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Development of biphasic transdermal nitroglycerin delivery systems

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Summary

A number of transdermal systems exist which provide steady nitrate levels over a period of 24 h. Recent investigations have identified the potential for development of nitrate tolerance with these dosage regimes. Therefore, novel delivery systems have been developed to reduce the incidence of tolerance. The design strategy and in vitro testing of such a delivery device is described. In vitro release across hairless mouse and human skin is compared. The data generated from these experiments are used to predict in vivo blood levels. The results are substantiated using computer simulations and experimentally determined in vivo levels.

Introduction

Currently marketed transdermal delivery systems (TDS) containing nitroglycerin (GTN) maintain fairly constant blood levels of GTN over the 24 h application (Müller et al., 1982). When higher GTN doses are therapeutically required, the constant drug input may lead to nitrate tolerance. This provides a possible explanation of the clinical results which show decreasing anti-ischaemic effect within 8–12 h after patch application. Tolerance may also be responsible for the decreased clinical response noted after repeated administration (Reineger and Rudolph, 1985). It is therefore desirable to develop a GTN-TDS that offers a time-dependent, non-constant drug delivery input rate which would minimise tolerance. Additionally, new concepts in transdermal GTN administration should take into consideration the necessity to reduce production and hence patient costs.

One approach is represented by a new biphasic release system [S 917 (Phasonit, Biophase), manufactured by Schwarz Pharma AG, Monheim, F.R.G.] which was developed to reach high GTN blood levels within the first 12 h after application. This should prevent exercise-induced anginal attacks and provide low GTN levels during the night to reduce the development of tolerance. In order to optimise the delivery system a range of factors should be considered. These include the physicochemical properties of both the drug, the TDS and the skin. The major parameters which are important in formulation design are presented in Table 1. A high thermodynamic activity of the drug with appropriate time-dependent release characteristics from the polymeric matrix should be achieved by the formulation strategy.

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TABLE 1

Factors affecting drug release rates from transdermal delivery systems (TDS)

(I) System factors
drug concentration
total drug content
drug solubility
drug dispersity
polymer viscosity
water uptake
matrix crystallinity
(II) Biological factors
permeability of stratum corneum (sc)
lipid content and composition
water content
solubility of drug in sc
permeability of viable tissue (vt)
partitioning between sc and vt
metabolism
(III) System and biological factors
partitioning between device and sc
interactions between skin and TDS components
hydration effects
uptake/release of substances besides drug
irritancy
drug and formulation components
adhesion between TDS and skin
microflora between TDS and skin

The Biphasic Transdermal GTN system has been developed with the above pharmaceutical concepts. The main factors (Table 1) that can influence the delivery of the drug into the systemic circulation may be attributed to the physicochemical properties of the TDS (I), the skin (II) and a combination of both (III). The factors listed in Table 1 represent important considerations in formulation development. High thermodynamic activity of the drug as well as an appropriate viscosity of the TDS matrix system should be achieved.

Since the transdermal absorption rate of GTN can be limited by the barrier properties of the skin, the provision of time-dependent release for the TDS has to be checked in vitro and in vivo. The complexity of factors that may control the drug release include interactions between skin and TDS components. Substances beside GTN must be regarded (e.g. water), which may be absorbed or retained by the skin, or the TDS matrix, and which may lead to a changed release capacity of the pharmaceutical dosage form and/or to a changed skin permeability. Like some other marketed GTN patches, the biphasic TDS can be classified as an adhesive-type matrix system. Its structure (Fig. 1), reveals similarities to the multi-

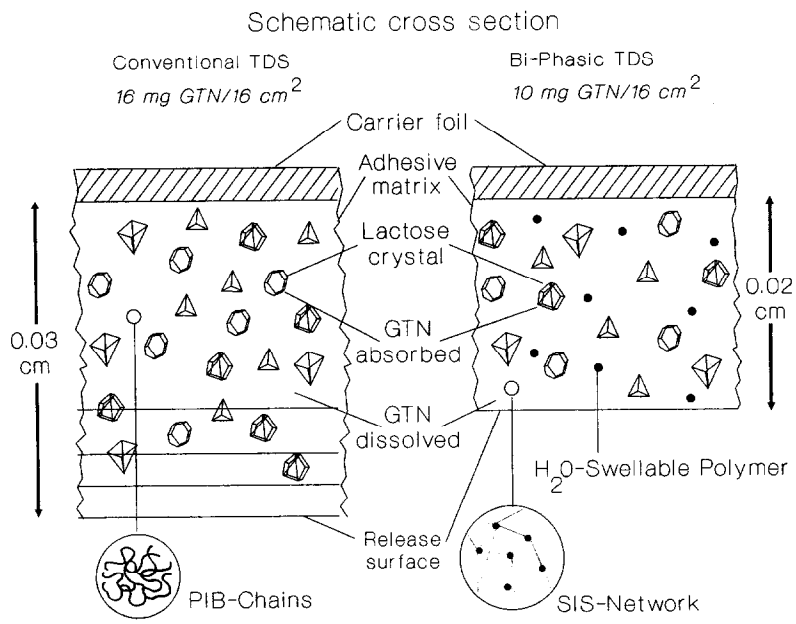

Fig. 1. Schematic structure of two different matrix-type TDS for GTN.

layered matrix system, Deponit (Schwarz Pharma AG, Monheim) (Wolff et al., 1985). Both systems consist of a GTN-loaded self-adhesive matrix that is supported by a carrier foil. The schematic cross-section illustrates that the matrix of the biphasic TDS:

(i) is 30% thinner than Deponit (0.02 cm in comparison to 0.03 cm);

(ii) has a mono-layered structure with a homogeneous distribution of all ingredients whereas Deponit is constructed in several layers to enhance the concentration of the GTN absorbed on lactose crystals towards the carrier foil;

(iii) contains an additional water-swellable ingredient to improve skin compatibility and modify release characteristics;

(iv) contains a different polymeric backbone than Deponit; the polyisobutylene (PIB) chains incorporated are exchanged by shorter *p*-styrene-*p*-isoprene-*p*-styrene (SIS) molecules that form a flexible, three-dimensional network by interaction of their *p*-styrene endblocks. The chemical structure of the different monomer units composing the polymer skeleton of the adhesive is shown in Fig. 2.

The in vitro experiments required to validate the release profiles are described and comparisons made with an existing membrane moderated TDS and Deponit. Studies were conducted to examine the intrinsic release rates, and the transport of GTN across both hairless mouse and human skin. The release rates can then be used in a mathematical model for transdermal delivery to predict the plasma levels of GTN (Guy and Hadgraft, 1985). In vivo human volunteer studies were then conducted and show that the model used was predictive.

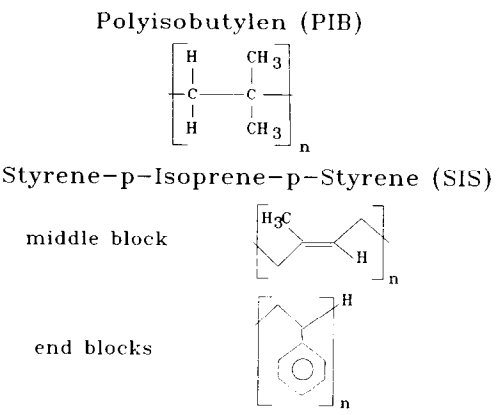

Fig. 2. Monomer units of SIS and PIB elastomers constituting the adhesive-type TDS that are shown in Fig. 1.

Experimental

In vitro release profiles

The intrinsic in vitro release was measured in a conventional manner by determining, by HPLC, the amount of GTN appearing in isotonic saline in direct contact with the delivery system. Comparisons were made with Deponit and a currently marketed membrane moderated system. Fig. 3 shows the results and clearly demonstrates the differences in release patterns. The membrane moderated system, designed to release at a constant rate, achieves this objective extremely well. The slightly increased release rate in the first time interval is caused by the presence of the loading dose of GTN in the adhesive layer. The biphasic TDS system, in contrast, releases 80% of its contents in the first 6 h and only a small fraction is released in the 18–24 h time interval. Deponit has an intermediate profile but still produces relatively constant release over the 6–24 h period. This is achieved by a sophisticated design technology without recourse to membrane moderation.

Validation studies have been conducted, in the first instance, using excised hairless mouse skin. The full-thickness mouse skin was mounted in conventional diffusion chambers and the patches adhered to the skin surface. The GTN content in the receptor phase (distilled water) was measured using HPLC and the observed release patterns for the three products are presented in Fig. 4. The results are expressed as a percentage of the mean cumulative amount released over the 24 h. This method of presentation is used to normalise the results to facilitate comparison, since the GTN contents of the products are different. Fig. 4 confirms the intrinsic release characteristics given in Fig. 3. The membrane moderated and Deponit systems provide constant fluxes whereas the biphasic system gives maximum flux in the first 6 h. By 24 h the flux has dropped by approximately a

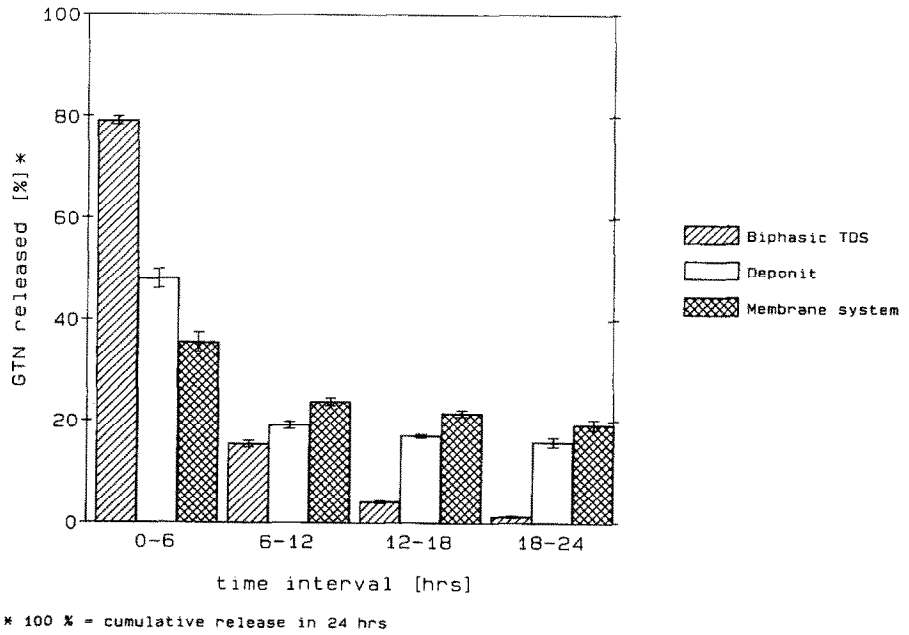

Fig. 3. Mean in vitro GTN release rates (±S.D.) measured at 32°C for different TDS ($n = 6$).

factor of five and the time-dependent release designed into the system is clearly demonstrated. The results are not quite as pronounced as for release in the absence of skin. This is because the skin contributes to the overall rate of penetration and produces a moderating effect.

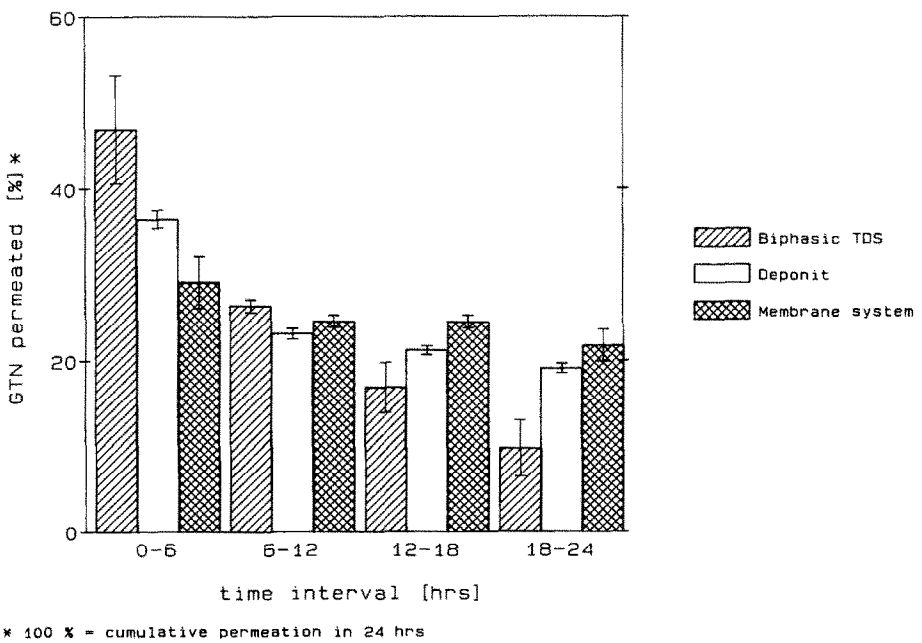

Fig. 4. Mean in vitro GTN skin permeation rates (±S.D.) measured at 32°C across hairless mouse skin for different TDS at several time intervals ($n = 6$).

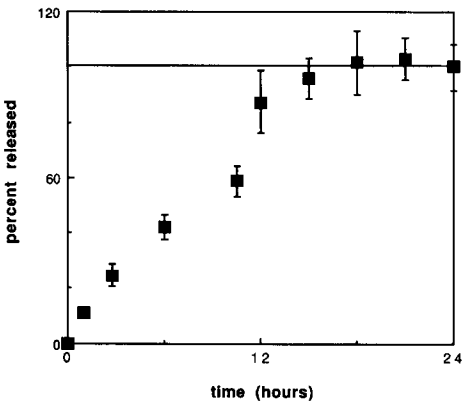

Fig. 5. Time profile of GTN skin permeation across human cadaver skin from a biphasic TDS ($n = 3$; 32° C).

Final in vitro evaluation was conducted on excised human skin dermatomed to 220 μm. This thickness was chosen to reflect the diffusional path length from the skin surface of the capillary network. The skin was mounted in conventional, all-glass, Franz diffusion cells and the biphasic system adhered to the outer face of the skin. Regular samples were removed from the pH 7.4 phosphate-buffered receptor phase and analysed for GTN content by HPLC. The results were conducted in triplicate and no comparisons made, in this instance, with the Deponit or the membrane moderated system. Fig. 5 shows the results and demonstrates again that the biphasic system delivers the majority of its payload in the initial period after application with 40 and 90% release after 6 and 12 h, respectively.

In vivo release profiles

Human volunteer studies were conducted following ethical approval and GTN content in the patch, after various application times, measured. Fig. 6 illustrates the time profile for apparent GTN release determined by measuring the residual GTN in the patch after 6, 12, 18 and 24 h, respectively. Further moderation in release, compared to Fig. 4, is seen since human skin, in vivo, contributes more to the overall permeation rate than in vitro excised hairless mouse skin. Nevertheless, comparison with human in vitro skin permeation is good, and shows that the system releases 40% of its contents in the first 6 h of application. For a patch of size 16 cm^2 (GTN content 10 mg), 5 and 7.5 mg were absorbed by

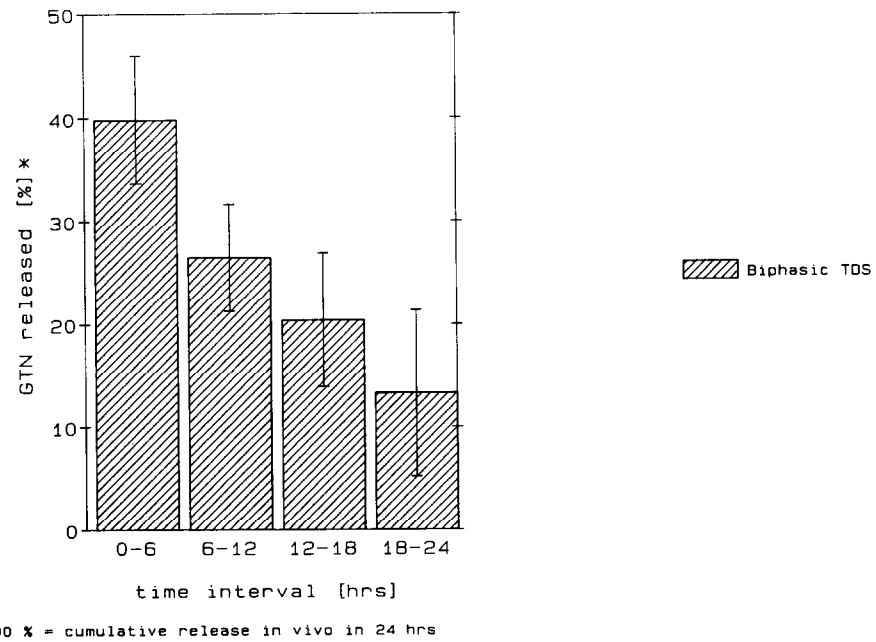

Fig. 6. Apparent mean (±S.D.) GTN release rates in vivo (in human volunteers) of biphasic TDS over 24 h ($n = 11$).

the skin after 12 and 24 h, respectively. A second volunteer study was also conducted to compare the effect of area of application. 16 and 32 cm^2 systems were applied to the skin and residual GTN determined after 24 h application. The results are presented in Fig. 7 and show the expected linear relationship between amount of drug absorbed and area of application.

Fig. 7 also gives an indication of absorption reproducibility with a coefficient of variation of less than 20% for the mean apparent drug release in 24 h. The apparent drug release has also been compared, using a similar experimental protocol, with commercial TDS systems having declared release rates of 5 and 10 mg GTN/24 h. The results are provided in Fig. 8 and demonstrate the good reproducibility of the biphasic system in comparison with several conventional TDS (Noonan et al., 1990).

Plasma concentration determinations

A phase I study was conducted in eight human volunteers with repeated application of the biphasic system over a 5-day period (Wiegand et al., 1988). The GTN plasma concentration was measured by capillary gas liquid chromatography with

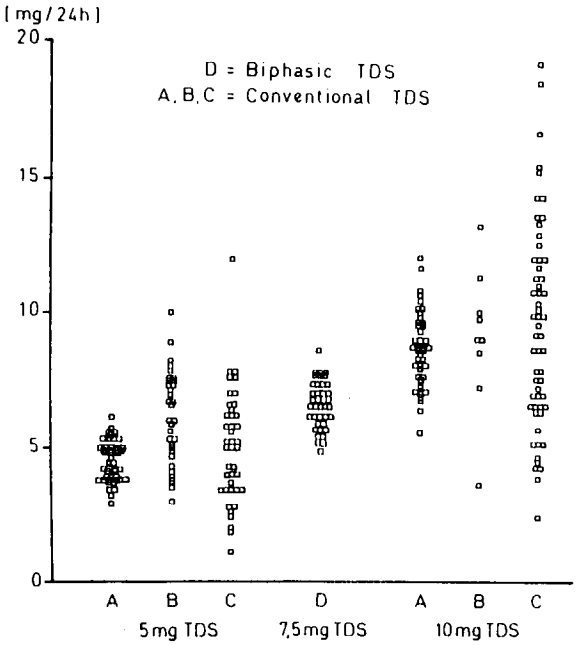

Fig. 8. Apparent GTN release in vivo over 24 h of several conventional 5/10 mg TDS (A–C) and a biphasic 7.5 mg TDS (D); values of B and C adapted from Noonan et al. (1990).

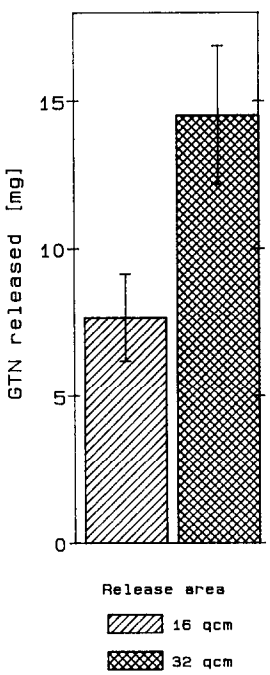

Fig. 7. Influence of the patch size (biphasic TDS) on the apparent GTN release (±S.D.) in vivo during 24 h ($n = 12$, human volunteers).

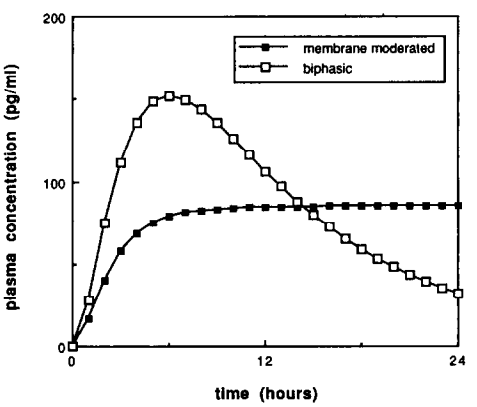

Fig. 9. Predicted GTN plasma concentration over a 24 h period for the biphasic system and a membrane moderated system. Using the notation from Guy and Hadgraft (1985), the rate constants are k_1 (0.15 h^{-1}); k_2 (2.36 h^{-1}); k_3 (53 h^{-1}); k_4 (18.24 h^{-1}); V_d (231 l). For the membrane moderated system; k_0 (0.036 mg/cm^2 per h), k_a (1.3 h^{-1}), loading dose in adhesive (2 mg), area of application (10 cm^2).

an electron capture detector (Boertz et al., 1987). The GTN plasma levels are shown in Fig. 10. More frequent plasma levels were determined both after the initial application and from 96–120 h. The results show a rapid rise in the GTN plasma levels and significantly higher amounts during the first 12 h after patch administration. At the end of each application the GTN levels had dropped to below 50 pg/ml. This latter low delivery rate of GTN may be useful in preventing ischaemic episodes during this time.

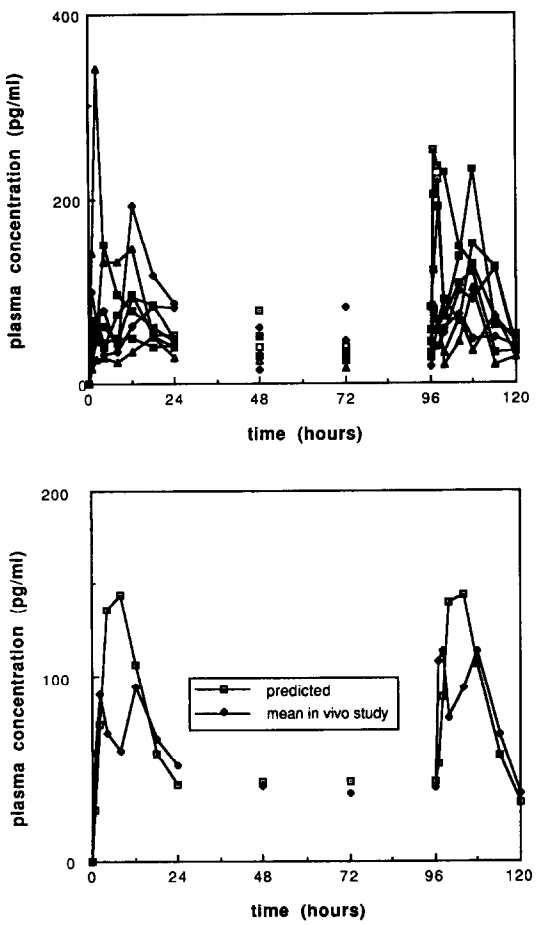

Fig. 10. Experimental ($n = 8$) and predicted GTN plasma concentration time profiles during repeated once-a-day application of a biphasic TDS. The data were collected at short time intervals during the first and fifth day and at daily intervals during the interim times.

The plasma levels of GTN may be predicted using a kinetic model for transdermal delivery. Guy and Hadgraft (1985) described a model which predicted GTN levels after the application of a membrane moderated system. The input function from such a device was described as the sum of a first- and zero-order rate constant. The release pattern for the biphasic system is more complex but recent developments using a commercially available software package (STELLA, High Performance Systems) has allowed graphical input of the release behaviour. Using the release pattern described by Fig. 3 and the rate constants given in the corresponding figure legend, it is possible to predict the GTN levels after single or multiple application. The predictions are given in Figs 9 and 10. Fig. 9 shows the difference in predicted plasma levels after application of the biphasic system and a membrane moderated system. Fig. 10 demonstrates a striking similarity between the predicted and the measured in vivo levels showing the utility of a computer based predictive model. In Fig. 10 the peak plasma values at times between 24 and 96 h have been omitted for clarity and the data points plotted to coincide with those determined in vivo.

Conclusion

In contrast to the tested conventional TDS already described in the literature, the new matrix system is characterised by an initial fast drug input followed by a pronounced decline of drug release rate during the 24 h application period. The biphasic or exponential release pattern has been proved by in vitro and in vivo experiments including determination of GTN plasma levels in human volunteers. The desired release profile was achieved by modifying the composition and structure of an already marketed multi-layered matrix system. The new device releases in vivo approx. 5 mg GTN/16 cm^2 per 12 h and approx. 7.5 mg/16 cm^2 per 24 h. The reduced drug content as well as a high bioavailability generated from a relatively small system area is beneficial in both safety and economic aspects in TDS development.

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