Transdermal Patch Release Testing Using Vertical Diffusion Cells

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Summary

The Phoenix™ RDS dry heat diffusion system was evaluated against the standard paddle-over-disk Apparatus V, and an immersion cell. The Phoenix RDS data was similar to the Apparatus V data, although it showed a slightly higher release rate making it a choice for quality control labs due to its small space requirements. The small cells used in the Phoenix also reduce the amount of buffer needed. The immersion cell showed a higher release rate than the other two methods.

Introduction

The skin is commonly used as a path to administer pharmaceutical products for both systematic and topical action. Systemic drugs are delivered via patches which release the active product into the blood stream through the skin for treating the whole body. Transdermal patches have been gaining popularity over other methods of administering medications. Transdermal patches are used to deliver painkillers such as lidocaine, vasodilators such as nitroglycerine, muscarinic receptors such as scopolamine, and many others. In this study, lidocaine is used as a typical example.

Diffusion-cell testing of topical and transdermal products has been known to be cumbersome, time-consuming, and subject to inconsistencies due to variations in operational procedures. A dissolution system using the diffusion cell apparatus, USP apparatus V is a generally accepted procedure to measure release from transdermal patches. The Phoenix RDS and dissolution system immersion cell are typically used for release studies for other topical medicines such as gels and creams. A patch is conceptually similar to those transdermal delivery systems, with the major difference being that the medicine is encapsulated within the patch.

Materials and Methods - App 5

A transdermal lidocaine hydrochloride patch containing 4% lidocaine HCl was used in the study.

Also used was a potassium phosphate buffer solution of pH 6.8 vacuum filtered through 47 mm 0.45 µm filter paper. The media was made by dissolving 6. 8 g potassium phosphate per 1 L water followed by adjusting the pH to 6.8 with phosphoric acid.

The App 5 method used a Teledyne Hanson Vision® Elite 8 dissolution tester. Six 1-Liter vessels were used in each run, with a Hanson USP Apparatus V, paddle-over-disk, setup.

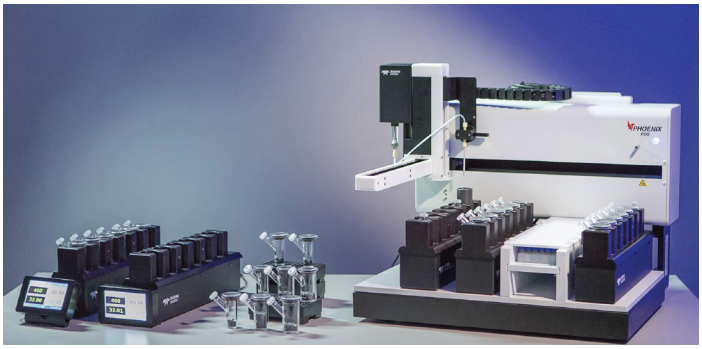


Image 1: Phoenix RDS Dry Heat Diffusion System

The patch size was reduced by cutting to 2" x 2" to fit the instrument sample requirements, and the results normalized to the patch area used. The disk assemblies were placed in each vessel, 250 mL of media was added to each vessel, and paddles were installed in the dissolution tester. During the test, the rotation speed of the paddles was 25 rpm, with the media maintained at a temperature of 32 °C.

Two runs were performed. 6 patch samples were run concurrently in each run. Samples were collected every 15 minutes for two hours and analyzed as per the HPLC procedure discussed in the following paragraph. The results of each group of six patches at each time point, were averaged to generate the data in the results table.

Chromatographic analysis was conducted using a Shimadzu LC20A HPLC system, equipped with a SPDM20A PDA detector set at 240 nm, a LC-20AD pump, a SIL-20AC HT Autosampler, a CTO-20AC column oven, and a CBM-20A communications bus module, all controlled via the Shimadzu Lab Solutions software. Separation was performed using a C18 reverse phase Kromasil (Sigma Aldrich) 1.6 x 250 mm column, at room temperature (25 ˚C). A mixture of 25:75 Acetonitrile: sodium acetate buffer solution (pH 3.4, 50 mL glacial acetic acid in 900 mL water, pH adjusted to 3.4 with 0.1 N sodium hydroxide) was used as the mobile phase, at a flow rate of 1 mL/min and injection volume of 50 µL.

Results – App 5

Table 1 shows the results of the two runs. The data shows the average of the cumulative amount released of each group of six patches at each time point. The %RSD (percent relative standard deviation) is also shown for each result. The release-rate (slope m) was calculated for each run.

Apparatus V—Paddle-over-disk Cummulative Amount Released of Lidocaine HCl µg/cm²										
Run Number	Time Minutes	15	30	45	60	75	90	105	120	Slope (m)
1	Average	231.3	336.5	403.1	467.4	539.1	599.8	665.8	712.3	68.1
	%RSD	11.9	8.9	6.8	5.5	3.2	2.9	2.5	2.2	
2	Average	201.1	293.9	370.9	439.7	508.6	571.9	630.9	689.3	69.1
	%RSD	8.2	5.1	3.4	2.8	2.6	2.3	2.4	2.4	

Table 1: Apparatus V—Paddle-over-disk Cummulative Amount Released of Lidocaine HCl µg/cm²

Materials and Methods—Vertical Diffusion Cells

A transdermal lidocaine hydrochloride patch containing 4% lidocaine HCL was used in the study. Also used was a potassium phosphate buffer solution of pH 6.8 vacuum filtered through 47 mm 0.45 µm filter paper. The media was made by dissolving 6.8 g potassium phosphate per 1 L water followed by adjusting the pH to 6.8 with phosphoric acid.

For this method, a Teledyne Hanson Phoenix RDS vertical cell diffusion system was used. This system is an automated dry-heat system with 6 cells. (Note: The automated sampling was not used, and the samples were taken manually.) Medium cells were used a with nominal volume of 21 mL, 13 mm mixer-inserts, and 15 mm orifice diameter cell tops. The cells were filled with the receptor media, 25 mm 0.45 µm Tuffryn synthetic membrane were placed on the dosage wafer, and the evaporation covers (glass lids) were set in place. Any air bubbles beneath the membrane were removed. The temperature of the heating block was set at 32.5 °C to maintain the diffusion cell at 32 °C ± 0.1 °C and stirrer speed was set to 400 rpm. The system was equilibrated for at least 30 minutes prior to starting the test. The lidocaine hydrochloride patch was cut using a 9/16" diameter hollow punch and hammer to fit on the dosage wafer. The patch was placed on the membrane with the sticky side facing the membrane. An evaporation cover was placed on top of the dosage wafer. At 15-minute intervals, samples were manually withdrawn via the sampling arm and the volume was replaced with receptor solution maintained at 32 °C ± 0.1 °C. (Note: Automated sampling can be performed by a user generated protocol with the diffusion master software.) A mixture of ethanol and DI Water in the ratio of 50:50 was used as a wash solution. Collected samples of 400 µL were assayed by HPLC to determine the amount of lidocaine released from the patch.

The patch size was reduced by cutting to fit the instrument sample requirements, and the results normalized to the patch area used.

Two runs were performed. 6 patch samples were run concurrently in each run. Samples were collected every 15 minutes for two hours and analyzed as per the HPLC procedure discussed in the following paragraph. The results of each group of six patches at each time point, were averaged to generate the data in the results table.

Chromatographic analysis was conducted using a Shimadzu LC20A HPLC system, equipped with a SPDM20A PDA detector set at 240 nm, a LC-20AD pump, a SIL-20AC HT Autosampler, a CTO-20AC column oven, and a CBM-20A communications bus module, all controlled via the Shimadzu Lab Solutions software. Separation was performed using a C18 reverse phase Kromasil (Sigma Aldrich) 1.6 x 250 mm column, at room temperature (25 ˚C). A mixture of 25:75 Acetonitrile: sodium acetate buffer solution (pH 3.4, 50 mL glacial acetic acid in 900 mL water, pH adjusted to 3.4 with 0.1 N sodium hydroxide) was used as the mobile phase, at a flow rate of 1 mL/min and injection volume of 50 µL.

Results—Vertical Diffusion Cells

Three tests were completed on different days by different chemists using freshly prepared solutions. The results are consistent with acceptable %RSD values as shown in Table 2.

Materials and Methods—Immersion Cell

A transdermal lidocaine hydrochloride patch containing 4% lidocaine HCL was used in the study.

Also used was a potassium phosphate buffer solution of pH 6.8 vacuum filtered through 47 mm 0.45 µm filter paper. The media was made by dissolving 6. 8 g potassium phosphate per 1 L water followed by adjusting the pH to 6.8 with phosphoric acid.

The Immersion Cell method (USP <1724>) used the Teledyne Hanson Vision Elite 8 dissolution tester with an immersion cell setup in small volume (150 mL) flatbottom vessels and mini-spin paddles. 75 mL of media was used in each vessel.

The patch size was reduced by cutting to 9/16" to fit the instrument sample requirements, and the results normalized to the patch area used. The prepared immersion cells were placed in each vessel, 75 mL of media was added to each vessel, and the mini-paddles were installed in the dissolution tester. During the test, the rotation speed of the paddles was 50 rpm, with the media maintained at a temperature of 32 °C. Two runs were performed. 6 patch samples were run concurrently

Phoenix Vertical Diffusion Cells Cummulative Amount Released of Lidocaine HCl µg/cm²										
Run Number	Time Minutes	15	30	45	60	75	90	105	120	Slope (m)
1	Average	166.5	298.2	399.4	480.1	554.1	619.9	678.7	719.9	78.9
	%RSD	10.7	9.0	8.5	7.6	7.3	6.6	6.4	6.1	
2	Average	178.0	313.2	416.2	505.6	561.1	618.2	663.4	707.3	68.1
	%RSD	7.3	8.8	10.2	10.8	11	11.4	11.0	11.3	

Table 2: Phoenix Vertical Diffusion Cells Cummulative Amount Released of Lidocaine HCl µg/cm²

Immersion Cell Cummulative Amount Released of Lidocaine HCl µg/cm²										
Run Number	Time Minutes	15	30	45	60	75	90	105	120	Slope (m)
1	Average	262.4	419.3	542.3	640.9	755.8	838	882.7	921.5	115.4
	%RSD	8.6	8.9	9.2	9.4	9.1	8.5	8.1	7.7	
2	Average	289	769.9	602.1	710.4	790.6	848.8	901.8	943.8	112.2
	%RSD	10.4	8.7	7.4	6.5	6.0	5.3	4.9	4.2	

Table 3: Immersion Cell Cummulative Amount Released of Lidocaine HCl µg/cm²

in each run. Samples were collected every 15 minutes for two hours and analyzed as per the HPLC procedure discussed in the following paragraph. The results of each group of six patches at each time point, were averaged to generate the data in the results table.

Chromatographic analysis was conducted using a Shimadzu LC20A HPLC system, equipped with a SPDM20A PDA detector set at 240 nm, a LC-20AD pump, a SIL-20AC HT Autosampler, a CTO-20AC column oven, and a CBM-20A communications bus module, all controlled via the Shimadzu Lab Solutions software. Separation was performed using a C18 reverse phase Kromasil (Sigma Aldrich) 1.6 x 250 mm column, at room temperature (25 ˚C). A mixture of 25:75 Acetonitrile: sodium acetate buffer solution (pH 3.4, 50 mL glacial acetic acid in 900 mL water, pH adjusted to 3.4 with 0.1 N sodium hydroxide) was used as the mobile phase, at a flow rate of 1 mL/min and injection volume of 50 µL.

Results—Immersion Cell

Table 3 shows the results of the two runs. The data shows the average of the cumulative amount released of each group of six patches at each time point. The %RSD (percent relative standard deviation) is also shown for each result. The release-rate (slope m) was calculated for each run.

Comparison Results and Discussion

The Phoenix Dry Heat system, typically used for in vitro release testing of semisolid formulations, was evaluated for testing transdermal patches, by comparison to the Elite 8 with the immersion cell and Elite 8 with apparatus V.

The immersion cell is a mix of paddle over disk and vertical cell diffusion. Like paddle-over-disk, the patch is submerged in the cell, with the stirrer above it. It needs a smaller volume of buffer. However, the release rate was significantly faster than the Apparatus V and the Phoenix. The curve was also noticeably non-linear with a faster release early in the experiments.

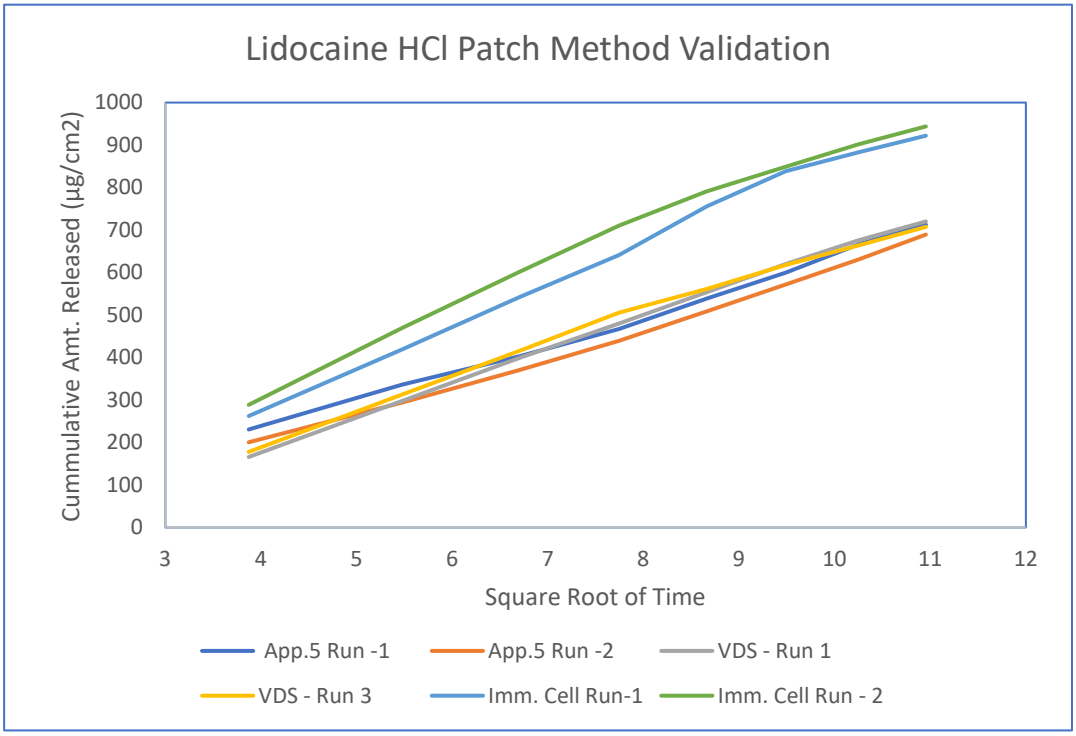
The immersion cell and Phoenix indicated higher release over time than the accepted Paddle-over-disk (Apparatus V)

$$m = 2C_0\sqrt{\frac{D}{\pi}}$$

test. The release rate is measured by the slope of a plot of the amount of drug released per cm2 and the square root of time, where the slope is:

Where m is the slope, C_0 is the drug concentration in the releasing patch, D is Diffusion coefficient and π is the constant 3.1415. As the same patch material was used for all experiments, the lidocaine concentration is the same for all experiments so changes in the release are caused by changes in the diffusion.

The increased slope in the vertical diffusion cell experiments suggests a higher diffusion from the patches in the vertical diffusion cells, possibly due to increased diffusion area from the cut edges, created when the patch was "punched" to create a smaller patch to fit within the cells. However, the results from the Phoenix system tracked well with the Apparatus V. The amount of drug released as a function of time was measured by HPLC in all cases as previously discussed.



Graph 1: Licocaine HCl Patch Method Validation

Conclusion

The Phoenix dry heat system provides in-vitro release data similar to the USP Apparatus V and it shows a slightly higher release rate, possibly due to the edges exposed by cutting the patch to size to fit in the cell.

However, the results are reproducible allowing use in a QC environment. The Phoenix system is smaller and very easy to set up and needs very little buffer. The vertical diffusion cell gave significantly different results compared to the immersion cell.

These tests were conducted at the Analytical Research Center of Teledyne Hanson (https://www.teledynehanson.com/analytical-research-center) in accordance with all applicable in-house standard operating procedures (SOPs) prepared in compliance with GMP requirements. These facilities are available to help test customer protocols.

About Teledyne Hanson

Teledyne Hanson is a global technology company specializing in test instruments for the pharmaceutical industry. Founded by the innovator of modern dissolution test technology, Teledyne Hanson helps ensure that the world's pharmaceuticals are pure, safe, and effective by manufacturing equipment that sets the global standard for quality, innovation, and long-term value. Teledyne Hanson instruments are used by scientists in over 75 countries worldwide and are supported by the industry's top customer service team. For more information, please visit teledynehanson.com.

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