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Development and Validation of an UPLC-MS/MS Method for Stimultaneous Determination of Imatinib and its Metabolite N-desmethyl Imatinib in Beagle Plasma

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***SUMMARY*. A method for the simultaneous determination of imatinib and its metabolite n-desmethyl imatinib in beagle plasma by UPLC-MS/MS was developed and validated. The two analytes and diazepam (internal standard, IS) were extracted by acetonitrile precipitation and separated on an Acquity UPLC BEH C18 column using acetonitrile-0.1% formic acid as mobile phase with gradient mode. In positive ion mode, two analytes and IS were monitored by multiple reaction monitoring (MRM) using tandem mass spectrometry. The mass transfer pairs were *m/z* 494.3→394.2 for imatinib, *m/z* 480.3→394.2 for n-desmethyl imatinib, and *m/z* 285.0→154.0 for IS. Under the conditions of this experiment, this method exhibited a good linearity for imatinib and n-desmethyl imatinib. The inter-day and intra-day precision did not exceed 8.73%, the accuracy values were from -2.20% to 3.52%, the recovery values were all between 79.78% and 85.14%, the matrix effect (ME) and stability were also within acceptable criteria. The developed UPLC-MS/MS method for simultaneous determination of imatinib and n-desmethyl imatinib in beagle plasma was accurate, reproducible, specific, and it was found to be suitable for the pharmacokinetics of imatinib and drug-drug interactions. Finally, this method had been successfully applied to the pharmacokinetics of imatinib and n-desmethyl imatinib in beagles after oral administration of 7.0 mg/kg imatinib.**

RESUMEN. Se desarrolló y validó un método para la determinación simultánea de imatinib y su metabolito n-desmetilimatinib en plasma de beagle por UPLC-MS/MS. Los dos analitos y el diazepam (patrón interno, IS) se extrajeron por precipitación con acetonitrilo y se separaron en una columna Acquity UPLC BEH C18 usando acetonitrilo-ácido fórmico al 0,1% como fase móvil con modo gradiente. En el modo de iones positivos, dos analitos y el IS fueron analizados por monitoreo de reacción múltiple (MRM) usando espectrometría de masas en tándem. Los pares de transferencia de masa fueron *m/z* 494.3→394.2 para imatinib, *m/z* 480.3→394.2 para n-desmetilimatinib y *m/z* 285.0→154.0 para IS. Bajo las condiciones de este experimento, este método exhibió una buena linealidad para imatinib y n-desmetilimatinib. La precisión entre días e intra-días no superó el 8,73%, los valores de precisión fueron del -2,20% al 3,52%, los valores de recuperación estuvieron entre 79,78% y 85,14%, el efecto de matriz (EM) y la estabilidad también estuvieron dentro criterios aceptables El método desarrollado UPLC-MS/MS para la determinación simultánea de imatinib y n-desmetilimatinib en plasma de beagle fue preciso, reproducible, específico y se encontró que era adecuado para la farmacocinética de las interacciones entre imatinib y fármaco-fármaco. Finalmente, este método se ha aplicado con éxito a la farmacocinética de imatinib y n-desmetilimatinib en beagles después de la administración oral de 7,0 mg/kg de imatinib.

KEYWORDS: beagles plasma, imatinib, n-desmethyl imatinib, pharmacokinetics, UPLC-MS/MS.

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