

Extraction of Nitroglycerin from Transdermal Patches by Accelerated Solvent Extraction

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 cleanup steps are required before the analysis can be completed. These extraction and cleanup steps may take hours and may use solvents that are expensive, toxic, and require costly disposal.

Accelerated solvent extraction 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 cleanup 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 accelerated solvent extraction for the extraction of nitroglycerin from prototype transdermal matrix patches. The results obtained using accelerated solvent extraction were compared to those obtained using the standard extraction method, which is a sonication procedure.

Equipment

- Thermo Scientific™ Dionex™ ASE™ 200 Accelerated Solvent Extractor system*
- Thermo Scientific Dionex DX-500 HPLC system equipped with a Thermo Scientific Dionex AD20 Absorbance Detector

*Dionex ASE 150 and 350 Accelerated Solvent Extractor systems 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)
- Sand (Ottawa Standard, Fisher Scientific, Cat. No. S23-3)

Accelerated Solvent Extraction Conditions

System Pressure: 10.3 MPa (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 accelerated solvent extraction applications.

HPLC Conditions

Column: Thermo Scientific™ Dionex™ Acclaim™ C18, 10 µm, 150 × 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 cm². 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 cm² patches, prepare 11 mL cells for use; for the 20 cm² patches, use the 22 mL cells.
2. Fill the extraction cell with clean sand. 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 accelerated solvent extraction method as given.
7. After extraction has been completed, the resultant extract is diluted to 50 mL for the 10 cm² patch or 100 mL for the 20 cm² 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 cm² accelerated solvent extraction patches. The data for the accelerated solvent extraction 20 cm² patches are presented in Table 2. As is typical for pharmaceutical method validation, both peak area and peak height data were obtained.

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

Table 1 Accelerated solvent extraction of nitroglycerin from 10 cm² transdermal patches (n=10); recovery of nitroglycerin per patch.

	Area Data	Height 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. Accelerated solvent extraction of nitroglycerin from 20 cm² transdermal patches (n=10); recovery of nitroglycerin per patch.

	Area Data	Height 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

Table 3. Comparison of extraction methods.

	Current Method	Accelerated Solvent Extraction
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

Accelerated solvent extraction 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 accelerated solvent extraction because the extracts pass through 10 µm frits as they exit the extraction cells. Since the Dionex ASE 200 Accelerated Solvent Extractor system is fully automated, extractions can be performed in an unattended manner.

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