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Technical Note: Comparison of USP Apparatus 5 and 7 for In Vitro Drug Release from Nicotine Transdermal Systems

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ABSTRACT

To monitor in vitro drug release in nicotine transdermal systems, USP Apparatus 5 (paddle over disc) and Apparatus 7 (reciprocating holder) were selected for comparison. Two nicotine transdermal systems marketed in United States for the controlled release of 7.0 mg of nicotine in a 72-hour period were evaluated. The results demonstrate that the drug release profiles obtained using USP Apparatus 5 and 7 are equivalent. Repeatability was measured using Apparatus 7 and found acceptable.

KEYWORDS: Dissolution, nicotine, USP apparatus 5, USP apparatus 7

INTRODUCTION

Transdermal drug delivery (TDD) systems are drug-loaded adhesive patches that, when applied to the skin, deliver the therapeutic agent, at a controlled rate, through the skin to the systemic circulation and to the target organs (*1*). Pressure-sensitive adhesives (PSAs) have been used for decades in medical devices, tapes, and dressings. Naturally, since the development of TDD devices in the 1980s, the use of PSAs has been extended to these devices (*2*).

In the early 1990s, the United States Food and Drug Administration (FDA) approved four different nicotine TDD systems as adjuvants in smoking cessation. Drug plasmatic levels can be safely assured using these commercial devices for approximately 16–24 hours to provide relief of symptoms related to nicotine abstinence (*3*). Various procedures have been recommended in United States Pharmacopeia (USP) for the evaluation of nicotine patches, including paddle over disc (Apparatus *5*), rotating cylinders (Apparatus 6), and reciprocating holders (Apparatus 7) (*4*).

There are five dissolution test methods mentioned in the USP for nicotine transdermal systems. Three different apparatus, i.e., USP Apparatus 5, 6, and 7, are used for these methods. Four tests in the USP list take at least 12 hours to complete the dissolution, and with wide range of amount dissolved. The purpose of this study is to find a more time-efficinet method with a narrower range of amount dissolved and to verify these drug release methods using USP Apparatus 5 and 7 as a routine quality control test method of nicotine transdermal systems.

MATERIALS AND METHODS

Reagents and Equipment

Nicotine patch formulation was prepared by Bionex Pharmaceuticals LLC (North Brunswick, NJ, USA) containing 4.1 mg nicotine (batch no: 117-180420). All chemicals and solvents used were of analytical grade. PBS Tablets (MP Biomedicals, LLC, Solon, OH, USA) were used for preparation of PBS buffer solutions (PH 7.4). Distilled water was used for all analytical purposes.

The equipment used were: USP Apparatus 5, UST-814 (Logan Instruments Corp., Somerset, NJ, USA) (Fig. 1); USP Apparatus 7, Disso III-7 (Logan Instruments Corp.) (Fig. 2); High-performance liquid chromatography (HPLC), Agilent 1100 (Agilent Technologies Inc., Santa Clara, CA, USA); and HPLC column, Gemini C18, 150 × 4.6 mm, 5-µm particle size (Phenomenex Inc., Torrance, CA, USA).

Preparation of Solutions and Standards

The dissolution medium was pH 7.4 buffer selected for the reference listed drug product, 30 PBS tablets, is 3 L distilled water; potassium chloride (KCl): 200 mg/L; potassium phosphate monobasic (KH_2PO_4): 200 mg/L, sodium chloride (NaCl): 8000 mg/L; sodium phosphate dibasic (Na_2HPO_4): 1150 mg/L.

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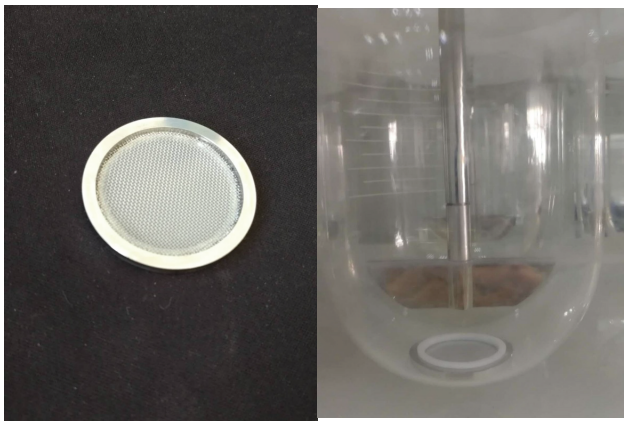

Figure 1. Photograph of USP Apparatus 5 (Model: UST-814, Logan Instruments Corp., Somerset, NJ, USA).

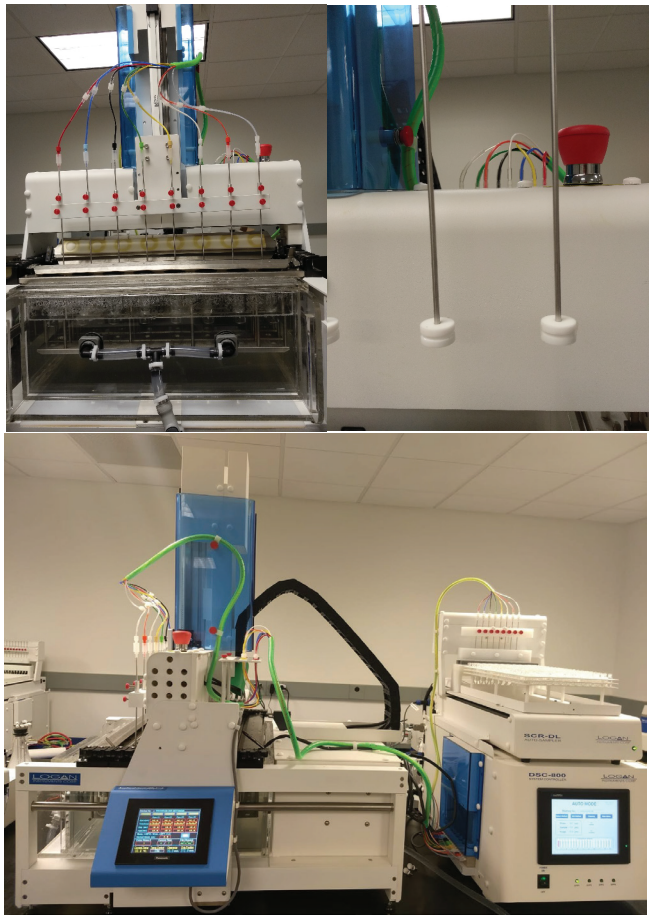

Figure 2. Photographs of USP Apparatus 7 (Model: Disso III-7 and Auto Sampler, Logan Instruments Corp., Somerset, NJ, USA).

Dissolution Conditions

For USP Apparatus 5 (paddle over disk method), the medium volume per vessel was 200 mL. The temperature should be maintained at 32 ± 0.5 °C. During the test, we maintained a distance of 25 ± 2 mm between the paddle blade and the surface of the disk assembly. The rotation speed was 50 rpm. The number of transdermal systems per test was 12 at seven time points: 1, 2, 4, 8, 24, 48, and 72 hrs. At each time point, a 2-mL sample was withdrawn and 2 mL of fresh media was added.

For USP Apparatus 7 (reciprocating holder method), the medium volume per vessel was 20 mL. The solution containers were partially immersed in a suitable water to permit maintaining the temperature inside the containers at 32 ± 0.5 °C. We attached the system to be tested to a suitable sample holder with 2-cyano acrylate glue. Each sample holder was suspended from a vertically reciprocating shaker so that each system is continuously immersed in dissolution medium at reciprocated at a frequency of about 30 dips per min with an amplitude of about 2 cm each time point (1, 2, 4, 8, 24, 48, and 72 hrs). At each time point, 2-mL sample was collected by the autosampler.

Chromatographic Analysis

The mobile phase flow rate was 1.0 mL/min. The mobile phase was A/B 72/28; mobile phase A was 50 mg Na_2HPO_4 in 1 L water, and mobile phase B was acetonitrile. The column temperature was 40 °C. The injection volume was 10 µL. The diode array detector (DAD) UV detection wavelength was 260 nm. The typical retention time of nicotine was about 4.5–5 min. The run time per injection was 10 min. The analytical method was validated for its accuracy, precision, linearity, limit of quantitation, specificity, solution stability, and robustness, which included varying the mobile phase buffer concentration, aqueous-to-organic mobile phase ratio, and column temperature. The detailed method validation results are not presented here. The original USP method was not adopted but modified to make it more time efficient.

Calculations

The concentration was calculated using Equation 1:

$$C_n = \frac{R_{Sample}}{R_{STD}} C_{STL} \quad (1)$$

C_n is the concentration of time point n in mg/mL; C_{STD} is the concentration of standard in mg/mL; R_{Sample} is the peak area of nicotine in a sample; and R_{STD} is the average peak area of nicotine standards.

For USP Apparatus 5, the accumulative release of nicotine at each time point in percent of label claim LC_n (%) was calculated using Equation 2:

$$LC_n = \frac{200 \cdot C_n + \sum_{i=1}^{n} 2 \cdot C_{i-1}}{LC} \cdot 100 \quad (2)$$

For where C_{i-1} is the concentration of time point i–1 in mg/mL; and LC is the label claim of the product in mg/mL.

Table 1. Dissolution Data Using USP Apparatus 5

Time (h)	A	B	C	D	E	F	G	Mean	SD	RSD/%
0	0	0	0	0	0	0	0	0	0	N/A
1	47.2	47.4	48.4	49.9	44.4	39.4	44.1	45.8	3.2	7.1
2	60.2	59.7	60.7	62.2	56.5	51.4	55.9	58.1	3.4	5.9
4	74.8	73.6	76.3	77.0	71.4	67.1	71.4	73.1	3.2	4.4
8	86.0	89.4	88.2	87.7	83.1	80.4	83.2	85.4	3.0	3.6
24	97.1	92.9	100.9	101.0	97.1	96.1	96.1	97.3	2.7	2.7
48	99.3	94.9	102.9	103.0	99.6	99.6	97.3	99.5	2.7	2.7
72	103.0	99.1	107.1	105.0	102.0	105.5	102.6	103.5	2.4	2.4

RSD: Relative standard deviation; N/A, not applicable.

Table 2. Dissolution Data Using USP Apparatus 7

Time (h)	A	B	C	D	E	F	G	Mean	SD	RSD/%
0	0	0	0	0	0	0	0	0	0	N/A
1	46.0	45.9	42.7	43.0	42.8	44.8	43.0	44.0	1.4	3.1
2	65.2	65.4	62.9	63.3	62.9	64.3	64.5	64.0	1.0	1.5
4	79.5	80.2	77.3	77.5	77.5	78.5	80.7	78.7	1.3	1.7
8	89.1	90.1	87.0	87.0	87.3	88.4	90.7	88.5	1.4	1.6
24	95.6	95.5	92.1	91.8	92.6	93.9	93.3	93.5	1.4	1.5
48	96.1	96.9	96.0	92.1	94.5	95.5	95.0	95.2	1.4	1.5
72	98.1	99.1	98.6	98.1	98.1	99.1	98.9	98.6	0.4	0.4

RSD: Relative standard deviation; N/A, not applicable.

Table 3. Dissolution Data Using USP Apparatus 7, Test 2

Time (h)	A	B	C	D	E	F	G	Mean	SD	RSD/%
0	0	0	0	0	0	0	0	0	0	N/A
1	43.0	42.2	46.9	44.0	39.1	39.8	40.4	42.2	2.7	6.5
2	61.5	61.9	66.4	63.7	57.8	59.2	60.1	61.5	2.9	4.7
4	76.6	77.6	80.6	79.4	74.1	75.5	75.7	77.1	2.3	3.0
8	86.7	87.9	89.0	89.3	85.5	86.1	85.8	87.2	1.6	1.8
24	92.3	93.3	92.7	94.1	92.0	92.1	90.9	92.5	1.0	1.1
48	93.5	94.4	93.3	94.9	93.5	93.1	92.0	93.5	0.9	1.0
72	93.7	94.6	93.5	85.2	93.8	93.4	92.3	93.8	0.9	1.0

RSD: Relative standard deviation; N/A, not applicable.

For USP Apparatus 7, the LC_n (%) was calculated using Equation 3:

$$LC_n = \frac{\sum_{i=1}^{n} 20 \cdot C_i}{LC} \cdot 100 \quad (3)$$

where C_i is the concentration at time i in mg/mL.

RESULTS AND DISCUSSION

The comparison of dissolution profiles of TDD systems can be achieved by comparing relative standard deviation [RSD] and standard error [SE] bars through the mathematical treatment of dissolution data. The one with lower RSD and SE shows stability of the Nicotine TDD systems.

Comparison of Drug Release Using Apparatus 5 and 7

The drug release test on nicotine transdermal systems was performed using USP Apparatus 5 and 7 (n = 7). The RSD for all time points was within 2.4–7.1% and 0.4–3.1% for Apparatus 5 and 7, respectively, as shown in Tables 1 and 2. The drug release profiles were similar, as shown in Figure 3.

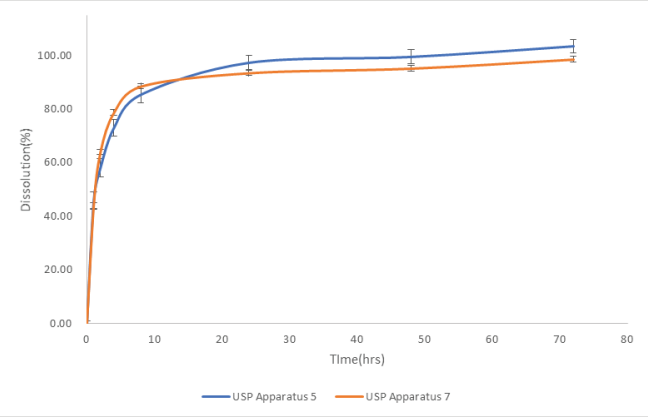

Figure 3. Comparison of drug release profiles obtained from USP Apparatus 5 and 7.

Repeatability Analysis

The drug release test on nicotine transdermal systems was repeated on a different day by using the same USP Apparatus 7. The RSD for all time points was within 0.4–3.1% and 0.92–5.96% for Test 1 and Test 2, respectively, as shown in Tables 2 and 3. The drug release profiles are shown in Figure 4. Due to the variation within the drug product, there might be differences in the samples used that contributed to the slight difference in profiles. Overall, reproducibility is achieved.

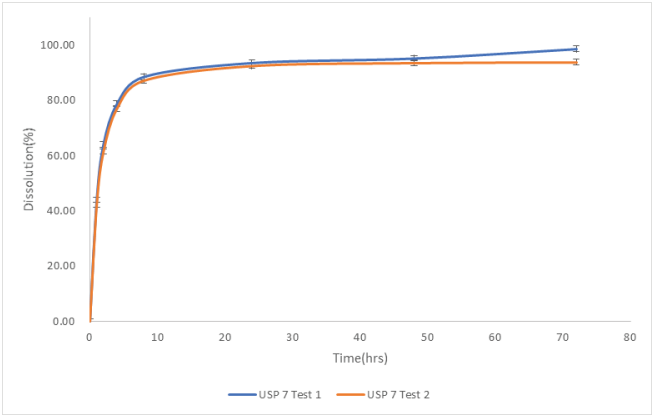

Figure 4. Comparison of drug release profiles obtained on different days by USP Apparatus 7.

CONCLUSION

Drug release profiles obtained using USP Apparatus 5 and 7 are equivalent, though Apparatus 7 produced data with less variability. In this experiment, Apparatus 7 was more time-saving than Apparatus 5 because Apparatus 7 works together with an autosampler. These results indicate that the USP Apparatus 7 assembly, which is cost-effective and easier to operate, uses smaller volume of medium and can replace the conventional USP Apparatus 5 setup to determine drug release for transdermal patch products.

Our study demonstrated day-to-day repeatability of dissolution profiles using the Apparatus 7 system. Apparatus 7 has various sample holders to adapt various drug dosage forms (implants). For a large TDD system, Apparatus 5 cannot be used to determine the drug release property because of its limited sample holder area.

CONFLICTS OF INTEREST

Ming Li is an employee of Logan Instruments. Hock Tan is an employee of Bionex Pharmaceuticals.

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