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Drug migration from the adhesive matrix to the polymer film laminate facestock in a transdermal nitroglycerin system

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Abstract

The apparent loss of nitroglycerin in a prototype transdermal nitroglycerin system was investigated by attenuated total reflectance infrared (ATR-IR) microspectroscopy and high performance liquid chromatography (HPLC). Several transdermal nitroglycerin lots placed under controlled storage conditions exhibited loss of drug potency (up to 10%) along with the appearance of a defect in the polymer film laminate facestock. A significant loss of nitroglycerin from the transdermal drug/adhesive matrix may reduce the bioavailabilty of nitroglycerin to the patient. ATR-IR analysis confirmed that nitroglycerin migrated from the drug/adhesive matrix to the facestock polyester layer under storage conditions and that nitroglycerin was retained in the facestock polyester layer. An alternate sample extraction solution successfully removed the nitroglycerin from both the adhesive matrix and facestock polyester layer with nearly 100% labeled strength recovered. The relationship between the migration of nitroglycerin into the facestock polyester layer and the appearance of the defect in the facestock aluminum layer is discussed and a nitroglycerin–aluminum metal reaction mechanism is proposed. © 1997 Elsevier Science B.V.

Keywords: Nitroglycerin; Transdermal; Attenuated total reflectance infrared microspectroscopy; High-performance liquid chromatography; Aluminum metal

1. Introduction

Nitroglycerin pharmaceutical dosage forms have historically been subject to potency and stability problems [1–9]. Sublingual nitroglycerin tablets lose potency due to inter-tablet migration, volatilization, and absorption onto plastic containers [1–4]. Intravenous nitroglycerin solutions lose potency through absorption onto plastic filters, containers, and administration sets [1,5–9]. Similar migration, volatilization, and potency loss of nitroglycerin have been reported in the propellants/explosives industry [10–17].

This study examined the loss of potency in a prototype transdermal nitroglycerin system under stability test conditions. Coincident with the loss of nitroglycerin potency was the appearance of a defect in the facestock aluminum layer. The investigations that identified the cause of the nitroglyc-

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erin potency loss and the facestock aluminum layer defect in the transdermal nitroglycerin samples are described. These problems were related and, in part, due to the same phenomena—the migration of nitroglycerin from the drug/adhesive matrix to the facestock polyester layer.

Chi [18] reported that nitrate esters, such as nitroglycerin, are used as plasticizers in polyester and polyether polymers. Low molecular weight plasticizers like nitroglycerin lack permanence in the polymer systems [19]. Thus a plasticizer like nitroglycerin will exhibit high diffusion, volatility, migration, and extractability in a polymer matrix, and when the plasticizer containing polymer matrix is in contact with a suitable sink (i.e. a rigid plastic) the plasticizer will migrate from the matrix to the sink [19]. The drug/adhesive matrix is a nitroglycerin reservoir, the facestock polyester layer is a rigid plastic sink, and nitroglycerin can migrate to the facestock polyester layer by time–temperature dependent diffusional processes. Attenuated total reflectance infrared (ATR-IR) microspectroscopy was used to identify that nitroglycerin migrated from the drug/adhesive matrix to the facestock polyester layer under stability test conditions. High performance liquid chromatography (HPLC) was used to quantitate the extent of nitroglycerin uptake in the facestock polyester layer.

2. Materials and methods

2.1. Materials

Methanol optima grade was purchased from Fisher (Fair Lawn, NJ). Distilled deionized water was passed through the Mill-Q UV Plus Ultra Pure Water System (Millipore, Milford, MA). Solvents used for sample extraction were ethanol USP grade from Pharmco (Bayonne, NJ) and acetone ACS certified grade from Fisher (Fair Lawn, NJ). Nitroglycerin USP reference standard, 1% w/w in propylene glycol was obtained from USPC, (Rockville, MD). The 1-mononitroglycerin, 1,2-dinitroglycerin, and 1,3-dinitroglycerin standards were purchased from Radian (Austin, TX). The polymer film laminate facestock Scotchpak™ 1109 was obtained from 3 M Pharmaceuticals (St. Paul, MN). The prototype transdermal nitroglycerin lots were manufactured at Schering-Plough (Miami, FL). Storage conditions were 4°C, 25°C/60% relative humidity (RH), 30°C/60% RH, and 40°C/80% RH and testing was performed at the Schering-Plough Research Institute, Kenilworth, NJ.

2.2. HPLC

The HPLC system consisted of a Waters WISP 712 sample injection module (Millipore, Milford, MA), a Waters 590 HPLC pump, and a Waters Lambda-Max 481 LC spectrophotometer. Nitroglycerin content was quantitated by UV detection at 214 nm, using a mobile phase of methanol–water (45:55, v/v) at a flow rate of 1.5 ml min^{-1}, and a Waters μBondapak™ C18 (10 μm, 3.9 mm × 150 mm) HPLC column (Millipore, Milford, MA) at ambient temperature. All mobile phase solutions were filtered and degassed. Nitroglycerin degradation products 1-mononitroglycerin, 1,2-dinitroglycerin and 1,3-dinitroglycerin were quantitated by UV detection at 214 nm, using a DuPont Zorbax CN (5 μm, 4.6 mm × 250 mm) HPLC column at 40°C and a gradient methanol—water (20:80, v/v) to 100% methanol.

2.3. Nitroglycerin extraction

Several sample extraction methods were employed during the study. The samples were extracted in either ethanol, acetone or ethanol–acetone (50:50, v/v) by an orbital shaker at 300 rpm. Ethanol containing extraction solutions were preferred because nitroglycerin has a 4.5-fold greater solubility in ethanol as compared to methanol [1,20]. Method 1: samples were extracted twice in ethanol. Method 2: twice extracted ethanol samples were extracted a third time in acetone. Method 3: samples were extracted twice in ethanol–acetone (50:50, v/v).

2.4. ATR-IR microspectroscopy

ATR-IR spectroscopy was performed on a Nicolet Magna-IR™ 550 series FTIR spectrome-

Table 1
HPLC quantitation results of nitroglycerin in aged transdermal nitroglycerin samples after ethanol extraction

Lot	Time point/condition (months/°C)	Nitroglycerin content package (% label strength)		
		X	Y	Z
A	24/4		98.9	
A	24/25 60% RH		95.3*	
A	24/30 60% RH		93.6*	
B	24/4	96.9	99.3	103
B	24/25 60% RH	94.5*	96.9*	101*
B	24/30 60% RH	91.1*	93.5*	97.1*
C	12/4	103	103	104
C	12/25 60% RH	104	105	105
C	12/30 60% RH	96.8*	97.9*	95.6*

The appearance of the facestock aluminum layer defect for a given sample/condition is indicated by *.

ter with OMNIC™ software, Nic-Plan™ microscope with an ATR objective (ZnSe crystal), and a MCT-A liquid nitrogen cooled detector (detection range 4000 cm^{-1}–650 cm^{-1}). Spectra were obtained at 8 cm^{-1} resolution and the spectra were not smoothed. Interferograms from 128 scans were coadded with one level of zero filling and apodized with a Happ-Genzel function before Fourier transformation. Spectra were obtained by lowering the ATR-IR objective to the polymer sample surface until crystal contact was achieved, the sample spectrum was acquired, the objective was lifted off the sample surface, the ATR crystal was cleaned, and the background spectrum was acquired. Spectra were baseline corrected by drawing a line at three points (at approximately 650, 1850 and 4000 cm^{-1}).

3. Results and discussion

3.1. Stability testing

Several transdermal nitroglycerin lots, placed under controlled storage conditions, produced decreased nitroglycerin potency over time of up to 10% as compared to initial values (Table 1). This loss of nitroglycerin was not accompanied by a corresponding increase in nitroglycerin degradation products. Coincident with the loss of drug was the appearance of a defect in the facestock aluminum layer (indicated by * in Table 1). The polymer film laminate facestock is composed of a medium density polyethylene (MDPE) layer, a vapor deposited aluminum metal layer and a polyester layer (Fig. 1). The drug/adhesive matrix is in contact with the polyester layer of the facestock and the aluminum layer is beneath this polyester layer (Fig. 1). Microscopic examination of the transdermal nitroglycerin samples with the aluminum layer defect, after the removal of the adhesive/drug matrix layer, showed that the facestock polyester layer was intact and the aluminum layer had formed small channels void of aluminum metal along the transdermal patch perimeter (Fig. 2). Infrared spectroscopic analysis was used to investigate the cause of the loss of nitroglycerin and the aluminum layer defect in aged transdermal nitroglycerin lots.

3.2. ATR-IR microspectroscopic analysis of transdermal nitroglycerin samples

Nitroglycerin can migrate from the drug/adhesive matrix to the polymer film laminate facestock [18,19]. If the extractability of nitroglycerin from the polymer film laminate facestock is different from the extractability of nitroglycerin from the adhesive matrix, then an apparent loss of nitroglycerin would result. This hypothesis was examined by ATR-IR microspectroscopy [21–27]. ATR-IR microspectroscopy allows the direct

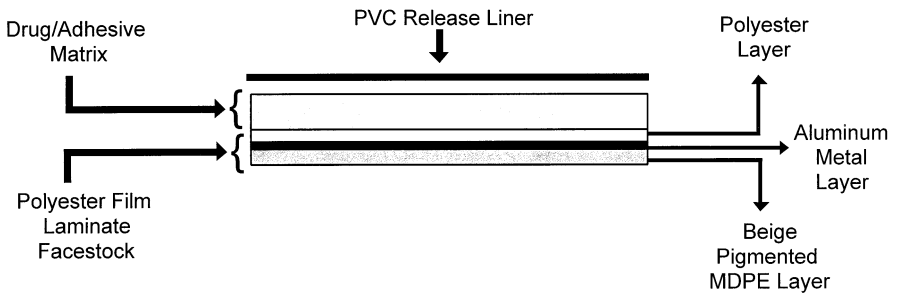

Fig. 1. Schematic of the prototype transdermal nitroglycerin patch.

analysis of highly absorbing materials without altering the sample (i.e. KBr pellets, etc.) and provides a fixed reproducible pathlength for accurate qualitative/quantitative information [24,25]. ATR-IR is a nondestructive technique that provides infrared spectral information from the sample surface through the intimate contact between the sample and the ATR-IR crystal. The depth of infrared light penetration from the ATR crystal to the sample is a function of wavelength, angle of incidence, refractive index of the ATR crystal, and the refractive index of the sample, and typically the ATR objective can analyze the upper 1–2 μm of a sample [24–26].

ATR-IR analysis of the drug/adhesive matrix of an aged sample (Lot B, 24 months @ 30°C/60% RH) showed that ethanol extraction is sufficient to completely remove nitroglycerin from the drug/adhesive matrix (Fig. 3a). Fig. 3a shows the characteristic IR bands of nitroglycerin in the drug/adhesive matrix (top spectrum). These IR bands include the NO_2 asymmetric stretch ($\nu_{as}NO_2$) at 1650 cm^{-1}, the NO_2 symmetric stretch ($\nu_{s}NO_2$) at 1275 cm^{-1}, and the NO stretch (νNO) at 850 cm^{-1}. These bands are clearly absent in the placebo/adhesive matrix (middle spectrum, Fig. 3a) and the ethanol extracted drug/adhesive matrix (bottom spectrum, Fig. 3a). Analysis of the same sample (Lot B, 24 months @ 30°C/60% RH), after the removal of the adhesive/drug matrix layer, revealed that nitroglycerin had migrated from the adhesive/drug matrix into the facestock polyester layer (middle spectrum, Fig. 3b) as indicated by the characteristic nitroglycerin IR bands at 1650 cm^{-1} ($\nu_{as}NO_2$) and at 850 cm^{-1} (νNO). Ethanol extraction was not sufficient to remove all of the nitroglycerin from the facestock polyester layer (bottom spectrum, Fig. 3b). Note that the nitroglycerin IR band at 1275 cm^{-1} ($\nu_{s}NO_2$) is obscured by a polyester IR band (top spectrum, Fig. 3b).

The stability data in Table 1 shows that the loss of nitroglycerin potency is temperature dependent. Fig. 4 shows the polyester layer spectra of lot B at different storage conditions (24 months @ 4°C, 25°C/60% RH and 30°C/60% RH) after the removal of the drug/adhesive matrix. These spectra show that the intensity of the nitroglycerin IR bands at 1650 cm^{-1} ($\nu_{as}NO_2$) and at 850 cm^{-1} (νNO) increased with increasing storage temperature (i.e. 4°C < 25°C < 30°C). In addition, these samples exhibited a varying degree of defects in the facestock aluminum layer. Samples stored for 24 months at 4°C had no observable aluminum layer defect. Samples stored for 24 months at 25°C/60% RH had hairline fractures in the aluminum layer that increased in both number and width at the 30°C/60% RH storage condition (similar to that shown in Fig. 2).

3.3. Quantitation of absorbed nitroglycerin in the facestock

Aged samples were extracted with ethanol (extraction method 1, Section 2), then extracted with acetone (extraction method 2, Section 2) and the resulting extraction solutions analyzed for nitroglycerin content. The results in Table 2 indicate

that the samples still contain anywhere from 0.1–6% nitroglycerin after ethanol extraction. The facestock from these samples were analyzed by ATR-IR spectroscopy both before and after acetone extraction (not shown). Spectra from the

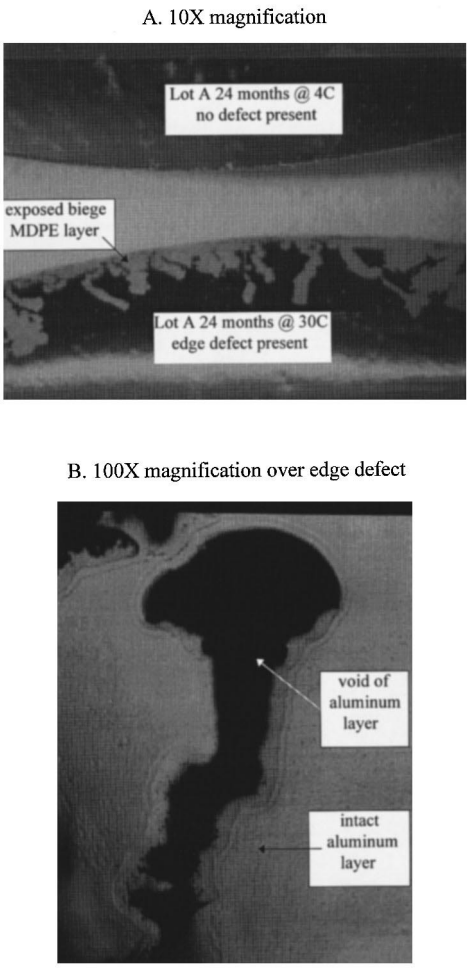

Fig. 2. (a) Photograph at 10 × magnification of the transdermal nitroglycerin sample lot A with (bottom, 24 months @ 30°C) and without (top, 24 months @ 4°C) the aluminum layer defect, after the removal of the adhesive/drug matrix layer. (b) Photograph at 100 × magnification of the transdermal nitroglycerin sample (lot A 24 months @ 30°C) over the aluminum layer edge defect taken after the removal of the adhesive/drug matrix layer. The view for both photographs is down on the facestock polyester layer near the transdermal patch perimeter.

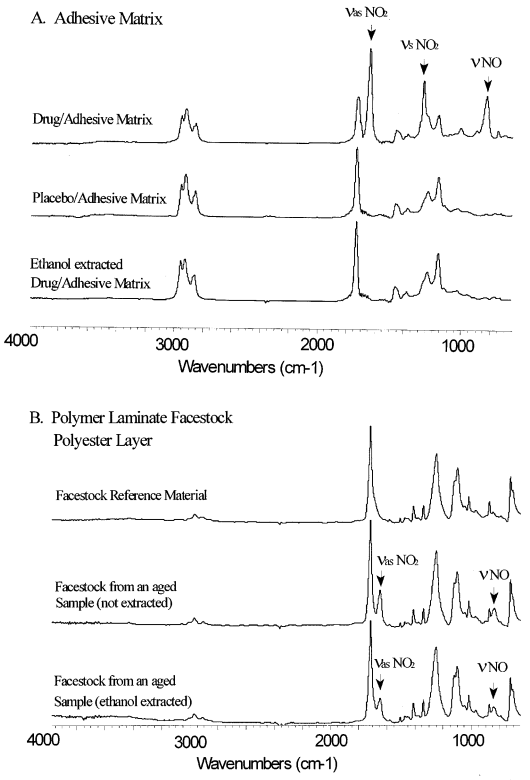

Fig. 3. ATR-IR spectra of the transdermal nitroglycerin sample (a) drug/adhesive matrix and (b) facestock polyester layer before and after ethanol extraction. IR spectra of the placebo adhesive matrix and the polyester layer from virgin polymer film laminate facestock are included as references.

ethanol extracted samples exhibited the characteristic nitroglycerin IR bands at 1650 cm^{-1} ($\nu_{as}NO_2$) and 850 cm^{-1} (νNO) in the facestock polyester layer. Spectra from the acetone extracted samples contained no detectable nitroglycerin IR bands, which demonstrate that the ATR-IR technique has a detection limit of at least 0.1% nitroglycerin in the facestock polyester layer.

A final nitroglycerin extraction method (method 3, Section 2) was developed to simultaneously extract nitroglycerin from both the adhesive matrix and the facestock polyester layer. The results in Table 3 show that nearly 100% of the label strength was obtained using this extraction technique. Fig. 5 compared the sample facestock spectra after the acetone–ethanol extraction and after the ethanol extraction. This figure shows

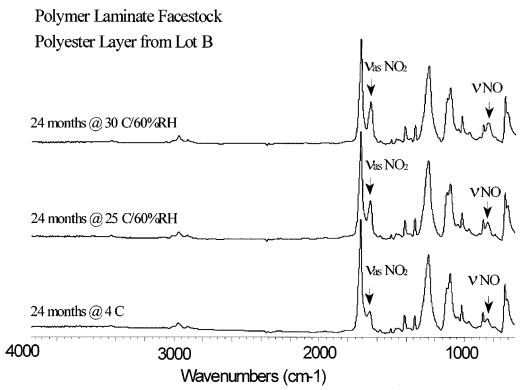

Fig. 4. ATR-IR spectra of the facestock polyester layer after the removal of the adhesive/drug matrix layer from aged transdermal nitroglycerin samples. The spectra from lot B, 24 months @ 30°C/60% RH (top spectrum), lot B, 24 months @ 25°C/60% RH (middle spectrum) and lot B, 24 months @ 4°C (bottom spectrum). The spectra show an increased intensity of the characteristic nitroglycerin IR bands at 1650 cm^{-1} ($\nu_{as}NO_2$) and 850 cm^{-1} (νNO) with increasing stability temperature.

that the nitroglycerin IR bands at 1650 cm^{-1} ($\nu_{as}NO_2$) and 850cm^{-1} (νNO) were absent in the acetone–ethanol extracted sample facestock and present in the ethanol extracted sample facestock.

Since ATR-IR microspectroscopy examined the top 1–2 μm of the 0.56 mil (14 μm) thick facestock polyester layer (i.e only 10% of the polyester thickness), additional evidence was required to determine if nitroglycerin extraction was complete. The adhesive-side polyester surface and the aluminum-side polyester surface of the facestock from previously extracted samples were analyzed (refer to Fig. 1) by ATR-IR. The lack of nitroglycerin on either side would suggest complete nitroglycerin extraction. This assumption is valid because the extracting solvent can only permeate through the adhesive-side polyester surface to the aluminum-side polyester surface of the facestock polyester layer. The MDPE polymer layer and the vapor-deposited aluminum metal were removed by razor blade thus exposing the aluminum-side polyester surface of the facestock. Spectra from both sides of the polyester surface of an acetone–ethanol extracted sample is shown in Fig. 6. The spectra show no detectable nitroglycerin IR bands at 1650 cm^{-1} ($\nu_{as}NO_2$) and 850 cm^{-1} (νNO) on either side of the facestock polyester layer which confirms complete or nearly complete nitroglycerin extraction.

Table 2
HPLC quantitation results of nitroglycerin in aged transdermal nitroglycerin samples after ethanol extraction and acetone extraction of the same ethanol extracted samples

Lot (package)	Time point/condition (months/°C)	Nitroglycerin content (% label strength)	
		Ethanol extraction	Acetone extraction
A (Y)*	24/30 60% RH	95.7	3.6
B (X)*	24/30 60% RH	89.4	4.8
B (Y)	24/4	99.5	0.5
B (Y)*	24/30 60% RH	93.5	5.4
B (Z)*	24/30 60% RH	96.5	3.9
C (Y)	12/4	103	0.2
C (Y)	12/25 60% RH	104	0.7
C (Y)*	12/30 60% RH	98.1	2.4
C (Y)*	6/40 80% RH	92.5	6.0
C (Z)	12/4	104	0.1
C (Z)	12/25 60% RH	104	0.5
C (Z)*	12/30 60% RH	95.5	1.7

The appearance of the facestock aluminum layer defect for a given sample/condition is indicated by an *.

Table 3
Comparison of HPLC quantitation results of nitroglycerin in aged transdermal nitroglycerin samples after acetone–ethanol extraction and after ethanol extraction

Lot (package)	Time point/condition (months/°C)	Nitroglycerin content (% label strength)	
		Acetone–ethanol extraction	Ethanol extraction
A (Y)	24/4	103	98.9
A (Y)*	24/30 60% RH	99.8	93.6
B (Y)	24/4	99.8	98.1
B (Y)*	24/30 60% RH	96.6	92.9
C(Y)*	6/40 80% RH	100	94.0

The appearance of the facestock aluminum layer defect for a given sample/condition is indicated by an *.

3.4. Facestock aluminum layer channeling

Several phenomena coincide with the appearance of facestock aluminum layer channeling in the transdermal nitroglycerin samples. Samples placed under stability test conditions (≥ 25°C) for prolonged periods produced facestock aluminum layer channeling (see * notation in Tables 1–3). The size of the facestock aluminum layer channels increased with age and temperature suggesting a temperature–time related mechanism. The extent of nitroglycerin migration into the facestock polyester layer also increased with age and temperature. Finally, placebo transdermal samples exposed to conditions sufficient to produce channeling in active nitroglycerin transdermal samples (i.e. 11 months @ 40°C/80% RH) did not exhibit facestock aluminum layer channeling. Therefore a correlation exists between the presence of nitroglycerin in the facestock polyester layer and the facestock aluminum layer defect in transdermal nitroglycerin samples.

To determine the extent of nitroglycerin migration as a function of the appearance of the aluminum layer defect, spectra from both sides of the facestock polyester layer of unextracted aged samples were examined. This was accomplished by first removing the adhesive layer by razor blade and acetone–methanol wash then removing the MDPE layer and the aluminum layer by razor blade (refer to Fig. 1). The spectra from 24 month

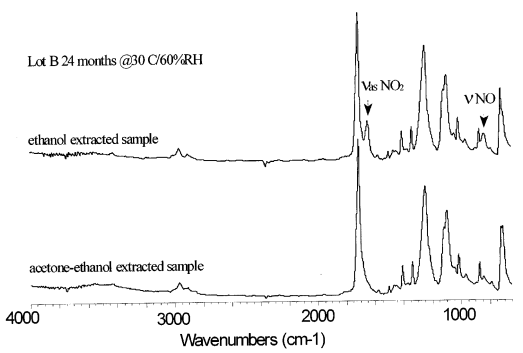

Fig. 5. ATR-IR spectra of the facestock polyester layer of transdermal nitroglycerin samples after the acetone–ethanol extraction (method 3) and after the ethanol extraction (method 1). Shown are example spectra from lot B, 24 months @ 30°C/60% RH which were extracted in acetone–ethanol and ethanol.

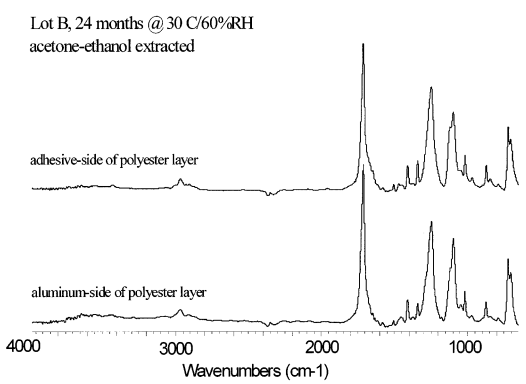

Fig. 6. The ATR-IR spectra of the facestock polyester layer from both the adhesive side and the aluminum side of the acetone–ethanol extracted sample (lot B, 24 months @ 30°C).

old samples (Lot A) maintained at 4°C (no aluminum layer defect), 25°C/60% RH (aluminum layer defect present) and 30°C/60% RH (aluminum layer defect present) are shown in Fig. 7 and the results summarized in Table 4. These results show that nitroglycerin migrated into the facestock polyester layer from the adhesive side down and the from the edge towards the center of the sample and that the extent of nitroglycerin migration depends on the storage condition temperature (24 months @ 30°C/60% RH > 24 months @ 25°C/60% RH > 24 months @ 4°C). These results suggest that nitroglycerin–aluminum metal contact along the aluminum-side polyester surface perimeter is required for aluminum layer channeling to occur.

Nitroglycerin degradation products were found in these aged transdermal nitroglycerin samples. For example, 0.4% of 1,2-dinitroglycerin and 0.6% of 1,3-dinitroglycerin were found in lot C (12 months @ 30°C/60% RH). The amount of 1-mononitroglycerin was between 0.05 and 0.1%. Nitrates (NO_3^-) form through the degradation of nitroglycerin [1,28]. In addition, the drug/adhesive matrix contains approximately 4% water. Therefore nitroglycerin, nitrates, water and aluminum metal are present in the aged transdermal nitroglycerin samples.

3.5. Proposed nitroglycerin–aluminum metal reaction mechanism

Lurie et al. [17] reported that aluminum metal can react with both inorganic nitrates and/or organic nitrates (including nitroglycerin) in the presence of water to form AlO(OH), $Al(OH)_3$, AlO_2^-, $Al(NO_3^-)_3$, and $(AlO)NO_3$. Aluminum metal reacts with nitrates (NO_3^-) and water (H_2O) to form water-insoluble boehmite (AlO(OH)) by the following reaction mechanism [17]:

$$Al + NO_3^- + H_2O \rightarrow AlO(OH) + NO_2^- + H^\cdot$$
$$NO_3^- + 2H^\cdot \rightarrow NO_2^- + H_2O$$

$$2Al + 3NO_3^- + H_2O \rightarrow 2AlOOH + 3NO_2^-$$

Boehmite (AlO(OH)) can react with water (H_2O) to form aluminum hydroxide $Al(OH)_3$ which can

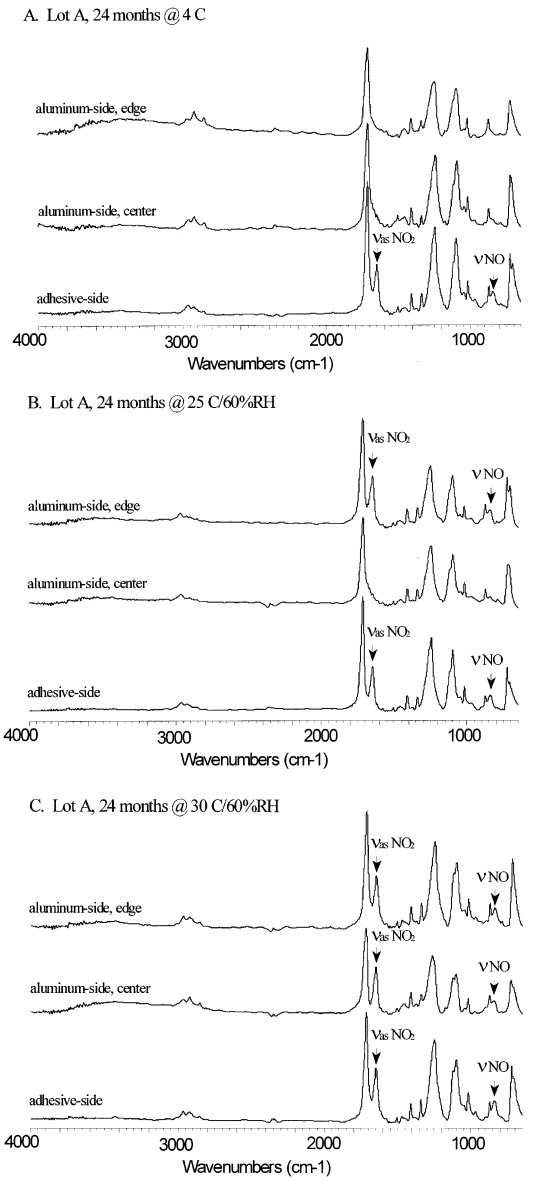

Fig. 7. The ATR-IR spectra of the facestock polyester layer from both the adhesive side and the aluminum side (center and edge) for the transdermal nitroglycerin samples (lot A) maintained at (A) 24 months @ 4°C, (B) 24 months @ 25°C/60% RH and (C) 24 months @ 30°C/60% RH. These samples had the drug/adhesive matrix and the MDPE/aluminum layers removed by razor blade prior to ATR-IR analysis of the facestock polyester layer.

Table 4
Summary of the presence of nitroglycerin on both sides of the facestock polyester layer of 24 month old samples (Lot A) maintained at 4°C, 25°C/60% RH and 30°C/60% RH conditions as detected by ATR-IR microspectroscopy

Lot (package)	Time point/condition (months/°C)	Adhesive-side	Aluminum-side	
			Edge	Center
A (Y)	24/4	+[a]	−[b]	−
A (Y)*	24/25 60% RH	+	+	−
A (Y)*	24/30 60% RH	+	+	+

Spectra shown in Fig. 7).
The appearance of the facestock aluminum layer defect for a given sample/condition is indicated by an *.
[a] +, Nitroglycerin present (observable IR band at 1650 cm^{-1} $\nu_{as}NO_2$).
[b] −, Nitroglycerin absent (no observable IR band at 1650 cm^{-1} $\nu_{as}NO_2$).

further react with hydroxide (OH^-) to form aluminate (AlO_2^-) as shown below [17]:

$$AlO(OH) + H_2O \leftrightarrow Al(OH)_3$$
$$Al(OH)_3 + OH^- \rightarrow 2H_2O + AlO_2^-$$

$$AlOOH + OH^- \rightarrow H_2O + AlO_2^-$$

Nitrates (NO_3^-) can also stabilize the newly formed aluminum compounds AlO(OH) and $Al(OH)_3$ by forming the equilibrium species $(AlO)NO_3$ and $Al(NO_3^-)_3$, respectively while also increasing the alkali (OH^-) concentration [17].

$$Al(OH)_3 + 3NO_3^- \leftrightarrow Al(NO_3^-)_3 + 3OH^-$$

$$AlOOH + NO_3^- \leftrightarrow (AlO)NO_3 + OH^-$$

From the above information, several aluminum compounds including AlO(OH), $Al(OH)_3$, AlO_2^-, $Al(NO_3^-)_3$, and $(AlO)NO_3$ are formed when aluminum metal is in contact with nitrates (NO_3^-) and water (H_2O). The compounds AlO_2^- and $Al(NO_3^-)_3$ are water soluble and $Al(OH)_3$ forms a gel on prolonged contact with water [29].

This information provided a plausible mechanism for the facestock aluminum layer channeling of the transdermal nitroglycerin samples under the prolonged exposure to 25°C/60% RH, 30°C/60% RH, and 40°C/80% RH stability conditions. It is theorized that these conditions are sufficient for aluminum metal to form the above mentioned aluminum compounds resulting in the observed facestock aluminum layer channeling. Further experiments are necessary to identify which potential aluminum compounds are present. Since all IR spectra of the facestock polyester layer show that water does not penetrate into the facestock (no νOH band in the 3200 to 3500 cm^{-1} region), then this proposed mechanism would predict that the water–nitrates–aluminum metal reaction can only occur around the perimeter of the facestock (where water is present in the adhesive) and expand radially towards the center of the facestock over time. All aged transdermal nitroglycerin samples exhibited the aluminum layer channeling defect in this manner.

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