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REGULATORY CONSIDERATIONS IN TRANSDERMAL CONTROLLED MEDICATION

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On behalf of the Food and Drug Administration, I wish to thank Rutgers University, College of Pharmacy, for extending me the invitation to participate in this symposium dealing with "Transdermal Controlled Release Medication."

A milestone for the evolution of "Controlled Release Dosage Forms" was recently made with the development of several new innovations, primarily the invention of polymer-mediated controlled release drug delivery systems for long-term medications. It is exemplified by the development of progesterone-releasing Progestasert IUD for one year intrauterine contraception, the pilocarpine-releasing system for weekly management of glaucoma and the scopolamine-releasing transderm-V system for the prevention/treatment of motion sickness. Regulatory approval of these controlled release drug delivery systems has been granted only in the past 5 years. More recently, the FDA has granted approval on three separate transdermal nitroglycerin drug delivery systems, and it is

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anticipated that newer drug delivery systems are likely to be approved in the foreseeable future.

Perhaps one needs to ask "Why all this interest in transdermal drug delivery systems?" Aside of economic interests, there are a number of scientific reasons for the development of transdermal drug delivery systems. Among these reasons are the avoidance of first pass liver or G-I metabolism, long term therapy from a single dose, improved patient compliance and minimal drug exposure by significant reduction of the dose. Indeed it is possible to accomplish all of these goals with transdermal drug systems. The avoidance of first pass metabolism often can result in a significant reduction in dose and better patient compliance over a longer period of time by pre-set delivery rates of drug over several days. The zero-order drug delivery can also minimize side effects by avoiding toxic plasma levels. It should be feasible to develop transdermal systems which will facilitate patient titration to predetermined therapeutic plasma levels and such systems will facilitate bi-weekly or even weekly dosage administration.

This presentation will deal with both the regulatory and biopharmaceutic aspects of transdermal drug delivery systems. The drug examples referred herein are employed to illustrate specific scientific viewpoints as well as to illustrate the basis of biopharmaceutics approval of the new drug application. These statements should not be viewed as an Agency endorsement of specific drug products but rather as my own personal views endorsing the scientific principles or hypotheses put forth. Further, it is my opinion that these examples best illustrate a new trend in drug delivery system in the United States which opens new scientific horizons which needs to be encouraged. By the same token, our data is too limited to establish strict guidelines; and the Agency needs to be flexible in

establishing requirements as a basis of drug approval. The newness of this technology and the limited biopharmaceutic and clinical data particularly explains the various basis of drug approval.

Regulatory Requirements

Transdermal controlled release medications regardless of the active therapeutic moiety employed is regarded as a new drug within the meaning of the Federal Food, Drug and Cosmetic Act, Section 201(P) and as such require submission of scientific documents to substantiate clinical safety and efficacy. Furthermore, all such drugs are considered by the FDA to be controlled release dosage forms and, therefore, require demonstration of controlled release characteristics to support drug labeling.

Transdermal controlled release drugs are considered by the Agency to be new drugs intended for the treatment or prevention of a systemic disease as opposed to the topical drugs intended for a local effect. This does not negate the possibility of a controlled release medication exerting a local effect nor does it necessarily restrict such drugs to the systemic circulation. Perhaps the best examples of the latter is the pilocarpine-releasing system, Ocusert, used for glaucoma and the progesterone-releasing Progestasert IUD.

Transdermal controlled release medications require demonstration of safety both in terms of local irritations and systemic toxicity. In the event that the systemic toxicity of an active therapeutic moiety is well defined in the scientific literature, e.g., nitroglycerin, scopolamine, etc., the Agency may waive the demonstration of animal systemic toxicity, but may require additional clinical testing for safety in human

patients. Where blood level comparisons of the transdermal medication to an already-established systemic route of administration of the same drug, e.g., I.V., I.M., P.O. is available, the systemic safety issues may be ruled out if the blood levels are within established safe and efficacious limits in treated patients administered the currently approved labeled dosages. The latter is particularly applicable where the daily dose of the transdermal drugs far exceed current clinical usage or the circulating systemic blood levels of the drug far exceeds other systemic routes of administration due to by-passing first-pass metabolism.

Clinical testing for efficacy is always required of transdermal controlled release medications involving new drug entities (drugs not well defined in the scientific literature) and may be required to support new efficacy claims on old drugs. Biopharmaceutic considerations can play an immense role in the latter determinations since the FDA may be able to rely on blood level comparisons where the pharmacodynamic effects of the drug are well defined employing a systemic route of drug administration, i.e., intravenous, intramuscular, oral routes. The latter will be illustrated with the TTS-scopolamine system.

Clinical efficacy data would always be required to support a new medical claim or any claim of superior efficacy. Biopharmaceutics claim as to enhanced superior reproducibility or prolonged therapy will require appropriate bioavailability/pharmacokinetic studies to support labeling. Because of the nature of such studies, i.e., generally steady-state and the potential for safety considerations, an Investigational New Drug (IND) exemption is currently required of the firm prior to initiating such studies.

In certain instances, additional metabolism studies in man may be required to define the metabolism of the drug where it is suspected that

significant alteration in metabolic pathways may be encountered due to difference in hepatic-portal metabolism or by-passing G-I metabolism. In instances where kidney function plays an important role in the drug and metabolite elimination of transdermal drug, pharmacokinetic studies in patients with renal impairments or patients undergoing hemodialysis may be further required unless such data is currently available in the literature to support dosage administration.

The types of studies required as a basis of approval of a new drug application need to be customized and are largely dictated by the following considerations:

1) Critical nature of the active drug.

2) Availability of already-marketed systemic dosage form of the same drug.

3) Medical and biopharmaceutic rationale.

4) Current literature data on the drug entity.

5) Agency experience with the drug and/or drug delivery system.

It should be stressed that these novel drug delivery systems require careful scientific evaluation based on the pharmacologic and pharmacokinetic properties of the drug and drug delivery system. Critical drugs (drugs with narrow therapeutic index) or drugs which require careful patient titration may need additional specialized studies to define both the safety, efficacy, and labeling requirements. Such studies, in my opinion, need to be customized. In most instances where systemic toxicity of the drug entity is well known, further animal

toxicity testing is obviated. Where toxicity data is required, such requirements should parallel other systemic drugs of the same pharmacological class.

Biopharmaceutic Considerations

Biopharmaceutic considerations are pivotal in the evaluation of transdermal controlled release medications. There is an absolute need to define the dosage form delivery system in terms of its rate and extent of drug delivery as well as its reproducibility. Additionally, there may be a need to define the pharmacokinetics and metabolism of the active therapeutic moiety itself where such information is lacking. It should be stressed that the pharmacokinetic and metabolic profile of the active therapeutic moiety in a transdermal delivery system may differ significantly from the oral routes of administration due to the by-passing liver of G-I metabolism. In such instances, the pharmacokinetic profile of the drug should parallel an intravenous infusion which delivers the drug by a zero-order mechanism.

From my perspective in evaluating transdermal drug delivery systems, there is the need to evaluate the site of drug administration in order to optimize the dosage delivery. One further needs to consider such parameters as area of drug administration, blood flow at the site, and perhaps even the consequence of physical activity. There is the further need to assess the role of the skin in controlling (and in some instances, sustaining) drug delivery to the systemic circulation. The example of ipsolateral versus controlateral plasma levels from Searle's MDD-Nitroglycerine discussed by Dr. Karim points out the need to define the optimal site of drug absorption.

Ideally, transdermal controlled release medications are best defined in comparison to an intravenous dose. Such an example is shown in the next figure which compares Alza's trandermal scopolamine to an intravenous infusion (courtesy of Dr. Jane Shaw, Alza Corporation). It can be readily seen that following the sudden bolus observed in the initial 12 hours, scopolamine is released at a zero order rate over a 3-day period. Beyond 24 hours, urinary excretion rate in (mg/hr) was fairly constant, i.e., 0.5 ng/hr over an 84 hour period for the TTS-scopolamine. This study demonstrates that TTS-scopolamine delivers the drug at comparable to a zero order infusion over a 3-day period (Figure 1).

These findings are in marked contrast to that obtained from a parenteral I.M. dose of 200 mcg of scopolamine hydrobromide which is equivalent to

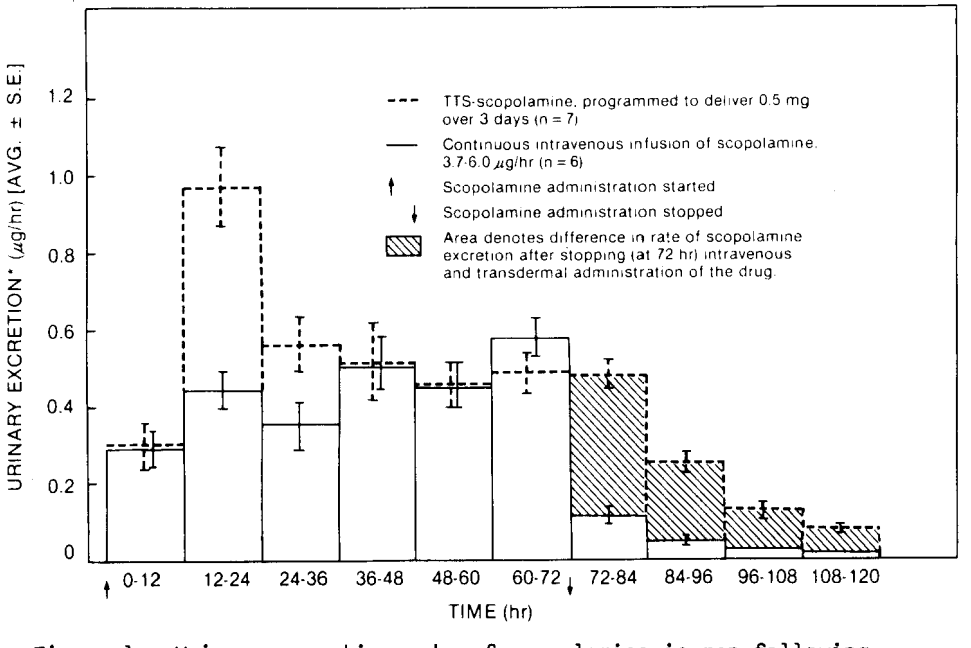


Figure 1 - Urinary excretion rate of scopolamine in man following TTS-scopolamine and intravenous infusion (Courtesy of Alza Corporation).

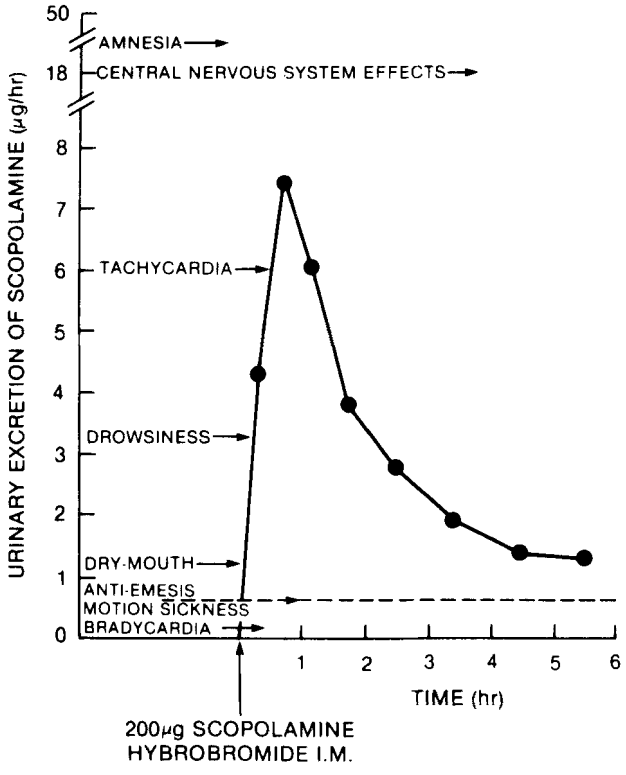


Figure 2 - Urinary excretion of scopolamine and pharmacodynamic effects following intramuscular administration (Courtesy of Alza Corporation).

the amount administered in 1 hour I.V. The I.M. dose achieves rapid peak plasma levels which are associated with the side effects, e.g., drowsiness, tachycardia (Figure 2).

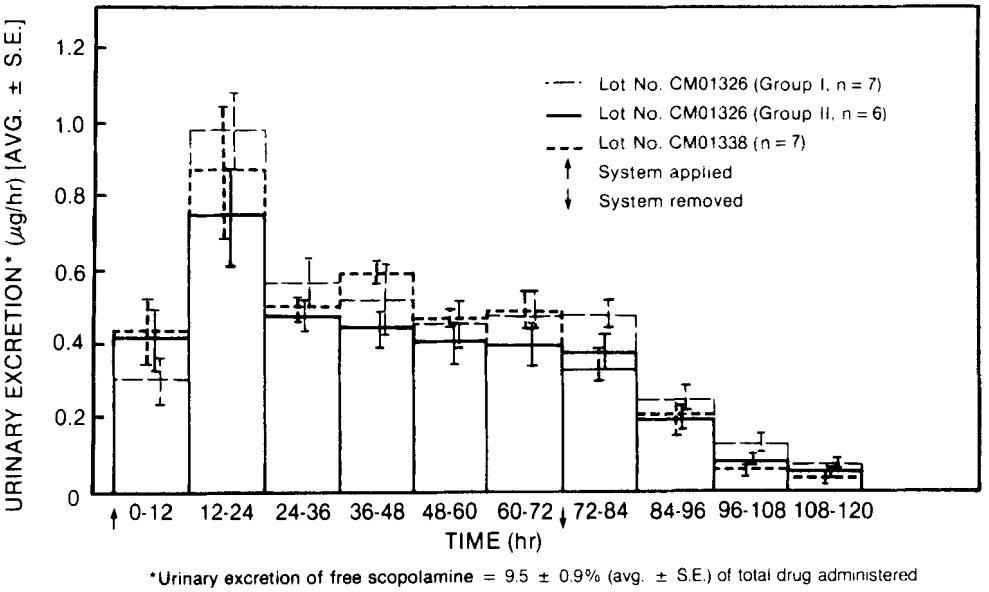
It should be noted that in the case of TTS-scopolamine, the skin behaves as a source of drug reservoir maintaining levels at least for 12 hours after removal of the TTS delivery system. This can be readily observed by comparing urinary excretion rates at 72-84 hours after removal of the drug delivery device.

It should be noted that the TTS scopolamine was so designed so as to deliver the drug at a rate which resulted in a urinary excretion rate of

less than 1 mcg/hr well below the toxicity range which occurs at higher levels.

As well as defining the pharmacokinetic profiles of a new drug delivery system, it is necessary to demonstrate the reproducibility of such systems. This involves both demonstrating reproducibility in manufacturing as well as in intra-and inter-patient variability. This can be achieved by comparison of different batches of a drug delivery system in the same patients. This is best illustrated in the next figure (Figure 3) (courtesy of Dr. J. Shaw, Alza Corporation).

In considering systemically effective drug delivery systems using absorptive surfaces other than the upper GI tract, one cannot ignore the likelihood that such dosage forms will result in significantly different pharmacokinetic profiles than the oral dosage forms. For example, it should be possible to demonstrate that a systemically effective



*Urinary excretion of free scopolamine = 9.5 ± 0.9% (avg. ± S.E.) of total drug administered

Figure 3 - Comparison of two lots of TTS-scopolamine (Courtesy of Alza Corporation).

transdermal drug delivery system avoids first-pass liver metabolism and/or is a far more reliable drug delivery system. Bioavailability data may further indicate that the dosage form delivers the drug for a longer period of time. Both the latter hypotheses can be readily demonstrated by comparing two systemically effective nitroglycerin products, a sublingual dose of nitroglycerin and a new transdermal drug delivery system (courtesy of Dr. Cohen of Key Laboratories). Studies performed by Dr. Pitt and coworkers at the University of Michigan Medical Center clearly demonstrated that cutaneous absorption of nitroglycerin from the transdermal drug delivery system (TNG Polymer, Key Laboratories) resulted in detectable plasma levels for 24 hours (Figure 4) in contrast to plasma levels for only 16 minutes after a sublingual dosage form (Figure 5).

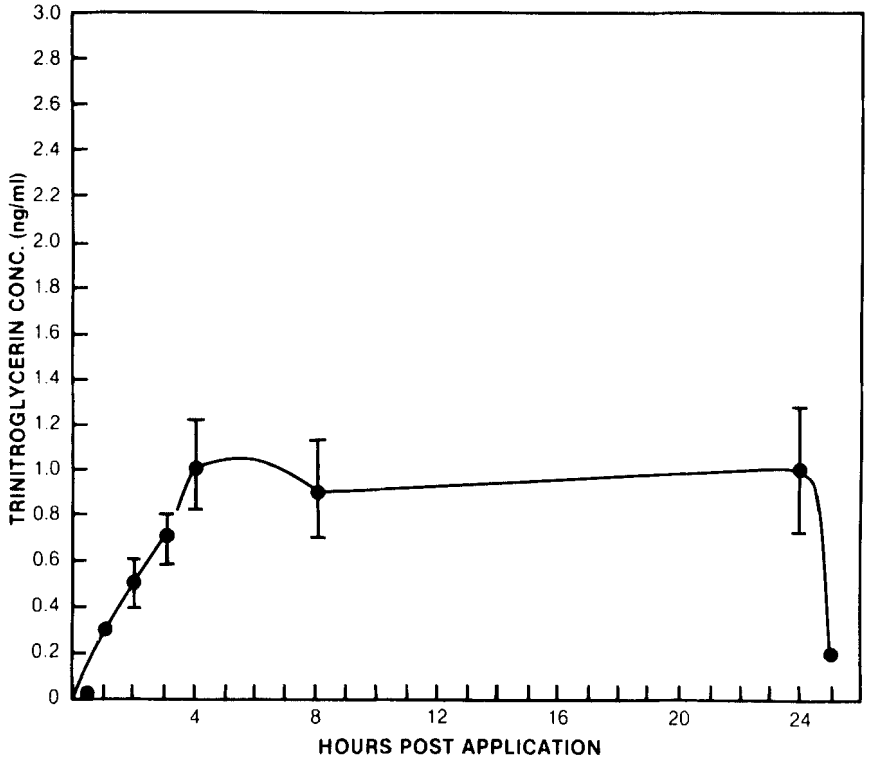


Figure 4 - Cutaneous absorption of nitroglycerin from a transdermal drug delivery system, TNG Polymer (Courtesy of Key Laboratories).

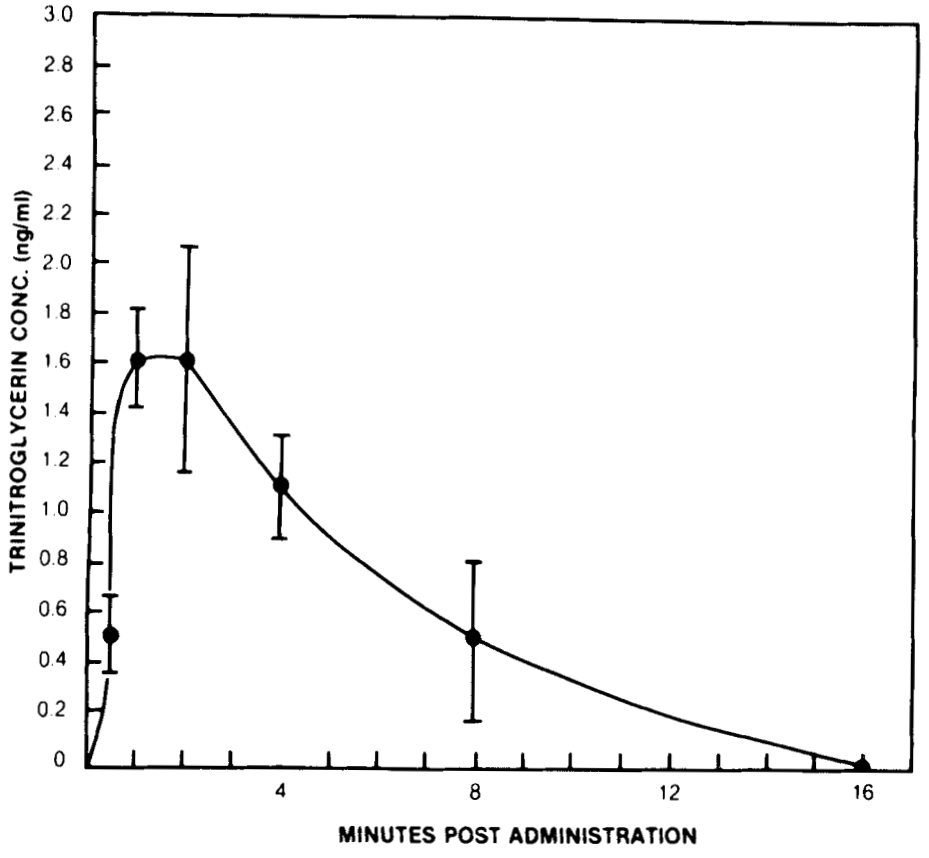


Figure 5 - Plasma concentration of nitroglycerin following sublingual dose (Courtesy of Key Laboratories).

The basis of approval of such a dosage form from a biopharmaceutics standpoint consists of demonstration of:

1. reproducibility of plasma levels
2. defined pharmacokinetic parameters to support drug labeling; and
3. demonstration that the plasma concentration are within reasonable therapeutic limits of those achieved with the oral sublingual dosage form. Additional clinical trials are needed to support the once-a-day dosage regimen, and to rule out physiological tolerance. Such trials may not only support maintenance dosage recommendations but may also document more reliable drug delivery.

It is not always feasible to define the bioavailability profile of a transdermal drug relative to an I.V. dose (bolus or zero order infusion), and often the use of other routes of drug administration may provide additional pharmacokinetic data so as to permit appropriate labeling.

Illustrated in Figure 6 are comparative plasma levels of nitroglycerin following administration of this drug either in an ointment (Nitro-Bid) every 8 hours or as TTS-nitroglyercin once a day (courtesy of Dr. J. Shaw, Alza, Corporation).

In this study involving 12 human subjects, the ointment containing 9.2 mg per 10 cm^2 area was administered every 8 hours for a total daily dose of 27.6 mg. The TTS-nitroglycerin containing 25.6 mg per 10 cm^2 device was administered as two separate patch (20 cm^2) once a day. Each drug

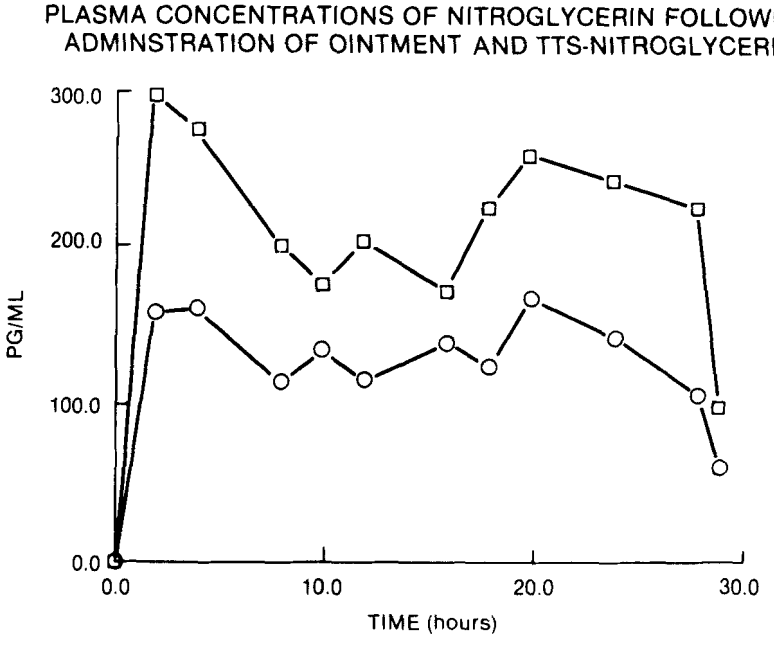


Figure 6 - Plasma concentrations of nitroglycerin following administration of Nitro-Bid (○) ointment, Marion Laboratories and TTS-Nitroglycerin (□), Alza Corporation (Courtesy of Alza Corporation).

was administered to the human subjects over a 28 hour period employing a balanced random design. It can be readily seen that following an initial spiking in plasma levels of nitroglycerin, both drug administration resulted in reasonably well-controlled pseudo steady-state plasma levels over the 28 hour period, and a rapid decline in nitroglycerin plasma levels was manifest upon cessation of dosage at 28 hours.

Since both dosage forms were administered at different dosages and area of skin applications, i.e., 10 cm^2 vs 20 cm^2, it was necessary to normalize the data by comparing the nitroglycerin plasma levels normalized for area of skin application (Figure 7). It can be readily seen that the TTS-nitroglycerin is slightly higher but statistically equivalent to the Nitro-Bid Ointment over the entire 28 hour period. On the average, plasma levels of 12-15 pg/ml was achieved per cm^2 area of

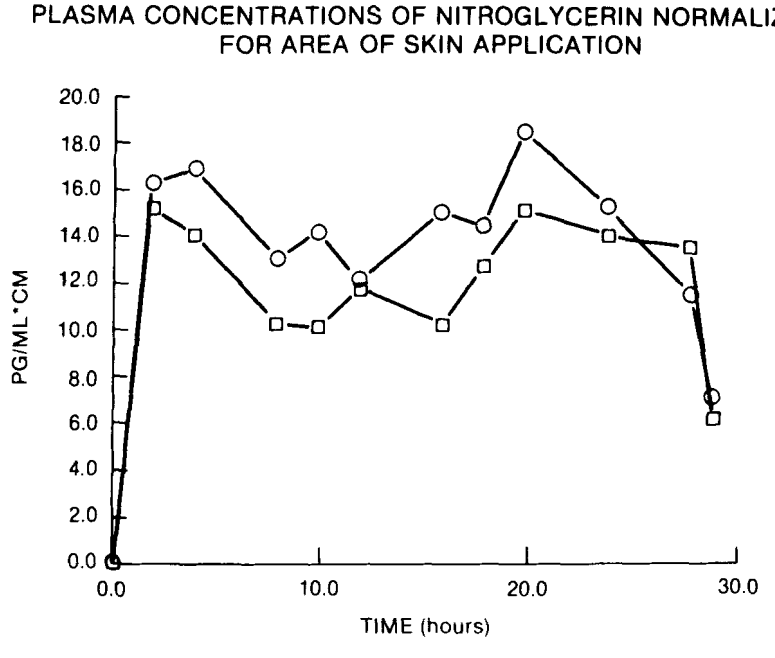


Figure 7 - Plasma concentrations of nitroglycerin normalized for area of skin application, Nitro-Bid ointment (O), TTS-Nitroglycerin (□) (Courstesy of Alza Corporation).

skin application over the 28 hours. Upon cessation of dosing the plasma levels of nitroglycerin precipitously dropped to about one-half these levels within 1 hour indicating that the skin does not serve as a tissue reservoir (in contrast to TTS-scopolamine).

During the course of the study the firm assayed the residual amount of nitroglycerin within each TTS-Nitroglycerin patch at the end of 28 hours and the residual amount in the Nitro-Bid Ointment (Marion) at the end of the 8 hour dosage regimens. This additional analysis permitted the assessment and comparison of absolute bioavailability, total "apparent" plasma clearance of nitroglycerin following both dosage regimen and rates of drug delivery over the 28 hour period in the individual subjects. Additionally, this study design permits assessment of the reproducibility of each patch and ointments within any given subject.

The latter was made possible since 2 TTS-Nitroglycerin patches and 3 Nitro-Bid Ointment applications were made for each subject. Assuming equivalent clearance values for each drug delivery system, this analysis permits further normalization of plasma levels of nitroglycerin based on an equivalent absorbed dose, i.e., 10 mg absorbed dose. It should be stressed that this comparison was made possible because both the TTS-Nitroglycerin and the Nitro-Bid Ointment were administered in a rigorously pre-measured dosage and pre-defined area of skin applications for both drugs. The latter data could not be feasibly obtained employing the current labeled instructions for the ointments and would be expected to perhaps result in higher plasma of nitroglycerin of shorter duration because of the rapid partitioning of this drug when administered over a large skin area.

Comparison of clearance values (Cl) indicate comparable clearance of nitroglycerin in both systems, i.e., 42.7 L/min ($\pm$ 26.4% C.V.) for

TTS-Nitroglycerin vs 47.8 L/min (± 31.7% C.V.) for Nitro-Bid ointment respectively. Similarly, comparison of the reproducibility of unit dosage delivery in each subject indicated no statistical difference. Thus, it was possible to normalize the plasma levels to an equivalent absorbed dose (Figure 8), which demonstrates the equivalent plasma levels can be achieved when administered equivalent doses are absorbed.

Of particular interest was the findings that with both dosage forms, approximately one-third of the dose was absorbed in 28 hours on average, i.e., 30.9 ± 40.6% C.V. and 36.0 ± 28.4% C.V. with the flux being about .030 mg/hr/cm^2 Nitroglycerin for both drugs. Closer examination of the data obtained in individual subjects revealed that there were slow absorbers and fast absorbers regardless of what dosage form was employed (range 17-58 percent of dose per 28 hour administration). Of particular interest to the FDA is the fact that TTS-Nitroglycerin delivers drug at a constant

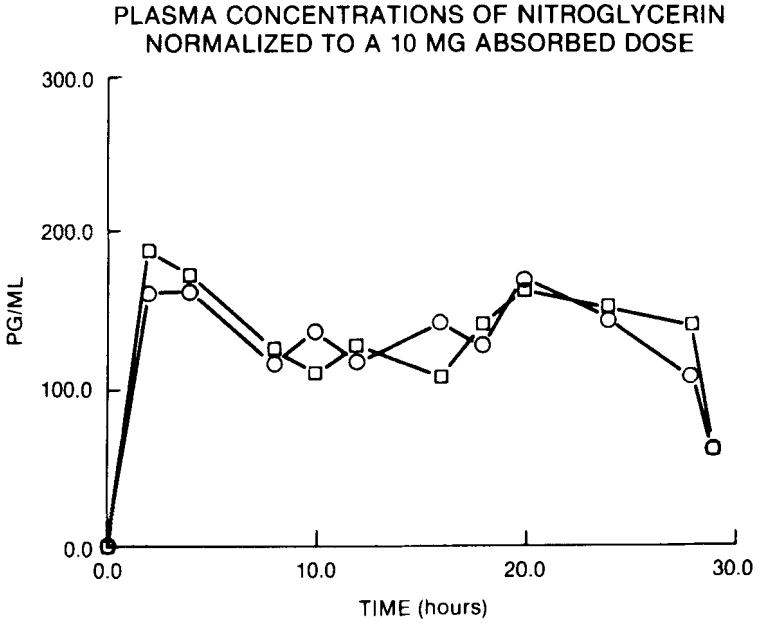


Figure 8 - Plasma concentrations of nitroglycerin normalized to a 10 mg absorbed dose.

rate (zero order rate) over the 28 hour period and further suggest the strong possibility that plasma levels could be maintained 48 to 72 hours with such a drug device.

To warrant such a labeling claim the firm would be required to demonstrate (1) that equivalent plasma levels are maintained when such drug devices are administered once a day for 2 or 3 consecutive days as opposed to a single 3-day dosage application; and (2) no physiological tolerance is manifest when the drug is administered once a day.

Similar results were also demonstrated by Searle Laboratories as a basis of approval of the Nitroglycerin Microsealed Drug Delivery System (MDD-NG). Comparison of MDD-NG administered as 2 X 16 mg pad over a total 16 cm^2 skin application area to that of a 2% Nitro-Bid ointment (Marion Laboratories) administered as a 16 mg dose over an area of 53 cm^2 once a day, revealed comparable plasma levels over a 36 hour period (Figure 9).

Systemic plasma levels of 300 pg/ml nitroglycerin were achieved within one hour of dosing and remained essentially constant for 36 hours. The mean nitroglycerin remaining in the MDD-NG system at the end of 48 hours was similar in the two pads in each subject and on the average accounted for 30 percent of the total dose. No attempt was made to normalize the plasma levels in proportion to the area of skin applications (as previously described in Figure 6), but this data indicates that the drug release rates per cm^2 skin applications differ significantly for these two drugs since Nitro-Bid was applied over a significantly larger area; 53 cm^2 for Nitro-Bid vs 16 cm^2 for MDD-NG.

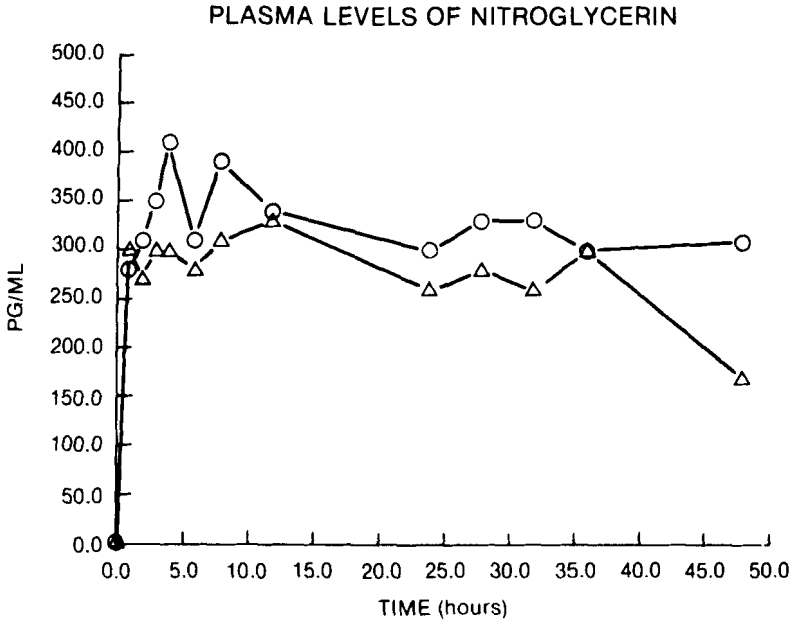


Figure 9 - Plasma concentrations of nitroglycerin following single application of Nitro-Bid (O) ointment, Marion Laboratories and Searle's Nitroglycerin Microsealed Drug Delivery System (△) (Data Courtesy of Searle Laboratories).

Irrespective of the above findings, the steady-state plasma levels for both drugs would strongly suggest comparable rates and extent of drug absorption, i.e., approximately .47 mg per hour over a 48 hour period on average for both drugs. This rate of drug delivery is very similar to that reported for the TTS-Nitroglycerin (Alza) i.e., 0.56 mg/hr and probably accounts for the similar plasma levels reported earlier (Figure 6).

On the basis of the above findings, the Agency has come to a better understanding of transdermal nitroglycerin drug delivery systems and will be able to recommend specific study designs for future drugs. In particular, there is the need to define both the rate and extent of drug

delivery to establish comparable clearances in the crossover design and to evaluate the effects of surface area of skin applications and dose on the absorption. In my opinion, the rate of drug absorption as a function of daily activity and blood circulation may be pivotal. Additionally, one should not rule out the effect of skin temperature.

In summary, this presentation has dealt with both the regulatory and scientific considerations involved in evaluating transdermal controlled release medications. There is much more data that needs to be considered prior to establishing study guidelines, and each drug entity needs to be considered on its merit.