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Delivery of triazolam and baclofen by gastrostomy tubes

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DELIVERY OF TRIAZOLAM AND BACLOFEN BY GASTROSTOMY TUBES

By

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Delivery of Triazolam and Baclofen by Gastrostomy Tubes (86 pp.)

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Delivery of potent drugs by gastrostomy tubes to critically ill patients has become a major concern in recent years because of the increased number of reported drug-plastic interactions. Delivery of two potent drugs, triazolam a hypnotic and sedative and baclofen a skeletal muscle relaxant were studied in teflon coated silicon rubber Foley catheters and in Ross flexiflo replacement G-tubes. Sorption studies were conducted under static (equilibrium), dynamic (flow) and clinical simulation conditions in Foley catheters for triazolam. Sorption, dynamic and clinical simulation studies were conducted in Foley catheters for baclofen and in Ross tubes for both drugs. The variability in drug loss to different Foley catheters also was studied.

Drug loss (20-70%) to delivery tubes was evident for triazolam in both the tubes. No loss was observed for baclofen in either tube. Drug loss to delivery tubing was related to the chemical nature, water solubility and physicochemical properties of the drugs and tube materials.

Sorption of triazolam to the Foley and Ross tubes was observed for up to 72 hours. Equilibrium conditions were not reached in this period and drug loss was irreversible in both tubes. Drug loss was dependent upon concentration of the test solution, amount of drug presented to the tube surface, time and flow rate. Drug loss was greater at higher concentrations, longer time of contact, larger volumes (and amounts) of drug solution and at slower flow rates. The observed drug loss was consistent with diffusion controlled absorption of the drug into the tube, and was attributed to interaction between drug and the lipophilic tube materials. Slow equilibration and irreversibility of drug loss in repeated trials in the same tube indicate a multi-layer formation or possibly chemisorption even before drug diffused into the tube matrix. Greater inter-tube variability than intra-tube variability in the extent of drug sorption was observed. This variability in drug sorption among different Foley catheters was attributed to differences in tube construction and physicochemical properties. It was observed that materials leached from the Foley catheters into the drug solutions stored in these tubes.

Sorption problems, low therapeutic dose and high ratio of dose related complications with triazolam necessitate further investigation of absorption, distribution and elimination kinetics of this drug in tube fed patients. These studies can be extended to other drugs and other types of delivery tubes.

ACKNOWLEDGEMENTS

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INTRODUCTION

Enteral feeding

In certain disease conditions, patients cannot swallow food or medicines by mouth. In those situations patients are fed by the parenteral route or by enteral feeding tubes (1-24). When parenteral feeding is not necessitated and patients have to be fed for longer periods, enteral tube feeding is recommended. Situations where tube feeding is necessary include anorexia resulting from trauma, burns, cerebrovascular accidents, or disease (1,6-10). Other conditions such as mechanical impediments to eating, depression or coma may also prevent patients from oral intake (5).

The method of feeding depends on the status of the gastrointestinal tract and the quantity of calories required (2). Enteral feeding promotes more efficient utilization of nutrients and better preservation of intestinal integrity than does parenteral administration (11). The gut is the preferred route when it is functioning and accessible. Enteral alimentation is generally safer and more economical than parenteral alimentation and, when tolerated, is the preferred route of nutrient administration for patients requiring intensive nutritional support (4).

There is evidence both theoretical and practical suggesting that enteral feeding is superior to parenteral alimentation with regard to substrate utilization (1). Unlike parenteral feeding, which exposes the tissues to unmetabolized nutrients, enteral alimentation preserves the physiologic sequence of nutrient absorption, metabolism and utilization, prior to delivery to the peripheral circulation (19).

Tube enterostomy refers to the operative placement of a tube or catheter into any segment of the gastrointestinal tract, from the pharynx to the colon (26). The surgical placement of a tube or a catheter into the gastrointestinal tract for nutrient delivery is indicated when the

nasoenteric route is unavailable or when long term enteral alimentation of more than four weeks is anticipated (1). Enterostomy is required in situations such as tumors of the esophagus, and stomach or benign conditions such as strictures or collagen-vascular diseases (1). In such situations, the operative insertion of a feeding tube distal to the obstruction will allow the normal process of intestinal digestion and absorption to continue. Even if the upper gastrointestinal tract is mechanically intact, central neurologic disorders (multiple sclerosis, cerebral vascular accidents, infection or tumor) or primary muscular disfunction may interfere with swallowing and reduce or prevent oral intake (5,6,8,9,10). If the condition appears to be chronic, a tube enterostomy offers a more secure, manageable access site for enteral nutrition.

Gastrostomy, in which the tube is surgically implanted between the stomach and the abdominal surface, is the most commonly used method of enterostomy (26). This technique is widely accepted because of its wide applications, limited side effects, greater reservoir capacity, economy and high patient compliance. Gastrostomy is particularly useful for prolonged or permanent feeding (36). Gastrostomy requires a stomach uninvolved by primary disease, normal gastric and duodenal emptying, no significant esophageal reflux, and intact gag reflexes (26). Utilization of the stomach is important because of its reservoir capacity which allows intermittent bolus feeding without the need for a continuous pump infusion.

The development of percutaneous endoscopic gastrostomy (PEG), in 1980 by Gauderer and Ponsky opened a new era in the field of enteral feeding (39). In PEG, flexible endoscopes are placed in 15-20 minutes without general anesthesia. The procedure involves the placement of a gastrostomy catheter through a guide needle and sheath. PEG is a less expensive, non surgical procedure with fewer complications. Because of its ease and the rapidity of the

procedure, low procedure related mortality, very few major and minor complications, and easier maintenance and replacement, PEG has become the procedure of choice in recent years (37). PEG is receiving wide acceptance including paediatric patients, debilitated neurologic cases, and elderly patients, who usually have more complications with anaesthesia and surgery (38).

Gastrostomy tubes (G-tubes) made of rubber and latex are commonly used for long term delivery of feeding. There are number of feeding tubes available. The large-bore gastrostomy tube is more advantageous for delivery of medication and high-viscosity nutrient formulae. Most of the feeding tubes for different routes of administration are made of polyurethane, polyvinylchloride, silicone, silicone rubber or polyethylene (28). Softer, more pliable enteral feeding tubes made of silicone and polyurethane are less reactive with body tissue, and have been widely used in recent years (40). These tubes are divided into nasoenteral feeding (naso-gastric, naso-duodenal and naso-jejunal) and enteral feeding (jejunostomy, gastrostomy, ileostomy, and colostomy) categories (1,28). The only differences among these three types of tubes are their dimensions (length, diameter). Gastrostomy tubes are shorter (76.2 cm or 30 in) and range from 5 French to 24 French in diameter (measured in French size) (28).

Administration of medication by enteral feeding tubes

Drugs are most commonly administered through the oral route, where the drug is prepared (disintegration, dissolution) by the stomach and delivered to the absorptive sites of the small intestine. Patients who are being fed by enteral feeding tubes frequently are given medication via the feeding tube, either with the nutrient formula or separately. When the entry route is altered by the placement of enteral feeding tubes, the pharmacologic agent and its mode of delivery are often modified depending on the size

and placement of tubes and also on the type of dosage form (1). Large drug particles (crushed tablets, granules, powders, suspensions) are administered along with bolus enteral feedings by large-bore, nasogastric or gastrostomy tubes. If the tubes are placed beyond the stomach where disintegration and dissolution is a problem drugs must be in liquid form with low viscosity and the tubes should be flushed with water after each dose. Studies indicate that drugs generally are better absorbed in the fasted state than in the fed. So the most suitable time for drug administration by feeding tubes is one hour before or two hours after a meal (62).

The rate of absorption of food or drugs delivered into the stomach by oral or tube feeding is dependent upon the gastric emptying rate (GER). There are several factors which directly or indirectly affect GER. Physiologic factors included disease states such as ulcer, severe trauma, myocardial infarction and gastric carcinoma (1). The GER can be delayed by drugs (e.g. belladonna alkaloids, chlorpromazine, amitriptyline.), or increased by drugs (e.g. metaclopramide, anticholinergic, reserpine) (1). Food can also effect the absorption of drugs, either to decrease absorption (e.g ampicillin, tetracycline and phenobarbital), or to increase absorption (e.g propranolol, metoprolol and griseofulvin) (1). Since absorption is slow from the stomach, faster gastric emptying leads to rapid absorption of drugs and quicker onset of action. Therefore, in tube fed patients one must evaluate carefully, factors affecting GER, type of dosage forms, particle size, volume, rate of feeding and other factors such as compatibility with food and other drugs.

It is recommended that a commercial liquid dosage form should always be used when it is available. Solid dosage forms should be used only when liquid products are not available. When a liquid dosage form of a drug is not available one must prepare a solution or a suspension from

solid oral dosage forms. While reprocessing solid dosage forms into a liquid form for enteral administration, problems such as non-uniformity of particle size, choice of an improper suspending agent and production of an unstable drug product must be carefully viewed. Knowledge of interfacial phenomenon, colloidal dispersion and flocculation is very important in making pharmaceutically viable liquid formulations (134). At no time, should enteric coated or slow released drug formulations or drugs contraindicated for oral use be administered by feeding tubes.

Problems of drug administration by enteral feeding tubes

Enteral feeding tubes are generally made of polyurethane, polyethylene, polyvinyl chloride (PVC), silicon, or silicon rubber. They represent a chamber with possible sorptive capacity. Some recently conducted studies reported that problems may occur with drug delivery through feeding tubes (81-111).

One of the potential problems of administering drugs through G-tubes is binding interaction between the drugs and the non-polar materials of the tubes which results in decreased delivery of drugs to the patients (80). Drugs with low water solubility and high affinity for lipids present the greatest potential for sorptive loss to plastic tubing.

Administration of different drugs, nutrients and other fluids concurrently or within a short time span is likely to increase the potential for problems of interactions with each other or with the tube material (46-80). A major concern is the delivery of drugs by G-tubes with and without food. Although there is very little data available regarding the delivery of drugs by gastrostomy or other types enteral feeding tubes, there are literature reports showing loss of drugs to intravenous tubing and other materials which are directly comparable to enteral feeding tubes (81-111).

The complications involved in the delivery of drugs by

polymeric materials are well documented. Insulin is reported to be adsorbed to glass containers, PVC surfaces, IV tubing, polyolefin infusion bottles and plastic containers (81-84,87-89). Vitamin A is reported to be sorbed to polyvinyl, polyolefin IV tubing and plastic IV infusion bags (85,86,94,95,97). Binding of drugs to plastics appears to be a major problem when polymeric delivery devices are used to administer drugs (90,96,101). Interaction of drugs with plastics has been well documented for diazepam and nitroglycerin (102-111). Drugs are also reported to be interactive with food and electrolytes (46-80). Binding of drugs to caseinate salts, calcium and other electrolytes has been reported (66,72). Drug interaction with protein nutrient formulas is also a problem in the delivery of drugs by feeding tubes (78-80). Stability problems for drugs in total nutrient admixtures for gentamicin, phenytoin, carbamazepine and warfarin have been evaluated (46,48,50,55). Leaching of plasticizer into the solution is well documented (111-132). Toxicity from leached substances, drug binding to plasticizer and drug degradation by leached material have been reported to be other problems in the tube fed patient (114,118,119,126-132).

From the literature reports it is clear that a wide range of interactions may occur between tube materials, drugs and enteral nutrient formulas. These interactions may lead to degradation of essential nutrients present in the formula or antagonism or altered bioavailability of drugs administered by the feeding tubes. In order to knowledgeably use this procedure for the administration of drugs it is necessary to evaluate further the delivery of drugs by feeding tubes. Other aspects such as interactions between food and drugs, drugs and drugs, food and tube material, drugs and tube materials must also be evaluated. The above studies should be extended to different drugs with different food formulas in a variety of enteral feeding tubes. It is essential to have delivery as well as pharmacokinetic data

available for drugs most commonly administered by enteral feeding tubes to critically ill patients for long term use. Data concerning quantitative delivery of drugs by feeding tubes and pharmacokinetics may permit a clear understanding of the effectiveness of treatment and evaluation of the patient's recovery. Considering the problems associated with the delivery of drugs by enteral feeding tubes it will be essential to conduct delivery studies for drugs by different feeding tubes. Studies should be conducted with and without nutrient formulas.

Since all types of feeding tubes, IV tubes and infusion bags are made of similar materials, results from one study can be used to correlate to other tubes made of the same material, i.e., to the other feeding tubes made of the same material.

Sorption of drugs and chemicals to polymeric materials

Sorption is a physicochemical phenomena that can occur when a solution is in contact with a solid phase (86). Sorption can occur as a result of two phenomena. If the solute interacts with the surface of the solid then it is adsorption whereas if the solute penetrates into the solid matrix then it is termed absorption. Absorption occurs as a result of diffusion of the solute molecule into and within the matrix of the solid (90). Since solute absorption is a diffusion process it takes a longer time and can involve larger amounts of material when compared to adsorption (96). Adsorption occurs more rapidly (86). It reaches equilibrium faster, and desorption is easier unless the interaction between the drug and the solid material is quite strong (96). The amount of drug adsorbed is likely to be smaller than the amount absorbed.

Since sorption is a physicochemical phenomenon, sorption of drugs to tubing material is directly related to the chemical structure of the drug and the physical and chemical properties of the tubing material (98). Other

factors such as concentration, solvent system, other agents in the solution, pH of the solution, temperature, time of contact, amount of surface exposed to solution, purity of material and possible changes in the material after exposure to solution may also be involved in this process. Interactions may be ion-ion, ion-dipole, dipole-dipole or through secondary valance forces such as Van der Waals forces or perhaps a combination of these (98). The affinity of a drug for a specific plastic material can be indicated in terms of standard chemical potential. If the rate determining step in the sorption process is diffusion of the drug into the matrix of the plastic, then importance is placed upon the diffusion constant or coefficient. Solute molecules within the solvent diffuse toward the surface of the plastic and become adsorbed. When most of the adsorption sites are occupied, there will be sufficient energy to permit these solute molecules to penetrate the surface and to travel or diffuse into the amorphous zone of the plastic where new binding sites become available (98). If no more sites are available then equilibrium has been reached at that particular solute concentration and time.

Plastic or rubber polymers are composed of crystalline regions dispersed throughout amorphous regions. The permeability of polymers may differ due to molecular weight, molecular weight distribution, branching, degree of crystallinity and the presence of other ingredients (136). Extensive cross linking within the polymer retards the movement of solute particles, thus less permeation occurs. Since an amorphous zone has low crosslinking, more permeability (easier diffusion) is observed in this region than in a moderate to high crystalline region. A low diffusion constant results for high crystalline region (136). Highly crystalline polymers are rigid in nature. To make formulated polymers soft and flexible, plasticizer and other additives such as stabilizer, filler and lubricant are added to the material. In any formulated plastics there is

always a propensity for one of the ingredients to migrate into the environment which has intimate contact with the material (130). Leaching may modify the structure of the plastic matrix, thereby altering its permeability. Additives leached from any of the polymer materials may interact with the drug. The chemistry of a number of polymers utilized in plastics suggest that a medicinal agent conceivably could be bound to certain polymers (96). Polymers containing charged negative centers such as carboxyl groups could react with proton donating agents forming an intermolecular complex. A number of such intermolecular interactions have been reported for macromolecules having acidic hydrogens (137). Reactivity due to sorption (absorption and/or adsorption) has been found to occur frequently with the polyamide polymers (137). Though the exact mechanism is not determined it could be that the carbonyl groups of the polyamides acted as negative charged centers attracting the proton donating groups of phenols, the main forces of bonding being through hydrogen bonds. In dilute solutions, drug molecules are not hindered in approaching the binding sites on the surface and within the polymer, but as the concentration is increased there is hindrance to the approach of the molecules for the remaining sites (137). However there appears to be a critical concentration level where the solution can literally break through the polymer matrix. Once this has occurred a great many sites are available (137).

Thus, loss of drug could occur by adsorption of a nonpolar drug onto the tubing surface, absorption of the nonpolar drug into the tubing, or partitioning of the drug into the tubing (97).

Purpose and objectives of this study

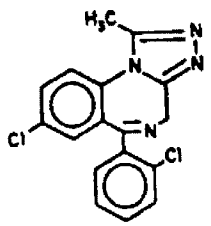
Triazolam (Halcion^{R}) and baclofen (Lioresal^{R}) are commonly administered to spinal cord injury and post-stroke patients through G-tubes. Since these patient conditions prevent them from taking food and drugs by mouth they are

fed through feeding tubes. Both triazolam and baclofen are available only in tablet form, so they must be crushed to make a slurry and administered through feeding tubes. No data has been reported regarding the quantitative delivery of these drugs by G-tubes or any other drug delivery devices made of similar materials.

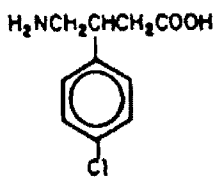
This study was conducted in-vitro using the two most common G-tubes in practice, the rubber Foley catheter and a replacement G-tube (Ross flexiflo #154). The major purpose of this thesis was to study the sorptive interaction between triazolam and baclofen with two types of G-tubes in current clinical use. This was studied by evaluation of the delivery of triazolam and baclofen by G-tubes using conditions which simulate but do not duplicate the clinical conditions used for administration of these agents. Thus delivery of 10 mg of baclofen or 0.25 mg of triazolam in 10 ml of water was evaluated. Two types of studies were conducted for each drug and each tube under study, static (equilibrium) studies and dynamic (flow) studies. Depending on the drug loss in static (equilibrium) studies, further studies at different concentrations and at various intervals were done.

This project could serve as the initial phase of studies to characterize the absorption and disposition of drugs in patients requiring medication delivery by G-tubes. Results of the delivery of these drugs by G-tubes could be used to make recommendations regarding the selection of an appropriate G-tube with minimal or no drug loss for patients requiring long term use. This study may also be helpful in the development of suitable dosage forms which would enhance the delivery of these and other drugs through G-tubes.

Chemical Structures



Triazolam



Baclofen

EXPERIMENTAL

MATERIALS

Gastrostomy tubes:

1) Foley Catheter
   Bard Urological Division
   C.R. Bard, Inc., Covington, Georgia 30209
2) Flexiflo Gastrostomy Tube, 18 French #154
   Ross Laboratories, Columbus, Ohio 43216
   Lot numbers: 45-429-GZ & 46-455-GZ

Drugs:

1) Baclofen [Lioresal^R] 10 mg tablet
   Geigy, Ardsley, NY 10502
   Lot numbers: IT108066, IT115898 & IT119303
2) Triazolam [Halcion^R] 0.25 mg tablet
   The Upjohn Co., Kalamazoo, MI
   Lot number: 440 DY
3) Triazolam (8-chloro-6-(2-chlorophenyl)-1-methyl-4H-1,2,4-triazolo [4,3-al]-1,4-benzodiazepine) $C_{17}H_{12}Cl_2N_4$ (M.W. 343.21)
   Sigma Chemical Co., T-9772, Lot-19F4021
4) Baclofen (4-amino-3-[4-chlorophenyl butanoic acid) $C_{10}H_{12}ClNO_2$ (M.W. 213.67)
   Sigma Chemical Co., B-5399, Lot-38F0508

Reagents:

1) Methanol, HPLC grade, Fischer Chemical
2) Monobasic Potassium Phosphate, Allied Chemical
3) Sodium Acetate GR, EM Science
4) Acetone
5) Sodium Hydroxide, Reagent Grade, J.T. Baker Chemical Co.

Foley catheters are 43 cm in length, Ross Flexiflo G-tubes measured 26 cm and both are 18 French in diameter. The internal diameters for Foley catheter and Ross tubes are 0.3 cm and 0.45 cm respectively. Triazolam is a tan crystalline powder and is very slightly soluble in water. Baclofen is crystalline and is slightly soluble in water.

METHODS

Analytical Methods

Triazolam was analyzed by the reversed phase HPLC procedure described by Inoue and Suzuki (141), and baclofen by the procedure of Wuis et al. (142). A LDC/MILTON ROY series 3000 high performance chromatograph equipped with a variable wave length UV/visible detector and a CI 4000 computing integrator was used. The analytical column was an Altech econosphere (250 mm x 4.6 mm, 5 micron reversed phase C18 column). Triazolam was eluted with a mobile phase of methanol:10mm phosphate buffer pH 8, in a ratio of 65:35 at a flow rate of 0.8 ml/min, with analysis at a wavelength of 220 nm at 0.02 aufs or 0.1 aufs, dependent upon concentration.

The procedure for baclofen utilized a mobile phase of methanol: 0.02 M sodium acetate in a ratio of 85:15 at a flow rate of 0.7 ml/min using a wavelength of 220 nm at 0.2 aufs.

Retention times for triazolam and baclofen were 9.5 ± 0.1 and 5.6 ± 0.1 minutes, respectively.

Procedure:

The column was prepared by elution with the water followed by mobile phase for at least 10 to 15 column volumes each. The detector was adjusted for wave length, absorption units full scale (AUFS), and response time. The pump flow rate was adjusted based on the peak times of authentic samples. Sample injections were made using a 20 mcl injection loop which was filled using 60-100 mcl of sample solution. Relative peak areas were determined by the integrator, which was set for appropriate baselines and skim ratios. Sample quantification was made based on the integrated area under peak. All injections were made at least in triplicate. Sufficient column washing time was allowed between the sample injections. At the end of the sample analysis the column was thoroughly washed with mobile

phase followed by water and finally parked under methanol. After a series of injections were completed, the data could be recalled from computer memory and reprocessed to evaluate the baseline and peak area integration. If the baseline was not consistent with initial baseline corrections, then the injection data was reprocessed to correct the error in the peak area calculation.

Standard curves for triazolam and baclofen

Standard curves for triazolam and baclofen were prepared using authentic samples of drugs in known concentration in water. Serial dilutions were made from the highest concentrations. Additionally, standard curves were made from tablet solutions under identical conditions. These standard curves covering the concentration ranges used in all experiments, were used to set the instrumental conditions for sample analysis, to correlate peak area and concentration, to evaluate the extent of drug dissolution from the powdered tablet, to study the reproducibility of experiments and to determine the amount of drug lost to the G-tubes from the drug solutions.

Standard curves for triazolam were made in two concentration ranges (25-100 and 2-25 mcg/ml) using tablet solutions and one concentration range using triazolam standard (10-100 mcg/ml). Standard curves using baclofen tablet solution and authentic sample were made from a concentration range of 200-1000 mcg/ml. Standard curves for triazolam and baclofen are shown in Figures 1-5.

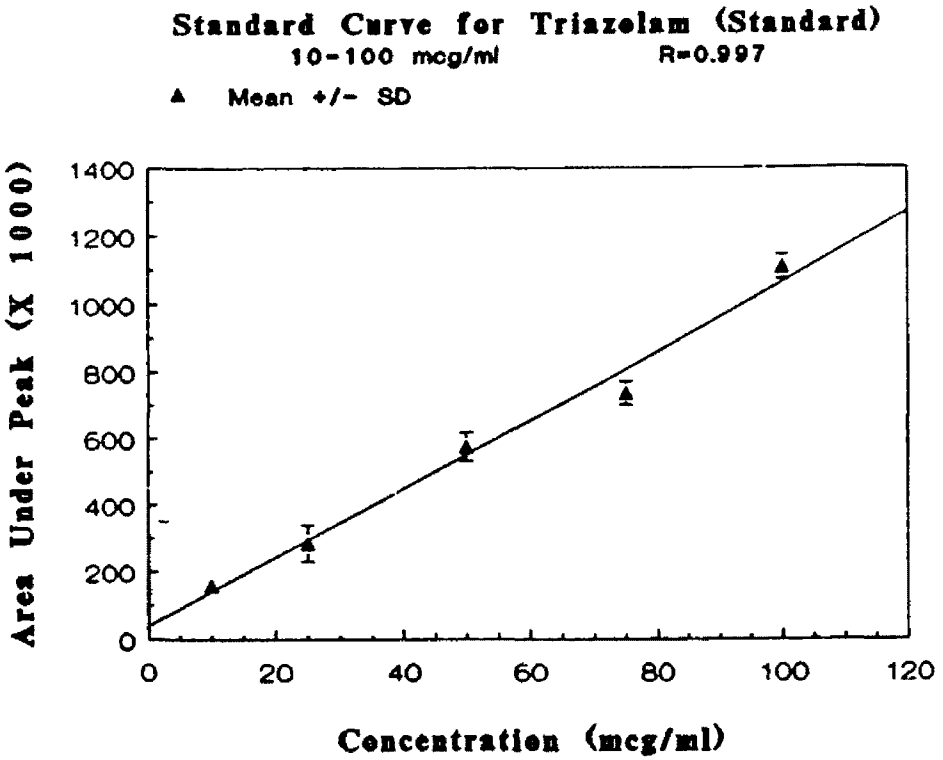


Figure 1. Standard curve for Triazolam standard in water (10-100 mcg/ml)

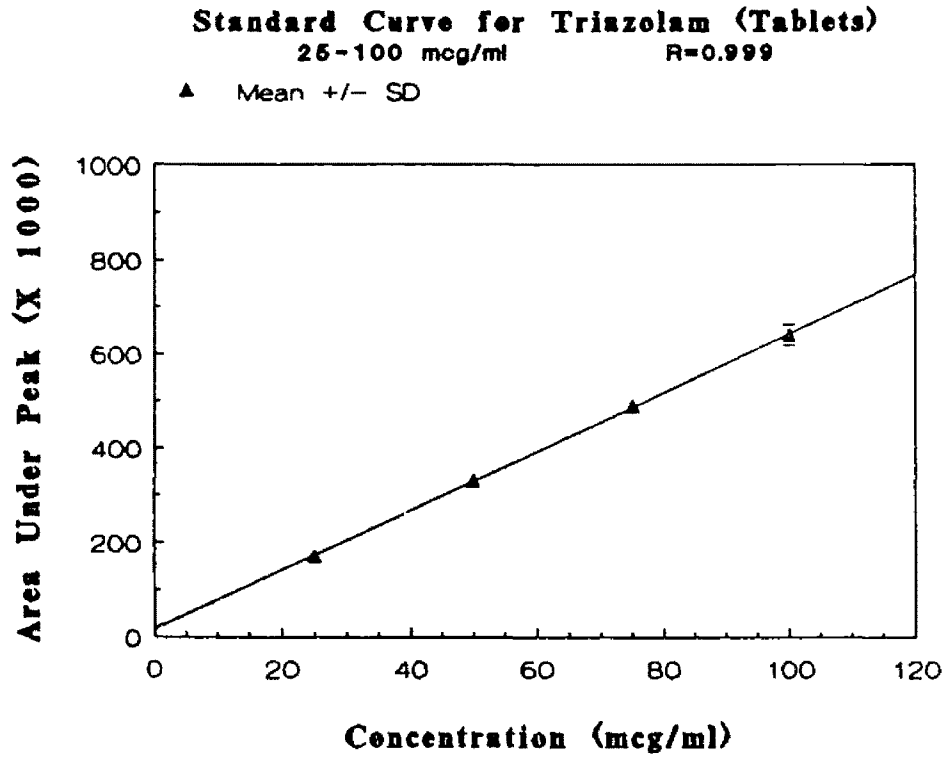


Figure 2. Standard curve for Triazolam tablets in water (25-100 mcg/ml).

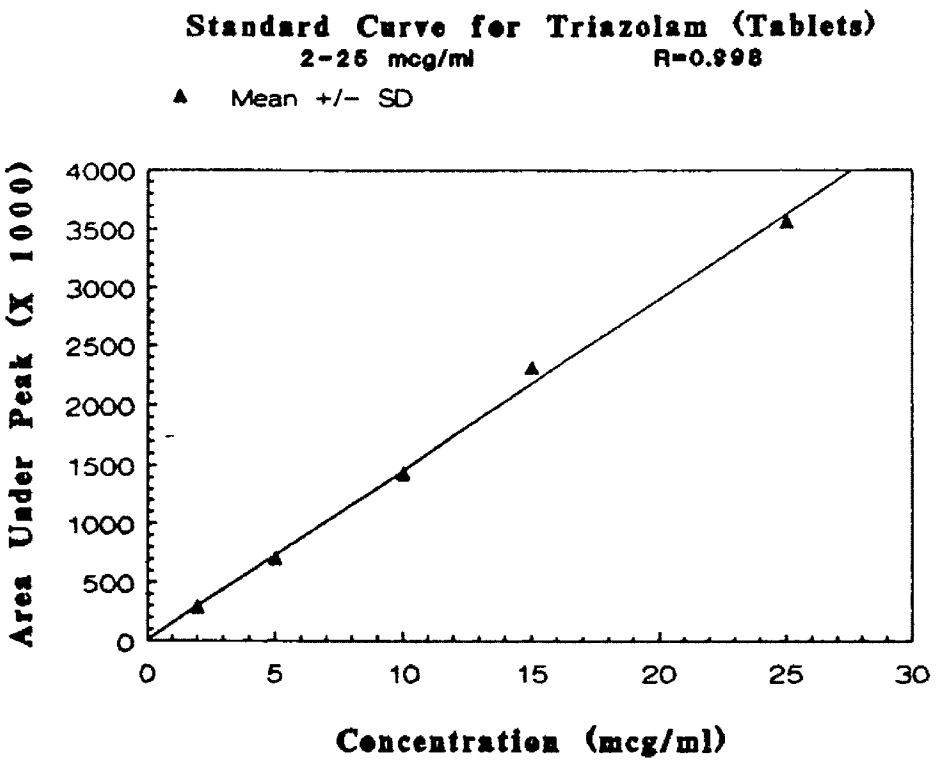


Figure 3. Standard curve for Triazolam tablets in water (2-25 mcg/ml)

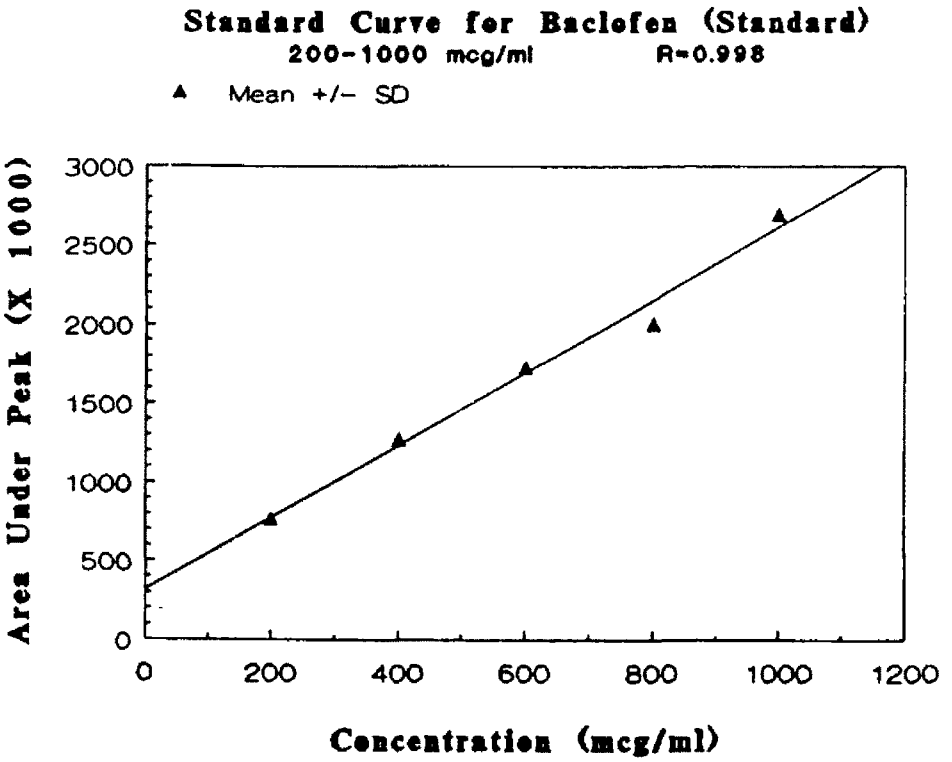


Figure 4. Standard curve for Baclofen standard in water (200-1000 mcg/ml).

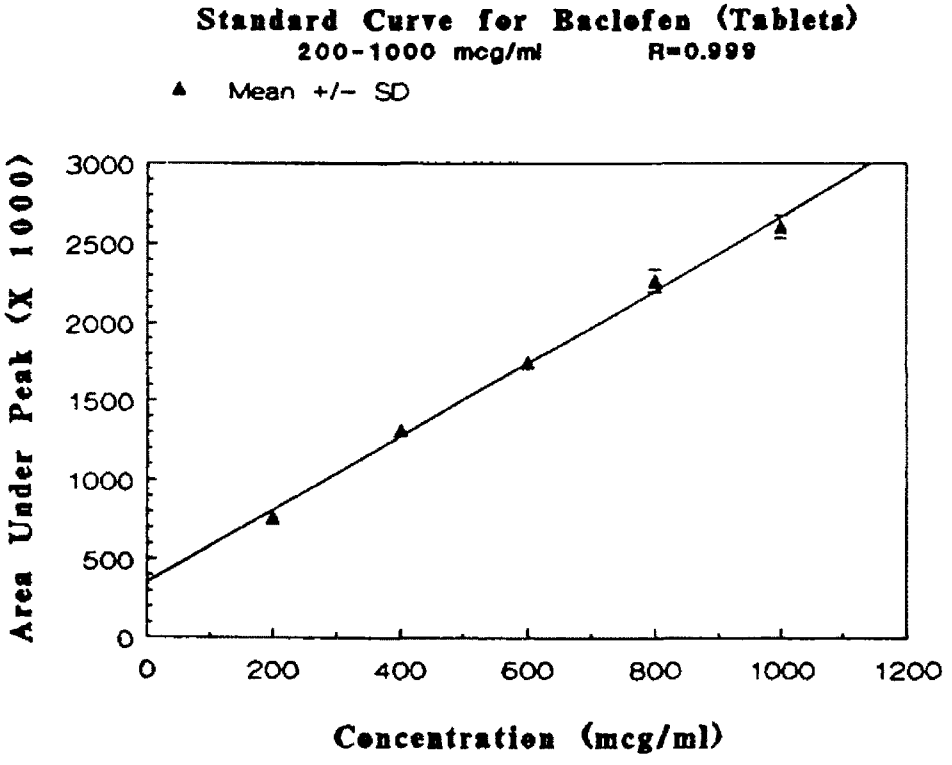


Figure 5. Standard curve for Baclofen tablets in water (200-1000 mcg/ml).

Dissolution study for triazolam

Since triazolam is very slightly soluble in water dissolution studies were conducted to study the extent of solubility in water. Two triazolam tablets were dissolved in 50 ml water at a stirrer speed of 50 rpm. Samples were drawn at regular intervals, filtered and analyzed for the dissolved drug (Figure 6).

Preparation of test solutions

Tablets were powdered in a porcelain mortar and the powder was dissolved in water to obtain the required concentration. The solution was stirred on a magnetic stirrer at a speed of 250 rpm for 30 min, and was filtered under suction through a No.2 Whatman filter paper to remove undissolved excipients. The filtered test solutions were stored in glass vials with plastic screw caps.

Triazolam

Solution A: Six Halcion^{R} 0.25 mg tablets were dissolved in 15 ml distilled water to obtain a concentration of 100 mcg/ml. This solution was used to make further dilutions of required concentration.

Solution B: Two Halcion^{R} 0.25 mg tablets were dissolved in 20 ml distilled water to obtain a drug concentration of 25 mcg/ml. This solution was used to make further dilutions.

Baclofen

Four Lioresal^{R} 10 mg tablets were dissolved in 40 ml distilled water. Further dilutions were made from this 1000 mcg/ml solution.

Delivery (Sorption) Studies

The tubes or cut tube segments were filled with the drug solution using a plastic syringe, clamped at both ends and allowed to stand at ambient temperature (20^{o}C) for 24 hours. After 24 hours the solutions were drained and analyzed for drug content. This result was compared to the control, which was obtained from the solution stored in

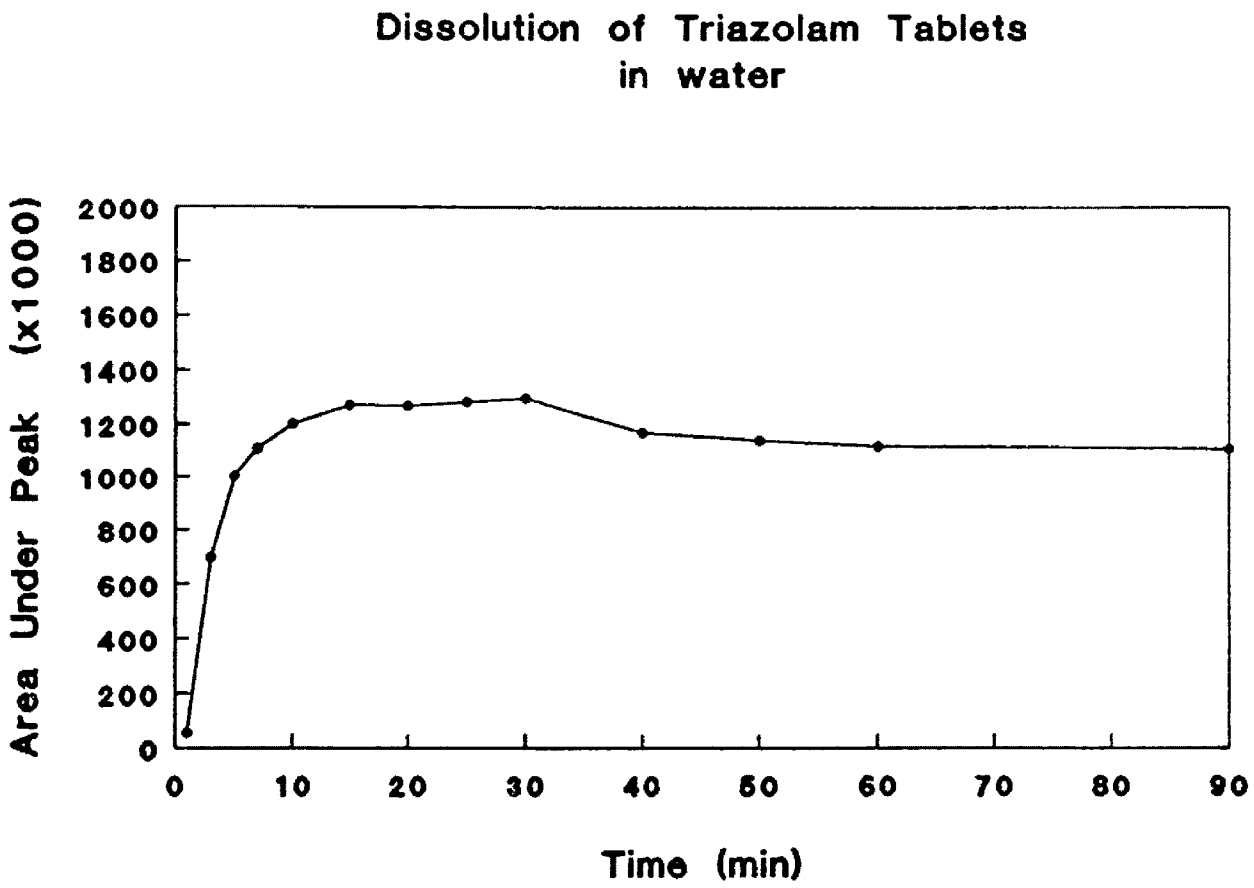


Figure 6. Dissolution study for Triazolam tablets in water.

glass vials for an equal time. To evaluate the possibility of drug loss to glass, the test solution was analyzed before and after storage in the glass vial. Similarly, loss of drug to the plastic syringe used to inject the sample into the tube also was evaluated by comparing the control stored in glass to that of the syringed control. The results from the stability analysis of the solution stored in glass vials were also applicable to potential drug loss to the glass used in mixing and to the glass syringe used to inject samples into the column.

The 24-hour sorption studies described above were performed in order to evaluate the drug loss to the G-tube under "worst-case" conditions. In the clinical environments the drug normally is in contact with the G-tube only for a matter of minutes, never for hours. Therefore, exposure of the drug solution to the G-tube for 24 hours would evaluate the maximum drug loss in any clinical setting. Loss of drug was observed only with triazolam but not with baclofen. Therefore, with triazolam further studies to evaluate the drug loss were performed as below.

I) Static (equilibrium) studies:
   A) 24-hour sorption studies
   B) if loss was observed in part A
      1) reversibility of loss (desorption)
      2) variability of tubes: inter and intra
      3) dependence of loss on:
         a) time of contact with internal surface
         b) concentration of the sample
         c) surface area of the tube exposed
         d) prewashing of tubes

II) Dynamic (flow) studies:

III) Clinical simulation studies:

IV) Other Studies:
   A) study of leaching
   B) study of nature of loss
   C) study of extent of loss

IA) 24-hour Sorption Studies (Baclofen and Triazolam):

The 24-hour studies were performed as described above.

IB) Further Studies (Triazolam):

1) Reversibility of loss (desorption):

Into the same tubes used in experiment IA water was stored for 24 hours at ambient temperature. After 24 hours the water was drained from the tube and was analyzed for recovered drug. Control for this experiment was water not stored in the tube and also water stored in a fresh tube for the same amount of time.

2) Variability in tubes:

Tubes were tested for variability of drug loss within the tubes and between the tubes. Variability was studied with the same sample concentration as well as for different concentrations.

a) Inter-tube variability with the same solution concentration:

Different tubes of the same kind were studied for variability between the tubes. The same drug solution was used to fill different tubes and the experiment was repeated as in IA. All the samples were analyzed under identical conditions and compared against the control solution stored in glass.

b) Inter-tube variability with different solution concentrations:

As in experiment 2a, solutions of different concentrations were placed into different tubes and the conditions of experiment IA were repeated. Control solution for each tube was that of the test solution stored in glass. The results were compared to that of the control, and the variability in sorption with respect to concentration in different tubes was evaluated.

c) Intra-tube variability:

Each tube was cut into four pieces. The first and third sections were filled with a 100 mcg/ml solution of triazolam and the second and fourth sections were filled with a 50 mcg/ml solution. All sections were clamped at both ends and the experiment was repeated as in IA. Samples were analyzed and compared against control (100 mcg/ml solution for section 1 and 3 and with 50 mcg/ml for section 2 and 4). The variability in drug loss within the same tube and with respect to different concentrations was evaluated.

The above experiment was repeated with 25 mcg/ml and 10 mcg/ml concentrations in a separate tube. These results were combined to evaluate the variability between the tubes, and within the tubes for the same as well as different concentrations.

3a) Dependence of loss on time:

Two tubes were cut into four pieces each, into each part the same test solution was placed, and the tubes were clamped at both ends. Samples were drained from the tubes at the following intervals.

Tube	Section	Time
A	1	0.5 hr
	2	1 hr
	3	2 hr
	4	4 hr
B	1	4 hr
	2	8 hr
	3	12 hr
	4	24 hr

Samples were analyzed and the results were compared to that of control stored in glass.

3b) Dependence of loss on concentration:

Four different concentrations of the test solution (100, 50, 25 and 10 mcg/ml) were placed into four different tubes and the experiment was performed as in IA. Samples were drained and analyzed for the drug. The results were

compared to that of the control solution for each tube (100, 50, 25 and 10 mcg/ml) and loss of drug with respect to the concentration was determined.

The above experiment was repeated using a fresh tube cut into four pieces. Into each section different concentrations were placed. The samples were analyzed and compared to the respective control.

3c) Dependence of loss on the surface area of the tube exposed:

The following experiment was conducted to study the relationship between drug sorption and the surface area (internal surface) of the tube to which the drug was exposed. In this experiment, tubes of the same internal surface area were exposed to three different volumes of the same drug solution. Into three tubes, was placed 1, 2 and 3 ml of the drug solution (100 or 25 mcg/ml) and the tubes were clamped at both ends. The tubes were attached to a rotating blender and revolved at a speed of 30 rpm for 2 hours, samples were drained and analyzed for drug content. Results were compared to that of control to evaluate the loss of drug with respect to surface area of the tube.

3d) Effect of prewashing of tubes on delivery of drug:

One tube was cut into four equal parts and each part was washed with water for different periods of time at the same washing rate.

Section	Washing time
a	2 min
b	10 min
c	water stored in tube for 24 hr
d	unwashed

After the washing procedure, the tubes were used to study the effect of washing on leaching of substances from the tube as well as sorption of drug. Test solutions of the

same concentration was stored in each section of the tube and experiment IA was repeated. Test results were compared to the control to identify the effect of washing.

II. Dynamic (flow) Studies (Triazolam):

In order to evaluate the delivery of drugs through G-tubes, it was necessary to study the loss of drug in a dynamic mode as drug solutions pass through the tube. Therefore, to understand the delivery more clearly this study was conducted with triazolam at two different flow rates, 1 ml/min and 25 ml/min.

Two 0.25 mg tablets of triazolam were crushed and dissolved in 50 ml water and this solution was placed in a 30 ml syringe. The G-tube was attached to the needle attachment hub of the syringe and the solution was run through the tube at 1 or 25 ml/min by means of a syringe pump (Sage instruments, model 355). Samples were collected every 5 min for 1 ml/min and every 0.2 minutes (12 sec) for 25 ml/min. Samples were filtered and analyzed for drug content. The results were compared against three controls. The first control was the solution before taking into the syringe, the second control was the solution from syringe but before the experiment and the third control was the solution collected towards the end of the experiment from the syringe. After all the solution was expelled from the syringe, the G-tube and syringe were washed with about 50 ml water. The water washings were collected and analyzed for the drug content.

III. Clinical Simulation Study (Baclofen and Triazolam):

In hospitals patients fed through gastrostomy tubes are given "oral" medications via the G-tube. Medications available as tablets are crushed and made into a slurry in about 10 ml of water in order to facilitate the delivery through tubes. After the drug is given the tube is washed with 50 ml water to wash the possible remains of the drug as

well as to avoid any clogging in the tube.

The following procedure was used to simulate the delivery of drugs via G-tubes. Two tablets were crushed and made into a slurry in 20 ml water. The slurry was shaken manually for several minutes, then 10 ml of the slurry was drawn into the syringe and injected through the feeding tubes in about 1/4 to 1/2 minute. This solution contains about one tablet quantity of drug. The syringe and tube were washed with 50 ml water. Drug solution from the tube was collected in one volume and the washings were collected in 10 ml portions each. The remaining 10 ml portion of the initial drug solution was used as control. The test results were compared against the control to see how much drug was delivered through the G-tube, and the water washings were analyzed to see if a measurable amount of recoverable drug remained in the tube. This simulation study was also repeated with filtered solutions.

IV. Other studies:

A) Study of leaching:

From the previous studies it was noted that the solutions exposed to the G-tubes contained several peaks in the HPLC chromatograms which were not present in the control solutions. One peak, which eluted prior to the drug, appeared to increase as the solution was stored longer in the tubes. This peak decreased as the tube was used repeatedly, i.e., it was more prominent in the fresh tubes than in the older ones. Several experiments were done in order to evaluate this leaching of material from the G-tubes.

Leaching into water:

Water was stored in two tubes for 24 hours, drained and analyzed for the presence of leached material under the same conditions as in the other experiments. The above experiment was repeated with drug solution in the same tube and fresh

tubes, and the appearance of leached material and total amount of drug lost was compared between the two tubes.

In the experiment on the effect of leaching on drug sorption, one tube was cut into two pieces and one part was filled with water and the other part with drug solution. The results were compared to determine if the leaching varies with the nature of the solution (e.g pH, polarity). This experiment was repeated with the same parts of the tube but with the drug solution into both sections. Results were compared to determine if the loss was the same or if a prior water wash has any effect on the leaching or drug sorption.

Effect of solvent pre-treatment on leaching and sorption:

Two tubes were cut into two pieces each. One part of each tube was filled with methanol and acetone separately for 12 hours. Solvents were drained and tubes were dried for about an hour in the room temperature. Experiment IA was repeated for each section of each tube with the drug solution. Results were compared to study the effect of pre-treatment of the tube with organic solvents on leaching, and subsequent sorption of drug.

B) Study of nature of loss:

One tube was cut into two pieces and drug solution was stored in each piece for two hours, then samples were drained and analyzed. One part of the tube was not washed with water before repetitions whereas the other part of the tube was washed with water between experiments. The above experiment was repeated 10 times and the results of each trial was compared with the control and also to the previous trials. This experiments provide information as to whether the loss was due to adsorption or absorption and also if the washing promotes or inhibits the loss. In each trial, the same sample solution was used in the washed and unwashed sections. The washed tube was dried in air before filling with the solution.

C) Extent of drug loss:

Pseudo-equilibrium study:

One fresh tube was washed with 10 liters of water and then cut into four equal parts. Into each part of the tube drug solution was placed, the tubes were clamped at both ends and samples were collected in the following order for analysis.

Tube section	Time of sample collection
a	12 hrs
b	24 hrs
c	48 hrs
d	72 hrs

Results of each sample was compared with the control and with each other to evaluate the equilibration of drug loss to the tubing.

DATA INTERPRETATION

Test samples and controls were analyzed under the same conditions using the same analytical procedure. All experiments were repeated at least 3 times and the results were compared for reproduceability. In all experiments, test results were compared to that of the appropriate controls. Data corresponding to all variables were evaluated for one-way analysis of variance.

Drug loss is reported as percent of loss in comparison to controls. Quantification of drug present in samples was made by integrated peak areas of the HPLC chromatogram. No internal standard was used. The difference between the amount of drug remaining in solution exposed to the tube and that in the control solution stored in glass for the same amount of time (as indicated by differences in the areas under peaks) was assumed to be the drug sorbed by the tube.

Results of the surface area experiments were reported as loss per square centimeter of the tube. The total surface area which the drug solution was exposed to was determined

from the interior dimensions of the tubes under study. In the reversibility of drug loss (desorption) studies, water was used as control and recovery was estimated as percent of recovery of the sorbed drug. Intra- and inter-tube variability was studied by comparing the percent drug loss within different parts of the same tube and different tubes of the same kind. Samples in the flow studies were collected in fractions and the loss was reported for the particular fraction. In the clinical simulation study, drug loss was estimated only for bolus administration.

Since controls of authentic samples did not show any additional peaks other than the sample peak, peaks that appeared with the test solutions stored in tubes were attributed to the leached substances from the tubes. Identical peaks were observed following storage of water in the tubes, substantiating that the peaks were due to the presence of leached substances and not due to drug break down. Since peaks of leached substances had different peak (elution) times and appeared not having any effect on the sample peak, they are not considered in the data analysis.

RESULTS

STATIC (EQUILIBRIUM) STUDIES IN FOLEY CATHETERS:

SORPTION STUDIES FOR TRIAZOLAM:

The results of sorption studies in which solutions of triazolam were stored in Foley catheters are shown in Table I. Concentrations in all studies are in mcg/ml.

Table I: Sorption studies for Triazolam in Foley catheters

Exper	Tube	Conc	% loss	% R	Loss Mcg/cm^2	Final conc
1	I	100	36	100	2.70	64
2	I	100	42	101	3.15	58
3*	I	0	0	0	0.00	0
4	I	100	62	100	4.65	38
5	I	100	39	104	2.92	61
	II	100	25	104	1.87	75
6	I	50	25	103	0.94	38
	II	100	35	100	2.62	65

* Experiment to evaluate desorption of triazolam from the tube.
%R Percent remaining control.

From the results in Table I it can be seen that between 25-62% of triazolam was lost to the tubing when solutions of the drug were stored in the tubes for 24 hours. No loss was observed for the control solutions stored in glass during the same period. Tube I showed a variability in loss depending on the pre-treatment of the tube and on the concentration of the solution studied. After the desorption study in experiment 3, this tube showed greater loss in experiment 4 than in the other trials. A smaller drug loss was observed in tube I when the concentration of the test solution was decreased from 100 mcg/ml to 50 mcg/ml in experiment 6. Even after four trials, tube I showed more drug uptake than tube II in its first or second trials as seen in experiments 5 and 6.

DEPENDENCE OF DRUG LOSS ON CONCENTRATION:

Drug uptake by G-tubes was studied in different Foley catheters and in the different sections of the same Foley catheter with different concentrations. The results of these studies are shown in Tables II, III and in Figure 7.

Table II: Sorption studies for Triazolam: Different drug concentrations in different Foley catheters.

Tube #	Conc	% loss	% R	Loss Mcg/cm^2	Final conc
I	100	41	102	3.07	59
II	50	30	100	1.12	35
III	25	21	97	0.39	20
IV	10	11	100	0.08	9

% R: Percent remaining control.

Table III: Sorption studies for Triazolam: Different drug concentrations in different sections of the same Foley catheter.

Sect	Conc	% loss tube I	% loss tube II	% R	Loss Mcg/cm^2 I	Loss Mcg/cm^2 II	Final conc I	Final conc II
a	100	62	63	100	4.43	4.50	38	37
b	50	55	65	100	1.96	2.32	23	18
c	25	59	34	100	1.05	0.60	10	17
d	10	22	39	101	0.16	0.28	8	6

% R: Percent remaining control.

The results in Table II show a concentration dependent loss in four different Foley catheters. The percent of drug lost to tubing decreased as the concentration decreased from 100 mcg/ml to 10 mcg/ml. The percent of drug loss was 41% with the 100 mcg/ml solution followed by 30%, 21% and 11% with 50, 25 and 10 mcg/ml solutions respectively.

Results from experiments on loss of triazolam at different concentrations in different sections of the same Foley catheters showed a variable drug loss. The results in Table III showed higher drug loss in sections a and b, in

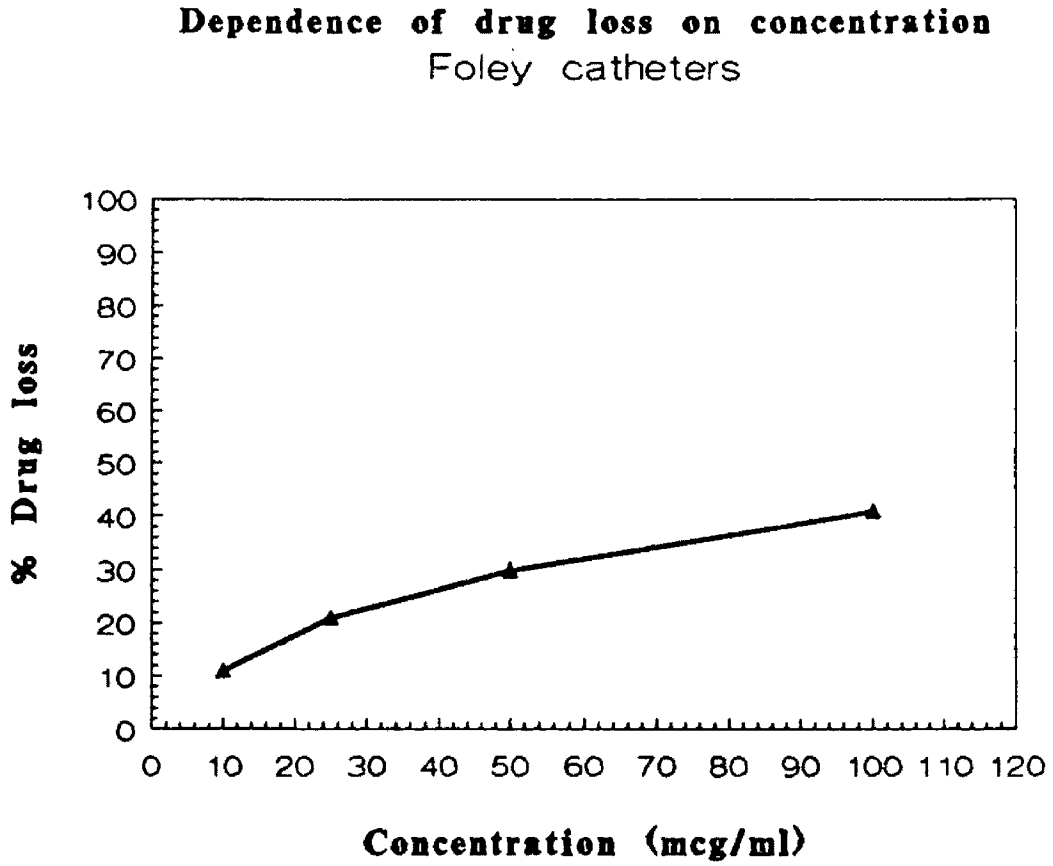


Figure 7. Dependence of Triazolam loss on concentration in Foley catheters.

which 100 and 50 mcg/ml solutions were placed. Sections c of tube I, b and d of tube II showed higher drug loss than the preceding higher concentrations. The overall trend in drug loss seemed to be concentration dependent in both tubes; i.e., a greater percent was lost at higher concentrations.

DEPENDENCE OF THE LOSS ON TIME:

Experiments on loss of drug with respect to time were conducted in two Foley catheters cut into four sections each. The dependence of drug loss on time is also shown in Figure 8 for 25 mcg/ml solution and Figure 9 for 100 mcg/ml drug solution. Table IV shows the results of loss of drug with respect to time with 25 mcg/ml solution and table V with 100 mcg/ml solution.

Table IV: Sorption studies for Triazolam: Dependence of loss on time with 25 mcg/ml solution.

Time(hr)	Tube	% loss	% R	Loss Mcg/cm^2	Final conc
0.5	Ia	23	100	0.41	19
1	Ib	23	100	0.41	19
2	Ic	24	101	0.43	19
4	Id	24	101	0.43	19
4	IIa	26	101	0.46	19
8	IIb	27	105	0.48	18
12	IIc	33	97	0.59	17
24	IId	52	97	0.93	12

Table V: Sorption studies for Triazolam: Dependence of loss on time with 100 mcg/ml solution.

Time(hr)	Tube	% loss	% R	Loss Mcg/cm^2	Final conc
0.5	IIIa	39	100	0.70	15
1	IIIb	35	100	0.62	16
2	IIIc	46	101	0.82	14
4	IIId	48	101	0.86	13
4	IVa	30	101	0.54	18
8	IVb	36	98	0.64	16
14	IVc	47	98	0.84	13
24	IVd	51	97	0.91	12

% R: Percent remaining control.

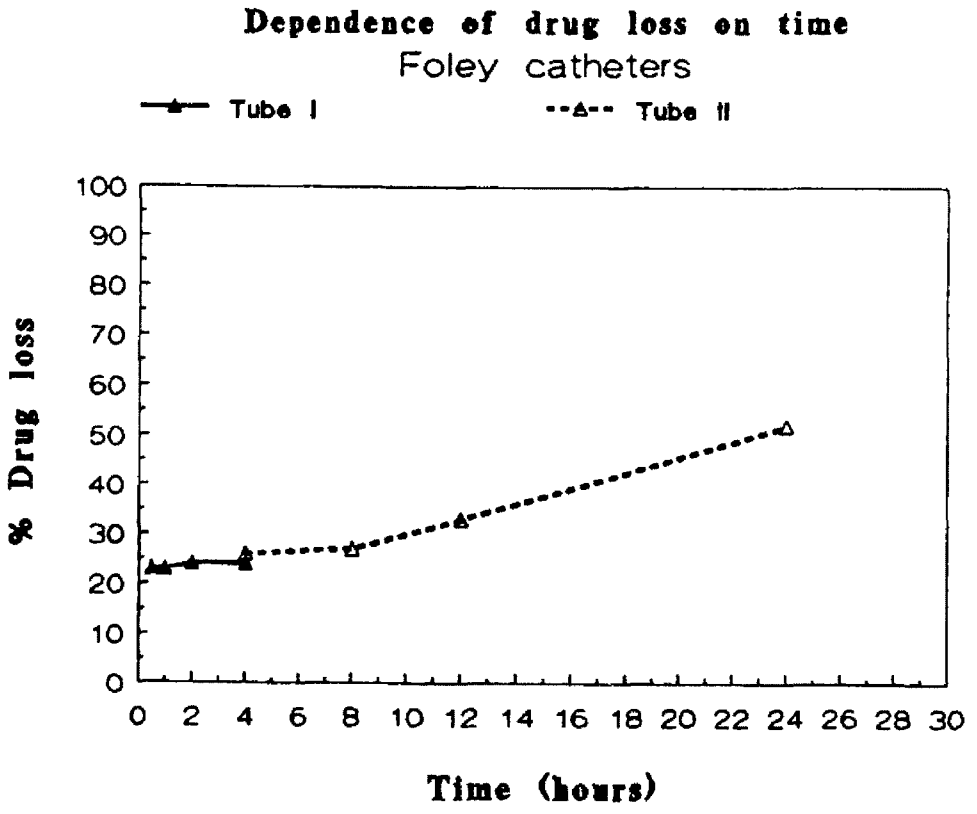


Figure 8. Dependence of Triazolam loss in Foley catheters with 25 mcg/ml solution.

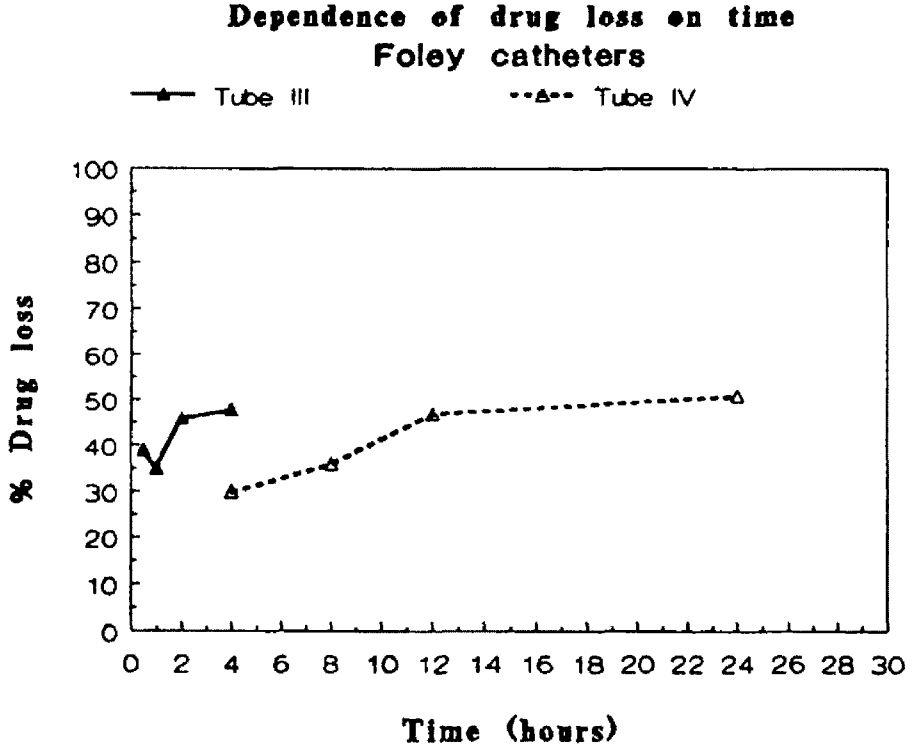


Figure 9. Dependence of Triazolam loss in Foley catheters with 100 mcg/ml solution.

From Tables IV and V and Figures 8 and 9, it can be seen that drug loss to tubing is time dependent with both 25 mcg/ml and 100 mcg/ml drug solutions. Significant drug loss was observed within one half hour. The rate of drug loss appeared to decrease after the initial rapid loss. This was evident from table IV, in which 23% of the initial drug was lost in the first half hour, but it increased to only 27% at eight hours, to 33% at 12 hours and to 52% at 24 hours. Similar drug loss was observed with 100 mcg/ml drug solution as shown in Table V except for the inter-tube variability between tubes III and IV. There was no significant inter-tube variability between tubes I and II as shown in Table IV.

STUDY OF EXTENT OF DRUG LOSS:

Drug loss observed for extended periods of time (12, 24, 48 and 72 hours) in different sections of the Foley catheters is shown in Table VI and in Figure 10. In these experiments two different Foley catheters were cut into four sections each.

Table VI: Sorption studies for Triazolam: Drug loss for extended periods in Foley catheters.@

Tube	Time (hr)	%loss tube I	%loss tube II	% R	Loss Mcg/cm^2 I	Loss Mcg/cm^2 II	Final conc I	Final conc II
a	12	26	27	100	0.46	0.48	19	18
b	24	27	26	101	0.48	0.46	18	19
c	48	56	51	100	1.00	0.91	11	12
d	72	62	52	99	1.10	0.93	10	12

% R: Percent remaining control.
@: Concentration 25 mcg/ml.

As observed in the previous experiments there was an initial rapid drug loss followed by a slower, time-dependent drug loss. About 26-27% of the initial drug was lost in 12 hours. No significant drug loss was observed during the next 12 hours. Another 25-26% of the drug was lost from 24 to 48 hours, but little loss was observed in the next 24 hours.

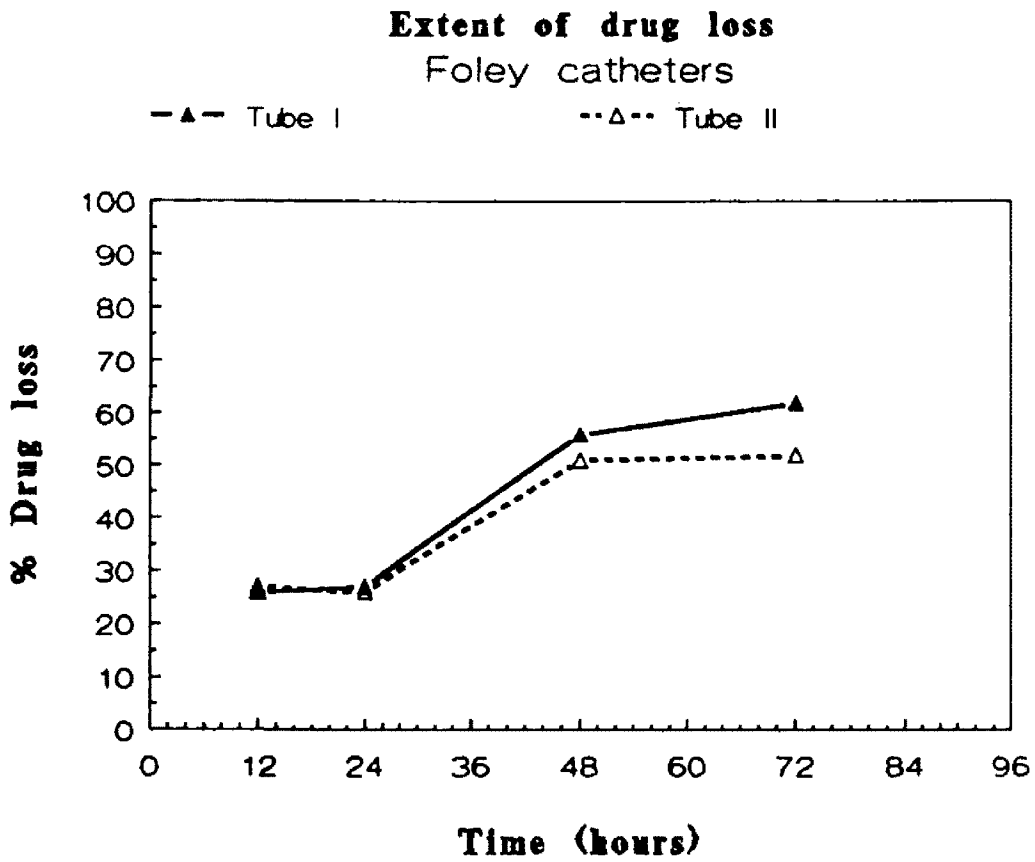


Figure 10. Extent of Triazolam loss in Foley catheters with 25 mcg/ml solution.

DEPENDENCE OF LOSS ON VOLUME OF DRUG SOLUTION AT CONSTANT SURFACE AREA OF THE TUBE:

Experiments to determine the dependence of drug loss on the exposed surface area of Foley catheters were conducted in three different Foley catheters. Each catheter was studied with a different volume (1, 2 or 3 ml of drug solution). Results of these experiments are shown in Table VII.

Table VII: Sorption studies for Triazolam: drug loss with respect to the volume of solution at constant surface area* of the tube.@

Tube #	Volume	% loss	Initial amount	Mcg loss	Mcg rem.	Loss Mcg/cm^2	Final conc
A	3 ml	10	75	7.5	67.5	0.19	22.5
B	2 ml	11	50	5.5	44.5	0.14	22.2
C	1 ml	12	25	3.0	22.0	0.08	22.0
D	3 ml	12	75	9.0	66.0	0.23	22.0
E	2 ml	12	50	6.0	44.0	0.15	22.0
F	1 ml	15	25	3.8	21.3	0.10	21.3

@: concentration 25 mcg/ml.
*: Surface area of the tube to which the drug solution was exposed was calculated from the internal dimensions of the tube.

These results show that while the percent of the drug loss was about the same for the 3 different quantities of drug solution used, the amount of the drug lost (in mcg) is dependent upon the total amount of drug exposed to the tube. Thus approximately 7.5 mcg of drug was lost in tube A, 5.5 mcg in tube B and 3 mcg in tube C. Similarly, 9, 6 and 3.8 mcg of drug was lost in tubes D, E and F respectively. The amount of drug loss per cm^2 of the tube exposed is related to the total amount of drug exposed, i.e., more drug is lost with higher volumes and greater amounts. Final concentration of the drug solution is same for all volumes.

TUBE VARIABILITY:

Inter-tube variability (Variability between Foley catheters):

Tube variability between different Foley catheters was studied both with different drug concentrations and with equal drug concentration. These results are shown in Tables VIII and IX.

Table VIII: Sorption studies for Triazolam: Variability between different Foley catheters with a constant concentration.

Tube #	Conc	%loss	% R	Loss Mcg/cm^2	Final conc
V	100	37	102	2.77	63
VI	100	25	104	1.87	75
VII	100	70	97	5.25	30
VIII	100	75	97	5.62	25
IX	100	41	102	3.07	59
X	100	46	102	3.45	54

% R: Percent remaining control.

Table IX: Sorption studies for Triazolam: variability between different Foley catheters with different drug concentrations.

Tube #	Conc	%loss	% R	Loss Mcg/cm^2	Final conc
I	100	41	102	3.08	59
II	50	30	100	1.12	35
III	25	21	97	0.39	20
IV	10	11	100	0.08	9

% R: Percent remaining control.

Table VIII showed a variable drug loss of 25-75 % with equal concentration (100 mcg/ml) in six different Foley catheters. As seen in Table IX, four different Foley catheters showed a concentration dependent drug loss of 41, 30, 21, and 11% with 100, 50, 25 and 10 mcg/ml drug solutions respectively.

Intra-tube variability (Variability within the Foley catheter):

Different sections (a-d) of the same Foley catheter were studied for variability of sorption within the tube. Results of intra-tube variability in two Foley catheters with four different drug concentrations 100, 50, 25 and 10 mcg/ml were shown in Table X.

Table X: Sorption studies for Triazolam: variability within the Foley catheter with different drug concentrations.

Section	Conc	% loss		% R	Loss Mcg/cm^2		Final conc	
		tube I	tube II		I	II	I	II
a	100	62	63	100	4.4	4.5	38	37
b	50	55	65	102	2.0	2.3	23	18
c	25	59	34	97	1.1	0.6	10	17
d	10	22	39	101	0.2	0.3	8	6

% R: Percent remaining control.

Both tubes I and II showed a concentration dependent drug loss. Variability in drug loss was observed among different sections of tube I and II. In tube I, section c showed a higher percentage of loss with 25 mcg/ml drug solution than with 50 mcg/ml solution in section b. Similarly, sections b and d in tube II showed slightly higher drug loss than the preceding higher concentrations.

Tube variability within the Foley catheters was studied in four Foley catheters cut into two sections each. Each tube was studied with 100, 50, 25 and 10 mcg/ml drug solution separately. The results of variability within the tube with equal concentrations are shown in Table XI.

Table XI: Sorption studies for Triazolam: Variability within the Foley catheter with the same drug concentration.

Exper	Tube	Conc	% loss	% R	Loss Mcg/cm^2	Final conc
1	Ia	100	77	103	5.5	23
	Ib	100	79	103	5.6	21
2	IIa	50	34	99	1.2	33
	IIb	50	39	99	1.4	31
3	IIIa	25	29	101	0.5	18
	IIIb	25	47	101	0.8	13
4	IVa	10	20	99	0.1	8
	IVb	10	24	99	0.2	8

% R: Percent remaining control.

From Table XI it was again observed that drug loss to tubing was concentration dependent. In three of the experiments there was no significant variability in drug loss within the tube with equal concentration. Only tube III with 25 mcg/ml drug solution showed variability in sorption within the tube. As observed in the earlier experiments, drug loss was higher (77-79%) with the highest concentration of 100 mcg/ml and dropped to the lowest (20-24%) with the lower concentration of 10 mcg/ml.

REVERSIBILITY OF DRUG LOSS (DESORPTION):

Sorption studies for triazolam in Foley catheters showed significant drug loss to tubing in 24 hours. Following the sorption studies, the tubes used in the sorption studies were tested for desorption of the sorbed drug. Results of the sorption and desorption studies are given in Table XII.

Table XII: Sorption studies for Triazolam: Reversibility of drug loss in Foley Catheters.@

Exper	Tube	% loss	% Recovery	% R Control
1	I	37	NE	102
2	I	42	NE	101
3*	I	NE	12	0
4	II	50	NE	100
5*	II	NE	0	0

*: Desorption study.
NE: Not Evaluated.
% R: Percent remaining.
@: Concentration 100 mcg/ml.

There was 37% and 42% of the drug lost to the tubing in experiments 1 and 2. However, in the desorption study from this tube in experiment 3 only 12% of the lost drug was recovered. In experiment 4 with tube II there was a 50% drug loss. No recovery was observed in the subsequent desorption study.

EFFECT OF PRE-WASHING OF TUBES ON DRUG LOSS:

Two Foley catheters were cut into four equal parts each and each part was subjected to different washing treatments before the experiment. Treatments and results are shown in Table XIII.

Table XIII: Sorption studies for Triazolam: Effect of prewashing on drug loss in Foley catheters.

Section	Treatment	% loss tube I	% loss tube II	% R	Loss Mcg/cm^2 I	Loss Mcg/cm^2 II	Final conc I	Final conc II
a	unwashed	71	75	97	5.1	5.4	29	25
b	water, 2 min	46	63	97	3.3	4.5	54	37
c	water,10 min	58	56	97	4.1	4.0	42	44
d	water,24 hrs	64	58	97	4.6	4.1	36	42

% R: Percent remaining control.
@: Concentration 100 mcg/ml.

The results of the effect of pre-washing of tubes showed more drug loss with untreated sections of the tubes (71% and 75%) than after washing. Tubes I and II showed variability in drug loss in section b with 2 minute treatment. Drug loss in the unwashed sections was followed by 10 minute and 24 hour treatment.

STUDY OF THE NATURE OF DRUG LOSS:

The percent of drug loss in two sections of the same Foley catheter is shown in Table XIV. Experiments refer to repetitions with section I-UW, which was not washed with water between trials, and section I-W which was washed with water and dried in air between the experiments.

Table XIV: Sorption studies for Triazolam: Loss of drug in washed and unwashed tubes.@

Expt #	% loss I-UW	% loss I-W	% R Control
1	13.0	12.0	101
2	7.4	4.5	101
3	2.8	8.3	100
4	5.0	4.1	100
5	2.0	5.7	100
6	8.8	9.2	101
7	2.8	10.3	101
8	3.9	8.0	101
9	7.6	8.7	101
10	11.8	9.7	101

I-UW: Unwashed tube. I-W: Washed tube.
% R: Percent remaining control.
@: Concentration 25 mcg/ml.

A loss of 2-13% was observed in unwashed and washed sections of the Foley catheter in ten trials. The results between unwashed and washed sections of the tube and between the trials showed a large variability. There was an average loss of 6.5% and 8.0% in unwashed and washed tubes respectively, in 10 trials. Drug loss was significant even after 10 repetitions.

DYNAMIC (FLOW) STUDIES FOR TRIAZOLAM:

Loss of triazolam from solutions delivered at a flow rate of 25 ml/min and 1 ml/min was studied in Foley catheters. Results are shown in Tables XV and XVI.

Table XV: Delivery of Triazolam in Foley catheter at a flow rate of 25 ml/min.@

Fraction	% loss		Loss Mcg/cm^2		Final conc	
	tube I	tube II	I	II	I	II
1	0.6	3.3	0.01	0.04	9.9	9.7
2	2.8	4.0	0.04	0.05	9.7	9.6
3	3.2	2.8	0.04	0.04	9.7	9.7
4	3.8	2.9	0.05	0.04	9.6	9.7
5	2.2	1.1	0.03	0.01	9.8	9.9

@: Concentration 10 mcg/ml.

Table XVI: Delivery of Triazolam in Foley catheter at a flow rate of 1 ml/min.@

Fraction	% loss		Loss Mcg/cm^2		Final conc	
	tube I	tube II	I	II	I	II
1	5.8	9.7	0.04	0.07	9.4	9.0
2	0.0	2.5	0.00	0.02	10	9.8
3	2.7	+0.25	0.02	0.00	9.7	10
4	4.0	+2.1	0.03	0.00	9.6	10
5	1.8	0.9	0.01	0.01	9.9	9.9

+: Increase in apparent concentration.
@: Concentration 10 mcg/ml.

It was evident from these data that little drug loss occurred when solutions of the drug were passed through the tubes under these conditions. A loss of about 1-4% was observed in Foley catheters at a flow rate of 25 ml/min in both tubes. At the flow rate of 1 ml/min, 5-10% of the drug was sorbed to both tubes in the first fraction. No significant drug loss was observed in the later fractions in both experiments. The data from fraction 5 suggests that the drug loss may decrease as more of the solution passes through the tube. This was evident at both 25 ml/min and 1 ml/min flow rates.

ROSS FLEXIFLO G-TUBE:

SORPTION STUDIES FOR TRIAZOLAM IN ROSS FLEXIFLO G-TUBE:

Solutions of triazolam were stored in Ross Flexiflo G-tubes for 24 hours in experiments 1-9 (In experiment 2 a desorption study was conducted) and for 64 hours in experiment 10. The same untreated Ross Flexiflo tube was used in experiments 1 through 10. Results are shown in Table XVII.

Table XVII: Sorption studies for Triazolam in Ross Flexiflo G-Tube.

Exper	Conc	% loss	% R	Loss Mcg/cm^2	Final conc
1	25	72	100	2.0	7.0
2@	water	0	0	0	0
3	25	65	100	1.8	8.8
4	12.5	43	102	0.6	7.1
5	12.5	35	101	0.5	8.1
6	25	51	101	1.4	12.3
7	12.5	30	98	0.4	8.8
8	12.5	30	98	0.4	8.8
9	25	47	101	1.3	13.3
10*	25	62	101	1.7	9.5

@: Desorption study.
*: Drug solution was stored in tube for 64 hours.
% R: Percent remaining control.

Results from Table XVII showed a variable drug loss to the tubing. A drug loss of between 30-72% was observed . The percent of drug uptake appeared to decrease as the concentration of the test solution was decreased and also as the number of trials increased. The desorption study in experiment 2 might have caused the increase in drug loss observed in experiment 3. Drug loss appeared to be time dependent, as a greater loss was observed in the 64 hour study in experiment 10 than with 24 hour study in the previous experiment.

REVERSIBILITY OF DRUG LOSS (DESORPTION):

Experiment 1 from Table XVII showed 72% of the drug loss to Ross Flexiflo G-tube. This same tube was used to study desorption of the sorbed drug. Results of this experiment are shown in Table XVIII.

Table XVIII: Reversibility of the sorbed Triazolam in Ross Flexiflo G-Tube.

Exper	Tube #	% loss	% recovery
1	I	72	NE
2*	I	NE	11

*: Desorption study.
NE: Not Evaluated.

Results from Table XVIII showed a 11% drug recovery from the Ross Flexiflo G-tube, in which 72% of the drug was sorbed from 25 mcg/ml solution in the previous experiment.

DYNAMIC (FLOW) STUDIES:

The effect of flow rate on the delivery of triazolam was studied in a Ross Flexiflo G-tube with 10 mcg/ml solution at a flow rate of 1 ml/min. Results are shown in Table XIX.

Table XIX: Delivery of Triazolam in Ross Flexiflo G-Tube at a flow rate of 1 ml/min.

Fraction	% loss	Loss Mcg/cm^2	Final conc
1	7.0	0.10	9.3
2	4.4	0.06	9.6
3	9.9	0.14	9.0
4	12.9	0.18	8.7
5	9.3	0.13	9.1

From Table XIX it was seen that there was a drug loss of 4-13% in the Ross flexiflo tube at a flow rate of 1

ml/min. Drug loss was significant even in the fifth fraction. Loss appeared to be greater in the final three fractions than in the initial two. The data from Tables XVI and XIX show that the loss of triazolam is greater in Ross Flexiflo tubes than in Foley catheters at a flow rate of 1 ml/min. Drug loss in Ross Flexiflo tube appeared to continue longer than in the Foley catheters.

CLINICAL SIMULATION STUDY:

The results of clinical simulation studies for triazolam in Foley catheters and in Ross Flexiflo tubes are shown in Table XX. In these studies, a slurry/solution prepared from triazolam tablets was passed through the tubing.

Table XX: Loss of Triazolam in clinical simulation studies in Foley catheters and in Ross tubes.

Exp #	Tube type	Tube #	% loss	Loss Mcg/cm^2	Final conc
1	Foley	I	+0.5	0.0	25
2	Ross	II	7.82	0.5	23
3	Ross	II	+1.0	0.0	25

+: Increase in apparent concentration.

The first trial in Ross tube (exp #2) showed a drug loss of 8% to the tube. No drug loss was observed in the second trial (exp #3) with the same tube. There was no significant drug loss when the studies were conducted following the procedure which is used to administer drugs via G-tubes in the clinic with both Foley catheters and Ross Flexiflo G-tubes.

EQUILIBRIUM STUDY:

Tables I, IV, V, VI and XIV contain data pertinent to the equilibrium study for triazolam in Foley catheters. The results of equilibrium studies for triazolam in Ross G-tubes are shown in to Table XVII. In Foley catheters, extensive

drug loss was observed in 24 hours even after the fifth exposure of the tube to the drug solution (Table I). The drug loss appeared to be time dependent as observed in Tables IV, V and VI. The rate of sorption appeared to decrease after the initial rapid loss, but then continued for extended periods. Drug loss appeared to be significant even after 10 trials with the same Foley catheter (Table XIV).

Ross Flexiflo G-tubes showed very extensive drug uptake in 24 hours. Table XVII shows concentration and time dependent drug loss in Ross G-tubes. The percent of drug loss appears to decrease as the trials were repeated in the same tube. Drug loss was significant even after nine trials.

BACLOFEN

STATIC (EQUILIBRIUM) STUDIES FOR BACLOFEN:

The results of sorption studies for baclofen in Foley catheters and in Ross Flexiflo G-tubes are shown in Table XXI.

Table XXI: Sorption studies for Baclofen in Foley catheters and Ross Flexiflo G-Tubes.

EXP #	TUBE TYPE	TUBE #	SAMPLE	CONC	% LOSS
1	Foley	I	tablet	1000	0.3
2	Foley	IIa	tablet	1000	0
3	Foley	IIb	standard	1000	2.5
4	Ross	I	tablet	1000	+3.5

+: Increase in apparent concentration.

Very little or no loss of drug to Foley catheters or Ross Flexiflo G-tubes was observed in 24 hours. These results indicate that there was minimal or no loss (< 5%) in both Foley catheter and Ross Flexiflo G-tubes. Therefore, further studies were not necessary.

CLINICAL SIMULATION STUDY FOR BACLOFEN:

Baclofen slurry/solution samples were injected into the tubes in a simulation of clinical conditions. The results are shown in Table XXII for Foley catheter and for Ross G-tubes.

Table XXII: Drug loss in clinical simulation studies in Foley catheters and in Ross Flexiflo G-Tubes.

EXP #	TUBE TYPE	TUBE #	SAMPLE	CONC	% GAIN
1	Foley	III	tablet	1000	0.68
2	Foley	IV	standard	1000	0.93
3	Ross	II	tablet	1000	1.85

As shown in Table XXII, no drug loss was observed to Foley catheters or to Ross G-tubes. The observed gain (increase) in baclofen was an artifact within experimental error.

STUDY OF LEACHING

When the drug solutions were stored in Foley catheters, some additional peaks in the HPLC chromatograms of the drugs were observed other than that of the drug. Peaks that appeared between 3.5 and 4.5 minutes with the drug solutions prepared from tablets stored in Foley catheters were partly due to excipients in triazolam tablets. These additional peaks which were not present in the drug control solutions stored in glass would suggest leaching of tube materials into the drug solution. Peak areas corresponding to the leached substances increased with the increase in time of contact and slowly disappeared after few treatments. This is illustrated in the chromatograms in figures 11 and 12 for triazolam and baclofen solutions respectively.

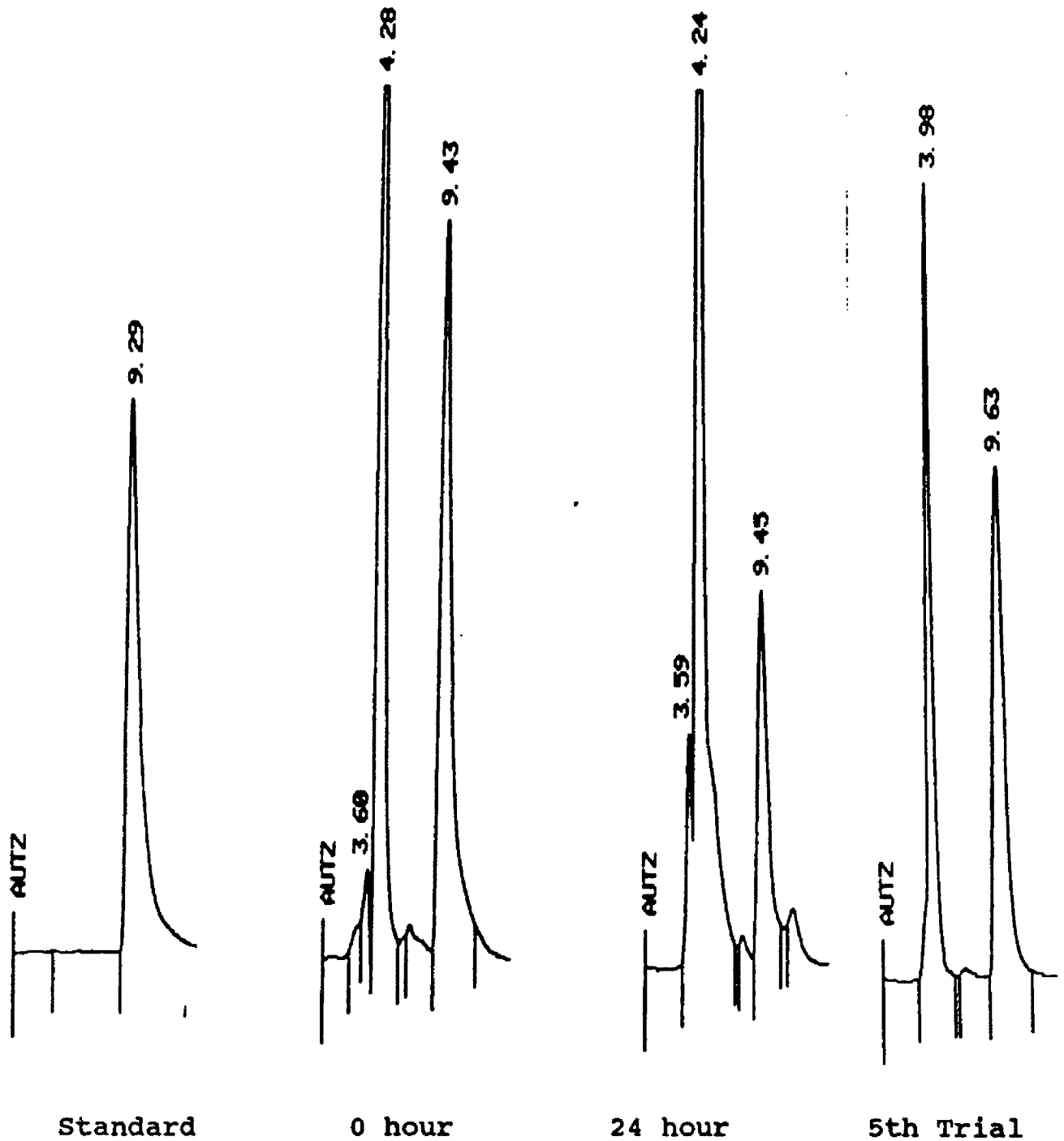


Figure 11. HPLC chromatograms showing leaching of tube materials from Foley catheters into Triazolam solutions.

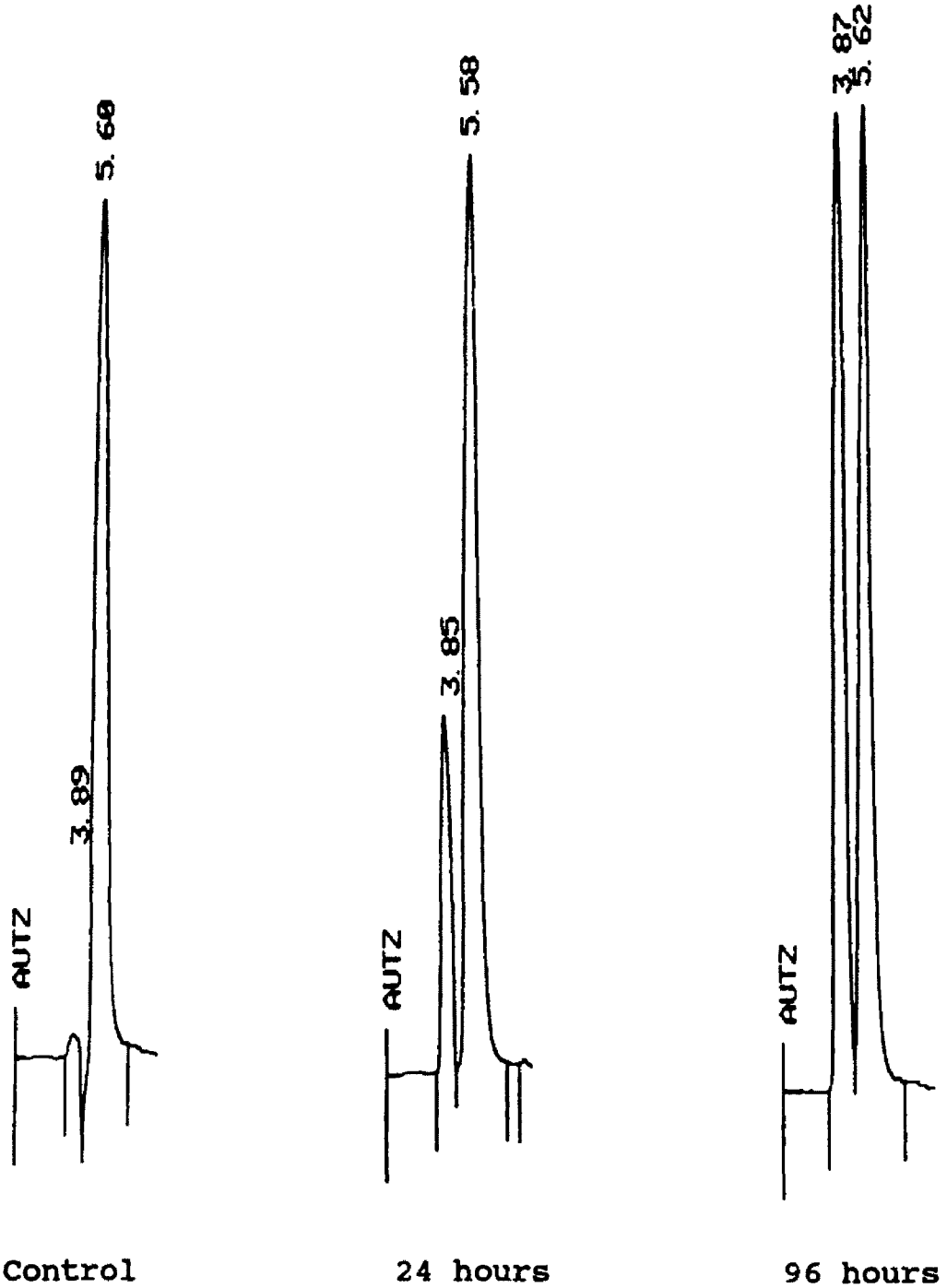


Figure 12. HPLC chromatograms showing leaching of tube materials from Foley catheters into Baclofen solutions.

DISCUSSION

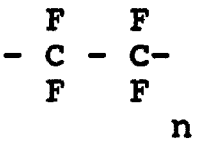
Physicochemical properties play a major role in drug absorption from the gastrointestinal tract and also in the delivery of drugs by G-tubes. A drug which has low water solubility and a lipid-water partition coefficient that favors lipid to water has the potential to adsorb onto and diffuse into the non-polar materials of delivery tubings. Weak organic acids and bases for which the non-ionized form has low water solubility will have an increased potential for sorption when the solution pH favors the non-ionized form. Poor hydrogen bonding capacity also suggests the poor water solubility of a compound.

Triazolam is a weakly basic drug with low polarity, low water solubility and moderate lipid solubility. Triazolam is poorly soluble in water and soluble in alcohol. Baclofen is a zwitterionic drug which is slightly soluble in water, freely soluble in alcohol and poorly soluble in organic solvents, and thus has low lipid solubility. Triazolam is mostly non-ionized in aqueous solution whereas baclofen is mostly in the ionized form. Since non-ionized drugs have increased affinity toward lipids and ionized drugs favor water, triazolam is more likely to be sorbed to the delivery tubings than baclofen.

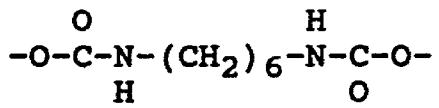
At a pH of 7.0, triazolam (pKa 1.52) has a non-ionized to ionized ratio of about 300,000:1 (> 99.99% non-ionized). The poor water solubility and high ratio of non-ionized to ionized molecules in aqueous solution suggests that triazolam would have a higher affinity for its own molecules and for lipids than for water molecules. This explains its poor water solubility and affinity towards the polymeric materials. Baclofen, which is highly ionized in water has a higher water solubility and lower affinity for lipids than triazolam.

Two types of gastrostomy tubes were used in these studies. They were teflon coated Foley catheters and Ross flexiflo replacement G-tubes made of polyurethane. The Foley

catheters are constructed with an outer layer of silicone rubber and inside this catheter teflon is glued as an inner protective layer. Teflon is polytetrafluoroethylene and belongs to the halocarbon class of polymer. Polyurethane is a member of the natural and synthetic rubber-type polymers class.



Tetrafluoroethylene



polyurethane

Chemically both types of polymers are non-polar, inert, non-wetable and lipoidal in nature. These polymers are very flexible and contain additives. The chemical nature, high flexibility and lipoidal nature of the tubes creates a high potential for sorption of non-ionized, poorly water soluble or lipophilic drugs with similar chemical nature. Between these two types of polymers polyurethane has more water permeability than teflon.

Baclofen showed very little or no sorption in both types of tubes. Triazolam on the other hand was lost in significant amounts to both tubes. Loss of triazolam to tubes was dependent upon the concentration of the drug solution, the time of exposure, the surface area to solution volume ratio, the amount of drug exposed and the flow rate. Drug loss was irreversible in that it could not be recovered from the tubes. Equilibrium was not reached in these studies even after extended exposure times. The loss of triazolam to the tubes is consistent with an initial adsorption of the drug onto the tube surface followed by absorption or diffusion of the drug into the tube matrix.

The results of static (equilibrium) studies in Tables I and XVII showed a variable loss (25-60%) of triazolam to Foley catheters and (30-70%) to Ross flexiflo tubes. This

loss indicates that triazolam has a high affinity toward the hydrophobic polymer substances and that the drug is attracted towards the solid tube material from the less favored aqueous solutions. This was substantiated by a calculation of the standard affinity of triazolam for Foley catheters according to the method shown below (136).

Calculation of the standard affinity ($\blacktriangle\mu$) of triazolam for the Foley tube from aqueous solutions:

- $\blacktriangle\mu$ = RT ln C2/C1
  where, C2 = concentration in the tube,
  C1 = concentration in the solution.
  The ratio of C2 to C1 is the slope of the plot of C1 verses C2 (Figure 13).

C2/C1 = 0.6372, R = 8.314, T = 298.15.

- $\blacktriangle\mu$ = 8.314 * 298 * ln 0.6372 = - 1117

$\blacktriangle\mu$ = 1117

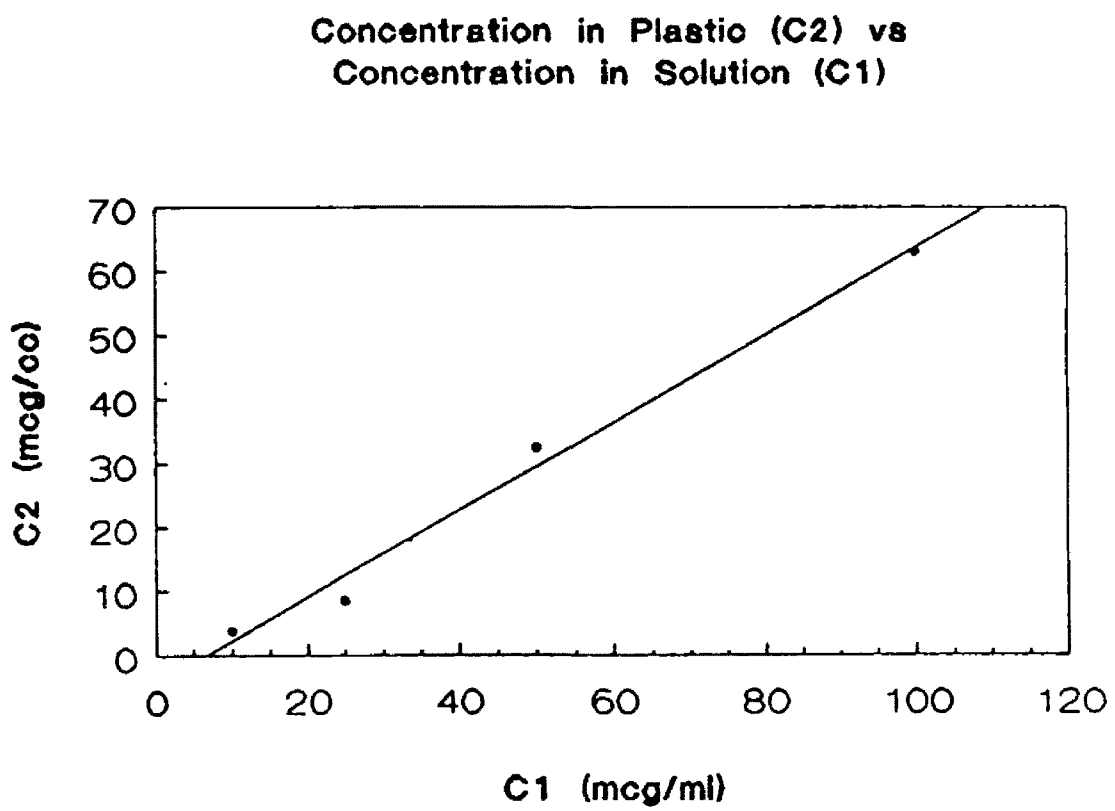


Figure 13. Plot of concentration of triazolam in the plastic versus concentration in solution.

Standard affinity is the quantitative measure of the tendency of a drug to move from its standard state in liquid to the plastic. Standard affinity can also be described as the chemical potential of the solute. Calculated standard affinity of 1117 indicate that chemical potential of the solute is greater in aqueous phase than in the plastic. Therefore there was a driving force moving the solute from the higher (aqueous) to the lower (plastic) phase. A measure of the relative affinity of a solute for the plastic can be approximated as the plastic-water partition coefficient. Since triazolam is poorly water soluble, liberation of drug molecules from water molecules was easier and would have required very little activation energy in the transfer (sorption) of drug molecules from aqueous solutions to tubings. Loss of triazolam to the tubing material could be either by adsorption onto the tubing surface or by absorption or partitioning of the non-polar drug into the tubing. The persistent drug loss observed in repeated trials (Table XIV) in the same tube with no tube washing between trials indicates that the drug loss is not consistent with a monolayer adsorption process. Therefore it could be a multi-layer formation or, most likely, diffusion into the tube materials. Since in most instances adsorption is rapid and instantaneous where as absorption is slow and continuous, slow equilibration indicates that the drug is absorbed, or partitioned, into the tubing.

The amount of drug adsorbed is likely to be smaller and more independent of concentration than the amount absorbed. The concentration dependent drug loss shown in Tables I, II and III for Foley catheters and Table XVII for the Ross tube supports the hypothesis of absorption into the tube material. Functional groups of plastic which attract or sorb the drug molecules act as binding sites in the drug plastic interaction. Dilute solutions do not show any significant hinderance to the drug molecules in approaching the binding sites on the surface of the polymer, but as the

concentration is increased there is hindrance to the approach of the molecules for the remaining sites. The relatively large amount of drug loss with respect to concentration in Foley catheters shown in Tables II and III indicates that there is no hindrance in approach to the binding sites at the concentrations used in this study. If there was hindrance then concentration dependent drug loss would not be possible, because at higher concentrations drug molecules compete for the same binding sites resulting decrease in sorption at higher concentrations. The relationship between concentration of the drug solution and the percent of drug loss indicates that uptake is probably a function of the total amount of drug available for sorption. It has been shown that at a critical concentration level, a solute can literally break through the polymer matrix of the tube creating a great many binding sites available for the solute molecules to sorb (137). The critical concentration level was not evaluated in these studies.

Drug loss in time studies (Tables IV, V and VI for Foley catheters and Table XVII for Ross tube) were done over time periods up to 72 hours. Equilibrium conditions were not reached even after this period, but the rate of loss appeared to decrease with increasing time. Time dependent drug loss was observed in both Foley catheters and Ross tubes. The time course of drug sorption was most compatible with absorption rather than adsorption. Since diffusion is the rate determining step in most absorption processes, extensive time dependent drug loss supports the phenomena of diffusion controlled absorption. When drug absorption is a diffusion process it takes a longer time and involves larger amounts of material when compared to adsorption. Therefore, the observed time course of drug sorption is consistent with absorption rather than adsorption. Initial rapid drug loss might be attributed to interaction of the drug with the surface of the tubing and partly due to absorption of water by the polymer at the earlier exposure. Since diffusion is

the rate determining step in sorption, the initial rapid loss followed by slower drug uptake is attributed to drug adsorption followed by diffusion of the drug into the plastic matrix.

It is possible to envision a model where, when the aqueous solutions of triazolam are stored in the tubes, triazolam molecules diffuse from solution towards the surface of the tube and become sorbed. As the surface area is filled there is sufficient energy to permit these solute molecules to penetrate the surface and diffuse into the amorphous zones of the plastic where new binding sites become available. When all sites are filled, equilibrium is reached, and no further sorption would occur.

The physicochemical properties of a polymer can be altered as a result of contact between drug and tube material. Changes in physicochemical properties of the tube can possibly change the sorptive nature and capacity of the tube material. In some cases when the solution is stored for extended periods of time, the solvent can swell and plasticize the tube material permitting entry of more drug molecules by opening up more passage ways. Since both teflon and polyurethane used in this study are poorly wetable hydrophobic material with low water permeability, they permit water only through porous amorphous zones which thereby acts as a plasticizer. It is possible that plasticizer from the tube might leach into the solution upon prolonged exposure with the drug solution. This opens more amorphous zones for drug molecules to diffuse into the tube matrix, hence extensive drug loss by diffusion into the tube matrix.

Drug uptake by the tube material was dependent on the total amount of drug exposed to the tube surface (Table VII). The amount of drug lost per square centimeter surface of the tube was dependent on the amount of drug exposed, that is, the volume of solution exposed. The total amount of drug lost from solution was greater for larger volumes of

test solutions stored. For an adsorption process, an increase in surface area should result in an increase in the total amount of drug sorbed, and a constant amount of drug should be adsorbed to a constant surface area. In this study, the extent of drug loss increased as the amount of drug exposed increased, that is, more loss occurred with larger volumes present in the tube. While the percent of drug sorbed was about the same for each volume exposed, the amount of drug sorbed per square centimeter area increased with higher volumes. Therefore, the total amount of drug sorbed was independent of the surface area, but was dependent upon the total amount of drug exposed to the surface. This is consistent with drug diffusion or penetration into the solid matrix rather than drug adsorption onto the tube surface. The amount of drug adsorbed can be expected to be smaller than the amount absorbed because adsorption is a surface phenomena whereas absorption can involve interaction of the solute with the entire polymer matrix. Also adsorption should reach equilibrium quickly since, the binding sites on the tube surface can rapidly become saturated. A slow sorption equilibrium was observed in this study.

Drug loss in the tube variability studies (Tables XIII, IX, X and XI) showed larger variation in drug sorption among different Foley catheters with the same as well as different concentration drug solutions. Variability in drug sorption within the same Foley catheter is minimal. The chemical structure within the polymer family can differ with the changes in manufacturing conditions at different time periods, which leads to differences in properties. Inter tube variability might be caused by variation in the composition of the polymer, molecular weight distribution, crystallinity, cross-linking and additives among different batches. Crystalline regions are generally very resistant to penetrating molecules and molecules pass only through the amorphous regions. Because high molecular weight regions are

highly crystalline, they have low permeability to drug molecules. Cross-linking may also decrease the swelling tendency of a plastic when in contact with a solvent having high affinity for the material, thus low permeability. Cross-linking stiffens the chains, therefore tightly cross-linked or stiff chained polymers retard diffusion.

Additives used in the tube manufacture might also alter the physicochemical properties of the polymers, producing variability in drug sorption. Leaching of additives into the solvent creates more lesions on the tube surface, which enhances drug sorption. Leaching was observed only from Foley catheters but not from Ross tubes. Leached substances from Foley catheters could be plasticizer, adhesives or other substances used to bind the teflon layer to the rubber. Leached substances could be toxic or incompatible with the drug. Tube variability in drug sorption was once again evident in the effect of pre-washing of tubes on drug loss studies (Table XIII).

Irreversible drug loss to delivery tubings was observed in the data in Table XII for desorption studies, Table XIV for the study of nature of drug loss in Foley catheters and Table XVII (experiment 2) in the Ross tube. As stated previously, it is possible that triazolam initially was adsorbed to the tube surface and slowly diffused into the tube matrix. Since there was no significant desorption of the sorbed drug, it indicates that the drug molecules were tightly bound to the tubing. Irreversible drug loss to the tubing might suggest that chemical binding was involved in the sorption process. However, since triazolam is predominantly non-ionized in aqueous solution, the most likely interactions would be either Van der Waals forces or weak dipole interactions. Poor water solubility and little or no hydrogen bonding capacity prevents desorption of the drug from the tube into the water. Irreversibility can also be explained by a higher affinity of the drug for plastic than water, therefore no recovery in water.

The results observed for baclofen further strengthens the above interpretation. Baclofen has both basic and acidic groups in its structure and is mostly in the ionized form. Therefore it is polar and water soluble. In contrast to triazolam, these physicochemical properties did not favor the sorption of baclofen to the delivery tubes. In solution baclofen should have strong hydrogen bonding with the water molecules, that is why it is not partitioning into the tube material from aqueous solutions. In the baclofen studies, leaching of tube material did not show any effect on the delivery. A negative absorption was observed, that is, the baclofen concentration appeared to increase upon exposure of the solution to Foley catheters. Solvent absorption by the tubes would explain the observed increase in concentration of the drug.

Amount of drug required for monolayer coverage per square centimeter of the tube surface was calculated using the density value of 1.1 g/cm^3 which is typical for chlorinated hydrocarbons. About 0.018 mcg (see Appendix A) of triazolam can form a single layer per square centimeter of the tube surface. The observed drug loss per square centimeter of the tube surface was far greater than the calculated monolayer value. Therefore loss of drug is not mainly due to monolayer sorption but it could possibly be multilayer formation or chemisorption followed by diffusion into the tube matrix.

Sorption of drugs can be predicted if the fraction remaining in solution is known at 24 hours (109). Using the fraction remaining data sorption numbers can be calculated using the following equation.

$$Sn.t = 0.75[\ln F_t + 1/2F^2_t - 1/2]$$

If the drug loss is governed by diffusion control then the predicted drug loss should be close to the observed drug loss.

Table XXIII: Sorption number calculation using fraction remaining data and calculation of predicted drug loss with the sorption number at 24 hours.

Time (hr)	Sn/hour	Drug loss	
		Predicted	observed
0.5	0.12	12.5	23
1	0.06	17	23
2	0.03	23	24
4	0.02	30	25
8	0.01	38	27
12	0.01	43	33
24	0.03	52	52

Sn: Sorption number.

Results in table XXIII showed variation in observed and predicted drug loss at earlier and later times. Higher observed drug loss than predicted at half hour indicates that the initial rapid drug loss is not due to diffusion. Close estimates of drug loss between one and four hours indicates that initially the drug is lost rapidly due to adsorption followed by diffusion. Decrease in rate of sorption at higher times further supports the diffusion controlled sorption mechanism. The mechanisms described in the recent publication (109) cannot be applied directly to this study because of differences in volumes, surface area and plastics (polyvinylchloride versus teflon and polyurethane) and different drugs. Since there was large variability in drug sorption among different tubes it is difficult to calculate the exact sorption number for triazolam in the tubes studied.

CONCLUSIONS

Delivery of triazolam and baclofen, two drugs commonly administered to critically ill patients by G-tubes, was studied in Foley catheters and Ross flexiflo tubes. Conclusions drawn from the observations and theoretical principles are:

Significant drug loss (20-70%) was observed for triazolam in both Foley catheters and Ross tubes in 24 hour sorption studies. Drug loss to tube materials could be related to the physicochemical properties of drug and tube materials. The slow equilibration was consistent with diffusion controlled penetration of the drug into the tube matrix. The large extent of drug loss was attributed to drug absorption into the matrix rather than adsorption to the tube surface. Concentration dependent drug loss was most consistent with absorption rather than adsorption, and was also consistent with drug penetration into the tube material. Persistent drug loss in repeated trials suggests diffusion of drug into the tube matrix, rather than a mono-layer adsorption. The irreversibility of triazolam sorption is consistent with a process in which the lipophilic drug partitions into the non-polar matrix of the tubing but does not redistribute back to water. The observed rapid initial loss of drug from solution followed by a slow perpetual loss suggests a rapid adsorption of drug onto the tube surface may occur followed by slow time dependent diffusion into the tube matrix. In surface area studies, the extent of drug loss was dependent upon the amount of drug presented to the tube and not on the total surface area exposed. A greater amount of drug was lost as the ratio of amount of drug exposed to total surface area was increased. Surface area independent drug loss was consistent with solute diffusion into the tube matrix but not adsorption onto the tube surface. Variability in drug loss was observed among different Foley catheters with equal and different concentrations. Changes in the tube construction and

physicochemical properties would explain the greater inter-tube variability than intra-tube variability in drug sorption. Tube materials from Foley catheters leached into the drug solution which was in contact with the tube. The leached materials were not identified but might be plasticizer, adhesives used to bind the teflon layer, or lubricants used in the tube manufacture. It is possible that the leached substances could be toxic and incompatible with the drugs.

APPLICATION OF RESULTS

Sorption of a significant amount of triazolam to both Foley catheters and Ross flexiflo G-tubes indicates that this drug has potential delivery problems in these tubes. Triazolam sorbs to tubes because of its low water solubility and high affinity for lipids. Sorption could be reduced by increasing the water solubility of the drug. Water solubility of this compound can be increased by increasing the percent ionized. The pH where triazolam is mostly ionized is highly acidic and therefore is not practical in clinical use. Use of co-solvents could possibly increase the solubility of triazolam in solution, leading to a decrease in sorption. Drug loss was dependent on the concentration, the time, the amount of drug exposed, and the flow rate. Therefore, to minimize drug loss to the tubes, dilute solutions should be administered in less than 30 mins for intermittent and bolus administration. Results from this study suggest that a triazolam concentration of less than 10 mcg/ml at a flow rate of 1 ml/min or greater would not have significant drug loss to either Foley catheter or Ross tubes.

Tubes should be washed with water after each dose to wash the residual drug from the tube surface. Drugs with low water solubility should not be administered with nutrient formulas because of the potential for interaction between food and drug or enhanced interaction of the drug with the tubes, due to a decrease in water solubility of the drug.

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Appendix A: Monolayer calculations for Triazolam

Fluid density (d) of triazolam = 1.1 g/cm^3

Radius of the molecule (r^3) = $(3/4\pi d) * 343 * (1/(6.02\ E23))$

$= 1.237 * 10\ E\text{-}22$

$r = 4.98 * 10\ E\text{-}8$

Area of the molecule = $4\pi r^2$

$= 3.12 * 10\ E\text{-}14\ cm^2$

Mass/cm^2 for monolayer coverage = $\frac{(343 * (1/(6.02 * 10E\text{-}23)))}{4\pi r^2}$

$= 1.827 * 10\ E\text{-}8\ g/cm^2$

$= 0.018\ mcg/cm^2$

Appendix B: Statistics and Symbols used in Appendices 1-16

Statistics:

A special case of anova is considered as a two sample t-test when there are only two groups. The t values can be obtained from the data tables by taking the square root of the F ratio value.

Symbols used:

aufs = absorption units full scale
aup = area under peak
n = number of observations
c = control
t = test
esd = standard deviation

measured values are 10^3 * values shown
(e.g 555 = 555,000)

Appendix 1: Sorption studies for Triazolam in Foley catheters

Exp. #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integrated AUP Control	Integrated AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
1	I	Tab (100)	100	0.2	555	353	2	5	17	11	358	<.0001
2	I	Tab (100)	100	0.2	634	370	5	7	24	35	212	<.0001
3	I	water	0	0.2	-	54	2	2	-	-		
4	I	Tab (100)	100	0.2	847	319	4	2	19	2	1351	<.0001
5	I II	Tab (100)	100	0.2	694.5	424 518	4	2 5	33	15 36	222	<.0001
6	I II	Tab (100)	50 100	0.2	332 634	249 415	3 5	4 5	10 24	7 10	359	<.0001

Appendix 2: Loss of Triazolam with respect to concentration in Foley catheter

Exp. #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integrated AUP Control	Integrated AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
1	Ia	Tab (100)	100	0.2	528	199	5	5	20	6	783	<.0001
	IIb	Tab (100)	50		222	101	3	3	8	8	555	<.0001
	IIa	Tab (100)	100		528	195	5	2	20	4		
	IIb	Tab (100)	50		222	78	3	4	8	2		
2	Ic	Tab (25)	25	0.02	3829	1559	6	3	113	97	285	<.0001
	Id	Tab (25)	10		1510	1185	5	2	40	124	81	<.0001
	IIc	Tab (25)	25		3829	2544	6	3	113	211		
	IId	Tab (25)	10		1510	918	5	3	40	60		
3	IIIa	Tab (25)	25	0.02	3561	1916	4	4	17	78	297	<.0001
	IIIb	Tab (25)	10		1453	790	2	4	74	47	144	<.0001
	IIIc	Tab (25)	25		3561	2082	4	3	17	182		
	IIId	Tab (25)	10		1453	869	2	3	74	21		

Appendix 3: Loss of Triazolam with respect to concentration in Foley catheter

Exp. #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integrated AUP Control	Integrated AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
4	IVa	Std	100	0.2	1073	242	2	2	53	58	384	<.0001
	IVb	Std	100			227		4		16		
	IVc	Std	50		495	150	2	3	23	6	684	<.0001
	IVd	Water	--		--	--	-	-	--	--		
5	Va	Tab (25)	25	0.02	3549	2538	4	3	50	68	761	<.0001
	Vb	Tab (25)	25			1884		3		54		
	Vc	Tab (25)	25		1485	1187	5	3	49	61	43	<.0001
	Vd	Tab (25)	25			1127		3		69		
6	VI	Std	50	0.05	283	207	4	4	13	23	22	.0002
	VIIIa	Std				184		2		22		
	VIIIb	Std				182		3		18		
	VII	Tab (100)	50	0.05	1943	1351	3	3	24	15	186	<.0001
	VIIIc	Tab (100)				1289		3		49		
	VIIId	Tab (100)				1187		3		65		
7	IX	Tab (100)	100	0.05	2592	1521	4	3	77	48	510	<.0001
	XIa	Tab (100)				1411		4		34		
	X	Tab (100)	50		1487	1038	4	4	29	16	997	<.0001
	XIb	Tab (100)				708				27		
	XII	Tab (100)	25	0.05	707.8	558	5	4	23	15	67	<.0001
	XIVa	Tab (100)				515		3		39		
	XIII	Tab (100)	10		267	239	4	3	7	1	80	<.0001
	XIVb	Tab (100)				209		4		8		

Appendix 4: Loss of Triazolam with respect to surface area in Foley catheter

Exp #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integ. Control	AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
1	A (3 ml)	Tab (25)	25	0.02	3382	3050	6	4	56	103	30	<.0001
	B (2 ml)					2997		5		60		
	C (1 ml)					2991		5		104		
2	A (3 ml)	Tab (100)	100	0.1	1161	1045	4	3	20	10	201	<.0001
	B (2 ml)					971		3		10		
	C (1 ml)					849		2		19		
3	A (3 ml)	Tab (25)	25	0.02	3405	3159	4	3	58	31	23	<.0001
	B (2 ml)					3423		4		52		
	C (1 ml)					3203		3		61		
4	D (3 ml)	Tab (25)	25	0.02	2287	2080	6	5	17	54	79	<.0001
	E (2 ml)	unstirred				1985		4		35		
	F (1 ml)					2015		5		36		
5	D (3 ml)	Tab (25)	25	0.02	2424	2143	2	5	0.7	53	54	<.0001
	E (2 ml)	unstirred				2141		5		29		
	F (1 ml)					4050		5		20		
6	D (3 ml)	Tab (25)	25	0.02	2748	2345	4	5	36	65	58	<.0001
	E (2 ml)					2355		5		69		
	F (1 ml)					2311		5		42		

Appendix 5: Equilibrium study of Triazolam in Foley catheter

Exp. #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integrated AUP Control	Integrated AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
1	Ia	Tab (25)	25	0.02	3793	2807	5	2	25	20	2681	<.0001
	Ib					2759		3		55		
	Ic					1661		2		22		
	Id					1444		3		36		
2	IIa	Tab (25)	25	0.02	3793	2766	5	3	25	84	1501	<.0001
	IIb					2828		2		10		
	IIc					1848		3		32		
	IId					1813		3		15		

Appendix 6: Equilibrium study of Triazolam in Foley catheter

Exp. #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integrated AUP Control	Integrated AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
1	Iuw	Tab (25)	25	0.02	3860	3360	4	3	45	113		
	Iw					3398		2		48		
2	Iuw					3576		2		19		
	Iw					3686		2		78		
3	Iuw					3752		2		59		
	Iw					3538		3		81		
4	Iuw					3668		2		17		
	Iw					3700		2		23		
5	Iuw	Tab (25)	25	0.02	3793	3717	5	2	25	62		
	Iw					3576		2		9		
6	Iuw	Tab (25)	25	0.02	3838	3499	3	2	108	18		
	Iw					3485		2		119		
7	Iuw					3730		2		4		
	fIw					3442		2		36		
8	Iuw					3688		2		8		
	Iw					3532		2		77		
9	Iuw					3545		2		82		
	Iw					3506		2		134		
10	Iuw					3386		2		69		
	Iw					3465		2		30		

Appendix 7: Effect of pre-washing on Triazolam sorption

Exp. #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integrated AUP Control	Integrated AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
1	Ia	Tab (100)	100	0.1	1064	314	5	2	50	9	194	<.0001
	Ib	Tab (100)	100			389		2		6		
	Ic	Tab (100)	100			580		2		33		
	Id	Tab (100)	100			444		3		48		
2	IIa	Tab (100)	100	0.1	1065	262	5	2	50	23	300	<.0001
	IIb	Tab (100)	100			447		2		28		
	IIc	Tab (100)	100			397		4		23		
	IId	Tab (100)	100			472		2		13		
3	IIIa	Tab (25)	25	0.02	3635	2783	5	3	55	55	173	<.0001
	IIIb	Tab (25)	25			2980		4		91		
	IVa	Tab (25)	25	0.02		2562		3		36	561	<.0001
	IVb	Tab (25)	25			2627		3		42		

Appendix 8: Clinical simulation study of Triazolam in Foley catheter

Exp. #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integrated AUP Control	Integrated AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
I	I	Tab (25)	25	0.02	3451	3467	3	4	15	51	2805	619

Appendix 9: Sorption studies for Triazolam in Ross tube

Exp. #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integrated AUP Control	Integrated AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
1	I	Tab (25)	25	0.02	3793	1051	5	4	25	29	24048	<.0001
2	I	water	--	0.02	--	307.7		3		0.6		
3	I	Tab (25)	25	0.02	3793	1325	5	4	25	28	19784	<.0001
4	I	Tab (12.5)	12.5	0.02	2021	1150	3	3	46	26	820	<.0001
5	I	Tab (12.5)	12.5	0.02	1981	1287	3	3	86	35	168	.0002
6	I	Tab (25)	25	0.02	3860	1876	4	3	45	69	2134	<.0001
7	I	Tab (12.5)	12.5	0.02	1936	1362	3	3	78	35	186	.0003
8	I	Tab (12.5)	12.5	0.02	1936	1359	3	3		54	98	<.0001
9	I	Tab (25)	25	0.02	3860	2040	4	3	45	57	2232	<.0001
10	I	Tab (25)	25	0.02	3860	1484	4	3		48	4449	<.0001

Appendix 10: Clinical simulation study of Triazolam in Ross tube

Exp. #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integrated AUP Control	Integrated AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
1	II	Tab (25) (Ud)	25	0.02	1927	1776	5	4	35	57	24	.0017
2	II	Tab (25)	25	0.02	3860	3898	4	3	45	66	0.86	.3962

Appendix 11: Sorption study for Baclofen in Foley catheter

Exp. #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integrated AUP Control	Integrated AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
1	I	tab	1000	0.2	2604	2595	4	4	72	40	0.03	0.97
	IIa	tab	1000	0.2		2604		4		72		
	IIb	8 td	1000	0.2	2698	2630	4	3	43	45	4.2	0.097

Appendix 12: Sorption study for Baclofen in Ross tube

Exp. #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integrated AUP Control	Integrated AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
1	I	tab	1000	0.2	2604	2697	4	3	72	11	4.76	0.0832

Appendix 13: Clinical simulation study for Baclofen in Foley catheter

Exp. #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integrated AUP Control	Integrated AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
1	III	tab	1000	0.2	2604	2622	4	3	72	28	0.16	0.70
	IV	std	1000	0.2	2698	2723	4	3	43	25	0.557	0.497

Appendix 14: Clinical simulation study for Baclofen in Ross tube

Exp. #	Tube #	Drug source	Conc. mcg/ml	AUFS	Integrated AUP Control	Integrated AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
1	II	tab	1000	0.2	2604	2653	4	3	72	34	1.12	0.337

Appendix 15: Loss of Triazolam with respect to time in Foley catheters

Exp. #	time	Tube #	Drug source	Conc. mcg/ml	AUFS	Integ. AUP Control	Integ. AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
1	.05	I	Tab (100)	100	0.2	528	413	5	4	20	12	199	<.0001
	1	I	Tab (100)	100	0.2		384		5		19		
	2	I	Tab (100)	100	0.2		295		3		10		
	4	I	Tab (100)	100	0.2		304		4		20		
	5	II	Tab (100)	100	0.2		257		3		13		
	20	II	Tab (100)	100	0.2		157		3		14		
2	0.5	III	Tab (25)	25	0.02	3829	2957	6	2	113	170	79	<.0001
	1	III	Tab (25)	25	0.02		2953		4		108		
	2	III	Tab (25)	25	0.02		2890		4		84		
	4	III	Tab (25)	25	0.02		2901		2		59		
	4	IV	Tab (25)	25	0.02		2834		3		120		
	8	IV	Tab (25)	25	0.02		2797		2		80		
	12	IV	Tab (25)	25	0.02		2582		3		159		
	24	IV	Tab (25)	25	0.02		1852		3		139		
3	0.5	V	Tab (25)	25	0.02	3561	2934	4	2	17	111	65	<.0001
	1	V	Tab (25)	25	0.02		2969		2		136		
	2	V	Tab (25)	25	0.02		2931		4		67		
	4	V	Tab (25)	25	0.02		3080		4		130		
	4	VI	Tab (25)	25	0.02		3393		3		109		
	8	VI	Tab (25)	25	0.02		3202		3		51		
	12	VI	Tab (25)	25	0.02		3538		2		20		
	24	VI	Tab (25)	25	0.02		2120		2		33		

Appendix 16: Loss of Triazolam with respect to time in Foley catheters

Exp. #	time	Tube #	Drug source	Conc. mcg/ml	AUFS	Integ. AUP Control	Integ. AUP Test	n C	n T	esd C	esd T	Statistics F-Ratio	Statistics Prob
4	.05	VII	Tab (100)	100	0.1	1044	637	5	2	22	38	92	<.0001
	1	VII	Tab (100)	100	0.1		682		4		23		
	2	VII	Tab (100)	100	0.1		566		3		12		
	4	VII	Tab (100)	100	0.1		538		3		29		
	4	VII	Tab (100)	100	0.1		729		4		52		
	8	VIII	Tab (100)	100	0.1		671		3		38		
	14	VIII	Tab (100)	100	0.1		554		4		32		
	24	VIII	Tab (100)	100	0.1		508		4		54		
5	0.5	IX	Tab (25)	25	0.02	3549	3134	4	2	50	65	111	<.0001
	1	IX	Tab (25)	25	0.02		3049		3		88		
	2	IX	Tab (25)	25	0.02		2853		3		110		
	4	IX	Tab (25)	25	0.02		2726		3		95		
	4	X	Tab (25)	25	0.02		2715		2		28		
	8	X	Tab (25)	25	0.02		2517		4		70		
	12	X	Tab (25)	25	0.02		2701		3		105		
	24	X	Tab (25)	25	0.02		1916		3		33		
6	0.5	XI	Tab (25)	25	0.02	4006	3459	4	2	90	3		<.0001
	1	XI	Tab (25)	25	0.02		3346		3		102		
	2	XI	Tab (25)	25	0.02		3306		3		28		
	4	XI	Tab (25)	25	0.02		3320		3		33		
	4	XII	Tab (25)	25	0.02		3450		4		91		
	8	XII	Tab (25)	25	0.02		2700		2		75		
	12	XII	Tab (25)	25	0.02		2287		2		79		
	24	XII	Tab (25)	25	0.02		2357		1				