International Journal of Pharmaceutics, 55 (1989) 147–155
Elsevier

IJP 01866

A comparative study of the release kinetics of trinitrine from transdermic therapeutic systems

J.-M. Aiache [1], J.-M. Cardot [2] and S. Aiache [1]

[1] *Biopharmaceutics Department, Faculty of Pharmacy, Clermont-Ferrand (France) and* [2] *Ciba-Geigy Ltd. Basle (Switzerland)*

(Received 23 January 1989)
(Accepted 25 March 1989)

Key words: Transdermal therapeutic system; In vitro release; In vitro control; Trinitrine in vitro release

Summary

The in vitro study of transdermal therapeutic systems is of first importance to ensure a good quality control of such drug dosage forms. As several national Pharmacopoeias have published different in vitro methods, the authors aimed at comparing two of them. The first method described in the French Pharmacopoeia is a cell, consisting of a reservoir which contains a central chamber designed to receive the transdermal therapeutic system and a lid which fits onto the reservoir in order to centre the transdermal therapeutic system and delimit the area of diffusion. The second method described in the USP is a hollow cylinder mounted on the end of a steel rod like a paddle; the transdermal therapeutic systems are stuck on the outside of the cylinder, horizontally. In both cases, the transdermal therapeutic systems are placed with the diffusion membrane outward, in direct contact with the medium (degassed distilled water). The transdermal therapeutic systems studied are composed of a reservoir one of the walls of which is a membrane of surface area 10 cm^2 when containing 25 mg of trinitrine, or 20 cm^2 when containing 50 mg of trinitrine. Released trinitrine was assayed using a HPLC technique. In spite of some small differences in the technique used (e.g. temperature 30 °C or 32 °C), the release of trinitrine is linear (zero-order) and the results are correlated by an equation of type $y = ax + b$ and thus validated.

Introduction

In vitro tests constitute a useful method to study the development of dosage forms, since if a good correlation with subsequent in vivo results is obtained, the development of the new dosage form is greatly facilitated. In addition, once the new dosage form is ready, the supplier requires a quality control method that ensures that the production of the dosage form meets imposed standards of quality, conformity and reproducibility. During the development stage, any of the methods described in the literature may be used in order to find the device giving the best in vitro/in vivo correlations; but it is more advisable to use a method described in a national Pharmacopoeia and therefore approved by regulating authorities. It is also clearly desirable for any method used during development work to be validated against the officially approved one.

The work described here sets out to do this for transdermic therapeutic systems delivering trinitrine.

Correspondence: J.-M. Aiache, Biopharmaceutics Department, Faculty of Pharmacy, P.O. Box 38, 63001 Clermont-Ferrand Cédex, France.

Materials and Methods

The transdermic therapeutic systems studied

These meet the definition given in the French Pharmacopoeia (1987): "Transdermic systems are therapeutic devices designed to be applied on the skin in a particular area. They hold or are the vector for one or more drugs designed to exert a general action after release and penetration through the skin.

They can be composed of: (a) either a semi-solid or solid preparation in which the drug(s) is (are) dispersed or dissolved at a defined concentration, usually high. This preparation, designed to release its drug according to a defined rate pattern, is placed directly on the skin, to which it is designed to adhere spontaneously due to its composition. The preparation is usually placed at the centre of an adhesive support which keeps it in contact with the site of delivery (e.g. a waterproof sticking plaster); or (b) a reservoir one of the walls of which is a membrane which, placed on the skin, has special permeability properties making possible the release and the diffusion of the drug from the reservoir through the skin with a defined rate pattern. This reservoir contains the active drug(s) at a defined concentration, usually high, dispersed or dissolved in the preparation, the composition of which does not affect the processes of release and diffusion of the drug through the membrane" (Fig. 1).

The two systems studied here correspond to the second type: one has a membrane of surface area 10 cm^2 and contains 25 mg of trinitrine (Nitriderm TTS5; Ciba-Geigy, Basel, Switzerland); the other has a membrane of surface area 20 cm^2 and contains 50 mg of drug (Nitriderm TTS10; Ciba-Geigy, Basel, Switzerland).

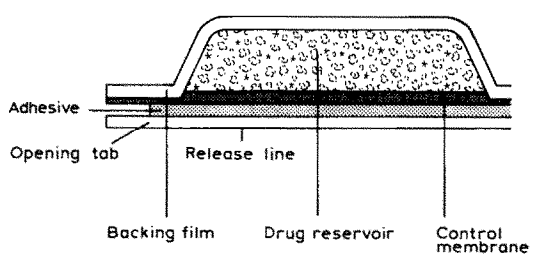

Fig. 1. Diagram of the therapeutic transdermic system.

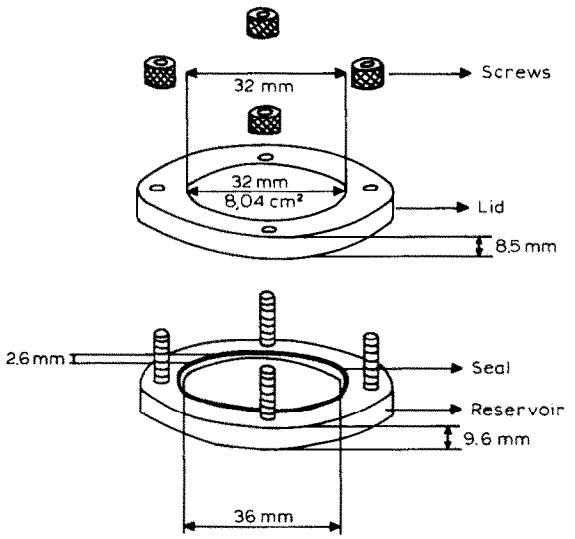

Fig. 2. Diagram of the cell.

Methods used for the study of the release pattern

The first method is the cell method described in the French Pharmacopoeia. The design of the cell is shown in Fig. 2. It consists of a reservoir and a lid. The reservoir contains a central chamber designed to receive the transdermic therapeutic system. The diameter of this chamber is 36 mm. The lid which fits onto the reservoir has a central aperture of diameter 32 mm. This is intended to centre the system and delimit the area of diffusion (here 8.04 cm^2). The lid is held on the cell by nuts traveling on threaded studs fixed around the cell. Here, the cell is used without a diffusion membrane since the dosage form has one.

The second method (recently published in the USP 8th Suppl., 1988) is the cylinder method, proposed by the supplier of the dosage forms. This uses hollow cylinders 4.4 cm in diameter and 5 cm high (Fig. 3). Slanting holes are bored in the upper part to facilitate flow of the dissolving medium (Fig. 4). These cylinders are mounted on the end of a steel rod like a paddle. The transdermic therapeutic systems are stuck on the outside of the cylinder, horizontally, at a defined height, with the diffusion membrane outward.

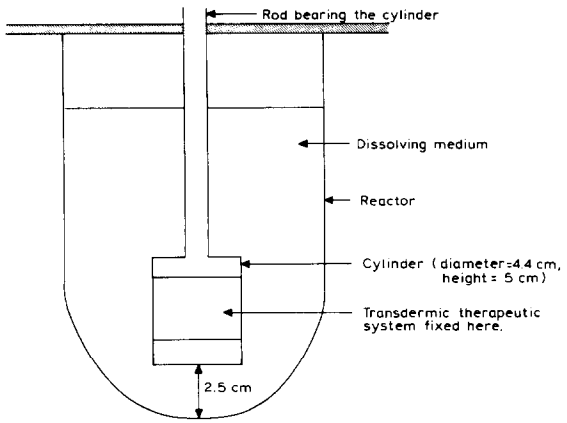

Fig. 3. Diagram of the cylinder.

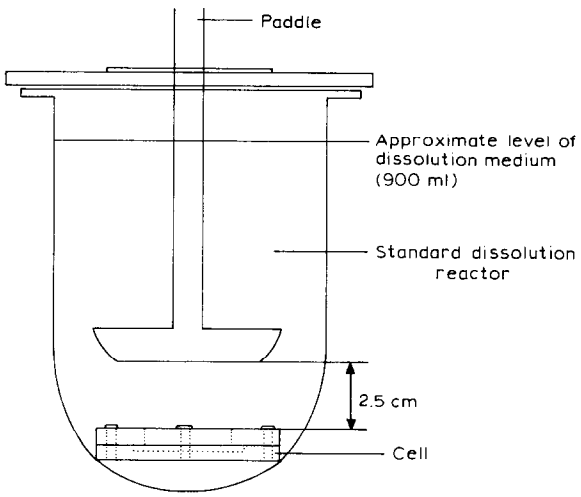

Fig. 5. Diagram of the cell in the reactor.

Operating procedure

First method: the cell method. The transdermic therapeutic system of surface area 10 cm^2 was placed in the cell as indicated above, with its membrane outward, i.e. placed in direct contact with the dissolving medium. Because of the shape of the transdermic therapeutic system, the surface actually in contact with the medium was 7.34 cm^2.

After closing, the cell was placed at the bottom of the reactor of a dissolver where it remained in a horizontal position due to its weight. The paddle was 2.5 cm above the cell (Fig. 5) and set to turn at 100 rpm to ensure satisfactory homogeneity of the medium as indicated in a previous study (Traisnel and Aiache, 1984; Vincent, 1985).

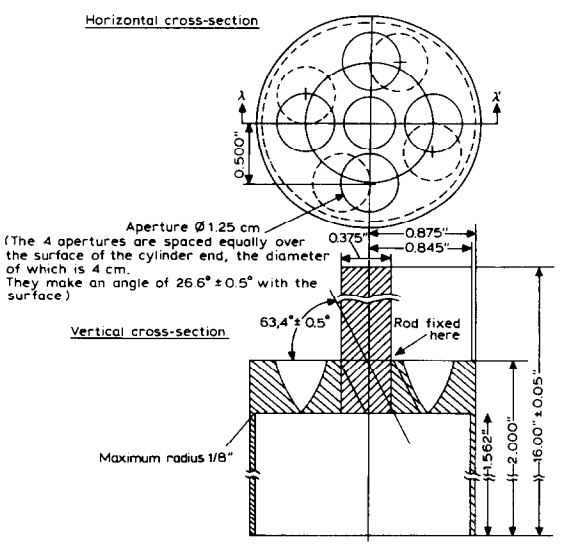

Fig. 4. Diagram of the cylinder (horizontal and vertical cross-sections).

The dissolving medium was 900 ml of degassed distilled water thermostatically regulated at 30 ± 0.5 °C, according to the monography. Six runs were performed concurrently.

The 20 cm^2 transdermic therapeutic system was folded in two and placed in the same cell as above, thus exposing the same surface area to the dissolving medium. No diffusion into the medium of the drug through the membrane in contact with the bottom of the cell occurs thanks to the imperviousness of the latter.

Second method: the cylinder method. The transdermic therapeutic systems were fixed on the predetermined area of the cylinder either with glue or with two elastic bands placed at the top and bottom of the system. The cylinder was placed 2.5 cm from the bottom of the reactor of the dissolving apparatus, which contained the same volume of medium as above, also thermostatically regulated at 30 ± 0.5 °C. The cylinders were set to rotate at 100 rpm to remain close to the conditions obtained in the first method.

Assay of released trinitrine. Eighteen successive experiments were carried out with each of these two methods.

In both cases, 1 ml of dissolving medium was sampled every hour for 8 h using a flexible tube

fitted with a non-woven non-sized paper filter. This tube was fixed so that the filter was halfway up the medium. The samples were used undiluted. A standard solution of trinitrine (10% in lactose) was made up containing 250 mg in 250 ml of mobile phase (methanol/water 65 : 35). After complete dissolution of the trinitrine, 1 ml of the solution was sampled using the same filter system as described above. This sample was used undiluted. For assay of released trinitrine, a high-performance liquid chromatography (HPLC) method was used. Conditions were as follows.

Apparatus: Kratos 1204 A variable-wavelength U.V. detector; Waters M 6000 A pump; Waters Wisp automatic injector; Delsi integrator; Waters C18 μBondapack column (10 μm) 30 cm, inside diameter 3.9.

Operating conditions: mobile phase = methanol/water 65 : 35; run time = 4; volume injected = 25 μl; flow rate = 1.5 ml/min; LP = 10, DI = 120, TF = 285; λ = 214 nm; sensitivity of detection = 0.1 Aufs.

With five injections of control solution, a percentage variation of 0.3% was obtained. The sensitivity of the method was evaluated at 0.7 μg/ml. Its linearity was checked and found satisfactory.

Calculations

Cylinder method

For the transdermic therapeutic system of surface area 10 cm^2, the proportion $X\%$ of drug released at time t is obtained from the following equation:

$$X = \frac{A_{Tt} \times C_C \times 100}{A_C \times CE} = \frac{A_{Tt} \times \frac{25}{250} \times 100}{A_C \times \frac{25}{900}}$$

$$= \frac{A_{Tt} \times 25 \times 100 \times 900}{A_C \times 25 \times 250}$$

$$X = \frac{A_{Tt} \times 360}{A_C}$$

where A_{Tt} = area under the recording of the test solutions sampled at time t; A_C = area under the recording of the control solution; C_C = concentration of control = 25 mg/250 ml.

The proportion released is based on a theoretical total concentration CE of nitroglycerine in the medium of 25 mg/900 ml. The quantity Q released is $\mu g/cm^2/h$ (from t_0 to $t = 6$ h) is:

$$Q = \frac{X(\%) \times 25\ (mg) \times 1000}{100(\%) \times 6\ (h) \times 10\ (cm^2)} = \frac{X \times 25}{6}$$

The factor 1000 is to convert mg to μg.

For the transdermic therapeutic system of surface area 20 cm^2, the proportion $X\%$ of drug released at time t is obtained from the following equation:

$$X = \frac{A_{Tt} \times C_C \times 100}{A_C \times CE} = \frac{A_{Tt} \times \frac{25}{250} \times 100}{A_C \times \frac{50}{900}}$$

$$= \frac{A_{Tt} \times 25 \times 100 \times 900}{A_C \times 50 \times 250}$$

$$X = \frac{A_{Tt} \times 900}{A_C \times 5}$$

where A_{Tt}, A_C and C_C are as above.

The proportion released is based on a total theoretical concentration CE of nitroglycerine in the medium of 50 mg/900 ml. The quantity Q released in $\mu g/cm^2/h$ (from t_0 to $t = 6$ h) is thus:

$$Q = \frac{X(\%) \times 50\ (mg) \times 1000}{100(\%) \times 6\ (h) \times 20\ (cm^2)} = \frac{X \times 25}{6}$$

where the factor 1000 is to convert mg to μg.

Cell method

The proportion $X\%$ of drug released at time t is obtained in the same way for both transdermic therapeutic systems studied, since unlike the cylinder method, the cell method always exposes the same surface area of membrane to the dissolving medium (see Experimental procedure).

$$X = \frac{A_{Tt} \times C_C \times 100}{A_C \times CE} = \frac{A_{Tt} \times \frac{25}{250} \times 100}{A_C \times \frac{25}{900}}$$

$$= \frac{A_{Tt} \times 25 \times 100 \times 900}{A_C \times 25 \times 250}$$

$$X = \frac{A_{Tt} \times 360}{A_C}$$

where A_{Tt}, A_C and C_C are as above.

The proportion released is based on a total theoretical concentration CE of nitroglycerine in the medium of 25 mg/900 ml. The quantity Q released in $\mu g/cm^2/h$ (from t_0 to $t = 6$ h) is:

$$Q = \frac{X(\%) \times 25\ (mg) \times 1000}{100(\%) \times 6\ (h) \times 7.24\ (cm^2)} = \frac{X \times 250}{43.44}$$

where the factor 1000 is to convert mg to μg. The actual surface area in contact with the dissolving medium is 7.24 cm^2.

Results

Results are given in Tables 1–4, which indicate the following.

- The kinetics of the release of trinitrine from the transdermic therapeutic system of surface area 10 cm^2 – batch 066700 (in % versus time) by the cylinder method (Table 1).
- The kinetics of the release of trinitrine from the transdermic therapeutic system of surface area 20 cm^2 – batch 067500 (in % versus time) by the cylinder method (Table 2).
- The kinetics of the release of trinitrine from the transdermic therapeutic system of surface area 10 cm^2 – batch 066700 (in % versus time) by the cell method (Table 3).
- The kinetics of the release of trinitrine from the

TABLE 1

Kinetics of the release of trinitrine from the transdermic therapeutic system of surface area 10 cm^2 – batch 066700 (% versus time): cylinder method

Test no.	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
1	7.24	9.18	9.93	12.00	12.58	14.52	16.06	19.46
2	6.61	7.78	9.60	10.96	13.11	14.86	16.68	17.21
3	6.89	8.19	11.07	12.63	13.58	15.39	17.23	18.72
4	6.62	9.86	9.83	12.81	15.35	16.32	17.26	18.55
5	6.76	7.40	9.92	11.87	15.28	14.04	17.16	18.79
6	7.21	8.60	10.02	11.99	13.62	14.61	16.10	18.98
7	5.81	7.54	10.06	13.29	16.66	17.21	19.14	21.32
8	6.37	6.92	13.03	13.99	16.25	16.54	21.12	21.47
9	7.78	9.25	11.95	13.46	15.44	17.88	17.99	21.85
10	4.73	8.61	11.82	12.82	15.95	15.18	17.37	19.24
11	7.70	7.94	11.58	12.60	16.87	17.03	18.22	19.53
12	7.74	8.01	10.29	12.00	13.23	13.43	14.33	17.00
13	6.72	9.09	10.89	12.52	13.03	16.03	19.06	19.35
14	6.73	8.46	7.61	12.33	13.42	14.23	16.78	17.95
15	6.47	8.58	9.30	11.95	15.09	16.84	16.98	19.06
16	7.27	7.71	9.78	13.52	14.45	16.35	18.19	20.59
17	6.53	8.67	9.97	11.61	13.5	15.54	17.86	19.80
18	6.62	7.44	8.63	11.59	14.37	16.28	17.45	19.96
$\bar{X}$	6.77	8.44	10.29	12.44	14.54	15.69	17.50	19.38
σ	0.73	0.75	1.27	0.78	1.35	1.23	1.44	1.34
% V	10.7	8.9	12.4	6.3	9.3	7.8	8.2	6.9
i.e. in total quantity released vs time:								
Q (mg)	1.69	2.11	2.57	3.11	3.63	3.92	4.37	4.84

TABLE 2

Kinetics of the release of trinitrine from the transdermic therapeutic system of surface area 20 cm^2 – batch 067500 (% versus time): cylinder method

Test no.	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
1	4.62	4.95	8.28	8.51	9.67	11.78	13.12	14.67
2	4.43	5.09	5.94	8.31	9.75	10.59	12.88	14.43
3	4.80	5.64	6.71	8.80	10.09	11.35	12.08	12.39
4	4.29	5.49	6.96	8.66	10.13	11.42	13.06	13.56
5	4.51	5.06	6.75	8.49	9.28	11.30	11.83	15.29
6	4.72	6	7.72	9.38	9.78	11.47	13.26	14.35
7	3.98	5.89	7.29	9.22	10.92	12.61	16.30	16.78
8	3.91	4.76	6.39	8.09	10.04	12.29	12.28	15.27
9	3.53	4.16	7.37	8.23	10.21	11.95	14.36	14.62
10	3.92	5.01	7.29	8.56	9.74	11.66	13.66	16.51
11	3.68	5.01	6.87	8.15	9.59	11.81	12.37	15.98
12	3.17	4.28	7.03	7.51	8.90	10.99	12.53	13.08
13	3.88	5.58	7.76	9.84	9.86	14.32	15.24	18.86
14	3.94	5.97	7.41	8.48	11.2	13.65	14.7	19.03
15	4.01	5.55	6.60	8.00	9.27	11.13	13.04	14.57
16	3.81	5.31	7.60	9.19	10.87	13.06	16.92	19.03
17	4.02	5.44	6.45	7.80	9.43	16.86	17.53	17.93
18	4.04	6.05	7.21	9.38	11.13	13.43	15.39	20.07
$\bar{X}$	4.07	5.29	7.09	8.59	9.99	12.31	13.92	15.91
σ	0.42	0.55	0.57	0.61	0.66	1.51	1.73	2.26
% V	10.4	10.4	8.1	7.2	6.6	12.3	12.4	14.2
i.e. in total quantity released vs time:								
Q (mg)	2.03	2.64	3.54	4.29	4.99	6.15	6.96	7.95

TABLE 3

Kinetics of the release of trinitrine from the transdermic therapeutic system of surface area 10 cm^2 – batch 066700 (% versus time): cell method

Test no.	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
1	3.54	4.39	5.39	6.95	8.37	8.94	10.64	12.2
2	3.54	4.96	5.96	7.09	9.50	11.21	12.63	14.05
3	3.69	4.68	5.96	7.23	8.51	8.94	10.50	15.46
4	3.26	4.25	6.10	7.94	8.65	10.07	13.05	13.62
5	3.69	5.11	6.24	8.37	9.50	11.35	11.21	12.06
6	3.12	4.25	5.39	7.52	8.51	10.50	12.06	15.04
7	3.14	4.28	6.71	6.71	9.0	11.29	13.0	13.29
8	2.86	4.71	5.86	6.86	10.72	10.86	12.14	13.86
9	4.0	5.57	6.71	6.71	10.57	10.57	12.14	14.43
10	2.71	4.0	5.57	6.71	9.86	10.0	12.86	12.86
11	3.57	4.28	6.57	7.57	9.29	11.0	12.29	14.29
12	4.57	6.43	8.29	10.72	13.43	15.0	17.86	20.29
13	2.91	3.93	6.12	7.57	9.03	9.76	11.95	13.26
14	3.2	4.22	6.55	7.57	9.47	10.78	12.38	12.53
15	3.06	4.22	5.97	7.72	8.89	10.34	11.22	13.26
16	3.35	4.81	6.55	7.87	9.47	11.36	12.09	14.13
17	3.35	4.95	6.26	7.72	9.47	11.36	12.09	13.84
18	4.52	6.41	8.3	10.2	12.24	14.13	17.34	17.34
$\bar{X}$	3.45	4.75	6.36	7.72	9.69	10.97	12.64	14.21
σ	0.51	0.74	0.81	1.10	1.33	1.52	1.95	1.96
% V	14.9	15.6	12.8	14.3	13.7	13.8	15.4	13.8
i.e. in total quantity released versus time:								
Q (mg)	0.86	1.18	1.59	1.93	2.42	2.74	3.16	3.55

TABLE 4

Kinetics of the release of trinitrine from the transdermic therapeutic system of surface area 20 cm^2 – batch 067500 (% versus time): cell method

Test no.	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
1	4.26	6.92	9.12	10.6	13.24	14.72	17.36	18.68
2	4.26	5.88	7.64	8.98	11.04	12.06	13.68	15.9
3	3.68	5.74	7.06	8.98	10.44	11.92	13.68	15.3
4	3.68	5.58	7.06	8.68	10.4	11.62	13.38	15.74
5	3.96	6.18	7.2	9.26	10.88	12.5	14.86	16.18
6	4.4	5.88	7.8	8.98	10.3	12.8	13.98	14.86
7	6.16	6.16	7.5	9.14	9.26	10.8	12.56	13.9
8	5.5	5.5	5.94	8.6	8.7	11.02	11.02	11.8
9	5.06	5.06	5.72	7.5	9.04	10.7	11.14	13.34
10	2.96	6.16	5.72	6.5	7.6	8.7	9.82	12.12
11	4.52	5.5	6.84	8.04	9.26	11.24	11.46	12.78
12	3.96	5.44	5.94	7.06	8.7	9.58	11.58	11.9
13	3.74	3.74	6.22	7.28	9.44	10.36	11.68	13.22
14	2.58	3.18	4.80	6.52	7.34	8.78	10.6	11.9
15	2.88	4.46	5.24	7.22	8.68	9.96	11.34	12.96
16	3.2	4.94	6.1	8.28	8.48	11.88	13.22	14.0
17	2.98	4.24	5.7	7.3	8.32	10.94	11.14	13.9
18	3.1	4.4	5.96	7.86	8.6	11.0	12.72	13.98
$\bar{X}$	3.94	5.27	6.53	8.15	9.43	11.14	12.51	14.02
σ	0.96	0.96	1.07	1.09	1.42	1.45	1.82	1.82
% V	24.3	18.2	16.4	13.4	15.1	13.1	14.5	13.0
i.e. in total quantity released vs time:								
Q (mg)	0.98	1.32	1.63	2.03	2.35	2.78	3.12	3.50

transdermic therapeutic system of surface area 20 cm^2 – batch 067500 (in % versus time) by the cell method (Table 4).

- The quantity of trinitrine released in $\mu g/cm^2/h$ (from 0 to 6 h) by the cylinder method (Table 5).
- The quantity of trinitrine released in $\mu g/cm^2/h$ (from 0 to 6 h) by the cell method (Table 6).

From these tables, curves for comparison and correlation of the two methods were plotted.

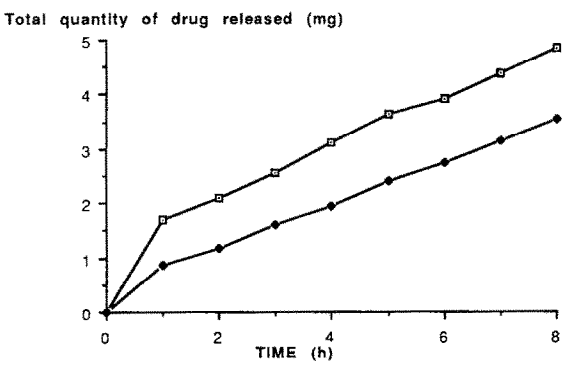

Fig. 6. Comparative curves for the kinetics of dissolution of the 10 cm^2 transdermic therapeutic system. Key: ⊡———⊡, cylinder method; ◆———◆, cell method.

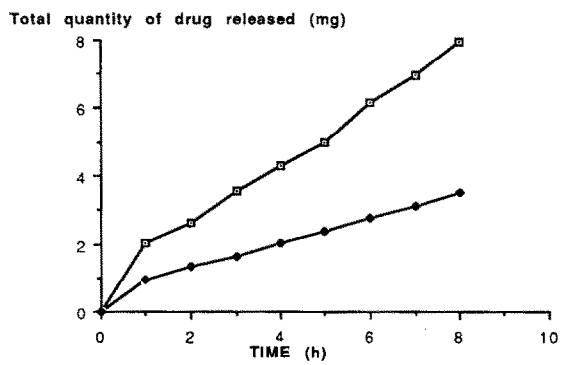

Fig. 7. Comparative curves for the kinetics of dissolution of the 20 cm^2 transdermic therapeutic system. Key: ⊡———⊡, cylinder method; ◆———◆, cell method.

TABLE 5

Quantity of trinitrine released in μg/cm²/h (period 0-6 h): cylinder method

Transdermic therapeutic system of surface area 10 cm²		Transdermic therapeutic system of surface area 20 cm²	
Test no.	$t = 6$ h	Test no.	$t = 6$ h
1	60.5	1	49.1
2	61.9	2	44.1
3	61.95	3	47.3
4	68	4	47.6
5	68.5	5	47.1
6	60.9	6	47.8
7	71.7	7	52.54
8	68.9	8	51.20
9	74.51	9	49.79
10	63.20	10	48.58
11	70.9	11	49.20
12	56	12	45.79
13	66.8	13	59.66
14	59.3	14	56.87
15	70.2	15	46.37
16	68.1	16	54.41
17	64.7	17	70.25
18	67.8	18	55.95
$\bar{X}$	65.77	$\bar{X}$	51.31
σ	4.95	σ	6.31
% V	7.5	% V	12.3

TABLE 6

Quantity of trinitrine released in μg/cm²/h (period 0-6 h): cell method

Transdermic therapeutic system of surface area 10 cm²		Transdermic therapeutic system of surface area 20 cm²	
Test no.	$t = 6$ h	Test no.	$t = 6$ h
1	51.45	1	84.71
2	64.51	2	69.40
3	51.45	3	68.60
4	57.95	4	66.87
5	65.32	5	71.94
6	60.43	6	73.66
7	64.97	7	62.15
8	62.50	8	63.42
9	60.83	9	61.58
10	57.55	10	50.07
11	63.30	11	64.68
12	86.32	12	55.16
13	56.17	13	59.62
14	62.04	14	50.53
15	59.50	15	57.32
16	65.37	16	68.37
17	65.37	17	62.96
18	81.32	18	63.30
$\bar{X}$	63.12	$\bar{X}$	64.13
σ	8.73	σ	8.37
% V	13.83	% V	13.05

– Comparative curves for the kinetics of dissolution of the transdermic therapeutic system of surface area 10 cm² (Fig. 6).

– Comparative curves for the kinetics of dissolution of the transdermic therapeutic system of surface area 20 cm² (Fig. 7).

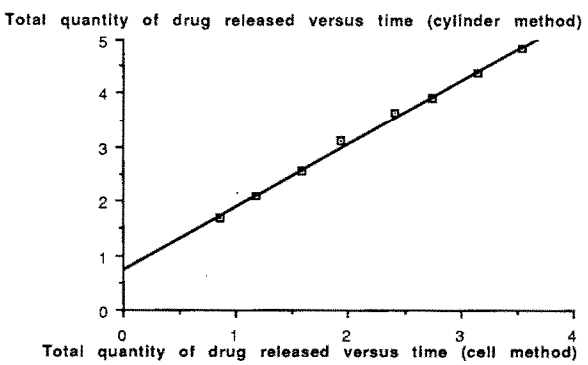

Fig. 8. Correlation between results with cells and with cylinders for the transdermic therapeutic system of surface area 10 cm². Key: Regression chosen: $1 \cdot y = ax + b$ with $a = 0.85778768$ and $b = -0.635104398$. Coefficient of correlation $r^2 = 0.996895954$.

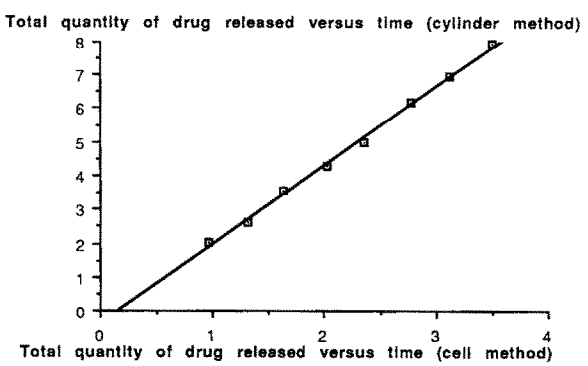

Fig. 9. Correlation between results with cells and with cylinders for the transdermic therapeutic system of surface area 20 cm². Key: Regression chosen: $1 \cdot y = ax + b$ with $a = 2.35495916$ and $b = -0.394540848$. Coefficient of correlation $r^2 = 0.997701585$.

- Correlation between results with cells and with cylinders for the transdermic therapeutic system of surface area 10 cm^2 (Fig. 8).
- Correlation between results with cells and with cylinders for the transdermic therapeutic system of surface area 20 cm^2 (Fig. 9).

Discussion

The results can be considered at several levels.

First, the results obtained with the cell described in the French Pharmacopoeia are practically identical for both systems tested (10 cm^2 and 20 cm^2) as regards percentage of drug released versus time, total quantities of drug released versus time and quantities released per cm^2. This is not unexpected since both systems have the same surface area of membrane exposed to the dissolving medium when they are held in the cell. Hence the membrane releases exactly the same amount of drug in the same time with the same kinetics (zero-order release after $t = 1$ h). A t-test applied to these values shows no difference at $P = 0.05$.

The results obtained using the cylinder method, in which the entire surface of the system is exposed to the dissolving medium, are similar as regards the proportion of drug released in a given time (zero-order release after $t = 1$ h), though the proportion released from the 10 cm^2 system is slightly higher than that released from the 20 cm^2 system in the same time. However, as might be expected, the total quantities released versus time are twice as high for the 20 cm^2 system (containing 50 mg of drug) as for the 10 cm^2 system (containing 25 mg of drug).

If the two methods are compared for each of the systems tested, we see that for the 10 cm^2 system, the quantity of drug released in $\mu g/cm^2/h$ (the best value for comparison) is not statistically different after 6 h of diffusion at $P = 0.05$, but for the 20 cm^2 system, there is a significant difference for this value at $P = 0.05$ (yet, the difference is here just within the limits).

However, for both systems, there is a linear relationship that relates the two methods of type $y = ax + b$ where for the 10 cm^2 system $a = 0.85$, and for the 20 cm^2 system $a = 2.35$ (Figs. 8, 9).

Finally, the results obtained here are close to those obtained by the supplier over the same test period with the same product batches (80 $\mu g/cm^2/h$ for the 10 cm^2 system and 73 $\mu g/cm^2/h$ for the 20 cm^2 system – extreme values 50–100 $\mu g/cm^2/h$).

The experimental conditions were slightly different, however; i.e. speed of rotation of the cylinders 50 rpm, temperature of the medium 32 °C.

Conclusion

The aim of this work was to compare the rate of release and dissolution of trinitrine from transdermic therapeutic systems using two different methods. The results show that, with these two methods, both systems yield practically the same results in terms of quantity of drug released per unit area per hour, which ensures a satisfactory quality control of the system.

Whichever method was used, the drug release is zero-order after 1 h diffusion and thereafter. The two methods are linearly correlated, results from one being obtainable from those from the other by means of an equation of type $y = ax + b$. Hence the method proposed by the supplier (the cylinder method) is hereby validated against that described in the French Pharmacopoeia.

References

French Pharmacopoeia, Xth Edn., July 1987.

Traisnel, M. and Aiache, J.-M., Les formes adhésives cutanées. Evolution de la Pharmacopée et contrôle. *Bulletin de la Société de Pharmacie de Lille, Tome 4*, 1984, pp. 57–73.

Vincent, J.-F., *Méthodes de Contrôle in Vitro des Préparations à Usage Cutané*, Doctorat Pharmacie, Clermont-Ferrand, 1985.