建置液相層析串聯式質譜儀應用β-內醯胺類抗生素污染動物用注射劑檢驗技術

動物用藥品檢定分所

林文華 副研究員兼系主任

摘要

目前國內動物用藥品中危害物質監測系統尚未完善，以β-內醯胺類致敏物為例，依據「動物用藥品優良製造準則」第 34 條規範「非青黴素類產品，必要時應予檢驗並確定未被青黴素類、荷爾蒙類及頭孢子菌素類藥品污染」。美國藥物食品管理局(FDA)規範在非 β-內醯胺類藥品檢測青黴素 G(penicillin G)和安比西林(ampicillin)殘留量為 0.03ppm，而在美國聯邦法規法典第 21 冊第 211.176 及第 436.104 部分對於交叉污染列入法規並且有最低偵測量為 0.006ppm。但國內藥品製造廠多為共用生產線，導致一般藥品受汙染風險性極大。目前未具備高敏感度與高特異性之精密分析儀器，對藥品進行β-內醯胺污染調查研究，故建立國內常用 12 種β-內醯胺類抗生素以超高效液相層析儀串聯式質譜儀(UHPLC-MS/MS)之多重檢驗技術。以正負離子電灑離子源切換方式，以電灑離子源(ESI)正負電離子切換，採用多重反應監測(Multiple reaction monitoring，MRM)模式下，純溶劑檢量線濃度範圍 0.5 至 50 ppb 下線性迴歸係數均大於 0.995 以上，偵測極限

為 0.2 ppb，定量極限為 0.5 ppb。於注射劑產品，添加 12 種 β-內醯胺類抗生素 0.5ppb 及 2.5ppb 回收率範圍為 80-101%，專一性檢驗於相同時間點無其它干擾物訊號出現；精密度部分，日內精密度相對標準差為 1.21-5.52，日間精密度相對標準差為 1.49-7.79。該方法可應用於未來國內動物用藥品 β-lactam 類致敏物污染監測，或提供國內製造廠清潔確效分析方法使用。

Development of liquid chromatography-tandem mass spectrometry method for testing animal injection solutions contaminated with β-lactam antibiotics

Wen-Hua Lin

Abstract

Currently the surveillance system for harmful substances in animal drugs in the domestic market is incomplete. For non-penicillin products, testing is necessary to ensure that there is no contamination of penicillin, hormone, or cephalosporin drugs, in accordance with Article 34 of the Guidelines of Good Manufacturing Practice (GMP) for Veterinary Drug Manufacturers. The U.S. Food and Drug Administration (FDA) requires the detection of penicillin G and ampicillin residues in non-beta-lactam drugs at the level of 0.03 ppm. The measurement of cross-contamination is codified at 21 CFR 211.176 and 436.104, with a minimum detection limit of 0.006 ppm. Because of the high risk of contaminating regular pharmaceuticals in the domestic market, it is necessary to establish multiple inspection technology for the twelve most used beta-lactam antibiotics, using the ultra-high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) method. This method employs positive and negative ions of the electrospray ionization (ESI) which are switched in multiple reaction monitoring (MRM) mode. The linear regression coefficients for the pure solvent calibration curve concentration ranging from 0.5 to 50 ppb were all greater than 0.995, with a limit of detection (LOD) of 0.2 ppb and a limit of quantification (LOQ) of 0.5 ppb. The recovery rate of twelve beta-lactam antibiotics in drug products of injection were found to be within the range of 80 to 101% for concentrations of 0.5 ppb and 2.5 ppb. The specificity check showed no interference signals at the same time point. The relative standard deviation (RSD) of intra-day precision was 1.21 to 5.52, and the RSD of inter-day precision was 1.49 to 7.79. This method could be used for monitoring non-beta-lactam drugs in domestic animal medicines or as a cleanliness analysis method for domestic manufacturers.