



Development of a novel topical formulation of glyceryl trinitrate for the treatment of erectile dysfunction

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Received: 5 September 2019 / Revised: 28 November 2019 / Accepted: 20 December 2019
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Abstract

Erectile dysfunction (ED), defined as the inability to initiate or maintain an erection sufficient for satisfactory sexual intercourse, is common, particularly in men aged ≥ 50 years. Existing treatments have significant limitations, and there remains a need for a fast-acting (to facilitate spontaneity during intercourse) and well tolerated local therapy. Topical glyceryl trinitrate (GTN) may meet this need because GTN undergoes rapid metabolism in penile smooth muscle and endothelial cells to produce nitric oxide, which plays a key role in the development of erection. This paper describes the rationale for the development of MED2005, a topical GTN formulation using DermaSys® technology, which is undergoing clinical trials for the treatment of ED. Pharmacokinetic studies have shown that MED2005 provides rapid delivery of GTN following application to the glans penis, and a Phase 2(a) trial in men with ED showed that MED2005 produced significant improvements in erectile function, compared with placebo. MED2005 was well tolerated in this trial, with only 21 cases of headache in 1003 intercourse attempts. It is anticipated that MED2005 will provide an effective therapy for ED, with a fast onset of action, good local tolerability, and fewer contraindications than phosphodiesterase 5 inhibitors, the current cornerstone of ED therapy.

Introduction

Erectile dysfunction (ED) is defined as the inability to initiate or maintain an erection sufficient for satisfactory sexual intercourse [1, 2]. It is a common disorder, and the incidence increases with age, particularly in men aged 50 years and older [3, 4]. Data from the United States suggest that ED affects more than 75% of men over 70 years of age [5], while other studies suggest that more than 40% of men over 60 years of age are likely to have ED [6]. ED is associated with a number of chronic disorders that are more common in older men, such as diabetes and cardiovascular or neurological disease [7], and this may at least partly explain the increased prevalence in older men. In addition, ED is a common comorbidity in obese men, particularly in the presence of other cardiovascular risk factors such as diabetes, dyslipidemia, or hypertension [8, 9]. However, ED

is not just a problem affecting older men: ~20–25% of cases occur in men under the age of 40 years [10], and the incidence is increasing in this age group [11].

ED can be a major factor contributing to an unsatisfactory sexual life, and this in turn may lead to severely impaired quality of life, both for affected men and their partners [1, 12–14]. In addition, ED is often associated with psychiatric symptoms, including symptoms of anxiety, depression, and somatization [15]. Treatment of ED has been shown to have a positive effect on the quality of life and overall satisfaction of both patients and their partners [12, 16]. Currently, phosphodiesterase 5 inhibitors (PDE5-Is) are recommended as first-line therapy for ED [2]. However, it is estimated that these agents are effective only in about 70% of patients [16], and failure rates of between 11 and 44% have been reported, depending on the population under study [17]. In a 2016 meta-analysis of 22 trials, involving almost 163,000 patients, the mean discontinuation rate was ~4% per month; thus, almost 50% of patients discontinued treatment within the first year [18]. Furthermore, PDE5-Is have to be taken between 30 min and 2 h before sexual activity, leading to a lack of spontaneity [19], and are associated with a number of adverse effects, including headache, back pain, facial flushing, and visual disturbances [1, 2, 20, 21]. Other limitations of PDE5-Is

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include potential interactions with food or alcohol, and contraindications in patients taking nitrates [1]. Reflecting these limitations, adherence to PDE5-I treatment has been shown to decrease over time. Approximately 50% of patients discontinue treatment beyond 1 year: reasons for this include lack of efficacy, adverse effects, cost, loss of spontaneity in sexual activity, and a feeling that medications are controlling their lives [19, 22–24].

Options for second-line therapies in men who are not satisfied with PDE5-Is, or who do not respond to these agents, include local therapies such as intracavernosal injection, intraurethral alprostadil, or vacuum erection devices, which may have been used alone or in combination with PDE5-Is. However, these therapies are invasive and are themselves associated with adverse events such as petechiae and hematoma with vacuum devices, and pain or priapism with intraurethral suppositories and intracavernosal injections [1]. There thus remains a strong unmet need for an effective local therapy that is easy to administer, fast-acting for spontaneity of sexual activity, and well tolerated with a low risk of systemic adverse effects. This paper describes the development of MED2005 (Futura Medical Ltd, Guildford, UK), a novel topical formulation of glyceryl trinitrate (GTN) that is currently undergoing clinical trials for the treatment of ED.

Anatomy and physiology of the penile erectile system

The penile erectile system comprises the twin corpora cavernosa, which form the main erectile compartment, and the corpus spongiosum (Fig. 1). These compartments are supplied with blood by the internal pudendal artery via the bulbourethral, cavernous, and penile dorsal arteries (Fig. 2). The most important of the dorsal arteries is the highly branched cavernous artery, which supplies the sinusoidal space of the corpus cavernosum. Venous return from the corpus cavernosum is via the emissary veins (Fig. 3), which run obliquely between the inner and the outer layers of the tunica albuginea; this anatomical arrangement is essential for venoocclusion and erectile function [25]. Erection results from relaxation of the cavernosal smooth muscle, which allows blood to enter the lacunar spaces of the corpora cavernosa, thereby compressing the subtunical vesicles and impeding venous outflow (Fig. 3) [1].

Nitric oxide (NO) plays a key role in the development of erection [26]. NO binds to soluble guanylyl cyclase in corporal smooth muscle cells, producing the signaling molecule guanosine monophosphate (cGMP), which ultimately induces relaxation of cavernosal smooth

Fig. 1 Anatomy of the penile erectile system [52]. Based on illustration published in [52].

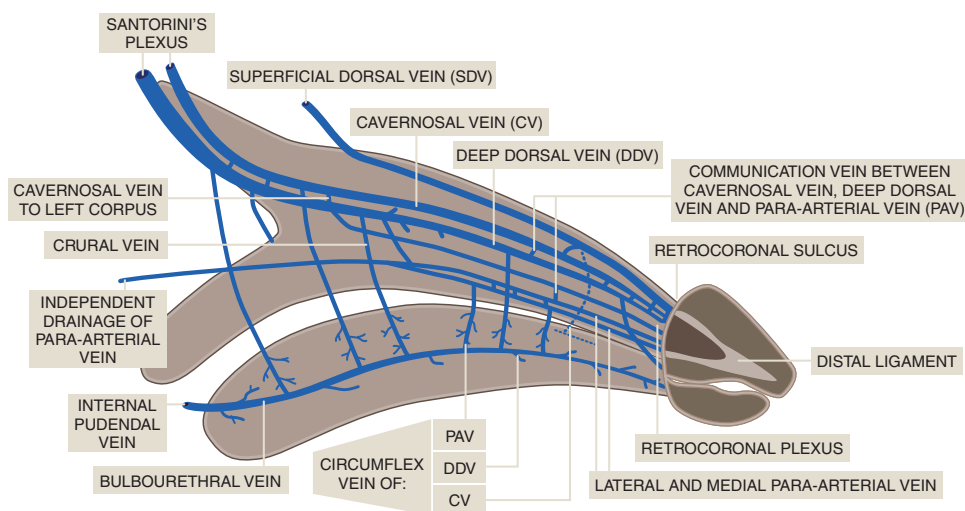


Fig. 2 The arterial blood supply to the penis [30]. Based on illustration published in [30].

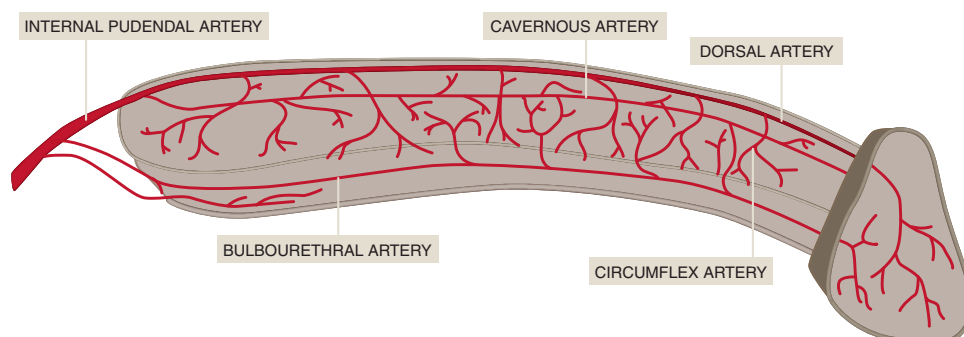


Fig. 3 The tunica albuginea bilayer and cavernosal emissary vein erectile system [26]. Schematic demonstrating the effect of increasing swelling of the cavernosal sinusoids to increase pressure on the lower tunica albuginea bilayer and occlude the emissary veins, thereby initiating, and sustaining penile erection. Based on illustration published in [26].

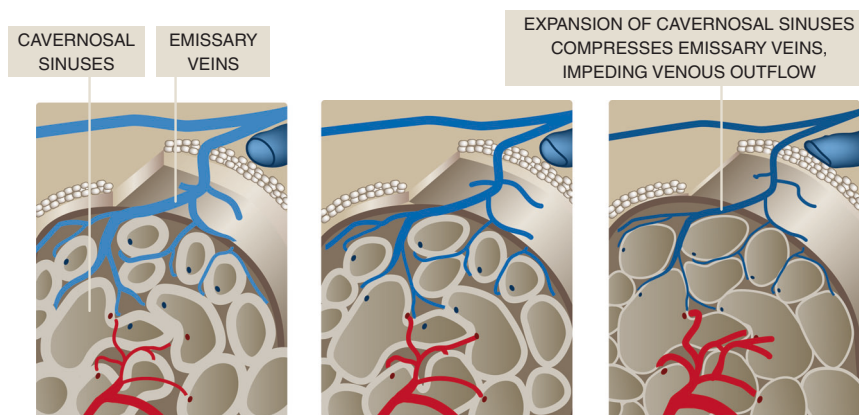
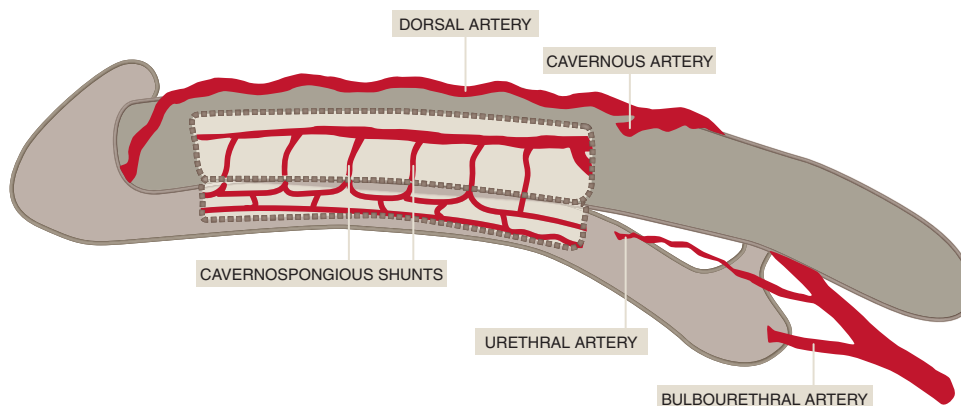


Fig. 4 Schematic representation of arterial shunts connecting the urethral artery (UA) and the cavernous artery (CA), causing retrograde blood flow from the corpus spongiosum to the corpus cavernosum. Based on illustration published in [29].



muscle. GTN is metabolized to NO in smooth muscle and endothelial cells [27], thereby increasing local cGMP production.

Delivery of vasoactive agents to the corpus cavernosum

Effective pharmacological treatment of ED requires the delivery of vasoactive agents to the corpora cavernosa and retention within this compartment.

Several studies, using microdissection [28, 29] or spongigraphic radiological contrast techniques [30, 31] have described the presence of both arterial and venous shunts, that could constitute a viable route for delivery of vasoactive drugs from the surface of the spongiosal glans penis to the cavernosal compartment. As shown schematically in Fig. 4, these vessels connect the urethral artery and the cavernous artery [29], allowing shunting between the spongiosal and cavernosal compartments. There is evidence that, following application of a vasoactive agent to the corpus spongiosum, increasing pressure within this compartment causes a retrograde flow from the spongiosum to the cavernosum, which may occur via arterial or venous shunts, or both [29, 31, 32].

Although relatively few publications have described the pharmacokinetics of vasoactive agents following topical application to the penis, the available evidence suggests that the penis can be regarded as a separate pharmacokinetic compartment. The results of the available pharmacokinetic studies are summarized in Table 1 [33–35]. These studies suggest that vasoactive drugs are retained in the penile tissues following compression of the subtunical veins and erection in responders, allowing sustained erection despite decreasing systemic plasma drug levels.

Development of a topical formulation for the treatment of ED

Drug selection

The potential for rapid delivery of a vasoactive drug to the corpus cavernosum, in order to achieve and sustain an erection, while minimizing systemic exposure, is clearly attractive. As noted above, NO plays a key role in the development of erection, and hence treatment with NO donors represents a potentially useful strategy for the treatment of ED. If this potential is to be realized, it is important to determine the most appropriate drug and

Table 1 Studies of pharmacokinetics of vasoactive agents administered to the penis.

Authors	Population	Drug, dose	Route of administration	Key pharmacokinetic findings
Cawello et al. [33]	Patients with erectile dysfunction ($n = 24$) –13 identified as responders to prostaglandin E1 prescreening	Alprostadil alfadex (prostaglandin E1), 20 µg	Intracavernous injection or 30 min intravenous infusion	–Peak plasma concentrations of prostaglandin E1 following intracavernous injection were 12.1 pg/mL in responders and 24.1 pg/mL in nonresponders. –AUC _{0–120} was 198 and 344 pg/mL min, respectively. –No significant change in these parameters was seen after intravenous administration.
Hakenberg et al. [34]	Patients with erectile dysfunction ($n = 13$) –5 identified as responders to papaverine/phentolamine combination	Papaverine 15 mg plus Phentolamine 0.5 mg	Intracavernous and intravenous injection	–Peak serum concentrations of papaverine after intracavernous and intravenous injection were 116 ng/mL (range 5.5–936 ng/mL and 507 ng/mL (range 175–3969 ng/mL, respectively. –Serum concentrations of phentolamine 24 h after administration were 5.2 ng/mL (range 0.5–53.5 ng/mL) and 24 ng/mL (range 9.7–113 ng/mL), respectively. –Peak serum concentrations of papaverine were reached after ~1 min after intravenous administration, and 20–30 min after intracavernous administration. Thereafter, concentrations declined to undetectable levels over 20 min and 240 min, respectively. –Similar concentration–time profiles were seen with phentolamine.
Van Ahlen et al. [35]	Patients ($n = 21$) with erectile dysfunction, or congenital or acquired penile deviation without erectile dysfunction	Papaverine Prostaglandin E1	Intracavernous injection	–At 5 min after injection, peak intracavernosal concentrations were ~300 ng/mL for prostaglandin E1 and 900 pg/mL for the primary metabolite 15-ketoPGE1. –No significant change in plasma prostaglandin E1 concentrations was observed, but after 30 min plasma concentrations of 15-ketoPGE1 had increased from ~60 to 110 pg/mL. –Papaverine drained into the systemic circulation more slowly than prostaglandin E1, with only slight increases in plasma concentrations at 30 and 60 min after administration.

AUC_{0–120} area under concentration–time curve to 120 min after dosing

formulation for topical application to the penis. This will involve consideration of drug potency and skin penetration, and the potential for both local adverse effects, such as local irritation or phototoxicity, and systemic adverse effects.

The numerical ratio of skin penetration/potency may be used to select candidate compounds from a pharmacological class based on their efficacy potential. For example, Cordero et al. used the ratio of maximum human skin flux in vitro (µg/cm²/h) to the drug concentration producing 50% inhibition (IC₅₀) of cyclo-oxygenase-2 (µg/cm³) in vitro to predict the topical anti-inflammatory activity of a series of nonsteroidal compounds [36]. The highest ratios, and thus the greatest therapeutic potential, were obtained with the compounds with the highest transdermal flux rates, and lower potency. In a comprehensive study of GTN permeability across a range of membranes, Minghetti et al. reported steady state flux values across fresh human skin (200 µm) and fresh

epidermal membrane (~100 µm) of 22 and 23.4 µg/cm²/h, respectively, which is consistent with the physical chemistry of GTN [37]. Hadgraft et al. reported similar in vitro human skin flux values from commercial transdermal GTN patches [38]. By contrast, a single study investigating the permeation of PGE1 through human skin in vitro reported steady state flux values of 0.70–1.66 µg/cm²/h [39]. In a US patent application, steady state in vitro PGE1 fluxes of up to ~12 µg/cm²/h were obtained with various formulations containing the skin penetration enhancer DDAIP (Dodecyl 2-N, N-dimethylaminopropionate), although it should be noted that these results were obtained with snake skin [40].

The in vitro vasoactive potency of GTN and PGE1 has been investigated in a number of studies. In one study, Taub et al. contracted human corpus cavernosal smooth muscle with phenylephrine (100 nM–100 µM). At 75% of maximum phenylephrine-induced contraction, the IC₅₀ values

for relaxation were 150 nM with GTN and 2 μ M with PGE1 [41]. Using the same protocol, Christ et al. reported GTN relaxation IC₅₀ values of 25 nM and 180 nM in responder and nonresponder donors, respectively [42].

Together, these findings suggest that GTN is a more potent vasoactive agent than PGE1, and is likely more permeable, at least through human skin. For these reasons, GTN was considered the drug of choice for the development of the experimental topical gel, MED2005 (see below).

Choice of application site

Intraurethral drug administration, and topical application to the glans penis and penile shaft, have been considered for the noninvasive treatment of ED. The surface of the glans penis consists of a thin squamous mucosal epithelium, similar to that of the inner lip [43]. Branches of the dorsal nerve of the penis extend ventrolaterally through the glans, such that it is filled with nerve endings supporting its function as a sensory structure [44]. Exploratory pharmacokinetic data show that GTN delivered via MED2005 is effectively absorbed via the glans penis in both circumcised and uncircumcised men (Holland et al. Unpublished data).

NO is synthesized by neuronal NO synthase and endothelial NOS within the corpora cavernosa. Topical application of a semi-solid spread onto the glans should lead to rapid signaling and release of endogenous NO into the corpus cavernosum. It is a significant formulation challenge for a NO donor formulation to deliver exogenous NO into the corpus cavernosum within this time frame, but this is likely to be advantageous for erectile function.

Factors influencing choice of drug formulation

Drug delivery from the surface of the glans penis into the body of the glans is a diffusional process, described by Fick's First Law of Diffusion. The rate of diffusion depends on three independent formulation factors: the thermodynamic activity of the drug in the residual, non-volatile phase of the formulation after application; the presence of a partition coefficient enhancer to increase drug solubility in the skin; and the presence of a diffusion coefficient enhancer to increase drug diffusivity in the skin.

Spontaneity and speed of action are important considerations in the treatment of ED. However, enhancers, particularly diffusion coefficient enhancers [45] require a significant time to establish their effect within the diffusional barrier. By contrast, drug thermodynamic activity, particularly in solution-type formulations, may be rapidly increased by loss of volatile solvents from thin films applied to the skin. This concentration process can result in the formation of saturated or supersaturated solutions of active drug; since transdermal drug delivery is directly

proportional to the degree of supersaturation, this will lead to enhanced delivery [46].

The DermaSys® drug delivery system

DermaSys® (Futura Medical Ltd, Guildford, UK) is an enhanced topical drug delivery system containing both volatile (ethanol) and nonvolatile (propylene glycol) solvents and volatile (water) and nonvolatile (glycerol) nonsolvents. Upon application, the volatile solvents evaporate, creating a super-saturated solution of the drug which drives the drug rapidly into tissue. Thus, no harsh penetration enhancers are used; this is an important consideration for topical application to the glans, given the sensitivity of this site. Analysis of the solubility of GTN in a range of water–ethanol and glycerol–propylene glycol cosolvent systems [47] showed that the saturated solubility increased with the residual phase glycol concentration (i.e., the concentration remaining after evaporation of the volatile solvent). As a result, the rate of delivery of GTN across the skin can be varied by altering the composition of the cosolvent system.

The DermaSys® formulation has been designed to optimize the rate of solvent evaporation. Typically, topical products are applied at concentrations of up to 5 mg/cm², equivalent to a thickness of ~5 μ m (approximately one tenth the thickness of a sheet of normal printer paper), and solvent loss from these thin films may be rapid. However, the oil phase of creams, often described as a barrier, can significantly reduce solvent loss. For this reason, MED2005 uses an open-structured Carbopol Ultrez-10 gelation system, in which diffusion of the volatile solvents and of GTN is directly related to the viscosity of the gel. While the macroviscosity of a Carbopol Ultrez-10 gel may be ~50,000 cP (5000 Pa·s), the route for diffusion of the volatile solvents and of GTN (the microviscosity) is only 10 cP (1 Pa·s), which is similar to that of diffusion through water [48]. This combination of high levels of saturation or supersaturation of GTN, and unhindered diffusion of volatile solvent and GTN through the gel, combine to produce rapid delivery of GTN—and hence NO—into the glans penis (Fig. 5). The formulation has been designed to achieve a rate of delivery that is broadly similar to the rate of endogenous NO production following stimulation.

In vivo human pharmacokinetics of GTN from DermaSys® MED2000-range formulations

Pharmacokinetic–pharmacodynamic studies of vasoactive therapies in patients with ED are difficult to conduct because the laboratory conditions lead to stress and inability to form an erection, even in known responders [35].

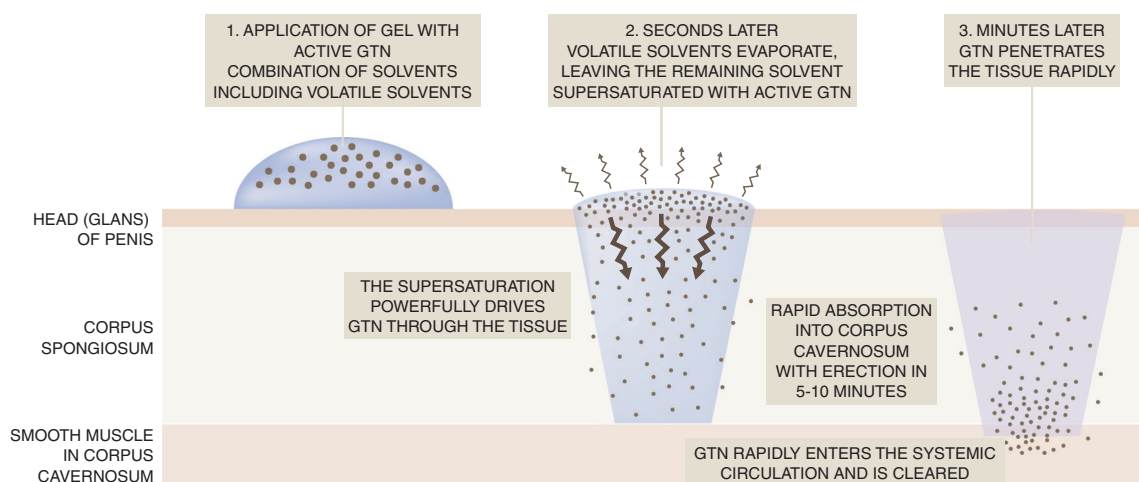
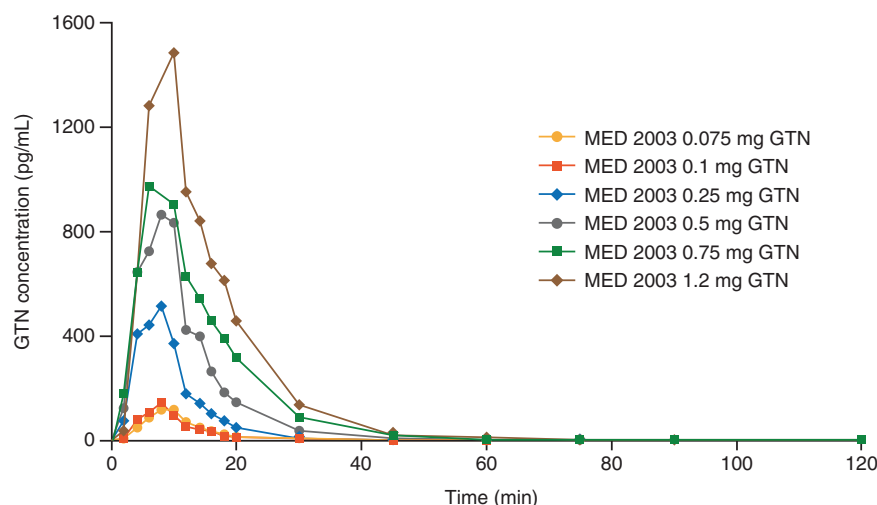


Fig. 5 Schematic representation of the delivery of glyceryl trinitrate GTN from MED2005 with DermaSys® technology.

Fig. 6 Systemic plasma concentrations of glyceryl trinitrate with following increasing doses of MED2003 and single doses of MED2004 and MED2005.



However, studies in normal volunteers can provide information about onset, rate, dose–response and duration of delivery following administration of GTN.

Pharmacokinetic studies were conducted in healthy volunteers to evaluate the delivery of GTN following application of a series of candidate products designated MED2003, MED2004, and MED2005. Figure 6 shows systemic plasma concentrations of GTN following application to the glans penis of increasing doses delivered via these formulations. With MED2003, GTN was measurable in systemic plasma at 2 min after application at all doses, with peak levels being attained at 8 min and total clearance by 60 min. There was a linear response between dose and peak plasma concentrations. Because GTN is very rapidly metabolized (even faster than the input rate, such that “flip-flop” pharmacokinetics apply [49]), control

of input rate from MED2004-5 is seen in the terminal, declining, phase of the concentration–time plot. The area under the plasma concentration–time curve over 60 min after administration (AUC_{0-60}) was linearly proportional to dose across MED2003-2005 formulations.

On the basis of these studies, it was determined that MED2005 offered the most optimal pharmacokinetics for the treatment of ED, and hence this formulation was chosen for further development. The pharmacokinetics of increasing doses of GTN delivered via MED2005 were evaluated in a randomized study involving 31 healthy volunteers (NCT04008732, ref. [50]). At all doses, GTN was measurable in plasma within 5 min, with peak plasma concentrations being attained after ~10 min. There was a linear relationship between dose and peak plasma concentration.

Clinical experience with DermaSys® MED2005

The efficacy of GTN delivery via MED2005 has been assessed in a pharmacodynamic study and a Phase 2(a) clinical study [51].

Pharmacodynamics

Historically, ultrasound doppler measurements of penile blood flow have been used to assess degrees of ED of mixed etiology. This technique was used to study the optimized MED2005 formulation at a variety of GTN doses by measuring hemodynamic changes within the cavernosal arteries (Holland et al. Unpublished data). A placebo-controlled, double-blind, dose-ranging, crossover study was conducted in 15 healthy adult men who received 0.01, 0.075, 0.25, and 0.6 mg (0.0033%, 0.025%, 0.083%, and 0.2%, respectively) doses of GTN, applied to the glans penis via MED2005. Significant differences in penile blood flow, compared with placebo, were seen only with the 0.6 mg dose, although there was a trend toward increased blood flow with the 0.25 mg dose. The most prominent hemodynamic changes with the 0.6 mg dose were increases in diastolic velocity, pulsatility index, and overall waveform; all of these would be positively associated with the ability to obtain an erection. All doses were well tolerated, and there was no clear evidence of headache as a drug-related adverse event. No falls in blood pressure, or symptoms associated with hypotension, were reported.

Clinical efficacy and tolerability

On the basis of these results, the 0.6 mg (0.2%) GTN dose was chosen for a randomized Phase 2(a) study with MED2005 [51]. This study involved 232 men with ED, who received MED2005 or placebo for 4 weeks each, with a 1-week washout period between treatments. The primary endpoint was the International Index of Erectile Dysfunction erectile function domain (IIEF-EF) score. The mean (SD) IIEF-EF score at baseline was 17.1 (5.7), and the mean scores after MED2005 and placebo treatment were 19.6 (7.5) and 18.5 (6.7), respectively ($P = 0.0132$ for MED2005 versus placebo). Following MED2005 treatment, there were significant increases in IIEF-EF scores, compared with placebo, in subgroups of patients with mild ED (least squares mean treatment difference 1.81, 95% confidence interval [CI] 0.93–2.68, $P < 0.0001$) or mild and moderate ED (mean treatment difference 1.18, 95% CI 0.38–1.99, $P = 0.0043$). In total, 23.1% of patients showed a clinically relevant (≥ 4 -point) increase in IIEF-EF scores after treatment with MED2005 only, compared with 14.5% who responded after MED2005 and placebo, 14.0% who responded after placebo

only, and 48.4% who did not respond after either treatment; the difference in response rates between treatment was statistically significant ($P = 0.027$). MED2005 was also associated with improvements in other IIEF domains. Importantly, the start of erection was noticed within 5 min in 44.2% of all intercourse attempts with MED2005, and within 10 min in 69.5%. Overall, 40.4% of patients, and 38.0% of partners, reported preferences for MED2005, compared with 22.2% ($P = 0.0007$) and 22.2% ($P = 0.003$), respectively, for placebo. MED2005 was very well tolerated. The most common adverse events reported by both patients and partners were headache (7.9% and 1.3%, respectively) and nasopharyngitis (5.7% and 0.9%, respectively); only 21 instances of headache (patients: $n = 18$; partners: $n = 3$) were reported in 1003 intercourse attempts, of which 17 were considered to be related to treatment (patients: $n = 14$; partners: $n = 3$).

A potential concern with topical therapies for ED would be the risk of local application site reactions. In this context it is reassuring that, in the Phase 2(a) study with MED2005, application-site reactions such as coldness, irritation, or pain occurred in $<1\%$ of patients, and there were no cases of priapism [51]. Similarly, the low incidence of headache in female partners suggests that the risk of drug transfer to partners is small. This is supported by data from the pharmacokinetic study in healthy volunteers [50], in which the geometric mean recovery of GTN from penile swabs taken 5 min after application of MED2005 was 22%, suggesting 100% absorption within 6–10 min. The risk of overdosing, which could potentially result in an increased risk of local reactions or transfer to sexual partners, is likely to be low because the gel is packaged in a single-dose tube to limit the potential for overdosage.

In this study, the effect of MED2005 was greatest in patients with mild and mild-to-moderate ED. Based on the linear relationship between dose and peak plasma concentration, and the favourable adverse event profile observed with higher doses in a pharmacokinetic study (NCT04008732, ref. [50]), it was decided to investigate higher doses of GTN. Thus, a 12-week, double-blind, parallel group, multicenter Phase 3 study (NCT03813992) is underway, evaluating the effect of 0.6, 1.2, and 1.8 mg (0.2%, 0.4%, and 0.6%, respectively) doses versus placebo in 1000 patients.

Conclusion

The MED2005 formulation has been developed in an attempt to optimize topical GTN therapy for men with ED. It is likely that this formulation will provide a fast onset of action, with acceptable efficacy and limited local adverse effects, and fewer contraindications than PDE5-Is.

MED2005 could therefore be an important advance in the management of ED, offering an opportunity to improve sexual activity and satisfaction for couples affected by this common condition.

Acknowledgements Medical writing assistance in the development of this paper was provided by Dr Michael Shaw (MScript Ltd, Hove, UK), and funded by Futura Medical Developments Ltd (Guildford, UK).

Funding Medical writing assistance in the development of this paper was funded by Futura Medical Developments Ltd (Guildford, UK).

Compliance with ethical standards

Conflict of interest AD provides consultancy services to Futura Medical Developments Ltd, and holds stock options and shares in the company. YR reports no conflicts of interest in relation to this paper. The medical writer, Dr Michael Shaw, reports no conflicts of interest in relation to this paper.

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