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Review

Pharmaceutical aspects of transdermal nitroglycerin

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Abstract

Transdermal delivery has become an important method for the delivery of nitroglycerin in the treatment of angina. Developments have been made over the decade and the purpose of this mini-review is to highlight some of the more important developments in a critical manner. Many of the concepts are of general relevance to the transdermal field and it is instructive that many of the system designs for other drugs that are delivered transdermally have been based on the information gained from GTN delivery. Safety is of paramount importance but for a product to be successful it must also have good patient compliance. The future of transdermal delivery must consider these two aspects and the role that basic physical chemistry has to play in this cannot be underestimated. From first principles it is possible to predict that GTN is a good transdermal candidate, from an in vitro assessment it is possible to predict the expected plasma levels. The more difficult aspect to predict is the potential side effects from the drug itself and problems such as tolerance.

Keywords: Transdermal drug delivery; Nitroglycerin; Skin absorption

1. Introduction

Transdermal delivery of nitroglycerin from polymeric devices has been around for over a decade and significant advances have been made in this field. The objective of this paper is to review the development of this route of nitrate delivery and to assess its relative merits. GTN is an ideal substance to deliver transdermally, its physicochemical properties, partition characteristics, solubility (and low melting point) and small size predicate a high skin permeability. It is a potent drug with required therapeutic levels of the order of hundreds of pg/ml and it has a short biological half-life with extensive first pass metabolism. In order to maintain therapeutic levels over a 24-h period about 10 mg of drug are required. It is relatively easy to deliver this amount over a skin area of less than 50 cm^2.

In the development of transdermal GTN it is easy to monitor the advances that have been made and the techniques used to control the delivery of the drug typify the approaches made for other passively delivered transdermal drugs. The review therefore has relevance to the general aspects of transdermal delivery in which physical

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techniques for enhancing skin permeability (e.g. iontophoresis) have not been used.

The simplest and least elegant, but least costly, method for delivering GTN transdermally is using a conventional topical base. Nitrobid ointment for example is delivered by applying a predetermined length of the ointment base, rubbing it into the application area (usually the chest) and covering the area with an occlusive plastic sheet. The GTN plasma levels that are obtained are shown in Fig. 1 (Chu et al., 1984). It is necessary to re-apply the ointment on an 8-hourly basis in order to sustain the therapeutic levels of GTN.

The first generation of transdermal patches that were marketed can be divided into two major sub-divisions: those based on polymeric matrices and those containing a rate-controlling membrane.

2. Matrix systems

In these the GTN is dispersed throughout a polymer. The polymer may be adhesive in its own right. If not, a further adhesive layer is required to adhere the delivery system to the skin. Nitrodur was one of the first examples of this type of

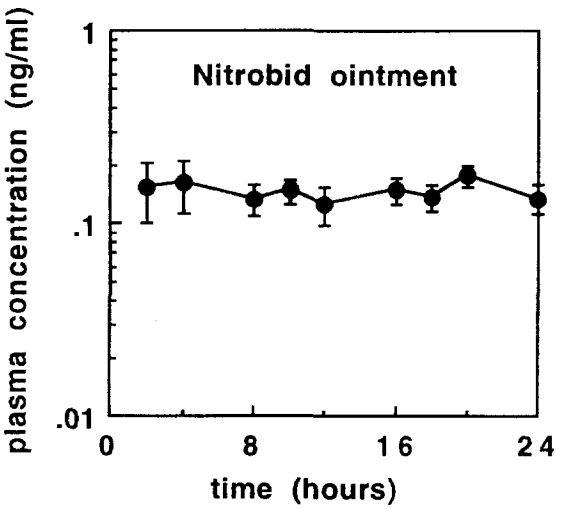

Fig. 1. The plasma levels obtained after the transdermal delivery of GTN from Nitrobid ointment (data adapted from Chu et al., 1984).

device. A schematic diagram of the device is given in Fig. 2. The original system was based on a plasticised poly (vinyl) pyrrolidone poly (vinyl) alcohol polymer into which the GTN was homogeneously dispersed. The system characteristics (size, drug load, etc.) are given in Table 1.

The in vivo plasma levels obtained are shown in Fig. 3 (Noonan et al., 1986). The patch acts as a reservoir of the GTN which penetrates through the skin to provide constant drug levels in the plasma over a 24-h period. Refinements to the patch were made and Nitrodur II introduced onto the market. It is composed of a cross-linked acrylate polymer and its characteristics are given in Table 1. It provides a similar plasma profile to Nitrodur and has been shown to be bioequivalent (Noonan et al., 1986). It too is a homogeneous system but is thinner and smaller in size than the original system making it more pliable. The size and pliability together with the adhesive used are important determinants in patient acceptability of the product. It is important to produce patches which are comfortable to wear and stay in place over the lifetime of application.

The area of patch in direct contact with the skin is important since the plasma levels obtained are in direct proportion to the contact area. The patch should be small enough but sufficiently pliable that it is able to follow the contours of the skin. The flow properties of the adhesive are also an important consideration. 'Bleeding' of the adhesive from the edges of the patch both during storage and after application should not be significant.

Another type of matrix system, slightly more complex than Nitrodur was the micro-sealed drug delivery system (Nitrodisc). In this system, small solvent droplets (e.g. PEG 400/water and hydrophobic solvents, e.g. isopropyl palmitate) are dispersed in a silicone polymer. GTN is dissolved both in the droplets and in the silicone. The polymer is not adhesive and an adhesive annulus is required to keep the patch in contact with the skin (Fig. 2). Details of the system are provided in Table 1. The plasma levels obtained from this system are given in Fig. 3 (Karim, 1983).

More complex still in design and manufacture is the Deponit system. This consists of a multi-

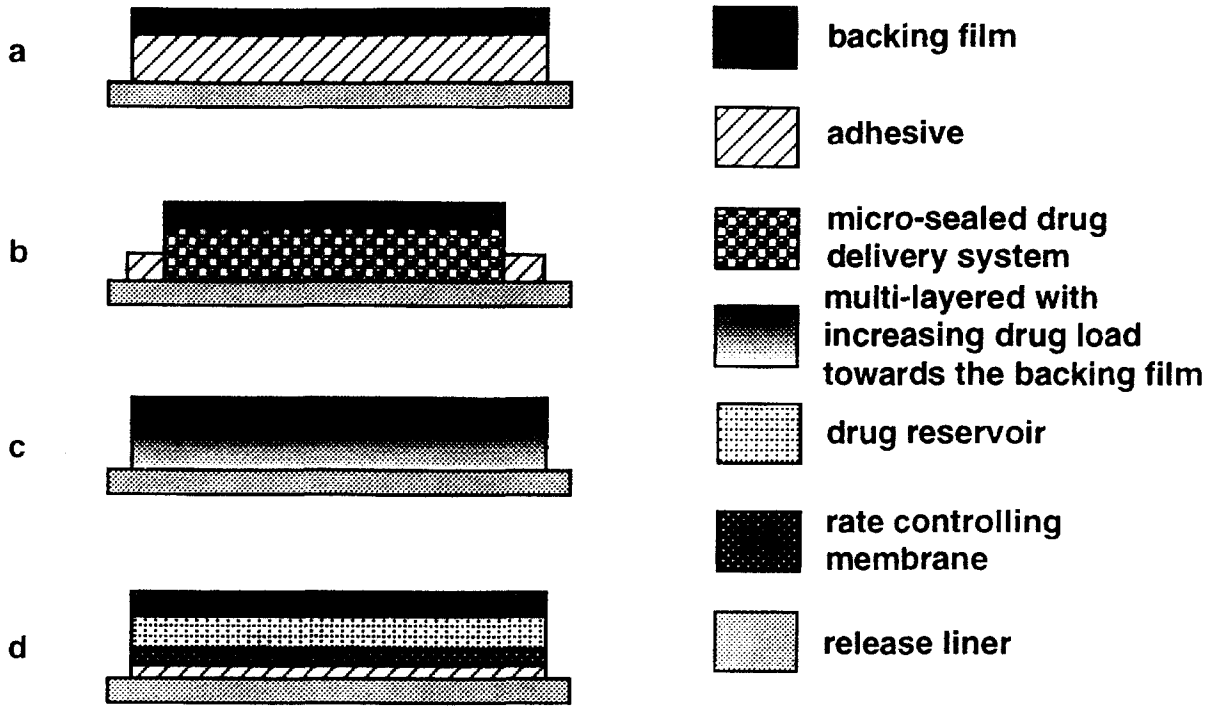

Fig. 2. Schematic representation of the various transdermal patches. (a) Homogeneous matrix system. (b) Microsealed drug delivery system. (c) Matrix system, a layered drug concentration profile. (d) Membrane moderated system.

layer device in which GTN is in solution in the polyisobutylene layers and also adsorbed onto lactose which is inhomogeneously dispersed throughout the system (Fig. 2). There is a carefully controlled amount of GTN absorbed onto the lactose in each of the layers. The further from the skin surface the larger the amount of lactose dispersed and hence the greater the amount of GTN. This gives rise to release characteristics which are significantly different to the two devices described above; this point will be discussed later. The characteristics of the Deponit system are provided in Table 1. Plasma levels are shown in Fig. 3 (Wolff et al., 1985).

Table 1
Characteristics of some GTN patches which release 0.4 mg/h in vivo.

	Contact area (cm^2)	Thickness (mm)	GTN content (mg)
Nitrodur II	20	0.13	80
Nitrodisc	16	3	32
Minitran	13.3	0.17	36
Deponit	32	0.3	32
SPM 751	18	0.1	37.4
Transderm Nitro	26	0.5	50

3. Penetration enhancers

One of the ways in which the device size can be reduced is to incorporate a penetration enhancer which will reversibly improve the permeation characteristics of the skin to the GTN. The enhancer should be identified such that it selectively enhances the penetration of the GTN. It can achieve this by increasing the solubility of the GTN in the skin lipids or lowering the diffusional resistance of the skin lipids. One of the matrix systems which adopts this approach is Minitran. It is a homogeneous polymeric system based on

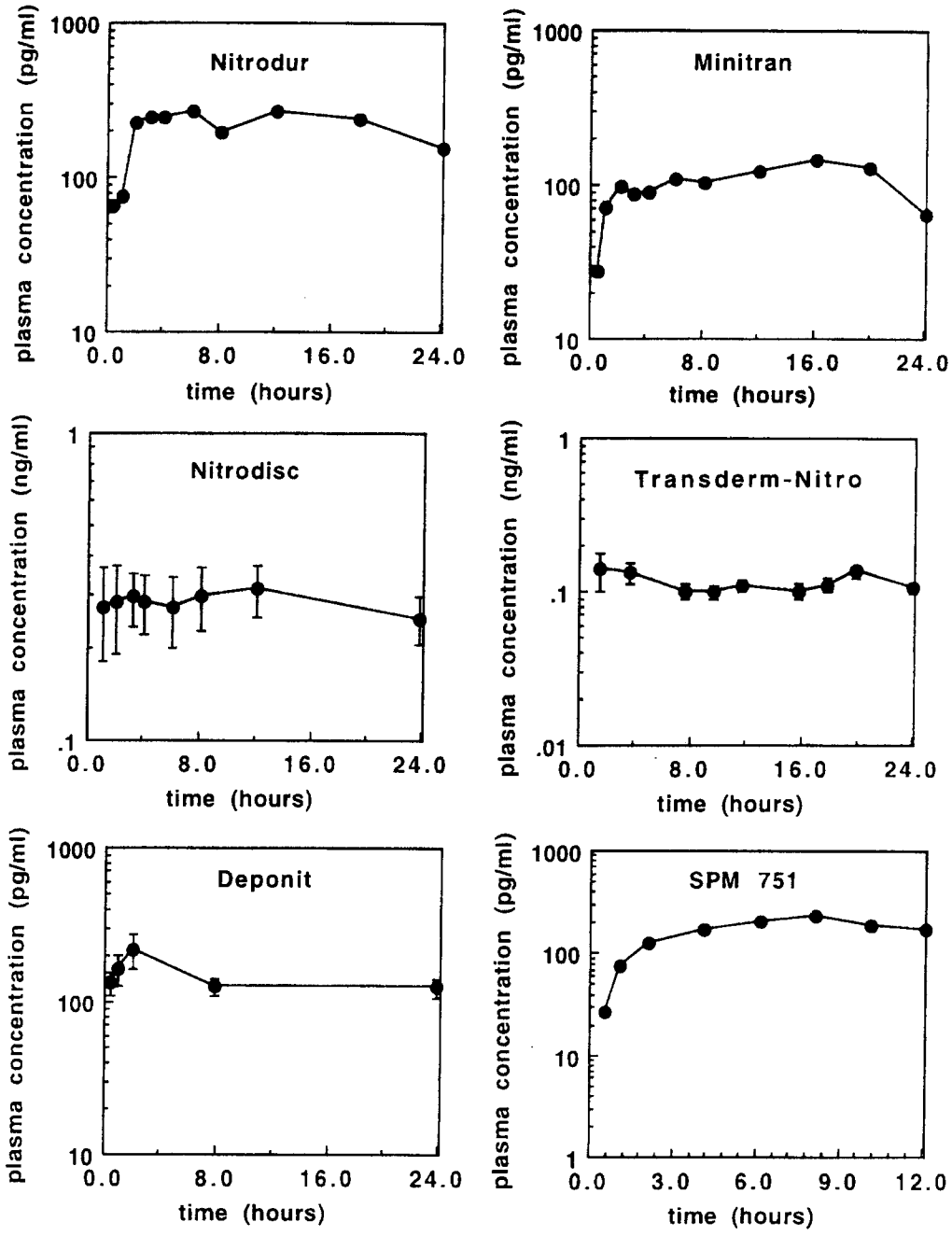

Fig. 3. Plasma levels obtained after the transdermal delivery of GTN from various patches. Data adapted from references provided in the text.

acrylate adhesives but additionally contains glyceryl monolaurate and ethyl oleate. The dimensions and other details of the patch are provided in Table 1. An example of the plasma levels obtained after transdermal application is provided in Fig. 3.

A more recent system that has been released onto a limited market is Nitrosylon which contains approximately 10% sorbitan mono-oleate in a Durotak adhesive. The presence of the sorbitan mono-oleate is thought to optimise the transdermal penetration of the GTN.

4. Membrane moderated devices

The most complex design and one which was pioneered by the company Alza contains a rate-controlling membrane (Fig. 2). This controls the delivery rate to the skin surface and therefore the maximum rate at which the GTN can be delivered to the systemic circulation. In order to maintain zero order release kinetics the GTN is dispersed in a reservoir such that it remains at saturation. This keeps the thermodynamic activity of the GTN at unity and, as long as GTN is maintained in the reservoir above its saturated solubility level, the patch will continue to provide drug at a constant rate. This is seen in the in vitro release kinetics shown later. The reservoir is a silicone oil base and the rate-controlling membrane is based on poly(ethylene vinyl acetate). The rate-controlling membrane is kept in place on the skin surface by a poly-isobutylene adhesive. The overall dimensions are given in Table 1 and plasma levels in Fig. 3 (Chu et al., 1984).

5. Tolerance

One of the problems in the development of transdermal GTN was the prevalence of patients experiencing tolerance if the devices were kept in contact with the skin for 24 h and replaced on a 24-h basis. This dosing schedule results in continuous and constant levels of the GTN and its metabolites in the plasma. For these nitrates this results in considerable tolerance difficulties and the way of circumventing this problem was to relabel the patches such that they were applied for a 12–16-h period. This regimen usually means that the patient has the patch in place during the day and the body is given a resting period overnight (the 8-h period whilst the patch is removed). A new patch is applied first thing in the morning. Under these conditions tolerance is avoided but there are problems of attacks of angina during the night and patient compliance is not as good as when patch removal time coincides with application of a new patch. An interesting consequence of discovering the problems concerning tolerance has been the renewed interest in the precise mechanism of action of the nitrates and the underlying cause of tolerance.

It has also resulted in an interest in the design of patches which can be applied for a 24-h period but which do not produce constant plasma levels. One such homogeneous matrix system is the Phasonit device (Hadgraft et al., 1990). The system contains GTN adsorbed onto lactose, water swellable polymers to modify release characteristics and an adhesive based on *p*-styrene *p*-isoprene *p*-styrene. The device provides a high activity of the drug with time-dependent release characteristics such that the GTN levels attained are high during the first 12 h of application and then they fall over the subsequent 12 h of application. This minimises potential tolerance but allows patch replacement on a 24-h basis. The design of transdermal systems which possess special programmed pulsatile delivery regimes will be significantly easier with the use of iontophoresis.

In order to optimise the delivery and to produce systems which are flexible and well tolerated it is desirable to have a high ratio of drug to polymer adhesive. This creates problems in design since a high drug ratio can significantly affect the adhesive properties of the polymer. Also for this compound it is important to design a matrix which is stable; it should not be forgotten that GTN possesses explosive properties. A novel design (SPM 751) has been described in which the drug loading is very high (40%) but the choice of adhesive is such that it retains excellent qualities. Mixtures of acrylate adhesives are used and the GTN is dissolved in these (Hadgraft et al., 1993a). One element of the adhesive is relatively hydrophilic which allows a

small but significant uptake of water. Excess water does not build up due to a water permeable backing. The small amount of water produces a high activity state for the GTN and enhanced delivery is possible. The plasma levels are shown in Fig. 3. It is likely that the GTN becomes supersaturated and phenomena such as those described by Davis and co-workers are possible. If excess water was allowed to build up the adhesive properties of the patch would diminish.

6. In vitro release

There are two main methods by which drug release can be determined. The first is the 'intrinsic' release in which the device is allowed to release its payload into an inert solvent sink such as water. This type of experiment is thus similar to a tablet dissolution study. It is useful in quality assurance and can be used to determine batch to batch variability. It cannot be used to predict the performance of the device in vivo. A number of methods for determining in vitro release characteristics have been described but in general they are based on the publication of Shah et al., 1986. The in vitro release characteristics of a number of representative devices are given in Fig. 4.

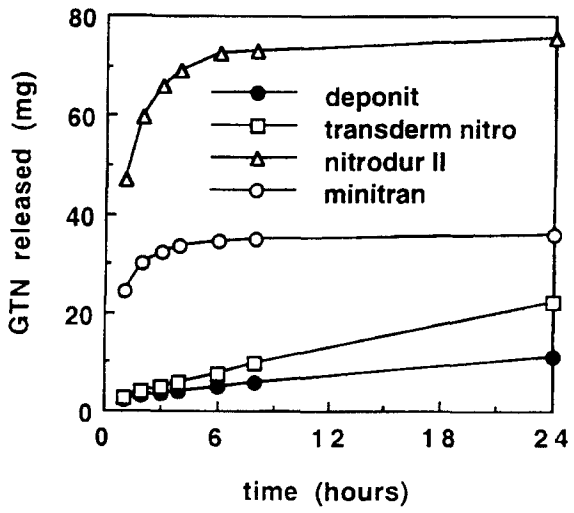

Fig. 4. The in vitro release profiles of four transdermal systems (data adapted from Hadgraft et al., 1991).

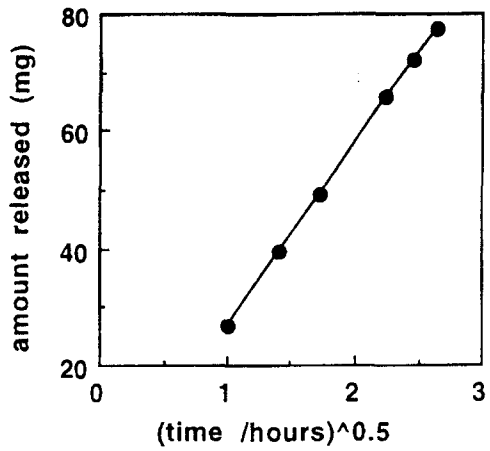

Fig. 5. The relationship between the amount of GTN released from Nitrodur and the square root of time. Data adapted from Shah et al., 1986.

As would be expected from the diffusion theory the release of GTN from homogeneous matrix systems follows square root of time kinetics (Fig. 5).

If the GTN is inhomogeneously dispersed, as it is in the Deponit system, the release kinetics approximates to zero order and a release profile similar to a membrane-moderated device is obtained. The membrane-moderated devices will, after an initial burst effect, produce zero order release (Fig. 4) (Hadgraft et al., 1991). In all cases the process that determines the rate at which the GTN is delivered to the skin surface is the diffusion through the polymer(s) that comprise the devices.

Some difficulty may be experienced if the polymer contains a high loading of the GTN or if it contains hydrophilic excipients. An example of this is shown for the prototype patch SPM 751 where its contents are released in the USP XXII method within 60 min (Fig. 6) (Hadgraft et al., 1993b).

The release could be even more rapid with release occurring within minutes; in these cases reproducibility of release from batch to batch may be difficult to prove. In these circumstances it may be appropriate to choose an inert receptor medium or to place a 'non-rate-controlling' membrane between the device and the receptor

medium. It should be remembered that this type of experiment is only to prove batch to batch conformity and not to predict in vivo performance.

As can be seen from Fig. 4 the in vitro release characteristics for the systems shown are significantly different from one another despite the fact that they have been specifically designed such that they deliver 10 mg in 24 h when used in vivo. In order to get a more realistic in vitro assessment which may be used to predict in vivo absorption it is necessary to conduct the in vitro release experiment through samples of human skin. It is possible to use epidermal tissue or skin which has been dermatomed to 200 μm. This thickness is chosen since it is readily achievable practically and also it is representative of the depth where the GTN would encounter the circulation and hence be distributed into the systemic pool. If experiments on skin are conducted with non-viable tissue there may some discrepancies between in vitro and in vivo data due to the lack of metabolism in non-viable tissue. Data in the literature suggest that this is not a major problem which substantiates the view that the rate-controlling step is in the stratum corneum and that there is little metabolism of GTN in this layer.

Typical in vitro release through dermatomed skin results are shown in Fig. 7 (Hadgraft et al., 1993a). It is a simple matter to compare the 24-h

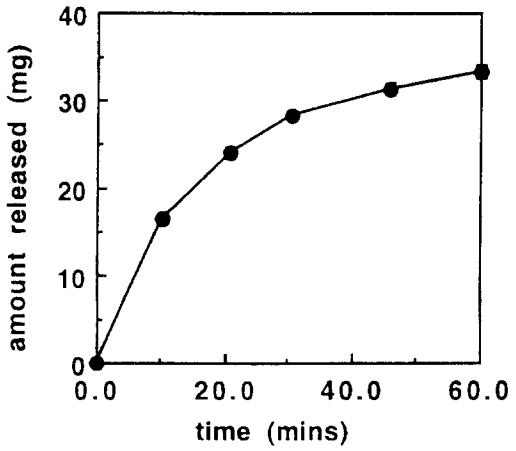

Fig. 6. The release profile of SPM 751. Data adapted from Hadgraft et al., 1993b.

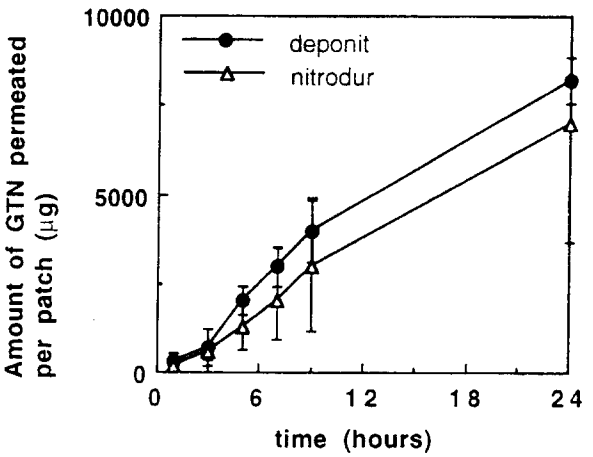

Fig. 7. The in vitro permeation of GTN through excised human skin dermatomed to 200 μm. Data adapted from Hadgraft et al., 1993a.

data points with the known amounts delivered in vivo (viz. 10 mg). There is good agreement. Other in vitro-in vivo correlations are possible; these will be considered after in vivo data have been considered.

7. In vivo evaluations

The best in vivo evaluation must be to consider the blood levels of the GTN and its metabolites. Since the levels of these are very low there have been analytical problems in these determinations and complex capillary GC techniques have been developed. The clearance kinetics of GTN are very variable which results in variable plasma levels even from constant infusion. This has made interpretation of in vivo transdermal data more complicated. Typical plasma levels are shown in Fig. 8 which demonstrate the variability between volunteers (Bonn et al., 1993).

Another simpler way of assessing in vivo absorption is to measure the residual GTN in the patch after removal. This can be assessed at any time point after application giving a dynamic determination of uptake of the drug. Since GTN is a very volatile material it is important to ensure that an experimental design is used such that the amount of GTN lost to the atmosphere is mini-

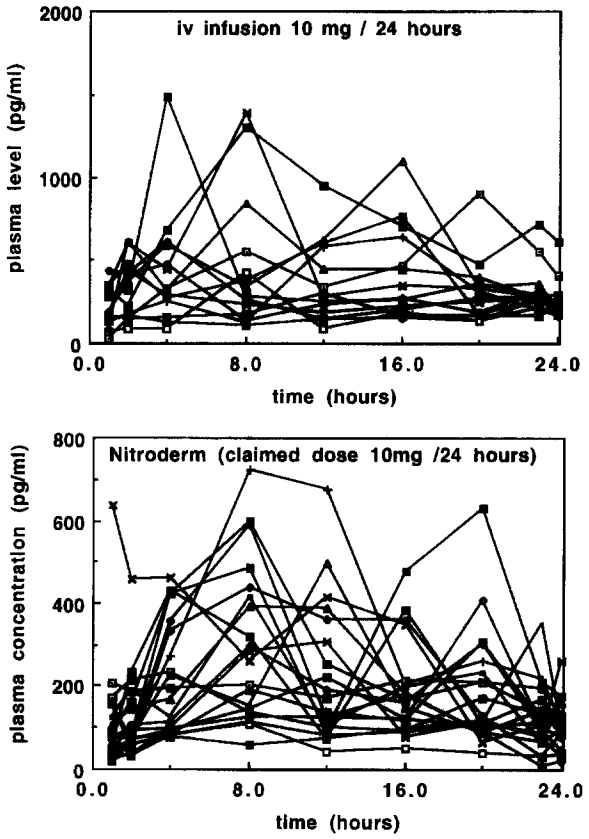

Fig. 8. Plasma levels of GTN following i.v. infusion and application of Nitroderm. Data adapted from Bonn et al., 1993.

mal. Typical results for the amount of GTN absorbed after 24 h are shown in Fig. 9 (Hadgraft et al., 1991). The spread of the data is interesting and is probably a reflection of the relative control from the skin and the device. This aspect will be considered later.

In vivo studies should also consider the biological effect of the GTN. Numerous studies have been conducted and these lead to the discovery of tolerance difficulties in long-term GTN delivery and the consequent need to give the body a resting period from therapy (Elkayam, 1991). As previously mentioned, initial labelling of the application of devices for 24 h was changed to a 12–16-h period. Various evaluations of the pharmacodynamics of GTN delivery have been published but a review of these is beyond the scope of this paper.

8. In vitro-in vivo correlations

One of the interesting aspects that is possible for the transdermal delivery of GTN is to examine in vitro-in vivo correlations. From an in vitro assessment of the absorption of the GTN across the skin it is possible to calculate the input function of the drug into the systemic circulation. If this is then equated to the known clearance kinetics of GTN an estimate can be made of the anticipated blood levels (Hadgraft et al., 1993b). The actual and estimated levels for two systems are shown in Fig. 10. There is good agreement between the two showing the utility of the approach. If the data are available it is also possible to compare the in vitro absorption with the in vivo absorption as determined from the residual concentration in the patch. Such an analysis has

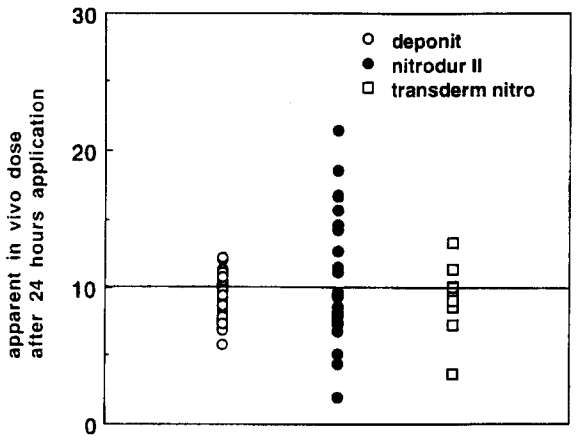

Fig. 9. The apparent dose of GTN determined by measuring the residual GTN in the patch after it has been applied for 24 h. Data adapted from Hadgraft et al., 1991.

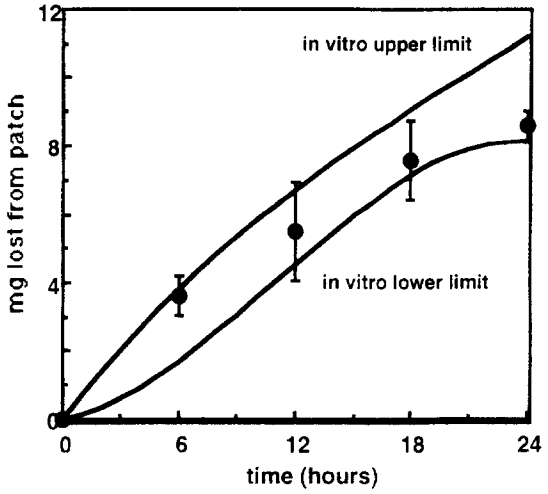

Fig. 11. The predicted and measured amounts of GTN lost from a Deponit patch in vivo. Data from Hadgraft et al., 1993a.

been conducted for Deponit and the results are given in Fig. 11. Again there appears to be good correlation showing the general utility of conducting in vitro evaluations of skin permeation.

It is now instructive to consider in vitro release studies in comparison with the in vivo levels. As mentioned earlier the intrinsic release (as shown in Fig. 4) does not necessarily give a good indication of in vivo performance. The reason for this is that the absorption into the systemic circulation is governed by two factors, the release from the device and the rate of transfer across the stratum corneum. From the difference between the known in vivo uptake and the amount released in vitro (without skin present) it is possible to calculate

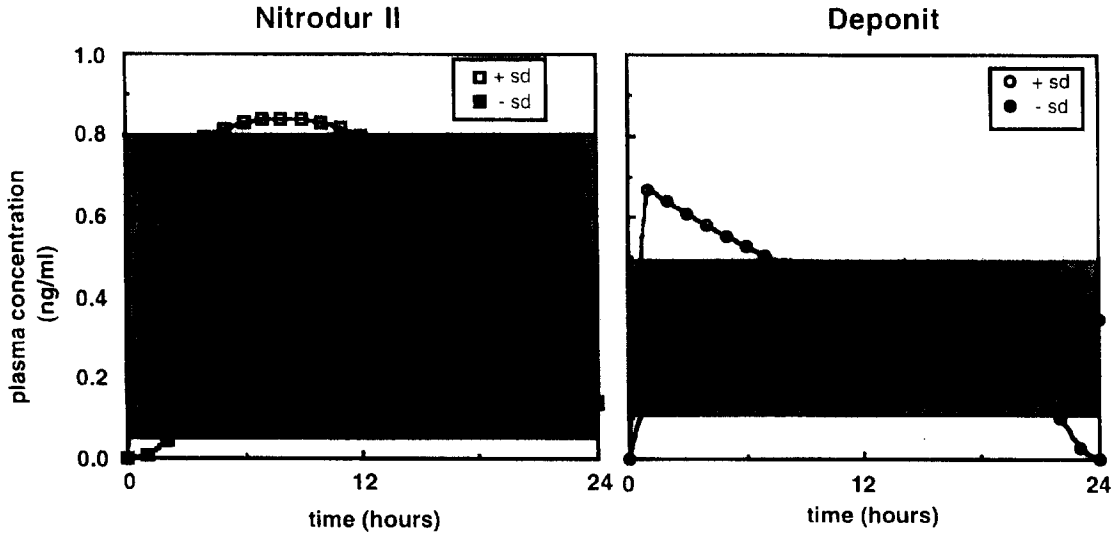

Fig. 10. Predicted plasma levels of GTN following transdermal delivery from Nitrodur and Deponit. For comparison the mean ± S.D. in vivo levels are shown. Data from Hadgraft et al., 1993a.

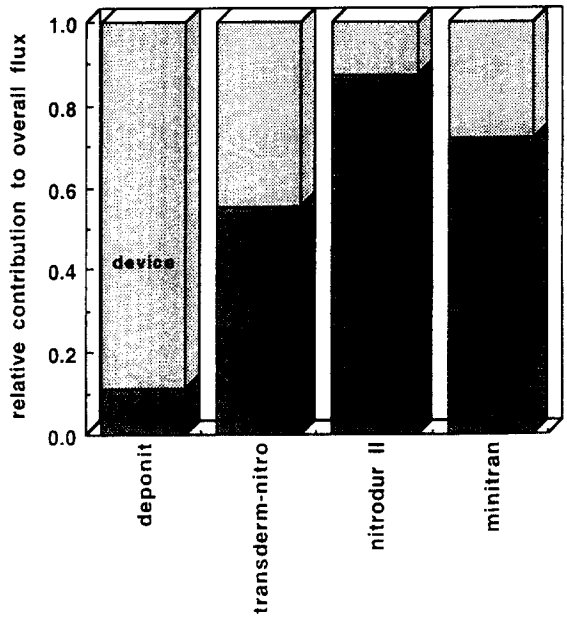

Fig. 12. Histogram showing the relative control from the device and the skin. Data from Hadgraft et al., 1991.

the relative control of input into the body from the skin and from the device. The histogram in Fig. 12 shows the results (Hadgraft et al., 1991).

Considering the data in Fig. 9 it is now possible to postulate reasons for the spread in the data. It is well documented that the permeability of skin (both inter and intra subject) is very variable (Southwell et al., 1984. If a device is placed on the skin and the skin is rate controlling then the input into the body will be subject to this variability. As the device becomes more significant in controlling the input the variability will be reduced. In the case of Fig. 9 the comparison is made between two devices where the rate control from the device is 90% for Deponit and 10% for Nitrodur. The spread in the data in Fig. 9 would therefore be expected to be less for Deponit.

9. Metabolism

One of the major advantages of transdermal delivery is that first pass metabolism is avoided. This is a significant problem for this drug. However metabolism is not totally circumvented and there is evidence to suggest that non-specific enzymes within the skin can contribute to the metabolism of GTN (Wester et al., 1983). Another aspect which always needs to be taken into account is that there are bacteria on the skin surface which have metabolic activity. One of the commonly occurring bacteria is *Staph. epidermidis* which has been shown to be capable of metabolising GTN (Denyer et al., 1985). The exact significance of this in the transdermal delivery of this drug has not been investigated.

10. Ideal properties for system design

The drug content should be as small as possible commensurate with delivering the required dose in vivo. The closer the total drug content is to the amount delivered the closer the bioavailability is to 100% and therefore the possibility of overdosing through application to a particularly permeable site is minimised.

The adhesive properties of the patch need to be such that it will remain in place over the required time frame and under a variety of conditions. The drug should be released at an appropriate rate under these variable conditions which should take into consideration elevated temperatures (in tropical climates) and the differences in transepidermal water loss between subjects. The latter will be a function of exercise, relative humidity and temperature. It is clear from the literature that some of the more recent developments in adhesives that are being used are more appropriate than some of the original adhesives. Whatever type of adhesive chosen it must have no adverse reaction with the skin and residual monomer, solvents and other potential contaminants must be minimal.

For good patient compliance the patch should be as small and as thin as possible. This can be achieved using a high payload and by the incorporation of chemical enhancers or by using high activity states of the GTN. If a chemical enhancer is used it needs to be one which is ideally specific to the GTN and which has no skin reaction of its own. It is important to determine that the chemical enhancer does not have any adverse effects with other components of the patch, i.e. other excipients. It is possible for any enhancer incorporated into the polymer matrix to promote the permeation of other substances (monomers, residual solvents, etc.) into the skin where they could react adversely. Also the enhancer should not have a deleterious effect on the adhesive properties.

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