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目 录

论文编号：07–001

高端药物制剂开发技术新进展

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摘要正文：

新药研发投入风险愈来愈大，化合物新药开发需投入高昂费用且新化学实体的发现速度逐年变缓。新型给药系统的开发具有成本低、周期短、见效快等优点，药物研发进入了制剂创新时代。中国市场对创新制剂技术的需求潜力巨大，但我国与国外发达国家医药工业相比仍存在较大差距，创新制剂产业的关键技术远远落后于国外，创新制剂产业化程度低，导致自主创新产品缺乏，国内制剂企业出口能力不强，特别是打入高端市场能力薄弱。本报告就国际创新制剂核心技术的现状进行了分析，探讨了我国创新制剂的实际情况，进一步结合本实验团队在创新制剂开发领域的关键技术，对我国创新制剂核心技术的未来发展提出了展望。

论文编号：07–002

以缓控释新药为例阐述二类新药 505(b)(2)产品的开发

闻晓光

泰州越洋医药开发有限公司

摘要正文：

报告包括三方面内容：第一，简要介绍行业背景——505(b)(2) 或者改良型新药的优势；第二，结合FDA已批准上市的缓控释新药产品的开发案例进行分析——505(b)(2)的开发路径；第三，掌握和发明缓控释平台技术是解决改良新药来源问题的关键——505(b)(2)开发的基础和关键；最后我会简要分享一下我公司越洋医药在缓控释新药领域的产品开发进展，也期望能够与致力于改良型新药开发的公司一道在创新制剂新药上有所突破有所合作。

论文编号：07–003

中药口服固体制剂处方智能设计

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摘要正文：

制剂处方研究是根据制剂原料性质、剂型特点、临床用药要求等，筛选适宜的辅料，确定制剂处方的过程。制剂处方研究是制剂成型研究的基础。口服固体制剂（OSD）是已上市中成药和中药新药开发的主体。中药制剂具有原料组分复杂、载药量高、辅料可调节空间少的特点。生产过程受原料波动的影响、主药收率、理化性质存在波动，制剂稳健性收到挑战。为提高制剂处方可靠性，缩短制剂处方开发周期，作者建立了iTCM智慧中药系统[1-6]，包括：（1）iTCM数据库，即代表性中药原料和常用药用辅料物性数据库，存储原辅料粉体多维度参数信息；（2）iTCM模型库，给定中药原料和载药量、以及剂型目标，实现辅料智能筛选。报告将以中药颗粒剂和片剂为例，介绍中药OSD制剂处方智能设计系统的应用。

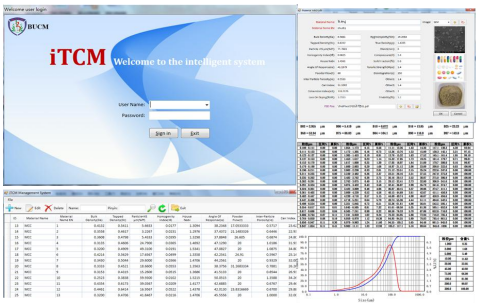

Fig. 1 The intelligent traditional Chinese medicine (iTCM) system

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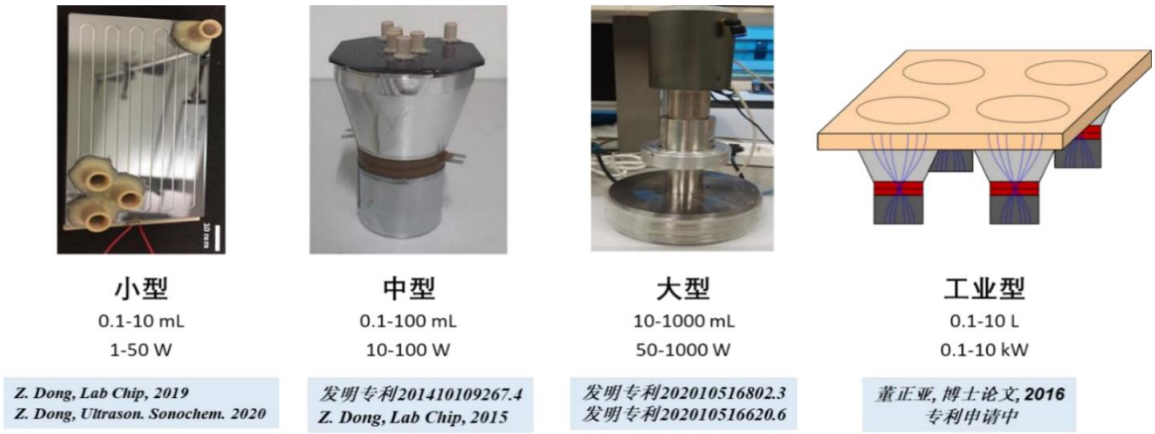

图 1 已开发的各种型号的超声微反应器。

关键词：纳米药物；纳米材料合成；微反应器；微流体；超声

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论文编号：07–004

肺部吸入小干扰RNA缓释制剂的肺内长期基因沉默效果及安全性研究

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摘要正文：

siRNA是一种短小双链RNA，可以特异性降解基因转录后的mRNA，从而达到基因沉默效果[1]。通过肺部吸入直接递送siRNA可以使siRNA迅速在局部达到较高的浓度，并且降低机体中广泛分布的核酸酶对siRNA的降解作用，与全身性给药方式相比可降低给药剂量与不良反应[2]。肺部吸入siRNA长效制剂可以调节siRNA释放速率，维持胞内siRNA水平，延长将靶基因表达水平控制在治疗所需阈值之下的时间，从而达到更好的治疗效果。本研究以针对EGFP的siRNA（anti-EGFP-siRNA）为模型药物，制备anti-EGFP-siRNA与阳离子脂质DOTAP混合形成的脂质复合物LPXs和以PLGA为基质的脂质-高分子杂化纳米粒（lipid-polymer hybrid nanoparticles，LPNs），以嵌入EGFP基因的转基因C57BL/6小鼠为动物模型，比较了气管内雾化给药后LPNs和LPXs在小鼠肺内抑制EGFP蛋白表达的效率，以及抑制该蛋白表达的时间。此外，以正常C57BL/6小鼠为模型，通过对急性炎症因子IL-6水平的考察评估了LPNs和LPXS通过气管内雾化给药后的肺部安全性。结果显示，LPNs经气管内雾化给药后，肺内基因沉默效果可以维持6天，而LPXs在末次给药后第1天表现出明显的基因沉默效果后，肺内基因表达量迅速恢复至与对照组相同的水平。在肺部滞留11天的过程中，LPXs引起的肺部炎性反应明显强于LPNs。课题结果表明包载siRNA的肺部吸入长效缓释制剂在肺内可以发挥出比速释制剂更稳定且延长的基因沉默效果，且安全性更好，具有一定的应用前景。

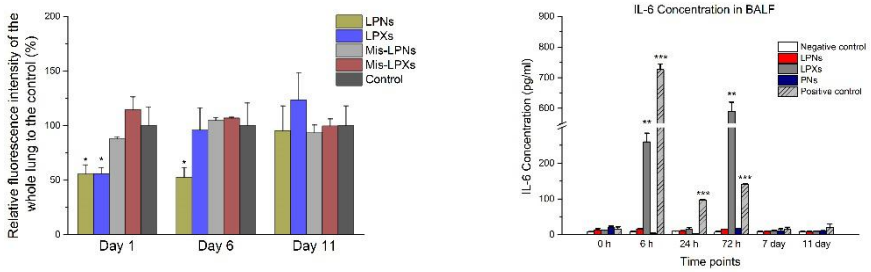

Fig. 1. *In vivo* gene silencing effects and cytokine level of the nanoparticles treated lung tissues (bars represent mean values ± SD, n = 3).

关键词：小干扰RNA；缓释纳米制剂；安全性

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论文编号：07–004

Long-term Gene Silencing Effects and Safety of Small Interfering RNA Loaded Sustained-release Formulations after Pulmonary Administration

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Abstracts:

Small interfering RNA (siRNA) is a short double-stranded RNA that can specifically cleave mRNA after gene transcription, thereby achieve specific gene silencing effect. Pulmonary delivery of sustained-release siRNA preparations may extend the time to control the target gene expression level below the threshold required for the treatment, so as to achieve the desired therapeutic effect. In this study, siRNA against enhanced green fluorescent protein (anti-EGFP-siRNA) was used as a model drug. First, anti-EGFP-siRNA was formulated into Lipoplexes (LPXs) with 1,2-dioleyl-3-trimethylammoniumpropane (DOTAP), a cationic lipid, which were further encapsulated in poly lactide-co-glycolide (PLGA) nanoparticles to prepare lipid-polymer hybrid nanoparticles (LPNs). LPNs showed extended gene silencing effects in mouse lungs 6 days after last administration while the gene silencing effects of LPXs diminished 1 day after last administration. In addition, the LPXs induced more severe inflammatory effects than LPNs after pulmonary administration.

Key words: Small interfering RNA, Sustained-release nano-preparations, Safety

论文编号：07–005

中药颗粒剂研究进展

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摘要正文：

中药颗粒剂作为一种在中药汤剂基础上发展起来的常用中药剂型,具有携带使用方便、稳定性好、吸收快等特点。近年来随着一些新辅料及制备技术工艺的使用,中药颗粒剂得到迅速发展，并展示出其巨大的应用价值和广阔的市场前景。亟待针对不足之处开展深入系统的研究,并制定统一、标准化的中药颗粒剂生产与应用标准,推进中药现代化发展进程。同时，课题组围绕经典名方，四逆汤等，对中药颗粒剂进行了全方位的探索，且从中药颗粒剂的过去、现在、未来概述了中药颗粒剂的研究进展。

关键词：中药；颗粒剂；四逆汤；生血丸；存在问题；应用前景

论文编号：07–006

Prediction of in vitro dissolution profile and in vivo performance of solid dispersions by the integrated computational tools（用集成计算工具预测固体分散体的体外溶出曲线和体内性能）

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Abstract:

Current formulation development of solid dispersions lacks effective theoretical guidance and is mainly based on a random large-scale formulation screening method, which requires a large amount of time, manpower and material resources. Current research aims to integrate various computational tools, including machine learning, molecular dynamic simulation and physiologically based pharmacokinetic modeling, to accelerate the development of solid dispersion formulations. 674 solid dispersion formulations were collected from the Web of Science database. A classification model was established to distinguish two types of dissolution profiles of solid dispersions: “spring-and-parachute” profile and “maintain supersaturation” profile. The results showed that this ensemble model presented good performance (0.85) to distinguish the dissolution profiles. Furthermore, a regression model was constructed to predict the whole “maintain supersaturation” dissolution profiles. The vemurafenib (VEM) solid dispersion formulations with two model polymers (HPMCAS and Eudragit) were investigated by molecular dynamics (MD) simulations. MD simulation results presented that the drug molecules from HPMCAS formulation were released much faster than those from Eudragit formulation, which agreed with the reported experimental results. PBPK model was developed to predict the in vivo absorption of two vemurafenib formulations. The predicted pharmacokinetic profile of formulations was consistent with the reported human pharmacokinetic curves. In conclusion, the integration of data-driven machine learning, MD simulation and PBPK models is able to predict the in vitro drug release and in vivo pharmacokinetics of solid dispersion formulations. The integrated computational tools will significantly facilitate pharmaceutical formulation development than the traditional trial-and-error approach in the laboratory.

Keywords: solid dispersion, dissolution profile, machine learning, molecular dynamics (MD) simulations, physiologically based pharmacokinetic modeling

论文编号：07–007

Programmed Therapeutics to Reverse Idiopathic Pulmonary Fibrosis（程序化纳米粒用于特发性肺纤维化治疗）

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Abstract:

Here, we present surface-engineered nanoparticles (PER NPs) loading astaxanthin (AST) and trametinib (TRA) adhered to monocyte-derived multipotent cell (MOMC) forming programmed therapeutics (MOMC/PER). Specifically, the cell surface is designed to backpack plenty of PER NPs that reach directly to the lungs due to the homing characteristic of the MOMC and released PER NPs retarget injured AEC II after responding to the matrix metalloproteinase-2 (MMP-2) in IPF tissues. Then, released AST can enhance synergetic effect of TRA for inhibiting myofibroblast activation, and MOMC can also repair injured AEC II to promote damaged lung regeneration. Our findings provide proof of concept for developing a strategy for cell-mediated lung-targeted delivery platform carrying dual combined therapies to reverse IPF.

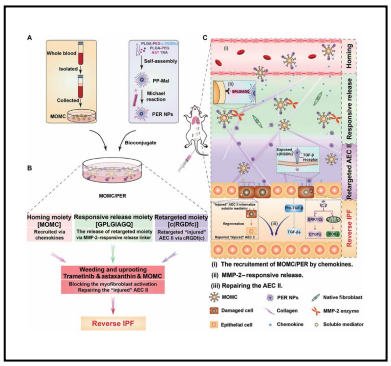

Fig. 1 Schematic illustration of lung-targeted programmed MOMC/PER therapeutic designed to reverse IPF. (A) Bioconjugated MOMC/PER was prepared by incubating PER NPs with MOMC. (B) MOMC/PER has multifunctional moieties including a homing moiety, responsive release moiety, and retargeting moiety to reverse IPF. Then, a weeding and uprooting strategy contributes to IPF reversion. (C) Schematic illustration of MOMC/PER for improved drugs accumulation and antifibrotic effect in IPF lung microenvironment.

Key words： surface-engineered nanoparticle; monocyte-derived multipotent cell; Idiopathic pulmonary fibrosis.

论文编号：07–008

喷雾干燥过程中甘露醇结晶对颗粒形成的影响与作用机制

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摘要正文：

喷雾干燥所得甘露醇粉体可作为药物载体或活性药物成分制备吸入剂，部分甘露醇吸入剂药物已在数个国家上市，还有些正在进行上市评估。吸入剂中甘露醇颗粒的粒径和形貌对活性成分在支气管及肺中的给送和生物利用率具有重要影响。而甘露醇是一种易于结晶的材料，喷雾干燥过程中雾化液滴经历的不同干燥动力学可影响甘露醇析出和形成颗粒的历程，导致干粉中颗粒及颗粒中晶簇的形貌差异。明确甘露醇在喷雾干燥中的颗粒形成机理，对粉体理化和功能特性的精确调控具有重要意义。本文采用均一颗粒微流控喷雾干燥技术，制备形貌大小均一、性质性能一致的甘露醇颗粒，研究进料液固形物含量及喷雾干燥温度对颗粒形貌及性质的影响。研究结果发现甘露醇的颗粒形成行为与常见肺部吸入剂载体乳糖具有较大差异，可通过调控干燥条件制备球形或具有不同程度凹陷的中空甘露醇颗粒。采用单液滴干燥实验研究甘露醇颗粒的形成过程，发现析出的甘露醇固形物倾向于在液滴表面富集形成较硬的表层，而溶解度相似的乳糖则未表现出这种倾向。本文探究了喷雾干燥过程中甘露醇结晶对颗粒形成的影响机理，所制备的甘露醇粉体具有较高的球形度和优秀的流动性，与市售的甘露醇样品相比具有较好的理化特性。

关键词：喷雾干燥；甘露醇；单液滴干燥；颗粒形成机理；粉体性质

论文编号：07–009

“里应外合”新策略——基于异形纳米结构的深部肿瘤治疗

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摘要正文：

目前，纳米药物对肿瘤的深度穿透仍然是肿瘤治疗的主要障碍。本工作将金-银中空纳米三角和二氧化硫前药精巧地整合于一体，构建了一种有效的肿瘤深部治疗纳米系统。利用该系统良好的光热转换能力和肿瘤部位的酸性微环境，可以通过pH值精确控制SO_2气体释放，实现“内部”气体治疗和“外部”光热治疗。光热-气体联合治疗可以同时激活细胞凋亡通路，即上调线粒体上凋亡因子Bax的表达，下调Bcl-2的表达，从而诱导Caspase-3表达，加速肿瘤细胞的凋亡，实现双赢。结果表明，该纳米系统在体内外对深部肿瘤均有良好的治疗效果。这种pH触发的SO_2气体治疗有望为改善纳米药物在肿瘤中的渗透性和异质性分布提供一种新策略。

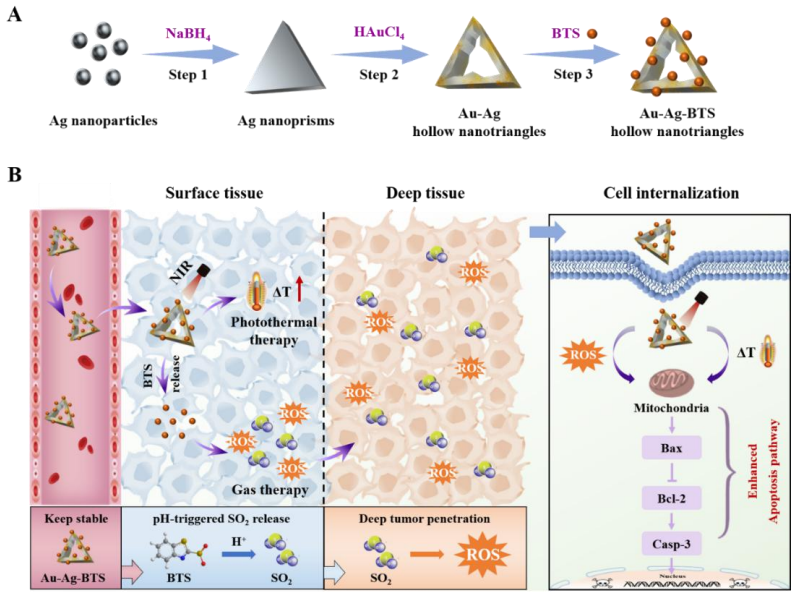

Fig. 1. Schematic illustration of (A) synthetic procedure of Au-Ag-BTS HTNs, and (B)“Collusion inside and outside” therapeutic mechanism of Au-Ag-BTS HTNs by acting together on apoptosis protein-Bax and enhanced tumor penetration.

关键词：金-银空心纳米三角；二氧化硫前药；肿瘤深部治疗；气体治疗

论文编号：07–009

“Collusion inside and outside” for deep tumor therapy based on abnormal-shaped nanostructures

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Abstracts:

Nowadays, limited deep tumor penetration is still the major obstacle in nanomedicines for cancer therapy. Here, we developed high-efficiency nanocomposites, SO_2 prodrug (BTS) loaded Au-Ag hollow nanotriangles (Au-Ag-BTS HNTs), which could not only inhibit superficial tumor but also deep tumor. Taking advantages of excellent photothermal conversion ability as well as acidic microenvironment in the tumor sites, SO_2 gas release could be precisely controlled by pH, thus realizing “collusion inside” gas therapy and “outside” photothermal therapy. More importantly, the combined therapy could simultaneously upregulate the expression of Bax as well as downregulate Bcl-2 in mitochondria, which would induce an increase of Caspase-3 expression to accelerate the apoptosis of tumor cells. The results indicated that deep tumor therapeutic effect based on Au-Ag-BTS HTNs was realized in vitro and in vivo. Such SO_2 therapy offered a novel strategy for improving penetration and heterogeneity distribution of nanotherapeutics in tumor.

Keywords: Au-Ag hollow nanotriangles; sulfur dioxide prodrug; deep tumor therapy; gas therapy

论文编号：07–010

超临界快速膨胀结晶工艺（RESS）制备辅酶Q10脂质体中的应用

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摘要正文：

辅酶Q10（CoQ10）是存在于人体所有细胞中的脂溶性醌类化合物，CoQ10的水中溶解度和细胞膜渗透性极大地制约着其在人体中的生物利用度，从而制约其临床的应用[1-2]。本实验采用超临界溶液(RESS)快速膨胀法，以卵磷脂为载体材料，制备了纳米CoQ10脂质体，并采用透射电镜(TEM)对CoQ10脂质体的粒径进行表征，采用紫外光谱(UV)对CoQ10脂质体的包封率进行评价。通过压力的优化对比发现，当压力在25-35MPa时，超临界快速膨胀结晶工艺可以制备获得包封率在95%以上的CoQ10脂质体样品，并采用透射电镜(TEM)对CoQ10脂质体的粒径进行表征。当压力小于25MPa或大于35MPa时，CoQ10的包封率明显下降。通过这一方法制备得到的CoQ10脂质体的粒径均小于100nm，粒径分布非常均匀。通过这一方法制备得到的CoQ10脂质体拥有分散性高，水溶性好等特点，对于提高其在人体中的生物利用度有非常大的促进作用。

关键词：超临界快速膨胀结晶；辅酶 Q10；生物利用度；超临界流体技术

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论文编号：07–011

Gene regulations and delivery vectors for treatment of cancer（肿瘤治疗的基因调控与递送载体）

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Abstract:

Backgrounds: Resistant residual cancer and cancer stem cells after comprehensive treatment often result in the recurrence of cancer. The refractory nature of cancer is an important scientific problem to be solved.

Area covered: An emerging gene regulation strategy of cancer is involved in the cross field of chemistry, genomics, bioinformatics and pharmaceutical sciences, which could offer a possible solution to a curative strategy of cancer.

Expert Opinion: In this talk, we dealt with the advances and applications of major gene regulation strategies, including DNA modification, gene editing and RNA regulations. Moreover, we also analyzed the representative transfection carriers for delivering the genetic material into cancer cells, including viral and non-viral vectors. Herein, we conclude that the gene regulation by a safe and high efficient transfection vector would be promising to provide a new treatment strategy for full recovery of cancer disease.

论文编号：07–012

聚合物纳米颗粒佐剂构建、效果及安全性初步评价

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摘要正文：

疫苗在传染病的防治中发挥着重要作用，随着科技的发展，疫苗由传统的减毒活性疫苗、灭活疫苗等逐步发展为亚单位疫苗和基因重组疫苗等，其安全性得到了稳步提高，但是免疫原性越来越弱，因此需要添加佐剂来提高免疫效果。尽管铝盐佐剂是目前最常用的人用疫苗佐剂，但在一些新型疫苗尤其是重组蛋白抗原中，存在难以诱导有效免疫，因此，开发新型疫苗佐剂势在必行。

可生物降解聚合物颗粒佐剂因具有良好的生物相容性、可模拟病原体尺寸和结构、有效递送和呈递抗原，诱导高效体液与细胞免疫应答，是有潜力的新型疫苗佐剂系统。本团队前期构建了聚乳酸类脂质纳米粒，如图所示，构建的纳米颗粒尺寸为100 nm左右，可以通过静电吸附携载抗原，形成纳米疫苗；细胞水平评价结果显示，纳米疫苗能够被DC细胞大量摄取，并有效诱导DC的活化与成熟；体内抗原转运研究显示，纳米疫苗能够通过引流淋巴结被动靶向和DC细胞主动运输两种方式，将抗原转运至淋巴结，通过活化DC诱导T/B细胞的活化，诱导高效的体液与细胞免疫应答，同时，诱导了持久的免疫记忆水平。并且，采用此纳米体系携载不同抗原，开展了免疫效应评估，均诱导了较高的体液与细胞免疫应答，因此，构建的聚乳酸类脂质纳米粒是有潜力的疫苗佐剂平台。细胞和动物水平的初步安全性评价显示，构建的聚乳酸脂质纳米粒具有很好的体内安全性。

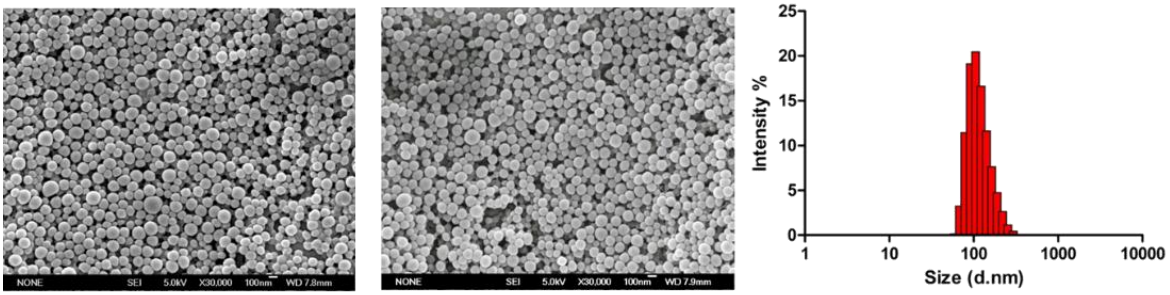

Fig. 1 SEM micrographs and size distributions of prepared nanoparticles

关键词：脂质纳米粒；颗粒佐剂；免疫应答

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论文编号：07–013

医学检测用生物颗粒创制

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摘要正文：

生物颗粒是疾病诊断和个体化治疗的重要内容。特别是近些年发展的纳米生物颗粒技术，可基于同一颗粒实现影像学上的增强显像和随后肿瘤影像引导治疗和疗效评估。报告人聚焦纳米生物颗粒在肿瘤诊断、医学影像和干预方面的特异性、敏感性和医用性等科学技术问题，利用材料、化学和工程等手段，构建蛋白仿生型诊疗生物颗粒探针。主要研究内容及学术成果：1.提出在超声波作用场下利用蛋白仿生修饰纳米颗粒，解决纳米颗粒非特异性吸附引发的诊断假阳性、病灶增强不显著等问题；2.证实相关氨基酸的仿生功能，提出多功能纳米生物颗粒的蛋白仿生集成概念，增强肿瘤多模诊疗效果；3.发现蛋白仿生合成后仍具活性，并用于肿瘤微环境高特异超敏诊疗。

关键词：生物颗粒；蛋白仿生；医学影像

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论文编号：07–014

基于核酸适体的靶向药物传递系统

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摘要正文：

近年来，基于核酸适体（aptamer）的给药系统（DDSs）成为疾病靶向和减少毒副作用的具有吸引力的平台。核酸适体是单链RNA或DNA，能与多种靶物质特异性结合，其与靶物质如金属离子、多肽、蛋白质和细胞膜蛋白具有高的结合亲和力和特异性。与传统抗体相比，核酸适体具有体积小、免疫原性小、批间差异小、成本低、易于修饰等优点，是一种很有前途的药物靶向配体。通过细胞膜受体介导的内化，偶联的DDSs可被靶向细胞选择性地摄取。目前，已有多种核酸适体介导的DDSs被构建出来，以实现对疾病的特异性给药，提高治疗效果。这里，我们报道在核酸适体介导的靶向递药系统上的最新研究成果，我们通过将光敏剂焦脱镁叶绿酸a（Pyro）与亲水性核酸适体Aptamer-sgc8连接，制备共轭物（APCs），使其具有增强的水溶性，实现对PTK7受体过表达肿瘤球体的特异性靶向和穿透，并发挥光动力治疗作用（图1A）。体外细胞毒性实验表明，APCs对Hela和MCF-7细胞具有选择性毒性，而对非靶向细胞（L02和HepG2细胞）的毒性较弱。我们还制备了基于二维材料和核酸适体的肿瘤靶向药物递送系统AS1411-NGO/B3（图1B），其中纳米氧化石墨烯(NGO)片作为药物载体，并将核酸适体AS1411偶联到氧化石墨烯上用于肿瘤靶向，氧化石墨烯具有独特的理化特性，可以吸附药物，通过在其表面吸附我们之前合成的具有抗癌活性的小檗碱衍生物用于肿瘤的治疗，氧化石墨烯光照后实现光热转换，并促进B3的释放，还可实现化疗和光热治疗联合应用于肿瘤的治疗。以上递药系统的研究为肿瘤治疗提供了具有较好应用前景的平台。

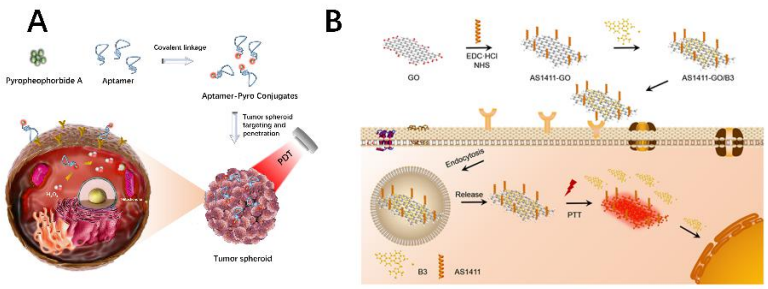

Fig. 1 (A) Sgc8 aptamer-Pyropheophorbide A conjugates with enhanced spheroid targeting and penetration abilities for tumor photodynamic therapy. (B) Graphene oxide (GO) loaded with drug berberine 9-*O*-pyrazole alkyl derivative B3 and modified with aptamers for cancer chemo-photothermal synergetic therapy.

关键词：核酸适体；光敏剂；肿瘤靶向；光动力治疗；化疗-光热联合治疗

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论文编号：07–014

Aptamer-Based Targeted Drug Delivery Systems

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Abstracts:

Recently, aptamer-based drug delivery systems (DDSs) emerged as attractive platforms for precise medicine by targeting to disease cells and reducing the side effects. Here, we report the aptamer-pyropheophorbide A (Pyro) conjugates (APCs) by linking Pyro to hydrophilic nucleic acid aptamer sgc8, which endowed it with enhanced water solubility, specific targeting and penetration to PTK7 overexpressed tumor spheroid for photodynamic therapy (Figure 1A). The *in vitro* cytotoxicity assays demonstrated that the APCs showed selective toxicity to Hela and MCF-7 cells, while alleviated toxicity to the control groups (L02 and HepG2 cells). We also prepared drug delivery system, namely, AS1411-GO/B3 for tumor targeting, in which nano-graphene oxide (NGO) sheets were employed as drug carrier, and the aptamer AS1411 was conjugated onto GO for tumor targeting. GO promoted the release of drug from GO as well as the generation of thermal cytotoxicity to cells. This AS1411-GO/B3 provided a promising platform for tumor treatment.

论文编号：07–015

A Modular Process Analysis Platform to Promote the Industrialization of DPIs（用于DPIs快速检测的模块化分析平台）

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Abstracts:

Dry powder inhalations (DPIs) had attracted enormous attention worldwide in lung diseases on account of direct lung delivery, good drug stability and satisfactory patient compliance. However, insurmountable technical barrier, high cost and long cycle restricted the industrialized development of DPIs, which was resulted from the indistinct understanding of pulmonary delivery processes (PDPs). It was attributed to the drawbacks of current evaluation methods that could not investigate the whole and consecutive PDPs separately, or explored with simplified models that neglected some crucial powder properties of DPIs. In the present research, a modular process analysis platform (MPAP) was developed to explore the PDPs mechanism of DPIs in real-time and consecutively. MPAP was composed of a laser particle size analyzer, an inhaler device, artificial throat and pre-separator (Fig.1A~C, representing Configuration A~C, respectivly), in order to monitor the fluidization and dispersion, transportation, detachment and deposition of DPIs.

The effects of carrier particle size (CPS), flow rate and inhaler device on PDPs were investigated in detail by the MPAP. Reliable results were obtained after careful comparison with the results of NGI. Take the CPS for example, the model carrier-based DPIs was prepared by blending micronized salbutamol sulfate (MSS) and lactose (LAC) with different CPS at a ratio of 1:15 (w/w). The measurements were conducted under the air flow of 60 L/min. The release profiles (R), maximum of release amount (R_{max}) and total release amount (R_{AUC}) of drug, drug aggregation and carrier were obtained.

With Configurantion A, the following information about the fluidization and dispersion of DPIs was available. The R values showed increment in the first place and decrement subsequently, which was similar to the breath of human. With the decrease of CPS, the R_{max} (Fig. 1E) and R_{AUC} (Fig. 1F) of DPIs increased. DPI_1 exhibited the highest R_{max}, which was 1.43-fold, 1.60-fold, 2.41-fold of DPI_2, DPI_3 and DPI_4, respectively. Meanwhile, the R_{AUC} of DPI_1 was much higher than DPI_4 (2.98-fold). There were good linear relationships between R_{max} and D_{50} of corresponding LAC (R^2 = 0.9967) (Fig. 1E). It was indicating that DPIs with smaller CPS was prone to be transported into deeper airway instead of premature deposition. Meanwhile, the detachment between drug/drug aggregation and carrier increased with smaller CPS. More information about the transportation, detachment and deposition of DPIs could be obtained in Configurantion B and Configurantion C. Thus, the constructed innovative MPAP is promising to promote the industrialization of DPIs.

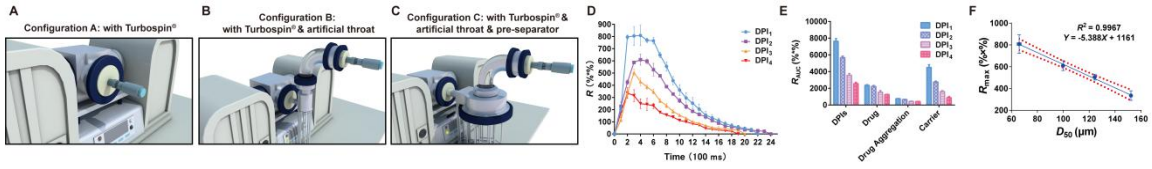

Fig. 1 (A~C) Schematic diagram of MPAP; (D) Release profiles of DPIs; (E) Total release amount; (F) the correlation between D_{50} of LAC and R_{max}; (n=3).

Keywords: Dry powder inhalation; Pulmonary delivery process; Process analysis platform; Real-time monitor

论文编号：07–016

人血清白蛋白纳米粒载甲氨蝶呤靶向治疗类风湿关节炎研究

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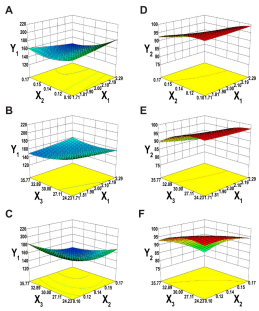
摘要正文：

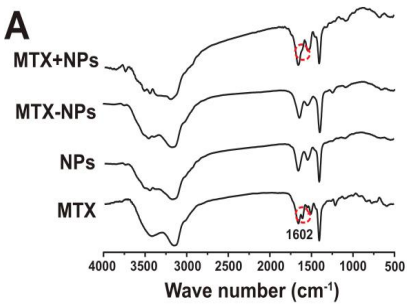
目的：将甲氨蝶呤（Methotrexate, MTX）包载于人血清白蛋白（Human serum albumin, HSA）纳米粒，并将配体甘露糖（Mannose, Man）通过酰胺化反应修饰于纳米粒表面，制备具有靶向性的新型递药系统MTX-M-NPs；克服MTX难溶性的缺点，延长药物半衰期，增强药物的靶向性，降低毒副作用，提高患者的依从性；实现MTX既抗炎镇痛又抑制血管新生的双重作用。考察目标递药系统MTX-M-NPs的粒径、包封率、形态、体外释放率、体内外毒性、药代动力学参数、体内外靶向性以及对类风湿性关节炎（Rheumatoid arthritis, RA）的治疗作用。

方法：首先，本课题在单因素筛选后利用星点设计优化制备载药纳米粒（MTX-NPs）的工艺处方；对甘露糖（Man）进行结构改造合成甘露糖衍生物，然后将其修饰于MTX-NPs表面，制备得到目标递药系统MTX-M-NPs；并用红外光谱分析验证配体是否连接成功。随后，通过细胞毒性试验和溶血实验对MTX-M-NPs的体外毒性进行考察；并通过细胞摄取试验研究RAW264.7和NEs细胞对MTX-M-NPs的体外摄取情况；通过鸡胚尿囊膜实验考察MTX-M-NPs对新生血管是否有抑制作用。接着，对MTX-M-NPs进行药代动力学研究，并考察其组织分布情况。最后，通过构建胶原诱导型关节炎（Collagen-induced arthritis, CIA）模型，对MTX-M-NPs进行体内药效学评价。

结果：实验结果表明，本课题制得的MTX-NPs呈球形，大小均匀，经星点设计优化后，包封率显著提高（Figure 1）。通过红外光谱分析，结果证明了Man成功修饰于纳米粒表面（Figure 2）。在相同给药浓度和相同时间条件下，MTX-NPs组和MTX-M-NPs组对RAW264.7和NEs细胞毒性明显减小；MTX-NPs组和MTX-M-NPs虽然有一定的溶血性，但均小于5%。MTX-NPs和MTX-M-NPs都能被RAW264.7和NEs细胞有效摄取，且MTX-M-NPs组均强于MTX-NPs组，具有显著性差异，这表明MTX-M-NPs对两种细胞的靶向性比MTX-NPs更强。在鸡胚尿囊膜实验中，MTX-M-NPs对新生血管显示出明显的抑制作用，且其抑制作用明显强于游离的甲氨蝶呤（Free-MTX）和MTX-NPs（Figure 3）。药代动力学研究表明，MTX-NPs和MTX-M-NPs的半衰期相比于Free-MTX都明显延长；组织分布研究表明，MTX-M-NPs对于CIA模型大鼠具有明显的关节靶向性。体内药效学实验表明，MTX-M-NPs对类风湿性关节炎的治疗效果明显优于其他治疗组，且其毒副作用相对于Free-MTX明显降低（Figure 4）。

结论：本课题成功构建了纳米靶向给药系统MTX-M-NPs，该给药系统延长了MTX半衰期，降低了MTX毒副作用；使MTX能特异性靶向到炎症部位，实现MTX既抗炎镇痛又抑制血管新生的双重作用，对类风湿性关节炎具有较好的治疗效果。





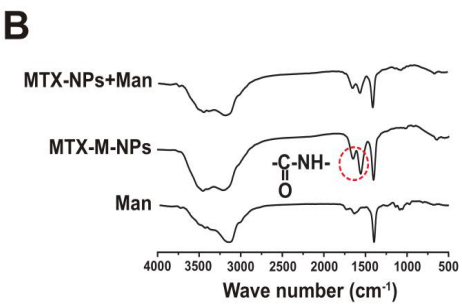


Fig. 1 Response surface plot and contour map of the combined effect of X1 and X2 (A, D), X1 and X3 (B, E), X2 and X3 (C, F) on the mean size and encapsulation efficiency (EE).

Fig. 2 Results from the infrared spectroscopy analysis. Comparison of MTX, NPs, MTX-NPs and the physical mixture of MTX and NPs (A) and comparison of Man, MTX-M-NPs, and the physical mixture of Man and MTX-NPs (B).

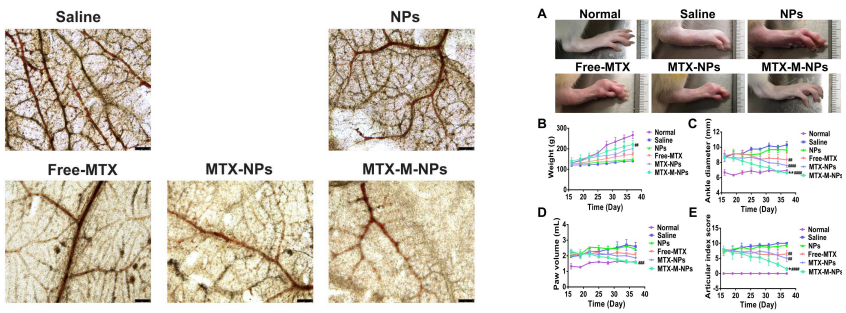


Fig. 3 The effect of the different formulations on the neovascularization of the chicken embryo allantoic membrane. The fertilized chicken eggs were incubated for 7 days at 37 °C with a 55% relative humidity. On the seventh day post-incubation, eggs were swabbed with 75% ethanol solution and a hole was opened in the middle of the air chamber, and another hole is made in the middle body of the egg to form a false gas chamber. Follow incubation for 48 h, different formulations of Saline, NPs, Free-MTX, MTX-NPs, MTX-M-NPs were added respectively. After an incubation period of 24 h, the blood vessel was separated and photographed using microscope, the magnification is 40 times.

Fig. 4 Treatment effects of various formulations on CIA model rats. The CIA rats randomly assigned into six groups and given the different formulations every three days for 10 times. The photographs of representative hind legs were taken on the 36th day (A). The weight (B), ankle diameter (C), paw volume (D) and articular index score (E) were recorded every three days. The significance of the differences was evaluated using 1 way ANOVA (each group vs saline group, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$, and $^{\#\#\#\#}P < 0.0001$; MTX-M-NPs vs Free-MTX, $^{*}P < 0.05$ and $^{**}P < 0.01$). Data are shown as the mean ± SD in each group (n≥3).

关键词：甲氨蝶呤；人血清白蛋白；纳米粒；甘露糖；类风湿性关节炎

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论文编号：07–017

纳米光遗传学药物调控新技术

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摘要正文：

利用合成生物学，设计肠道工程菌，构建“在体制药工厂”，已取得系列进展。然而，如何精准调控“在体制药工厂”的药物生产，一直是应用转化的痛点。针对上述现状，天津大学王汉杰团队独辟蹊径，率先利用“纳米光遗传学”策略，开创性地为肠道工程菌装配“感光元件”，利用近红外光线，实现在体药物生产的精准调控。该技术已申请系列发明专利，并于退行性脑疾病、糖尿病、肿瘤、病毒感染等动物模型中同步进行验证实验，均可实现因子（药物）调控作用，取得了一定的疾病防治效果。

关键词：纳米光遗传学；肠道工程菌；蛋白质调控；药物绿色智造

论文编号：07–018

用于胰岛素口服递送的环糊精胰岛素包合物

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摘要正文：

目的：设计一种环糊精胰岛素包合物（NAC-HP-β-CD-Arg@insulin），用于胰岛素的口服递送。方法与结果：首先，合成得到羟丙基-β-环糊精衍生物（NAC-HP-β-CD-Arg）载体，并通过FT-IR和^{1}H-NMR分析对产物进行表征，之后，利用NAC-HP-β-CD-Arg的疏水空腔对胰岛素的疏水部分进行包载，制备成NAC-HP-β-CD-Arg@insulin包合物；利用荧光光谱确定了包合物的形成，利用XRD分析出胰岛素以无定型形式存在于包合物中，并利用等摩尔浓度变化法确定包合物的包合比为1.5：1。圆二色谱结果证明，包合物并未改变胰岛素的二级结构，胰岛素仍具有其生物活性。体外酶促降解实验显示，包合物可以有效减缓α-糜蛋白酶和胰蛋白酶对胰岛素的降解；Caco-2细胞转运实验显示，包合物中的胰岛素比游离胰岛素的表观渗透系数高8倍；大鼠体内粘膜粘附性实验显示，包合物可以延长胰岛素在胃肠道的停留时间；大鼠体内降糖实验显示，包合物具有优异且持续的降糖效果。结论：环糊精胰岛素包合物是一种很有应用前景的用于胰岛素口服递送的载药体系。

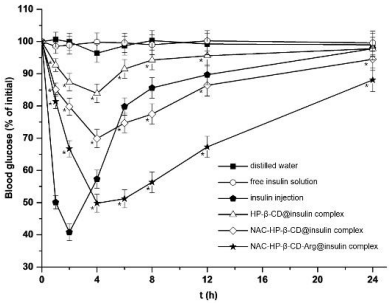

Fig. 1 Plasma glucose levels after administration of various insulin samples.

关键词：羟丙基-β-环糊精；N-乙酰-L-半胱氨酸；胰岛素；口服递送

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论文编号：07–019

序贯式克服肠道屏障并靶向至肝脏的口服胰岛素纳米载体

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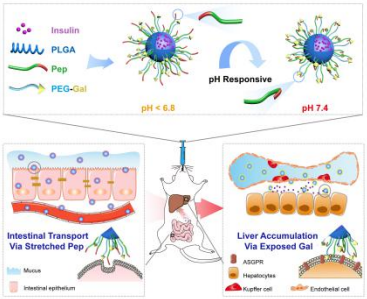
摘要正文：

正常生理条件下内源性胰岛素经胰岛β细胞分泌后首先经门静脉被运送至肝脏，因此肝脏中的胰岛素浓度是外周的2-4倍[1]。与皮下注射的方式相比，通过口服给药将胰岛素递送至肝脏可以更好地模拟内源性胰岛素的分泌过程，调节外周胰岛素水平并降低低血糖发生率[2]。然而，胰岛素在到达肝脏前首先需要克服胃肠道屏障，这也是限制胰岛素口服吸收的关键因素[3]。针对以上问题，为使口服胰岛素序贯地跨过肠道屏障并靶向至肝脏发挥作用，我们设计了一种功能型口服胰岛素纳米载体（Pep/Gal-PNP），其以聚乳酸-羟基乙酸共聚物（PLGA）作为基质材料，内部包载胰岛素，并在表面同时修饰具有伸缩折叠特性的穿膜肽（Pep）以及肝脏靶向的半乳糖分子（Gal）两种配体（**Fig.1**）。由于Pep/Gal-PNP表面的Pep配体具有pH响应作用（**Fig.2a-b**），可在胃肠道酸性环境中发生伸展并暴露出一端的穿膜肽，显著提高了胰岛素在肠上皮细胞的转运效率（**Fig.2c**），约为游离胰岛素的8.7倍。入血后Pep在中性环境中发生折叠并暴露出Gal配体，增加了Pep/Gal-PNP在肝脏的分布，约为对照组的6.9倍（**Fig.2d**）。在I型糖尿病大鼠模型中，Pep/Gal-PNP显示出良好、持续的降血糖作用（**Fig.2e**），可将糖尿病大鼠的血糖水平维持在正常范围（约为初始的21.2%），且肝门静脉中胰岛素含量为外周的3.2倍（**Fig.2f-g**），与内源性胰岛素的分布模式相似。因此，本研究中设计的双功能口服胰岛素纳米载体，可序贯式克服肠道屏障并将胰岛素递送至肝脏，高度模拟了内源性胰岛素的分布模式，避免了外周高胰岛素血症的发生，安全高效，在胰岛素的口服递送研究中具有良好的应用前景。



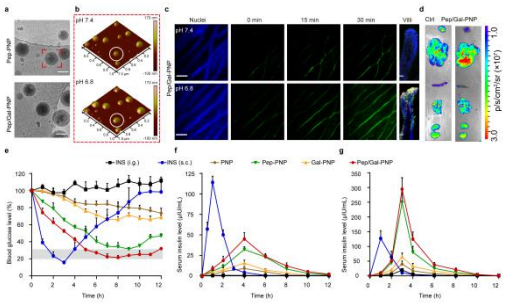


Fig.1 Schematic illustration of synthesis of Pep/Gal-PNP and its oral delivery route

Fig.2 The characterization of Pep/Gal-PNP and its i*n vivo* biodistribution and therapeutic effect on diabetic rats. a) Cryo-TEM images of nanoparticles. b) The AFM images of Pep-PNP under different pH conditions. c) Intravital two-photon images of the absorption of nanoparticles in intestinal villi. d) The accumulation of nanoparticles in major isolated organs imaged by IVIS. e) Therapeutic effect on type I diabetic rats. f) Peripheral and g) portal serum insulin level versus time profiles of diabetic rats following oral administration.

关键词：口服胰岛素；序贯式转运；可伸缩穿膜肽；肝靶向；pH响应

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论文编号：07–020

Impact of different excipients on spray dried microparticles: morphology, solid state characteristics and intrinsic dissolution（不同赋形剂对喷雾干燥微粒的影响:形貌、固态特性和本征溶出度）

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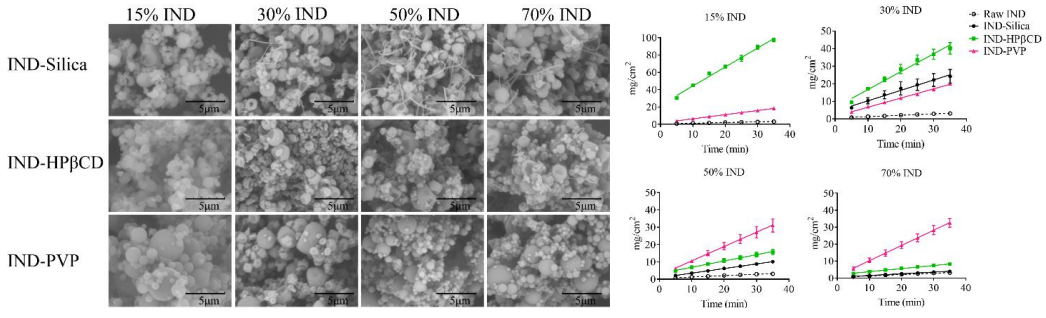
Abstracts:

Purpose Spray drying is widely used for constructing inhalable microparticles in the pharmaceutical industry. Excipients are normally introduced during spray drying process in order to modify the characteristics of the microparticles such as morphology, solid state, and dissolution properties. The aim of this study was to investigate three different types of excipients i.e. colloidal particles, long-chain polymers, cyclic oligosaccharides, and their impact on the characteristics of the spray dried microparticles.

Methods Indomethacin (IND) was used as a model drug and spray dried at different drug loadings using colloidal silica, 2-hydroxypropyl-β-cyclodextrin (HPβCD) or polyvinylpyrrolidone (PVP) as excipients. The morphology, solid state and dissolution behavior of the spray dried microparticles were studied.

Results All the resultant microparticles were between 1-3 μm in diameter, the samples with silica and HPβCD had narrow size distributions. X-ray powder diffraction results showed that IND was amorphous in all three spray dried samples. The IND-Silica sample re-crystallized, while the IND-PVP sample remained amorphous after 4-months of storage [1]. The excipients also showed different impact on the intrinsic dissolution rate of spray dried IND. The dissolution rate of IND with silica or HPβCD increased with an increase in the fraction of excipients in the spray dried microparticles whereas samples with PVP showed an opposite trend.

Conclusions The long-chain polymer i.e. PVP exhibited the best stabilizing effect for IND among all the excipients studied. However, HPβCD in represent of the cyclic oligosaccharides is more efficient for forming microparticles with narrow size distribution and improving the dissolution rate of the IND at low drug loadings.



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论文编号：07–021

原料药微粉化的粒度控制与大生产关键技术研究

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摘要正文：

CN 210449445 U：本实用新型涉及粉碎装置技术领域，具体来说是一种可拆卸可更换材质的圆盘式气流粉碎装置，上出料口设于上盘的顶部，上盘内衬、下盘内衬、粉碎环和粉碎环内衬均设于粉碎装置的内部，上盘内衬设于粉碎装置内的顶部，粉碎环设于粉碎装置内的中部，下盘内衬设于粉碎装置内的底部，粉碎环的内环上环绕设有若干喷嘴，粉碎环内衬圆周方向上环绕设有若干通孔，粉碎环内衬设于粉碎环的内环内，喷嘴的孔道包括大孔和小孔。本实用新型通过在粉碎环内衬设置通孔，喷嘴可以经粉碎环内衬的通孔与粉碎环连接，喷嘴无需单独拆卸，粉碎环内衬可以避免黏性物料的粘附；喷嘴孔道为发射锥面结构，喷嘴孔道的大孔和小孔设计，可以起到引流和稳定气流的作用。

CN 210449444 U：本实用新型涉及物料喷吹装置技术领域，具体的说是一种用于解决管道物料堆积问题的喷吹装置，喷吹装置设于运输管道上，喷吹装置包括上盘和下盘，上盘内壁与下盘外壁间留有间隙，喷吹装置的外壁设有三进气通道，三进气通道连通于一气体缓冲腔，气体缓冲连通于上盘内壁与下盘外壁的间隙，进气装置包括三输气管道和压力调节器，三进气通道分别通过三输气管道连接于压力调节器。本实用新型气体缓冲腔和上盘内壁与下盘外壁的间隙设计，高压气体进入气体缓冲腔内，可以稳定气流并进行压缩，随后稳定的气流经过下盘与上盘之间的间隙进入积粉的运输管道，高速气流在运输管道内以360度无死角的方式全面喷出，对运输管道的积粉进行全方位清扫。

论文编号：07–022

基于颗粒技术天然产物新型给药系统开发

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摘要正文：

随着制剂新技术的发展，开发能更有效满足小分子天然产物临床治疗需求的新剂型有望实现该类药物的二次开发，为相应疾病治疗提供新的选择。本研究借助多种颗粒技术，在纳米颗粒、微米颗粒与毫米颗粒三个尺度对包括苏子油、穿心莲内酯等在内的多种天然产物单体化合物或混合物开展新剂型研究，实现了对应药物的静脉递送、长效缓释、口服掩味、肠壁贴附控释及口服生物利用度提升，为相应新产品的开发奠定了基础。

苏子油富含α-亚麻酸等多不饱和脂肪酸及天然抗氧化物质，可用于化疗及ICU应激状态的肠外营养支持。本研究明确了甾醇对植物油脂静脉应用安全性的影响，联合硅胶柱层析法、水蒸气蒸馏等手段将甾醇含量降低至100 mg/100 g油以下[1]，低于所有市售静脉营养脂肪乳。制备的苏子油脂肪乳平均粒径301.1 nm，PDI为0.176，zeta电位-32.9 mV，稳定性良好。本品血管刺激性与生理盐水无异，且无致敏性，安全性良好。在小鼠化疗损伤模型中，低剂量苏子油脂肪乳与中剂量某市售品种具有相同的体重维持效果。

针对穿心莲内酯（AND）生物利用度低及味苦问题，采用液相研磨法，以HPMC E5为稳定剂制备了AND纳米晶混悬液，D_{50}约500 nm，并采用液相层积法将药物混悬液层积于MCC丸芯上。研究确定了AND的苦味阈值为3.50 μg/mL，并以丙烯酸树脂IV号为阻滞材料进行包衣掩味。掩味微丸人工唾液中2 h溶出量低于药物苦味阈值。比格犬口服药动学研究表明，自制微丸C_{max}是市售滴丸的2.7倍，相对生物利用度可达市售滴丸的1.5倍[2]。

盐酸小檗碱（BER）可在肠道通过抑制α-糖苷酶活性、下调SGLT1、抑制肠道apoB48合成等途径发挥降糖降脂效果[3]。针对这一机制，本研究联合湿法研磨-流化床上药及流化床包衣工艺制备了粒径250-430 μm的BER贴壁控释微丸，与大粒径微丸（1-1.2 mm）相比，小粒径微丸在家兔体内的滞留百分比提升近一倍。基于这一理念，又针对胃内不稳定的三七总皂苷开发了肠溶型口服速释制剂，通过贴壁滞留提高三七总皂苷生物利用度，为胃肠道滞留制剂的研发提供了新的思路[4]。

银杏内酯水溶性差，口服生物利用度低。本研究针对其成分的复杂性，联合HPMC、SDS、磷脂等多种稳定剂制备平均粒径370 nm的银杏内酯纳米混悬剂。借助甘露醇的支撑效应确保流化床上药后的再分散性，载药微丸复溶后纳米晶平均粒径396 nm，主要成分30 min内溶出度大于90%。比格犬药动学研究表明，以微丸制剂给药，银杏内酯A和银杏内酯B的相对生物利用度分别为原料药的2.21倍和4.37倍[5]。

关键词：颗粒技术；天然产物；静脉脂肪乳；长效注射剂；口服功能性制剂

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论文编号：07–023

What is the future for nanocrystal-based drug delivery systems?（刍议纳米晶药物递送系统发展方向）

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Abstract：

Nanocrystal is a platform technique for delivery of poorly water-soluble drugs and has gain great commercial success in oral drug delivery. We argue that the future of this technique lies in the cancer treatment and development of parenteral preparations. For this purpose, breakthroughs in technique for uniform and high quality nanocrystals as well as deciphering the in vivo fate of nanocrystals are critical. The bottom-up technique may be capable of better controlling the particle properties, while hybrid nanocrystal technique provides a novel approach to explore the in vivo fate of nanocrystals. Breakthroughs in these two technique to further the development of nanocrystals are also discussed.

Keywords： nanocrystals; parenteral delivery; bottom-up; particle size; in vivo fate

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多重光散射技术研究药物粉体稳定性对流动性的影响

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摘要正文：

化学原药粉体、药物辅料粉体及中药浸膏粉体的流动性，在生产工艺、传输、储存、装填以及中药制剂中的不同成分的混合，颗粒剂、片剂、散剂、胶囊剂的成型及装量有着重要的意义。影响药物粉体流动性的因素非常复杂，重力、颗粒间的黏附力、粒径分布、颗粒形状、空隙率、堆密度、粘结指数、内部摩擦系数等因素都对的流动性产生影响。这些因素受粉体在空气中放置稳定性的影响，粉体的团聚直接改变颗粒间的黏附力、粒径分布、颗粒形状、空隙率、堆密度、粘结指数、内部摩擦系数，是影响药物粉体最重要因素。

药物粉体的聚团现象大致分成液接团聚（软团聚）和分子间团聚（硬团聚）两大类。软团聚是粉体颗粒间的静电力和范德华力以及表面吸附的液膜共同作用形成的，较容易分散；而硬团聚经过很多科学工作者的研究认为，它主要是由化学键作用形成的，较难分散。 粉体表面改性技术改善药物粉体团聚，改善中药浸膏粉体吸湿性、润湿性及流动性等，是近年国内药剂学工作者关注的重点。

本文利用TURBISCAN多重光散射技术，研究了药物粉体在不同储存条件下颗粒平均粒径随时间变化的图谱，并区分是液接团聚还是分子间团聚。研究了药物粉体改性剂的种类和浓度对粉体稳定性的影响以及药物粉体的稳定性对流动性的影响。

关键词：药物粉体；稳定性；流动性；聚团；表面改性

论文编号：07–025

Bio-Responsive Nanodrugs Generators for Enhancing Chemo-Immunotherapy and Modulating Tumor Microenvironment（纳米药物生物反应器用于增强化学免疫治疗和调节肿瘤微环境）

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Abstract：

Bio-responsive nanoscience has received extensive attention and become mainstream strategies for treating cancer. Herein, an innovative implantable bio-responsive nanoarray (DOX/JQ1-IBRN) is developed to eliminate tumor cells and reprogram immunosuppressive tumor microenvironment (ITME). Chemotherapeutics doxorubicin (DOX) and epigenetic modulator JQ1 are first co-loaded into tumor-targeting nanoparticles (HP-DOX/JQ1 NPs), which are then linked up through the bio-responsive linker to construct the nanoarray loading with another part of JQ1. Under high level of H_2O_2 in TME, the implanted DOX/JQ1-IBRN could disaggregate and release JQ1 while generating small-sized HP-DOX/JQ1 NPs. On one hand, JQ1 selectively blocks programmed death-ligand 1 (PD-L1) and regulatory T cells (Tregs)/-disruptive effect to relieve ITME. On another hand, HP-DOX/JQ1 NPs destroy residual tumor precisely and stimulate strong antitumor immunity. It is demonstrated that DOX/JQ1-IBRN prevents post-surgical recurrence/metastasis and prolongs survival with negligible toxicity. The 'clusterbomb' nanoarray (a simple, valid, and safe scaffold) is expected to provide crucial insights for post-surgical treatment.

Keywords: Post-surgical, Precise treatment, Tumor microenvironment, Implantable nanoarray, Immunotherapy

论文编号：07–026

药物粉体的加工过程对制剂产品质量的影响

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摘要正文：

固体制剂与普通液体制剂相比，制备过程复杂，质量控制的风险比较大。固体制剂的起始原料一般是药物粉末，药物本身的理化性质由药物的结构确定，是个定数，但药物的粉体性质，不用说是不同药物，就是同一种药物由粒径开始到流动性乃至压缩成形性等都是千变万化的变数。为保证固体制剂的产品质量和生产过程的顺利进行，我们借助辅料的帮助，采用适宜的制备工艺和制剂设备，对药物进行加工和处理，如粉碎、分级、混合、制粒、干燥、压片等，实际上每一步单元操作都是粉体的处理过程。

本次报告重点介绍粒子的加工过程（粉碎，制粒，压片）对产品质量的影响。即如何根据药物的粉体性质正确选择制备工艺，反过来制备工艺又如何影响药物的粉体性质？如，粉碎是在制剂过程中粒子加工的第一步，粒径大小是影响产品质量的最关键性质。粒子大小影响药物的混合均匀度，药物的溶出，甚至影响药物的压缩成形性，从而影响最终产品质量，因此根据需要选择适宜的粉碎机；粒子大小和密度也会影响制粒过程的顺利进行，小而轻的药物粉末与稀释剂混合，流化床制粒时，物料在气流中容易分层，不易得到含量均匀的颗粒，必须对工艺参数上下功夫，或选择其他制粒技术；过分制粒和制粒不足，不仅影响物料的流动性，而且影响压片过程的顺利进行，出现粘冲，裂片，含量不均等不良现象发生。粉体性质很多，其中重点关注的性质是药物粉体的粒度，制粒后的粉体性质，如粒径，密度，流动性，压缩性。这些是使生产工艺的顺利进行，保证产品质量的关键性质。

关键词：药物；粉体性质；粉碎；制粒；压片

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论文编号：07–027

The effect of organic ligand modification on the protein corona formation of nanoscale metal organic frameworks

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Abstract:

As one of the most stable Nanoscale Metal Organic Frameworks (NMOFs), zirconium (Zr)-based UIO66 is widely employed as a drug carrier for their high surface-area-to-volume ratio, easy surface modification and excellent biocompatibility[1]. The organic ligand modification is a well-established strategy to improve the loading capacity of UIO66. When NMOFs were administrated *in vivo*, the proteins in biological fluids would inevitably bind to their surface and formed the protein corona (PC), affecting its biodistribution, pharmacokinetics and drug release, which made the therapeutic effect of NMOFs unpredictable *in vivo*, which led to the difficulty of clinical transformation[2].

In order to investigate the effect of organic ligand modification on PC formation of NMOFs, we chose BSA as model protein as its similar physicochemical properties with human serum albumin, and UIO66, UIO66-2COOH and UIO66-NH_2 as model NMOFs. Transmission electron microscope (TEM) was used to observe the morphology of NMOFs. The bicinchoninic acid (BCA) assay was introduced to determine the relative BSA adsorption amount, the specific surface area and porous structure changes were studied using an automatic surface area and porosity analyzer and analyzed by Brunauer-Emmett-Teller (BET) formula.

As shown by TEM image, all NMOFs were nanometer scale and exhibited regular cubic shape (Fig. 1A-1C). After the soft PC was removed by separation, the hard protein adsorption capacity was determined by BCA assay. Compared with UIO66 and UIO66-NH_2, the relative adsorption amount of BSA on UIO66-2COOH is the largest (Fig. 1D). In addition, the BET surface area of UIO66-2COOH also decreased most significantly, demonstrating that its surface was remarkably adsorbed by BSA to occupy the pore (Fig. 1E). The hard PC formation on porous structure of NMOFs was also analyzed by BET characterization (Fig. 2A-2C). It was shown that UIO66 and UIO66-NH_2 exhibited I-type adsorption isotherms, while UIO66-2COOH exhibited IV-type adsorption isotherms. The different adsorption of N_2 at low $p/p°$ indicated the nanopores structure (< 2 nm) of UIO66 and UIO66-NH_2 and the mesoporous structure (2-50 nm) of UIO66-2COOH. After BSA adsorption, the adsorption isotherms of UIO66-2COOH decreased significantly, implying the reduction of porosity with the hard PC formation. The different types of PC formation may be ascribed to the mesoporous structure of UIO66-2COOH which enables BSA to be embedded, leading to the stronger interaction. Thus, it can be concluded that the UIO66-2COOH mainly forms an irreversible hard PC due to its larger pore size, while the other two formed fragile soft PC.

These results demonstrate that the BSA adsorbed on the surface of NMOFs in different forms. Due to the different porous structures, BSA can be embedded in mesoporous UIO66-2COOH to form a hard PC and change its porosity while adsorbed on micropores UIO66 and UIO66-NH_2 to form soft PC (Fig. 3). The specific mechanism needs to be further studied.

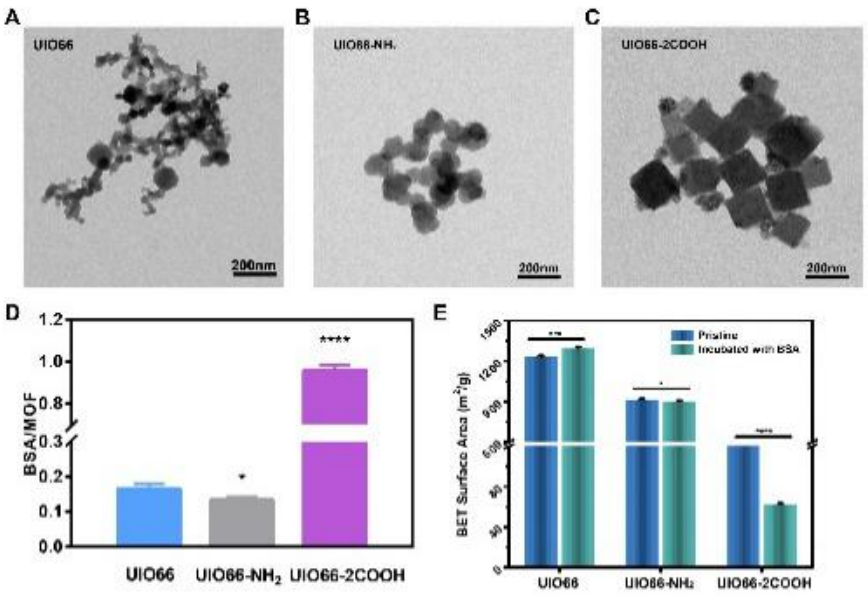

Fig. 1 The TEM images of UIO66 (A), UIO66-NH_2 (B) and UIO66-2COOH (C). The relative adsorption amount (D) and BET surface area change (E) of NMOFs.

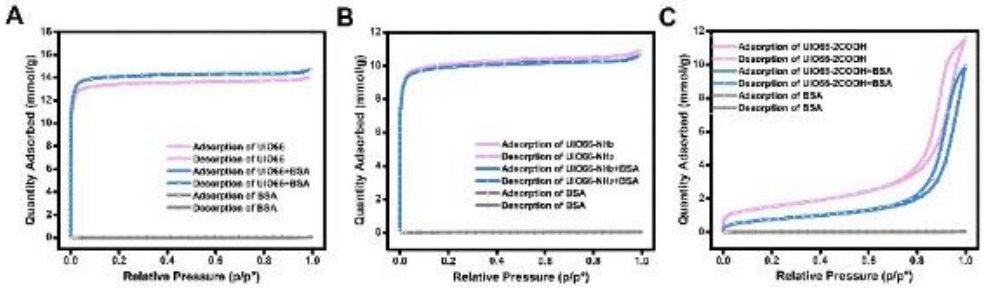

Fig. 2 The adsorption isotherms of UIO66 (A), UIO66-NH_2 (B) and UIO66-2COOH (C).

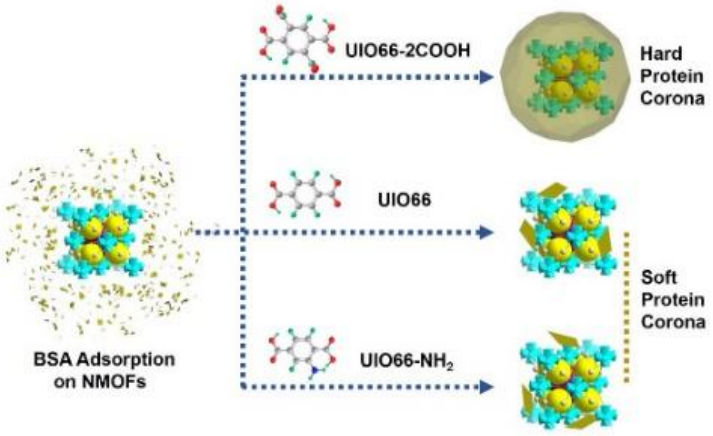

Fig. 3 PC formation process of NMOFs.

Keywords: Metal Organic Frameworks; Organic Ligand Modification; Protein Corona

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论文编号：07–028

An oral drug delivery system with particular properties for orthotopic colon cancer therapy

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Abstract:

Investigation the application of the programmed drug release system to improve premature exposure and poor real-time monitoring of drugs in oral delivery systems. Methods: Inspired by the characteristics of pH changes of gastrointestinal tract (GIT) and specific enzymes secreted by colonic microflora, we anchored poly(acrylic acid) (PAA) and chitosan (CS) on the Gd3+-doped mesoporous hydroxyapatite nanoparticles (Gd-MHAp NPs) to realize programmed drug release and magnetic resonance imaging (MRI) in tumor sites. Results: The drug release rate was of only 10.2% ± 0.3% in the gastric acid environment, and the system has an MRI function. The results showed that the system could improve the survival rate of mice with orthotopic colon tumors. Conclusion: This study demonstrated that this novel drug system (Gd-MHAp/5-FU/Gef/CS/PAA NPs) could protect, transport and programmed release drugs locally in the colonic environment, and exhibited good therapeutic effect, providing a promising novel treatment strategy for orthotopic colon cancer.

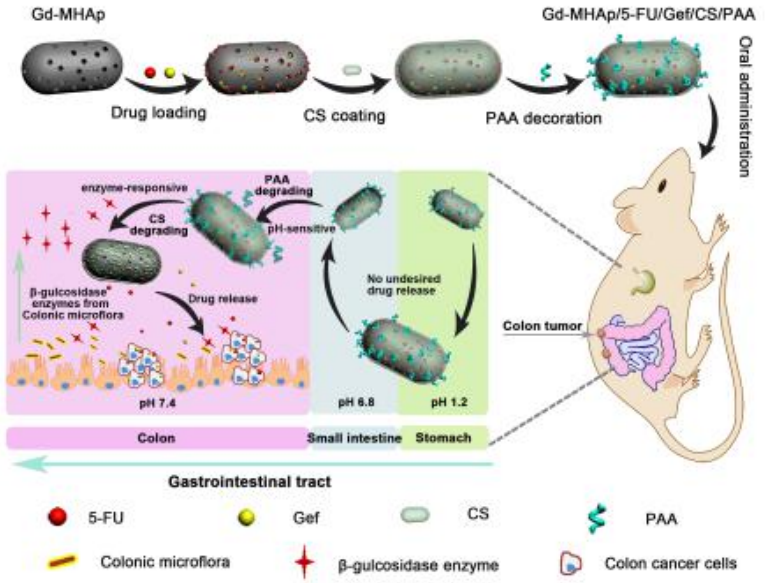

Fig. 1 Schematic illustration of the preparation of Gd-MHAp/5-FU/Gef/CS/PAA NPs and the mechanism of drug release in different physiological environments in the GIT.

Keywords: Programmed drug release; orthotopic colon cancer; theranostic; combination therapy

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论文编号：07–029

Understanding Integrity and Size Effect of Polymeric Nanocarrier on System Circulation and Sequestration by Macrophage in Zebrafish Larvae

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Abstract:

This research aimed to investigate biological fate of intravenously injected polymeric nanoparticles combined FRET (Förster Resonance Energy Transfer) method using zebrafish larvae model. Firstly, FRET pair (DiO and DiI)-loaded PEGylated poly(caprolactone) nanoparticles with small and large particle size (S-PEG-PCL, 103±11.6 nm and L-PEG-PCL, 214±5.3 nm) and unmodified poly(caprolactone) nanoparticles with large particle size (L-PCL, 207±12.9 nm) were fabricated via emulsification/solvent evaporation method to evaluate integrity of nanoparticles in zebrafish. Then DiI was loaded into nanoparticles to study pharmacokinetic properties and macrophages sequestration *in vivo*. Results showed that L-PCL disassociated rapidly and PEG-PCL had a better integrity. DiI-loaded S-PEG-PCL performed the longest circulation, whereas DiI-loaded L-PEG-PCL showed a shorter half-life than L-PCL as a result of high sequestration of intact L-PEG-PCL by macrophages. Moreover, polymers were eliminated through hepatobiliary pathway after nanoparticles disassociation. The elimination rate was consistent with their disassembly rate. In summary, this study demonstrated significant influence of particle size and integrity on circulation behavior, macrophage sequestration and elimination rate of polymeric nanoparticles in zebrafish larvae model.

Keywords: Polymeric Nanocarriers; Zebrafish Larvae Model; In Vivo Integrity; Size Effect; Bio-fate

论文编号：07–030

Celastrol noisome take anti-inflammatory effect on skin keratinocytes topically without systemic exposure on imiquimod-induced psoriasis mice model

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Abstract:

Psoriasis is an inflammatory disease, where keratinocytes play pivotal roles in its pathogenesis. We aimed to explore the therapeutic target and anti-psoriasis mechanism of Celastrol Niosome (Cel Nio). Cel Nio with the particle size of 133 nm was topically administered on imiquimod (IMQ) -induced psoriasis mice, which significantly decreased the psoriasis area severity index (PASI) scores and levels of inflammatory factors in skins and blood. Pharmacokinetic study revealed that Cel Nio was accumulated mainly in skin without exposure in blood and lymphatic system. When Hacat cells stimulated by IMQ and treated with Cel in vitro, the levels of several inflammatory factors were obviously reduced. In vivo results also confirmed that the expression of inflammatory factors and Ki67 in skin were decreased. Cel Nio achieved the anti-psoriasis effect through inhibiting the inflammation of keratinocyte in the skin and further suppressing the inflammatory response of the system in the blood. Our study may provide an example for the design of the topical drug delivery system without systemic exposure to take anti-psoriatic effects both locally and systemically.

Keywords: Psoriasis; Celastrol; Niosome; Topical delivery; Keratinocytes

论文编号：07–031

Nano-enable intracellular zinc (II) interference for preferential tumor energy exhaustion

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Abstract:

The interference of ion homeostasis is a novel tactic for tumor therapy. Herein, we found melanoma features a relatively low level of Zn(II) compared with normal cells, inspired by the pivotal functions of Zn(II) homeostasis in glucose-derived energy metabolism pathway, an “ion nanogenerator”, which embedded Zn(II) initiated GLUT1 DNAzyme into ZIF-8 and capped with HA, is rationally designed for preferential tumor energy exhaustion. As a robust carrier of DNAzyme, ZIF-8 is also used as Zn(II) generator: (i) selectively inducing Zn(II) overloading in tumor cells; (ii) inhibiting glycolysis which is abnormally high in tumor cells; (ii) serving as a cofactor to initiate GLUT1 DNAzyme for cutting off glucose supply, synergistic with glycolysis inhibition for complete energy exhaustion. The effective performance of this system in tumor growth suppression, as well as neglectable systemic toxicity was validated in vivo. This study suggests that intracellular Zinc(II) interference is an efficient strategy for tumor therapy.

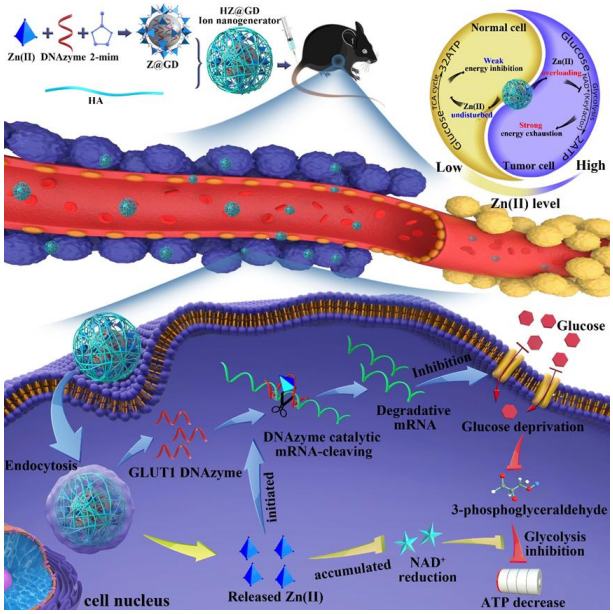

Fig.1 The scheme of ZIF-8-based “ion nanogenerator” for Zn(II)-mediated energy inhibition and Zn(II)-initiated gene silencing therapy.

Keywords: ion nanogenerator, Zn(II) interference, self-initiated gene silencing, energy exhaustion

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论文编号：07–032

Novel Nanotechnology-based Medicine For Enhanced Treatment Against Pancreatic Cancer

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Abstract:

Pancreatic cancer remains one of the deadliest solid tumors in humans. The dense tumor stroma surrounding tumor cells form a physical barrier for chemotherapy. Moreover, the immunosuppressive microenvironment hindered antitumor immunity. To elevate the therapeutic results and prevent metastasis of pancreatic cancer, herein, we have developed a series of drug delivery systems to elevate therapeutic results for pancreatic cancer. A thermal sensitive liposome encapsulating albumin nanoparticle of paclitaxel (HAS-PTX) and IR-780 was formulated in the aim of overcoming the stromal barrier and achieving deep tumor penetration. IR-780 produced hyperthermia under irradiation to kill tumor cells and further promoted deep penetration of small HSA-PTX. Besides, to alleviate the immunosuppressive environment, a tumor targeted micelle consisting of P-selectin inhibitor low molecular weight heparin (LWMH) and D-α-tocopheryl succinate (TOS) was developed, which could inhibit MMP-9 secretion and suppress the infiltration of MDSCs. These drug delivery systems provide promising solutions for pancreatic cancer treatment.

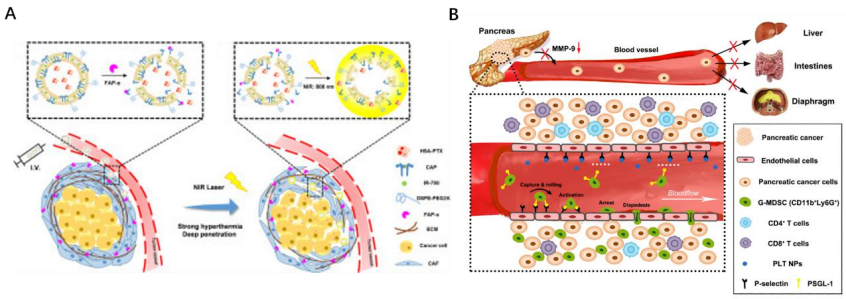

Fig. 1 Novel nanomedicine for enhanced treatment against pancreatic cancer. (A) Diagram of cancer associated fibroblast-targeted thermosensitive liposome delivery of HSA-PTX for enhancing deep tumor penetration and combination therapy against pancreatic cancer. (B) Mechanism of self-delivery micellar nanopartcles against orthotopic pancreatic tumor and its spontaneous metastasis.

Keywords: pancreatic cancer, stromal cells, deep penetration, immunosuppressive, micelle.

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论文编号：07–033

ROS响应脂质体远程激活CAR-T细胞免疫应答规避脱靶效应研究

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摘要正文：

近年来发展的利用基因改造技术表达肿瘤特异性嵌合抗原受体(chimeric antigen receptor，CAR)的T细胞治疗技术进展迅猛，在体外和临床试验中显示出良好的靶向性、杀伤活性和持久性，为过继性细胞免疫治疗提供了新的有效解决方案，展示了巨大的应用潜力和发展前景[1,2]。CAR-T细胞临床应用的首要问题是脱靶效应，导致针对正常组织的自身免疫反应[2]。为解决现有CAR-T细胞的脱靶效应的问题，本课题构建靶向间皮素高表达的卵巢癌细胞的ON-switch CAR-T细胞（Fig.1）。这种ON-switch CAR-T细胞在基因构建阶段就将CAR基因分成两段分别构建，分别转染T细胞实现独立表达。当异源二聚化小分子存在时可实现两段肽链链接，CAR-T细胞被激活。本课题创新性地设计ROS响应脂质体（ROS，reactive oxygen species，光敏感型活性氧自由基）包封控制CAR-T细胞的二聚化诱导药物分子，CAR-T细胞携载这种ROS响应脂质体同时达到肿瘤部位。近红外光照条件下在肿瘤部位启动CAR-T细胞免疫应答，精确控制T细胞的活性水平，妥善处理CAR-T细胞引起的各种副作用。

1.构建靶向间皮素的ON-switch CAR-T细胞

首先构建mesoCAR和ON-switch mesoCAR的重组质粒，接着通过慢病毒载体转染人T细胞，然后培养获得Conventional mesoCAR-T细胞和ON-switch mesoCAR-T细胞。采用流式细胞仪检测转染效率。然后以分别以间皮素不同表达水平的卵巢癌细胞株为靶细胞，进行不同效靶比下CAR-T细胞的杀伤活性检测。

2.ROS响应脂质体制备

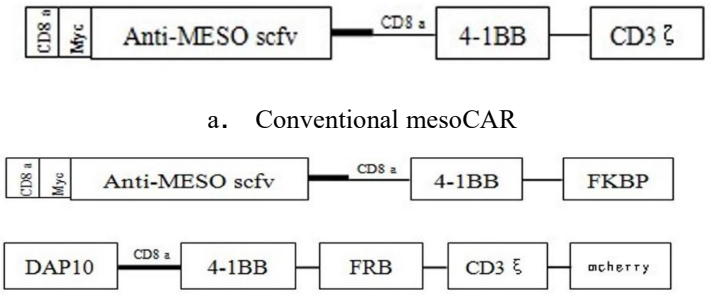
首先合成光敏剂$PdPC(OBu)_8$,通过紫外检测进行结构鉴定。接着建立雷帕霉素（Rapamycin）和$PdPC(OBu)_8$的含量测定方法。采用HPLC法测定雷帕霉素含量，其在0.2-40ug/mL浓度范围，线性回归方程为A=0.6377C-0.0246（R^2=1）。利用紫外分光光度法考察$PdPC(OBu)_8$，其在2-12ug/mL浓度范围内，线性回归方程为A=0.0696C+0.0142（R^2=0.9999）。

然后，进行脂质体处方筛选及表征检测。DSPC用量70%（摩尔比），DLPC用量5%，胆固醇用量20%，DSPE-PEG2000用量5%。雷帕霉素投药量为药脂比（m：m）1:25，$PdPC(OBU)_8$投药量为药脂比（m：m）1:200。所得脂质体粒径为216.4nm，PDI为0.249。

3.携载光敏脂质体的CAR-T细胞体外抗肿瘤效果

首先将光敏脂质体与ON-switch mesoCAR-T细胞共培养，获得携载光敏脂质体的ON-switch meso CAR-T细胞。然后以分别以间皮素不同表达水平的卵巢癌细胞株为靶细胞，调节NIR照射条件，进行不同效靶比下ON-switch mesoCAR-T细胞的杀伤活性检测。

本课题采用二聚化小分子激活的ON-switch CAR-T细胞的新设计，创新性地提出将载二聚化小分子光敏脂质体通过CAR-T细胞载体在实体瘤部位聚集，实现远程光控释药，启动CAR-T细胞免疫应答。构建的新型光敏脂质体携载能够控制CAR-T细胞的二聚化小分子递药系统为细胞免疫治疗提供了一种新的方法，对细胞免疫的拓展具有一定的实用价值。本课题独特地提出以CAR-T细胞为载体，通过构建新型的以CAR-T细胞介导的局部高效治疗系统，为解决现有CAR-T细胞治疗和纳米制剂体内实体瘤靶向效率差的现状问题提供了重要的思路。



a． Conventional mesoCAR

b． ON-switch mesoCAR

Fig. 1 Construction of Conventional mesoCAR(a) and ON-switch mesoCAR（b）

关键词：CAR-T；间皮素；卵巢癌；光敏剂；脂质体

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论文编号：07–034

崩解剂和赋形剂的比表面和粒度分析

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摘要正文：

物的众多性能中溶出度是一项备受关注的性能，溶出度直接影响到药物在体内的崩解、溶解和吸收。本文从粒度和比表面积两个参数评价崩解剂和赋形剂的相关性能，以低取代羟丙纤维素和甘露醇为例，比较了两类样品的粒度和比表面积的相对差异，也是针对2020版《中国药典》的新规做更全面的表征。

总所周知，药物的众多性能中溶出度是一项备受关注的性能，溶出度直接影响到药物在体内的崩解、溶解和吸收。影响溶出度的因素有很多，比如配方以及辅料的选择，药物生产的工艺，其中大家比较关注的两个参数为粒度和比表面积的影响。

以前大家对于药物及其辅料的粒度及其分布都比较关注，而比表面积因为和颗粒粒度存在一定的关系，所以很多时间都通过粒度的表征来辅助判断。但实际上因为颗粒大小分布，颗粒形状以及形态分布，孔径的分布不一会导致实际的比表面积的值与粒度之间的关系不那么一致，所以对于比表面积更加准确的表征方法还是应该通过特定仪器来做科学地表征。

2020版《中国药典》将于2020年12月1日正式实施，《中国药典》2020年版四部通则第二批增修订地理化分析内容中，也明确规定了药物粉体比表面积的测定方法，需要测试的样品包括药物中的稀释剂(填充剂)、粘合剂、崩解剂、润滑剂以及各助剂等等。

针对《中国药典》的新规，我们选取了两类样品-低取代羟丙纤维素和甘露醇，进行了比表面积和粒度分析，更全面地对这两类样品进行了分析。

低取代羟丙基纤维素，主要用作固体制剂崩解和粘合剂，由于它的粉末有较大的表面积和孔隙率，故能快速吸水膨胀，用于片剂时，使片剂快速崩解，同时它的粗糙结构与药物和颗粒之间有较大的镶嵌，可明显提高片剂硬度，同时不影响崩解，从而加速药物的溶出度，提高生物利用度。

甘露醇在医药上是良好的利尿剂，降低颅内压、眼内压及治疗肾药、脱水药、食糖代用品、也用作药片的赋形剂及固体、液体的稀释剂。作为片剂用赋形剂，甘露醇无吸湿性，干燥快，化学稳定性好，而且具有爽口、造粒性好等特点，用于抗癌药、抗菌药、抗组织胺药以及维生素等大部分片剂。甘露醇因溶解时吸热，有甜味，对口腔有舒服感，故更广泛用于醒酒药、口中清凉剂等咀嚼片的制造，其颗粒专作直接压片的赋形剂。

关键词：2020版《中国药典》；比表面积测定；崩解剂和赋形剂；粒度表征

论文编号：07–035

冷冻干燥法制备枸橼酸喷托维林微粉

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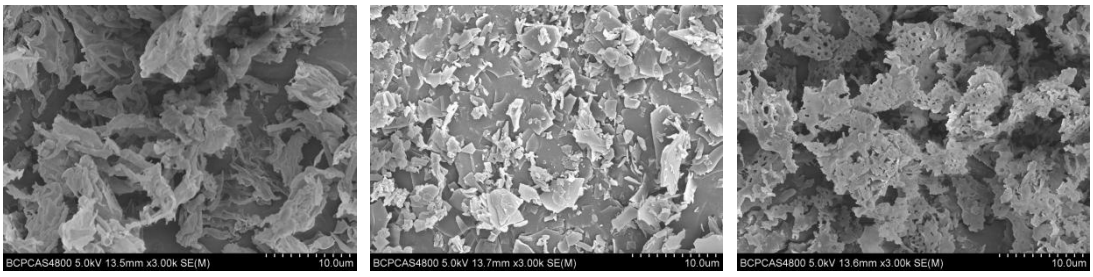
摘要正文：

干粉吸入剂（Dry Powder Inhalation，DPI）在药理学、药动学和药效学等方面具有给药方便直接、吸收表面积大、药物交换距离短、膜通透性好、局部酶活性较低、避免肝脏首过效应等独特的优越性，受到原来越多的关注。枸橼酸喷托维林是一种应用广泛的非成瘾性镇咳药，对呼吸中枢具有直接抑制作用，并有微弱的阿托品作用，可轻度抑制支气管内感受器，减弱咳嗽反射，并可松弛痉挛的支气管平滑肌，减小气道阻力，适于采用 DPI 形式给药直接作用于呼吸道病灶。

低密度多孔性大颗粒（Low Density and Large Porous Particles，LDLPPs）由于具有较低的有效密度，在满足DPI空气动力学粒径要求的同时，具有较大的几何学粒径，从而能够降低颗粒的聚集，提高微粉的雾化和流动性能等，被认为是优选的DPI制剂形式。冷冻干燥工艺制备过程操作简单，灭菌封装贮存方便，避免低熔点的枸橼酸喷托维林经历高温作用，且特别有利于低密度多孔性大颗粒的构建。

本文采用冷冻干燥法制备枸橼酸喷托维林微粉，筛选了药液浓度、预冻方式等工艺条件，考察了乳糖、甘露醇、聚乙烯醇、羟丙基甲基纤维素、氨基酸、山梨醇、海藻糖、聚乙二醇等冻干保护剂对微粉性能的影响。研究结果表明，在药液浓度0.6-0.9倍饱和度、预冻温度-70℃、预冻时间3 hr、真空干燥时间16 hr、未添加冻干保护剂的工艺条件下，能够得到满足DPI制剂粒度分布要求的可吸入微粉，且颗粒具有明显的低密度多孔性结构（几何学平均直径约10 μm、空气动力学质量中值粒径小于5 μm），但由于冻干脱水过程破坏了药物与水分子之间的氢键，促使药物分子发生融合与团聚，微粉缩塌现象严重。添加糖类与醇类保护剂后，在冻干的过程中，保护剂带有的羟基结构可替代失去的水分子，与药物极性基团结合形成氢键，对药物分子进行保护，维持微粉结构的完整性，能够有效避免缩塌现象的出现。添加不同冻干保护剂得到的微粉形貌具有显著差异，如添加10%乳糖作为保护剂时，微粉颗粒为不规则片状结晶，几何学粒径为3-5 μm，低密度多孔性特征减弱；而添加10%甘露醇作为保护剂时，能够得到典型的低密度多孔性絮状颗粒，几何学粒径5-10 μm，空气动力学质量中值粒径小于2.5 μm，流动性与分散性良好。



(a) protectant free　　(b) 10% lactose　　(c) 10% mannitol

Fig.1 Micro-morphologies of pentoxyverine citrate powders

关键词：枸橼酸喷托维林；冷冻干燥；干粉吸入剂；低密度多孔性大颗粒

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论文编号：07–036

补骨脂种子提取物水分散粒剂的制备

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摘要正文：

补骨脂是豆科草本植物补骨脂（Psoralea corylifolia L.）的干燥成熟果实。到目前为止，已从补骨脂中分离出 90 余种化学成分，主要为黄酮类[1-2]、香豆素类[3]和单萜酚类[4]化合物，此外还包括豆甾醇、烷烃、糖等化合物。补骨脂作为中医常用药材，有明显的抗肿瘤[5]、抗氧化、雌激素样[6]和免疫调节特性。在农业方面，补骨脂种子提取物可作为植物源杀菌剂防治植物病害，补骨脂种子提取物微乳剂对水稻稻瘟病菌、苹果腐烂病菌、黄瓜炭疽病菌等 11 种植物病原菌有较好的抑制活性[7]。同时，近年来研究表明，补骨脂种子提取物可促进苜蓿与水稻种子的萌发，提高植物根系活力和相关酶活力[8] 。其作为一种绿色环保的植物源农药在农业生产使用方面具有巨大的市场前景。

目前，市面上常见的植物源农药的剂型有乳油、粉剂、水分散粒剂、微胶囊、微乳剂等，其中传统的剂型中乳油的有机溶剂含量大，不环保；粉剂在施药时易产生漂移，对施药区域外的作物造成伤害[9]。微胶囊剂作为新型、环保农药剂型具有缓控释功能，且有较好的稳定性，对外界因素引起的农药分解和流失有一定的抑制作用[10]；微乳剂是目前研究较多的的一种新剂型，毒性低，便于贮存和运输。农药水分散粒剂作为目前开发的一种新剂型，能在水中迅速崩解形成均匀的悬浮液，具有有效成分含量高，不需溶剂，且产生的粉尘少，使用极其简便、对环境的影响小等优点，已成为一种安全环保的农药新剂型[11]，在国内外市场上备受欢迎。

论文通过单因素实验筛选出补骨脂种子提取物水分散粒剂的最佳配方及加工工艺。经筛选得补骨脂种子提取物水分散粒剂配方为：补骨脂种子提取物 30%、LT-Q90 3.3%、蔗糖 43.33%、白炭黑 16.67%、Q303 6.7%；加工工艺为湿法工艺中的挤压造粒法。将辅料分别粉碎过 200 目筛，混合研磨一段时间后，将原药加入，边加边搅，混合均匀后加入适当有机溶剂制软材，实验室挤压造粒机制粒，烘干，整粒。工艺流程如下:

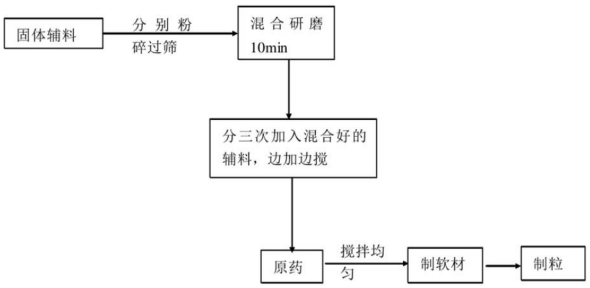

图 1 水分散粒剂加工工艺

对补骨脂种子提取物粒剂进行质量控制指标检测，检测结果为：补骨脂种子提取物水分散粒剂外观为棕褐色颗粒，在室温下遇水分散性良好，崩解时间小于 3min，静置 2h 后仍保持透明状态，热贮、冷贮物理性质稳定，达到质量控制各项指标。

关键词：补骨脂种子提取物；植物源杀菌剂；水分散粒剂

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