频繁给药使得患者感染风险极大增加[4]。与注射相比, 口服肽递送患者依从性更好, 便利性更高。

1.2 口服肽类药物面临的挑战

肽类药物分子质量高、亲水性强, 在肠道中溶解度有限、半衰期短、易被酶降解, 加之胃肠道生理屏障的影响 (图1), 导致其口服生物利用度极低[4-12]。此外, 口服给药过程中, 药物易受肝首过效应的影响, 药物利用率低。

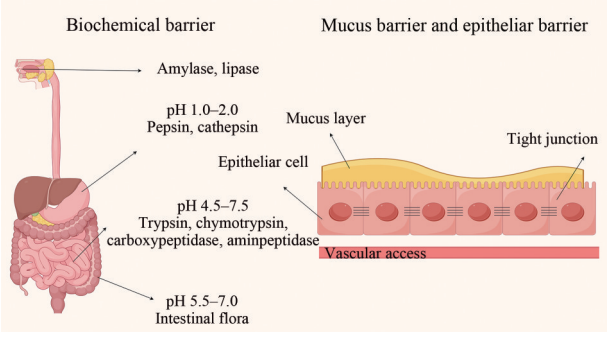


Figure 1 Gastrointestinal physiological barrier. Created with Figdraw

1.2.1 肽类药物稳定性

肽类药物通常具有较差的化学稳定性, 容易被酸、碱、高温或有机溶剂等因素破坏, 从而失去活性。此外, 多肽链本身的结构也会影响其稳定性, 使其在体内快速降解。

1.2.2 生理屏障

1.2.2.1 生化屏障 肽类药物进入胃肠道后会遇到各种消化酶的攻击, 胃中胃蛋白酶、小肠中的多种蛋白水解酶 (胰蛋白酶、羧肽酶、二肽基肽酶-4等)、结肠中的微生物蛋白酶等[5,8,12-14]。胃肠道中不同部位的pH差异较大, 胃内1.0～2.0, 小肠4.5～7.5, 结直肠5.5～7.0[15-18]; 这种多变的pH梯度易导致药物变性甚至失去活性[4,19]。

1.2.2.2 黏液屏障 消化道黏液覆盖整个胃肠道, 呈现黏弹性凝胶网状结构, 可有效清除潜在有害物质, 同时对药物的摄取显著降低[20-24]。此外, 黏液能够与存在于黏膜表面的物质等发生多种低亲和力的相互作用 (静电相互作用、氢键、疏水相互作用等), 减缓药物扩散[8,25-27]。

1.2.2.3 上皮屏障 药物穿过黏液层后, 主要通过跨细胞和细胞旁途径进入上皮细胞[18]。前者依赖特定细胞的内吞, 生物利用度低; 后者受紧密连接、黏附连接和桥粒构成的致密屏障限制, 肽类药物难以通过[13,23,28,29]。

2 渗透增强剂的分类与作用机制

渗透增强剂是一类能够促进药物分子穿越细胞膜并进入细胞的化合物, 能提升药物在肠道黏膜的渗透性和吸收率[30-33]。PEs的作用机制 (图2) 基于可逆的物理作用[34], 如提高细胞膜流动性、降低黏液黏度、短暂打开紧密连接、瞬时破坏消化道上皮细胞的完整性、延长制剂滞留时间等[5,15,29,35-38]。

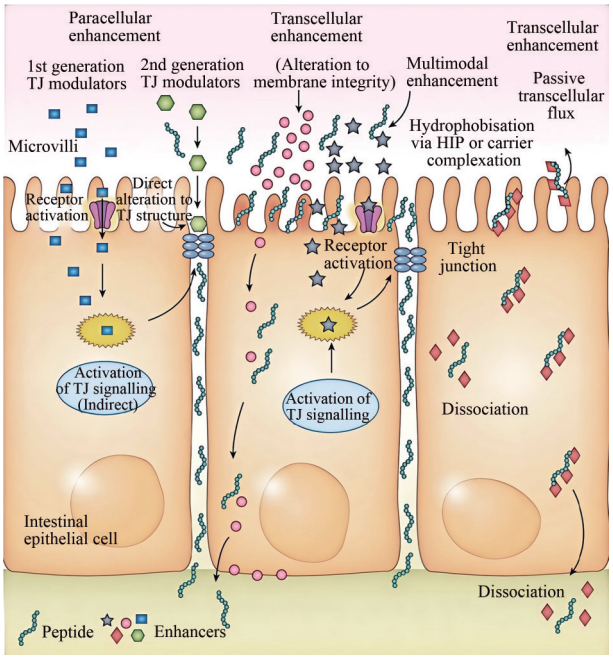


Figure 2 Mechanism of action of penetration enhancers (PEs). TJ: Tight junction; HIP: Hydrophobic ion pairing. Reprinted with permission from Ref. 38 Copyright ©2016 Elsevier

PEs可以分为表面活性剂、螯合剂、胆盐、烷基糖苷、阴离子和阳离子聚合物、脂肪酸及其衍生物、细胞穿透肽等[5] (表1)。理想的PEs应该具有安全无毒、无刺激性、无过敏性等特性[5,39], 但是PEs提高肽类药物吸收是非特异性的, 可能会增加将毒素或过敏原输入的风险[1,40], 目前只有少数渗透增强剂展现出足够的安全性和有效性可进入临床试验[5,39,41]。

Table 1 Common penetration enhancers and their mechanisms of action. TDM: *N*-Tetradecyl-*β*-*D*-maltoside; DDM: *N*-Dodecyl-*β*-*D*-maltoside; EDTA: Ethylenediaminetetraacetic acid; DTPA: Diethylenetriaminepentaacetic acid; Tat: *trans*-Activator of transcription peptide

Category	Example	Mechanism of action
Surfactants	Sodium dodecyl sulfate, laureth-9, sodium taurodihydrofusidate, poly oxyethylene ethers	Perturbation of intercellular lipids, lipid order, orientation and fluidity. Inhibition of efflux mechanisms
Fatty acids and their derivatives	Octanoic acid, decanoic acid, oleic acid, linoleic acid, acyl carnitines, mono and di-glycerides	Increase fluidity of phospholipid membranes, contraction of actin myofilaments, opening of TJ
Bile salts	Sodium deoxycholate, sodium taurocholate, sodium glycocholate, sodium glycodeoxycholate	Form reverse micelles and disrupt membrane, open up TJ, enzyme inhibition and mucolytic activity
Alkyl polyglycoside	TDM, DDM	Accelerate biofilm flow and enhance cell membrane endocytosis, briefly opening up TJ between cells
Calcium-chelating agent	EDTA, DTPA	Interferes with Ca^{2+}, chelation disrupts intracellular junctions and decreases transepithelial electrical resistance
pH adjuster	Citric acid, salicylic acid, tartaric acid	Because of the pH change, local proteases are inhibited, acting as a chelating agent to improve paracellular transport
Cationic polymer	Chitosan and its derivatives	Combined effect of mucoadhesion and opening of TJ *via* ionic interactions with the cell membrane
Anionic polymer	Polyacrylic acid derivatives	Combined effect of enzyme inhibition and opening of TJ through removal of extracellular Ca^{2+}
	N-Acetylcysteine	Reduce the viscosity of mucus layer by breaking down disulfide bonds
Cell penetrating peptide	Tat, penetratin	Entry into cells through endocytosis and direct translocation

2.1 表面活性剂

2.1.1 辛酸钠及其衍生物

辛酸钠 (sodium caprylate, C8) 是饱和8碳中链脂肪酸, 可作PEs的辛酸钠衍生物主要有*N*-(8-(2-羟基苯甲酰基)-氨基)辛酸钠 [sodium *N*-(8-(2-hydroxybenzoyl) amino) caprylate, SNAC]、*N*-(8-(2-羟基-5-氯苯甲酰基)-氨基)辛酸钠 [sodium *N*-(8-(2-hydroxy-5-chlorobenzoyl) amino) caprylate, 5-CNAC]、*N*-(8-(2-羟基-4-甲氧基苯甲酰基)-氨基)辛酸钠 [sodium *N*-(8-(2-hydroxy-4-methoxybenzoyl) amino) caprylate, 4-MOAC] 等 (图3, **1**～**3**)。

SNAC分子上的疏水芳香基团 (2-羟基苯甲酰氨基) 可与多肽发生疏水相互作用并改变其构象, 形成亲脂性更高的SNAC-多肽复合物, 增加其在细胞膜中的溶解度, 提高跨细胞转运效率[42-44]。在与肝素、胰岛素等复合物中可观察到这种非共价相互作用。此外, 辛酸钠通过提高膜流动性并诱导胞内蛋白外排, 增强胃肠道上皮通透性, 提高生物利用度。

SNAC能有效地促进胰岛素、肝素等的口服吸收, 安全性良好[45]。4-MOAC可促进的大鼠和猴对甲状旁腺激素 (parathyroid hormone, PTH) 的口服吸收, 相对生物利用度为2.1%。5-CNAC可与鲑鱼降钙素 (salmon calcitonin, sCT) 联合制成口服制剂[46], 安全、有效且耐受性良好, 绝对生物利用度为0.5%～1.4%[47-49]。

2.1.2 癸酸钠及其衍生物

癸酸钠 (sodium caprate, C10) 是饱和10碳中链脂肪酸 (图3, **4**), 与SNAC同为脂肪酸衍生物但作用机制不同。C10可激活磷脂酶, 升高三磷酸肌醇并触发Ca^{2+}释放; 肌动蛋白收缩瞬时打开紧密连接[24,41,50,51] (图4)。高剂量C10可诱导温和且可逆的膜扰动, 辅助药物跨膜进入胞内[52]。C10与细胞间紧密连接处的各种离子螯合造成的肠细胞损伤具有可逆性, 毒性较小[53]。

肽的分子质量大小、脂化程度、理化特性及吸收部位等均会影响C10促进吸收等能力, 例如, FITC标记葡聚糖-4生物利用度比MEDI7219肽高2～4倍[54,55]; C10可使GLP-1类似物生物利用度提高35～40倍, 脂化程度与肠道吸收增强呈正相关[56]。C10联合依比拉肽渗透速率空肠1.5倍, 结肠3.84倍。

2.1.3 烷基糖苷类

烷基糖苷 (alkyl polyglucoside, APG) 可瞬时提高膜流动性并加强细胞膜内吞作用, 加快细胞对药物的摄取可逆性打开紧密连接, 增大细胞旁路通量[57-59]。十二烷基麦芽糖苷 (*n*-dodecyl-*β*-*D*-maltopyranoside, DDM, 图3, **5**) 与十四烷基麦芽糖苷 (*n*-tetradecyl-*β*-*D*-maltopyranoside, TDM, 图3, **6**) 已被证实可显著增强小分子及多肽类药物的口服吸收, 应用较为广泛。

Arnold等[60]证实DDM对降钙素和生长激素的促渗效应随预处理时间延长而迅速衰减, 紧密连接的开放短暂且可逆。FITC-胰岛素荧光标记实验证明, TDM除瞬时可逆松弛紧密连接外, 还能加速膜流动并增强内吞。大量毒性研究显示, APG会造成黏膜损伤, 损伤程度与APG的碳链长度、单聚糖基团及浓度有关。

2.1.4 胆盐类

胆盐 (图3, **7**～**10**) 可螯合Ca^{2+}, 破坏细胞之间的

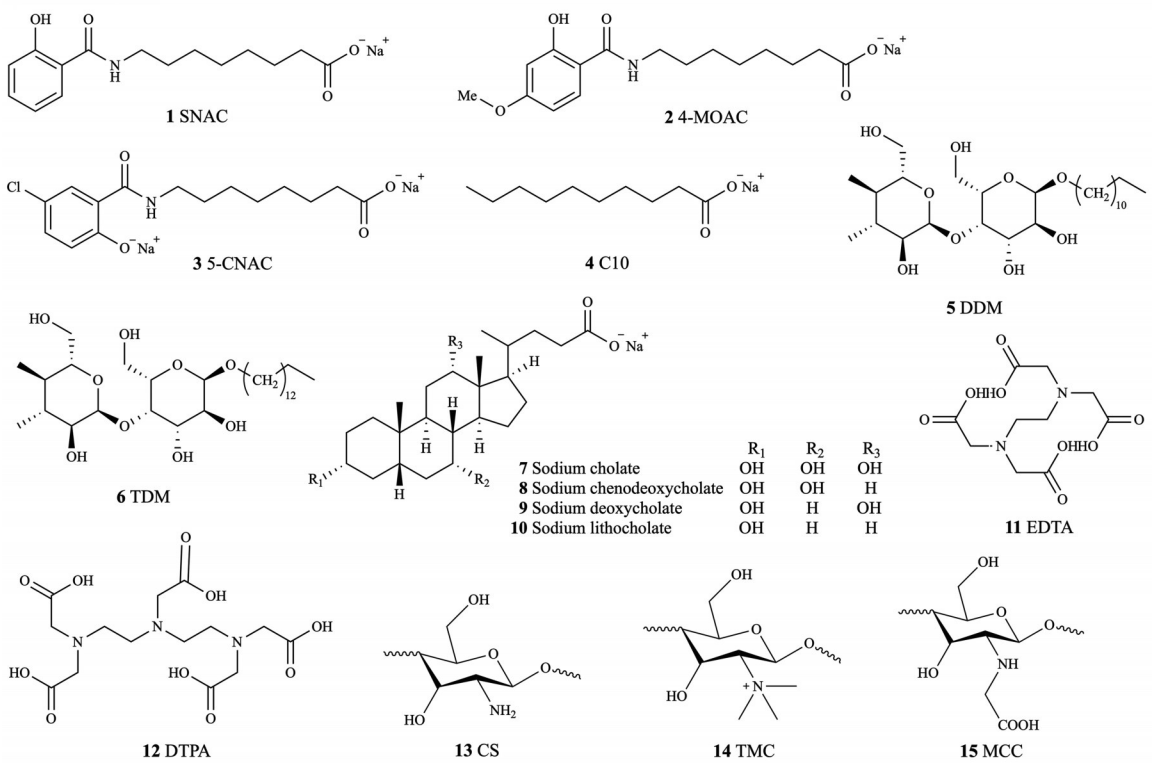


Figure 3 Chemical structure of common PEs. SNAC: Sodium *N*-(8-(2-hydroxybenzoyl) amino) caprylate; 4-MOAC: Sodium *N*-(8-(2-hydroxy-4-methoxybenzoyl) amino) caprylate; 5-CNAC: Sodium *N*-(8-(2-hydroxy-5-chlorobenzoyl) amino) caprylate; C10: Sodium caprate; CS: Chitosan; TMC: *N*-Trimethylchitosan chloride; MCC: *mono*-*N*-Carboxymethyl chitosan. Created with Chemdraw

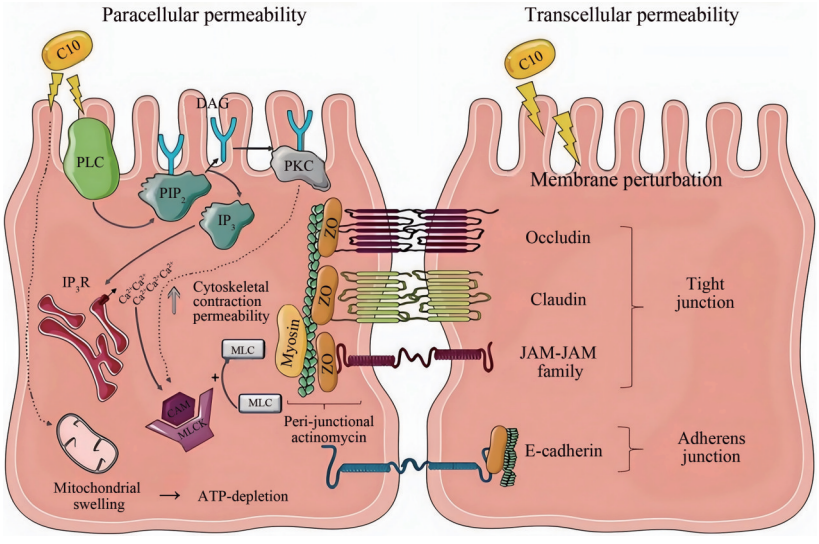


Figure 4 Mechanism of action of C10. DAG: Diacylglycerol; PLC: Phospholipase C; PIP_2: Phosphatidylinositol 4,5-bisphosphate; IP_3: Inositol 1,4,5-trisphosphate; PKC: Protein kinase C; IP_3R: IP_3 receptor; MLC: Myosin light chain; ZO: Zonula occludens. Reprinted with permission from Ref. 52 Copyright © 2019 Multidisciplinary Digital Publishing Institute

紧密连接, 增加细胞旁渗透性[61]。低浓度时, 其可形成胶束或脂质体, 增溶促渗, 而浓度高于临界胶束浓度时, 胆盐可能会与细胞膜的磷脂结合, 致使膜溶解[62,63]。此外, 胆盐可以降低黏附在所有黏膜表面的黏液层的黏度和弹性, 从而增加上皮膜渗透性[64]。

Choi 等[65]研究发现 Jaspine B 的口服生物利用度为6.2%, 胆汁耗竭大鼠中降至1.6%, 在补充牛磺胆酸盐后增至41.2% (正常) 和23.5% (胆汁耗竭), 证实胆盐的促渗作用。Chen等[66,67]研究发现胆酸钠对甲氨蝶呤渗透存在浓度依赖效应, 高浓度下, 紧密连接打开, 渗透性增加; 低浓度下, 跨细胞渗透降低。胆盐对黏膜具有不可逆损伤和纤毛毒性, 其在高浓度下会破坏细胞膜结构[64]。

2.1.5 其他

常用表面活性剂类PEs还包括十二烷基硫酸钠、聚山梨酯、月桂酸酯及酰基肉碱等, 其可瞬时开放紧密连接或提高药物亲脂性以提升肠道渗透吸收。Unigene公司在开发的口服PTH中加入月桂肉碱, 其II期临床疗效优于注射剂。

2.2 螯合剂

螯合剂可直接通过降低膜完整性、增加膜流动性、螯合Ca^{2+}打开紧密连接、或改变肠道pH, 抑制上皮转运蛋白等方式来增强药物渗透。如乙二胺四乙酸盐(ethylenediaminetetraacetic acid, EDTA, 图3, **11**) 可调节Ca^{2+}含量, 影响细胞间紧密连接, 并降低跨上皮电阻, 促进药物渗透[5,10]。此外, EDTA为细胞旁PEs, 与跨细胞PEs相比, 细胞旁PEs增加低分子质量亲水肽肠道吸收的潜力更大[68]。

二乙烯三胺五乙酸 (diethylenetriaminepentaacetic acid, DTPA, 图3, **12**) 为新型螯合剂, 具有蛋白酶抑制活性, 可螯合细胞外Ca^{2+}破坏黏连[11], 打开细胞间的紧密连接。Su等[69,70]用DTPA、壳聚糖和聚γ-谷氨酸组成纳米递送系 (γ-PGA-DTPA) 口服输送胰岛素, 相对口服生物利用度约20%, 其中γ-PGA-DTPA抑制了肠道蛋白酶, 并产生了短暂和可逆的细胞旁渗透性增强。

2.3 壳聚糖及其衍生物

壳聚糖 (chitosan, CS, 图3, **13**) 在中性和碱性下均不溶, CS在弱酸中质子化, 其与带负电荷的紧密连接蛋白相互作用, 瞬时开放上皮细胞间的紧密连接[71,72]。CS的生物黏附特性使其能够与肠道上皮结合并增加药物停留时间, 加之其打开紧密连接及酶抑制作用, 药物吸收增强[73]。此外, 壳聚糖还可形成纳米颗粒 (nanoparticles, NPs), 增强药物的生物利用度[74]。

壳聚糖在中性pH下因缺乏良好的溶解性而无效, 引入烷基或羧甲基等修饰基团提高其溶解性, 如*N*-三甲基壳聚糖氯化物 (*N*-trimethylchitosan chloride, TMC, 图3, **14**) 和单-*N*-羧甲基壳聚糖 (*mono*-*N*-carboxymethyl chitosan, MCC, 图3, **15**)[75-77]。修饰后的壳聚糖在更宽的pH和浓度范围内表现出高水溶性[78,79]。TMC可与阴离子大分子形成配合物, 在水环境和中性pH值下与阳离子或中性化合物形成凝胶或溶液[76,77], 可显著增加中性和阳离子肽在Caco-2肠上皮中的渗透。10% TMC可使奥曲肽的生物利用度从1.7%提高到25%, 吸收增强14.5倍。MCC能够在水环境中和中性pH值下与阴离子大分子药物形成黏弹性凝胶[77]。3%的低黏度MCC可使低分子质量肝素的AUC和C_{max}分别增加7.0和5.4倍[80]。

此外, 巯基化的壳聚糖促吸收, Pratap-Singh等[81]研究了巯基烟酸激活硫醇化壳聚糖 (MNA-TG-CS), 与CS和TG-CS相比, 细胞摄取率提高1.5和4.4倍, 表观渗透系数 (apparent permeability coefficient, Papp) 提高了40%和150%。

2.4 细胞穿透肽

细胞穿透肽 (cell-penetrating peptide, CPP) 是一类由5～30个氨基酸组成的短肽, 富含碱性氨基酸, 一般带正电荷或具两亲性[82], 具有细胞膜穿透能力。CPP被分为阳离子肽、阴离子肽、两性肽和疏水肽。阳离子CPP可与细胞膜上带负电荷的羧基、磷酸和硫酸基团发生静电相互作用, 扰乱膜结构, 内吞进入细胞; 疏水肽可通过与细胞膜的疏水区域发生疏水相互作用, 直接易位进入细胞, 但该机制具体方式目前尚不完全明确[83-85]。

Shi等[86]结合绿色荧光蛋白GFT和细胞穿透肽Tat, 构建了GFP-Tat融合蛋白, 该结构输送效率和稳定性提高, 体内肿瘤保留率提高7.79倍。Lakkadwala等[87]开发了一种转铁蛋白和细胞穿透肽Pen介导的脂质体, 能穿越血脑屏障, 靶向胶质母细胞瘤, 可使肿瘤部位多柔比星和厄洛替尼的累积分别增强12和3.3倍。

3 渗透增强剂的在口服肽类药物中的应用

3.1 SNAC

美国Emisphere开发的SNAC不需要保护性肠道涂层, 是一种跨细胞、基于载体的PEs[52]。2009年SNAC被美国食品药品监督管理局 (FDA) 授予“一般认为安全”的地位[38,52,88]。2014年, FDA首次批准了氰钴胺/SNAC口服制剂用于维生素B_{12}缺乏性贫血[88-90]。SNAC首先被用于开发肝素的口服制剂, 在I/II期研究中其与皮下肝素具有相似的活性, 但III期试验中活性并不优越, 其开发被停止[52,91]。

Buckley等[92]研究了semaglutide/SNAC片剂的吸收, 与大多数药物在肠道中吸收不同, semaglutide在胃中吸收且吸收区域仅限于片剂附近。Semaglutide片在胃中被完全侵蚀, SNAC通过局部缓冲作用防止semaglutide被酶降解, 并短暂增强吸收[9,14,93,94] (图5)。Granhall等[95]的两项随机、双盲、安慰剂对照试验显示semaglutide口服制剂安全且耐受性良好, 大多数不良事件为轻度胃肠道疾病。Semaglutide口服制剂已于2019年被FDA批准用于治疗2型糖尿病[1,5], 这是第一个获批上市的口服肽类药物。

Fattah等[96]研究发现SNAC对奥曲肽促渗效果存在区域差异, 结肠效果最好, Papp增加了1.5～2.1倍。Weng等[97]利用Eudragit®S100包埋SNAC/胰岛素微球, Papp增加了6.6倍, 降血糖活性持续超10 h, 口服生物利用度约为6.3%。Itin等[98]将替度鲁肽与SNAC结合, 替度鲁肽在胃中吸收, 血浆水平5 min内迅速升高, 15 min达到C_{max}。Tran等[99]开发了含有SNAC和GIP/

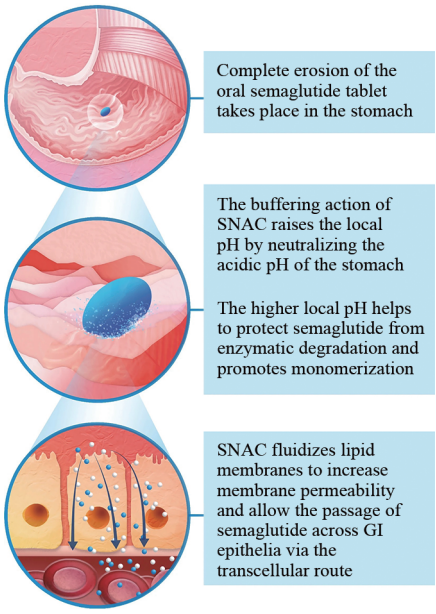


Figure 5 Mechanism of action of SNAC in Semaglutide tablets. GI: Gastrointestinal. Reprinted with permission from Ref. 94 Copyright © 2022 Springer Nature

GLP1 双重激动剂肽 (LY) 的黏膜黏附片剂, 定位递送肽并减少胃中的稀释效应, 其溶出速率比 SNAC 对照片慢, 但口服生物利用度相似。

离子液体 (ionic liquid, IL) 是既能提高药物的溶解度和稳定性, 又能改善药物通过黏液的扩散。IL 可通过增强细胞膜的流动性、破坏细胞膜的完整性或打开紧密连接来增强药物的肠道上皮运输[100]。诺和诺德的研发团队[101]利用 SNAC 的有机阴离子 *N*-(8-(2-羟基苯甲酰基)氨基)辛酸酯和胆碱作为反离子, 开发了一种 IL 制剂——CHONAC 递送 GLP-1 类似物。CHONAC 负载能力高、释放快、起效快, 绝对生物利用度与片剂相当。基于 SNAC 的 IL 既保留了 SNAC 的促吸收作用又解决了固体片剂释放慢、载药低的问题, 为口服递送提供了新平台。

3.2 癸酸钠

C10 主要通过短暂打开紧密连接和可逆地增加膜流动性, 通过细胞旁和跨细胞途径促进肽的吸收[50,52,53]。C10 的渗透增强作用会受到浓度、肽的物理化学性质及胃肠道环境的影响, 如大鼠对 FITC 标记葡聚糖-4 的吸收随着 C10 浓度的增加而增加[102]; C10 仅在高浓度和 pH 值 7.4 时, 对依那普利拉有渗透增强作用[55]。

Vetter 等[103]基于磺化聚卡波非和谷胱甘肽结合 C10 设计了小肠靶向的口服磺达肝素, 肠黏膜吸收提高 4.1 倍, 绝对生物利用度提高 6.2 倍。LY 肽与 C10 联用可使迷你猪相对生物利用度为达到 2%[104]。Tran 等[105]开发了基于 C10 和 SNAC 的速释片剂递送 LY 肽, 口服生物利用度分别为 5.7% 和 4.2%。Niu 等[106]发现 SNAC 及 C10 合用对 GLP-1 类似物和 PCSK9 抑制剂有协同作用促吸收效果, 其 AUC 较 SNAC 增加 22%、51%, 较 C10 增加 34%、65%。但人体中的 SNAC/C10 制剂的效果仅为 SNAC 制剂的 0.94 倍。

印度 Biocon 的 Tregopil 胰岛素 (IN-105) 是聚乙二醇化胰岛素, 其通过酰胺键将 PEG 附着在胰岛素的 Lysβ29 的 ε-氨基上, IN-105 利用 C10 增强吸收, 治疗窗口广泛, 起效快[107-109]。IN-105 已完成 11 项 I 至 III 期临床试验, 涵盖印度、美国和欧洲, 参与者包括正常健康志愿者 (4 项试验)、T1DM 患者 (2 项试验) 及 T2DM 患者 (5 项试验)[110]。IN105 已完成 T1DM 患者的 I 期临床和 T2DM 患者的 III 期临床, 其改善糖化血红蛋白 (hemoglobin A1c, HbA1c) 效果没有显著更优, 但患者餐后 1 h 血糖显著改善, 没有严重不良反应或者低血糖[110]。Biocon 正把开发重心放在餐后血糖控制和减少低血糖风险的方向, 而并非追求传统 HbA1c 优效。

3.3 烷基糖苷

TDM 可通过瞬时扰动肠上皮屏障, 提高其在胃肠道的跨膜通透性; 0.125% TDM 可使依诺肝素相对生物利用度增加 2.4 倍, 0.25% TDM 增加 3.5 倍[111]。Petersen 等[112]证实 TDM 对降钙素具有显著促渗作用, 使其绝对生物利用度从 1.0% 提高到 4.6%。口服利拉鲁肽制剂为 DDM、GLP-1 激动剂、胆盐的静电络合纳米胶束, 胆盐胶束可增强肽的稳定性, 并通过 ASBT 介导的途径增强药物的肠吸收, DDM 进一步优化胶束结构, 协同提升药物的稳定性与口服生物利用[113]。

Intravail® 利用 DDM 作 PEs, Intravail® 结合瘦素类似物 [(*D*-Leu-4) OB3] 的鼻喷剂存在双相吸收特征 (鼻黏膜, 胃肠道)[114,115], 0.25% DDM 有较好的促进口服吸收效果, (*D*-Leu-4) OB3 使用剂量可减少至 1/10。Maggio 等[116]研究发现浓度为 0.5% Intravail® 能改善其半衰期且能将奥曲肽的口服相对生物利用度从 1.0% 提高至 4.0%, 但是更高浓度的 Intravail® 不会进一步增强。

3.4 胆盐

胆盐通过改变膜流动性、破坏紧密连接、抑制酶活性、形成胶束或脂质体等方式增强药物的渗透[63]。Niu 等[117]利用大豆磷脂酰胆碱和胆盐制成脂质体口服递送胰岛素, 该脂质体胃肠道滞留时间长、细胞摄取高效, 毒性低, 口服生物利用度 10.2%, 有持续降血糖作用。Wang 等[118]利用熊脱氧胆酸钠作膜材制备了包载硅素的脂质体, 口服可有效抑制酒精引起的肝脏损伤、氧化应激和脂肪积累。

Zhou 等[119]设计并合成了一种基于 PLGA、离子液体和脱氧胆酸的纳米颗粒 (DCA-PLGA@IL) 递送重

组人类生长激素。DCA-PLGA@IL室温稳定性好, 且具有高封装效率和体外完全释放; 大鼠口服生物利用度提高2.09倍。

3.5 壳聚糖

壳聚糖可瞬时打开紧密连接, 并通过静电吸附促进药物与细胞膜负电荷的相互作用, 提高跨膜转运效率。CS兼具PEs与纳米载体双重功能[120], 可显著提高药物在胃肠道中的稳定性和摄取率。Sonaje等[121]用CS/γ-PGA NPs负载胰岛素, 冻干后装入肠溶胶囊, 其口服生物利用度能达到20%。Guo等[122]利用生物素化三甲基化壳聚糖包载艾塞那肽, 其具有肠溶特性, 相对生物利用度比未修饰的高27倍。Yang等[123]以TMC封装艾塞那肽, 并用海藻酸钠提高其稳定性, 1 h内释放量达90%, 口服生物利用度为9.16%。

Maria等[124]用巯基乙酸和巯基烟酸修饰CS并用离子凝胶技术封装奥曲肽, 其黏膜黏附特性较CS提高了3和16倍, 后者口服生物利用度提高7.2倍。Ziebarth等[125]通过离子凝胶化制备壳聚糖纳米粒包封利拉鲁肽, 其可保护超过80%的利拉鲁肽在模拟胃液和肠液中不被降解。Lee等[126]开发了一种由有机黏土、壳聚糖和Eudragit®S100组成的纳米系统口服递送胰岛素, 该制剂pH敏感且增强了药物渗透性和吸收性, 显著降低了糖尿病大鼠的血糖水平。

3.6 细胞穿透肽

细胞穿透肽能通过细胞内吞作用和直接易位等机制促进药物的口服吸收, 安全性高。但是CPP易被胃肠道降解破坏, 常与纳米递送系统联用防止其降解。Li等[127]研究了含有细胞穿透肽SAR6EW的壳聚糖纳米颗粒递送胰岛素, 该制剂口服降血糖效果优于无SAR6EW的制剂。此外, 其可通过壳聚糖保护及SAR6EW竞争蛋白水解酶的双重作用保护胰岛素免受降解, 胰岛素留存率提高4倍。

Guo等[128]设计了带细胞穿透肽Tat的壳聚糖纳米颗粒 (Tat-CS-NPs) 口服递送胰岛素。对糖尿病大鼠研究表明, Tat-CS-NPs的降血糖效果是PVA-NPs的6.89倍, CS-NPs的1.79倍。Zhu等[129]利用细胞穿透肽Pen和具有N端硬脂化的分泌肽Sec联合修饰纳米颗粒, Sec-Pen-NPs的Caco-2细胞Papp是Pen-NPs的2倍; Sec-Pen-NPs的大鼠胰岛素的相对生物利用度是Pen-NPs 1.71倍。

4 渗透增强剂的临床研究与专利技术

目前仅有少数PEs技术兼具足够的安全性与有效性, 得以进入临床试验阶段; 相关专利技术包括Eligen™、TPE™、GIPET™、POD™、Peptelligence™等, 已上市或正处于临床研究阶段的代表性药物汇总于表2。

4.1 Eligen™技术

Eligen™由美国Emisphere开发, 主要是通过蛋白质构象的可逆变化及抑制药物的胃肠道降解发挥作用[130]。Emisphere的研究团队[91]认为, 他们的PEs是肽输送的“载体”(图6), 主要通过跨细胞途径运输药物。肽类药物和载体产生的非共价相互作用会改变药物的理化性质; 但这种非共价作用是可逆的, 当非共价复合物将药物经上皮细胞运输到血液循环后, 载体与药物

Table 2 Oral peptide drugs already marketed or in clinical development. R&D: Research and development; HTBT: Hefei Tianmai Biotechnology Development Co., Ltd.; Biolaxy: Shanghai Biolaxy Pharmaceutical Technology Co., Ltd.; sCT: Salmon calcitonin; C8: Sodium caprylate; Cap-NPs: Bioadhesive calcium phosphate nanoparticles; MCFA: Medium-chain fatty acid

Drug code	R&D company (Country)	Durg	Technology/permeation enhancer	Development stage
Rybelsus®	Novo Nordisk (Denmark)	Semaglutide	Eligen™: SNAC	Approved
Mycapssa®	Chiasma (USA)	Octreotide	TPE™: C8	Approved
Korsuva™	Cara Therapeutics (USA) Enteris Biopharma (USA)	Difelikefalin	Peptelligence™	Approved
ORMD-0801	Oramed (Israel) HTBT (China)	Insulin	POD™: EDTA, bile salt	Oramed: Phase III completed, study suspended HTBT: Phase III completed, under regulatory review for marketing approval
SMC021	Novo Nordisk (Denmark)	sCT	Eligen™: 5-CNAC	Phase III completed, study suspended
TBRIA™	Enteris Biopharma (USA) Tarsa Therapeutics (USA)	sCT	Peptelligence™	Phase III
IN105	Biocon (India)	Insulin	GIPET™: C10	T1DM phase I T2DM phase III
OI338	Merrion (Ireland)	Insulin	GIPET™: C10	Phase II
Capsulin	Diabetology (USA)	Insulin	Axcess™: Aromatic alcohol	Phase II
Ovarest®	Enteris Biopharma (USA)	Leuprorelin	Peptelligence™	Phase II
Nodlin	Biolaxy (China)	Insulin	NOD™: Cap-NPs, bile salt or MCFA	Phase I
ORMD-0701	Oramed (Israel)	Leptin	POD™: EDTA, bile salt	Phase I
ORMD-0901	Oramed (Israel)	Exenatide	POD™: EDTA, bile salt	Phase I

分离, 药物恢复具有生物活性的原生构象。载体中应用最广泛的是SNAC、4-CNAB、SNAD、5-CNAB和4-MOAC[38], 目前为止Eligen™载体已经评估了胰岛素、肝素、人生长激素、肽YY3-36、sCT、PTH和GLP-1类似物的口服输送[37]。

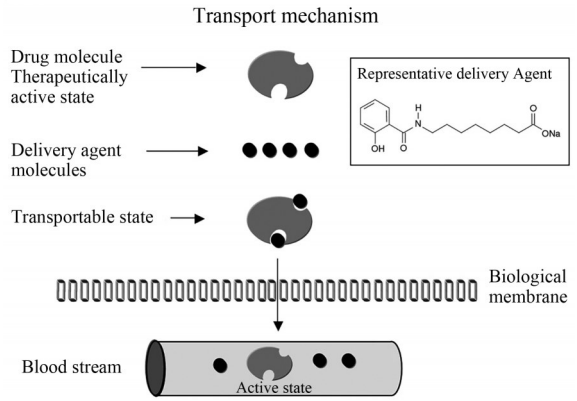


Figure 6 Eligen™ mechanism schematic diagram. Reprinted with permission from Ref. 91 Copyright © 2006 Springer Nature

Novo Nordisk公司利用SNAC开发了口服索马鲁肽 (Rybelsus®) 用于治疗2型糖尿病, 这是首个获批口服给药的GLP-1受体激动剂。在10项PIONEER临床试验中[131-146], 共9 543例成人2型糖尿病患者参与, Rybelsus®的疗效和安全性较好, 且HbA1c降幅大, 减重获益大[94]。但是Rybelsus®的生物利用度仅约1%, 其成本显著高于长效注射剂[95]。

SNAC是Eligen™技术最为先进的载体, 除Rybelsus®外, Novo Nordisk公司研发的新型GLP-a激动剂 (NNC0113-2023) 现处于I期临床; 双重GIP/GLP-1受体激动剂 (NNC0090-2746) 现已完成IIb期临床; 胰高血糖素/GLP-1受体共激动剂 (NNC9204-1177) 已完成I期临床, 但因其意料之外的安全信号已放弃其开发[147]; PCSK9抑制剂 (NNC0385-0434) 已完成II期临床。此外, 含有5-CNAC的sCT肠溶片 (SMC021) 现已完成III期临床研究, 但其未降低新发椎体骨折风险, 胃肠道不良事件发生率略高于安慰剂; 由于缺乏预防骨折的功效, 其研发最终停止[46-49,148-151]; 4-CNAB应用于胰岛素, I期临床试验已经完成[152]。

4.2 TPE™技术

美国Chiasma Pharmaceuticals开发的TPE™由制成冻干颗粒的亲水药物和疏水的油性悬浮液组成[153]。TPE™以C8为PEs, 打开紧密连接, 瞬时增强渗透[154]。由于肽水解酶在油中不表现出酶活性, 油性悬浮液可保护药物防止其降解。此外, 油相中的赋形剂可与生物膜相互作用, 引起额外的渗透增强效应。

Chiasma利用TPE™开发口服奥曲肽制剂 (Mycapssa®) 用于治疗肢端肥大症, 完成了3项III期临床试验及11项药理学和药代动力学I期研究, 并获得FDA批准上市[155]。I期临床试验显示20 mg口服制剂和0.1 mg奥曲肽注射剂具有等效的药代动力学参数, 且显著抑制了生长激素水平, 其相对口服生物利用度为0.7%[156]。奥曲肽胶囊的2项III期临床试验达到了主要终点, 但是达到终点所需的剂量是皮下注射的200倍以上, 成本较高[7,157]。

4.3 GIPET™技术

GIPET™由爱尔兰Merrion Pharmaceuticals开发, 主要包括基于中链脂肪酸的GIPET I、基于肠衣片或胶囊中配制的中链脂肪酸甘油酯的微乳液系统的GIPET II和基于中链脂肪酸衍生物的GIPET III[158]。GIPET™可形成胶束或囊泡, 其在肠道环境的影响下不断形成和重组; 只要药物与PEs在目标吸收区域共同释放并保持浓度高于CMC, 即可促进药物渗透[158]。此外, 肠溶衣可在肠内快速分解, 确保PEs和药物在适当浓度下共同释放, 改善肠道上皮细胞渗透。

Amory等[159]研发了基于GIPET™的Acyline口服制剂, 其I期临床研究表明, 其可以显著抑制正常男性的睾丸激素和促性腺激素水平, 而不会产生不良影响。此外, GIPET还被用于递送胰岛素、去氨加压素和低分子质量肝素[160], 口服低分子肝素相对生物利用度为3.9%～7.6%[52]; 基于GIPET™口服去氨加压素的平均生物利用度为2.4%, 而已上市的DDAVP®生物利用度仅有0.2%[5]。

口服胰岛素338 (I338) 是利用GIPET I技术将胰岛素与C10共配制成的片剂, Halberg等[161]进行了II期临床试验, 治疗效果与注射剂无显著差异, 可安全改善2型糖尿病患者的血糖控制; 但因商业原因, 诺和诺德最终决定终止该项目。Thomas等设计并制备了两种口服长效蛋白酶稳定胰岛素类似物OI338和OI320并利用GIPET I技术递送, OI338在IIa期临床试验血糖控制效果与胰岛素注射剂一致, 且无严重的不良事件[162], OI338使狗的口服生物利用度达到3.0%[163]。

4.4 POD™技术

POD™由以色列Oramed研究开发, 该技术分别将胰岛素、酶抑制剂、渗透增强剂 (EDTA、胆盐) 微球化; 各种微球注入肠溶胶囊, 形成双重保护。Oramed利用POD™开发的ORMD-0801是一种口服重组人胰岛素肠溶制剂, 生物利用度达18%, 疗效与皮下注射相当, 且不会增加体重和低血糖发生率。2023年1月, Oramed宣布ORMD-0801的III期临床试验结果没有达到主要终点和次要终点, Oramed随后停止了该药的2型糖尿病的

临床研究[164-168]。Oramed再次分析发现具有特定参数的患者亚群对口服胰岛素反应良好, HbA1c降低超过1%, 现计划在美国启动一项III临床试验; 合肥天麦生物已完成中国III期 (CTR20201644), 并于2023年4月申报上市 (受理号: CXSS2300021)。此外, 目前ORMD-0801正在进行用于治疗非酒精性脂肪性肝炎的临床II期研究和I期高胰岛素−高血糖钳形研究[169,170]。此外, Oramed还研发了基于瘦素的ORMD-0701和基于GLP-1类似物艾塞那肽的ORMD-0901, 现处于I期临床试验[171,172]; ORMD-0901在模型猪及模型犬中均表现出良好的耐受性且降血糖作用显著[165,173]。

4.5 Peptelligence™技术

Peptelligence™由Enteris研发, 是一种肠溶胶囊配方, 该配方有两种主要成分, 一种是表面活性剂PEs, 如酰基肉碱, 可打开紧密连接改善渗透性, 同时其也是强大的溶解剂; 另一种是柠檬酸, 它既是钙螯合剂和膜渗透增强剂又是增强吸收的pH调节剂和膜润湿/电荷分散剂[39,174]。

Enteris BioPharma利用Peptelligence™开发了用于治疗子宫内膜异位症的口服GnRH激动剂——亮丙瑞林片 (Ovarest®), 目前已完成IIa期临床研究[175]。Tarsa Therapeutics研发的口服sCT肠溶片 (TBRIA™), 其ORACAL试验评估了sCT的疗效和安全性, 其脊柱骨矿化改善优于鼻腔sCT喷雾剂[176]。TBRIA™已通过III期临床试验, 但因其缺乏显著疗效及鼻喷剂的安全警告, 未通过FDA审评, 目前项目处于搁置状态[36,150,177]。Korsuva™ (CR845/difelikefalin) 是由Cara Therapeutics与Enteris合作开发的选择性靶向外周*κ*-阿片类受体激动剂, 用于治疗与慢性肾病相关的中度至重度瘙痒, 2021年8月获得FDA批准上市[178,179], 首个获批的静脉抗瘙痒药。III期临床试验显示, 与接受安慰剂的患者相比, 使用Korsuva™治疗的患者瘙痒强度明显降低, 瘙痒相关生活质量有所改善[180]。

5 总结与展望

口服肽类药物相较于注射剂具有高便利性, 高依从性, 但口服制剂的口服生物利用度极低, 目前已上市口服肽类药物Mycapssa®生物利用度约为0.5%, Rybelsus®约为1%。PEs能够通过提高细胞膜流动性、降低黏液黏度、打开紧密连接等方式提升药物在肠黏膜中的渗透和吸收。PEs缺乏特异性, 可能会增加将有害物质输入的风险, 存在安全隐患。尽管目前研究了很多PEs的专利技术, 但大多处于临床前研究, 通过临床试验并上市的药物极少, 药物长期安全性和临床有效性有待深入探究。

不同肽类药物的理化性质千差万别, 合理选用PEs并设计处方,“一药一策”, 最大限度地提高其疗效与安全性, 开发出具有显著临床优势、安全性良好的口服药物, 是当前口服肽制剂亟需突破的核心瓶颈, 也是制药行业下一阶段努力的重点方向。此外, 新型的纳米药物递送系统及离子液体与PEs联用亦可显著提高药物的生物利用度, 目前含有胆盐及壳聚糖的纳米递送系统处于临床研究阶段, 这为下一代高效、安全的口服制剂提供了新的发展方向。

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利益冲突: 本文所有作者声明不存在利益冲突关系。

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