Percutaneous Absorption of 1,3-Dinitroglycerin and a Trial of Pharmacokinetic Analysis

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In order to estimate the pharmaceutical usefulness of 1,3-glycerol dinitrate (1,3-GDN), an active metabolite of nitroglycerin, a trial transdermal delivery system designed to sustain a suitable plasma concentration of 1,3-GDN was produced using a porous membrane (Hipore 2100 or 4500) and it was a gel base or ethylhexyl acrylate-based adhesive (adhesive) and was applied to rats. Additionally, for practical use of the transdermal system, a simple pharmacokinetic model to describe plasma 1,3-GDN levels after percutaneous (p.c.) application is presented.

As a result, the drug was penetrated through the rat skin in vitro at a zero-order rate, although the penetration rate from the gel base was significantly greater than that from the adhesive. In vivo, the drug was rapidly absorbed through the rat skin, with a peak plasma level of 581 ± 151 and 265 ± 62 ng/ml for the gel ointment and adhesive systems without a porous membrane, respectively. The plasma levels after application of the systems with a membrane were relatively constant for a long time, indicating that the membranes act as a controlled-release barrier. The bioavailability of 1,3-GDN after gel base systems with and without a membrane was relatively high. The model presented was successfully able to describe the time course of plasma 1,3-GDN concentrations following p.c. application of the systems.

Keywords 1,3-dinitroglycerin; transdermal delivery system; percutaneous absorption; gel ointment system; adhesive system; sustained plasma level; pharmacokinetic model; rat

Nitroglycerin is a drug effective in angina pectoris. Several types of the pharmaceutical dosage forms, such as tablets, sublingual tablets, topical ointments and intravenous fluid, are available commercially. The usual dosage form is a sublingual tablet, which has the disadvantage of a short duration (10—30 min) of action, due to the inherently rapid elimination (half-life = 1.3—4.4 min) of nitroglycerin.11 Additionally, transdermal nitroglycerin delivery systems have been developed for transdermal-controlled administration of the drug over a 24 h period.

The dinitrate metabolites of nitroglycerin, 1,2- and 1,3-glycerol dinitrate (1,2- and 1,3-GDN), have been shown to be active and to be approximately 2 to 10% of the activity of the parent drug.23) On the other hand, the elimination half-life for the dinitrate metabolites are approximately twentyfold longer than that found for the parent drug.44 Therefore, there is a possibility that the active metabolites may be available as transdermal delivery systems exerting a more prolonged effect.

The present studies were undertaken to estimate the absorbability of 1,3-GDN via skin and the disposition after an intravenous (i.v.) injection. In addition, in order to investigate the pharmaceutical usefulness of 1,3-GDN, a transdermal therapeutic system was prepared and the plasma concentrations were measured after percutaneous (p.c.) application of the system to the rat abdomen. For practical use of the system, a simple pharmacokinetic model to describe plasma 1,3-GDN levels after p.c. application is proposed.

Materials and Methods

Materials 1) Reagent: 1,3-GDN and a mixture of 1,2- and 1,3-GDN, trinitroglycerin (GTN) and glycerol mononitrate, produced by the partial nitration of glycerin, were generous gifts of Nipponkayaku Co., Ltd. Hiviswako 104, a gel base, and ethylhexyl acrylate suspension (7927/8) were obtained from Wako Junyaku Co. and Rōhm Pharma, respectively. Isosorbide dinitrate, an internal standard for high-performance liquid chromatography (HPLC), was obtained from Banyu Seiyaku Co. Microporous membranes, made of polyolefin, Hipore 2100 (mean pore size: 0.23 μm, thickness: 100 μm) and Hipore 4050 (mean pore size: 0.30 μm, thickness: 50 μm) were generous gifts of Asahi Kasei Co. Other chemicals and solvents used were of reagent grade or HPLC quality. 2) Animals: Male Wistar rats, weighing 220—300 g, were used throughout this experiment. The animals had free access to a MF diet (Oriental Yeast Co.) for 3—4 d prior to the experiment.

Purification of 1,3-GDN A mixture of glycerol nitrates was applied on the LiChroprep Si 60 column (310.25, 40—63 μm, Merck) and 1,3-GDN was eluted with benzene-ethylacetate mixture (4:1, v/v). The 1,3-GDN was monitored by ultraviolet (UV) absorption at 254 nm. The fractions of 1,3-GDN were concentrated under reduced pressure.

Preparation of Ointment, Adhesive and Their Transdermal Systems 1,3-GDN was dissolved in an ethanol and propylene glycol mixture and then mixed with an ointment base (Hiviswako 104) containing water. For an adhesive, ethylhexyl acrylate suspension was heated at 140°C for 30 min and after cooling 1,3-GDN was gently mixed with the ethylhexyl acrylate-based adhesive (adhesive). Details of the preparations are listed in Table 1. The transdermal system with or without a microporous membrane, having 0.12 g of the ointment (1,3-GDN 2.4 mg) or adhesive (1,3-GDN 4.8 mg) and 1 cm² of an absorption area as depicted in Fig. 1, was prepared.

I.v. Administration On the day before the experiment, the rat jugular vein was cannulated with silicon tubing.56 On the next day, 1,3-GDN dissolved in saline was administered intravenously at a 300 μg/kg dose. After administration, blood samples were withdrawn from the cannulated jugular vein periodically into a heparinized syringe.

Table 1. Composition of 1,3-GDN Ointments

| Rp. 1 | Hiviswako 104 | 1.0 g |
|       | Propylene glycol | 20.0 g |
|       | Ethanol | 30.0 g |
|       | Diisopropylamine | 1.1 g |
|       | 1,3-GDN | 2.0 g |
|       | Purified water | 100.0 g |
| Rp. 2 | Ethylhexyl acrylate-based adhesive | 96.0 g |
|       | 1,3-GDN | 4.0 g |

Fig. 1. Diagrammatic Illustration of Transdermal 1,3-GDN Delivery System
In Vitro p.c. Absorption Experiment On the day before the experiment, the hair of the abdominal area of the rats was removed with an electric clipper and an electric razor. On the next day, pieces (3 x 3 cm area) of full-thickness abdominal skin were excised from the rats. The adherent fat and other visceral debris were removed from the skin surface. The dermal side of the skin was soaked in a buffer solution (0.9% NaCl—10 mM phosphate buffer, pH 7.41 for 14 h at 37°C, 0.1 g of ointment (1,3-GDN: 2 mg) or adhesive (1,3-GDN: 4 mg) was uniformly spread over the stratum corneum surface of the skin, which was immersed in a Franz diffusion cell (reservoir volume 13.0 ml, a 1.0 cm i.d. O-ring flange), and occluded with a sheet of aluminum foil. The incubation was carried out at 37°C. Aliquots (50 μl) of the receptor fluid were withdrawn periodically for 10 h and stored frozen until assay.

In Vivo p.c. Absorption Experiment On the day before the experiment, the rat jugular vein was cannulated with silicon tubing5-8 and the hair of the abdominal area was carefully removed with an electric clipper. On the next day, the transdermal system was applied to the rat abdomen. The system was fixed with an adhesive tape for 48 h. Blood samples (0.2 ml) from the cannulated jugular vein were collected periodically for 48 h after dosing. The plasma was separated immediately by centrifugation and stored frozen until assay.

Determination of 1,3-GDN All glassware used were previously silanized with a 5% hexamethyldisilazane in benzene to prevent adsorption. 1,3-GDN in plasma samples was determined by the HPLC method of Baaske et al.3) with slight modification. A 100 μl aliquot of plasma was mixed with 50 μl of the internal standard solution (10 μg/ml) and 100 μl of saline, and then 1,3-GDN was extracted with ether (2 ml each) twice. Following centrifugation, the combined upper fluid was concentrated and the residue was dissolved in the mobile phase (acetoni-trile: tetra-hydrofuran: water, 20:10:70, v/v). The solution was filtered through a membrane filter (0.45 μm, Chromatodisc 4N, Biofe ld Co.) The filtrate was injected into a reversed-phase LichroCART RP-8 column (7 μm, 4 mm x 25 cm, Cica-Merck, Tokyo) using a Shimadzu liquid chromatograph (model LC-6A) equipped with a UV spectrophotometer (model SPD-6AV).

Analysis of Data The in vitro percutaneous parameters were calculated from the penetration data by using the following equations8):  
\[ D = \frac{\delta^2}{6\pi} \] 
\[ J_s = \frac{D}{\delta^2} \frac{K_m \cdot C_s}{C_i} \]
where \( J_s \) is the penetration rate, \( K_m \) is the skin/vehicle partition coefficient of drug, \( D \) is the diffusion constant within the skin, \( \delta \) is the lag time and \( \delta \) is the thickness (0.071 ± 0.004 cm) of skin, \( K_p \) is the permeability coefficient through the skin, and \( C_i \) is the drug concentration in the ointment or adhesive.

Kinetic parameters were calculated by using the least-squares fit program MULTII.9) The plasma concentration data after i.v. administration were fitted to the equation:  
\[ C_t = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \]
where \( C_t \) is the drug concentration at time, \( t \) and \( A, \alpha, B, \) and \( \beta \) are the biexponential equation constants. The half-life (1/2) of the terminal phase was calculated as \( t_{1/2} = 0.693/\beta \). The area under the plasma concentration-time curve (AUC) after i.v. administration was calculated by the following equation:  
\[ AUC = \frac{A \cdot (\alpha + B) \beta}{\alpha \cdot (\alpha + B)} \]

The area under the first moment curve (AUMC) and the mean residence time (MRT) were calculated by means of the following equations:
\[ AUMC = \frac{A \cdot (\alpha^2 + B) \beta + \alpha}{\alpha \cdot (\alpha + B) \beta + \alpha} \]
\[ MRT = \frac{AUMC}{AUC} \]

The total clearance (CLt) and apparent volume of distribution (Vd) at a steady state were estimated according to the following equations:
\[ CL_{tot} = \frac{X_0}{AUC} \]
\[ Vd_{app} = \frac{X_0 \cdot MRT}{AUC} \]

where \( X_0 \) is the dose.

The AUC0-48 after p.c. administration was determined by the trapezoidal method. The absolute bioavailability was calculated by the following equation:

\[ \text{bioavailability} = \frac{\text{AUC}_{p.c.} \cdot X_{0, p.c.}}{\text{AUC}_{p.c.} \cdot X_{0, p.c.}} \times 100 \]

To analyze the plasma 1,3-GDN concentration after a single p.c. dosing, the data were fitted to the model (flip-flop model) including a first-order absorption process and the parameters were determined by the simulation:

\[ C_t = F \cdot X_0 \cdot \frac{K_s}{V_d (k_e - k_s)} \left( e^{-k_s t} - e^{-k_e t} \right) \]

where \( k_s \) is the apparent absorption rate constant, \( k_e \) is the elimination rate constant and \( F \) is the fraction of drug absorbed.

The time \( t_{max} \) needed to reach the peak plasma concentration was calculated by the following equation:

\[ t_{max} = \frac{1}{(k_e - k_s) \cdot k_s} \]

The means of all data are presented with their standard deviation (mean ± S.D.). Statistical analysis was performed by using the non-paired Student’s t-test, and a p value of 0.05 or less was considered to be significant.

Results

Plasma Concentration of 1,3-GDN after Single i.v. Administration The plasma concentration-time curve for 1,3-GDN after a single i.v. administration (300 μg/kg) is shown in Fig. 2. The plasma decay curve after dosing showed biexponential kinetics, as shown for nitroglycerin.30) Pharmacokinetic parameters calculated by using the two-compartment open model are listed in Table II. The half-

Fig. 2. Plasma Concentration of 1,3-GDN after a Single i.v. Administration

Each point represents the mean ± S.D. (n = 4). The dose was 300 μg/kg.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (ng/ml)</td>
<td>250 ± 47</td>
</tr>
<tr>
<td>α (h−1)</td>
<td>21.78 ± 9.96</td>
</tr>
<tr>
<td>B (ng/ml)</td>
<td>247 ± 79</td>
</tr>
<tr>
<td>β (h−1)</td>
<td>2.59 ± 0.83</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>0.293 ± 0.007</td>
</tr>
<tr>
<td>Vd (l/kg)</td>
<td>0.911 ± 0.116</td>
</tr>
<tr>
<td>CL (ml/kg/h)</td>
<td>0.782 ± 0.11</td>
</tr>
<tr>
<td>AUC (ng·h/ml)</td>
<td>109 ± 18</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>0.333 ± 0.095</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.D. of 4 experiments.

Table II. Pharmacokinetic Parameters after i.v. Administration of 1,3-GDN
life ($t_{1/2,p}$) of the β-phase, 17.6 min, was longer than that of nitroglycerin.

**In Vitro Percutaneous Absorption Studies** The *in vitro* p.c. absorption study was carried out to compare the penetration of the drug from both bases. The penetration profile of 1.3-GDN through the skin is shown as a function of time in Fig. 3 and the penetration parameters, being apparent parameters, calculated are shown in Table III.

The drug penetrated through the skin at a rate profile which can be described fairly well by zero-order kinetics during the first several hours. The penetration rate, $J_p$, of 1.3-GDN from the gel base (Rp. 1) was significantly greater than that from the adhesive (Rp. 2), ($p < 0.01$). The $K_p$ and $K_{p2}$ values for Rp. 1 were also much larger than those of Rp. 2. Almost all of the drug (2 mg) in the gel base penetrated through the skin in 10 h.

**In Vivo Percutaneous Absorption Studies** The plasma concentration after the topical application of the gel base transdermal systems throughout the experiment period are shown in Fig. 4A. The drug was rapidly absorbed through the rat skin. The peak plasma concentration ($C_{max}$) at 2 h was $581 ± 151$ ng/ml for the system without a release rate-controlling membrane (Hipore 2100). On the other hand, the time course of the plasma concentration of 1.3-GDN after the application of the system with the membrane was relatively constant for a long time; the

![Fig. 3. Penetration Profiles of 1.3-GDN through Rat Skin](image)

Each point represents the mean ± S.D. of 3 experiments. Applied dose was 0.1 g/0.785 cm². ●, gel ointment (Rp. 1); ○, adhesive (Rp. 2).

![Fig. 4. Plasma Concentration of 1.3-GDN after Percutaneous Application of the Systems with or without Release Rate-Controlling Membrane](image)

Each point represents the mean ± S.D. (n = 3–9). A, 2% 1.3-GDN gel ointment; B, 4% 1.3-GDN adhesive. Applied dose was 0.12 g/1 cm². ●, without and ○, with release rate-controlling membrane (HP 2100 or HP 4050).

### Table III. Apparent Percutaneous Penetration Parameters of 1.3-GDN

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gel ointment (Rp. 1)</th>
<th>Adhesive (Rp. 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{lag}$</td>
<td>1.091 ± 0.200</td>
<td>0.486 ± 0.164</td>
</tr>
<tr>
<td>$J_p$</td>
<td>401.4 ± 106.6</td>
<td>91.4 ± 8.1</td>
</tr>
<tr>
<td>$K_{p1}$</td>
<td>20.07 ± 5.33</td>
<td>4.57 ± 0.40</td>
</tr>
<tr>
<td>$K_{p2}$</td>
<td>2.161 ± 0.816</td>
<td>0.162 ± 0.047</td>
</tr>
<tr>
<td>$D_p$</td>
<td>0.787 ± 0.141</td>
<td>1.872 ± 0.650</td>
</tr>
</tbody>
</table>

a) Lag time (h). b) Penetration rate (μg/h cm²). c) Permeability coefficient (10⁻² cm/h). d) Partition coefficient (10⁻³). e) Diffusion constant (10⁻³ cm²/h).

### Table IV. Model-Independent Pharmacokinetic Parameters Following Percutaneous Administration of 1.3-GDN Systems

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gel ointment</th>
<th>Adhesive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None (n = 7)</td>
<td>+ HP 2100 (n = 9)</td>
</tr>
<tr>
<td>$k_{e}$ (h⁻¹)</td>
<td>0.0739 ± 0.0298</td>
<td>0.0251 ± 0.0170&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>10.8 ± 4.2</td>
<td>38.3 ± 18.1&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>$C_{max}$ (ng/ml)</td>
<td>9360 ± 1300</td>
<td>3910 ± 2070&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>$C_{max}$ (ng/ml)</td>
<td>581 ± 151</td>
<td>167 ± 78&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>$t_{max}$ (h)</td>
<td>3.7 ± 0.1</td>
<td>5.1 ± 2.2</td>
</tr>
<tr>
<td>$t_{max}$ (h) (calc.)</td>
<td>3.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>280.4</td>
<td>117.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> p < 0.001, <sup>b</sup> p < 0.05, <sup>c</sup> p < 0.01 and <sup>d</sup> p < 0.02, respectively, compared with none. <sup>e</sup> p < 0.001 compared with gel ointment. $k_{e}$, terminal elimination rate constant. The $t_{1/2}$ was calculated as 0.693/$k_{e}$. 

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plasma concentration range of 80—146 ng/ml was sustained for about 34 h. The pharmacokinetic parameters obtained are shown in Table IV. The plasma 1,3-GDN concentrations after the application of the adhesive transdermal systems are shown in Fig. 4B. The C_{max} after the application of the system without Hipore 4050 was 250 ng/ml. The value was much smaller than that following the gel base system. The system with Hipore 4050 also gave relatively sustained plasma levels, although the levels were slightly lower than those after the gel base system with Hipore 2100.

As shown in Table IV, the t_{1/2} values were much longer in both systems with porous membranes than in those without the membranes. The MRT values were also greater in the membrane-controlled systems than in the systems without membranes. These indicate that the membrane-controlled systems may be an efficient drug delivery system for achieving a prolonged effect. The bioavailability of 1,3-GDN after the application of the gel base systems with and without membranes was much higher than that of the equivalent adhesive system.

**Analysis of Plasma Drug Concentration Data Using the Model**

It is frequently shown that drugs requiring multicompartmental analysis after i.v. administration can be described by a one-compartment model after oral and rectal administrations. Additionally, in clinical therapeutics, pharmacokinetic analyses to model the data must be performed by a simple method. Therefore, we analyzed the plasma concentration—time profiles after p.c. application of the systems using a simple, flip-flop model. In the analysis, in order to simplify the complex process of p.c. absorption, the penetration of the drug through the stratum corneum of the skin was assumed to be first-order kinetics. Figure 5 shows the plasma concentration of 1,3-GDN after the application of the systems and fitting curves calculated according to our model. The kinetic parameters calculated are shown in Table V. The k_{e}’s were smaller in both systems with the porous membranes than in the systems without the membranes, indicating that the membranes act as a controlled-release barrier. The k_{w} was the smallest in the gel system with Hipore 2100, which has the smallest pore size. The k_{e} values were very large in all systems, these being close to the value (β) after an i.v. dosing. Thus, the flip-flop model presented would be favorable to the analysis of the plasma levels of 1,3-GDN after p.c. administration.

**Discussion**

Yap and Fung studied the pharmacokinetics of nitroglycerin in rats after intracardiac, oral and topical administrations and indicated that nitroglycerin has a half-life of ca. 4 min after intracardiac administration and showed “flip-flop” kinetics after oral administration. 1,3-GDN and 1,2-GDN are reported to accumulate to concentrations that should be pharmacologically active after topical (ointment) and sublingual administration of nitroglycerin to humans. Therefore, the dinitrate metabolites may be contributing to the overall activity of nitroglycerin. Additionally, the dinitrate metabolites are metabolized more slowly than nitroglycerin and are only poorly bound to plasma proteins. Thus, in order to estimate the potential of 1,3-GDN for a drug delivery system, we measured the kinetics of 1,3-GDN after the administration of the transdermal system.

The half-lives for 1,3-GDN following i.v. bolus dose of the nitroglycerin to man and dog are shown to be 42.6 and 68 min, respectively. Although there are no literature values for the t_{1/2} after an i.v. dosing of 1,3-GDN, the values reported were greater than that (17.6 min) observed by us. The discrepancy may be mainly due to the species differences in drug metabolism. The rapid penetration of 1,3-GDN in the in vitro experiment (Fig. 2 and Table II), as compared with the in vivo absorption, may be due to excess hydration of skin, because the skin was previously soaked in a buffer solution for 14 h at 37°C. Therefore, the parameters obtained appear to be apparent ones and so were not used for pharmacokinetic analysis in the in vivo p.c. absorption experiment.

The easy absorption of 1,3-GDN from the transdermal systems may be due to its low molecular weight and adequate lipophilicity. The relatively smaller amount of 1,3-GDN absorbed from the adhesive system than from the gel base system may be attributed to the slow release of the dinitrate from the adhesive (Table III).

The absolute bioavailability of 1,3-GDN following topical administration of the gel base systems was much higher than that of the adhesive system (Table IV). The difference in the availability is probably due to a rapid release of 1,3-GDN from the gel base.

The extremely high bioavailability (280% and 117%) after the gel base systems may be ascribed to the following reasons: The first is that 1,3-GDN accumulated most in blood vessels and then the drug would slowly release into

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**Table V. Model-Dependent Pharmacokinetic Parameters Following Percutaneous Administration of 1,3-GDN Systems**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gel ointment</th>
<th>Adhesive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None + HP 2100</td>
<td>None + HP 4050</td>
</tr>
<tr>
<td>k_e (h^{-1})</td>
<td>0.0734</td>
<td>0.0247</td>
</tr>
<tr>
<td>k_w (h^{-1})</td>
<td>0.694</td>
<td>1.167</td>
</tr>
<tr>
<td>FD/V_a (ng/ml)</td>
<td>6166</td>
<td>6506</td>
</tr>
</tbody>
</table>

The parameters were calculated using the mean plasma 1,3-GDN concentration-time data.
plasma, resulting in the apparently increased availability. Fung and coworkers have shown that nitroglycerin accumulates most in rat blood segments closest to the site of i.v. infusion.\textsuperscript{15} In addition, as the infusion rate of nitroglycerin is increased (at 10, 20 and 40 μg/min), the steady-state concentrations increase disproportionately, probably due to either end-product inhibition or saturable binding to blood vessels.\textsuperscript{16} It is also suggested that since the half-lives for the dinitro metabolites are about 10 times that for nitroglycerin, these metabolites are likely to accumulate during therapy with nitroglycerin.\textsuperscript{13} The second is that 1,3-GDN might inhibit its metabolism in vivo. The dinitro metabolites are shown to inhibit both blood and tissue metabolism of nitroglycerin.\textsuperscript{17} The 1,3-GDN in the circulation, which is quantitatively much more after p.c. absorption than i.v. administration, may extensively inhibit the metabolism. The high bioavailability and the sustained plasma level of 1,3-GDN after the application of the transdermal systems with porous membranes suggest that the systems may be efficacious for the treatment of angina pectoris.

A definite therapeutic plasma concentration range of nitroglycerin has not been defined. However, nitroglycerin administration results in venous plasma concentrations ranging from <50 pg/ml to 10 ng/ml, depending on the route of administration.\textsuperscript{18-20} Assuming that 1,3-GDN is to be 20-fold less potent than nitroglycerin, the effective plasma concentration is thought to be approximately 1 to 200 ng/ml. The transdermal systems with porous membranes, used in this experiment, gave an effective plasma concentration of 1,3-GDN over a prolonged time, due to sustained absorption of the drug. Thus, the advantages of these preparations may be comparable to transdermal nitroglycerin delivery systems, such as Nitro-Dur and Nitro-Disc.

The pharmacokinetic analyses are preferably performed by a simple method using limited data and parameters. In this study, plasma 1,3-GDN levels were well described by the simple model presented. The proposed simple model might be useful for developing insight into the description of the plasma concentration–time course during p. c. dosing of the 1,3-GDN delivery systems.

In conclusion, the transdermal systems with porous membranes were found to be useful in terms of the sustained absorption of 1,3-GDN, the longer duration of effective plasma levels and high bioavailability. The simple model presented in this paper adequately described the time course of the plasma 1,3-GDN concentration following application of the transdermal systems.

References