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基于中子活化法制备 **99Mo** 的新型 **99Mo/99mTc** 发生器关键技术研究

摘要

基于中子活化法制备 99Mo 的新型 99Mo/99mTc 发生器关键技术研究

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摘要
99mTc 作为单光子发射计算机断层成像（SPECT）全球范围应用最广的放射性核素，其稳定供应对于现代核医学至关重要。当前，我国临床使用的 99mTc 主要依赖进口裂变 99Mo 制备的发生器。随着 99Mo 主要生产堆临近寿期，全球 99Mo 供应稳定性面临巨大挑战。为实现医用同位素的自主可控并充分利用国内现有反应堆资源，本文聚焦基于中子活化法制备低比活度 99Mo 的新型 99Mo/99mTc 发生器关键技术研究，旨在避免采用浓缩铀为原料的裂变技术路线，攻克低比活度 99Mo /99mTc 高效分离纯化的技术瓶颈，开发一套符合药品生产质量管理规范（GMP）要求的生产工艺及全自动工程化装备，以期为我国 99mTc 的自主化、规模化生产提供切实可行的解决方案。
通过三批次（辐照时间分别为 3 天、5 天、7 天）的反应堆辐照实验，系统研究了天然 MoO3 与富集 98MoO3 靶材辐照的理论计算和辐照工艺参数。根据结果分析了两种辐照路线的 99Mo 产额及放射性杂质，确定了工程阶段的辐照时间和路线。
筛选活性炭进行 99Mo /99mTc 的分离研究。利用化学性质相似的 Re 稳定同位素模拟 99mTc 进行系统冷实验，全面探究了溶液初始 pH 值、色谱柱径高比、吸附流速、淋洗剂组成与体积、洗脱温度等关键参数对 Mo/Re 分离效率的影响规律。确定工艺路线后，冷实验实现约 83% 的 Re 回收率，热实验表明对实际 99mTc 的回收率达 82.1%，且最终产品中 99Mo 残留低于检测限，初步验证了技术可行性。基于此，研制了初代自动化分离样机，在模拟处理 5 Ci 99Mo 的放大实验中，获得 81.7% 的 99mTc 回收率，展现了工程化潜力。
鉴于后续实验发现活性炭批次间性能差异，进而深入探索了 PEG 树脂分离体系。研究发现，在 5.0 mol/L NaOH 强碱性环境中，PEG 树脂对以 ReO4-形式存在的 99mTc 模拟物具有极高的选择性吸附能力。通过系统柱实验优化确立了最佳工艺条件，冷实验 Re 回收率稳定在 94% 以上。在三次不同 99Mo 活度（2.3 至 8.7 mCi）投料的热实验中，99mTc 平均回收率超过 85%，且产品放射性核纯度完全达标。以此为核心，成功设计并开发了新型 GMP 级全自动 99Mo/99mTc 分离纯化工程样机，其运行稳定可靠，分离效率持续高于 85%，产品中 99Mo 残留始终低于检出限。
工程化开发与验证阶段，在 C 级洁净区对生产热室、关键设备（活度计）及自动化样机各模块性能验证基础上，采用 PEG 树脂工艺开展了连续三个批次的工艺性能验证。结果表明，99mTc 平均回收率达到 84.67%，所制备的最终产品溶液为无色澄明液体，其 pH 值、放射性核纯度、放射化学纯度、无菌检查、细菌内毒素含量及标记合成效率等质量指标，均符合《中华人民共和国药典》对高锝 [99mTc] 酸钠注射液的法定标准。这标志着从实验室工艺到符合药品生产质量规范的成功转化。
通过本文的研究，成功构建了一套基于中子活化法制备的 99Mo 的新型 99Mo /99mTc 发生器工程样机。该装置已在 GMP 环境下完成工程化验证，连续三批次产品全部符合《中国药典》标准，单批次处理能力达 4000 mCi，99mTc 平均回收率 84.67%，具备明确的产业化前景。本研究为满足核医学诊疗需求和保障医用同位素供应链安全提供了切实可行的工程解决方案。

关键词

新型 99Mo/99mTc 发生器；低比活度；中子活化；活性炭；PEG 树脂；工程样机

Abstract

Key Technologies of a Novel ^{99}Mo/^{99m}Tc Generator Based on Neutron-Activated ^{99}Mo

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As the most widely used radionuclide globally for Single Photon Emission Computed Tomography (SPECT), the stable supply of 99mTc is critically important for modern nuclear medicine. Currently, clinical 99mTc in China primarily relies on generators prepared from imported fission-produced 99Mo. As the main production reactors for 99Mo approach the end of their operational lives, the stability of the global 99Mo supply faces significant challenges. To achieve self-sufficiency in medical isotopes and fully utilize existing domestic reactor resources, this study focuses on key technologies for a novel 99Mo/99mTc generator based on neutron-activated, low-specific-activity 99Mo. The aim is to avoid the fission technology route that uses enriched uranium as feedstock, overcome the technical bottleneck of efficiently separating and purifying 99mTc from low-specific-activity 99Mo, and develop a production process and fully automated engineering equipment compliant with Good Manufacturing Practices (GMP). This research intends to provide a feasible solution for the autonomous, large-scale production of 99mTc in China.

Through three batches of reactor irradiation experiments (with irradiation times of 3, 5, and 7 days, respectively), the theoretical calculations and irradiation process parameters for natural MoO_3 and enriched $^{98}MoO_3$ targets were systematically investigated. Based on the results, the ^{99}Mo yield and radioactive impurities from the two irradiation routes were analyzed, leading to the selection of the irradiation time and route for the engineering phase.

Activated carbon was selected for $^{99}Mo/^{99m}Tc$ separation studies. Stable rhenium (Re) isotopes, which have similar chemical properties, were used as a surrogate for ^{99m}Tc to conduct systematic cold tests. The influence of key parameters on Mo/Re separation efficiency was comprehensively investigated, including initial solution pH, column aspect ratio, adsorption flow rate, eluent composition and volume, and elution temperature. After determining the process route, cold tests achieved an Re recovery rate of approximately 83%, and hot tests demonstrated an actual ^{99m}Tc recovery rate of 82.1%, with residual ^{99}Mo in the final product below the detection limit, preliminarily validating the technical feasibility. Based on this, a first-generation automated separation prototype was developed. In scale-up experiments simulating the processing of 5 Ci of ^{99}Mo, a ^{99m}Tc recovery rate of 81.7% was achieved, demonstrating its engineering potential.

Subsequently, due to observed performance variability between batches of activated carbon, the research explored the PEG resin separation system in greater depth. The study found that in a highly alkaline environment of 5.0 mol/L NaOH, PEG resin exhibits exceptionally high selective adsorption capacity for the ^{99m}Tc surrogate, present as ReO_4^-. Optimal process conditions were established through systematic column experiments, achieving a stable Re recovery rate above 94% in cold tests. In three hot tests with varying ^{99}Mo activities (2.3 to 8.7 mCi), the average ^{99m}Tc recovery rate exceeded 85%, and the radionuclidic purity of the product fully met the required standards. Based on this core technology, a novel GMP-grade fully automated $^{99}Mo/^{99m}Tc$ separation and purification engineering prototype was successfully designed and developed. Its operation is stable and reliable, with separation efficiency consistently exceeding 85% and residual ^{99}Mo in the product always below the detection limit.

During the engineering development and validation phase, after verifying the performance of the production hot cell, key equipment (dose calibrator), and various modules of the automated prototype in a Grade C cleanroom, three consecutive process performance validation runs were carried out using the PEG resin process. The results showed an average ^{99m}Tc recovery rate of 84.7%. The final product solution was a colorless, clear liquid, and its quality indicators—including pH, radionuclidic purity, radiochemical purity, sterility test, bacterial endotoxin content, and labeling synthesis efficiency—all complied with the statutory standards of the Pharmacopoeia of the People's Republic of China for Sodium Pertechnetate [^{99m}Tc] Injection. This marks the successful translation of the laboratory process to compliance with GMP standards.

Through this research, a novel engineering prototype of a $^{99}Mo/^{99m}Tc$ generator based on neutron-activated ^{99}Mo was successfully established. The device has undergone engineering validation in a GMP environment. Three consecutive batches of the product all met the standards of the Chinese Pharmacopoeia. This system demonstrates clear prospects for industrialization. This study provides a practical engineering solution to meet the diagnostic and therapeutic demands of nuclear medicine and ensure the security of the medical isotope supply chain.

Keywords

Novel 99Mo-99mTc generator; low-specific-activity; Neutron activation; Activated carbon; PEG resin; Engineering prototype

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