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Technical Note

In Vitro Release Profiles of Clonidine Transdermal Therapeutic Systems and Scopolamine Transdermal Patches

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INTRODUCTION

A simple, reliable, and reproducible *in vitro* methodology is essential for assuring batch-to-batch uniformity and bioequivalence of transdermal drug delivery systems. Recently, the Food and Drug Administration has developed a procedure for determining the release rate of nitroglycerin (NG) in transdermal patches (1,2). In addition to nitroglycerin patches, scopolamine patches for the control of motion sickness, clonidine patches as an antihypertensive agent, and estrogen patches for estrogen therapy in menopausal women are approved and marketed. We test here the utility of the procedure developed for NG patches for determining the release rate of drugs from other transdermal patches. Clonidine and scopolamine transdermal patches were investigated. The apparatus, Reciprocating Disk–Apparatus 5 (3) (release rate tester), used by the manufacturer in its quality-control procedure for clonidine and scopolamine patches is not readily available and is not official in the USP. An attempt was made to standardize the dissolution procedure for determining the *in vitro* release profile of clonidine and scopolamine in transdermal patches, and the results were compared to those obtained with the manufacturer's method.

MATERIALS AND METHODS

Transdermal Patches

Clonidine patches of three different strengths (Boehringer–Ingelheim Ltd., Ridgefield, Conn.) and scopolamine patches of one strength (Ciba Geigy) were evaluated (Table I).

Table I. Transdermal Patches

Product	Surface area (cm^2)	Claimed *in vivo* delivery rate (mg)	Labeled patch content (mg)
Clonidine TTS-1	3.5	0.1/24 hr	2.5
Clonidine TTS-2	7.0	0.2/24 hr	5.0
Clonidine TTS-3	10.5	0.3/24 hr	7.5
Transdermal scopolamine	2.5	0.5/72 hr	1.5

In Vitro Release Method

FDA Procedure

Transdermal Patch Holders. A transdermal patch holder, as described earlier (1), was used for these studies. For clonidine, a 9-cm-diameter watchglass with a 9-cm-diameter aluminum screen was used (Fig. 1A).

For scopolamine, which is comparatively a smaller patch, a 6-cm-diameter watchglass and a 6-cm-diameter aluminum mesh screen were used.

Dissolution Apparatus. The dissolution test was performed using a six-spindle USP apparatus 2 (4) employing glass vessels (Hanson Research Corp., Northridge, Calif.) and a paddle speed of 50 rpm at 32 ± 0.5°C (skin temperature). For clonidine patches, 500 ml of distilled; nondeaerated water was used and the paddles were lowered to a height of 1.5 cm above patches. The vessels were covered with aluminum foil (Fig. 1B) to minimize evaporation. Two-milliliter samples were collected without filtering or fluid replacement at intervals of 8, 24, 48, 72, 96, and either 168 or 192 hr and analyzed for clonidine content by high-performance liquid chromatography (HPLC).

For scopolamine patches, the medium volume was 300 ml and sample collection times were 6, 24, 48, and 72 hr.

Manufacturer's Procedure (Reciprocating Disk Method)

Clonidine Patches. Each patch was removed from its package, and the release liner was discarded from the system. The patch was gently pressed to a dry, unused, square piece of Cuprophane membrane (Enka Ag, Corona Del Mar, Calif.), an inert, porous cellulose material, with the adhesive side against the membrane. The membrane/patch assembly was attached to a stainless-steel holder with a Viton O-ring, or equivalent, such that the backing of the system was adjacent to and centered on the bottom of the sample holder. For different sized clonidine patches, different sized sample

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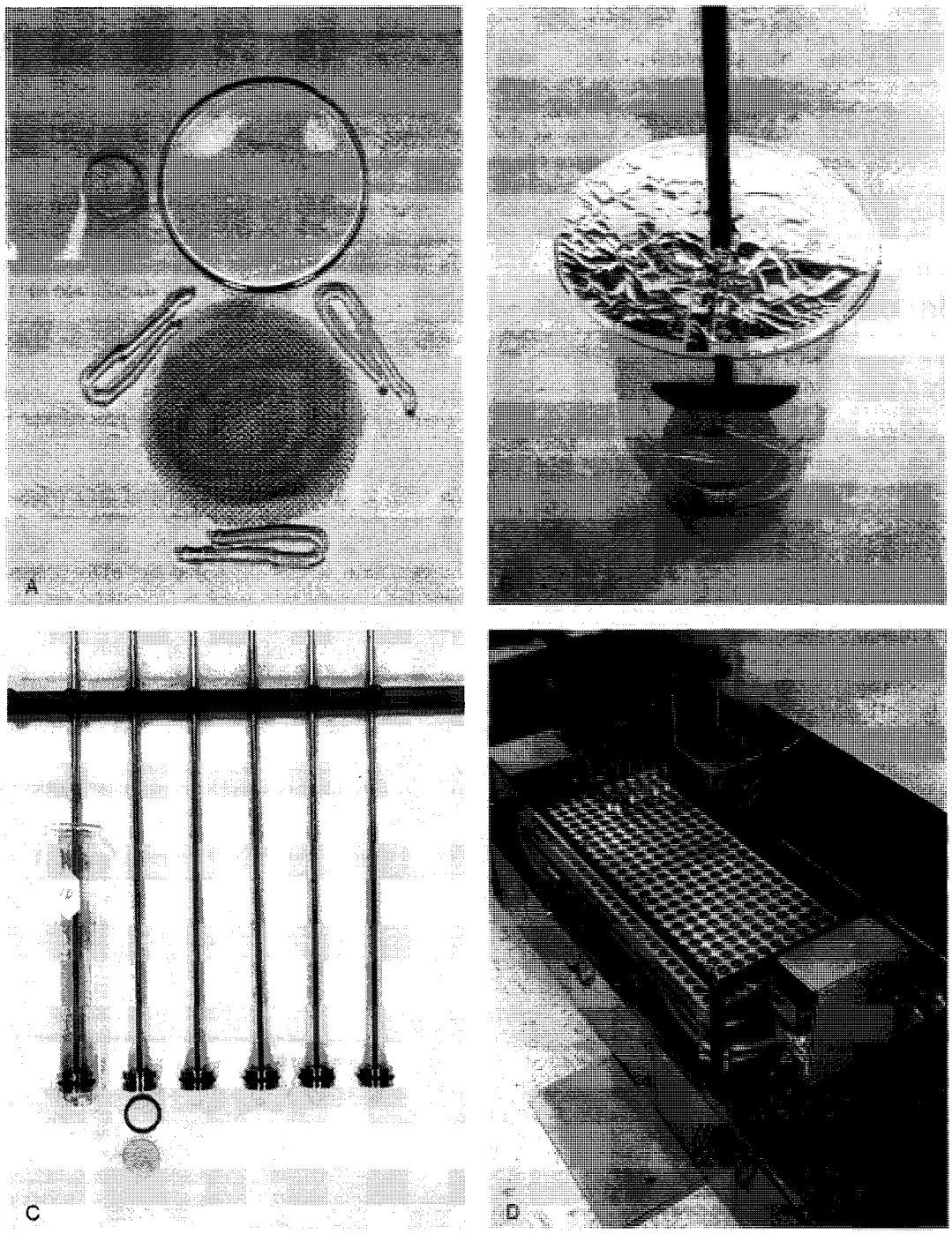

Fig. 1. Transdermal patch dissolution setup. FDA apparatus components: watchglass–patch–wiremesh screen and clips (A) and final setup with paddle apparatus (B). Manufacturer's apparatus components: stainless-steel holder–O-ring–Cuprophane film and patch (C) and final setup (D).

holders had to be used. The excess Cuprophane was trimmed with scissors. The sample holder was suspended from the arm of a reciprocating shaker (Figs. 1C and D) such that each patch (system) was continuously immersed in a beaker containing 80, 80, and 200 ml of 10^{-3} *M* H_3PO_4 for the 3.5^-, 7.0^-, and 10.5-cm^2 patch, respectively. The filled beakers were weighed and preequilibrated to 32.0 ± 0.3°C prior to immersing the test sample. The sample was agitated in an up–down motion at a frequency of ½ cycle/sec with an amplitude of 20 mm. At the end of each time interval, the test sample was transferred to a fresh beaker containing the specified volume of 10^{-3} *M* H_3PO_4, weighed, and preequilibrated to 32.0 ± 0.3°C. Before analysis, the beakers were allowed to cool to room temperature, and the water loss due to evaporation was made up by adding distilled water to the original weight. Samples were collected without filtering at time in-

tervals of 8, 24, 48, 72, 96, 120, 144, and 168 hr and analyzed for clonidine content by HPLC.

Scopolamine Patches. The scopolamine patches were attached to the same reciprocating apparatus in the same way as the clonidine patches. The dissolution vessels were 25 × 150-mm test tubes containing 20 ml of water as the dissolution medium. Samples were collected without filtering at time intervals of 6, 24, 48, and 72 hr and analyzed for scopolamine content by HPLC.

Liquid Chromatographic Analysis

All sample aliquots from the FDA and manufacturer procedure were analyzed by HPLC. The liquid chromatographic system consisted of a high-pressure pump (Series 10, Perkin Elmer Corp., Norwalk, Conn.), an auto injector (WISP 710A, Waters Associated, Milford, Mass.), a variable-wavelength UV detector (Spectroflow 757, Kratos Analytical Instruments, Ramsey, N.J.), an integrator-recorder (Model 3390A, Hewlett–Packard, Avondale, Pa.), and an octadecylsilane column (30 cm × 3.9 mm) (μ-Bondapak C18, Waters Associates).

Clonidine Analysis

A 15-μl sample, unfiltered and without further dilution, was injected onto the HPLC system. The mobile phase was 50% acetonitrile:50% of a 0.05% solution of triethylamine in water, with the pH adjusted to 4.8 with dilute phosphoric acid, and the flow rate was 1.3 ml/min. The clonidine peak at 4.5 min was measured at 200 nm and compared with the response from an injection of clonidine standard.

Scopolamine Analysis

A 50-μl sample, unfiltered and without further dilution, was injected onto the HPLC system (described above). The mobile phase was 60% acetonitrile:40% 0.01 *M* ammonium acetate, and the flow rate was 1.6 ml/min. The peak response of scopolamine, around 3.5 min, in the sample was measured at 200 nm and compared with the response from an injection of scopolamine standard.

RESULTS AND DISCUSSION

Clonidine Patches

The content of clonidine in transdermal patches currently on the market ranges from 2.5 to 7.5 mg per patch. A HPLC procedure was employed to assay the dissolution samples. The response was linear between 0.1 and 15 μg/ml and the limit of detection was 3 ng (50 μl of a 0.06 μg/ml clonidine solution).

Dissolution was performed on clonidine patches using 15 different media consisting of different buffers, acid solutions, wetting agent solutions, and water, all without filtering or deaerating. Medium temperatures of 32 and 37°C and paddle speeds of 75 and 50 rpm were used.

Problems encountered using the different media consisted of a low release rate for clonidine, reaction with the patches and/or patch holders, and interference in the chromatogram. Water and 0.005 *M* phosphoric acid gave the highest dissolution release rate for clonidine, and water was selected as the dissolution medium. Increasing the paddle speed from 50 to 75 rpm had no effect on the release rate of clonidine but increasing the medium temperature from 32 to 37°C increased the release rate in water from 21 to 28% in 24 hr. Since 32°C is the skin temperature and medium evaporation was much lower than at 37°C, the lower temperature was chosen for the dissolution of clonidine patches.

The release rates using the FDA procedure are slightly lower than those using the manufacturer's procedure (Table II). The differences in the two procedures consist mainly of the apparatus, patch holder, and dissolution medium. Since the dissolution of clonidine uses separate fresh solutions of media in the manufacturer's procedure, the assay results of these solutions had to be added together for each patch to obtain the accumulated amount, before they could be compared to the results from the FDA procedure. The release rate profiles of three sizes of clonidine patches using the FDA procedure and the manufacturer's procedure are similar (Fig. 2). Further, the fraction of drug released from all the three patches is similar. This result is expected because all sizes of the patch are generally made of the same formulation. These results show that the FDA procedure developed for nitroglycerin patches (1) can be readily applied to all sizes of clonidine patches. The FDA procedure was easier to use, and no changes of the apparatus were needed when the dissolution of different sized patches was performed. During the dissolution runs using the manufacturer's procedure, water had to be added to each vessel to keep the

Table II. Percentage of Label Release Characteristics for Clonidine Transdermal Patches

Labeled patch content (mg)	Sample time (hr)	FDA procedure		Firm procedure	
		%[a]	RSD %	%[a]	RSD %
2.5	8	14.6	3.3	20.0	11.8
	24	21.2	4.7	33.2	5.8
	48	30.2	3.7	48.3	4.0
	72	38.0	2.8	59.6	5.1
	96	45.0	4.1	68.6	5.3
	120			75.7	6.0
	144			80.8	5.6
	168	62.5	3.8	84.5	5.3
5.0	8	12.0	5.0	14.2	2.7
	24	17.8	4.6	21.5	8.4
	48	25.8	3.2	32.8	10.3
	72	34.5	5.5	42.9	9.9
	96	41.0	3.2	52.1	9.5
	120			61.1	9.1
	144			68.5	8.7
	168			74.9	8.0
	192	64.6	4.8		
7.5	8	12.8	7.3	15.2	2.4
	24	20.6	1.5	24.1	4.9
	48	28.8	2.1	36.2	6.4
	72	38.1	2.4	46.6	6.9
	96	47.8	3.0	56.0	7.2
	120			64.3	7.1
	144			71.6	7.0
	168	68.5	3.2	78.0	6.6

[a] Data represent the mean and RSD of six determinations.

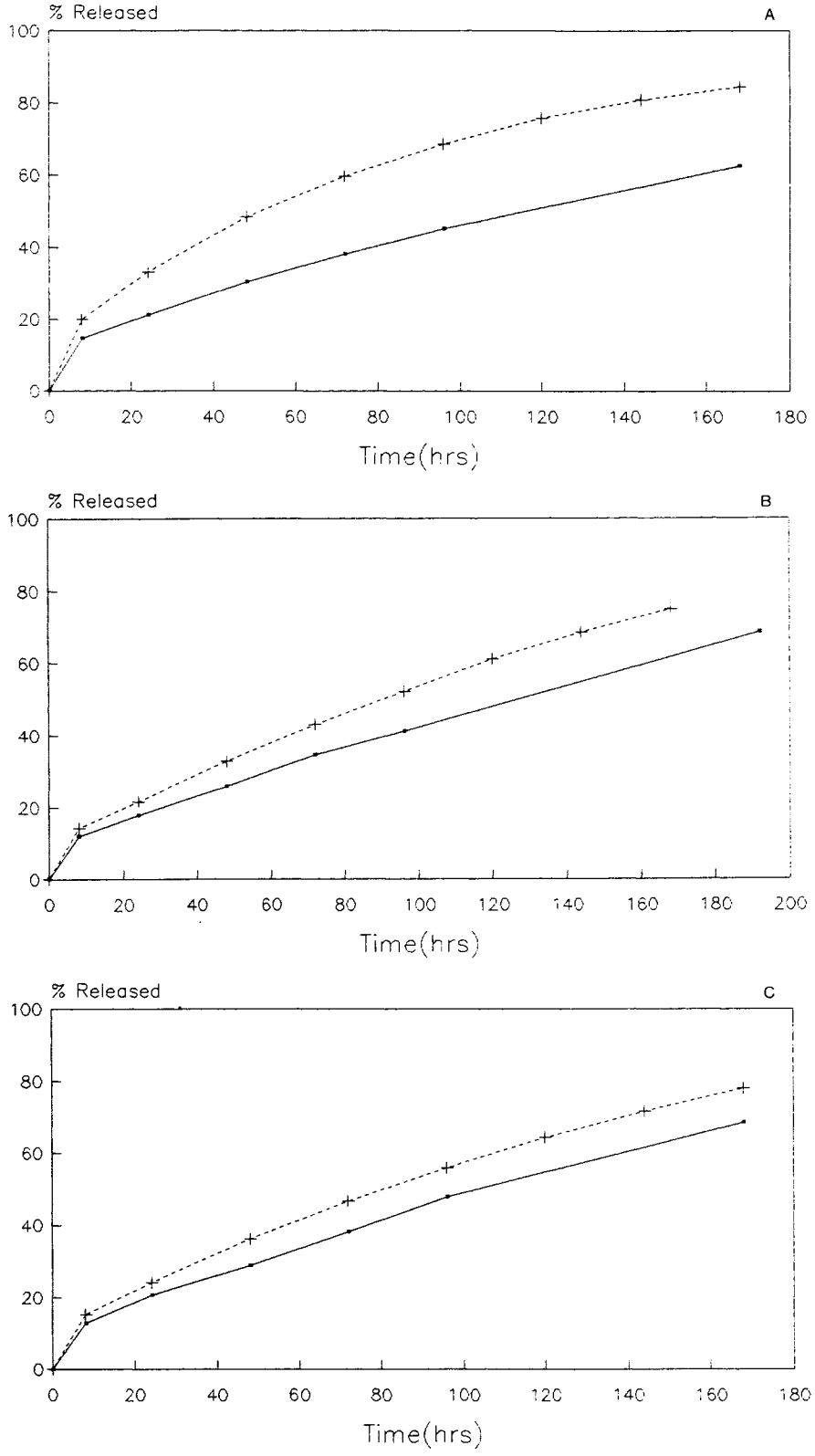

Fig. 2. Dissolution profiles of clonidine patches: (A) 2.5 mg, (B) 5.0 mg, and (C) 7.5 mg. FDA procedure (——) and manufacturer's procedure (---).

Table III. Percentage of Label Release Characteristics for Scopolamine Transdermal Patches

Labeled patch content (mg)	Sample time (hr)	FDA procedure		Manufacturer procedure	
		%[a]	RSD %	%[a]	RSD %
1.5	6	37.8	8.7	37.0	7.9
	24	54.6	5.0	55.8	5.0
	48	73.7	4.4	75.3	2.7
	72	88.0	4.0	91.3	1.5

[a] Data represent the mean and RSD of six determinations.

patches emersed, while no problems were encountered using the FDA procedure.

Scopolamine Patches

There is currently one size of scopolamine transdermal patch commercially available from one manufacturer. The HPLC assay used to analyze scopolamine gave a linear response between 1 and 20 μg/ml, and the detection limit was 25 ng (50 μl of a 0.5-mg/ml scopolamine solution). A 300-ml volume of dissolution medium in the FDA procedure was sufficient to keep the paddles fully submersed. The medium loss in the FDA procedure over 72 hr due to evaporation was 3%, and the assay results were not adjusted for this small loss. The assay results from each time period in the manufacturer's procedure were added to give the cumulative percentage scopolamine release. This was necessary because the dissolution began with fresh medium for each time period.

The *in vitro* dissolution data are summarized in Table III; the percentages scopolamine released for both methods compare well. Further, similar *in vitro* release–time profiles are shown with both procedures (Fig. 3).

While only one scopolamine patch is currently available, other sizes as well as manufacturers of these patches are likely in the future. A simple dissolution procedure using existing laboratory equipment should be developed as a standard procedure. The FDA procedure previously developed for nitroglycerin patches (1) is generally applicable when the diameter of the patch holder was decreased from 9 to 6 cm. This smaller-diameter holder was necessary to accommodate the lower volume dissolution medium of 300 ml. The FDA procedure was easier to use than the manufacturer's procedure; with readily available equipment, and no problems were encountered. On the other hand using the manufacturer's procedure, problems were encountered when the sample holders moved to the next set of dissolution test tubes.

The need for an *in vitro* release test method (dissolution procedure) for the patches can be argued against and criticized, since the patches contain excess drug, and the skin functions as a rate-limiting organ/step for drug penetration/absorption. However, a control procedure is needed for assuring product quality. If the drug release characteristics are erratic due to the formulation of the patch, it is anticipated that it will be detected by the *in vitro* quality-control procedure. From the present results and the previous work on nitroglycerin patches (5), it is clear that the release profile for a given patch is comparable, irrespective of the procedure adopted.

CONCLUSION

The *in vitro* release test procedure developed was simple, reliable, reproducible, and applicable to all sizes and shapes of scopolamine and clonidine transdermal patches. The ruggedness and flexibility of the method are also well documented. This simple procedure can easily be employed

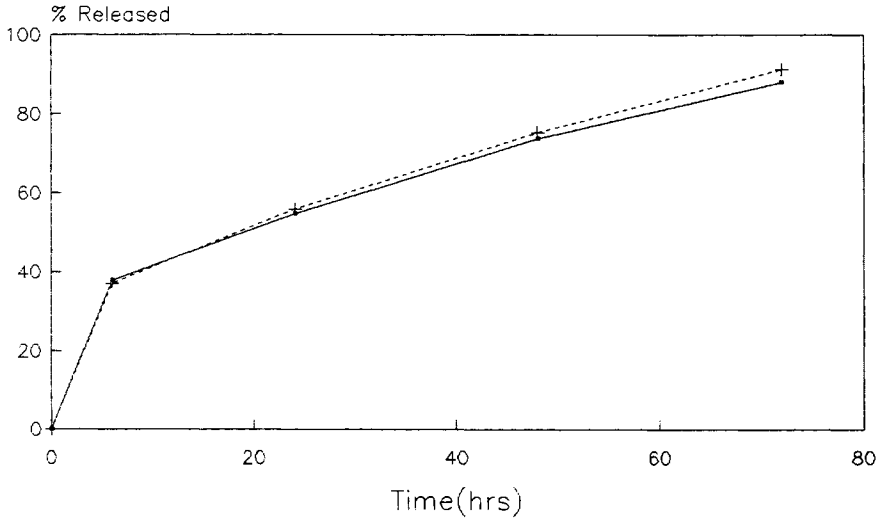

Fig. 3. Dissolution profiles of 1.5-mg scopolamine patch using FDA procedure (——) and manufacturer's procedure (---).

for studying *in vitro* release profiles of transdermal patches and for assuring batch-to-batch uniformity and quality of the product.

REFERENCES

1. V. P. Shah, N. W. Tymes, L. A. Yamamoto, and J. P. Skelly. *Int. J. Pharm.* 32:243–250 (1986).
2. V. P. Shah, N. W. Tymes, W. Ment, and J. P. Skelly. *Pharm. Forum* 14:3458–3462 (1988).
3. In *Pharm. Forum* 14:3860–3865 (1988).
4. In *U.S. Pharmacopeia XXI,* U.S. Pharmacopeial Convention, Inc., Rockville, Md., 1985, p. 1243.
5. V. P. Shah, N. W. Tymes, and J. P. Skelly. *J. Control. Release* 7:79–86 (1988).