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低水溶性药物口服增溶促吸收制剂的研究进展与临床转化展望

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摘　要

口服给药是小分子药物的理想给药途径，但低水溶性导致的生物利用度低已成为新药研发与临床转化的共性难题。统计研究提示，相当比例的候选化合物存在不同程度的溶解度不足，多集中于生物药剂学分类系统(biopharmaceutics classification system, BCS) II类或IV类。传统增加剂量或改换给药途径的策略难以兼顾疗效与安全性。目前已发展出固体形态工程、纳米制剂、脂质载体、环糊精包合等多种增溶促吸收策略，作用于溶出、过饱和、跨膜转运及淋巴吸收等环节。本文以完整吸收链条为主线，系统梳理难溶性药物口服吸收的限制环节，整合目前主要制剂策略的作用机制、优势与局限，并从临床转化视角提出一体化设计与评价思路。

关键词

低水溶性药物，口服制剂，生物利用度，增溶促吸收

Research Progresses and Clinical Translation Prospects of Solubilization and Absorption Enhancement Oral Preparations for Poorly Water-Soluble Drugs

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Abstract

Oral administration is an ideal route for small-molecule drugs. However, poor oral bioavailability caused by low water solubility has become a common challenge in the research and development and clinical translation of new drugs. Statistical studies indicate that a considerable proportion of drug candidates suffer from insufficient solubility to varying degrees, most of which are classified as Class II or Class IV in the biopharmaceutics classification system (BCS). Traditional strategies such as dose escalation or alternative administration routes can hardly balance efficacy and safety. To date, various strategies for solubility enhancement and absorption promotion have been developed, including solid-state engineering, nanoformulations, lipid-based carriers, and cyclodextrin inclusion complexes. These strategies exert effects on drug dissolution, supersaturation, transmembrane transport, and lymphatic absorption. Taking the complete oral absorption cascade as the main line, this review systematically summarizes the limiting factors of oral absorption for poorly soluble drugs, integrates the mechanisms, advantages, and limitations of current mainstream formulation strategies, and proposes an integrated design and evaluation paradigm from the perspective of clinical translation.

Keywords

Poorly Water-Soluble Drugs, Oral Formulations, Bioavailability, Solubilization and Absorption Enhancement

1. 引言

口服给药作为小分子药物的理想给药方式，凭借无创便捷、患者依从性高、便于长期治疗管理的优势，在临床用药中占据主导地位，据统计其在临床各类给药途径中的占比超过 70% [1]。近年来，随着药物研发逐渐向结构复杂、靶点特异性结合的方向推进，低水溶性导致的口服生物利用度低下，已成为制约新化合物成药与临床转化的关键瓶颈[1]。

根据生物药剂学分类系统(Biopharmaceutics Classification System, BCS)，药物的口服吸收特性主要由溶解度与通透性两大核心指标决定，其中约 75%的药物候选分子属于 BCS II 类(低溶解度、高通透性)或 IV 类(低溶解度、低通透性)。这类难溶性药物的口服吸收过程并非单一环节限制，而是受到胃肠道内溶出、过饱和维持、跨黏液及上皮屏障转运、外排蛋白介导的外排作用与肝脏首过代谢等多环节的协同制约，单纯依靠传统的剂量增加或给药途径调整，无法从根本上解决吸收不确定性问题，还可能引发毒副作用增加、治疗成本上升、患者依从性下降等一系列问题[2]。

近年来，难溶性药物口服增溶促吸收研究已逐步摆脱传统经验性处方筛选的局限，进入机制驱动的

理性设计阶段，研究重点从单纯提升体外溶解度，转向对药物体内吸收关键机制的深入探究，形成了固体形态/微观结构调控与体内过程调控两大互补技术主线[3]。各类增溶促吸收策略不断涌现，包括共晶、无定形体系、固体分散体、纳米晶等固体形态调控技术，以及脂质基递送系统、聚合物胶束、脂质前药等体内过程调控技术，同时组合化策略(如“弹簧–降落伞”策略)的应用的也日益广泛，为解决难溶性药物口服吸收难题提供了多样化的技术路径。

然而，目前多数增溶促吸收技术仍停留在实验室研究阶段，临床转化效率偏低，且不同策略的作用机制、适用范围、优势与局限存在显著差异，缺乏系统的梳理与整合。基于此，本文以难溶性药物口服完整吸收链条为主线，系统综述难溶性药物口服吸收的多环节限制机制及不同 BCS 分类药物的吸收瓶颈差异，全面整合当前主流药剂学增溶促吸收策略的作用机制、研究进展、优势与局限，剖析临床转化过程中的共性瓶颈，并提出“机制驱动、转化导向”的一体化设计思路与未来展望，为难溶性药物口服制剂的研发优化、技术创新与临床转化提供理论参考与技术指引，助力推动药剂学领域的技术进步与临床用药水平的提升。

2. 难溶性药物口服吸收的多环节限制机制与 BCS 分类差异

2.1. 口服吸收的多环节耦合限制

难溶性药物口服生物利用度偏低并非单一环节导致，而是溶出、过饱和、跨屏障转运、外排与首过代谢等多个环节协同限制的结果，各环节相互关联、相互影响，构成完整的吸收限制链条[4]。难溶性药物口服吸收关键屏障及药剂学策略干预位点见图 1。

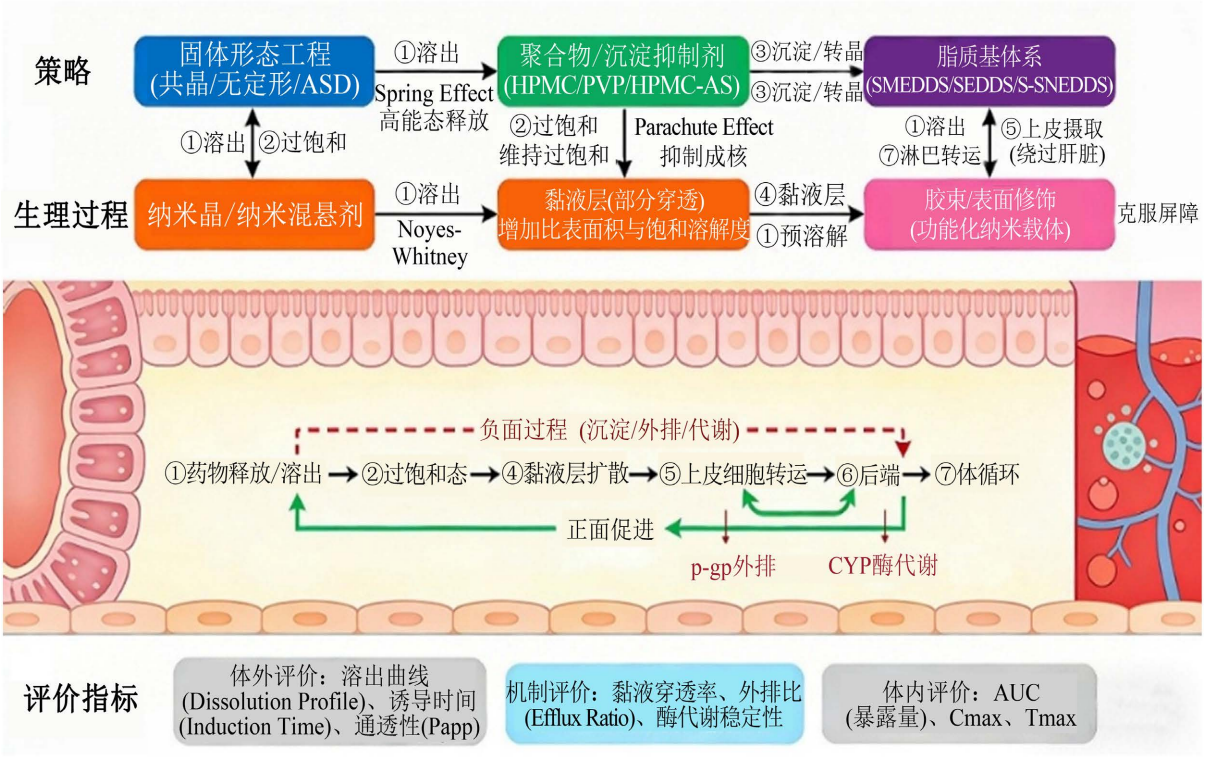

Figure 1. Schematic diagram of key barriers to oral absorption of poorly water-soluble drugs and intervention sites of pharmaceutical strategies

图 1. 难溶性药物口服吸收关键屏障及药剂学策略干预位点示意图

1) 溶出与溶解度不足：这是难溶性药物口服吸收的初始瓶颈。在胃肠道水性环境中，难溶性药物的溶出速率缓慢、饱和溶解度极低，难以在吸收窗内形成足够的溶解态药物浓度，无法为后续吸收提供充足动力。典型代表药物为紫杉醇，其水中溶解度仅约 0.006 mg·mL^{-1}，常规制剂难以在肠腔形成有效浓度，同时还受到多重因素影响，属于多重限制型药物[5] [6]。

2) 过饱和与沉淀不稳定：许多制剂策略通过无定形化、共晶、固体分散体或脂质系统在体内构建过饱和状态，以提高瞬时溶解度和吸收驱动力。但过饱和状态具有热力学不稳定性，极易通过结晶或沉淀快速“坍塌”，导致药物有效浓度急速下降。例如，布洛芬共晶可在体外短时间形成较高过饱和度，但在接近体内的复杂环境中易发生晶型转变或析出，说明快速溶出并不能必然转化为稳定吸收[7] [8]。

3) 跨黏液/上皮屏障转运受限：药物溶出后需穿越肠黏液层与上皮细胞屏障才能进入体循环。黏液的网状结构和非特异性吸附会降低药物颗粒或分子的扩散效率；上皮细胞的紧密连接限制了旁细胞通路，大部分药物需依赖跨细胞扩散或转运机制，而疏水性强、分子量大的难溶性药物往往通透性不足，进一步阻碍吸收[9] [10]。

2.2. BCS II 类与 IV 类药物的吸收瓶颈差异

不同 BCS 分类的难溶性药物，其口服吸收的核心瓶颈存在显著差异，需针对性制定干预策略：

1) BCS II 类药物：核心特征为低溶解度、高通透性，口服吸收的主要瓶颈是溶出/溶解效率与过饱和稳定性，需有效提升药物的溶出速率、维持过饱和状态，即可显著改善口服生物利用度[2]。

2) BCS IV 类药物：核心特征为低溶解度、低通透性，口服吸收面临双重瓶颈，不仅需要解决溶出与过饱和问题，还需改善药物的跨膜通透性、抑制外排转运、减轻首过代谢，需采用“增溶 + 促转运 + 减清除”的综合干预策略[12] [13]。

综上，难溶性药物口服递送的核心目标并非孤立提高单一体外参数，而是需精准识别药物的主导限速环节，结合其 BCS 分类特征，制定针对性的干预方案[14]。低水溶性天然活性成分口服增溶促吸收主流药剂学策略汇总见表 1。

Table 1. Summary of mainstream pharmaceutical strategies for solubilization and absorption enhancement of poorly water-soluble natural active ingredients via oral administration
表 1. 低水溶性天然活性成分口服增溶促吸收主流药剂学策略汇总表

药剂学策略	核心技术	作用环节	天然活性成分	药物实例	参考文献
固体形态/微观结构调控	共晶	溶出－过饱和－沉淀	疏水性天然多酚类、黄酮类、类胡萝卜素类	槲皮素、水飞蓟宾、姜黄素、黄芩苷、叶黄素	[6] [8] [16] [22] [63]
	无定形、共无定形体系		皂苷类、萜类、黄酮类、木脂素类	人参皂苷 Rg3、青蒿素、紫杉醇、葛根素、五味子酯甲	[1] [11] [16] [18] [24] [58]
	固体分散体		黄酮类、萜类、生物碱类、蒽醌类	姜黄素、穿心莲内酯、汉防己甲素、大黄素、紫草素	[22] [23] [29] [33] [36] [76]
	纳米晶、纳米混悬剂		黄酮类、多酚类、萜类、木脂素类、二萜类	槲皮素、水飞蓟宾、姜黄素、人参皂苷 Rh2、丹参酮 IIA、隐丹参酮、五味子酯甲	[1] [8] [24]-[27] [31] [35] [67] [60]

续表

体内过程调控	脂质基递送系统、自纳米乳	肠腔分散－跨黏液/上皮转运－外排与首过效应	萜类、黄酮类、皂苷类、多酚类、倍半萜类	青蒿素、姜黄素、人参皂苷 Rg3、红景天苷、紫杉醇、白藜芦醇、橙花叔醇	[1] [9] [13] [35]-[39] [41] [42] [60] [71] [72]
	磷脂复合物与脂质体		生物碱类、黄酮类、萜类、黄烷酮苷类	汉防己甲素、姜黄素、丹参酮 IIA、小檗碱、新橙皮苷	[2] [34] [42] [68]
	聚合物胶束及表面修饰纳米载体		萜类、皂苷类、多酚类、木脂素类	紫杉醇、人参皂苷 Rg3、姜黄素、白藜芦醇、五味子酯甲	[1] [9] [17] [45] [47] [51]
	脂质前药		萜类、酚类、类胡萝卜素类	青蒿素、姜黄素、白藜芦醇、虾青素	[10] [40] [77]
	药物离子液体		生物碱类、黄酮类、皂苷类	小檗碱、葛根素、黄芩苷、三七皂苷 R1	[40] [55]
	环糊精包合体系	溶出－过饱和－沉淀	萜类、多酚类、黄酮类、挥发油类	姜黄素、槲皮素、橙花叔醇、厚朴酚、新橙皮苷	[2] [5] [6] [9]
组合化(弹簧－降落伞)	共晶/无定形/固体分散体/高能态纳米晶(弹簧) + 聚合物沉淀抑制剂/脂质体系/胶束网络(降落伞)	溶出－过饱和－沉淀－跨黏液－上皮转运	多重吸收限制型天然活性成分、BCS IV 类成分	姜黄素、紫杉醇、人参皂苷 Rg3、槲皮素、五味子酯甲	[1] [13] [44]-[46] [57]
	SSNEDDS (脂质增溶 + 聚合物稳溶集成)	溶出－过饱和－沉淀－跨黏液上皮转运－外排与首过效应	低溶解度低通透性天然活性成分、BCS IV 类成分	青蒿素、姜黄素、丹参酮 IIA、葛根素、厚朴酚	[5] [13] [30] [42] [49] [50]
	磷脂/环糊精杂化纳米体系	溶出－过饱和－沉淀－跨黏液－上皮转运	黄烷酮苷类、黄酮类、多酚类	新橙皮苷、姜黄素、白藜芦醇	[2]
	纳米晶－脂质体复合体系	溶出－过饱和－沉淀－跨黏液－上皮转运	多酚类、萜类、BCS IV 类天然成分	姜黄素、青蒿素、丹参酮 IIA	[4]
	自组装纳米胶束体系	肠腔分散－跨黏液/上皮转运	木脂素类、酚类、萜类	厚朴酚、五味子酯甲、白藜芦醇	[5]

3. 难溶性药物口服增溶促吸收的主流药剂学策略

针对难溶性药物口服吸收的多环节限制，目前已形成两条互补且可组合的技术主线，各类策略通过作用于吸收链条的不同环节，实现增溶促吸收效果，同时逐步向组合化、一体化方向发展[1] [3]。

3.1. 固体形态/微观结构调控策略

该策略主要作用于“溶出－过饱和－沉淀”环节，通过改变药物的晶体结构、能态或粒径大小，提高溶出速率、表观溶解度，构建可控的过饱和来源，从而提升肠道内有效药物浓度，适用于各类难溶性药物，尤其对 BCS II 类药物效果显著[15]。

1) 核心技术类型：包括共晶、无定形与共无定形体系、固体分散体、纳米晶与纳米混悬剂四大类。其中，共晶、无定形与共无定形体系通过降低药物晶格能、提高固相化学势，实现快速溶出与过饱和形成[16]-[19]；固体分散体将药物以分子、无定形或微晶形式分散在水溶性聚合物载体中，改善润湿性与分散性[20]-[23]；纳米晶与纳米混悬剂通过将药物粒径降至纳米级别，大幅增加比表面积，加快溶出速率[24] [27]。

2) 关键机制与实例：根据 Noyes-Whitney 方程，溶出速率与比表面积成正比，纳米晶通过减小粒径、增加比表面积，缩短扩散路径、降低扩散阻力，同时提升表面能，提高表观饱和溶解度与跨膜浓度梯度[28]。以槲皮素为例，微流体制备的纳米晶粒径分布更均一，体外溶出显著提升，体内药代研究中 AUC 明显增加，形成“可控混合→粒径分布→体内暴露”的清晰技术路径[29]-[31]。

3) 优势与局限：该类策略无须显著改变化学结构，对药物的适用性较广，部分技术(如固体分散体的热熔挤出、喷雾干燥工艺)已具备一定产业化基础[32]。但存在明显局限：共晶、无定形体系的过饱和稳定性差，易发生结晶或相分离[8]；纳米晶面临奥斯特瓦尔德熟化、聚集等物理稳定性问题，且晶型差异会显著影响体内行为[26] [33]；固体分散体在长期储存中易老化，核心是药物在载体中处于热力学亚稳态，长期储存会自发结晶；同时载体可能结晶、降解，且温度、湿度等环境因素会加速这一过程，破坏分散体系稳定性。且固体分散体实验室处方难以直接工业化放大，主要因实验室与工业化的工艺参数、设备特性差异大，传热传质效率不均；处方组分的规模化适配性不足，原料批次差异影响质量；工业化批量增大后，关键质量指标难以精准把控[22] [23]。

3.2. 体内过程调控策略

该策略主要作用于“肠腔分散－跨黏液/上皮转运－外排与首过效应”环节，通过构建递送系统改善药物在肠道内的分散状态、促进跨屏障转运、抑制外排与代谢，实现体内暴露量的提升，尤其适用于 BCS IV 类药物及首过效应显著的难溶性药物[34] [35]。

核心技术类型：主要包括脂质基递送系统、磷脂复合物与脂质体、聚合物胶束及表面修饰纳米载体，以及脂质前药、药物离子液体等新型策略。其中，脂质基递送系统(SMEDDS/SEDDS、自纳米乳、过饱和自纳米乳 SSNEDDS)应用最广泛[36]-[39]；脂质前药通过分子设计改变药物亲脂性，实现转运效率提升[40]。

关键机制与实例：脂质基递送系统通过向疏水药物提供良好的溶解环境，使其在肠腔形成细小油滴分散，同时模拟膳食脂质消化行为，与胆盐、磷脂形成混合胶束，促进药物胶束转运，部分体系可通过淋巴通路吸收，减少首过代谢[35] [41]。SSNEDDS 作为集成化系统，在传统自纳米乳基础上引入聚合物沉淀抑制剂，实现“弹簧(油相增溶) + 降落伞(聚合物稳溶)”协同作用，延长过饱和维持时间[13] [42]。脂质前药通过将脂肪酸、甘油酯等片段与药物共价连接，提高亲脂性与膜通透性，借助脂质吸收通路减少首过代谢，在体内酯酶作用下释放活性药物[40]。

优势与局限：该类策略可直接干预药物体内转运过程，实现“增溶 + 促转运 + 减清除”的综合效果，能有效解决 BCS IV 类药物的双重吸收瓶颈[13]。但存在转化瓶颈：脂质体系表面活性剂用量较高，安全性需充分论证考察，载药量受油相溶解度限制[43]；脂质前药、离子液体等新型策略多处于概念验证阶段，体内代谢可控性、长期安全性及工艺放大难度较大[40]。

3.3. 组合化(弹簧－降落伞)调控策略

单一策略往往难以同时解决难溶性药物口服吸收的多环节限制，因此组合化设计成为临床转化的重要方向，其中“弹簧－降落伞(spring-parachute)”策略最为典型。该策略以共晶、无定形、固体分散体或

高能态纳米晶作为“弹簧”，快速产生短时高过饱和浓度；以聚合物沉淀抑制剂、脂质体系或胶束网络作为“降落伞”，延缓结晶、抑制沉淀，维持足够的溶解态暴露时间，实现增溶与稳溶的协同[13] [44]。

SSNEDDS 是该策略的典型代表，其将脂质增溶与聚合物稳溶集成于一体，进一步提升吸收程度并降低食物效应。但组合体系结构复杂，体内行为受消化、胆盐、pH、食物等多因素影响，对体内外相关性(IVIVC)的要求更高，需建立机制关联的评价指标[45] [46]。

4. 难溶性药物口服制剂临床转化的共性瓶颈

尽管各类增溶促吸收策略在体外实验与动物药代研究中均显示出显著的暴露提升效果，但向临床产品转化时，仍面临体内外相关性(IVIVC)不足、稳定性欠缺、安全性风险及工艺放大困难四大共性瓶颈，制约了实验室成果的临床落地[14] [45]。这些瓶颈相互关联、相互影响，其中 IVIVC 不足是核心衔接障碍，稳定性与安全性是基础保障短板，工艺放大则是规模化转化的关键制约，共同构成了难溶性药物口服制剂从实验室到临床应用的主要障碍。

4.1. 体内外相关性(IVIVC)不足

IVIVC 是连接处方筛选与临床效果的关键桥梁，其核心价值在于通过体外评价数据预测体内吸收行为，减少临床实验成本、缩短转化周期，而难溶性药物复杂递送体系的体内暴露同时受过饱和﹣沉淀动力学、脂质消化/相行为变化、黏液渗透、外排与首过代谢等多因素影响，单一体外溶出曲线无法反映全部关键过程，导致处方筛选的可预测性差成为临床转化的首要瓶颈[4] [45]。例如，共晶、无定形体系体外溶出极快，但体内可能因快速沉淀缩短吸收窗口，这一现象在布洛芬共晶、伊曲康唑无定形固体分散体中均有报道[8] [48]；SSNEDDS 体外乳化粒径与体内消化后的真实相结构存在差异，体外评价难以精准匹配体内消化吸收过程[49] [50]；纳米载体的吸收更多依赖黏液渗透、内吞与外排蛋白相互作用，溶出不再是决定性因素，传统溶出实验无法体现其体内转运特征[51] [52]。此外，生理药代动力学模型(PBBM)的参数优化，可通过整合药物理化性质、制剂特征与体内生理参数，提升 IVIVC 的预测能力，为制剂处方优化提供新路径[14] [53]-[55]，而监管层面对 IVIVC 的应用也有明确规范，进一步凸显了其在临床转化中的核心地位[47] [56]。研究表明，基于 PBBM 模型构建的 IVIVC，可显著提升难溶性药物复杂制剂体内吸收行为的预测准确性，减少临床实验的盲目性[57]。

4.2. 稳定性不足：储存与体内过程双重挑战

稳定性问题贯穿各类制剂策略的研发与转化全过程，直接决定制剂的有效性与安全性，主要包括储存稳定性与体内过程稳定性两个层面[44]。储存稳定性方面，无定形/共无定形体系因热力学不稳定易发生成核结晶，导致增溶效果丧失[22] [58]；固体分散体在长期储存中易出现相分离与老化，尤其热熔挤出工艺制备的固体分散体，在高温、高湿环境下易发生载体结晶与药物析出，影响制剂质量[23] [33] [59]；纳米晶易发生奥斯特瓦尔德熟化与聚集，导致粒径增大，降低溶出速率与体内暴露量[26] [27]；脂质体系易出现析油、相分离与氧化，影响制剂的均一性与有效性[22] [23] [26] [33]，这一问题在 SMEDDS、SEDDS 等脂质基递送系统中尤为突出[60] [61]。体内过程稳定性方面，制剂进入胃肠道后，会经历稀释、pH 变化、胆盐/酶消化等多重扰动，可能导致结构破坏、过饱和崩塌或药物释放异常，最终影响体内暴露效果[13] [41]。例如，无定形固体分散体在胃肠道酸性环境中易发生快速沉淀，SSNEDDS 在肠道稀释过程中可能出现药物析出，这些均会导致体内吸收效果与体外评价结果偏差[62] [63]。传统稳定性研究多聚焦储存稳定，对体内过程稳定性的关注不足，缺乏贴合体内真实环境的评价模型，成为临床转化的重要障碍[44]。

4.3. 辅料与长期安全性风险

增溶制剂的安全性主要依赖辅料的合理选择，而各类增溶策略均存在不同程度的辅料安全性隐患：SMEDDS/SEDDS 等脂质体系需使用高剂量表面活性剂，这类辅料可能破坏肠道黏膜屏障，引起肠道刺激或全身不良反应[43] [65] [66]；纳米与表面修饰载体可能导致特定组织蓄积、免疫反应或长期毒性[53] [54]，例如纳米晶在肝脏、脾脏的蓄积可能增加器官负担[67]-[69]。新型稳定剂、功能性高分子、离子液体等辅料的代谢途径、长期毒性数据通常有限[55]，缺乏长期用药的安全性证据，难以满足临床转化的监管要求[70]。此外，长期或高频用药场景下的安全边际、特殊人群(儿童、肝肾功能不全者)的风险评估，仍缺乏充分的实验证据，进一步制约了临床转化进程[43] [56]。

4.4. 工艺放大与质量一致性困难

许多复杂增溶体系在实验室小试阶段可获得理想的粒径、晶型、溶出效果，但进入中试与工业化放大后，粒径分布、晶型、含量均匀性、粉体流动性、残留溶剂等关键质量属性容易出现漂移，导致放大后药效与安全性不可预测、批间差异增大，影响药品注册与临床使用，这是难溶性药物口服制剂规模化转化的核心瓶颈[57] [73]。其核心原因在于缺乏可放大的工艺路线，以及在线监测与闭环控制体系，难以实现工艺与质量的稳定控制[74] [75]。不同增溶策略的工艺放大难度、关键控制点及质量风险存在显著差异，这也进一步凸显了策略选择与工艺放大协同考量的重要性，具体对比如下：对于共晶策略，实验室多采用溶液法、研磨法制备，工业化放大的核心难点在于晶型控制与收率提升，易出现晶型转变、杂质增多等问题，尤其高熔点药物的共晶制备需精准控制反应温度与时间，否则易导致共晶解离，其质量风险主要集中于晶型一致性与稳定性[22]；对于纳米晶策略，实验室常用微流控、超声法制备，放大后易出现粒径分布不均、聚集等问题，且奥斯特瓦尔德熟化现象更显著，需优化分散稳定剂用量与搅拌参数，质量风险主要为粒径漂移与物理稳定性下降[27] [53]；对于固体分散体策略，喷雾干燥、热熔挤出是主流工业化工艺，放大过程中温度、转速、进料速度等参数的微小变化，均会导致药物分散状态改变，高熔点药物需更高的熔融温度，易造成载体降解与药物降解，实验室处方难以直接适配工业化设备的传热传质特性，质量风险集中于药物分散均匀性与长期老化[22] [76]；对于脂质基递送系统(如 SMEDDS/SEDDS)，工业化放大易出现相分离、粒径不均等问题，高 logP 药物的载药量易受油相溶解度限制，放大过程中需严格控制乳化温度与搅拌速率，质量风险主要为制剂均一性与储存稳定性[60] [77]。

例如，纳米晶的实验室制备多采用微流控、超声等小试工艺，放大后易出现粒径分布不均、聚集等问题，影响制剂质量一致性[27] [53]；固体分散体的喷雾干燥、热熔挤出工艺，放大过程中温度、转速、进料速度等参数的微小变化，均会导致药物分散状态改变，影响溶出效果[22] [76]；脂质体系的工业化放大易出现相分离、粒径不均等问题，降低制剂的均一性与有效性[60] [77]。因此，质量源于设计(QbD)与过程分析技术(PAT)的引入，成为解决该问题的关键[58] [66]。QbD 理念通过在研发早期识别关键质量属性(CQA)与关键工艺参数(CPP)，设计可工业化放大的工艺路线，结合 PAT 技术实现对工艺过程的在线/近线检测，实时监测关键指标，建立工艺–质量的闭环控制，保障批间一致性与可追溯性[74] [75]。研究表明，基于 QbD 与 PAT 的工艺设计，可显著提升难溶性药物增溶制剂的工艺放大稳定性，降低批间差异，加快临床转化进程[74] [78]。同时，工艺放大的可行性也应作为策略选择的重要考量因素，避免选择实验室效果优异但工业化难度极高、质量难以控制的策略。

5. 结语与展望

低水溶性药物口服生物利用度不足，是长期制约新药成药转化、现有药物疗效优化的核心瓶颈，尤其在 BCS II 类(低溶解度、高通透性)与 BCS IV 类(低溶解度、低通透性)药物中表现突出，这一问题不仅

增加药物研发成本、延长研发周期，更限制了临床用药的有效性与安全性。本文以难溶性药物口服完整吸收链条为主线，系统梳理了其口服吸收过程中的多环节耦合限制机制，明确溶出不足、过饱和不稳定、跨黏液/上皮屏障转运受限、外排与首过代谢干扰四大核心障碍，清晰剖析了 BCS II 类与 IV 类药物的吸收瓶颈差异——前者以溶出与过饱和稳定性为单一核心瓶颈，后者面临溶出与通透性双重制约，为精准制定增溶促吸收策略提供了坚实的理论根基。在此基础上，本文整合了当前难溶性药物口服增溶促吸收的主流药剂学策略，明确固体形态/微观结构调控、体内过程调控两条互补技术主线的核心逻辑与应用场景，详细阐述了共晶、纳米晶、脂质基递送系统、SSNEDDS 等关键技术的作用机制、优势与局限，重点分析了组合化“弹簧–降落伞”策略的协同效应，通过具体药物实例与数据佐证各类策略的应用效果，全面呈现了该领域的研究现状与技术迭代趋势[1] [3] [44]。同时，本文从临床转化视角出发，剖析了实验室研究向临床落地过程中面临的四大共性瓶颈——体内外相关性(IVIVC)不足、储存与体内过程双重稳定性欠缺、辅料与长期安全性风险、工艺放大与质量一致性困难，揭示了实验室效果显著、临床转化滞后的核心瓶颈，为后续研究提供了攻坚方向[14] [45]。

回顾难溶性药物口服增溶促吸收领域的发展历程，研究范式已实现从传统经验性处方筛选向机制驱动理性设计的根本性转变，从单一环节增溶向多环节协同调控的升级，从独立技术研发向组合化、一体化系统设计的跨越，这一转变推动了该领域理论体系的完善与技术水平的提升。但不可忽视的是，当前研究仍存在诸多亟待突破的短板：一是策略选择的精准性不足，多数研究仍存在“技术导向”而非“机制导向”的误区，未能充分结合药物 BCS 分类、理化性质及吸收瓶颈实现精准匹配，导致部分策略应用效果不佳、资源浪费；二是体内外评价体系的关联性不强，传统体外溶出实验难以模拟体内复杂的生理环境(如胃肠道 pH、胆盐浓度、黏液屏障等)，导致 IVIVC 模型构建困难，无法有效预测临床吸收效果，成为制约临床转化的核心衔接障碍；三是临床转化的系统性不足，对制剂稳定性、辅料安全性、工艺放大可行性的关注多局限于单一环节，缺乏“研发–评价–放大–临床”的全链条设计，导致许多实验室阶段的优质处方难以实现工业化生产与临床应用；四是新型策略的临床落地能力薄弱，脂质前药、药物离子液体、功能化纳米载体等新型技术多处于概念验证或动物实验阶段，其体内代谢可控性、长期安全性及规模化生产工艺仍需进一步探索，未能形成成熟的临床转化路径。其中，策略选择的盲目性是制约研发效率与转化成功率的关键因素之一，亟需建立清晰的决策框架，指导研究者根据药物特性与吸收瓶颈选择最优策略。

基于药物理化性质(熔点、logP、剂量)、BCS 分类及吸收瓶颈，本文构建难溶性药物口服增溶促吸收策略的决策框架，为实践应用提供明确指导，核心要点如下：

1) BCS II 类药物(低溶解度、高通透性)：核心瓶颈为溶出与过饱和稳定性，策略选择需优先聚焦提升溶出速率与维持过饱和状态。对于高熔点(>150℃)、高 logP (>3)、低剂量(<100 mg)的 BCS II 类药物，共晶策略成功率较高，其通过降低晶格能实现快速溶出，且无需复杂载体，工艺相对简单，质量风险主要为晶型一致性与储存稳定性；纳米晶策略同样适用，可通过增大比表面积显著提升溶出，但需解决粒径稳定性与聚集问题，工业化放大难度中等，适合高熔点、高 logP 且不易形成共晶的药物；固体分散体策略对高熔点药物的适用性有限，高熔点药物需更高的熔融温度，易导致载体降解与药物老化，成功率低于共晶与纳米晶，但其产业化基础相对成熟，适合剂量较高(100~500 mg)、难以制备共晶或纳米晶的药物，需重点优化载体选择与工艺参数以降低老化风险。

2) BCS IV 类药物(低溶解度、低通透性)：核心瓶颈为溶出与跨膜通透性双重限制，需选择“增溶 + 促转运”的综合策略。对于高 logP、高熔点的 BCS IV 类药物，脂质基递送系统(如 SSNEDDS)或脂质前药策略成功率较高，可通过模拟脂质吸收通路促进跨膜转运，同时实现药物增溶，减少首过代谢，但需关注表面活性剂用量与安全性，以及载药量限制；聚合物胶束及表面修饰纳米载体策略可通过表面修饰

(如 PEG 化、靶向配体修饰)改善黏液穿透性与跨膜转运效率，适合高熔点、高 logP 且剂量较低的药物，但其工业化放大难度较大，长期安全性数据不足；组合化策略(如纳米晶－脂质体复合体系)可实现“增溶 + 促转运”协同，适合多重限制型 BCS IV 类药物，但体系复杂，需优化各组分比例以保障稳定性与质量一致性。

3) 通用考量因素：药物剂量较高(>500 mg)时，优先选择固体分散体、脂质基递送系统等载药量较高的策略，共晶与纳米晶策略因载药量有限适用性较差；logP < 2 的难溶性药物，优先选择环糊精包合、固体分散体等水溶性载体相关策略，脂质类策略因药物亲脂性不足难以实现有效增溶；熔点较低(<100℃)的药物，可优先选择固体分散体(热熔挤出工艺)、脂质基递送系统，避免共晶策略因熔点过低导致储存过程中晶型转变。同时，策略选择需兼顾工艺放大可行性与安全性，例如纳米晶策略虽对高熔点、高 logP 药物增溶效果显著，但工业化放大难度较高，若缺乏成熟的 PAT 控制体系，可优先选择共晶策略。

面向未来，难溶性药物口服增溶促吸收制剂的研发与临床转化，应坚持“机制驱动、转化导向、安全优先、系统协同”的核心原则，聚焦以下关键方向：第一，机制驱动的策略匹配：基于本文构建的决策框架，结合药物的理化性质、BCS 分类及吸收瓶颈，精准选择单一或组合策略，实现“增溶、稳溶、促转运、减清除”的协同，避免技术的盲目叠加[2] [13]。第二，转化导向的评价体系：构建贴近体内真实环境的体外评价模型，将过饱和动力学、消化行为、跨屏障转运、外排与代谢等关键因素纳入处方筛选，建立可解释的 IVIVC 模型，提高处方筛选的可预测性[4] [45] [46]。第三，QbD 与 PAT 的深度引入：在研发早期识别关键质量属性(CQA)与关键工艺参数(CPP)，设计可工业化放大的工艺路线，通过在线/近线检测实时监测关键指标，建立工艺－质量的闭环控制，保障批间一致性与可追溯性[58]-[60]。第四，安全性与可持续性并重：在追求体内暴露提升的同时，系统评估辅料与新型材料的长期安全性，兼顾特殊人群与长期用药场景的风险，确保制剂的临床安全可用[43] [56]。第五，策略选择决策框架的完善：结合更多临床转化案例，补充不同药物理化参数下各类策略的成功率数据，优化决策逻辑，为研究者提供更精准的实践指导。

只有在“增溶可靠、体内可预测、工艺可放大、可长期安全使用”的综合框架下，结合精准的策略选择，难溶性药物的口服制剂才能真正完成从机制研究到临床产品的转化，为高效、安全的新药开发提供坚实的技术支撑。

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