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Question:

How to determine the concentration of naproxen in rabbit samples in order to apply it to pharmacokinetic studies?

Problem:

Naproxen, 2-(6-methoxynaphthalen-2-yl) propanoic acid, is a type of non-steroidal anti-inflammatory medication. It is commonly used to manage chronic and acute pain, swelling, fever, and inflammation. Naproxen is also rapidly absorbed from the gastrointestinal tract, and overdoses can easily and quickly occur. These reasons have necessitated the development of an accurate, precise and rapid method of measuring naproxen concentrations.

Proposed Solution:

Liquid chromatography – mass spectrometry would provide the most accurate and sensitive results. This method however is very expensive and therefore not accessible to everyone. Furthermore, these studies use solid-phase extraction technique which is also a very expensive method which means it is not readily accessible. It appears then that the most practical analytical method is gas chromatography – mass spectrometry. The extraction method for this is liquid-liquid extraction which is a very inexpensive and simple extraction technique that can be completed in one step.

Technique:

The rabbits were given a single oral administration of 40 mg kg^{-1} and 2.0 mL of blood samples were incrementally collected 12 times over 16 h. Blood samples were put into EDTA collection tubes and stored at -20 °C until analysis on the GC-MS. To analyze, 0.5 mL of rabbit plasma was combined with 0.1 mL naproxen standard solution, 0.1 mL of ibuprofen solution, and 0.5 mL of dihydrogen phosphate and vortexed for 5 seconds. Next, 4 mL of hexane and ethyl acetate (3:2, v/v) was added and the sample was vortexed for 30 seconds. The plasma sample was then centrifuged for 10 minutes at 4500 rpm. The organic phase was transferred to another tube and vaporized under nitrogen gas. The dry residue was dissolved using the acetonitrile mixture. GC-MS was used to examine a 1 µL of plasma sample.

The Requirements:

Ten minutes is required for the liquid-liquid extraction procedure. Rabbits were administered with naproxen and the samples were collected up to 16 h. The overall, in lab procedure requires one hour to two hours.

Instruments and Reagents:

The GC-MS system suggested includes an HP-5 MS column (30 m x 0.25mm, 0.25 µm). The spitless injection mode was selected for the analysis. Helium was used as the carrier gas, with a flow rate of 1 mL min^{-1}. For electron ionization, the MS detector was employed at 70 eV. Fragment ions of naproxen and internal standard ibuprofen were selected as 185 and 73 (m/z), respectively. Acetonitrile was used to make naproxen standards. Hexane and ethyl acetate mixture (3:2, v/v) was used for the liquid-liquid extraction. All chemicals were of reagent grade acquired from Sigma- Aldrich (St. Louis, MO, USA).

Precision and Limits:

The extraction procedure provides 94.2% to 99.3% recovery of naproxen. The detector response for naproxen is concentration linear over a range of 0.1 to 5.0 µg mL^{-1}. The percent standard deviation of naproxen from plasma samples was 4.17% and the accuracy was detected to be within ± 2.18%. The limit of detection and the limit of quantitation for this method were 0.03 and 0.10 µg mL^{-1}.

Precautions:

Acetonitrile should be glass distilled and all glassware should be washed in distilled water. After the glassware should be rinsed in ethanol. No other precautions were listed in the article.

Practical Applications:

This is a quick and efficient procedure for analyzing naproxen in blood samples. This method uses a single extraction step in a short time using inexpensive chemicals. Alternate procedures may be more accurate but require more time to complete and use more expensive chemicals or instruments.

Seach technique:

A chemical dictionary was consulted to find the chemical name of naproxen. Chemical abstracts were then consulted using “naphthalene-2-propanoic acid” as the key phrase. The research summary of Yilmaz proved to be the most helpful.

References:

1. Yilmaz, B. *Journal of the Institute of Science and Technology,* ***2022,*** *1*2(3): 1635 -1643.
2. Sondnara, N.; Sawathee, S.; Atipairin, A. *Research Journal of Pharmacy and Technology,* ***2018****, 11(10): 4332-4338.*
3. Hirai, T.; Matsumoto, S.; Kishi, I. *Journal of Chromatography and Biomedical Applications,* ***1997,*** *692: 375-388.*