increased. This is a characteristic feature of polymers which are not compatible in all proportions (9), and it eventually leads to the appearance of two glass transitions when the compatibility limit is exceeded: one for the compatible phase and the other for the excess polymer additive. (Because the glass transition of PEG 1000 could not be detected, the appearance of its melting endotherm was considered as indicating incompatibility). T_g spread changed very little above the compatibility level. Incompatibility results when the solubility limit of the polymer additive in the main polymer is exceeded. Above this limit, two phases are formed: main polymer/polymer additive and polymer additive alone. Based on the concentration of the polymer additive at which a second glass transition (melting endotherm in the case of PEG 1000) was first observed, the polymer mixtures are compatible up to the following concentration of the additives: 40 wt % (PVA), 20 wt % (PEG 400) and 15 wt % (PEG 1000).

The difference between the experimental and predicted T_g data for the plasticized systems may be due, in part, to large variations in the molecular weight distributions of the polymers as has been noted by Entwistle and Rowe (16). Molecular weight variations may also explain the complex thermograms observed at plasticizer concentrations above 5 wt %.

Abbreviations and Symbols

HPMC	= Hydroxypropyl methylcellulose
PVA	= Polyvinyl alcohol
PEG	= Polyethylene glycol
X	= Main film former, i.e. HPMC
Y	= Polymer additive
C_X	= Concentration of HPMC
C_Y	= Concentration of polymer additive
$\eta(C_X, C_Y)$	= Viscosity of polymer blend
$[\eta_X]_{C_Y}$	= Intrinsic viscosity of polymer blend
$[\eta_X]$	= Intrinsic viscosity of polymer X in pure solvent
$\eta_{(C_Y)}$	= Viscosity of polymer Y in pure solvent
B	= Polymer blend
M	= Mass fraction
T_g	= Glass transition temperature
ΔC_H	= Heat capacity change at glass transition

References

(1) Kanig, J. L., Goodman, H. (1962) J. Pharm. Sci. 51, 77–83.
(2) Allen, D. J., De Marco, J. D., Kwan, K. C. (1972) J. Pharm. Sci. 61, 106–109.
(3) Krigbaum, W. R., Wall, F. T. (1950) J. Polymer Sci. 5, 505–514.
(4) Cragg, L. H., Bigelow, C. C. (1955) J. Polymer Sci. 16, 177–191.
(5) Gray, A. P. (1970) Thermochim. Acta. 1, 563–579.
(6) Fried, J. R., Karasz, F. E., MacKnight, W. J. (1978) Macromolecules 11, 150–158.
(7) Michaels, A. S., Bixler, H. J. (1961) J. Polymer Sci. 50, 413–439.
(8) Burrell, H. (1962) Official Digest 34, 131–161.
(9) Min, B. Y., Pearce, E. M. (1981) Proc., 11th North American Thermal Analysis Soc. (NATAS) Conf. New Orleans, USA, Vol. II, 557–563.
(10) Okhamafe, A. O., York, P., (1983) J. Pharm. Pharmacol. 35, 409–415.
(11) Lecourtier, J., Lafuma F., Quivoron, C. (1982) Makromol. Chem. 183, 2021–2031.
(12) Beaman, R. G., (1952) J. Polymer Sci. 9, 470–472.
(13) Droste, D. H., Dibenedetto, A. T. (1969) J. Appl. Polymer Sci. 13, 2149–2168.
(14) Couchman, P. R., (1978) Macromolecules 11, 1156–1161.
(15) Shalaby, S. W., Turi, E. A., Werner, W. M., (1978) in: Thermal methods in polymer analysis (Shalaby, S. W., ed.) 35–62, The Franklin Institue Press, Philadelphia.
(16) Entwistle, C. A., Rowe, R. C. (1979) J. Pharm. Pharmacol. 31, 269–272.

In Vitro and *In Vivo*-Release of Nitroglycerin From a New Transdermal Therapeutic System

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Abstract: A new transdermal therapeutic system (TTS) for nitroglycerin is presented that controls release of the active substance by means of desorption and diffusion. The drug release, in the dosage range examined under sink conditions, is independent of electrolytes and pH of the aqueous acceptor medium, but it does depend on its temperature as expected. Batches obtained on a production scale were highly reproducible. The validity of an *"in vitro"* dissolution model is demonstrated by the good correlation between the amount of nitroglycerin liberated *"in vitro"* and *"in vivo"*. The amount of nitroglycerin released *in vivo* is approximately 10 µg/cm²/h from 4 hours after application, and, it is controlled by the system. The plasma concentration reaches a maximum of 255 ± 151 pg/ml at 2 hours after drug application followed by a plateau level of 125 ± 50 pg/ml which is maintained between 8 and 24 hours after application. In a crossover study with a reference product characterized by the same release rate *in vivo* of 5 mg/24 h, both transdermal therapeutic systems proved to be bioequivalent.

Transdermal Therapeutic Systems (TTS) combine the principle of percutaneous application of drugs in order to avoid the first-pass effect after oral administration with the attainment of active drug levels sustained for 24 h or more (1). In order to control the absorption of the active substance, the release of active substance from the TTS should be the rate limiting step of the *in vivo* release. If the transdermal absorption rate is too

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slow to ensure a therapeutic effect from a TTS of acceptable size, vehicles that promote absorption or in special cases dilate the vessels can be applied (per)cutaneously together with the drug. However, if there is insufficient release control by the preparation, individual fluctuations in skin permeability can lead to different drug levels in the body. Whether this variability is acceptable depends on the therapeutic range of the drug (2). The only advantage of a TTS may lie in the attainment of longer lasting active substance levels compared with other topical formulations such as ointments, and the question arises whether such systems can rightly be called "TTS".

True Transdermal Therapeutic Systems regulate the release of an active substance independently of inter- and intraindividual fluctuations in skin permeability. For such systems the rate of release of the drug per unit time over a defined period is the sole important parameter. This parameter is more relevant to the therapeutic application than the total content of pharmaceutical substances in the TTS, which are often present in excess.

The focal point of the present study was to investigate the *in vitro/in vivo*-correlation of the release of the active substance and the batch-to-batch reproducibility on the industrial production scale of a new product intended for the controlled transdermal application of nitroglycerin (NG) (tradename: Deponit®). Nitroglycerin is particularly suitable for transdermal application because of its physico-chemical properties, its high first-pass metabolism after oral administration and its short biological half-life.

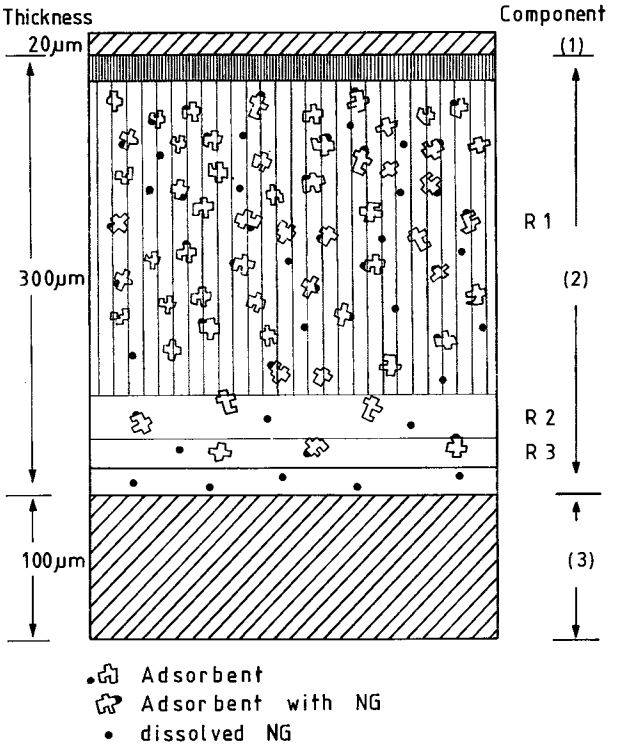

Fig. 1 Cross section through Deponit®.

Material and Methods

Galenical Structure of Deponit® TTS

Deponit® TTS consists of three main components (Fig. 1):
1. A flexible carrier foil about 20 µm thick, impermeable to nitroglycerin,
2. an adhesive film charged with nitroglycerin, approximately 350 µm thick, that constitutes simultaneously the drug reservoir and the release-control system,
3. a protective foil approximately 100 µm thick that is impermeable to nitroglycerin and can be peeled off before use.

Component 2 is characterized by:
a) its content of lactose as a hydrophilic constituent in a skin-compatible, water-insoluble, adhesive mass of a polyisobutylene/resin base with adsorbed and dissolved nitroglycerin,
b) a nitroglycerin-lactose-concentration gradient that rises in stages towards the carrier foil (1), as a result of which the cross section of the adhesive film can be divided into different drug-dispersion or reservoir zones (R 1 to R 3, Fig. 1). The image of the TTS cross-section obtained with a scanning electron microscope (Fig. 2) does not show any particular structural elements such as cavities or micropores, but the lactose crystals suspended in the adhesive film, which serve to absorb the drug, are clearly visible.

The concentration gradient between the adhesive film and the site of application, which is necessary for continuous transport of the active substance and controlled release, is obtained by release of nitroglycerin from the reservoir layers by means of desorption and diffusion.

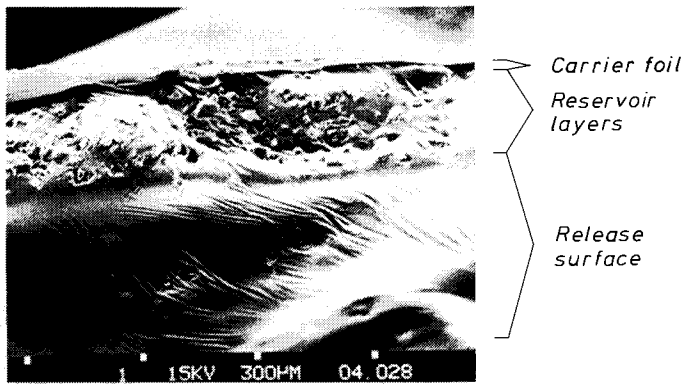

Fig. 2 SEM image of Deponit® TTS. Plan view 100×.

Determination of in vitro-Drug-Release

The release of nitroglycerin was determined using the apparatus described in NF XIII (3), with 80 ml isotonic sodium chloride solution as an acceptor medium for a TTS with a release area of 16 cm^2. After each sample withdrawal – as a rule after 2, 4, 6, 8 and 24 h – the acceptor medium was replaced to preserve sink conditions. In this method the TTS is placed with the acceptor medium in tightly closed, cylindrical glass vessels rotating at a speed of 10 r.p.m. perpendicular to their longitudinal axes in a thermostated water-bath of 37°C. Preliminary experiments showed that the hydrodynamics, i.e. the mechanical movement of the release medium, has practically no influence on the rate of liberation and that the nitroglycerin fraction diffusing from the open edges of the films into the acceptor medium is approximately 0.53 mg/16 cm^2/24 h at 37° C. The quantity of nitroglycerin released from the TTS was determined by HPLC (18) with the following modifications: eluent: 50 vol-% methanol/water, detection wave-

length: 220 nm. Suppliers of the equipment and chemicals were: HPLC system from Du Pont, Bad Nauheim, consisting of a pump, column oven, an SP 4100 integrator, a spectrophotometer, and an automatic sample dispenser.

The solvent (Lichrosolv) and reagents (analytical grade) were from Merck, Darmstadt. Separation column was a Zorbax ODS (length = 25 cm, diam. = 4.6 mm, Du Pont). The relative standard deviation of the method was 1.3 % (n = 10 × 3 injections).

Determination of in vivo-Drug-Release

The determination of the quantity of nitroglycerin released from the TTS into human skin was based on the "difference method" (4), i.e. the difference is determined between the total content of drug in the TTS before and after application of the TTS (samples from the same batch) on the skin of volunteers for 24 h. The nitroglycerin is determined by HPLC after shaking the nitroglycerin-containing adhesive film with 100.00 ml of a 15 vol-% solution of 2-propanol in hexane (extraction agent) until the polymeric constituents are completely dissolved. After filtering off the components that are insoluble in the extraction agent (lactose, carrier foil), 20 µl of undiluted solution are injected three times into the high-pressure liquid chromatograph.

The HPLC-conditions were:

Separation column:	Zorbax SIL (length = 25 cm, diam. 4.6 mm, ex Du Pont)
Eluent:	15 vol-% 2-propanol in hexane
Flow rate:	1 ml/min
Quantity injected:	20 µl
Detection wavelength:	220 nm.

The quantitative evaluation was performed against a standard solution of nitroglycerin prepared from a 1 % ethanolic nitroglycerin solution (Merck) by dilution with the extraction agent (= eluent). The relative standard deviation of the method was 0.47 % (n = 10 × 3 injections). The nitroglycerin content in the system can vary with a standard deviation of ± 6 % with maximal variations of 10 % and more. This is not correlated to the standard deviation of the *in vitro* release rate, which is smaller, but must be taken in mind when evaluating the *in vivo* release value obtained by the difference-method. A variation of 10 % = 1.6 mg nitroglycerin per patch leads to an experimental error of 32 % related to a release rate of 5 mg nitroglycerin.

In the experiments in humans the TTS was applied to a dry, clean region of chest-, abdominal- or upper-arm-skin with minimal hair covering. After the scheduled period of application the films could be removed from the skin leaving scarcely any residues.

Pharmacokinetics

The plasma concentration-time curves of nitroglycerin were determined after application of Deponit® to investigate the bio-equivalence, in comparison with a reference product with the same declared *in vivo* release of 5 mg/24 h, but which has a contact area of 10 cm^2 (System C, Table V). The pharmacokinetic study was carried out with six healthy male volunteers who had given their written consent to participate in the study after receiving an explanation as to the purpose and content thereof and regarding possible side effects and risks involved in the use of the active substance.

The average age of the volunteers was 37.8 ± 5.2 (32–44) years and their average weight 77.2 ± 8.2 (71–93) kg. Using the open, randomized, crossover mode, the test product and the reference product (system C) were applied to the left upper quadrant of the chest. The two test periods were separated by a wash-out phase of at least 3 days. Before application and 0.5, 1, 2, 8 and 24 h thereafter a sample of venous blood was withdrawn fom the volunteers. The nitroglycerin concentrations in the plasma were determined by capillary gas chromatography using the method of Kühn et. al. (5).

For determination of the actual drug quantities released by the system, the TTS were removed 24 h after application and the residual, non-absorbed fraction was analyzed by HPLC.

Results

Release of Nitroglycerin in vitro

Fig. 3 shows the *in vitro* drug-release from Deponit® TTS over 24 h at a temperature of 34° C with an application area of 16 cm^2. Within 24 h, 5 mg nitroglycerin were released, which is equivalent to 0.31 mg/cm^2. Within the first hour 0.84 mg of this amount was released, corresponding to 52.5 µg/cm^2/h.

System C shows a similar release profile *in vitro* (Fig. 4). This liberation behavior distinguishes the two test systems from simple nitroglycerin containing adhesive strips which

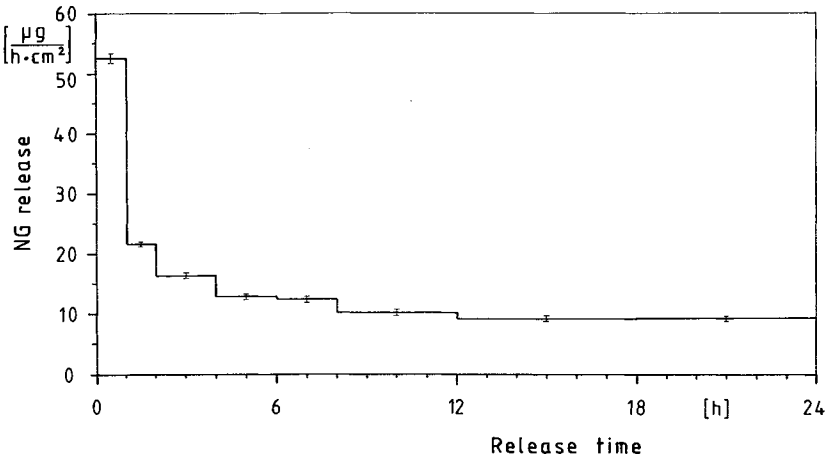

Fig. 3 Release of nitroglycerin from Deponit® TTS (differential). Mean values ± S.D. (n = 4), 34°C.

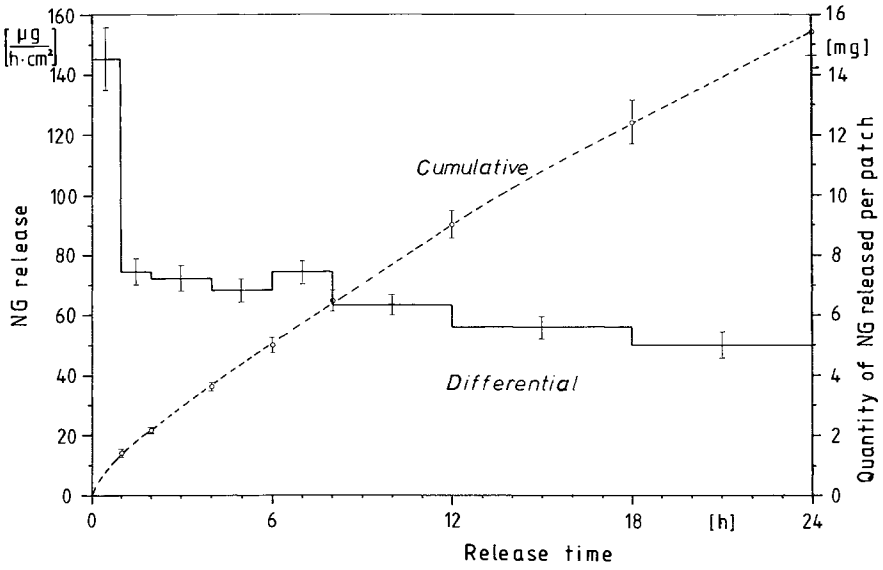

Fig. 4 Release of nitroglycerin from System C.

release the drug considerably more rapidly under comparable conditions (6) and show only a limited control function.

Influence of temperature. The influence of temperature on nitroglycerin release *in vitro* was determined at four different temperatures using Deponit® systems of 20 cm^2 in size manufactured on a laboratory scale. As expected, the liberation rate (Q) increases as the temperature (T) rises and the log rate Q/t is linearly correlated with 1/T (T = time) (Fig. 5). Thus, between, 32 and 37° C a change in the flow rate by approximately 1–2 $\mu g/cm^2/h/°C$ is to be expected.

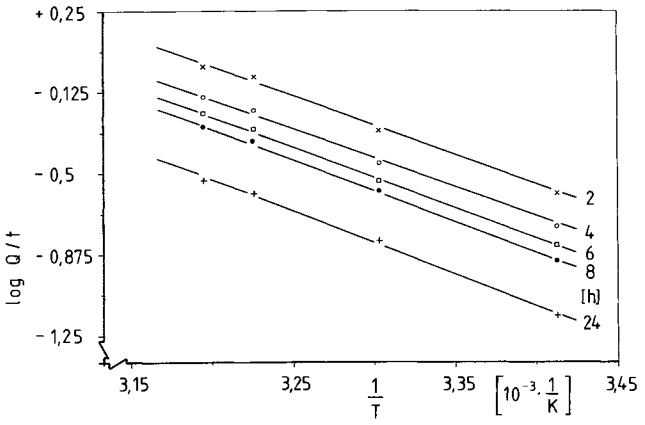

Fig. 5 Influence of temperature on nitroglycerin-release.

Influence of pH and electrolytes. The release of nitroglycerin was investigated in phosphate buffer (pH 5 to 7), in water and in isotonic sodium chloride solution. When sink conditions were maintained, changing the acceptor medium had virtually no effect on the rate of liberation (Fig. 6).

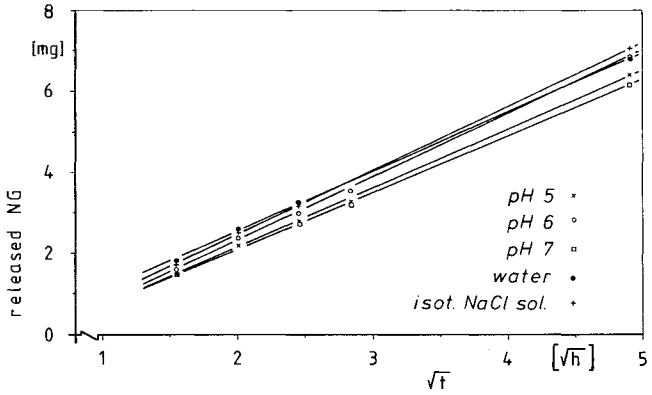

Fig. 6 Influence of pH and elektrolytes on nitroglycerin-release.

This result confirms that the release is essentially determined by the diffusion behavior of the drug in the adhesive matrix (7). The linear regression parameters determined on the assumption of a linear correlation between Q and the square root of time are presented in Table I.

Table I. Release of nitroglycerin from Deponit® in aqueous acceptor media

Acceptor medium (37°C)	Gradient $mg \cdot h^{-1/2}$
Phosphate buffer pH 5	1.42
Phosphate buffer pH 6	1.53
Phosphate buffer pH 7	1.35
Water	1.43
Isotonic NaCl solution	1.55

Batch-to-batch reproducibility. Table II shows the mean values and scatter of the release data within one batch (n = 5) in comparison with the results obtained with 10 production batches of the product Deponit®. The comparison of the cumulatively released quantities of nitroglycerin show good inter- and intra-batch reproducibility.

Table II. Cumulative release of nitroglycerin ($\bar{x} \pm$ S.D., n = 5) from one batch of Deponit® (A) in comparison with the corresponding means of 10 production batches (B) at 37°C

Time (h)	A $\bar{x} \pm$ S. D. (mg)	B $\bar{x} \pm$ S.D. (mg)
2	1.57 ± 0.06	1.71 ± 0.1
4	2.39 ± 0.10	2.57 ± 0.15
6	3.07 ± 0.15	3.24 ± 0.2
8	3.72 ± 0.20	3.87 ± 0.28
24	7.4 ± 0.35	7.2 ± 0.37

Release of Nitroglycerin in vivo

In a volunteer study (n = 17), determination of the cutaneous absorption of the active substance 24 h after application of Deponit® to the side of the chest yielded the individual results shown in Table III. On average a release of 4.52 mg nitroglycerin in 24 h was found. The relatively small scatter of 0.8 mg (S.D.) is indicative of good reproducibility of the cutaneously absorbed quantities of nitroglycerin, if one considers the assay-related scatter of the difference test.

Table III. Cutaneous absorption of nitroglycerin after 24 h of application of Deponit® to the side of the chest of volunteers

Volunteer No.	Nitroglycerin released (mg/24 h)
1	5.39
2	5.29
3	3.81
4	5.02
5	5.37
6	3.70
7	3.91
8	4.97
9	3.79
10	4.49
11	4.86
12	5.08
13	6.06
14	3.41
15	3.42
16	4.02
17	4.20
Mean ± S.D.	4.52 ± 0.8

Since Deponit® TTS releases nitroglycerin over the whole area in contact with the skin and its structure and composition do not vary over its area, there is a linear correlation between the size of the TTS and the dose released. To confirm this *in vivo*, three systems of different sizes (8, 16 and 32 cm^2) were studied to determine their respective release rates. The *in vivo* release rates of the TTS are presented in Fig. 7. Because of this characteristic of the system it is also possible to divide one TTS if smaller dosages are clinically required, e.g. in order to reduce headache in the beginning of treatment.

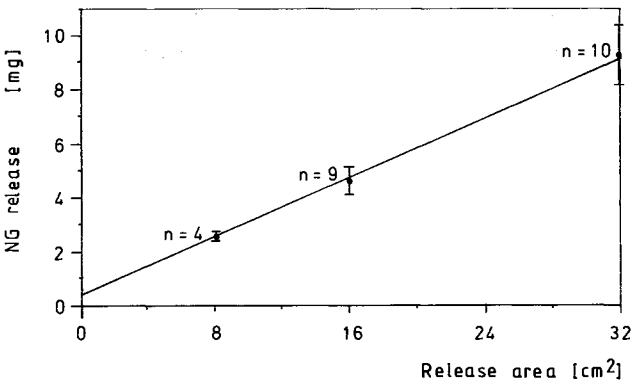

Fig. 7 *In vivo* nitroglycerin release (24 h) versus release area of Deponit® TTS.

Pharmacokinetics

The individual plasma level curves after application of Deponit® are shown in Fig. 8, and the mean plasma concentra-

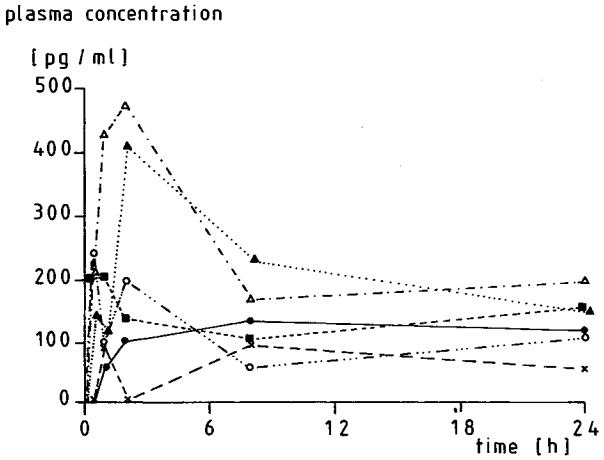

Fig. 8 Plasma concentration-time curves for nitroglycerin after application of Deponit® to 6 volunteers.

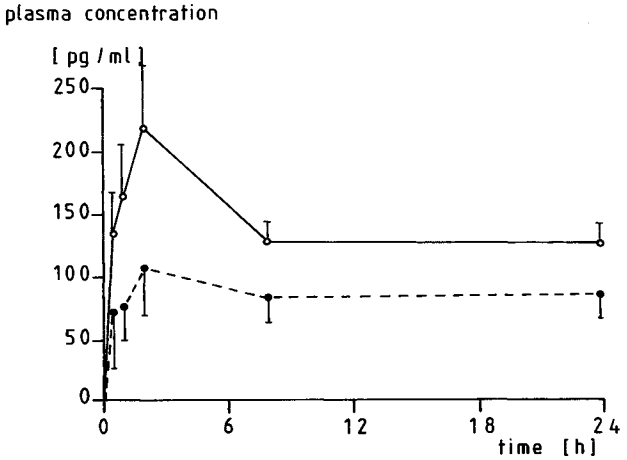

Fig. 9 Mean nitroglycerin plasma concentrations (n = 6) after application of Deponit® (——) and a reference product (---).

tion curves for the test and reference preparation are shown in Fig. 9. Model-independent pharmacokinetic parameters following administration of the test preparation are summarized in Table IV. At t_{max} = 3.6 ± 3.5 h (median 2 h) the plasma concentrations reach a maximum of c_{max} = 255 ± 151 pg/ml. A plateau value of 125 ± 50 pg/ml is maintained from 8 until 24 h after application. The TTS released 5.0 ± 0.7 mg of nitroglycerin during the exposure period. The total body clearance

$$Cl_{tot} = \frac{dose}{AUC}$$

was calculated on the assumption that the quantity released from the TTS is completely absorbed by the body.

Table IV. Pharmacokinetic parameters of nitroglycerin after transdermal application in Deponit®

C_{max} (pg/ml^{-1})	T_{max} (h)	AUC ($ng \cdot h \cdot ml^{-1}$)	Dose ($mg\ d^{-1}$)	CL_{tot} ($l\ min^{-1}$)
255 ± 151	3.6 ± 3.5	3.3 ± 1.6	5.0 ± 0.7	31 ± 19

C_{max} = Maximum plasma concentration
T_{max} = Time of C_{max}
AUC = Area under the plasma concentration-time curve
CL_{tot} = Total body clearance

Discussion

Correlation Between in vitro/in vivo Release

Fig. 10 shows the *in vitro*- and *in vivo*-release from Deponit®, with the *in vitro* determination performed at a temperature of 34° C, which approximates the average skin temperature during occlusion.

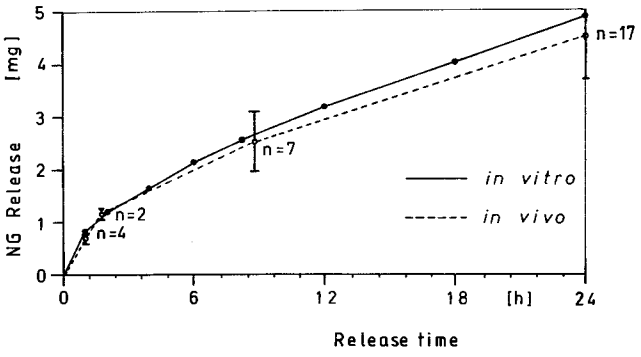

Fig. 10 Release of nitroglycerin from Deponit® TTS *in vitro* (34°C, n = 4) and *in vivo*. $\bar{x}$ ± S.D.

The mean values (± S.D.) of the *in vivo* release of nitroglycerin after 1, 1.75, 8.5 and 24 h were 0.69 (± 0.10), 1.18, 2.55 (± 0.57) and 4.5 (± 0.8) mg. The graph illustrates the good agreement between the *in vitro*- and *in vivo*-release over 24 h and confirms the informative value of the *in vitro* model.

Comparison of Application Systems

Currently there are four different nitroglycerin transdermal systems on the market. The relevant product specifications for these systems are shown in Table V. The *in vivo* release over a period of 24 h is approximately 5 mg nitroglycerin for all

Table V. Comparison of nitroglycerin release from different transdermal systems

Product specification	Product System A	System B	System C	Deponit® TTS
Release surface (cm^2)	8	10	10	16
Nitroglycerin content (mg)	16	51	25	16
Nitroglycerin release *in vivo* (mg/24 h)	5	5	5	5
Nitroglycerin release* *in vitro* at 37°C (mg/24 h)	14.2	43.7	13.0	7.1
Literature value** (8)	15.7 ± 0.02	40.9 ± 0.1	8.6 ± 0.35	

* Mean value (n = 3); the determination, based on (8), was peformed in a diffusion cell, with isotonic NaCl solution as receptor medium (100 ml) and change of the medium after 2, 4, 6, 8 and 24 h.
** Mean value ± S.D. (n = 4).

systems, while considerable differences exist in the *in vitro* release.

In system A the drug is distributed between microscopically small liquid compartments and a cross-linked silicone matrix (MDDS = Microsealed Drug Delivery System). System B consists of a hydrophilic gel matrix in which a drug/lactose trituration is homogenously dispersed (matrix system). In system C there is a microporous, release-controlling membrane provided with a thin adhesive layer between a suspension-like drug reservoir and the skin contact surface.

The data in Table V suggest that nitroglycerin uptake from systems A to C is primarily regulated by the skin. The thermodynamic activity of nitroglycerin provided by the systems leads to an *in vivo* release rate of approximately 21 µg/cm^2/h (equivalent to the mean *in vivo* release rate of 5 mg/24 h specified by the manufacturer). This value is comparable to the literature value (8, 9) for the *in vitro* permeation of skin by nitroglycerin of approximately 20 µg/cm^2/h.

The product Deponit® TTS achieves the same *in vivo* value of 5 mg nitroglycerin released in 24 h over its larger contact surface of 16 cm^2, so that after the first few hours the release rate is less than the rate of skin permeation for nitroglycerin, which suggests that the drug uptake is primarily controlled by the system (Fig. 11). This is consistent with the good correlation between nitroglycerin release from this preparation into aqueous solutions and into skin.

Pharmacokinetics

After transdermal application of nitroglycerin in a depot system the active substance rapidly reached the plasma: 30 to 60 min after application plasma concentrations are observed that correspond to the steady-state value. The relatively high initial flux rate of 52.5 µg cm^{-2} h^{-1} gives rise at the start of the dose-metering process to average peak values of 250 (90–470) pg/ml. Between the 8th and the 24th h after application a plasma level plateau of 125 ± 50 pg/ml is achieved.

Although the dose released by the TTS shows only a small range of variation (Tables II and III), the areas under the plasma concentration-time curves (AUC) have a variation coefficient of ± 47 %. The main reason for these strong fluctuations may be found in the large distribution volume of nitroglycerin of 3 l/kg. Consequently less than 1.5 % of the amount present in the body is localized in the plasma compartment (10, 11). Small fluctuations in the distribution in the

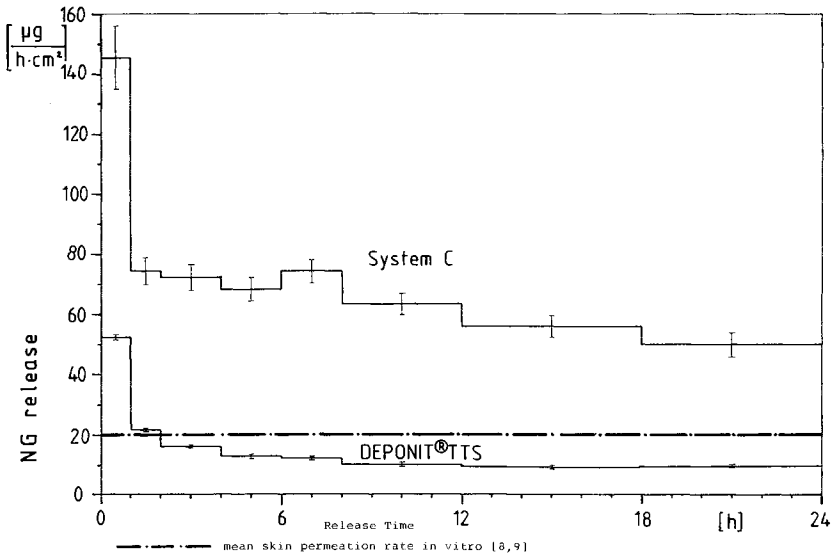

Fig. 11 Release of nitroglycerin from Deponit® TTS in comparison with system C (membrane type) and the mean dermal absorption rate.

peripheral compartment thus produce large fluctuations in the plasma level.

Similar findings have also been reported by other authors after transdermal application of ointment (12, 13) or TTS (14, 15) and even after intravenous infusion (16, 17).

The mean AUC (3.3 ± 1.6 ng·h·ml^{-1}) is in good agreement with corresponding literature data for the reference product used (3.6 ± 1.4 ng·h·ml^{-1}) (14). In the comparison study described here an AUC of 2.1 ± 1.7 ng·h·ml^{-1} was measured for this reference system, a value that did not differ from that of the test preparation either according to the paired t-test or according to Wilcoxon's sign rank test.

The dose-linearity of the plasma concentrations had been demonstrated by Jähnchen et al. (19) in 8 healthy volunteers treated simultaneously with two Deponit® systems for 8 h. Within this period of 1 to 8 h after application mean plasma concentrations between 200 and 270 pg/ml were determined, which correspond to twice the plateau level after application of one system.

References

(1) Shaw, J. E. (1980) Annual Reports in Medical Chemistry 15, 302–315.
(2) Fankhauser, P., Imhof, P., Shaw, J. E. (1982) Therap. Umschau 39, 857–867.
(3) American Pharmaceutical Association, National Formulary 13th Edition (NF XII), Washington (1979) 882.
(4) Stricker, H., Leber, A. (1983) Acta Pharm. Technol. 29, 265–273.
(5) Kühn, R., Luckow, V., Keppeler, D. (1984) Fresenius Z. Anal. Chem. 317, 668–669.
(6) Nippon Kayaku, K. K., Taiho Pharmaceutical Co. Ltd., Nichiban Co. Ltd., DE OS 3111734A1, A 61 K31/21, pp. 21 (1982).
(7) Kehne, K., Vogt, H., Merkle, H. P. (1981) Acta Pharm. Technol. 27, 17–31.
(8) Chien, Y. W., Keshary, P. R., Huang, Y. C., Sarpotdar, P. P. (1983) J. Pharm. Sci. 72, 968–970.
(9) Good, W. R. (1983) Drug Development and Industrial Pharmacy 9, 647–670.
(10) Jacobi, A., Amann, A. M., Baaske, D. M. (1983) Drug Intell. Clin. Pharm. 17, 255.
(11) Fung, H.-L. (1983) Am. J. Med. 74, 13–20.
(12) Armstrong, P. W., Armstrong, J. A., Marks, G. S., Phil, D. (1980) Nouv. Pr. Med. 9, 2429–2432.
(13) Gielsdorf, W., Schlegel, E., Settlage, J. A., Jaeger, H., Fink E. (1983) Arzneim.-Forsch/Drug Res. 33, 1677–1679.
(14) Müller, P., Imhof, P. R., Burkart F., Chu, L.-C., Gérardin, A. (1982) Eur. J. Clin. Pharmacol. 22, 473–480.
(15) Karim, A. (1983) Angiology 34, 11–22.
(16) Imhof, P. R., Sieber, A., Hodler, J., Müller, P., Ott, B., Fankhauser, P., Chu, L.-C., Gérardin, A. (1982) Eur. J. Clin. Pharmacol. 23, 99–106.
(17) Armstrong, P. W., Armstrong, J. A., Marks, G. S. (1980) Am. J. Cardiol. 46, 670–676.
(18) Crouthamel, W. G., Dorsch, B. (1979) J. Pharm. Sci. 68, 237–238.
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