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# Hydrophilic polymeric matrices for enhanced transdermal drug delivery

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**Abstract**

For many drugs with various chemical structures, delivery rates from the hydrophilic polyvinylpyrrolidone (PVP)-polyethylene oxide (PEO) based pressure sensitive adhesive (PSA) matrices of transdermal therapeutic systems (TTS) are higher compared to the hydrophobic TTS matrices. Delivery of propranolol, glyceryl trinitrate (GTN) and isosorbide dinitrate (ISDN) from the hydrophilic water soluble TTS matrix across human cadaver skin epidermis or skin-imitating polydimethylsiloxane-polycarbonate block copolymer Carbosil membrane in vitro is characterized by high rate values and zero-order drug delivery kinetics up to the point of 75–85% drug release from their initial contents in matrix. Both in vitro and in vivo drug delivery rates from the TTS hydrophilic diffusion matrix are controlled by the skin or membrane permeability and may be described by Fick's law. The contributions of various physicochemical determinants to the control of transdermal drug delivery kinetics are discussed. Pharmacokinetic and pharmacodynamic properties of hydrophilic TTS matrix with propranolol, GTN and ISDN are described.

*Keywords:* Polyvinylpyrrolidone; Polyethylene oxide; Propranolol; Glycerol trinitrate; Isosorbide dinitrate; Transdermal therapeutic systems

## 1. Introduction

Difficulties in drug delivery with transdermal therapeutic systems (TTS) arise when drugs have to be delivered transdermally requiring high therapeutic doses — up to 100 mg/day or more. This problem can be solved with the help of the skin penetration enhancers (Guy and Hadgraft, 1987; Barry, 1991; Hadgraft, 1991; Potts et al., 1991; Hadgraft, 1993). For this purpose TTS with enhanced drug release should also be developed. At the start of our TTS development the strategy was stated as follows:

(1) Developed TTS should have a universal PSA composition designed for the transdermal delivery of the drugs with various chemical structures.
(2) TTS should provide enhanced transdermal drug delivery rates to deliver drugs requiring administration in high therapeutic doses and to minimize the sizes of the device.

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Table 1
TTS examined

| Drug | TTS | Area ($cm^2$) | Drug content | | Claimed skin application period (days) |
|---|---|---|---|---|---|
| | | | mg | % | |
| Propranolol | Propercuten forte | 48 | 400 | 13.8 | 5 |
| | Propercuten mite | 48 | 200 | 7.4 | 5 |
| Glygerol trinitrate | Nitropercuten forte | 35 | 75 | 7.3 | 1 |
| | Nitropercuten mite | 35 | 20 | 1.9 | 1 |
| Isosorbide dinitrate | Sorbopercuten | 30 | 75 | 9.6 | 2 |

In 1985, we showed (Petrukhina et al., 1985) that transdermal delivery rates for ionogenic and polar drug molecules e.g. for hydralazine (1-hydrazinophtalazine) from polar hydrophilic medium can be much higher than from lipophilic nonpolar ones. Later this conclusion was confirmed for propranolol (Bodmeier and Paeratakul, 1990), diazepam (Touitou, 1986) and dihydroergotamine (Niazy et al., 1990). In the same year Guy and Hadgraft (1985) stated the criteria for the possibility of delivering drugs transdermally with predetermined pharmacokinetic constants and lipophilicity. As has been predicted theoretically, the transdermal delivery of propranolol in therapeutic doses from hypothetical TTS with a drug zero-order release rate of 35 $\mu g/cm^2$ h and TTS application area of 30 $cm^2$ can be realized in practice. Guy and Hadgraft (1985) made no attempt to answer how such a propranolol release rate from real TTS can be achieved.

Based on these considerations, in 1987 we developed the hydrogel PSA nontoxic TTS matrix composed of high molecular mass PVP and oligomeric PEO. This matrix is compatible with drugs of different chemical structure and provides high drug transdermal delivery rates even without skin penetration enhancers (Vasiliev et al., 1989; Vasiliev et al., 1995). Starting from this matrix we have developed TTS with propranolol (Propercuten TTS), GTN (Nitropercuten TTS), ISDN (Sorbopercuten TTS) and some other TTS and topical drug plasters. This paper is devoted mainly to the drug delivery kinetics from TTS Propercuten, Nitropercuten and Sorbopercuten both in vitro and in vivo. The conclusions are valid for hydrophilic TTS matrices with diverse drugs spanning a wide range of chemical structures, physicochemical properties and lipophilicity (Feldstein, 1995; Feldstein et al., 1996a; Feldstein et al., 1996b (in press)).

## 2. Materials

### 2.1. TTS

The main characteristics of TTS examined are given in Table 1. All TTS were produced in the 'Lekbiotech' R and D Center, J.S.Co. 'Biotechnologia' (Moscow, Russia). The equilibrium water content in hydrophilic TTS matrix was 8–11%.

### 2.2. Penetration barriers

Human cadaver skin epidermis was derived from thigh inner skin surface of male cadavers. The separation of epidermis from dermal tissues was prepared following the method suggested by Katz and Poulsen (1971).

The direct in vitro experimental measurement of drug release rate from water soluble TTS matrix as described by Shah et al. (1988) and Hadgraft et al. (1991) is impossible. To protect the matrices from dissolving in receptor solution they were combined with human skin epidermis or skin-imitating polymeric Carbosil-1 or Carbosil-2 (thickness 0.04 mm) membrane. This membrane is produced by 'Medpolymer' (Russia) from polydimethylsiloxane-polycarbonate block copolymer on a basis of 4,4′-bisdiphenylol-2,2′-propane carbonate ether. To obtain more information about matrix characteristics, we chose a membrane with

higher drug permeability than human skin epidermis. Carbosil-1 contains more polar polydimethylsiloxane blocks and has higher drug permeability in comparison with Carbosil-2.

## 3. Methods

**In vitro drug delivery determination** was based on the USP rotating cylinder paddle-over-disc method, as described earlier (Malkhazov et al., 1991; Malkhazov et al., 1993; Feldstein et al., 1993). The measurement of drug appearance rate in receptor solution (0.15 M NaCl for propranolol; water for GTN and ISDN) at 35.0 ± 0.5°C and paddle rotation speed 100 ± 1 rev./min was performed using the LKB Tablet Dissolution System combined with UV spectrophotometer (Ultrospec 4052), six-cell temperature-controlled bath (Sotax AT6), LKB multi-channel peristaltic pump and Olivetti M-240 computer. In experiments with cadaver skin epidermis, the drug concentration in the receptor solution was measured manually by means of a Hitachi F-4000 spectrofluorimeter (propranolol) or with the gas chromatography method described earlier (Feldstein et al., 1993) (GTN and ISDN). The precision of the drug concentration measurement was ±0.002 mg/ml (UV-spectrophotometry), ±20 ng/ml (spectrofluorimetry) and ±1.0 ng/ml (gas chromatography).

**The estimation of drug diffusion coefficients** in Carbosil membrane or human skin epidermis was carried out using our original Franz-type vertical diffusion cell with hydrostatic pressure compensator at 35.0 ± 0.5°C (Petrukhina et al., 1985). The drug solutions in donor (5-ml) and receptor (500-ml) chambers were mechanically stirred. The membrane-matrix drug partition coefficient was measured after TTS matrix lamination with Carbosil-2 at 25°C and after 48 h of contact.

**The drug reversible immobilization constants** with PVP and PEO were estimated by an equilibrium dialysis method at 35°C. Dialysis cellulose membrane (0.09 mm in thickness) was supplied by Visking Company. The dialysis sack with 5 ml of drug solution in liquid PEO-400 in the presence of variable PVP amounts was shaken in 100 ml PEO-400. After the dialysis, the free drug equilibrium concentration in the receptor solution was measured with a UV-spectrophotometer (Shimadzu UV-160).

**The mathematical simulation** of in vitro drug mass transfer kinetic profiles from TTS hydrogel diffusion matrix across skin-imitating protective polymer membrane into receptor solution was carried out using the Turbo-Pascall program of Markin and Iordanskii for IBM-PC (Markin et al., 1994; Feldstein et al., 1996a (in press)).

**Experimental pharmacokinetics** of TTS with propranolol, GTN and ISDN were investigated on male and female rabbits with weight 2.4–3.0 kg (Pyotrovsky et al., 1991; Pyotrovsky et al., 1993). TTS were applied on previously clean-shaven and damage-free skin of the back or shoulder-blades. The blood samples (3 ml) were taken from the rabbit's ear vein. The determination of drug concentration in rabbit's plasma was performed by gas chromatography (GTN, ISDN) (Blagodatskikh et al., 1986) or HPLC (propranolol) (Belolipetskaya et al., 1989). The drug concentration measurement experimental error was 1.0 ng/ml for propranolol; 0.05 ng/ml for GTN; 0.5 ng/ml for ISDN; 5.0 ng/ml for 2-ISMN and 10 ng/ml for 5-ISMN. The drug transdermal delivery rates from TTS into the systemic circulation were calculated according to Eq. (1) (Guy and Hadgraft, 1985):

$$J = (K_{el} C_{ss} V_d)/S \quad (1)$$

where:

(1) $J$ = transdermal drug delivery rate ($\mu$g/cm$^2$ h)
(2) $K_{el}$ = the drug elimination constant (h$^{-1}$)
(3) $C_{ss}$ = the steady-state drug concentration in blood plasma (ng/ml)
(4) $V_d$ = the drug distribution volume (l/kg)
(5) $S$ = TTS application area (cm$^2$/kg)

The individual values of $K_{el}$ and $V_d$ for every animal were estimated with the aid of drug intravenous infusion before TTS application.

**Clinical pharmacokinetics and pharmacodynamics** of TTS were studied in the course of TTS clinical trials, approved by the Pharmacological Committee of the Public Health Ministry of the

Russian Federation at leading Moscow Cardiology Clinics. Propercuten antihypertensive activity was investigated in 142 hypertensive patients and pharmacokinetics in 10 hypertensive patients. Antianginal activity of Propercuten was studied in 12 angina pectoris patients. TTS Nitropercuten and Sorbopercuten were examined in 104 and 115 angina pectoris patients, respectively. Propranolol concentration in human plasma after TTS application was determined by HPLC with fluorimetric drug detection (Feldstein et al., 1994a) with an accuracy of 1.0 ng/ml. Concentrations of ISDN and metabolites in human plasma were measured with electron-capture gas chromatography (Pyotrovsky et al., 1991).

## 4. Results and discussion

### *4.1. A comparative study of drugs delivery rates from the hydrophilic and the hydrophobic TTS matrices in vitro*

Drugs with various chemical structures are compatible with the PVP-PEO diffusion matrix and can be incorporated in the composition of this matrix up to a high drug content (10–20% or more). As is evident from the data in Table 2, in vitro drug delivery rates from the hydrophilic TTS matrix across Carbosil membrane are usually higher than from the hydrophobic TTS matrices measured without skin-imitating membrane. In accordance with the values of drug delivery rates from the hydrophilic TTS matrix all drugs in Table 2 can be classified into two groups:

(1) No. 1–7: drugs with high delivery rates from hydrophilic matrices ( $> 100$ $\mu g/cm^2$ h);
(2) No. 8–11: drugs with low delivery rates from these matrices ( $< 50$ $\mu g/cm^2$ h).

All the drugs from the first group have a high water solubility ( $> 0.1$ mg/ml) and (except verapamil) low melting points ( $< 120$°C). Apart from cytisine, all the drugs from the second group have a low solubility in water ( $< 0.1$ mg/ml) and high melting points ( $> 130$°C). The drug solubility–delivery rate relationship is more clearly expressed in comparison with the dependence between drug melting point and delivery rate from the hydrophilic matrix. A comparatively low steady state cytisine delivery rate may be attributed to the diffusion coefficient decreasing through hydration of cytisine molecules as a result of water transfer from the receiving solution across the Carbosil membrane into the TTS matrix (Feldstein et al., 1995a). It is notable that the delivery rate for a lipophilic drug such as silabolin is higher from the hydrophilic matrix than from the hydrophobic one. This paper reports mainly on the drug delivery kinetics from the TTS hydrophilic matrix for the first group of drugs — propranolol, GTN and ISDN.

### *4.2. In vitro drug delivery kinetics from TTS*

As shown in Fig. 1, in vitro delivery of propranolol, GTN and ISDN from the hydrophilic TTS matrix across the Carbosil membrane is characterized by high drug delivery rates (Table 3) and zero-order delivery kinetics at up to 85% propranolol release and 75% GTN and ISDN release of the initial drug contents in the matrix (Feldstein et al., 1994b). In vitro drug delivery rates from TTS across human cadaver skin epidermis (Table 3) are significantly lower than the drug delivery rates across the skin-imitating membrane. The rates of drug delivery from TTS hydrophilic matrix are controlled by penetration barriers (skin or membrane): the higher the drug diffusion coefficient in the penetration barrier, the higher the value of the drug delivery rate (Feldstein, 1995). The value of the drug delivery rate from the matrix increases in line with the drug concentration in the matrix (Fig. 2) up to the solubility limit. Propranolol crystallization in the matrix can be observed visually at a concentration greater than 15%. A similar dependence is also true for GTN and other drugs examined. As is obvious from the Table 3 data, the difference in the rates of GTN delivery from the matrix is 3.7 times, while the difference in the drug concentration in matrix is 3.8 times. Consequently, the drug delivery from TTS hydrophilic matrix across the penetration barrier may be described in Fick's law terms: the drug delivery rate varies in direct proportion to the drug concentration in the matrix.

Table 2
Physicochemical characteristics and in vitro delivery rates of various drugs from hydrophilic and hydrophobic TTS matrices

| Drug | MW | MP (°C) | Solubility[a] (mg/ml) | Delivery rate ( ± range, $\mu g/cm^2$ h) | | Composition of hydrophobic TTS matrix |
|---|---|---|---|---|---|---|
| | | | | Hydrophilic[b] | Hydrophobic | |
| 1. Aminostigmine | 223.26 | <0 | High | 625 ± 20 | 8 ± 1 | SBR[c], mineral oil |
| 2. Isosorbide dinitrate | 236.14 | 70 | 12 | 384 ± 78 | | |
| 3. Glycerol trinitrate | 227.09 | 13.5 | 1.25 | 160 ± 40 | 80 ± 10 | PDMS[d], silicone oil |
| 4. Anabasine | 162.24 | 9 | High | 150 ± 20 | | |
| 5. Silabolin | 345.58 | 120 | 0.36 | 131 ± 30 | 16 ± 7 | SBR, mineral oil |
| 6. Propranolol | 259.34 | 96 | 0.52 | 118 ± 25 | 56 ± 4 | SBR, mineral oil |
| 7. Verapamil | 454.59 | 245 | 0.94 | 110 ± 20 | | |
| 8. Cytisine | 190.24 | 155 | 7.7 | 21 ± 3 | | |
| 9. Nifedipine | 346.34 | 173 | 0.07 | 19 ± 3 | | |
| 10. Phenazepam | 348.61 | 227 | 0.014 | 6 ± 2 | | |
| 11. Clonidine | 230.10 | 130 | <0.1 | 5 ± 2 | 1.6 ± 0.2 | PIB[e], mineral oil |

[a]0.15 M NaCl, 35°C.
[b]From PVP-PEO matrix across Carbosil membrane.
[c]Styrene butadiene rubber.
[d]Polydimethylsiloxane: Nitroderm (Ciba-Geigy).
[e]Polyisobutylene: Catapres (Boehringer).

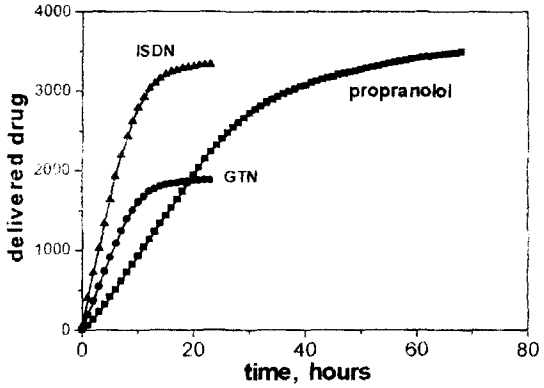


Fig. 1. In vitro delivery kinetics of glycerol trinitrate, isosorbide dinitrate and propranolol ($\mu$g/cm$^2$) from TTS Nitropercuten-forte, Sorbopercuten and Propercuten-mite across Carbosil-2 membrane.

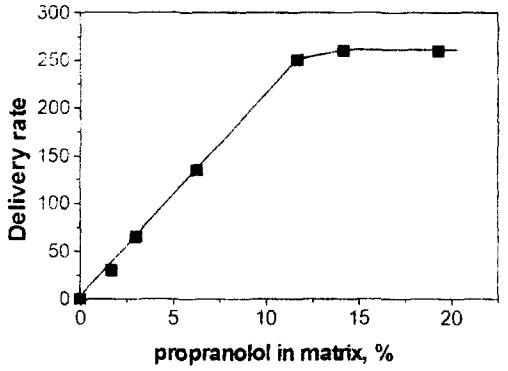


Fig. 2. Dependence between propranolol delivery rate ($\mu$g/cm$^2$ h) from TTS hydrophilic matrix across Carbosil-1 membrane in vitro and drug concentration in matrix (%).

It is known (Baker, 1974) that the drug release rate from matrix-type TTS decreases with time according to either an exponential law or to the Higuchi equation. From the results of our experiments, the drug delivery rate was essentially time-independent. We supposed that one of the reasons of this discrepancy may be connected with sorption (reversible immobilization) of drug molecules by macromolecules of the matrix or that the membrane was rate-limiting. To resolve this problem we have to assess the contributions of the different drug diffusion and drug complexation constants to the drug delivery kinetics from the TTS hydrophilic matrix.

### *4.3. The drug sorption in the TTS matrix*

It is well known that PVP can form complexes with drug molecules of various chemical structures. These complexes exist in aqueous solutions and dissociate in organic solvents (Plaizier-Vercammen and De Neve, 1982). We investigated the interaction of PVP with propranolol and some other drugs in ethanol and liquid oligomeric PEO and showed that drug binding with PVP macromolecules in organic medium occurs only if PVP and PEO are present together. The sorption of drug molecules with PVP chains in the presence of PEO cannot be described in Klotz equation terms, which is true for sorption of small molecules by the long linear macromolecule. It can be assumed therefore that the sorption of different drugs with long-chain PVP macromolecules and oligomeric PEO may be induced by a microphase separation in the PVP–PEO mixture (Cesteros et al., 1989) and results in the drug partitioning between microphases. The propranolol sorption constant

Table 3
In vitro drug delivery rates ($\mu$g/cm$^2$ h) from TTS hydrophilic matrix across Carbosil-2 membrane or human cadaver skin epidermis and drug diffusion coefficients within these penetration barriers

| TTS | Carbosil membrane | | Human cadaver skin epidermis | |
|---|---|---|---|---|
| | Delivery rate ($\pm$ range) | $D$ ($\times$ $10^{12}$ m$^2$/s) ($\pm$ range) | Delivery rate ($\pm$ range) | $D$ ($\times$ $10^{12}$ m$^2$/s) ($\pm$ range) |
| Propercuten-forte | 118 $\pm$ 25 | 22.0 $\pm$ 0.5 | 26.0 $\pm$ 15.0 | 0.91 $\pm$ 0.19 |
| Propercuten-mite | 80 $\pm$ 18 | | | |
| Nitropercuten-forte | 160 $\pm$ 40 | 17.1 $\pm$ 2.6 | 12.4 $\pm$ 4.0 | 4.5 $\pm$ 1.1 |
| Nitropercuten-mite | 43 $\pm$ 11 | | | |
| Sorbopercuten | 384 $\pm$ 78 | 250 $\pm$ 110 | 13.0 $\pm$ 4.3 | 2.9 $\pm$ 1.5 |

with PVP and PEO increases with an increase of PEO concentration in the mixture and attains 1 $\times$ $10^5$ l/mol. This phenomenon will be discussed in detail in a future publication.

### 4.4. The contribution of various physicochemical determinants in drug delivery kinetics

This was estimated from the matrix across skin-imitating protective membrane with the mathematical simulation analysis (Markin et al., 1994; Feldstein et al., 1996a (in press)). On the basis of the diffusion model of drug transfer via hydrogel matrix and hydrophobic membrane, it was shown using propranolol as a drug example that the drug diffusion coefficient in the membrane and the drug partition coefficient between membrane and matrix have a dramatic impact on the drug delivery kinetics. The closest approximation of the in vitro delivery kinetics profile with computed data was noted for $D = 1.1 \times 10^{-12}$ $m^2/s$ which is considerably lower than the experimentally observed value presented in Table 3 ($D = 22 \times 10^{-12}$ $m^2/s$). Physically, the explanation for this difference will be offered below. The contribution of the drug partition coefficient between membrane and matrix to drug delivery kinetics was so prominent that the variation in its value for propranolol within the limits of experimental error ($K = 0.22 \pm 0.04$) has a dramatic effect on drug delivery rate. The drug delivery rate from the hydrophilic TTS matrix depends only slightly on the value of the drug diffusion coefficient in the matrix. The rate of drug delivery from the TTS hydrophilic matrix across the membrane is controlled by the drug diffusion coefficient in the matrix only to a small extent compared to the drug diffusion coefficient in the membrane. The reason for this insignificant contribution of the drug diffusion in matrix to drug delivery kinetics lies in the matrix hydrogel structure and in fast drug diffusion in comparison with drug diffusion in a penetration barrier. The most satisfactory agreement between computed and experimental kinetic profiles is achieved if $D = 1 \times 10^{-11}$ $m^2/s$. It is one order of magnitude lower than the low-molecular mass compounds diffusion coefficient in a hydrogel $D = 1.1 \times 10^{-10}$ $m^2/s$ (Zaikov et al., 1988).

This dramatic decrease in the drug diffusion coefficient in the matrix in comparison to the predicted value can be explained by the effect of drug sorption in the matrix. The reversible sorption of drug molecules in the matrix produces a loss of their mobility and, as a result, a decrease in drug diffusivity in the matrix.

The mathematical method allows a computer simulation under imaginary conditions in which matrix dissolution in receptor phase does not occur and when membrane thickness is zero. Only without the influence of the membrane can the true kinetics of drug *release* from TTS be known. In experiments with rate-controlling membranes or skin we are only able to discuss the drug *delivery* from TTS. As was shown (Markin et al., 1994; Feldstein et al., 1996a (in press)), drug release kinetics without the membrane is described by an exponential curve, which is typical for all matrix TTS (Baker, 1974). For propranolol-containing TTS (7.4% in matrix), used for the simulation analysis, the computer-estimated drug release rate is 800 $\mu g/cm^2$ h (Feldstein et al., 1996a (in press)). Based on this value and applying a simple algorithm offered recently by Guy and Hadgraft (1992), we are able to assess quantitatively the fractional contributions of device, membrane or skin to drug delivery rate control. The permeation barrier control is found to average 88% for the Carbosil membrane in vitro and 97% for human skin both in vitro and in vivo. The device contribution to the drug delivery rate control varies from 12% in vitro across Carbosil membrane and up to 3% across the skin. These calculations support the conclusion presented above that the drug delivery kinetics from the hydrophilic polymeric matrices is almost totally controlled by the penetration barriers. In this connection the hydrophilic TTS matrices could be especially effective in combination with the skin penetration enhancers.

The fractional contribution of the device to drug delivery rate control depends slightly on the drug concentration in the matrix between 2 and 20%. Thus, for 13.8% propranolol in the matrix, this value in vivo is 1.5%. As the drug concentration in the matrix and the drug release rate decreases, the device control to drug delivery will increase. The transdermal drug delivery rate from

the hydrophilic TTS matrix with a high drug concentration characterizes the skin penetration of this drug. This value reflects the drug's real permeability across intact skin more correctly compared with a conventional procedure of skin permeability measurement involving the solvent action upon the skin. With hydrophilic matrices we can directly assess the in vivo skin penetration (Feldstein et al., 1995b). The reduced magnitudes of transdermal drug permeability coefficients (log $P$) compared with published data can be explained in view of the absence of a solvent effect. Thus, for the in vitro transdermal GTN delivery rates in Table 3, log $P = -3.77$ cm/h. The published value is considerably lower: log P = $-1.96$ cm/h (Pugh and Hadgraft, 1994). It is worthy of note that the published value is essentially higher than even log GTN permeability across the Carbosil membrane (log $P_m = -2.63$ cm/h) measured in the course of GTN delivery from the TTS hydrophilic matrix.

The contribution of all the different drug diffusion and drug sorption parameters individually or in combination to the drug delivery kinetics from the hydrophilic TTS matrix across the membrane cannot lead to a satisfactory approximation of computed and experimental drug delivery kinetic profiles. The reason of this inadequacy may be in the initial assumption that all the parameters analyzed are constants and do not alter with time up to the complete release of the drug from the matrix. In reality, the TTS skin application period in vivo or the duration of in vitro experiments may be sufficient for their variation in time. The drug delivery rate from the hydrophilic TTS matrix was shown above to be controlled by the drug mass transfer across the penetration barrier. Consequently, the assumption seems to be logical that the drug permeation through the human skin epidermis or membrane may not be constant and increases due to skin or membrane hydration. Similar modification of the barrier structure could be produced by the diffusion of oligomeric PEO molecules from a TTS matrix into the barrier. These changes in skin or membrane properties in the process of drug delivery may compensate for the decrease of drug concentration in the matrix because of an increase in the drug diffusion coefficient within the barrier. The introduction of the drug diffusion coefficient in membrane ($D$)-time relationship according to the simple linear Eq. (2):

$$D = Do + kt \tag{2}$$

where $Do = 1 \times 10^{-12}$ m$^2$/s and $k = 0.07 \times 10^{-12}$ h$^{-1}$ gives the best approximation of the kinetic profile from the computed curve (Fig. 3).

The changes in membrane structure mentioned were actually observed in the course of the experiment when propranolol release time was more than 100 h. This modification of membrane structure may be the reason for the noted imbalance between the experimental value for the propranolol diffusion coefficient in the membrane ($22 \times 10^{-12}$ m$^2$/s and the computed magnitude ($1.1 \times 10^{-12}$ m$^2$/s). The experimental value was estimated by measurement of the time it takes for half the drug transfer across the membrane in aqueous solution at 35°C (22–44 h depending on membrane thickness). These conditions are quite sufficient for complete membrane hydration.

### 4.5. In vivo transdermal drug delivery kinetics

Skin penetration is the central rate-limiting step of in vivo transdermal drug delivery from most of

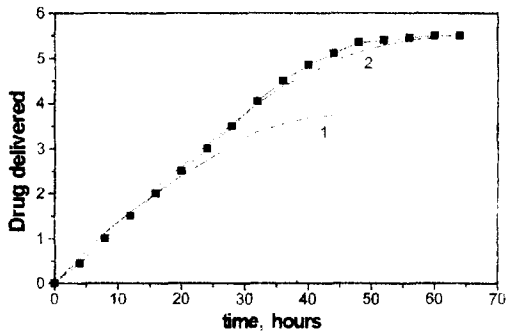


Fig. 3. Kinetics of propranolol (mg) delivered in vitro from 1 cm$^2$ TTS area across Carbosil-2 membrane. 1, Drug diffusion coefficient in membrane is time independent ($D = 1 \times 10^{-12}$ m$^2$/s); 2, $D$ is linear function of time (Eq. 2). Dash lines, computed curves (1,2), points are the experimental data. Drug diffusion coefficient in matrix is D= $1.1 \times 10^{-11}$ m$^2$/s. Membrane, matrix drug partition coefficient is 0.22. Membrane and matrix thickness is 0.04 and 0.6 mm, respectively.

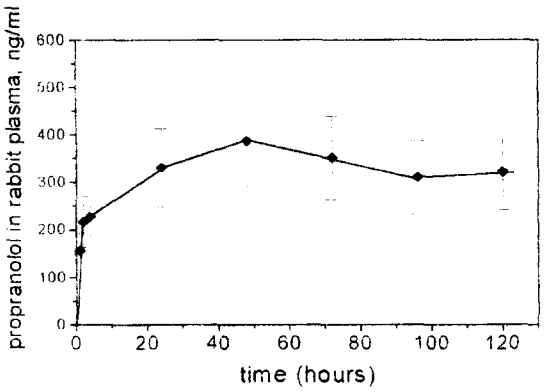


Fig. 4. Propranolol concentration in rabbit plasma (ng/ml) after Propercuten-forte TTS skin application ($S$ = 30 cm$^2$/kg, $N$ = 5).

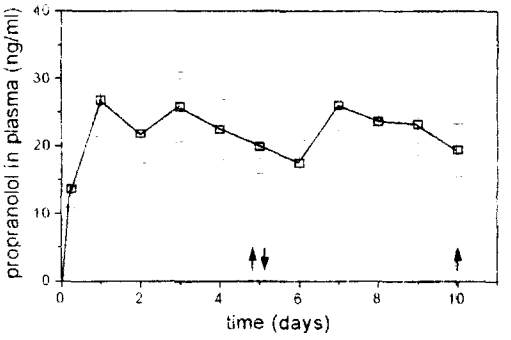


Fig. 5. Propranolol concentration in human plasma (ng/ml) ($N$ = 8) after TTS Propercuten-forte skin application ($S$ = 48 cm$^2$). Changes of applications are marked by the arrows.

the developed TTS (Hadgraft et al., 1991). The extrapolation of the in vitro test results to the in vivo situation may be reasonable only if the drug appearance in the receptor solution is controlled by the properties of the formulation, but not by the properties of the membrane (Guy and Hadgraft, 1990). The data presented above show that penetration barrier resistance to drug transfer is the dominating factor controlling drug delivery kinetics from the TTS hydrophilic matrix. It does not eliminate the necessity for investigation of in vitro drug delivery kinetics and comparison of in vivo and in vitro data. In our case the situation is facilitated in a qualitative sense because the fractional contributions of the Carbosil membrane and the skin to drug delivery rate control are close together and the skin resistance to transdermal drug transfer in vitro and in vivo is higher than the Carbosil membrane resistance in vitro. Hence, the in vivo transdermal drug delivery rate from the hydrophilic TTS matrix should be lower than the in vitro delivery rate across the membrane. In other words, in vivo transdermal drug delivery rates from the hydrophilic TTS matrix should be controlled by the skin permeability. For this reason, on the basis of our in vitro data for propranolol, GTN and ISDN zero-order transdermal delivery kinetics could be expected with a lower rate than that in vitro.

The pharmacokinetics of propranolol delivered transdermally to rabbits and humans from TTS Propercuten are presented in Figs. 4 and 5 (Pyotrovsky et al., 1993; Feldstein et al., 1994a). The steady state propranolol concentration in rabbit and human plasma is achieved not later than 24 h after TTS application. The propranolol plasma level is constant during the whole period of TTS application (up to 6 days), suggesting that in vivo transdermal drug delivery kinetics are zero-order. It follows from these data that observed in vitro and enhanced-in-time barrier permeability noted above could occur in vivo since the penetration barrier is the skin. The similar in vivo effects of drug enhanced-in-time skin permeability are well known (Barry, 1991): stratum corneum resistance to drug diffusion decreases with skin hydration produced by an occlusion. This phenomenon should be taken into account especially in long-term TTS application to the skin.

The rates of propranolol zero-order transdermal delivery in vivo from the hydrophilic TTS

Table 4
In vivo rates of propranolol transdermal delivery and release in rabbits and humans

| Parameter | Rate ($\pm$ range, $\mu$g/cm$^2$ h) |
|---|---|
| Mean rate of transdermal delivery: | |
| to rabbits | 80.0 $\pm$ 11.1 |
| to humans | 22.7 $\pm$ 4.9 |
| Mean rate of in vivo drug release to volunteers ($N$ = 6) | 20.0 $\pm$ 9.0 |

Table 5
Comparative pharmacokinetics of propranolol in humans under transdermal delivery from Propercuten TTS and as predicted theoretically by Guy and Hadgraft, 1985

| Parameter | As observed in clinical trials[a] | As predicted by Guy and Hadgraft, 1985 |
|---|---|---|
| Range of steady state concentration in human plasma, ng/ml | 22.0 ± 4.4 | 20 |
| Steady state concentration attainment period, h | 24 | 24 |
| Steady state concentration maintenance period, days | 7 | 7 |
| Range of zero-order transdermal delivery rate, $\mu g/cm^2$ h | 22.7 ± 4.9 | 35 |
| TTS application area, $cm^2$ | 48 | 30 |

[a]Feldstein et al., 1994a.

matrix to rabbits and humans calculated using Eq. (1) are presented in Table 4 together with the in vivo release rate determined from the remainder of propranolol content in matrix after TTS removal from the human skin. It is evident from the tabulated data that the in vivo propranolol transdermal delivery rate in humans is in close agreement to the in vitro propranolol delivery rates across a human cadaver skin (Table 3): 26 ± 15 $\mu g/cm^2$ h. The rate of propranolol transdermal delivery to rabbits was fourfold higher than to humans. From the comparison of in vivo propranolol transdermal delivery and release rates it is clear that propranolol bioavailability following transdermal administration in human is close to 100%.

The propranolol steady state concentration in human plasma is proportional to the TTS application area. Thus, TTS applications of 48 and 30 $cm^2$ produce $C_{ss}$ = 22.0 and 15.3 ng/ml, respectively. With a 1.6-fold increase of TTS application area, the drug steady state concentration in human plasma is 1.5 times higher. The rate of propranolol transdermal delivery in vivo is controlled by skin permeability. As is obvious from the pharmacokinetic data, propranolol permeability across human forearm skin is two times higher than across chest. In vivo rates of transdermal drug delivery to rabbits from TTS with 13.8 and 7.4% propranolol in the matrix were 80.0 and 73.0 $\mu g/cm^2$ h, respectively (Pyotrovsky et al., 1993), although in vitro delivery rates from these systems across Carbosil membrane differed markedly (Table 3). The pharmacokinetic data obtained for propranolol transdermal delivery from hydrophilic TTS to humans are in excellent agreement with the predicted results of Guy and Hadgraft (1985) (Table 5).

The pharmacokinetics of GTN and ISDN in rabbits after transdermal drug delivery from TTS Nitropercuten and Sorbopercuten are presented in Figs. 6 and 7 (Pyotrovsky et al., 1991). The steady state GTN concentration in rabbits plasma was achieved 1–2 h after TTS application and in 3 h for ISDN. The maintenance time of drug steady state concentration in rabbits plasma was > 24 h for GTN and 48 h for ISDN after TTS application to skin. The transdermal drug delivery rates, calculated from Eq. (1) after determination of

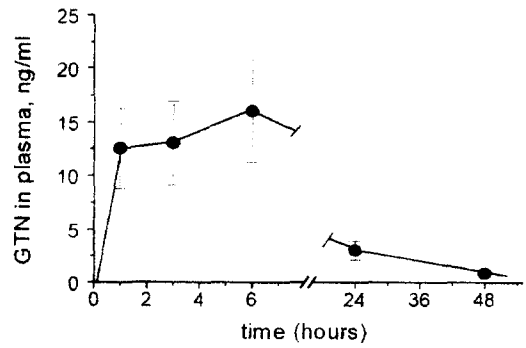


Fig. 6. Glycerol trinitrate concentration in rabbit plasma (ng/ml) after TTS Nitropercuten-forte skin application ($S$ = 10 $cm^2$/kg, $N$ = 5).

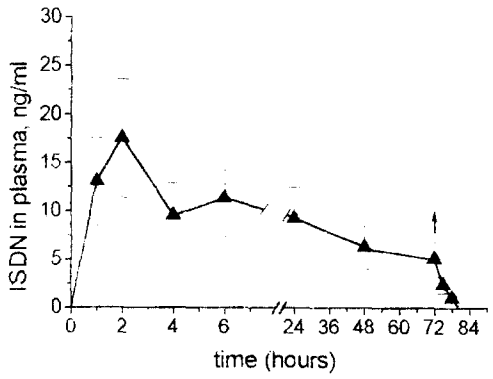


Fig. 7. Isosorbide dinitrate concentration in rabbit plasma (ng/ml) after TTS Sorbopercuten skin application ($S$ = 5 cm$^2$/kg, $N$ = 6). The time of TTS removal is marked by the arrow.

intravenous $V_d$ and $K_{el}$ values for experimental animals were 80 $\mu$g/cm$^2$ h for GTN and 32 $\mu$g/cm$^2$ h for ISDN. In vivo GTN release rate in human was estimated from the remaining GTN in the matrix after TTS removal from the skin. This rate was 24 $\pm$ 10 $\mu$g/cm$^2$ h.

A clinical pharmacokinetics study of TTS with GTN and ISDN is now in progress. As was shown in preliminary studies in two volunteers, in the course of transdermal ISDN delivery from TTS, partial biotransformation occurs in human skin with isosorbide mononitrate metabolites being formed, predominantly 5-ISMN. Thus, in the period 24–48 h after TTS application to skin of volunteers, the steady state concentrations in human plasma were 3–8 ng/ml (ISDN), 6–12 ng/ml (2-ISMN) and 25–61 ng/ml (5-ISMN) (Pyotrovsky et al., 1991). The data are in agreement with those obtained previously by Menke et al. (1987), for ISDN containing TTS 'Frandol tape '. The maximal drug concentration in human plasma after TTS Frandol tape skin application with area 100–300 cm$^2$ was 3 ng/ml (ISDN) and 20 ng/ml (5-ISMN). It is noteworthy that the hydrophilic TTS application area was 30–60 cm$^2$. Frandol TTS is based on a hydrophobic acrylate PSA matrix. The difference may be attributed to enhanced drug delivery from the hydrophilic TTS matrix.

The pharmacokinetics of ISDN, delivered transdermally across chest skin of two angina pectoris patients after TTS Sorbopercuten application with a dose 3·30 cm$^2$, is presented in Table 6 (Pyotrovsky and Blagodatskikh, unpublished data). ISDN and metabolite steady state concentrations in human plasma are achieved not later than 24 h after the first TTS application and remain steady up to 50 h. These data allow us to determine the in vivo ISDN transdermal delivery rate from the hydrophilic TTS matrix to humans in accordance with Eq. (1) and based on the values of ISDN and 5-ISMN intravenous infusion clearances of 4.05 l/min and 125 ml/min, respectively (Welling and Tse, 1985). In vivo drug delivery rates from hydrophilic TTS in human are 7.3 $\mu$g/cm$^2$ h for ISDN and 3.8 $\mu$g/cm$^2$ h for 5-ISMN. These rates correspond to the total ISDN delivery rate in vivo of 12.0 $\mu$g/cm$^2$ h. Taking into consideration that part of the ISDN delivered is transformed into 2-ISMN, an expected value for the in vivo ISDN total delivery rate from TTS Sorbopercuten of 15–17 $\mu$g/cm$^2$ h may be reasonable.

### 4.6. Results of TTS clinical trials

TTS with propranolol exhibits effective hypotensive and antianginal action beginning 20–24 h after the first TTS application with an area of 30–48 cm$^2$, which was maintained over the course of a 2-week alternate application with TTS replacement every 5 days. Negative chronotropic action was noted in 74% patients and was evident in a 12–15% systolic blood pressure decrease, an 11–15% diastolic blood pressure decrease and a 20–28% heartbeat frequency decrease. After 24–48 h of TTS application, antianginal action was recorded in 67% of patients and was expressed in a 37–39% increase in the mean time to development of moderate anginal attacks on a treadmill exercise test. The decrease in the daily requirement for GTN tablets was more than 50%. Adverse effects (mild erythema) were observed in 15% of patients.

Antianginal action of GTN TTS in 53% of patients was expressed 2 h after TTS skin application to an area of 35 cm$^2$. This effect was permanent over the course of $>$24 h of every TTS application. The daily requirements for GTN

Table 6
ISDN and metabolites concentration in human plasma after TTS Sorbopercuten application

| Time after TTS application (h) | Mean drug concentration in plasma ( ± S.D., ng/ml) | | |
|---|---|---|---|
| | ISDN | 5-ISMN | 2-ISMN |
| 24 | 3.8 ± 1.4 | 46.5 ± 4.5 | 7.2 ± 0.7 |
| 48 | 2.1 ± 0.1 | 43.5 ± 0.7 | |
| 50 | 2.1 ± 1.0 | 47.0 ± 0.3 | 6.5 ± 0.5 |
| Mean value | 2.7 | 45.7 | 6.9 |

tablets reduced to 45% on the first and second days after the first TTS application. For the other 27.5% of patients, the decrease in the above mentioned indexes was 25–50%. In patients with acute myocardial infarction, the antianginal effect was more evident (70%). Registered side effects were skin irritation (6%) and headache (15.5%).

The antianginal effect of ISDN TTS was determined from tolerance to physical exercises. For 57% of patients, a stable effect has been attained 6 h after TTS skin application and was permanent even after 48 h. In 92% of patients, the ISDN therapeutic dose was 1–2 patches (30–60 $cm^2$). This dose is significantly below the Frandol tape application area (100–300 $cm^2$) (Menke et al., 1987) and indicates that the ISDN transdermal delivery rate is enhanced from a hydrophilic matrix. The daily requirement for GTN tablets to prevent attacks was reduced to 50 and 64% on the first and second day, respectively, after Sorbopercuten application. Adverse effects were observed in 11.3% patients (skin hyperemia) and in 13% (headache).

## 5. Conclusions

The drug delivery rates from the hydrophilic TTS matrix are higher than from the hydrophobic ones and depend on the drug solubility in water. Drugs of various chemical structures may be incorporated in the PVP-PEO matrix. In vitro delivery kinetics of propranolol, GTN and ISDN from the hydrophilic TTS matrix have zero-order up to 75–85% of drug release. Drug delivery kinetics from hydrophilic TTS matrix are controlled by the penetration barriers: skin-imitating Carbosil membrane in vitro, skin in vitro and in vivo. The observed zero-order drug delivery kinetics from hydrophilic TTS matrix may be produced by the enhanced-in-time drug permeability across penetration barrier in the course of barrier hydration.

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