

Extraction of Nitroglycerin from Transdermal Patches by Accelerated Solvent Extraction (ASE)

INTRODUCTION

Pharmaceutical formulation assays are required for quality control and shelf-life studies. The most time-consuming part of the assay of the pharmaceutical formulations is often the sample preparation prior to analysis. This is especially true for transdermal formulations that have a more complex matrix than most other pharmaceuticals.

Existing procedures for extracting nitroglycerin from transdermal patches use copious amounts of organic solvents to isolate the active ingredient from the formulated final product. Often, additional clean-up steps are required before the analysis can be completed. These extraction and clean-up steps may take hours and may use solvents that are expensive, toxic, and require costly disposal.

Accelerated Solvent Extraction (ASE[®]) is a new extraction method that significantly streamlines sample preparation. Solvent is pumped into an extraction cell containing the sample, which is then brought to an elevated temperature and pressure. Minutes later, the extract is transferred from the heated cell to a standard collection vial for clean-up or analysis. The entire extraction process is fully automated and performed in minutes for fast and easy extraction with low solvent consumption.

The work reported here was undertaken to investigate the use of ASE for the extraction of nitroglycerin from prototype transdermal matrix patches. The results obtained using ASE were compared to those obtained using the standard extraction method, which is a sonication procedure.

EQUIPMENT

Dionex ASE 200 Accelerated Solvent Extractor*
Dionex DX 500 HPLC with AD20 (UV detector)
**ASE 150 and 350 can be used for equivalent results.*

REAGENTS AND STANDARDS

Ethanol, USP grade (190 proof) or equivalent
Nitroglycerin Reference Standard, USP
(1.00%, w/w solution in propylene glycol)
1-Chloro-2,4 Dinitrobenzene
(Sigma Chemical Company)

ASE CONDITIONS

System Pressure: 1500 psi*
Oven Temperature: Ambient
Sample Size: One patch, 10 or 20 cm²
Oven Heat-up Time: 5 min
Static Time: 3 min
Flush Volume: 100%
Cycles: 3
Solvent: Ethanol
Purge: 1 MPa (150 psi) nitrogen for 90 s

**Pressure studies show that 1500 psi is the optimum extraction pressure for all ASE applications.*

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HPLC CONDITIONS

Column: C18, 10 μm , 150 \times 3.9 mm i.d.
stainless steel, HPLC column
Mobile Phase: Methanol:Water (45:55, v/v)
Detection: UV, 214 nm
Temperature: Ambient
Flow Rate: 1.5 mL/min
Injection Volume: 15 μL

SAMPLE INFORMATION

Two sizes of prototype transdermal matrix patches were used for the investigations: 10 and 20 cm^2 . The amount of nitroglycerin present in each patch was approximately 32 mg and 65 mg, respectively. Ten replicate extractions of each patch size were performed.

SAMPLE PREPARATION

During the loading of the extraction cells, it is important not to touch the adhesive face of the patch. The following sample preparation guidelines were developed with this in mind.

1. For the 10 cm^2 patches, prepare 11 mL cells for use; for the 20 cm^2 patches, use the 22 mL cells.
2. Fill the extraction cell with clean sand [Fisher Scientific Standard Ottawa sand (S23-3)]. Pour the sand from the cell into a disposable weighing dish.
3. Peel off half of the backing from the patch and place it, adhesive side down, into the sand. The exposed adhesive surface should be completely covered with sand. Grasping the sand covered edge with tweezers, peel the remaining backing off (weigh both parts of the backing) and place the entire patch, adhesive side down, into the sand.
4. Remove the patch from the sand, curl the patch into a cylinder and place inside the extraction cell with the adhesive side now covered with sand and the center of the extraction cell, (i.e., the non-adhesive side facing out).
5. Pour the remaining sand in the weighing dish into the extraction cell, filling the void volume of the extraction cell on both sides, making sure the center of the curled patch is filled with sand.
6. Close the cell, load it into the carousel, and run the ASE method as given.

7. After extraction has been completed, the resultant extract is diluted to 50 mL for the 10 cm^2 patch or 100 mL for the 20 cm^2 patch.
8. Analysis for nitroglycerin in the resultant sample solution is performed using HPLC.

RESULTS

Table 1 summarizes the recovery data obtained for the 10 cm^2 ASE-extracted patches. The data for the ASE-extracted 20 cm^2 patches are presented in Table 2. As is typical for pharmaceutical method validation, both peak area and peak height data were obtained.

Table 1. ASE of Nitroglycerin from 10 cm^2 Transdermal Patches (n=10) Recovery of Nitroglycerin per Patch

	Area Data	Hight Data
Average (mg/patch)	31.4	31.0
% RSD	1.4	1.4
% Recovery versus Current Method	99.1	97.0
% RSD of Current Method	1.5	1.5

Table 2. ASE of Nitroglycerin from 20 cm^2 Transdermal Patches (n=10) Recovery of Nitroglycerin per Patch

	Area Data	Hight Data
Average (mg/patch)	62.0	62.9
% RSD	3.9	3.9
% Recovery versus Current Method	96.0	96.7
% RSD of Current Method	1.1	1.0

As shown in Tables 1 and 2, ASE produced recovery and precision results that were comparable to the data obtained using the current liquid extraction method. However, ASE uses significantly less solvent and is more time efficient (see Table 3).

Table 3. Comparison of Extraction Methods

	Current Method	ASE
Solvent	Ethanol	Ethanol
Solvent Volume	175 mL for 10 cm ² patches 275 mL for 20 cm ² patches	50 mL for 10 cm ² patches 100 mL for 20 cm ² patches
Post Extraction	Filtering, dilution	97.0
Analytical	HPLC	HPLC
Total Sample Preparation Time	2 h/sample	30 min/sample

CONCLUSION

ASE can be used as the extraction technique for determining nitroglycerin content in transdermal patches. Extractions can be performed faster and with less solvent consumption than the conventional extraction method, while yielding equivalent or superior extraction efficiencies and precision. Not only is the extraction step itself faster, but filtering is eliminated when using ASE because the extracts pass through 10 µm frits as they exit the extraction cells. Since the Dionex ASE 200 is fully automated, extractions can be performed in an unattended manner.

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