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RESEARCH ARTICLE

Evaluating elevated release liner adhesion of a transdermal drug delivery system (TDDS): A study of Daytrana™ methylphenidate transdermal system

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Abstract

Background: Complaints from healthcare providers that the adhesive on the Daytrana™ methylphenidate transdermal drug delivery system (TDDS) adhered to the release liner to such an extent that the release liner could not be removed prompted this study. Daytrana™ has a packaging system consisting of a moisture-permeable pouch contained within a sealed tray containing a desiccant; the tray is impermeable to ambient moisture. The objective of this project was to determine if the Daytrana™ packaging system influenced the difficulty in removing the release liner.

Method: Both a sealed tray and an open tray containing sealed pouches were placed into an environmental chamber at 25°C and 60% relative humidity for 30 days; afterwards, release liner removal testing using a peel angle of 90° and a peel speed of 300 mm/min was performed.

Results: TDDS from open chamber trays required less force to remove the release liner than did TDDS from closed chamber trays. For the 10 mg/9 h TDDS and the 15 mg/9 h TDDS (the dosages examined), there were substantial differences in release liner removal force between an old lot and a new lot for closed chamber trays but not for open chamber trays.

Conclusion: The results demonstrate that for this particular TDDS, storage conditions such as humidity influence release liner adhesion. This project also demonstrates that, to ensure adequate product quality, adhesion needs to become an important design parameter, and the design of a TDDS should consider the ability to remove the release liner under anticipated storage conditions.

Keywords: Adhesion, liner, methylphenidate, release liner, patch, transdermal delivery system

Introduction

Daytrana™ (methylphenidate transdermal patch) was approved by the USA Food and Drug Administration (FDA) in April 2006 for attention deficit hyperactivity disorder in pediatric patients of 6–12 years.[1–3], and Daytrana™ was launched in June 2006[4,5]. Daytrana™ is manufactured for Shire US by Noven Pharmaceuticals (Miami, FL) and is classified as a Schedule II (i.e. CII) controlled substance[6,7]. A box of Daytrana™ contains a sealed tray and Prescribing Information/Medication Guide. The tray contains a desiccant as well as either 30 or 10 sealed pouches. The pouch contains a transdermal drug delivery system (TDDS). The TDDS consists of three "layers" (Figure 1). Proceeding from the outer surface toward the surface adhering to the skin, the layers are (1) a polyester/ethylene vinyl acetate laminate film backing, (2) a proprietary adhesive formulation incorporating Noven Pharmaceuticals, Inc.'s DOT Matrix™ transdermal technology consisting of an acrylic adhesive, a silicone adhesive, and methylphenidate; and (3) a fluoropolymer-coated polyester liner which is attached to the adhesive surface and must be removed before the patch can be applied to the skin[6]. Hereafter, the backing/adhesive formulation combination is referred to as a "patch," the liner is referred to as a "release liner," and the backing/adhesive formulation/

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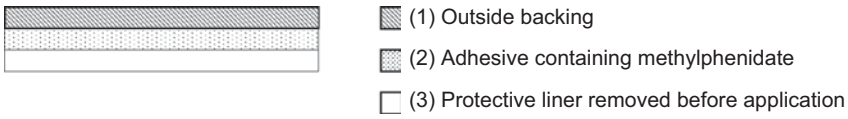

Figure 1. Drawing of Daytrana™ transdermal drug delivery system.

release liner combination is referred to as a "transdermal drug delivery system."

The release liner should peel easily from the patch without tearing the patch or removing the adhesive from the patch. Within less than 6 months following product launch, complaints about Daytrana™'s adhesive began appearing on internet message boards/blogs[8–24], and the FDA began receiving similar complaints. The complaints indicated that the adhesive (which contains the active pharmaceutical ingredient) adhered to the release liner to such an extent that the release liner could not be removed, or if the release liner was removed, very little adhesive remained on the patch (e.g. Figures 2 and 3). This could have resulted in the patch not adhering to the patient's skin as well as a possibly sub-therapeutic dosage[25].

On 4 September 2007, Shire announced the voluntary market withdrawal of Daytrana™ packages with an expiration date of 31 March 2009 or earlier as well as product from three additional lots. Shire stated that the withdrawal was not due to safety and efficacy issues, but due to feedback from patients and caregivers who had experienced difficulty removing the release liner from some Daytrana™ patches[26–29].

Noven and Shire attempted to enhance removal of the Daytrana™ release liner by increasing the release coating on the liner[26,30]. Despite this improvement, patients continued to experience difficulty removing the release liner. On 9 June 2008, two lots of Daytrana™ were recalled[31–33]; 25 August 2008, two lots of Daytrana™ were recalled[30,34]; 20 March 2009, 39 lots were withdrawn/recalled[35–37]; and 3 December 2009, six lots of Daytrana™ were withdrawn/recalled because of the release liner[38].

Typically, a TDDS is enclosed in a single unit pouch (e.g. polyester film, paper, metal foil) with a certain quantity of pouches contained in a cardboard box. Noven recognized that for a methylphenidate TDDS a moisture impermeable pouch produced relatively high amounts of related substances[39–41]. Noven's study concluded that this problem could be solved through creation of a packaging system that would allow moisture to be transmitted through a pouch (i.e. moisture-permeable pouch) contained within a moisture impermeable tray in which the relative humidity was controlled by the use of a desiccant material[39]. For the Daytrana™ packaging system, the pouches along with a desiccant are supplied in a sealed tray, and that tray is placed inside a box. Once the seal from the tray is removed in order to remove pouches containing the TDDS, the tray cannot be re-sealed. Both the Daytrana™ Prescribing Information and the Daytrana™ Medication Guide state that once a tray has been opened, the patches must be used or discarded within 2 months[6,7].

Figure 2. Difficulty in manually removing the release liner from the Daytrana™ patch.

The objective of this project was to determine if the Daytrana™ packaging system influenced the difficulty in removing the release liner. That is, are the TDDS release liner removal values for pouches stored in an open tray under controlled temperature and humidity different from those values obtained for pouches stored in the sealed closed tray under controlled temperature and humidity?

Materials and Methods

Samples

Thirty-count trays were chosen over 10-count trays because there were more complaints regarding the 30-count trays. The 10 mg/9 h (1.1 mg/h) dosage and the 15 mg/9 h (1.6 mg/h) dosage were chosen because there were more complaints for these two dosages than the 30 mg/9 h (3.3 mg/h) dosage. For each dosage, three boxes from each of two lots were purchased. Table 1 shows sample labeling scheme in text.

The TDDS were tested before their expiration dates. Also, according to Daytrana™ Prescribing Information[6],

Figure 3. Half of the release liner manually removed from the Daytrana™ patch; adhesive remains on the release liner that was removed. (This lot was later recalled by Shire).

Table 1. Methylphenidate transdermal drug delivery systems evaluated.

Labeled dose (/9 h)	Expiration date	Designation in text*
10 mg	08-2009	10 mg OLD
10 mg	01-2010	10 mg NEW
15 mg	10-2009	15 mg OLD**
15 mg	12-2009	15 mg NEW

* "OLD" signified an older expiration date, and "NEW" signified a newer expiration date.** The "15 mg OLD" lot was later recalled by Shire. Shire stated that since this recall was not due to product safety issues, the patches in this lot could continued to be used unless the release liner could not be removed or unless the patches were damaged while being opened[31,32].

Daytrana™ Medication Guide[7], Daytrana™ box, and Daytrana™ pouch, once a tray containing the patches has been opened, the patches must be used within 2 months or discarded. All tests reported here were performed within 2 months of the tray being opened.

Sample conditioning

Chamber closed samples

For each of the lots, one sealed tray was removed from its box, and the sealed tray was placed into a locked environmental chamber (Revco Environmental Test Chamber Model RTC10–99D) set at 25°C and 60% relative humidity for 30 days. These samples were identified as "10 mg OLD closed," "10 mg NEW closed," "15 mg OLD closed," and "15 mg NEW closed." "OLD" signified an older expiration date, and "NEW" signified a newer expiration date. "Closed" status signified that the tray was sealed when it was in the environmental chamber. The desiccant and the pouches containing the TDDS were in the sealed tray.

Chamber open samples

For each of the lots, one sealed tray was removed from its box, the seal and desiccant were removed from the tray, and the tray was placed into the locked environmental chamber set at 25°C and 60% relative humidity for 30 days. These samples were identified as "10 mg OLD open," "10 mg NEW open," "15 mg OLD open," and "15 mg NEW open," "Open" status signified that the tray was opened (i.e. the seal was removed) when it was in the environmental chamber. The pouches containing the TDDS were sealed while in the open tray.

Ambient closed samples

For each of the lots, the third box containing the sealed tray was kept in a locked cabinet under "ambient" laboratory conditions (22–26°C, 20–55% relative humidity). This was the "ambient" status.

The Daytrana™ Medication Guide states to store Daytrana™ at room temperature, 59–86°F (15–30°C)[7]. In this project, Daytrana™ was stored as per the guidelines.

Test procedure

After 30–35 days exposure in the environmental test chamber, each tray was removed, and release liner removal testing was performed on the TDDS. Chamber samples were held in the environmental test chamber for less than 2 months to allow time for testing the samples within the 2-month period stipulated in the prescribing information[6,7] for opened trays. For the pouches in the closed trays, a substantial static charge made it difficult to separate the pouches from each other. This phenomenon was not observed for the pouches in the open trays.

Release liner test procedure

The instrument used to remove the release liners, the Texture Analyser TA.XT.plus with a 5 kg load cell (Texture Technologies Corp., Scarsdale, NY) was calibrated on each day of use. The stainless steel test panels (3 × 6 inch; ChemInstruments, Fairfield, OH) were cleaned by rinsing the panel with a stream of methyl ethyl ketone from a squeeze bottle and wiping dry with Kimwipes®. The procedure of rinsing and Kimwipes drying was repeated a total of three times followed by air drying for a minimum of 10 minutes[42–44]. The width of each patch was measured using a digital caliper (Fowler PRO-MAX). Double-sided tape (3M 9877, 3M Medical Specialties, St. Paul, MN) was placed onto cleaned stainless steel test panels. A 4.5 lb. roller (HR-100; ChemInstruments) was rolled length-wise once in each direction (e.g. rolled from bottom-to-top and then top-to-bottom) over the double-sided tape. The release liner from the double-

sided tape was removed. The TDDS was bent along the score line. The top of the patch was folded back ~5 mm from its release liner. A tape leader (NT-9511-2, Dielectric Polymers, Holyoke, MA) was attached to ~3 mm of the exposed patch. The TDDS was placed onto the double-sided tape with the liner side down. The TDDS was rolled onto the test panel using a 4.5 lb. roller and rolled length-wise once in each direction. The test panel was placed into the instrument. After a 3-min dwell time from when the TDDS was applied to the test panel, the instrument and data acquisition systems (software TEE32 version 4.0.4.0 with 500 points per second data acquisition) were activated. Instrumentation was configured to peel samples at 90° with a peel speed of 300 mm/min[44].

Force measurement

The entire length of the patch was peeled. To calculate average force, the first point chosen was after the initial start force (indicated by a large peak). The last point chosen was just prior to the decline of the curve to zero, or if there was a large peak at the end of the curve, the last point taken was at the bottom of the valley prior to the large peak. Peel adhesion measurement is independent of sample length but is dependent upon the width of the sample[45,46]. Peel values are reported in force per unit of width (e.g. mN/mm).

Statistical analysis data

In this study, each TDDS was tested at the combination of two or three levels of three factors. The three factors were dose, age and status. Dose had two levels: 10 mg and 15 mg; age had two levels: old lot and new lot; status had three levels: open, closed and ambient. The samples were not run in a randomized experimental design because there was a concern that the chamber closed samples may act as chamber open samples if the chamber closed samples were not tested immediately after removing the seal.

Specifically, at each dose level, we were interested in assessing the following questions:

- Was there a statistically significant difference between age (new lot and old lot)?
- Was there a statistically significant difference between TDDS with different status (open tray, closed tray, and ambient tray)?

Statistical methods

Statistical analyses were carried out using linear models for each dose level.

The linear model analyzed is described in Equation (1)

$$y_{ijk} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + \varepsilon_{ijk} \begin{cases} i = 1,2 \\ j = 1,2,3 \\ k = 1,2,\ldots,m_{ij} \end{cases} \quad (1)$$

where y_{ijk} was the observed peel force at the ith age, jth status, and kth replicate, μ was the grand mean, α_i was the effect of ith age, β_j was the effect of the jth status, $(\alpha\beta)_{ij}$ was the effect of the interaction between ith age and jth status, m_{ij} is the number of observations for ith age and jth status, and ε_{ijk} was the unknown random error at the ith age, jth status, and kth replicate.

After the model was fitted to the data, the statistically significantly important factors and interactions were identified. The interaction term was removed from the model when it was not significant at the 0.05 level. When the interaction was statistically significant, comparisons involving two or more factor level means were constructed to assess the following difference in release liner peel adhesion force

- Between the open tray and the closed tray at each level of age
- Between the open tray and the ambient tray at each level of age
- Between the closed tray and the ambient tray at each level of age
- Between the old lot and new lot at each level of status (open, closed and ambient).

Results

This project focused on adhesion properties of Daytrana™. Table 2 shows the average release liner removal force obtained for each dose, age and status combination. The higher the measured release liner removal value, the more difficult it is to remove the patch from its release liner. For both dosages, TDDS from open trays have lower release liner removal values compared to values observed for TDDS from the closed trays; therefore, the patches from the TDDS stored in the open trays are easier to remove from their release liners than the patches from the TDDS stored in closed trays.

Analysis of release liner removal forces for 10 mg/9 h TDDS

The mean force required for release liner removal was substantially greater for the older lot than the newer lot for both closed and ambient trays, but not for the open trays (Figure 4).

Table 3 shows the results of tests of significance of the effects of age, status, and the interaction between age and status. These factors were significant, as expected from Figure 4.

The results of contrasts constructed to make comparisons between the selected groups are shown in Table 4. The differences between all selected groups are statistically significant at the 0.05 level.

Analysis of release liner removal forces for 15 mg/9 h TDDS

Figure 5 displays release liner removal force means vs. three levels of status for the 15 mg/9 h dose. The mean

Table 2. Summary of observed release liner removal peel force data.

Dose (mg/9 h)	Age	Status	Mean release liner peeling force (mN/mm)	Standard error of the mean	Number of observations
10	New	Closed	52.46	1.25	21
10	New	Ambient	86.42	2.91	21
10	New	Open	17.49	0.28	21
10	Old	Closed	79.04	2.54	21
10	Old	Ambient	121.12	1.85	21
10	Old	Open	28.41	0.96	21
15	New	Closed	33.02	0.86	21
15	New	Ambient	40.94	1.74	21
15	New	Open	13.10	0.33	21
15	Old	Closed	140.24	2.68	17
15	Old	Ambient	144.93	3.57	21
15	Old	Open	21.93	0.73	21

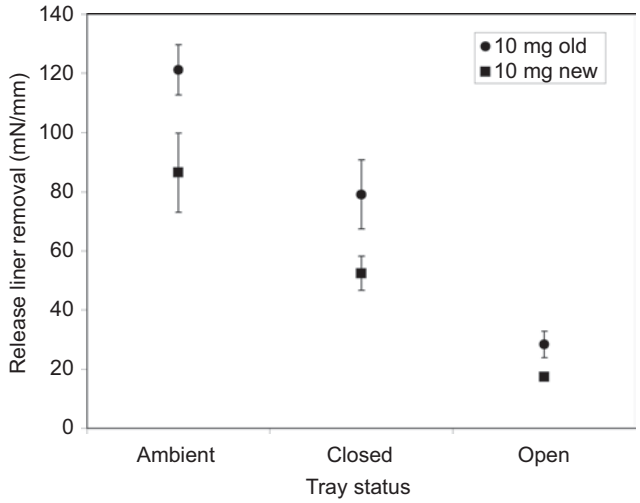

Figure 4. Mean release liner removal force vs. tray for 10 mg/9 h dosage.

release liner removal force required was substantially greater for the older lot than the newer lot for both closed and ambient trays, but not for the open trays.

Table 5 shows the results of tests of significance of the effects of age, status, and the interaction between age and status. These factors were significant, as expected from Figure 5.

The results of contrasts constructed to make comparisons between the selected groups for 15 mg TDDS patches are listed in Table 6. All differences were shown to be statistically significant except that for the comparison of 15 mg old closed lot with the 15 mg old ambient lot.

Discussion

For the 10 mg methylphenidate TDDS and the 15 mg methylphenidate TDDS, there were differences in release liner removal force between the old lot and new lot for closed and ambient trays but not for open trays. All selected comparisons showed statistically significant differences except the closed lot vs. ambient lot for 15 mg OLD patches. Shire recalled the lot identified in this study as "15 mg OLD" because it did not meet their release liner removal specification[32,33]. Based upon this information, the 15 mg OLD release liner removal results were expected to be higher than the release liner removal results for the 15 mg NEW lot, the 10 mg OLD lot, and the 10 mg NEW lot. The 15 mg OLD ambient release liner removal results and the 15 mg OLD closed release liner removal results were higher than the other release liner removal results; however, the 15 mg OLD open release liner removal results were lower compared to the 15 mg OLD closed and 15 mg OLD ambient results. This suggests that humidity influenced the decrease in the release liner removal values for this lot.

For the 10 mg methylphenidate TDDS and the 15 mg methylphenidate TDDS, there were differences in release liner removal force between closed trays and open trays. This seems to indicate that the sealed tray containing a desiccant provides some protection from higher humidity levels (i.e. the force required to remove the release liner is inversely related to the relative humidity). According to Kanios et al., moisture provides the catalyst for methylphenidate related substances formation[39–41], and since it was easier to remove the methylphenidate patch from its release liner when the TDDS was exposed to increased humidity, humidity seems to be a contributing factor in the ease of removing the Daytrana™ release liner for all the lots examined. In addition, Li et al. state that methylphenidate related substance formation is highly temperature dependent[47], and Arnold et al. state that temperature influences methylphenidate TDDS release liner removal[48].

Since the samples in the closed tray in the environmental test chamber and the samples in the ambient tray were in closed trays, the release liner removal values were expected to be similar. All selected comparisons showed statistically significant differences except the closed lot vs. ambient lot for 15 mg OLD patches. Differences between ambient and closed chamber results could arise if the tray is not moisture impermeable[49–51] or if the desiccant became saturated.

Table 3. Tests of significance of factors affecting release liner removal peel force for 10 mg/9 h methylphenidate transdermal drug delivery system.

Source	Degrees of freedom	Mean sum of square	F-Value	*P*-value
Age (old vs. new)	1.00	18,242.53	248.91	<0.0001
Status (ambient vs. closed vs. open)	2.00	68,669.07	936.96	<0.0001
Age × status	2.00	1534.22	20.93	<0.0001
Error	120.00	73.29		

Table 4. Analysis of comparisons in release liner removal peel force between factor levels for 10 mg/9 h methylphenidate transdermal drug delivery system (TDDS).

Contrasts for 10 mg/9 h TDDS	Estimate	Standard error	*P*-value of test of hypothesis that difference is 0.
New closed vs. new ambient	−33.96	2.64	<0.0001
New open vs. new closed	34.97	2.64	<0.0001
New open vs. new ambient	68.93	2.64	<0.0001
Old closed vs. new closed	−26.58	2.64	<0.0001
Old closed vs. old ambient	−42.08	2.64	<0.0001
Old ambient vs. new ambient	−34.7	2.64	<0.0001
Old open vs. new open	−10.92	2.64	0.0001
Old open vs. old closed	50.63	2.64	<0.0001
Old open vs. old ambient	92.71	2.64	<0.0001

Conclusion

The objective of this project was to determine if the Daytrana™ packaging system influenced the difficulty in removing the release liner by testing TDDS stored in an opened tray and in a sealed tray in an environmental chamber. TDDS from open trays in the environmental chamber required less force to remove the release liner than TDDS from closed trays. This project demonstrates that for this particular methylphenidate TDDS, Daytrana™, humidity can influence release liner adhesion. To provide a decrease in adhesion complaints and to ensure adequate product quality, adhesion needs to become an important design parameter[25,52–54]. Adhesion considerations include the attribute that a patch can be easily separated from its release liner prior to application of the patch to the patient.

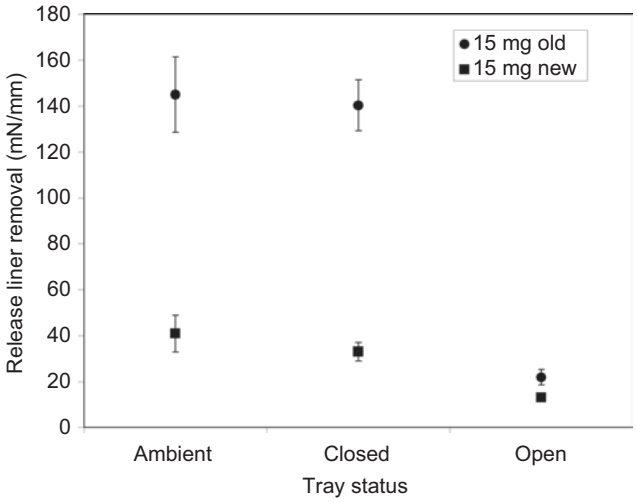

Figure 5. Mean release liner removal force vs. tray for 15 mg/9 h dosage.

Table 5. Test of significance of factors affecting fixed effects for analysis of release liner removal peel force for 15 mg/9 h methylphenidate transdermal drug delivery system.

Source	Degrees of freedom	Mean sum of square	F-Value	*P*-value
Age (old vs. new)	1.00	163,048.52	2061.06	<0.0001
Status (ambient vs. closed vs. open)	2.00	72,526.45	916.79	<0.0001
Age × status	2.00	32150.26	406.4	<0.0001
Error	116.00	79.11		

Table 6. Analysis of comparisons in release liner removal peel force between factor levels for 15 mg/9 h methylphenidate transdermal drug delivery system (TDDS).

Contrasts for 15 mg/9 h TDDS	Estimate	Standard error	*P*-value
New closed vs. new ambient	−7.92	2.74	0.0047
New open vs. new closed	19.92	2.74	<0.0001
New open vs. new ambient	27.84	2.74	<0.0001
Old closed vs. new closed	−107.22	2.90	<0.0001
Old closed vs. old ambient	−4.69	2.90	0.1087
Old ambient vs. new ambient	−103.99	2.74	<0.0001
Old open vs. new open	−8.82	2.74	0.0017
Old open vs. old closed	118.31	2.90	<0.0001
Old open vs. old ambient	123	2.74	<0.0001

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Declaration of interest

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References

1. Noven. (2006). Noven announces FDA approval of Daytrana™ methylphenidate transdermal system, April 6. http://www.noven.com.
2. Shire. (2006). Press release: Shire's Daytrana™ transdermal patch approved by FDA for treatment of ADHD. April 6. http://www.daytrana.com.
3. Shire News. (2006). Shire's Daytrana™ transdermal patch approved. April 7. http://www.shire.com.
4. Noven. (2006). Noven confirms availability of Daytrana™ methylphenidate transdermal system. June 29. http://www.noven.com.
5. Shire. (2006). Press release: Shire's Daytrana™ first transdermal medication for treatment of attention deficit hyperactivity disorder (ADHD) in children, now available in pharmacies. June 29. http://www.daytrana.com.
6. Daytrana™ (methylphenidate transdermal system) prescribing information. Wayne, PA: Shire, 03/07.
7. Daytrana™ (methylphenidate transdermal system) medication guide. Wayne, PA: Shire, 03/07.
8. ISMP. (2006–2007). Daytrana adhesive. Pediatrics/Neonatal Messages: Daytrana Adhesive. Available at: http://www.ismp.org/Forum/default.asp. Accessed 14 June 2007.
9. ISMP. (2007). Requirement #1 stick to patient. Institute for Safe Medical Practices Medication Safety Alert Community/Ambulatory Edition, June. http://www.ismp.org/newsletters/ambulatory/archives/200706_1.asp
10. ISMP. (2007). Requirement #1 patch should stick to the patient. Institute for Safe Medical Practices Medication Safety Alert Acute Care Edition. July. http://www.ismp.org/newsletters/acutecare/articles/20070712.asp
11. my3cents.com. (2007). Shire Pharmaceuticals complaint Daytrana patch defective. http://www.my3cents.com/showReview.cgi?id=19838. Accessed 14 June 2007.
12. Plumley K. (2006). Special needs education Daytrana patch chat. http://specialneedseducation.suite101.com/discussion.cfm/1964/1-6. Accessed 14 June 2007.
13. Plumley K. (2006). Special needs education Daytrana patch chat. http://specialneedseducation.suite101.com/discussion.cfm/1964/7-16. Accessed 14 June 2007.
14. Plumley K. (2006). Special needs education Daytrana patch chat. http://specialneedseducation.suite101.com/discussion.cfm/1964/17–26. Accessed 14 June 2007.
15. Plumley K. (2006). Special needs education Daytrana patch chat. http://specialneedseducation.suite101.com/discussion.cfm/1964/27–36. Accessed 14 June 2007.
16. Plumley K. (2006). Special needs education Daytrana patch chat. http://specialneedseducation.suite101.com/discussion.cfm/1964/37–46. Accessed 14 June 2007.
17. Plumley K. (2006). Special needs education Daytrana patch chat. http://specialneedseducation.suite101.com/discussion.cfm/1964/47–56. Accessed 14 June 2007.
18. Plumley K. (2006). Special needs education Daytrana patch chat. http://specialneedseducation.suite101.com/discussion.cfm/1964/57–66. Accessed 14 June 2007.
19. Plumley K. (2006). Special needs education Daytrana patch chat. http://specialneedseducation.suite101.com/discussion.cfm/1964/67–76. Accessed 14 June 2007.
20. Plumley K. (2006). Special needs education Daytrana patch chat. http://specialneedseducation.suite101.com/discussion.cfm/1964/77–86. Accessed 14 June 2007.
21. Plumley K. (2006). Special needs education Daytrana patch chat. http://specialneedseducation.suite101.com/discussion.cfm/1964/87–96. Accessed 14 June 2007.
22. Plumley K. (2006). Special needs education Daytrana patch chat. http://specialneedseducation.suite101.com/discussion.cfm/1964/97–106. Accessed 14 June 2007.
23. Plumley K. (2007a). Special needs education Daytrana patch chat. http://specialneedseducation.suite101.com/discussion.cfm/1964/107–116. Accessed 14 June 2007.
24. Plumley K. (2007). Special needs education Daytrana patch chat. http://specialneedseducation.suite101.com/discussion.cfm/1964/117–126. Accessed 14 June 2007.
25. Department of Health and Human Services. (2008). Warning letter FLA-08-05. January 4, www.fda.gov.
26. Megget K. (2007). ADHD transdermal patches withdrawn. September 05. http://www.in-pharmatechnologist.com/Materials-Formulation/ADHD-transdermal-patches-withdrawn. Accessed 18 January 2008.
27. Noven. (2007). Noven provides update on Daytrana™ Methylphenidate transdermal system: product licensee Shire undertakes voluntary market withdrawal of a limited portion of Daytrana™ product. September 4. http://www.noven.com.
28. Shire. (2007). Press release: Shire voluntarily withdraws a limited portion of Daytrana™ (methylphenidate transdermal system) patches. September 4. http://www.daytrana.com. Accessed 13 May 2008.
29. Shire News. (2007). Shire voluntarily withdraws a limited portion of Daytrana™ (methylphenidate transdermal system) patches. September 4. http://www.shire.com. Accessed 18 May 2009.
30. Macdonald G. (2008). Second Daytrana recall as liner problems continue. http://www.in-pharmatechnologist.com/Packaging/Second-Daytrana-recall-as-liner-problems-continue. Accessed 18 May 2009.
31. Noven. (2008). Noven provides update on Daytrana™ methylphenidate transdermal system: product licensee Shire undertakes voluntary recall of a limited portion of Daytrana™ product. June 9. http://www.noven.com.
32. Shire. (2008). Press release: Non-safety-related voluntary recall of a limited portion of Daytrana™ (methylphenidate transdermal system) patches announced. June 9. http://www.daytrana.com.
33. Shire News. (2008). Non-safety-related voluntary recall of a limited portion of Daytrana™ (methylphenidate transdermal system)

patches announced. June 9. http://www.shire.com. Accessed 9 June 2008.
34. Noven (2008). Noven provides update on Daytrana® methylphenidate transdermal system: Shire undertakes voluntary recall of two lots of Daytrana® product. August 25. http://www.noven.com/PR082508.htm.
35. Noven (2009). Noven provides update on Daytrana® methylphenidate transdermal system: Shire undertakes non-safety-related voluntary market withdrawal/recall of a limited portion of Daytrana® product: financial reserve established by Noven in 2008 expected to cover Noven's costs related to voluntary withdrawal/recall. March 20. http://www.noven.com.
36. Shire (2009). Press release: Non-safety-related voluntary market withdrawal of a limited portion of Daytrana® (methylphenidate transdermal system) patches announced. March 20. http://www.daytrana.com.
37. Shire News (2009). Non-safety-related voluntary market withdrawal of a limited portion of Daytrana® (methylphenidate transdermal system) patches announced. March 20. http://www.shire.com.
38. Shire (2009). Press release: Non-safety-related voluntary recall of a limited portion of Daytrana® (methylphenidate transdermal system) patches announced. December 3. http://www.shire.com.
39. Kanios DP, Mantelle JA, Johnson PA, Houze DW. (2006). The effect of primary and secondary packaging materials on the stability of drug-in-adhesive (DIA) transdermal drug delivery systems (TDDSs). http://www.noven.com/research.htm. Accessed 5 October 2007.
40. United States Patent Application Publication US 2005/0214354 A1. Publication date September 29, 2005. Inventors Kanios, DP, Mantelle, JA, Johnson, P, Li, C. Assignee: Noven Pharmaceuticals, Inc. (Miami, FL, US). Packaging system for transdermal drug delivery systems.
41. United States Patent 6905016. Publication date 14 June 2005. Packaging system for transdermal drug delivery systems. Inventors Kanios, DP, Mantelle, JA, Johnson, P, Li, C. Assignee: Noven Pharmaceuticals, Inc. (Miami, FL, US).
42. Wokovich AM, Brown SA, McMaster FJ, Doub WH, Cai B, Sadrieh N et al. (2008). Evaluation of substrates for 90 degrees peel adhesion–a collaborative study. I. Medical tapes. J Biomed Mater Res Part B Appl Biomater, 87:105–113.
43. Wokovich AM, Brown SA, Shen M, Doub WH, Cai B, Sadrieh N et al. (2009). Evaluation of substrates for 90 degrees peel adhesion–a collaborative study. II. Transdermal drug delivery systems. J Biomed Mater Res Part B Appl Biomater, 88:61–65.
44. Wokovich AM, Shen M, Doub WH, Machado SG, Buhse LF. (2010). Release liner removal method for transdermal drug delivery systems (TDDS). J Pharm Sci, 99:3177–3187.
45. American Society of Testing Materials. Standard test method for peel adhesion of pressure-sensitive tape. ASTM D 3330/D 3330M-02 2003.
46. Pressure Sensitive Tape Council. (2004). PSTC 101 test method: peel adhesion of pressure sensitive tape. Test Methods for Pressure Sensitive Tapes, 14th Edition. Northbrook, IL: Pressure Sensitive Tape Council, 101.1–101.10.
47. Li C, Cashman JS, Johnson PA, Kanios DP, Mantelle JA. (2002). Kinetic study of threo-methylphenidate degradation reaction to erythro isomer in MethyPatch transdermal system, November. http://www.noven.com/research.htm. Accessed 5 October 2007.
48. Arnold LE, Lindsay RL, López FA, Jacob SE, Biederman J, Findling RL et al. (2007). Treating attention-deficit/hyperactivity disorder with a stimulant transdermal patch: the clinical art. Pediatrics, 120:1100–1106.
49. Chen Y, Li Y. (2003). A new model for predicting moisture uptake by packaged solid pharmaceuticals. Int J Pharm, 255:217–225.
50. Chen Y, Li Y. (2008). Determination of water vapor transmission rate (WVTR) of HDPE bottles for pharmaceutical products. Int J Pharm, 358:137–143.
51. Farag Badawy SI, Gawronski AJ, Alvarez FJ. (2001). Application of sorption–desorption moisture transfer modeling to the study of chemical stability of a moisture sensitive drug product in different packaging configurations. Int J Pharm, 223, 1–13.
52. Food and Drug Administration. Q8 Pharmaceutical Development, May 2006. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128029.pdf
53. Food and Drug Administration. Q9 Quality Risk Management Guidance for Industry, June 2006. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128053.pdf
54. ISMP (Institute for Safe Medication Practices). (2001). Failure Mode and Effects Analysis can help guide error prevention effort. ISMP Medication Safety Alert! 17 October 2001 issue. http://www.ismp.org/Newsletters/acutecare/articles/20011017.asp. Accessed 1 February 2010.