(19) Storring, P. L., Zaidi, A. A., Mistry, Y. G., Lindberg, M., Stenning, B. E., Dicfalusy, E. (1982) Acta Endocrinol. 101, 339–347.
(20) Evans, R. M., Doelle, G. C., Lindner, I., Bradley, V., Rabin, D. (1984) J. Clin. Invest. 73, 262–266.
(21) Aiyer, M. S., Chiappa, S. A., Fink, G. (1974) J. Endocrinol. 62, 573–588.
(22) Nazian, S. J., Mahesh, V. B. (1979) Neuroendocrinology 29, 313–322.
(23) van Rees, G. P., Schuiling, G. A., de Koning, J. (1983) in Neuroendocrine Perspectives, Vol. 2 (Müller, E. E., Mac Leod, R. M., eds.), pp. 173–198, Elsevier Science Publishers B. V.
(24) Clayton, R. N., Shakespear, R. A., Duncan, J. A., Marshall, J. C. (1979) Endocrinology 105, 1369–1376.
(25) Reeves, J. J., Seguin, C., Lefebvre, F.-A., Kelley, P. A., Labrie, F. (1980) Proc. Natl. Acad. Sci U.S.A. 77, 5567–5571.

Cutaneous Absorption of Indomethacin From Two Topical Preparations in Volunteers

Hans Nowack[1,3], Udo Marin[1], Raimund Reger[1], Herta Böhme[1], Karl-H. Schriever[1], Peter Bocionek[1], Rembert Elbers[2] and Hermann-G. Kampffmeyer[2]

Received: January 21, 1985; accepted: March 2, 1985.

Abstract: The percutaneous absorption of indomethacin in 0.5 % or 1 % solution or 1 % gel at a dose of 50 mg or 100 mg indomethacin was compared in a randomized complete block design in seven healthy volunteers. The formulations were applied over an area of 12 dm^2 under an 8 h occlusion dressing. In addition, in the same volunteers the plasma concentration curves were determined after a single oral dose of 50 mg indomethacin. Indomethacin and some of its metabolites were determined with modified, existing assays using HPLC-fluorescence or gas chromatography-mass spectrometry. On the basis of a newly developed method, it was possible to separate and quantify *O*-desmethylindomethacin and *N*-deschlorobenzoyl-*O*-desmethylindomethacin. After cutaneous administration of the two drug formulations, peak indomethacin plasma concentration of 95 ng/ml and 130 ng/ml were found between 4 and 8 h; the cutaneous bioavailability was approximately 20 % of the oral dose, as judged by comparing the areas under the plasma concentration time curves (AUC) and the amount of metabolites excreted into the urine. Percutaneous absorption did not change the metabolic pattern in the urine that is obtained after oral administration.

In recent years there has been a dramatic development of interest world-wide in the dermal and transdermal delivery of drugs. The prime interest has centered on drugs such as scopolamine (1), nitroglycerine (2), and clonidine (3). All of these substances are delivered for systemic effect since the required blood levels to induce activity are extremely small.

Recently two products have appeared on the market containing indomethacin for application to the skin for local treatment of rheumatic and other pain (4). It is the aim of this study to determine if a substance such as indomethacin will penetrate the skin and to what degree the intact and metabolized drug appears in the blood and is excreted into the urine of volunteers. It must be clear that this study is concerned only with the absorption process and metabolism and in no way purports that the absorbed drug substance is present in quantities that will elicit a therapeutic response.

[1] Luitpold-Werk, Zielstattstraße 9–11, D-8000 München 70, Federal Republic of Germany
[2] Institut für Pharmakologie und Toxikologie der Ludwigs-Maximilians-Universität, Nussbaumstraße 26, D-8000 München 2, Federal Republic of Germany
[3] To whom correspondence should be addressed.

Materials and Methods

Experimental Design

Volunteers. Seven healthy male volunteers aged between 19 and 39 years, median 21 years, with a mean body weight of 72.7 ± 7.1 kg participated in the trial. Subjects with any type of skin disorder were excluded. According to the requirements the volunteers received a pre- and a post-medical examination, signed an informed consent, and were not allowed to take any drugs during the trial period.

Trial Products. The two solutions manufactured by Luitpold-Werk contained 0.5 % or 1.0 % indomethacin (Elmetacin®, 0.5 %: batch-No. V 80 033; 1 %: batch-No. V 80 023 in an alcoholic solution). The gel was commercially available (Amuno®-Gel, MSD-Frosst-Pharma, batch-No. 28 356), containing 1 % indomethacin. The commercial tablet (Amuno®, MSD Pharma, batch-No. 28 202) contained 50 mg indomethacin.

Trial Protocol. The trial was a cross-over of each of the cutaneously applied products in the seven volunteers with a washout period of at least two weeks between each. The products were applied to subjects 1 to 7 in a random sequence that was determined before initiation of the trial as indicated in Table I.

At the day of the first drug application each volunteer was allocated at random to a number to which a specific color was attached. The color code was unknown to the laboratory technician of the company. When this randomized block design was completed, each subject received a single oral dose of 50 mg indomethacin (140 μmoles) after a wash-out period of two weeks. In order to obtain standard conditions the products were applied to each volunteer for each trial on the same day at 5 min intervals.

Table I. Sequence of Drug Application to Each Subject.

Volunteer			
1	A	B	C
2	A	C	B
3	B	A	C
4	B	C	A
5	C	A	B
6	C	B	A
7	A	B	C

A	0.5 % solution
B	1.0 % solution
C	1.0 % gel

Sample Collection. After collecting blood (2 ml isotonic citrate solution to 25 ml blood sample) and urine, 12.5 ml corresponding to 10 g of the particular solution or the gel were applied to the backs of the volunteers over an area of 30 x 40 cm determined by frame, and massaged in with a gloved hand for 2 min. Thus, the amount of indomethacin applied was 50 or 100 mg, or 140 or 280 μmoles, respectively. The area was covered for 8 h with a plastic foil which was fixed on each side with plaster (Leukosilk); thereafter, the back was cleaned with cellulose. During this time period normal physical outdoor activity, like visiting lectures, was permitted. 24 h after drug application, the volunteers washed their backs with a bland soap (brand: Sebamed).

Blood samples were drawn after 1, 2, 4, 8, 24, 48 and 168 h. Blood was also drawn after 6 h in six volunteers following the third administration and after the oral application in each volunteer to get a more accurate estimate of the time of maximum indomethacin concentration.

Statistics

Mean data are presented with standard deviation. The comparison of the treatment-groups was carried out by using the individual areas under the curves of plasma concentrations vs. time calculated by the trapeze method. Because of the small number of subjects and unequal group variances the statistical analysis was based on non-parametric methods, i. e. Friedman test and Wilcoxon-test. Calculations of orthogonal contrasts within the framework of parametrical analysis of variance were also carried out.

Chemical Methods

Chemicals. Indomethacin was supplied by Welding, Germany, *N*-deschlorobenzoyl-indomethacin and heptafluorobutyric anhydride by EGA-Chemie (Steinheim, Germany), hexafluoroisopropanol and methyl stearate by Fluka (Neu-Ulm, Germany), and β-glucuronidase (18 000 000 fishman units/g), by Sigma (St. Louis, USA). *O*-Desmethylindomethacin was synthesized by demethylation with boron bromide and *N*-deschlorobenzoyl-*O*-desmethylindomethacin (DMBI) by alkaline hydrolysis under nitrogen of *O*-desmethylindomethacin. Acetonitrile was obtained from Promochem (Wesel, Germany). All other chemicals were of analytical grade and supplied by Merck (Darmstadt, Germany).

Instrumentation for HPLC. A Hewlett-Packard 1084-A high performance liquid chromatographic system with a stainless steel chromatographic column (25 cm x 3.2 mm) packed with Spherisorb ODS 2 (5 μm) was used for the assay of Bayne et al. (5). An URA 100-model (Kratos) with a coiled tubing (2 x 1.0 ml) and a heating block (75° C) in connection with a LKB-pump (2150) served as a post column in-line reactor. 0.1 N NaOH with a flow rate of 0.12 ml/min was introduced into the mobile phase, post-column. The mobile phase of 70 % methanol in 0.025 M KH_2PO_4, pH 4.0 was run at 0.6 ml/min at room temperature. For fluorescence analysis a Perkin-Elmer Model 650-40 detector was set at an excitation wavelength of 310 nm and an emission wavelength of 380 nm (slit-width 20 nm).

10 μl or 20 μl sample solution (oral or cutaneous application respectively) were injected automatically on the column. The samples that were hydrolyzed before chromatography were analyzed on a Spectraphysics Model 8100 high performance liquid chromatograph by fluorescence measurement (exictation: 286 nm, emission: 390 nm). Separation was performed at room temperature using an ODS column (7 μm, 25 cm x 4.6 mm, Nucleosil C 18), a mobile phase of 25 % acetonitrile in 0.05 M ammonium formate pH 3.5 and a flow rate of 1.5 ml/min. Sample sizes of 30 μl were injected.

Instrumentation for GC/MS. A Hewlett-Packard Model 5985 A gas chromatograph-mass spectrometer equipped with a direct interface was used. Separation were carried out on a fused silica capillary column (10 m x 0.2 mm) coated with CP Sil 5 CB (film thickness 0.11 μm). The split vent flow rate was 4 ml/min, and the column was operated with a head pressure of 0.4 bar. The injector was maintained at 250° C. The interface line temperature was 280°C, and the oven temperature was held constant at 180°C. Temperature of ion source was 200°C. The mass spectrometer was operated in the electron impact mode with an ionization potential of 70 eV. For selective ion monitoring the ions at *m/e* 356.2 and *m/e* 298.4 (corresponding to DMBI and the internal standard respectively) were measured.

Plasma Extraction for Post-Column Hydrolysis. The plasma samples were assayed by modifying a method described previously (5). 1.0 ml plasma was added to 1.0 ml 0.5 M citrate buffer pH 3.5 and 10 ml 1,2-dichloroethane in a silanized centrifuge tube. The tubes were shaken gently for 20 minutes and then centrifuged at 1000 g for 5 minutes.

The organic phase was transferred to a conical test tube and evaporated at 50°C under a stream of nitrogen. The residue was taken up with 200 μl methanol.

Every blood sample was extracted in duplicate at two different days and injected two times. Plasma standard curves were prepared by spiking blank plasma with indomethacin and *O*-desmethylindomethacin. Concentrations of indomethacin and *O*-desmethylindomethacin were determined from standard curves of peak height vs. concentration. The linearity of the method was evaluated in plasma in the concentration range from 10 ng to 1000 ng per ml plasma (5 standards, correlation coefficient always greater than 0.999). The recovery of indomethacin or *O*-desmethylindomethacin from plasma was 86 % (n = 46 plasma samples) or 62 % (n = 12), respectively, measured after spiking the blank plasma with 50 ng of these substances. 2 ng/ml plasma was the lowest concentration that could be measured accurately.

Urine Extraction for Post-Column Hydrolysis. 1 ml urine was incubated at 37°C for 30 min with 1 ml 0.5 M citrate buffer pH 5.0 containing 1660 U of β-glucuronidase. The subsequent procedure was the same as described for plasma in the preceding paragraph. The recovery of 1 μg indomethacin or

500 ng *O*-desmethylindomethacin added to urine was 95 % (n = 56) and 93 % (n = 60), respectively.

Plasma Extraction for Pre-column Hydrolysis. After hydrolysis of indomethacin and its metabolites the content of *N*-deschlorobenzoyl-indomethacin was determined by a modification of a previously described method (6). 1.0 ml plasma and 2.0 ml methanol were mixed, stored at −20°C for 20 min, and centrifuged (2500 g) at 4°C for 30 min. The supernatant was evaporated to dryness under a stream of nitrogen at 45°C. The residue was hydrolyzed with 0.2 ml 0.1 N NaOH for 30 min at 45°C and then centrifuged (2500 g, 10 min). The clear supernatant was then transferred to vials to be injected by the autosampler.

Standard curves were prepared by spiking blank plasma with indomethacin. A recovery of 74 % (n = 74 plasma samples) was found after addition of 70 ng indomethacin to blank plasma. Standard curves within the range of 10 ng and 1000 ng were linear. A minimum amount of approximately 5 ng calculated as indomethacin could be accurately measured.

Urine Extraction for Precolumn Hydrolysis. The urine was incubated with β-glucuronidase and extracted as described for plasma extraction for post-column hydrolysis. After evaporation of the organic phase the residue was taken up with 200 µl 0.1 N NaOH, hydrolyzed for 30 min at 45°C and centrifuged for 10 min at 2500 g. 20 µl of the clear supernatant was injected into the system. After spiking blank urine samples with 500 ng indomethacin a recovery of 93.3 % (n = 47 urine samples) was found.

Extraction Procedure for the Determination of N-deschlorobenzoyl-O-desmethylindomethacin (DMBI). Urine samples for GC/MS analysis were prepared by the same procedure as described for the determination of indomethacin and *O*-desmethylindomethacin, except that diethyl ether was used instead of 1,2-dichloroethane.

Derivatization. The dry urine extract was derivatized with 50 µl hexafluoroisopropanol and 50 µl heptafluorobutyric anhydride (7). The reaction mixture was heated to 75°C for 20 min. Following derivatization, the sample was evaporated to dryness under nitrogen in a 60°C water bath. The residue was redissolved in 200 µl ethyl acetate containing 5 µg methyl stearate/ml as internal standard, and the solution was mixed with a vortex mixer.

A standard calibration curve was prepared by spiking blank urine with DMBI. Each urine sample was injected in duplicate, and the analysis was immediately replicated. Concentration of DMBI was determined from standard curves of peak area vs. concentration.

Results

Plasma Concentrations

All plasma samples were analyzed by two different methods: a post-column method, by which indomethacin is determined, and a pre-column method by which the hydrolysis product, *N*-deschlorobenzoyl-indomethacin, is measured. Table II shows the mean plasma concentrations of indomethacin obtained by the post-column hydrolysis method. The data indicate maximum concentrations 4–8 h after topical drug application or 2 h following ingestion.

The maximum plasma concentrations of indomethacin were 95 ng/ml after application of the 0.5 % solution (140 µmoles) and 130 ng/ml after the 1 % solution, which was reached at the time when the occlusive dressing was removed. The concentration after 24 h had fallen to approximately 10 % of the maximum concentration.

After oral indomethacin administration, the maximum concentration was reached after 2 h, and it was approximately 10 times higher than following the corresponding cutaneous dose.

After gel administration the variance of the mean concentrations was larger than with the 1 % solution, which may have been caused by the abnormally high concentrations in subjects 3 and 5 (see Table III). Furthermore, subject 5 had a plasma concentration of 990 ng/ml at the second hour and subject 6 had 730 ng/ml at the fourth hour; however, these high values were not found after the precolumn method (subject 5: 162 ng/ml, subject 6: 94.6 ng/ml). If these high values had been deleted, the mean serum concentrations at the second and fourth hour following the 1 % gel would compare with that after the 1 % solution. However, no data have been omitted for the calculation of the area under the curve (AUC) since repeated chemical analysis with the post-column method had not revealed any simple plausible explanation for the discrepancy of these results.

The AUC for indomethacin for each volunteer after each topical and the oral administration is listed in Table III. Comparison of the mean areas after administration of the 0.5 % solution (1312.6) and the tablet (5756.5) indicated a relative bioavailability of approximately 20 % of the cutaneous dose.

The results of the nonparametric analysis of variance – including pairwise comparisons – may be summarized as follows.

a) Both the 1 % indomethacin-solution-group as well as the 1 % indomethacin-gel-group are statistically different from the 0.5 % indomethacin-solution-group ($p = 0.028$; $p = 0.043$).

b) There are no differences between the 1 % indomethacin-solution group and the 1 % indomethacin-gel-group ($p = 0.499$). Similar statistical results were obtained when the same group comparison was made by orthogonal contrasts within the framework of parametrical analysis of variance. Determination of the plasma concentration by the precolumn hydrolysis method gave values of about the same magnitude but of larger variance with lack of statistical difference between means.

Urinary Excretion

Table IV shows the time course of the urinary excretion of all the metabolites during the collection periods following the four drug applications. In Table V the amounts (µmoles) of indomethacin moieties determined after each treatment within 48 h are listed. Following oral administration, 34 % of the dose was found, approximately half as indomethacin, the other half as *O*-desmethylindomethacin and *N*-deschlorobenzoyl-indomethacin, free and conjugated in similar amounts. The same proportion of the indomethacin moieties was also found after the three topical drug applications, whereas the total amount was only 20 % of that recovered after the oral dose.

N-deschlorobenzoyl-*O*-desmethylindomethacin was determined in the urine of one subject. An amount of 0.68 µmoles was found after application of the 1 % solution, indicating that this route of metabolism is quantitatively only of minor importance.

Table II. Mean Plasma Concentration (ng/ml) of Indomethacin in 7 Volunteers Following Topical or Oral Administration.

Dose (μmoles)	Time (h) 1	2	4	6	8	24	48
				n=3			
1 % gel (280)	50.7 (±42.7)	234.3 (±343.7)	212.0 (±239.0)	134.4 (±91.2)	118.2 (±82.4)	17.6 (±8.5)	3.7 (±3.2)
				n=2			
1 % sol. (280)	11.2 (±7.1)	56.5 (±27.1)	106.9 (±30.8)	93.6 (±5.9)	127.2 (±33.3)	14.4 (± 2.2)	2.5 (± 2.3)
				n=1			
0.5 % sol. (140)	7.8 (±15.7)	33.2 (±43.8)	63.5 (±27.7)	99.3	95.2 (±39.5)	6.5 (± 4.0)	0.1 (±0.3)
				n=6			
Tabl. (140)	363.2 (±426.5)	849.1 (±455.7)	576.0 (±225.5)	258.3 (±111.3)	185.9 (±96.7)	36.4 (±18.0)	2.4 (±4.2)

Table III. Areas (ng x h/ml) (0–48 Hours) Under the Plasma Concentration Time Curves of Indomethacin after Administration of Indomethacin Topically or in Tablets.

Indomethacin (μmoles)	0.5 % sol. (140)	1.0 % sol. (280)	1.0 % gel (280)	tablet (140)
Volunteer				
1	246.7	2546.9	1707.6	4343.0
2	793.3	1521.6	1310.1	4701.0
3	2571.1	2371.1	4727.9	6225.8
4	1534.9	2116.0	1217.5	4920.3
5	1334.5	1638.0	4459.8	7455.3
6	1294.7	1738.9	3137.7	5069.9
7	1413.2	2113.4	1666.6	7580.5
$\bar{x}$	1312.6	2009.1	2603.9	5756.5
s	712.9	389.6	1501.0	1336.4

Peak concentrations and relative bioavailability are dependent on the experimental conditions, especially area of drug application, occlusion, etc. Inagi et al. (4) found a maximum concentration of only 20 ng indomethacin/ml when the same dose was applied to 9 dm^2 without occlusive dressing.

The total urinary recovery rate of 34 % after oral administration as determined by the free and conjugated moieties of indomethacin, *O*-desmethylindomethacin and *N*-deschlorobenzoyl-indomethacin is 10 % less than that found by Kwan et al. (8) using 50 mg of indomethacin-2-^{14}C which was given with a general hospital breakfast. These investigators found about 15 % of the administered radioactivity in feces. Duggan et al. (9) observed a total recovery rate of 90 % and nearly complete oral bioavailability with the same radioactively labeled drug, when the fasted volunteers drink 240 ml water every 2 h. Under these conditions, ⅔ of the dose was eliminated in the urine and ⅓ in the feces. Thus, the urinary recovery in this report following oral administration seems to be within a comparable range considering the different experimental conditions and chemical analysis.

Table IV. Mean Urine-Excretion (μmoles) of Indomethacin and Metabolites from 7 Volunteers Following Topical or Oral Administration.

	Applied dose (μmoles)	Time (h) 0–4	4–8	8–12	12–24	24–48	Σ0–48
1 % gel	280	1.3 ± 1.5	3.2 ± 2.0	1.8 ± 1.0	4.9 ± 2.6	2.7 ± 1.3	13.9 ± 6.8
1 % sol.	280	0.6 ± 0.7	2.3 ± 1.0	1.7 ± 0.8	4.5 ± 1.5	2.5 ± 1.1	11.6 ± 3.3
0.5 %sol.	140	0.3 ± 0.5	1.8 ± 1.0	1.5 ± 1.2	3.3 ± 1.8	1.6 ± 0.4	8.5 ± 3.2
tablets	140	12.2 ± 8.2	9.9 ± 6.3	5.9 ± 4.2	12.4 ± 4.8	7.6 ± 3.2	48.0 ± 10.8

Table V. μmoles of Indomethacin and Metabolites (Free and Conjugated) Detected in Urine.

Applied dose (μmoles)	Indomethacin	*O*-desmethyl-indomethacin	*N*-deschlorobenzoyl-indomethacin	Total	% of dose
1 % gel (280)	7.4 ± 5.2	3.0 ± 1.4	3.5 ± 2.8	13.9 ± 6.8	5.0
1 % sol. (280)	5.8 ± 2.2	3.0 ± 1.1	2.8 ± 1.3	11.6 ± 3.3	4.1
0.5 % sol. (140)	4.1 ± 1.7	2.3 ± 1.1	2.1 ± 1.4	8.5 ± 3.2	6.1
tablets (140)	22.9 ± 9.7	12.0 ± 4.0	13.1 ± 5.2	48.0 ± 11.0	34.3

Discussion

Indomethacin solution (0.5 % and 1.0 %, 10 g) containing 50 mg or 100 mg of indomethacin, respectively, applied to an area of 12 dm^2 under occlusive dressing, led to mean peak plasma concentrations of 95 ng/ml and 130 ng/ml, respectively, after 6 h. By comparing the areas under the plasma concentration-time curves after cutaneous and oral administration of equal doses (50 mg indomethacin), approximately 20 % of the cutaneously applied dose was absorbed.

The recovery rate of indomethacin and metabolites shown in Table V was 6 % for the 0.5 % solution, applied cutaneously, and it again reflects a relative bioavailability of 20 % under our experimental conditions when compared with the oral dose. The relative amounts of urinary metabolites were

similar to those published by Duggan et al. (9). Therefore, our results from the cutaneous and oral administration are essentially in agreement with the metabolic pattern reported by others for intravenous, oral and rectal routes, which suggests that the metabolism of indomethacin is independent of the route of administration.

References

(1) Price, N. M., Schmitt, L. G., McGuire, J., Shaw, J. E., Trobough, G. (1981) Clin. Pharmacol. Ther. 414–419.
(2) Armstrong, P. W., Armstrong, J. A., Marks, G. S. (1980) Am. J. Cardiology 670–676.
(3) Arndts, D., Arndts, K. (1984) Eur. J. Clin. Pharmacol. 26, 79–85.
(4) Inagi, T., Muramatsu, T., Nagai, H. (1979) Yakuri to Chiryo 7, Suppl. 1, 35.
(5) Bayne, W. F., East, T., Dye, D. (1981) J. Pharm. Sci. 70, 458–459.
(6) Bernstein, M. S., Evans, M. A. (1982) J. Chromatogr. 229, 179–187.
(7) Evans, M. A. (1980) J. Pharm. Sci. 69, 219–220.
(8) Kwan, K. C., Breault, G. O., Umbenhauer, E. R., McMahon, F. G., Duggan, D. E. (1976) J. Pharmacokin. Biopharm. 4, 255–280.
(9) Duggan, D. E., Hogans, A. F., Kwan, K. C., McMahon, F. G. (1972) Exp. Ther. 181, 563–575.

Kinetic Analysis of Transdermal Nitroglycerin Delivery

Richard H. Guy[1,3] and Jonathan Hadgraft[2]

Received: January 8, 1985; Accepted: March 25, 1985.

Abstract: The current success of transdermal nitroglycerin delivery systems has focussed much attention upon the skin as a portal of drug entry into the systemic circulation. Although there are multiple potential problems associated with this administration route to elicit central effects, considerable efforts are being made to identify transdermal drug delivery candidates and to determine whether a sufficient percutaneous input rate can be achieved such that therapeutic levels in the biophase may be maintained. The purpose of this work is to develop a physically-based kinetic model of percutaneous absorption, which includes delivery system input. Both zero-order and first-order situations are considered and the model is employed to analyze nitroglycerin plasma concentration *vs.* time data following transdermal delivery both from a controlled-release patch and from an ointment. The kinetic model includes rate parameters which relate to drug transport across the stratum corneum, to further diffusion across the viable epidermis and to the competition for substrate between these two layers of skin tissue. We show how these kinetic constants may be determined physicochemically and used, in conjunction with designated (delivery system) input rates and established systemic elimination kinetics, to predict plasma concentrations as a function of time. The agreement with human *in vivo* data for nitroglycerin, delivered from either a patch or a more conventional vehicle, is good and suggests that the simulation proposed may enable facile estimation of the feasibility of transdermal drug delivery.

The delivery of drugs via the skin to elicit systemic effects is attractive for many reasons (1–3). For example, hepatic first-pass metabolism may be circumvented, a steady, sustained plasma concentration of drug may be maintained, dosing frequency and dose magnitude may be reduced and, consequently, fewer side-effects and better patient compliance may be expected. Furthermore, a properly designed delivery device should lead to lower inter- and intra-patient variation, and a topical system has the unique advantage of permitting rapid termination of therapy in problematic situations. Of course, transdermal delivery also has limitations: the drug must be pharmacologically potent (normal daily dose requirements of a few milligrams or less) because the skin is a very good barrier to chemical ingress; thus the compound must be absorbable to some extent and its chemical properties should include, therefore, (1) a moderate molecular weight (in the order of 1000 daltons or less) and (2) reasonable oil and water solubility (*ca.* 1 mg/ml).

Transdermal delivery of nitroglycerin (GTN) is presently the most successful example of this mode of drug administration (4–6). In the U.S., three GTN devices are commercially available and are in competition with sublingual and ointment formulations of the vasodilating drug. The relatively recent acquisition of GTN pharmacokinetic data has allowed favorable conclusions pertaining to the efficacy of transdermal delivery to be drawn. Of the three marketed devices, two are of the matrix variety, the other is multi-laminate and includes a "rate-controlling" membrane. The degree of rate-control afforded by this membrane has been comprehensively defined in a recent paper by Good (4).

The purpose of the work described here is to present a novel analysis of GTN pharmacokinetics following transdermal delivery. The approach employs a physically based kinetic model of percutaneous absorption, the details and certain applications of which have been reported elsewhere (7–9). We make use of the *in vitro* and *in vivo* release characteristics, which have been described for the membrane-modulated GTN device (4, 10), and, where possible, compare the derived behavior to that expected and shown by the conventional ointment preparation. We show that the proposed kinetic model is able to simulate very adequately the observed *in vivo* disposition of GTN. The model accomplishes this correlation

[1] Departments of Pharmacy and Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, San Francisco, CA 94143, USA
[2] Department of Pharmacy, University of Nottingham, University Park, Nottingham, NG7 2RD, United Kingdom
[3] Correspondence