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In vitro dissolution profile of transdermal nitroglycerin patches using paddle method

Vinod P. Shah [1], Norlin W. Tymes [2], Lawrence A. Yamamoto [1] and Jerome P. Skelly [1]

[1] *Division of Biopharmaceutics, Food and Drug Administration, Rockville, MD 20857 and*
[2] *Baltimore District Lab, Baltimore, MD 21201 (U.S.A.)*

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Summary

A dissolution test procedure using an adaptation of the FDA paddle method (USP Apparatus 2) has been developed for the purpose of assuring uniform batch to batch release. The patch is held in position in the dissolution vessel by sandwiching it between a watchglass and an aluminum wire screen. The dissolution profiles of the three marketed brands (10 dosage forms) of transdermal nitroglycerin patches were determined over a 24-h period. All samples, were analyzed by HPLC. The results of patches manufactured by each firm indicate dose proportional release. While there is a qualitative difference in the dissolution pattern among manufacturers, the dissolution procedure was found to be simple, reliable and reproducible, suggesting this technique can be used as a quality control tool for assuring product uniformity.

Introduction

In the last decade the Food and Drug Administration has successfully employed the in vitro dissolution procedure to assure batch-to-batch bioequivalence reproducibility of solid oral drug products which have been shown to be bioavailable. The dissolution test has also been employed to assure the bioequivalence of solid oral drug products for which in vivo bioavailability studies were determined to be not necessary. The current trend in pharmaceutical research and development is towards novel drug delivery systems. In the last few years, several transdermal drug delivery systems, namely scopolamine (for the prevention and treatment of motion sickness), nitroglycerin (for the treatment of angina and congestive heart failure), and clonidine (for the treatment of hypertension) have been introduced. Presentations at some of the recent symposia on transdermal drug delivery systems indicate that an estrogen patch is likely to be introduced soon. (Symposium, 1985a and b). There is no information available in the literature on in vitro dissolution methodology for transdermal patches.

The transdermal nitroglycerin (NG) patches, currently are marketed by three manufacturers, in different strengths. Ciba manufactures patches in strengths of 2.5, 5, 10 and 15 mg/day delivery; Key manufactures patches in strengths of 2.5, 5, 7.5 and 10 mg/day delivery and Searle manufactures the patches in strengths of 5 and 10 mg/day delivery (Table 1). Each of these manufacturers

Correspondence: V.P. Shah, Division of Biopharmaceutics Food and Drug Administration, Rockville, MD 20857, U.S.A.

TABLE 1

MARKETED TRANSDERMAL NITROGLYCERIN PATCHES

Manufacturer	Surface area (cm^2)	Claimed in vivo release/24 h (mg)	Labelled patch content (mg)
Key	20	10.0	104
	15	7.5	77
	10	5.0	51
	5	2.5	26
Searle	16	10.0	32
	8	5.0	16
Ciba	30	15.0	75
	20	10.0	50
	10	5.0	25
	5	2.5	12.5

uses different dissolution methods as a quality control procedure. It is essential that a method which can be used to assure batch-to-batch uniform release of all these (and future) patches be available for regulatory purposes.

An in vitro dissolution method has been developed which will assure the batch-to-batch in vitro release reproducibility of these products. The method is very simple utilizing an adaptation of the FDA paddle method (USP Apparatus 2), which is employed in the dissolution testing of solid oral dosage forms.

Materials and Methods

Transdermal nitroglycerin patches

The four patches, marketed each by Ciba [1] and Key [2] and the two patches marketed by Searle [3] were evaluated.

Transdermal patch holders

A 9 cm diameter circle cut from aluminum window screens (about 18 mesh) was molded to fit a 9 cm diameter watchglass. A patch was removed from its protective package, excess adhesive tape was removed and the drug containing patch placed between the watchglass and the screen with the exposed drug side of the patch facing the screen. The watch glass–patch–screen sandwich was held together by 3, equally spaced 0.75 inch binder clips [4]. This assembly was placed at the bottom of a dissolution vessel containing 900 ml of water at 32°C. (Fig. 1). The assembly was centered, if needed, with the aid of a glass rod. Plastic clips [5] may be substituted for the binder clips (Fig. 1). The plastic clips are preferred because they are inert to aqueous dissolution media pH 1–8. The dissolution rate is not affected by the type of clip.

Dissolution apparatus

Dissolution was accomplished using a six spindle USP Apparatus 2 employing glass vessles [6], a paddle speed of 50 rpm and 900 ml deaerated water. The dissolution apparatus was calibrated using USP prednisone and salicylic acid calibrators and also using CDA (Center for Drug Analysis, St. Louis, MO) prednisone performance standard, before initiating the patch dissolution studies and also at the end of the studies. The dissolution results were found to be within the specified limits with all the three calibrators. The water bath temperature was maintained at 32 ± 0.5°C (the temperature of the skin). The ml aliquots, were collected without filtering or replacing media at 1, 2, 3, 5, 6, 7 and 23 h, and analyzed for nitroglycerin by a HPLC method.

Liquid chromatographic analysis

The liquid chromatographic system consisted of a high-pressure pump [7], an auto injector [8], a variable wavelength UV detector [9] and an integrator-recorder [10]. A 10 μl sample was injected on an octadecylsilane column (30 cm × 3.9 mm) [11] at ambient temperature with a flow rate of 1.5

[1] Ciba Pharmaceuticals Co., Summit, NJ.
[2] Key Pharmaceuticals, Miami, FL.
[3] Searle Pharmaceuticals, Chicago, IL.
[4] Lion Office Products.
[5] Central Notion Co., Brooklyn, NY
[6] Hanson Research Corp., Northridge, CA.
[7] Series 10; Perkin Elmer Corp., Norwalk, CT.
[8] WISP 710A; Waters Associates, Molford, MA.
[9] Spectroflow 757; Kratos Analytical Instruments, Ramsey, NJ.
[10] Model 3390 A; Hewlett-Packard, Avondale, PA.
[11] μ-Bondapak C18; Waters Associates.

ml/min. The mobile phase of methanol–water (50 : 50) was deaerated by filtration before use. The effluent from single injections of each sample aliquot was measured at 210 nm.

The standard curve was prepared by injecting (in triplicate) 0.01, 0.04, 0.05, 0.08 and 0.1 mg/ml of NG. Within run and between run coefficient of variation for standards was less than 5%. The area under the curve was determined and plotted against concentration. From the area of dissolution samples, concentration was determined and amount of NG in solution at each time calculated. This gave the amount (mg) of NG in solution. Knowing the amount of NG in the patch (declared on the label), the percent of label claim dissolved was calculated. Knowing patch size and amount of NG dissolved at each time interval, mg/cm^2 dissolved was also calculated.

Results and Discussion

The three presently marketed brands of transdermal NG patches, each employ different drug release technologies: Alza/Ciba, membrane permeation; Key, matrix-diffusion; and Searle, partition controlled microreservoir (Chien, 1982, 1983). The three systems each of which claims delivery of only 10 mg NG over a 24-h period (Table 1), contain widely varying amounts of active drug (32–104 mg). Because each of these transdermal drug delivery systems employs a different release technology, each exhibits a different in vitro release rate. It is anticipated therefore that the specifications for assuring batch-to-batch release uniformity will vary among the three brands.

One of the major problems in dissolution method development was keeping each patch 'flat', so as to prevent it from hitting the rotating paddle. This was analogous to the situation when developing a dissolution procedure for capsules using a paddle method. Capsules normally float, and hit the paddle. In order to avoid this, the capsules are placed in a wire helix, which keeps the capsules at the bottom of the flask. Several different approaches were tried: (i) attaching the patch to the watchglass with clips; (ii) holding the patch on the side of the dissolution flask with the aid of an adhesive tape; and (iii) sandwiching the patch between a watchglass and wire screen (4 or 18 mesh) using paper clips. Since in the preliminary studies the watchglass and wire mesh screen sandwich gave the most uniform and reproducible results, this method was used in all further studies.

The temperature of the dissolution medium was maintained at 32°C, rather than 37°C as in case of solid dosage forms such as tablets and capsules. Even though, the body temperature is maintained at 37 ± 0.5°C, the temperature of the skin surface is 32 ± 0.5°C (Pinson, 1952). Water, the simplest and most commonly used dissolution medium, and the paddle speed of 50 rpm were employed in these patch studies. It is expected that with increase in agitation, there will be an increase in dissolution release rate of the drug from the patches. The watchglass–patch–screen assembly was placed in the bottom of the round dissolution flask and centered, if needed, with the glassrod. The height of the paddle from the surface of the assembly was adjusted to 2.5 cm. In a few experiments this height was varied between 2.5 and 3.5 cm and was found that it had no effect on the dissolution (release) rate of the drug from the patch, suggesting that the geometrical arrangement of the patch assembly does not have significant influence on its release rate. The dissolution sampling from different locations at the same time revealed no difference in drug concentrations assuring uniform mixing in the dissolution flask.

The dissolution profiles of the tested NG patches are summarized in Table 2 and Fig. 2. Table 2 shows the cumulative amount (mg) released over a 24-h period. From this the percent of label claim dissolved and the amount (mg) of NG released per square centimeter patch area was calculated at each time interval and plotted in Figs. 2 and 3.

When plotted as percent label claim, the release pattern is virtually superimposable for each of Ciba's four strengths (Fig. 2B). In addition, when plotted as mg released, the release pattern exhibited by the four individual strengths of Ciba's products demonstrates dose proportionality (Fig. 2A). Similar observations are made for both the Key's products and the Searle's products (Fig.

TABLE 2

IN VITRO RELEASE (mg/patch) OF NITROGLYCERIN USING PADDLE METHOD

Manufacturer	Label Cont. (mg)	mg dissolved						
			1 h	2 h	3 h	5 h	6 h	7 h	23 h
Ciba-Geigy	75	Mean	4.5	6.2	8.3	11.8	13.5	15.5	41.4
		%CV	7.7	7.2	8.6	11.0	8.4	12.9	9.7
	50	Mean	3.0	4.4	5.6	7.7	8.8	10.0	25.8
		%CV	8.2	4.7	2.8	5.0	2.7	3.9	2.6
	25	Mean	1.5	2.2	2.8	4.0	4.2	5.0	13.0
		%CV	14.9	11.2	6.1	3.2	6.4	5.5	4.0
	12.5	Mean	–	1.1	1.3	1.8	2.2	2.4	6.4
		%CV	–	3.1	7.5	8.3	8.5	8.2	2.6
Key	104	Mean	26.9	39.4	49.2	65.7	72.2	77.5	104.8
		%CV	3.0	5.0	3.9	3.8	5.5	5.6	2.1
	77	Mean	17.1	27.3	34.6	46.0	51.0	55.4	
		%CV	3.1	2.2	1.4	1.0	1.2	1.4	
	51	Mean	13.5	19.9	25.4	33.1	36.1	38.9	53.8
		%CV	4.3	4.5	3.2	3.0	2.9	2.7	0.8
	26	Mean	6.6	9.7	12.5	15.9	17.7	19.3	26.9
		%CV	10.6	8.7	9.2	9.0	8.9	7.3	4.4
Searle	32	Mean	12.2	16.9	20.2	25.6	26.8	27.6	31.3
		%CV	7.0	4.4	2.7	4.0	3.3	1.8	2.2
	16	Mean	7.1	9.4	11.8	14.0	15.0	15.4	17.4
		%CV	5.7	4.4	5.1	5.0	3.0	2.2	1.8

Data represent mean of 12 (6 × 2) determinations.

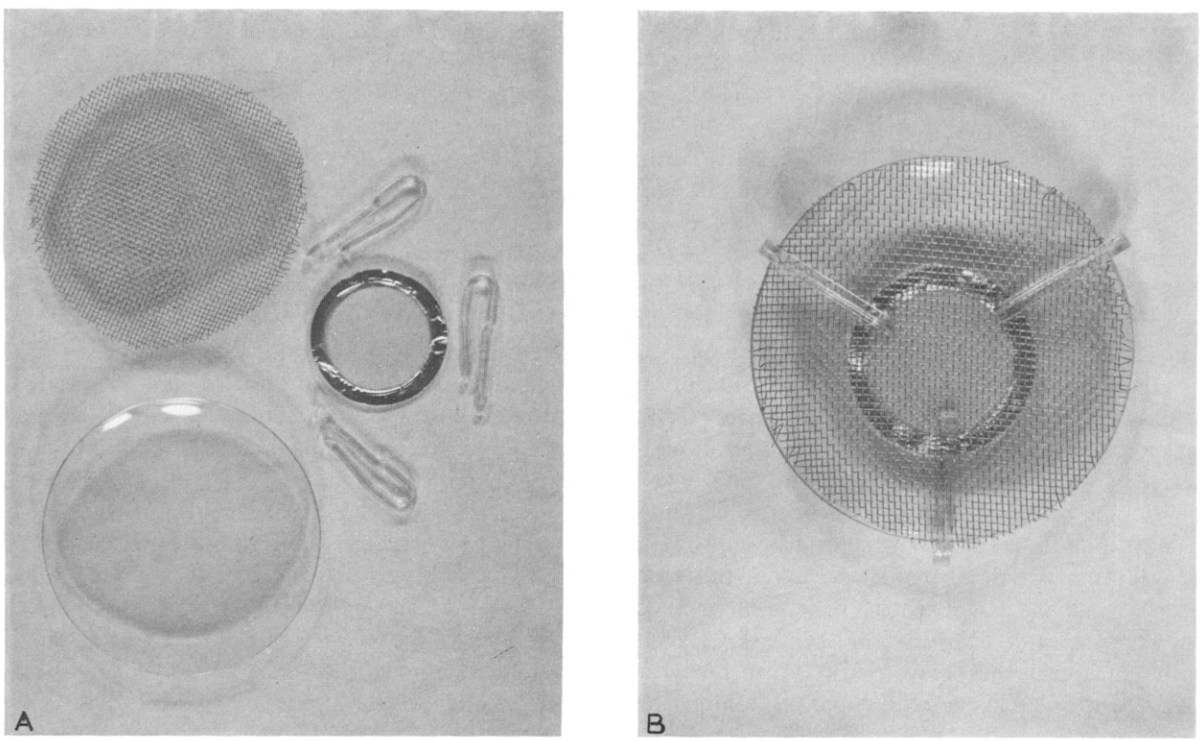


Fig. 1A and B.

2C–F). These results indicate that the in vitro method developed is reproducible and can be used for determining the drug release characteristics and for assuring batch-to-batch transdermal patch release uniformity.

The in vitro dissolution data summarized in Table 2 and Fig. 2 show that on an average, Key's patches released about 25% of the drug in the first hour, 45% in 3 h, 65% in 5 h, 75% in 7 h, and 100% in 23 h. Searle's patches released the drug somewhat faster on a percent label claim basis (40% in 1st hour, and 90% in 7 h). Ciba's patches, on the other hand released NG very slowly, less than 10% in the first hour, about 20% in 7 h and only about 55% in 23 h. Ciba's patch did not completely release the drug under our test conditions. These results indicate that, although consistent within a manufacturer, the release pattern from the three brands are different.

The comparative dissolution profile of the three products (Fig. 3) show similar in vitro release between Key's and Searle's products, but a distinctly different release for Ciba's product. This observed difference in release characteristics is attributed to different patch characteristics. Since all manufacturers use different manufacturing and drug release technology, the observed results are not surprising. Based on the amount of NG released per unit area (there is a 5–10-fold difference in the release rate among the patches) Key is faster than Searle which is faster than Ciba (Fig. 3). Ciba's patch released drug at constant rate (zero-order) where as the other two released the NG according to a 1st-order process. Different drug loading explains the difference in release rate profile seen between Key and Searle products. All three products exhibit different release properties, but still all claim the same in vivo absorption. In case of NG, skin serves as a rate-limiting membrane (Chien, 1983) and therefore controls the amount of drug delivery to the systemic circulation. Based on the observations here, it is clear

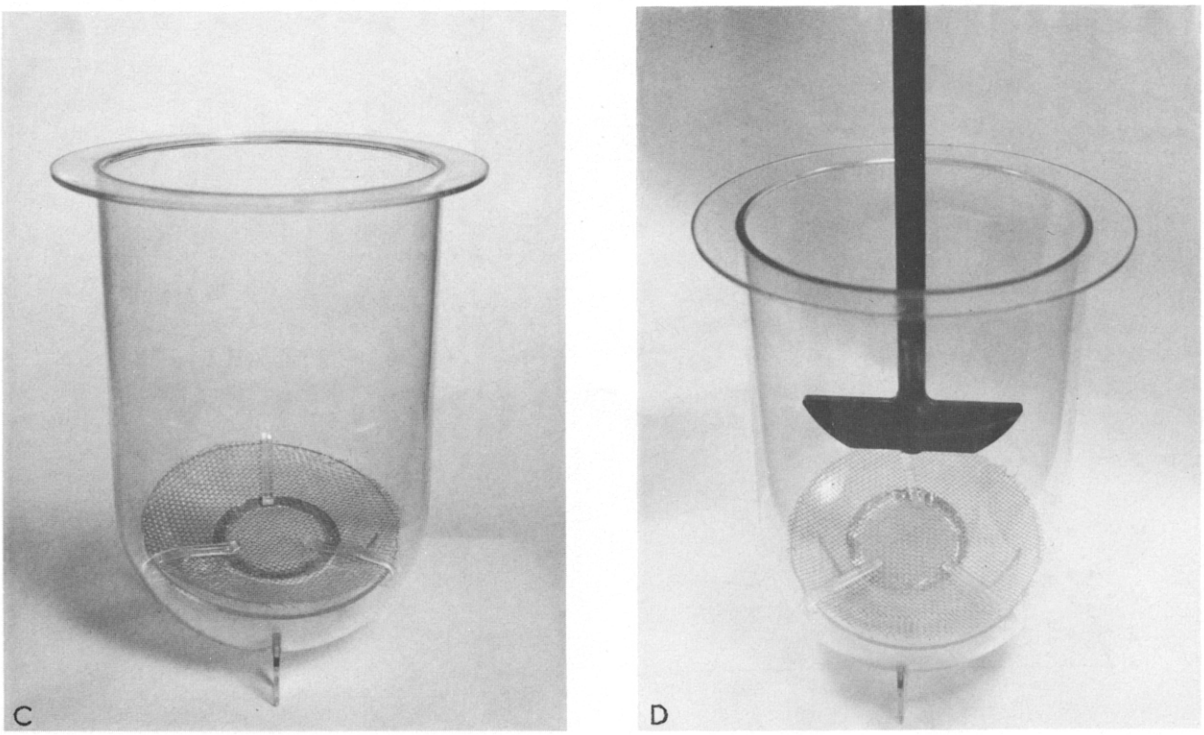


Fig. 1. Transdermal patch dissolution set up. Components: watchglass–patch–wiremesh screen and clips (A); assembly (B), assembly in dissolution flask (C); and final set up with paddle apparatus (D).

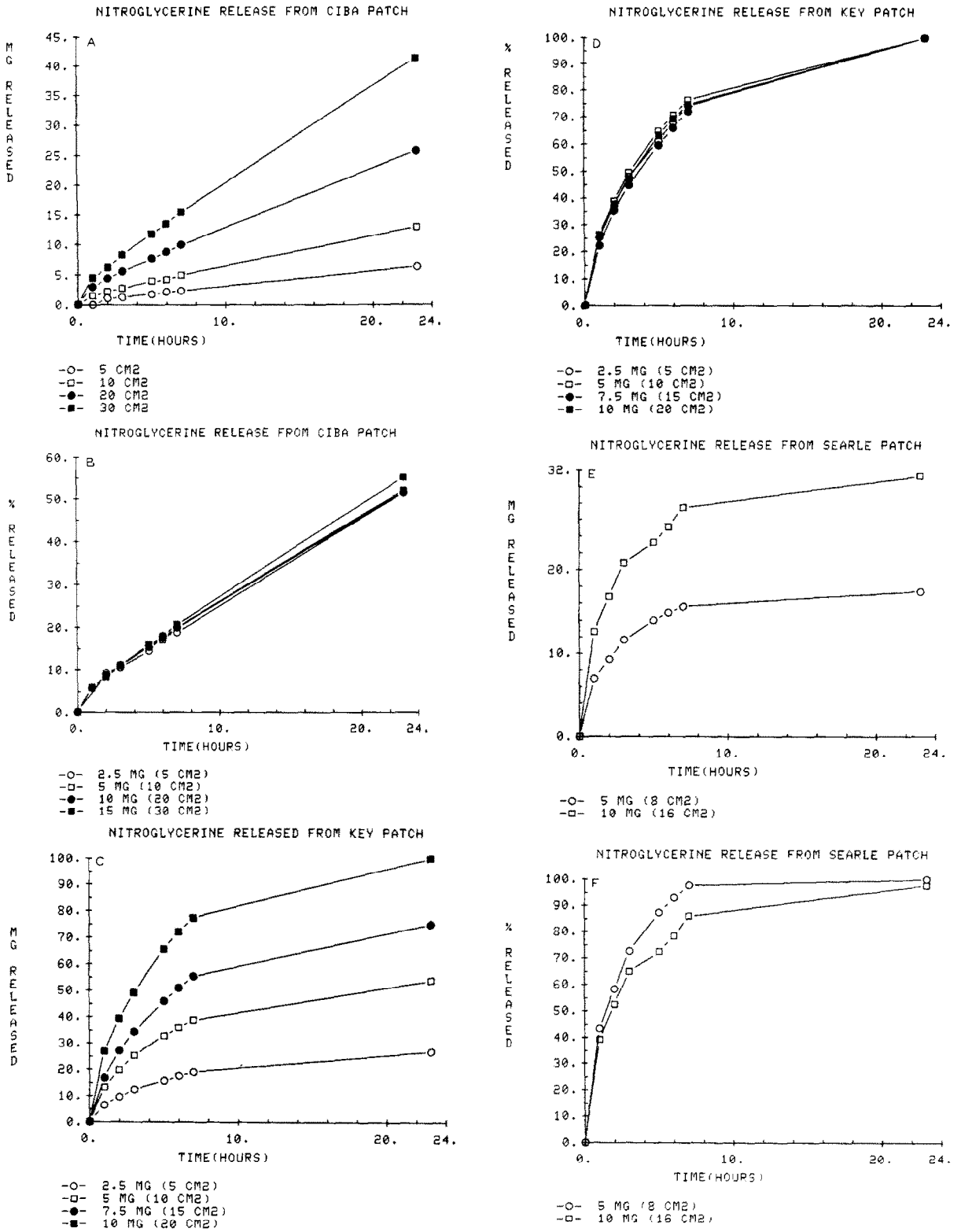
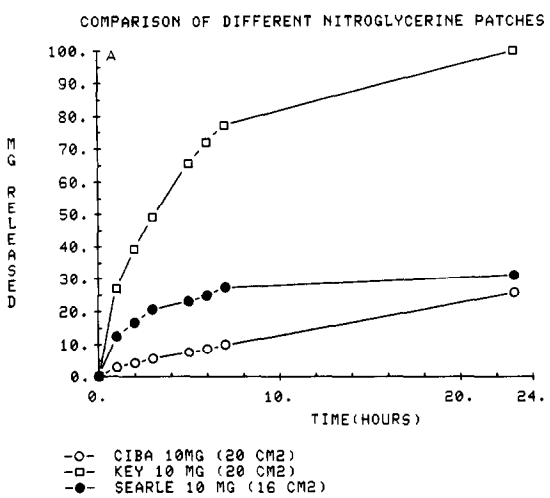
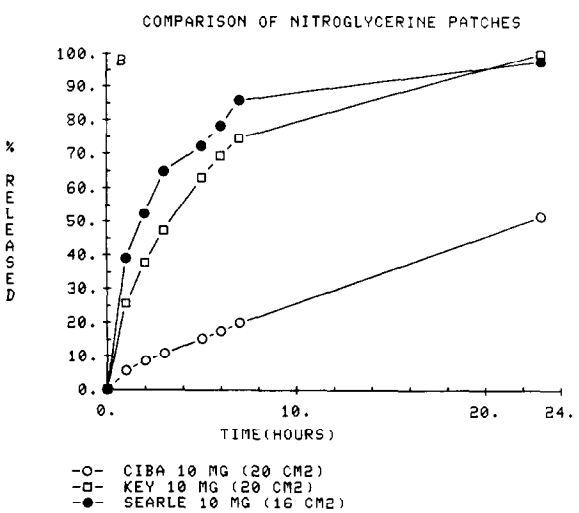


Fig. 2. In vitro release profile, mg/patch (A, Ciba; C, Key; E, Searle) and % label claim release (B, Ciba; D, Key; F, Searle) of transdermal nitroglycerin patches.

that each transdermal NG patch will have its own in vitro specification. This is similar to oral-controlled release preparations where again different manufacturers' products (containing same active ingredient) exhibit different in vitro dissolution patterns and they have their own specifications. In case of all controlled release products, the in vivo performance of the product is evaluated and if found satisfactory, the in vitro release pattern of that product is studied and specifications established. The transdermal patches are controlled release products, and therefore having separate in vitro release patterns for different patches is not surprising. From the studies, it is clear that





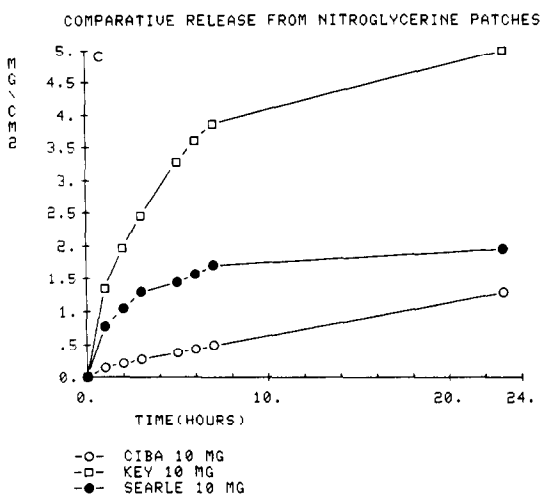


Fig. 3. Comparative dissolution data of three marketed nitroglycerin patches. A: mg of drug released. B: % label claim released. C: mg/cm^2 drug released.

all NG patches release the amount of drug claimed to be absorbed in 24 h.

An in vitro procedure is needed that can be used as a quality control tool to assure batch-to-batch uniformity. The in vitro procedure should be simple and should avoid unnecessary variables, which may complicate the results and its interpretation. The procedure described here is simple, and reproducible. The percent coefficient of variation for method variability and product variability was less than 10% in most cases. Only in the case of the initial time point determination, when the concentration is very low, was the percent coefficient of variation higher than 10%. The method developed utilizes an adaptation of the FDA paddle unit—officially known as USP Apparatus 2. This is used by almost all pharmaceutical laboratories for studying the dissolution of solid oral dosage forms. Recently Chien et al. (1983) have utilized a Franz diffusion cell assembly to study in vitro skin permeation as a method of determining in vitro patch release, for the purpose of relating in vitro release to in vivo absorption. Skin permeation studies involve, as the name suggests, use of animal skin or human cadaver skin and is subject to large variability. Use of the Franz diffusion cell for drug release testing is limited to exposure of only part of the patch

(limited to size of cell). As a result, even though patches may vary in size from 5 to 20 cm^2 in size and in shape from round to oval, the same area is exposed in the dissolution study. In addition the Franz diffusion cell has a very small volume (about 5–10 ml) and in order to maintain sink conditions in this small volume, the dissolution medium contained 20% polyethylene glycol 400. The influence of such agents on the patches is unknown. Lastly, Franz diffusion cell is not a common test unit in most of the pharmaceutical laboratories. On the other hand, use of the paddle method, and 900 ml of the water to determine the in vitro release profile of the patch, exposes the entire patch and maintains the sink conditions, obviating the problem noted with the Franz cell.

In summary, the results show that the paddle method developed for dissolution of transdermal patches is simple, reliable and reproducible. It can be used for determining drug release characteristics from all the marketed transdermal NG patches, and can be used as a tool to assure batch-to-batch release uniformity. Since different manufacturing technology has been employed to develop products with different release rates, separate specifications should be established for each system. However, the same method and procedure can easily be used for all three NG patches. This new procedure is now being employed to study and evaluate the in vitro release profile of marketed clonidine and scopolamine patches. The comparative evaluation of all in vitro dissolution procedures for transdermal patches is also underway, and will be published in the near future. It is anticipated that paddle procedure will be employed for other transdermal drug delivery systems.

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